The Effect of Dietary Intervention on Glycaemic Control in Patients with Type II Diabetes Mellitus

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DECLARATION

This thesis is the sole original work of the author and has not previously been submitted for or contributed to any comparable academic award at Thames Valley University (TVU) or any other academic institution.

Signed .....

(Rajadurai Akilen)

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LIST OF ABBREVIATIONS

ADA	American Diabetes Association
AHA	American Heart Association
BDA	British Dietetic Association
BGA	Blood Glucose Abnormalities
BMI	Body Mass Index
BMR	Basal Metabolic Rate
BP	Blood pressure
CAM	Complementary and Alternative Medicine
CE	Cinnamon Extract
CHD	Coronary Heart Disease
CONSORT	CONsolidated Standards of Reporting Trials
CP	Cinnamon Polyphenol
CVD	Cardio Vascular Disease
DBP	Diastolic Blood Pressure
DM	Diabetes mellitus
FBG	Fasting Blood Glucose
FPG	Fasting Plasma Glucose
GDM	Gestational Diabetes Mellitus
GLE	Gymnema Leaf Extract
GLUT-4	Glucose 4 Transporter vesicles
GS	*Gymnema Sylvestre*
GSK	Glycogen Synthesis Kinase
GA	Gymnemic Acid
HbA1c	Glycated Haemoglobin
HDL	High Density Lipoprotein
HOMA IR	Homeostasis Model Insulin Resistance index
IDDM	Insulin Dependent Diabetes Mellitus
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
IR	Insulin Resistance
IRS	Insulin Receptor Substrate
ITT	Intent to Treat
KRG	Korean Red Ginseng
LDL	Low Density Lipoprotein
LOCF	Last Observation Carried Forward
MC	Momordica Charantia
MHCP	Methyl Hydroxy Chalcone Polymer
MS	Metabolic Syndrome
MUFA	Mono Unsaturated Fatty Acids
NCCAM	National Center for Complementary and Alternative Medicine
NCEP	National Cholesterol Education Programme
NIDDM	Non Insulin Dependent Diabetes Mellitus
OGTT	Oral Glucose Tolerance Test
PI3K	Phosphatidal Inositol 3 Kinase
PPG	Postprandial Glucose

PQS	Panax Queguefolius Saponin
PUFA	Poly Unsaturated fatty Acids
RBC	Red Blood Cells
RCT	Randomized Controlled Trial
SBP	Systolic Blood Pressure
SFA	Saturated fatty Acids
T2DM	Type 2 Diabetes Mellitus
TFA	Trans fatty Acids
TE	Total Energy
TEI	Total Energy Intake
TG	Triglycerides
TTP	Tristetraprolin
TVU	Thames Valley University
VLDL	Very Low Density Lipoprotein
WC	Waist Circumference
WHO	World Health Organization

ABSTRACT

The prevalence of type 2 diabetes in the UK and Western society has continued to rise particularly given sedentary lifestyles and unhealthy food choices. There is growing evidence indicating that an effective dietary intervention could benefit patients by improving glycaemic control and the complications associated with type 2 diabetes mellitus.

In order to identify an effective dietary supplement for glycaemic control, a systematic review of randomized controlled trials (RCT) of *Mormordica, Ginseng, Gymnema* and *Cinnamomum* was conducted. The results of this review revealed that, although these supplements have shown a glucose lowering effect in patients with diabetes, there is insufficient evidence to actively recommend or discourage the use of these supplements, since the majority of the studies has not been confirmed by well defined, adequately powered RCTs. Prior to 2006, only one published human intervention trial of cinnamon and diabetes was accessible, however, this study had several important methodological limitations.

In order to evaluate the level of use of herbal dietary supplements, a survey of people with diabetes or features of metabolic syndrome was conducted by means of a questionnaire posted to 300 staff and students at Thames Valley University. Approximately 5% and 30% of the respondents reported that they either had diabetes or features of metabolic syndrome, respectively. It was concluded that individuals with diabetes or features of metabolic syndrome were more likely to use dietary supplements, especially herbal supplements, than individuals without diabetes or features of metabolic syndrome.

Based on the results of the systematic review and the survey, a randomized control trial was designed to evaluate the therapeutic effect of cinnamon on HbA1c, blood pressure and serum lipid profiles in patients with type 2 diabetes. A total of 58 patients (25 males and 33 females) with type 2 diabetes, aged 54.9 $\pm$ 9.8, treated only with hypoglycemic agents (not insulin) and with an HbA1c of more than 7% were recruited from Brent NHS. Patients were randomly assigned to receive either 2g of cinnamon (n=30) or placebo (n=28) every day for 12 weeks. The results of this RCT demonstrated that, after intervention, the mean HbA1c, systolic and diastolic blood pressures were significantly decreased ($P<0.05$) in the cinnamon group compared to placebo group. A decreasing trend in fasting plasma glucose (FPG), waist circumference and body mass index (BMI) was observed for both groups, however this decrease was more pronounced in the cinnamon group, but was not significant compared to placebo. There was no significant reduction in serum lipid profiles either between or within the groups.

In conclusion, dietary supplementation of 2g of cinnamon for 12 weeks may reduce the HbA1c, systolic and diastolic blood pressures among poorly controlled type 2 diabetic patients with HbA1c of $\geq$ 7%. The dose of cinnamon administered in our study was safe and well tolerated over the 12 weeks of treatment and shows promising effects. However, the sustainability and durability of the effect of cinnamon has not been tested nor has its long term tolerability and safety both of which will need to be determined and long term intervention trials will need to be conducted.

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CHAPTER 1

INTRODUCTION AND OVERVIEW OF THESIS

1 Introduction

This introductory chapter has provided an overview and the issues for people with diabetes to be considered in the design of the research. The different sections in this chapter present the classification of diabetes, brief literature review on the scale of the problem and the knowledge base which sets the context for the thesis. This chapter summarizes and enhances the understanding of the research results and provides additional details on some of the related areas that were not the specific focus of this research. The main chapters of this research work (chapter 2 to chapter 4) are then presented in the thesis, followed by a general conclusion and reflections of thesis (chapter 5).

This chapter consists of two main sections. Section 1.1 - The structure of the thesis, which gives details on arrangement of chapters, overview and aims of the thesis. Section 1.2 - Introduction to Diabetes Mellitus, which provides a brief description of the epidemiology of diabetes, its classification, diagnosis, associated pathology, and its treatment, especially dietary management.

1.1 The structure of the thesis

The key intention of this thesis is to introduce an effective dietary intervention which could be introduced alongside normal medication to improve glycaemic control in patients with type 2 diabetes mellitus. Therefore, identifying appropriate dietary intervention, studying the acceptability or the level of use of dietary supplements and investigating the efficacy of such dietary supplements in glycaemic control is essential.

The starting point, and to some degree the overall objectives and scope of this research work, originates in an interest to explore the applicability, tolerability and effectiveness of the dietary intervention of cinnamon on glycaemic control. People with diabetes are more likely to develop cardio vascular disease (CVD) than those without diabetes, and modifiable risk factors, such as hyperglycaemia, dyslipidaemia and hypertension that could be targeted in intervention programmes to decrease these risk factors.

This thesis is constructed in the following way,

1. Part 1 - Identifying appropriate dietary intervention
2. Part 2 - Study of the acceptability and the level of use of dietary supplements
3. Part 3 - Investigating the efficacy of dietary supplements on glycaemic control

Part 1 – Identifying appropriate dietary intervention

The previous studies of the use of dietary intervention for glycaemic control (Yeh *et al*, 2003; Khan *et al,* 2003) suggested different dietary supplements may be useful and that four supplements were promising and could be used as an effective anti-diabetic therapies; *Ginseng, Momordica, Gymnema,* and *Cinnamomum* (cinnamon). Therefore, based on the results of these studies, and considering the safety, tolerability and acceptability of dietary herbal supplements by the general population in the UK a detailed systematic review was conducted on *Momordica, Gymnema* and *Cinnamomum* and is presented in chapter 2. Furthermore a general literature review was performed on *Ginseng* and diabetes mellitus (chapter 2).

The proposed title of this thesis was initially registered with Thames Valley University (TVU) in February 2006. Prior to 2006 there were more human intervention trials published on the anti-diabetic efficacy of M*omordica, Gymnema,* and *Ginseng.* Furthermore the first human trial on *Momordica* and diabetes was reported in 1977 (Baldwa *et al,* 1977) and up until 2006, six human studies had been published on the anti diabetic effect of *Momordica.* Similarly, prior to 2006, three, five and one human trials respectively were published on anti diabetic effect of *Gymnema, Ginseng* and *Cinnamomum.*

Part 2 - Study the acceptability and the level of use of dietary supplements

A survey was conducted as part of this thesis to determine whether individuals with diabetes or features of metabolic syndrome were more likely to use different dietary supplements compared with individuals without diabetes or metabolic syndrome. This survey was carried out as a stepping stone, prior to the randomised controlled trial (in part 3) to investigate the acceptability or willingness to take dietary supplements by individual's diabetes or features of metabolic syndrome. The results of this study demonstrated that individuals with diabetes or features of metabolic syndrome were more likely to use dietary or herbal supplements than their counterparts. Furthermore this study suggested that introducing dietary or herbal supplements to individuals with diabetes or metabolic syndrome was likely to be acceptable and feasible.

Part 3 - Investigating the efficacy of dietary supplements on glycaemic control

Interestingly, prior to 2006, although the anti-diabetic potency of cinnamon had been demonstrated by numerous animal and *in vitro* studies, there was either very limited data in the literature on human intervention trials to support the clinical efficacy of cinnamon in glycaemic control. Only one published human intervention trial (Khan *et al,* 2003) of cinnamon was accessible prior to 2006 (Chapter 2). However, the results of this study were

ambiguous due to poorly described study design and clinical outcomes, especially the measurement of glycated haemoglobin levels (HbA1c). Therefore, the need for good human clinical data prompted the author to initiate a clinical trial in 2006 to further explore the anti diabetic potential of cinnamon in the management of type 2 diabetes mellitus. This thesis presents the first human intervention trial conducted in UK, to investigate whether cinnamon has the potential to control blood glucose (HbA1c), blood pressure and serum lipid profiles in patients with type 2 diabetes mellitus. The potential of cinnamon was subsequently recognised by other researchers, and studies increased with 4 more human studies published between 2006 and 2009 (Mang *et al,* 2006; Blevins *et al,* 2007; Vanschoonbeek *et al,* 2006; Altschuler *et al,* 2007). This study was finally completed in January 2009.

A randomized placebo controlled double blind clinical trial was designed to evaluate the anti diabetic potential of cinnamon (chapter 4). This study was initiated in January 2006 and completed in January 2009. In order to develop the study protocol, the feasibility of conducting such trial was reviewed with the support of the Research and Development office of West London Primary Care Research Network (WeLReN) and the Nutrition and Dietetics Department of NHS Brent, London. NHS Brent holds the NHS budget for a local population of around 347,500 people, and is one of the most ethnically diverse UK communities and has a high UK prevalence of diabetes.

1.1.1 Overview and aims of this thesis

The systematic review of dietary supplements of *Cinnamomum*, *Gymnema* and *Momordica* (chapter 2) illustrates the current impact of these herbal dietary supplements on glycaemic control and its potential effect for people with diabetes mellitus. In addition, it has highlighted some possible future directions. The recent rise in obesity and diabetes prevalence in UK demonstrates the urgent need for effective therapies. Therefore, the aim of this PhD thesis was to provide new information regarding dietary intervention that may improve existing therapeutic strategies in type 2 diabetes mellitus along with conventional medication.

This thesis is divided into 5 distinct chapters. This chapter (chapter 1) describes the structure and overview of the thesis and provides an introduction to diabetes. Chapter 2 explores the evidence for the effectiveness of some important RCTs of dietary supplements of *Ginseng*, *Gymnema*, *Momordica* and *Cinnamomum* in the management of diabetes mellitus. Chapter 3 describes and displays the results of a survey investigating the acceptability and level of use of dietary supplements by individuals with features of metabolic syndrome and/or diabetes mellitus. Chapter 4 presents the randomized placebo controlled double blind

clinical trial which explored cinnamon's ability to improve blood glucose, serum lipid profiles and blood pressure among type 2 diabetic patients. This is the first RCT in UK to evaluate the clinical efficacy of cinnamon in the management of diabetes.

The topic of cinnamon was chosen after close inspection of the literature to identify gaps in the evidence base, and to discover possible novel therapeutics that may be useful in the management of type 2 diabetes mellitus or metabolic syndrome. Chapter 5 discusses the reflections and general conclusions of the thesis.

In summary, the central aim of this thesis was to explore the management of type 2 diabetes mellitus, with a focus on the effectiveness of dietary intervention of cinnamon. This was achieved through the following objectives.

Main research aim -

1. To investigate whether cinnamon has the potential to improve glycaemic control, serum lipid profiles and blood pressure among type 2 diabetic patients using a randomized controlled trial.

Secondary research aim -

1. To examine the acceptability and level of use of dietary or herbal supplements by individuals with self reported features of metabolic syndrome or diabetes mellitus.
2. To systematically review the current evidence base for the effectiveness of dietary supplements especially *Cinnamomum, Momordica* and *Gymnema* for the management of diabetes mellitus and make suggestions for future research.

1.2 Introduction to Diabetes mellitus

Diabetes mellitus is a chronic medical condition that requires continuing medical care, patient self management and lifestyle modifications to prevent acute complications and reduce the risk of long term complications. Diabetes mellitus is a disease where blood glucose levels are above normal. This is due to glucose in the blood failing to enter cells, increases the glucose level in the blood (Hui *et al,* 2009). High blood glucose, also known as hyperglycemia, can damage nerves and blood vessels, leading to complications such as heart disease, stroke, kidney dysfunction, blindness, nerve problems, gum infections and amputation (Hui *et al,* 2009). Therefore, glucose-lowering drugs, lifestyle modifications such as exercise, weight control and diet therapy are recommended for the effective management of diabetes mellitus (Tuomilehto *et al,* 2001).

The incidence of late-onset diabetes is rapidly increasing in the UK as overweight and obesity becoming more prevalent (Soloman *et al,* 2007). Obesity affects more than 300 million people worldwide, representing a 50% increase in only 7 years (Torgerson *et al,* 2004). A number of studies have demonstrated that the risk of developing type 2 diabetes is closely linked to the presence and duration of overweight and obesity (Colditz *et al,* 1995; Hu *et al*, 2001; Must *et al,* 1999). Indeed approximately 90% of individuals with type 2 diabetes are either overweight or obese (Kumanyika *et al,* 2002). Obesity is recognised as an independent risk factor for type 2 diabetes mellitus and symptoms associated with metabolic syndrome (Solomon, 2007; Mokdad *et al,* 2003). Excess body fat, particularly abdominal visceral fat, leads to impaired glucose tolerance and changes in lipid metabolism, causing insulin resistance and hyperinsulinaemia (Goldstein *et al,* 2003).

1.2.1 Criteria for the diagnosis of diabetes mellitus

The methods used to diagnose diabetes, must also be confirmed by a repeated measurement on a subsequent day (American Diabetic Association, 2005; WHO 1999[b]). Table 1.1 shows the criteria for the diagnosis of diabetes. However, because of ease of use, acceptability to patients, and lower cost, fasting plasma glucose (FPG) is the preferred diagnostic test. Furthermore, the use of the glycated haemoglobin (HbA1c) test for the diagnosis of diabetes is not recommended at this time (American Diabetic Association. 2005). Patients diagnosed with diabetes are also recommended to maintain the following clinical parameters effectively based on American Diabetic Association (2005) and WHO (1999[b]) guidelines, as these guidelines are widely practiced in all countries (WHO 1999[b]); HbA1c < 7%, preprandial plasma glucose: 90 – 130 mg/dl (5 – 7.2 mmol/l), peak postprandial plasma glucose: <180 mg/dl (10 mmol/l), blood pressure < 130/80 mmHg, LDL cholesterol < 100 mg/dl (< 2.6 mmol/l), HDL cholesterol (> 40 mg/dl (> 1.1 mmol/l) and serum triglycerides <

150 mg/dl (< 1.7 mmol/l). There are no differences in ADA and WHO guidelines in the criteria for the diagnosis of diabetes.

Table 1.1 – Criteria for the diagnosis of diabetes mellitus based on American Diabetic Association (2005) and World Health organization (1999[b]) guidelines.

Symptoms of diabetes and a casual plasma glucose ≥ 200 mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.
FPG ≥ 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 hours
2 hours plasma glucose ≥ 200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.

1.2.2 Impaired glucose tolerance (IGT)

Impaired glucose tolerance (IGT) is the first abnormal stage in the natural history of type 2 diabetes that can be identified quite easily (Erikson *et al,* 1999). IGT is an intermediate category between normal glucose tolerance and overt diabetes (Harris, 1989; Tuomilehto *et al,* 2001), and it can be defined by an oral glucose tolerance test. Subjects with IGT have an increased risk of type 2 diabetes mellitus (The DECODE study, 1999). Therefore, IGT refers to an abnormal glucose regulation in the fasting state (FPG > 6.1 mmol/l and < 7.0 mmol/l) (Erikson *et al,* 1999). The overall prevalence of IGT varies greatly between studies, depending on the study population and survey methods. For the 45 – 54 year age group, the prevalence varies between 2-13.6% in European populations, and for the age group of over 65 years the corresponding figures are 6.8 - 23% (Valle *et al,* 1997). Therefore, subjects with IGT have a greater risk of developing diabetes and are a suitable group for testing the feasibility and effectiveness of the primary prevention of type 2 diabetes mellitus.

1.2.3 Glycated Haemoglobin (HbA1c)

The glycated haemoglobin (HbA1c) test has been suggested as one of the main diagnostic tests for type 2 diabetes (Bennet *et al*, 2007). Red blood cells (RBC) contain a molecule of haemoglobin, and glucose molecules stick to the haemoglobin to make glycated haemoglobin (Peters *et al,* 1996). RBC's live for 8 to 12 weeks before they are replaced in the body. Therefore, measuring the HbA1c represents an 8 to 12 weeks (2 to 3 months) average of blood glucose concentrations (Bennet *et al,* 2007). Furthermore, HbA1c can be measured at any time of the day regardless of the duration of fasting or the content of the

previous meal (Manley *et al,* 2006; Mannucci *et al,* 2003). Therefore, HbA1c remains the most important long term predictor of complications in diabetes, and the effect of any intervention on HbA1c is critical in determining its clinical usefulness (Altschuler *et al,* 2007).

The validity of HbA1c as a screening tool for diabetes has also been examined by using oral glucose tolerance test (OGTT) as the gold standard and FPG as the comparison (Bennet *et al,* 2007). This comparison suggested that HbA1c and FPG are equally effective screening tools for the detection of type 2 diabetes, and the HbA1c cut of point of $\geq$ 6.1% was the recommended optimum cut off point for HbA1c in most reviewed studies (Tanaka *et al,* 2001; Peters *et al,* 1996; Herdzik *et al,* 2002; Bennet *et al,* 2007). Different ethnic groups have been found to have different sensitivities to HbA1c which may be related to genetic differences in the concentration of haemoglobin, the rate of glycation and the life span of red blood cells (Ko *et al,* 1998; Saydah *et al,* 2002). Finally, any intervention measuring HbA1c as a primary study outcome should be tested for at least 12 weeks.

1.2.4 Classification of diabetes mellitus

According to the American Diabetic Association guidelines (American Diabetic Association, 2005), the classification of diabetes can be categorised into 4 clinical types; type 1 diabetes, type 2 diabetes, gestational diabetes and other specific types of diabetes.

1. Type 1 diabetes - results from β-cell destruction in the pancreas, usually leading to absolute insulin deficiency.
2. Type 2 diabetes - results from a progressive insulin secretory defect on the background of insulin resistance. This is the major form of diabetes, accounting for approximately 90 – 95% of all diabetic cases. This form of diabetes usually begins with insulin insensitivity, a condition in which muscle, liver and fat cells do not respond to insulin properly (Hui *et al,* 2009). The pancreas eventually loses the ability to produce and secrete enough insulin in response to food intake. Type 2 diabetes mellitus is preventable with lifestyle intervention (Lindstrom *et al,* 2003). The risk of diabetes was reduced by 58% in the previous intensive lifestyle intervention studies (Tuomilehto *et al,* 2001).
3. Gestational diabetes mellitus (GDM) – this is diagnosed during pregnancy caused by hormonal changes or insulin insufficiency during pregnancy.
4. Other specific types of diabetes – these are due to other causes, for example; genetic defects in β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas, and drug or chemical induced.

1.2.5 Prevalence of diabetes in UK

The prevalence and incidence of type 2 diabetes has increased in the UK over the past decade which may be mainly explained by the changes in obesity prevalence (Masso-Gonzalez *et al,* 2009). The diabetes statistics report published by the Diabetes UK association (Diabetes UK, 2009) has been used to report the prevalence of diabetes in the following section.

Currently, the UK is facing a rapid increase in the number of people with diabetes. Since 1996, the number of people with diabetes has increased from 1.4 million to 2.5 million. By 2025 it is estimated that over 4 million people will have diabetes in UK. More than 150,000 people were diagnosed with diabetes in 2007 in the UK, i.e. approximately 410 people diagnosed every day. Globally diabetes affects 246 million people and is expected to affect 380 million by 2025. The prevalence of diabetes in the adult population across the UK is given in Figure 1.1. This gives a UK average prevalence of 3.8%. For adults in the UK, it was estimated that 10% of people with diabetes have type 1 diabetes and 90% of people with diabetes have type 2 diabetes. Similarly, among children 15% and 85% of people have type 1 and type 2 diabetes respectively.

Country	Prevalence	No of people
England	3.9	2,088,335
Nothern Ireland	3.3	60,822
Scotland	3.7	200,669
Wales	4.4	138,988

Figure 1.1 - The number of people and prevalence (%) of diabetes in the adult population across the UK (England, Northern Ireland, Scotland and Wales) in 2008; Data from Diabetes UK, 2009. Data presented as prevalence rate (%) and number of peoples (n).

1.2.6 Risk factors associated with diabetes mellitus

The chances of developing diabetes may depend on an individual's genetic predisposition, lifestyle, obesity and/or environmental factors. The most commonly known risk factors associated with diabetes are; age, overweight or obesity, family history, lack of habitual physical activity, race or ethnicity, hypertension or hyper-cholesterolaemia and polycystic ovary syndrome in women (American Diabetic Association, 2004). On average if both parents have either type 1 or type 2 diabetes, the risk of individual developing diabetes is

between 30 or 75% respectively (Diabetes UK, 2009). Furthermore diabetes is more common among South Asian and African and African-Caribbean origins; for example, type 2 diabetes is up to 6 times more common in people of South Asian descent and up to 3 times more common among people of African and African-Caribbean's (Department of Health, 2001).

Type 2 diabetes has the strongest association with obesity and lifestyle factors (Williams & Pickup, 2004). Almost two in every three people in the UK are overweight or obese (62% of women and 66% of men) (World Health Organization, 2005). Deprivation is strongly associated with higher levels of obesity, physical inactivity, unhealthy diet, smoking and poor blood pressure control (All party parliamentary group for diabetes and Diabetes UK, 2006). Therefore, all these factors are inextricably linked to the risk of diabetes.

1.2.7 Dietary Management of Diabetes

1.2.7.1 Dietary carbohydrate management

Dietary and lifestyle modifications are the first line of treatment for type 2 diabetes, and other chronic conditions such as obesity and metabolic syndrome. Recently published reviews suggest that weight loss improves glycaemic control and reduces risk factors associated with type 2 diabetes (Anderson *et al,* 2003; Aucott *et al,* 2004). Weight loss can be achieved either through a negative energy balance; achieved by reducing total energy intake (diet control) or increasing energy expenditure or energy output (by regular physical activity). Evidence indicates that increasing physical activity is of great importance for long-term maintenance of weight loss (Ewbank *et al,* 1995). Low calorie diets produce rapid initial weight loss than conventional diets (Franz *et al,* 2002; Williamson *et al,* 200). The major determinant of energy requirement is basal metabolic rate (BMR), which is determined by body weight, age, gender and physical activity patterns (Department of Health, 1991).

People with diabetes should be encouraged to take 20 to 30 minutes of physical activity on most days based on their age and fitness (Diabetes & Nutrition study group of the European Association for the Study of Diabetes, 2000). Regular physical exercise improves insulin resistance, lipid profiles (reduce triglycerides and improve HDL cholesterol), and blood pressure (Ha & Lean, 1998), and can reduce HbA1c by 0.7% in type 2 diabetes (Boule *et al,* 2001).

1.2.7.2 Carbohydrate load or glycaemic load

Blood glucose concentration following a meal is determined by the rate of appearance of glucose into the blood stream and it's clearance from the circulation (Sheard *et al,* 2004; Schenk *et al*, 2003), and the rate of disappearance of glucose is largely influenced by insulin secretion and it's action on target tissues (Defronzo *et al,* 1982). The amount of carbohydrates has the greatest influence on blood glucose, and both the quantity (carbohydrate or glycaemic load) and type of carbohydrates found in foods influence postprandial glucose levels (Franz *et al,* 2002). Numerous studies have demonstrated improvements in glycaemia, glucose tolerance and lipid profiles with high carbohydrate diets (Brunzell *et al,* 1971; Kiehm *et al,* 1976; Swinburn *et al,* 1991; Vidon *et al,* 2001; Komiyama *et al*, 2002). In contrast high fat diets have repeatedly been associated with the development of insulin resistance (Parker *et al,* 1993; Mayer *et al,* 1993; Marshall *et al,* 1997). According to the Nutrition Subcommittee of the Diabetes Care Advisory Committee of Diabetes UK (2003), low carbohydrate diets are not recommended in the management of diabetes mellitus. Although dietary carbohydrate is major contributor to postprandial glucose concentration, it's an important source of energy, water soluble vitamin and minerals and fiber.

1.2.7.3 Glycaemic index

The glycaemic index is defined as the increase in blood glucose (over the fasting level) that is observed in the 2 hours following ingestion of a set amount of carbohydrate in an individual food; this value is then compare with the equivalent amount of reference food (white bread or glucose) (Jenkins *et al,* 1981).The glycaemic index is a measure of the change in blood glucose following ingestion of carbohydrate containing food (Sheard *et al,* 2004). Therefore, both the amount (load) of carbohydrate as well as the type of carbohydrate in a food will influence its effect on postprandial blood glucose levels.

1.2.7.4 Dietary fat management

The results of the Nurses' Health Study demonstrated that diets with high in fibre, have a low glycaemic load, a high poly unsaturated fatty acids (PUFA) and PUFA to saturated fatty acid (SFA) ratio (PUFA to SFA ratio) and a low trans fatty acid intake are important for the effective management of type 2 diabetes mellitus (Hu *et al,* 2001).

High amounts of dietary fats are thought to influence insulin sensitivity and cardiovascular risk by altering the fatty acid composition of phospholipids in the cell membranes of skeletal muscle (Pan et al, 1995; Vessby, 2000). These changes may then affect insulin receptor binding or affinity, the ability to translocate or insert glucose transporters (see section

1.2.8.1), ion permeability or cell signalling (Vessby, 2000). Furthermore, high polyunsaturated fatty acid (PUFA) intakes have been inversely associated with fasting glucose concentrations (Trevisan *et al,* 1990) and have been shown to improve glycaemic control in animal models (Field *et al,* 1990). The replacement of SFA with MUFA for three months has been shown to improve insulin sensitivity (Vessby *et al,* 2001), for example Mediterranean diets with low SFA and high MUFA are associated with lower rates of incidence of diabetes and cardio vascular diseases (CVD) (Gannon *et al,* 2003; Gannon & Nuttall, 2004). The harmful effects of SFA on total cholesterol and LDL cholesterol reported to increase the risk of CVD (Cromwell & Otvos, 2004). Therefore, dietary management of fats plays an important role in effective glycaemic control in diabetic patients.

1.2.8 Insulin regulation of glucose uptake in cells

Insulin is the most important hormone in the regulation of blood glucose concentration. In a healthy person, as the blood glucose concentration rises, pancreatic beta cells secrete insulin and stimulate glucose uptake into fat and muscle cells to promote the storage of sugar as intracellular triglycerides and glycogen in fat and muscles (Khan & Pessin, 2002). Further, insulin inhibits the production and release of glucose from the liver (gluconeogenesis and glycogenolysis process). In contrast, in patients with type 2 diabetes, the blood glucose concentration remains increased, despite the presence of normal insulin concentration in the blood stream (Khan & Pessin, 2002; Gould & Holman, 1993). This is due to a combined inability of muscle and adipose tissue to facilitate glucose uptake and of the liver to suppress glucose output in response to increasing amounts of insulin and is referred to as insulin resistance (Khan & Pessin, 2002). Figure 1.2 shows the insulin regulation of glucose uptake (Roberts *et al,* 2003)

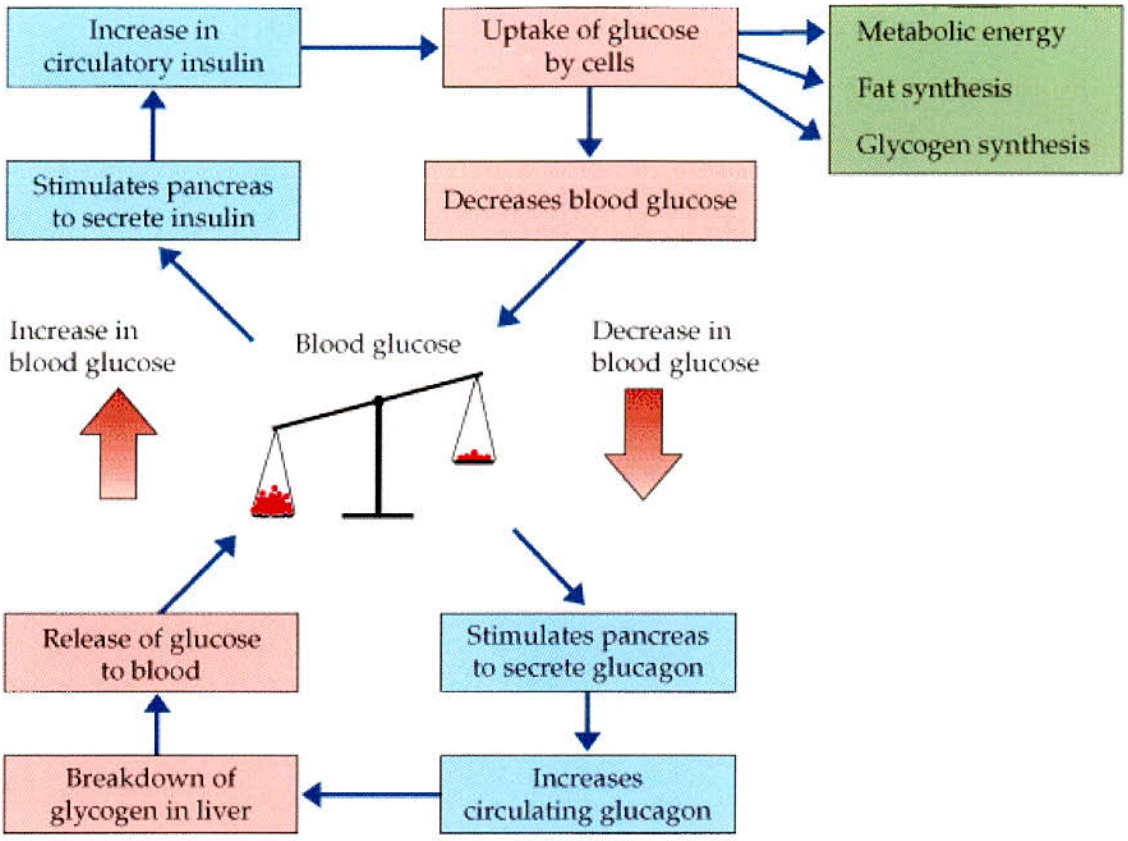


Figure 1.2 – Insulin mediated glucose regulation in human body (source: Roberts *et al,* 2003)

1.2.8.1 Glucose transport mechanism

Glucose transport is mediated through solute carriers of glucose transporter (GLUT) family in cells, and there are five established functional facilitative glucose transporter isoforms GLUT1 to GLUT-5 (Ramm *et al,* 2006; Watson & Pessin, 2001). Among the GLUT family, GLUT-4 is responsible for insulin stimulated glucose uptake predominantly in fat and muscles. In general, GLUT-4 is present in the intracellular compartment, while in the presence of insulin, GLUT-4 is start moving to the membrane of fat and muscle cells (Slot *et al,* 1991; Smith *et al,* 1991). This process is called translocation of GLUT-4 storage compartments to the plasma membrane. However, this process is readily reversible such that when circulating insulin levels decline; GLUT4 transporters are removed from the plasma membrane (by endocytosis) and are recycled back to their intracellular storage compartments (Watson & Pessin, 2001).

According to Youngren (2003), the insulin stimulated glucose uptake pathway occurs as follows; the effects of insulin on glucose uptake are mediated via the insulin receptor (IR) which, following insulin binding, undergoes autophosphorylation on tyrosine residues

activating tyrosine kinase activity. The activated IR then phosphorylates IRS-1 and other substrates (Shepherd & Khan, 1999). Tyrosine phosphorylated IRS-1 then serves as a docking protein for PI3-kinase, which is activated by this interaction. The necessity of PI3-kinase activation in the insulin effect is demonstrated by the complete ablation of the stimulatory effect of insulin on glucose transport when cells are incubated with specific inhibitors of this serine kinase (Robert, 2003). The serine phosphorylation cascade initiated by PI3-kinase involves activation of PI3K-dependent serine/threonine kinases (PDK), and, in turn, Akt and results in the translocation of intracellular GLUT4 to the cell surface. It is the increased amount of GLUT4 on the cell plasma membrane that results in an increased rate of glucose transport into the cell. The insulin signalling pathways involved in stimulating glucose transport in shown in Figure 1.3.

Even though the signaling mechanism by which insulin can mobilize GLUT4 to the plasma membrane has been extensively studied, many aspects are yet to be defined fully (Welsh *et al,* 2005). It is known that insulin, through the activation of its receptor tyrosine kinase, leads to the stimulation of the PI3Ks (phosphoinositide 3-kinases) and implicated in insulin-stimulated GLUT4 translocation (Zeigerer *et al,* 2004). The PI3K pathway is known to be essential for the action of insulin, since the promotion of GLUT4 translocation and the stimulation of glucose transport are both blocked by the PI3K inhibitor wortmannin and by dominant-negative mutants of this enzyme. Activation of PI3K is a major pathway in the mediation of insulin stimulated glucose transport and metabolism (Shepherd & Khan, 1999). Therefore, insulin-responsive tissues are balanced to respond rapidly and efficiently to fluctuations in circulating insulin levels. Unfortunately, the complexity of these regulatory processes provides numerous potential targets that may be defective and eventually result in peripheral tissue insulin resistance and possibly diabetes (for detailed mechanisms see sections 2.6.2 and 2.6.3).

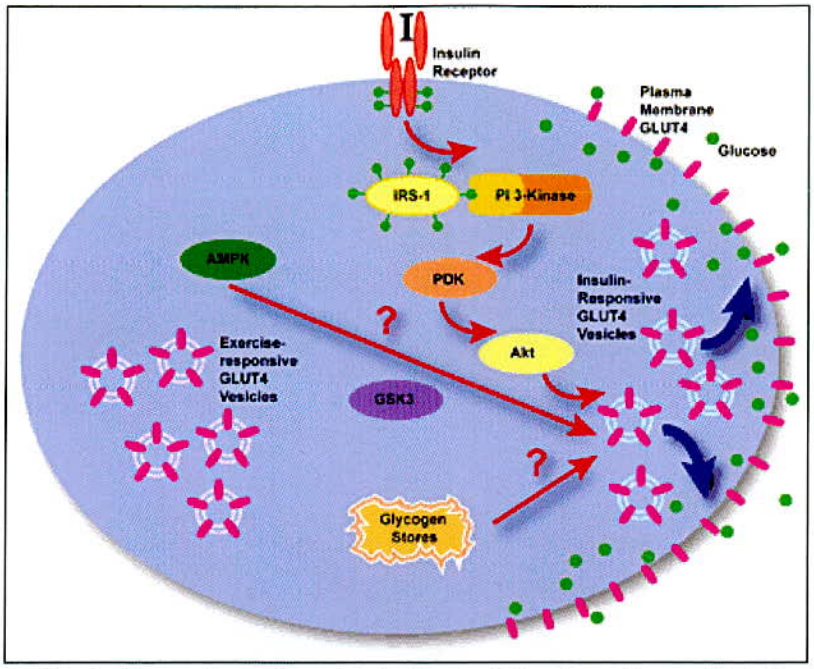


Figure 1.3 - Insulin signalling pathways involved in stimulating glucose transport in body cells

Insulin binding to the IR results in phosphorylation of tyrosine residues (in green) on the receptor and substrates such as IRS-1. Docking of the regulatory subunit of PI3-kinase to phosphotyrosine residues of IRS-1 activates its serine/threonine kinase activity and the phosphorylation cascade involving PDKs and Akt. While these steps are necessary for the recruitment of intracellular pools of insulin-responsive glucose transport to the plasma membrane, the mechanism connecting Akt to cellular trafficking of GLUT4 is not known (Source: Youngren, 2003)

1.2.9 Metabolic syndrome

The metabolic syndrome, previously named syndrome X (Reaven, 1988) or the insulin resistance syndrome (Zimmet, 1992), is a cluster of conditions, including abdominal obesity, glucose intolerance, insulin resistance, dyslipidaemia and hypertension (Eckel *et al,* 2005). There are numerous specific definitions of the metabolic syndrome; a number of expert groups have attempted to develop a unifying definition for the metabolic syndrome. The most widely accepted of these definitions have been produced by the World Health Organization (WHO, 1999), The European Group for Study of Insulin Resistance (EGIR) (Balkau *et al,* 1999) and the National Cholesterol Education Programme – Third Adult Treatment Panel (NCEP ATP III) (NCEP, 2001). All these groups agree on the components of the metabolic syndrome; obesity, insulin resistance, dyslipidaemia and hypertension (Alberti *et al,* 2006). However, they provide different clinical criteria to identify such a cluster (for metabolic syndrome).

The NCEP ATP III (NCEP, 2001) state that the metabolic syndrome may be diagnosed when a person has three or more of the following five components. The components are;

- Waist circumference: > 102 cm in men and > 88 cm in women
- Serum triglycerides: ≥ 1.7 mmol/l

- HDL cholesterol: < 1.0 mmol/l in men and < 1.3mmol/l in women
- Blood pressure: ≥ 130/85 mmHg
- Serum glucose: > 6.1 mmol/l

Most importantly NCEP ATP III definition includes waist circumference as the measure of obesity, and this guideline was used throughout the thesis. The elevated blood pressure associated with obesity and glucose intolerance and commonly occurs in insulin resistant patients (Alberti *et al,* 2006). Nowadays the obesity epidemic is one of the main drivers of the high prevalence of the metabolic syndrome, as the prevalence of obesity is increasing rapidly (Hu *et al,* 2004; Visscher *et al,* 2001; Dobson *et al,* 1998). Furthermore, obesity contributes to hyperglycaemia, hypertension, high serum triglycerides, low HDL and insulin resistance and is associated with higher cardio vascular disease risk (Alberti *et al,* 2006). Therefore, rapid BMI and weight gain during childhood and adolescence is a risk factor for metabolic syndrome (Fall *et al,* 2008).

1.2.9.1 Prevalence of metabolic syndrome.

The metabolic syndrome is estimated to affect approximately 19.4% of men and 17.2% of women aged over 24 years in Australia (Alberti *et al,* 2006). Another study revealed that metabolic syndrome generally affects twenty to twenty-five percent of the Australian and US adult populations (Dunstan *et al,* 2002; Ford & Giles, 2003). Therefore, it is expected that the UK prevalence is similar. Regardless of the definition used, the syndrome is associated with an increased risk of cardiovascular disease (CVD), morbidity and mortality (Dekker *et al,* 2005) and type-2 diabetes (Lorenzo *et al,* 2003). Table 1.2 shows the prevalence of components of the metabolic syndrome in men and women with out diabetes in Europe, and the UK prevalence may also expected to be similar to Europe.

Table 1. 2 - Prevalence of components of the metabolic syndrome in men and women without diabetes in Europe

Components of metabolic syndrome	Prevalence (%)	
	men	women
≥2 of the components	35.3	29.9
≥3 of the components	12.4	10.7
Hyperinsulinaemia plus any 2 of more of the other components	15.7	14.2
Hyperinsulinaemia plus any 3 or more of the other components	7.7	6.3

Components of metabolic syndrome are: obesity, dyslipidaemia, impaired glucose regulation and hypertension (source: Alberti *et al,* 2006; Hu *et al,* 2004).

1.2.10 Conventional therapies for type 2 diabetes mellitus

Today's clinicians are presented with an extensive range of oral anti-diabetic drugs for type 2 diabetes. The main classes are heterogeneous in their modes of action, safety profiles and tolerability (Krentz & Bailey, 2005). These main classes include agents that stimulate insulin secretion (sulphonylureas and rapid-acting secretagogues), reduce hepatic glucose production (biguanides), delay digestion and absorption of intestinal carbohydrate (alpha-glucosidase inhibitors) or improve insulin action (thiazolidinediones) (Krentz & Bailey, 2005).

The sulphonylureas are widely used as adjuncts to dietary measures in the treatment type 2 diabetes mellitus (Krentz *et al,* 1994). These drugs exert their hypoglycaemic effects by stimulating insulin secretion from the pancreatic β-cell (Frances, 1996). Their primary mechanism of action is to close ATP-sensitive K-channels in the β-cell plasma membrane, and so initiate a chain of events which results in insulin release (Frances, 1996). The main adverse effect associated with sulphonylureas is hypoglycaemia. This effect is a predictable consequence of the principal pharmacological effect of these drugs, i.e. sensitisation of the islet beta-cell to glucose, resulting in enhanced endogenous insulin secretion (Krentz *et al,* 1994). Sulphonylurea-induced suppression of hepatic glucose production may cause profound and protracted hypoglycaemia (Krentz *et al,* 1994).

Metformin is widely regarded as the drug of choice for most patients with type 2 diabetes (Ripudaman *et al,* 2000). Metformin reduces fasting plasma glucose concentrations by reducing rates of hepatic glucose production (Ripudaman *et al,* 2000). However, its effect on the relative contributions of hepatic glycogenolysis and gluconeogenesis remains controversial. Studies suggest that metformin works mostly by reducing rates of

gluconeogenesis or by reducing rates of hepatic glycogenolysis (Ripudaman *et al*, 2000). The insulin-sensitising thiazolidinedione class of anti-diabetic agents has potentially advantageous effects on multiple components of the metabolic syndrome (Krentz & Bailey, 2005).

Delayed early insulin response to glucose or a meal always accompanies chronic hyperglycaemia and is not normalized by non-pharmacologic treatment (Melander, 1996). Continuous exposure to high concentrations of sulphonylureas may down regulate beta-cell sensitivity (Frances, 1996). Metformin also improves insulin action. It is as antihyperglycaemic as sulphonylureas but does not cause hyperinsulinaemia, weight increase or hypoglycaemia (Frances, 1996). The risk of lactic acidosis can be minimized by avoiding metformin in subjects with renal impairment (Melander, 1996). Combined treatment with sulphonylurea and metformin can be highly effective even in advanced type 2 diabetes mellitus (Melander, 1996; Frances, 1996). The main oral antihyperglycaemic agents of sulphonylureas, metformin and alpha-glucosidase inhibitors can be used alone or in combination to obtain better metabolic control, sometimes with insulin (Scheen & Lafebvre, 1995).

1.2.11 Dietary intervention on insulin resistance or diabetes mellitus

The risk of obesity and related chronic health conditions such as insulin resistance or diabetes, cardiovascular disease (CVD) and dyslipidaemia are rapidly increasing nowadays. This may be due to the sedentary lifestyle of the population or the public perception that the effort required to improve health is too high. Therefore, introducing an alternative dietary supplement to improve the chronic conditions associated with obesity, especially diabetes mellitus is sensible.

It has been stated that there is an urgent need for new therapeutic approaches to target the various facets of type 2 diabetes mellitus, as currently, in more than half of all type 2 diabetic patients, glucose levels are poorly controlled six years after diagnosis, irrespective of which treatment is used (Marakis, 2000). Therefore, in view of the potential side effects of conventional drugs and the safe records that attend dietary supplementation (Marakis, 2000), an investigation into the potential value of a herbal dietary supplement approach is timely. As a result, following a search of the important herbal dietary supplements, we found that certain herbal supplements can improve glycaemic control in diabetes. Among these herbal supplements, human intervention trials on cinnamon were minimally reported. Enthused by this and the fact that herbal dietary supplement practices are widespread in the general population in UK (Felicity *et al,* 2008; Ernst & White, 2000), we attempted to

investigate the efficacy of cinnamon on glycaemic control among people with type 2 diabetes mellitus.

1.2.11.1 Cinnamon and diabetes mellitus

The potential hypoglycaemic effect or adipocyte glucose utilization of cinnamon in an *in-vivo* animal study was first reported by Khan *et al,* in 1990. After this study, a number of *in vitro* and *in-vivo* animal studies provide evidence of the glucose lowering potential of cinnamon (Qin *et al,* 2003; Broadhurst *et al,* 2000; Jarvil-Taylor *et al,* 2001; Roffey *et al,* 2006). The first human intervention trial of cinnamon and diabetes was published in 2003 by the same investigators Khan *et al,* (2003). The findings of this study demonstrated that, administration of 1g, 3g or 6g of cinnamon per day for 40 days significantly reduced fasting plasma glucose (FPG), serum total cholesterol and LDL cholesterol in type 2 diabetic patients (see section 2.6 for more details). However, this study did not investigate the effect of cinnamon on glycated haemoglobin (HbA1c), systolic and diastolic blood pressures and body mass index or waist circumference. Regardless of the convincing *in vitro* and *in-vivo* animal evidence of cinnamon, the picture in human intervention trials is less clear and further work is warranted. At the time of planning experimental work in 2006, the metabolic effect of cinnamon on HbA1c and blood pressure were unknown, and only Khan's publication (Khan *et al,* 2003) was available.

CHAPTER 2

SYSTEMATIC REVIEWS AND ANTI DIABETIC PROPERTIES OF SOME IMPORTANT HERBAL DIETARY SUPPLEMENTS

Momordica, Gymnema, Ginseng and Cinnamomum

2.1 General introduction

This chapter explores the use and effect of some important medicinal plants in the management of diabetes and glycaemic control. To date, over 400 medicinal plant treatments for diabetes have been reported (Bailey & Day, 1989). However, only a small number of these plants have been evaluated in order to assess their efficacy in glycaemic control through *in-vitro*, *in-vivo* animal studies and well defined human intervention trials. Yeh *et al,* (2003) systematically reviewed the anti diabetic potential of 14 different herbal dietary supplements and suggested that *Ginseng, Gymnema and Momordica* could be used as an effective herbal dietary supplement for diabetes. This review (Yeh *et al,* 2003) did not include the potential herb of *Cinnamomum* (cinnamon), as human intervention trials on cinnamon did not start until 2003. In 2003 Khan *et al,* published an article which showed that people suffering from type 2 diabetes who consumed cinnamon pills reduced their blood cholesterol and glucose levels considerably. Therefore, this chapter systematically reviews the anti-diabetic properties of three important herbal dietary supplements of *Momordica, Gymnema and Cinnamomum.* Furthermore, a general review on *Gymnema* and diabetes mellitus also included in this chapter.

The general methodology of systematic reviews of dietary supplements of *Momordica, Gymnema and Cinnamomum* is discussed in section 2.2. A systematic appraisal of randomized controlled trials (RCTs) of *Momordica* in the management of type 2 diabetes mellitus is discussed in section 2.3. Section 2.4 of this chapter includes; a systematic review of *Gymnema* in the management of type 2 diabetes mellitus. Section 2.5 explores the efficacy of *Ginseng* in the management of diabetes mellitus. However, this section did not include an extensive systematic review of *Ginseng*, as these plants are not widely used or studied for diabetes mellitus. A detailed and in-depth systematic review of randomized controlled trials of cinnamon and type 2 diabetes mellitus is discussed in section 2.6 as cinnamon was chosen to conduct RCT. The general conclusions of this chapter is discussed in section 2.7

Previous studies demonstrated that the following herbal dietary supplements showed anti diabetic or glucose lowering properties; such as, garlic (Sitprija *et al,* 1987), *Aloe vera* (Bunyapraphatsara *et al*, 1996; Yongchaiyudha *et al,* 1996), *Artocarpus* (Fernando *et al,* 1991), *Bauhinia forficate* (Russo *et al,* 1990); *Coccinia indica* (Azad Khan *et al,* 1979; Kamble *et al,* 1996), *Fiscus carica* or fig leaf (Serraclara *et al,* 1998), *Ginseng* (Sotaniemi *et al,* 1995; Vuksan *et al,* 2000; Vuksan *et al,* 2001), *Gymnema* (Baskaran *et al,* 1990; Shanmugasundaram *et al,* 1990), *Momordica* (Welhinda *et al,* 1986; Baldwa *et al,* 1977), *Ocimum sanctum* (Agrawal *et al,*

1996), *Trigonella* or fenugreek (Sharma *et al*, 1990; Madar *et al,* 1988), *Opuntia* (Frati *et al,* 1990) and cinnamon (Khan et al, 2003). However, most of these studies were published before 2000 and conducted in Asian countries and may not be feasible for western population.

The blood glucose lowering effects of herbal dietary supplements are subject to several factors (Hui *et al,* 2009). Firstly, each herb contains thousands of components, only a few of which may be therapeutically effective (Angelova *et al,* 2008). Secondly, different parts of herb have different ingredient profiles. Moreover, different extraction methods may yield different active ingredients (Shan *et al*, 2007).

There is a growing database of clinical trials investigating the effects of several herbs in diabetes *(www.clinicaltrials.gov)*. The efficacy, safety and potential mechanisms of herbal dietary supplements in glycaemic control have been well described in a recent systematic review of 42 randomized and 16 nonrandomized clinical trials (Yeh *et al*, 2003). However, the anti-hyperglycaemic efficacy remains inconclusive for the majority of these herbal dietary supplements especially *Mormordica, Gymnema, Ginseng and Cinnamomum* (Yeh *et al*, 2003).

2.1.1 Objective

The objective of this chapter was to systematically review and summarises the randomized controlled trials (RCTs) of *Momordica, Gymnema and Cinnamomum* for use in glycaemic control or diabetes management and to suggest recommendations for future studies.

2.2 General methodology

A systematic search of randomized controlled clinical trials of *Momordica, Gymnema, cinnamomum* and type 2 diabetes mellitus in human was conducted from the earliest possible date through 30 January 2009. Search terms included free text terms, MeSH (Medical Subject Heading), and Medline medical index terms. For instance, "diabetes mellitus", *"cinnamon", "Momordica", "Gymnema",* "type 2 diabetes mellitus" and each crossed with the term "diabetes mellitus". A search of the following databases was conducted.

- All evidence based medicine (EBM) reviews - Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effectiveness, CCTR, CMR, HTA and NHSEED, Allied and Complementary Medicine 1985 to January 2009,
- EMBASE 1986 to 2009 Week 3
- Ovid MEDLINE(R) 2004 to January Week 1 2009.
- JAMA, BMJ, High wire press and lancet database January 2003 to January 2009.

In addition hand searches of references of key articles were also carried out. The selection of RCTs based on the specific inclusion and exclusion criteria's and the systematic review flow diagrams (methods of inclusion) of *Momordica, Gymnema* and *Cinnamonmum* were explained in sections 2.3.2; 2.4.2 and 2.6.5 respectively.

2.3 Therapeutic effect of *Momordica* in the management of Diabetes Mellitus

2.3.1 Introduction

Momordica charantia belongs to the family of Cucubitaceae commonly known as bitter melon, balsam pear, bitter gourd, balsam apple or karela, and is used as an important medicinal plant (Virdi *et al,* 2003). *Momordica* is a vegetable indigenous to tropical areas, including India, Asia, South America and Africa and could be used as an alternative therapy to treat diabetes mellitus, because components of bitter melon extract appear to have structural similarities to animal insulin (Batran *et al,* 2006; Basch *et al,* 2003). Nutritional analysis showed that it is a rich source of iron, calcium and β-carotene and it also contains vitamin A, B and phosperous (Rosales & Fernando, 2001). In the recent past years there has been a high interest to screen *Momordica* for its anti diabetic potential.

***Momordica* fruit/vegetable**

Active constituents of *Momordica* and mechanism of action

The active components of bitter melon are thought to be charantin, vicine, and polypeptide-p (insulin like protein). It appears to increase insulin secretion, tissue glucose uptake, liver muscle glycogen synthesis, glucose oxidation and decrease hepatic gluconeogenesis (Basch *et al,* 2003; Baldwa *et al,* 1977; Yeh *et al,* 2003; Shibib *et al,* 1993). Studies carried out in animal models, mainly steptozotocin induced diabetic rats and mice, have shown significant lowering of blood glucose levels after supplementation with *Momordica* (Day *et al,* 1990; Higashino *et al,* 1992; Singh *et al,* 1989; Ahmed *et al,* 2001; Sitasawad *et al,* 2000; Ali *et al,* 1993). It has also been noted that the number of pancreatic beta cells increases among those (rat models) treated with *Momordica* (Ahmed *et al,* 1998). A number of phytochemicals have been isolated from bitter melon but the constituents responsible for the hypoglycaemic activities have not been determined yet (Harinantenaina *et al,* 2006). Cucurbitane triterpenoids of the ether fraction of *Momordica* methanol extract have shown blood hypoglycaemic effects *in vivo* studies (Harinantenaina *et al,* 2006). The alcoholic extracts of *Momordica charantia* (MC) induces a significant decrease in serum glucose levels, and which suggest that MC extract possesses antidiabetic and hypolipidemic effect in alloxan induced diabetic rats (Batran *et al,* 2006).

The hypoglycaemic effect of bitter melon is said to be mediated through an insulin secretogenic effect through an influence on the enzymes involved in glucose metabolism (Platel &

Srinivasan, 1997). Methanol extract of *Momordica* normalised blood glucose levels, reduces triglycerides and LDL levels and increased HDL level in diabetic rat models fed with high fat and low carbohydrate diet for 30 days (Chaturvedi *et al,* 2004). The anti oxidant activity of the aqueous extract of *Momordica* seeds exerts rapid protective effects against lipid peroxidation by scavenging of free radicals there by reducing the risk of diabetic complications in streptozotocin induced diabetic rats (Sathishsekar & Subramanian, 2005). It was suggested that the isolated active protein extract (polypeptide-p or p-insulin) from *Momordica* could be used as an effective hypoglycemic agent when administered subcutaneously to humans (Khanna *et al,* 1981). The phytochemicals of momordicin, charantin, and a few compounds such as galactose binding lectin and insulin like proteins isolated from various parts of *Momordica* plant have been shown to have insulin mimetic activity (Saxena & Vikram, 2004)

The water extract of *Momordica* fruit also effectively reduced blood glucose and serum insulin levels (Miura *et al,* 2001). Bitter melon has also been reported to depress the activities of key gluconeogenic enzymes, glucose 6 phosphatase and fructose 1,6 diphosphatase (Sekar *et al,* 2005) and these enzymes play an important role in elevation of fasting blood glucose levels. The hypoglycaemic effect of *Momordica* may also attribute to an inhibitory effect on glucose absorption in the intestine (Meir & Yaniv, 1985) and inhibit gluconeogenesis (Bailey & Day, 1989). The potential anti-diabetic properties of *Momordica* include; alcohol-extracted charantin consists of mixed steroids (Sarkar *et al,* 1996) and insulin-like polypeptide, polypeptide-P (Baldwa *et al,* 1977) compounds, which plays an important role in glycaemic control.

Shetty *et al,* (2005) carried out a study to find out the effect of the edible portion of *Momordica* by adding 10% to the diet in streptozotocin induced diabetic rats (animal study). The results of this study clearly provided experimental evidence that dried bitter melon powder when added to the diet at 10% (90% diet and 10% dried bitter melon powder) level improved diabetic status signifying its beneficial effect during diabetes in animal study. Fasting blood glucose level was observed to be 30% lower in animals consuming bitter melon when compared with controls. Therefore this study demonstrates that regular consumption of bitter melon in the diet may reduce the blood glucose level in primary development stages of diabetes mellitus.

Ahmed *et al,* (2004) investigated the beneficial effects and mechanism of action of the *Momordica* juice in streptozotocin induced diabetic rats. This study revealed that daily oral administration of *Momordica* juice exerted a marked beneficial effect in diabetic rats, and it can

regulate glucose uptake into jejunum membrane (small intestine) brush border vesicles and stimulate glucose uptake into skeletal muscle cells similar to the response obtained with insulin. During diabetes, structural and functional changes in the alimentary tract are known to take place resulting in increased absorption of intestinal glucose and alterations in the activities of brush border disaccharides (Kumar *et al,* 2005). Therefore, one of the other proposed mechanisms of the hypoglycaemic effect of *Momordica* have been attributed to an inhibitory effect on glucose absorption in the intestine (Meir & Yaniv, 1985)

2.3.2 Methods

Figure 2.1 shows the systematic review diagram where the inclusion and exclusion criteria were applied to select the studies. A total of 75 articles were identified, of these only 2 articles met the strict inclusion criteria for randomized controlled trials for *Momordica* and type 2 diabetes mellitus.

Inclusion and exclusion

Out of these 75 articles, 67 were excluded either because of duplicates, because they were *in vivo* animal studies, *in vitro*/laboratory studies, not published in English language, did not have an abstracts or author's name or did not include adequate study methodology or intervention. From the remaining studies of *in vivo* human intervention trials of *Momordica* (n=8), 6 studies were excluded because they were case series or case control trials of *Momordica* and diabetes (Rosales & Fernando, 2001; Ahmed *et al,* 1999; Srivastava *et al,* 1993; Welhinda *et al,* 1986; Letherdal *et al,* 1981; Baldwa *et al,* 1997). Finally 2 randomized controlled clinical trials of cinnamon and type 2 diabetes mellitus was included for further review and analysis (Dans *et al,* 2007; John *et al,* 2003). Data from 2 randomized controlled trials (RCTs) were included and analysed in detail for participant numbers, population characteristics, methodology, inclusion and exclusion criteria's and results in order to investigate the blood glucose lowering effect of *Momordica.*

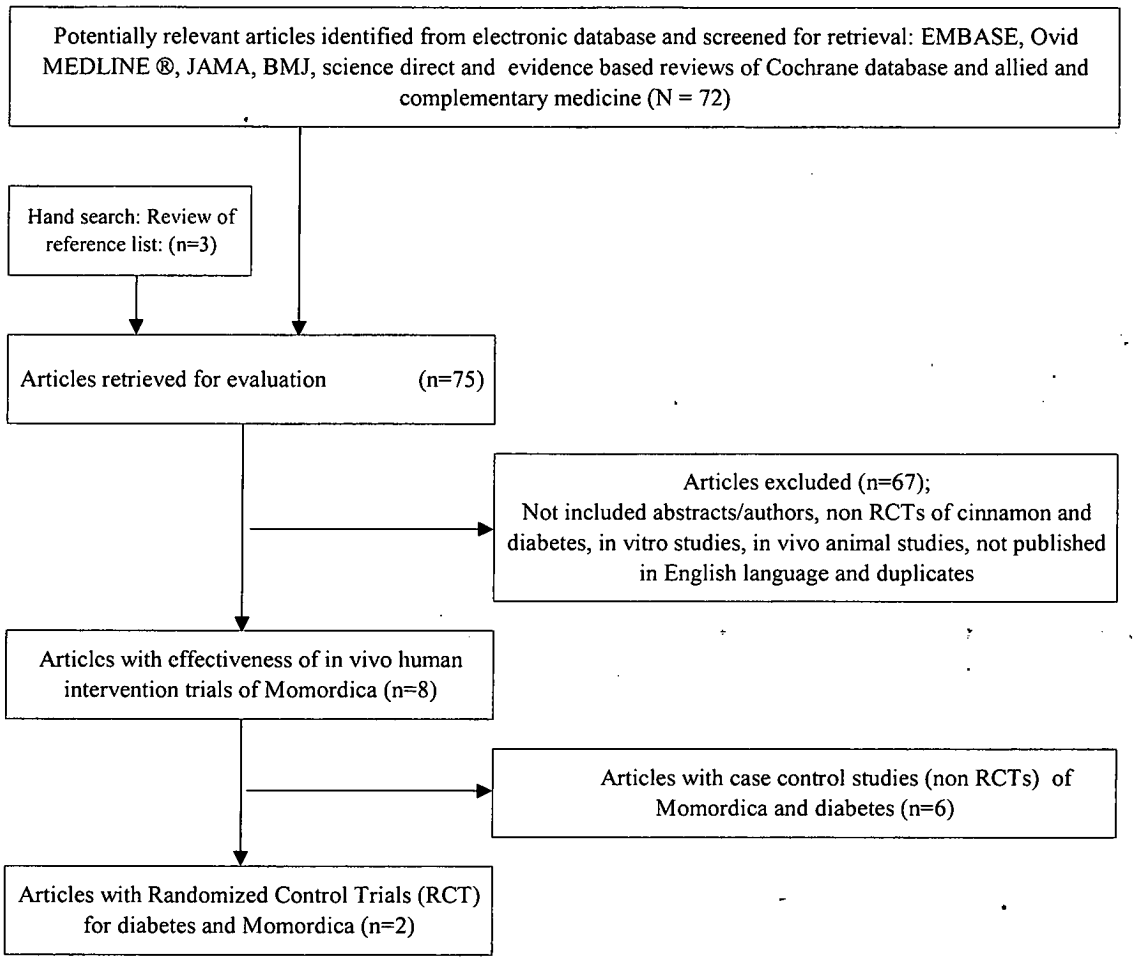


Figure 2.1 - Systematic review of *Mormodica* and diabetes mellitus, n = number of articles, RCT - randomized control trials. A total of 75 articles were identified, of these only 2 articles met the strict inclusion criteria for RCT for *Momordica* and type 2 diabetes mellitus

2.3.3 Results

Two randomized, placebo controlled trials of patients with type 2 diabetes mellitus were included in this review. These studies together considered a total of 90 patients who were followed up for a period of between 2 weeks to 3 months. Table 2.1 and Table 2.2, shows the baseline characteristics and methodologies of the selected RCTs. Among these 2 RCTs, only one was a randomized, double-blind, placebo-controlled clinical trial (Dan *et al,* 2007). Both trials administered the same *Momordica* species of *Momordica charantia.* The dose of *Momordica* in these studies ranged from 3g to 6g per day. One study provided *Momordica* powder (6g/day) in the intervention group (John *et al,* 2003) and the other RCT provided aqueous extract (3g/day) of *Momordica* (Dans *et al,* 2007).

Table 2.1 shows the baseline characteristics of the 2 RCTs. Gender, sample size, age and baseline fasting plasma glucose (FPG) was found to be approximately similar in both RCTs, and therefore it is less likely that heterogeneous factors contributed to these contrasting results. There are differences in ethnicity (Indians and Philippines) which might have contributed to the heterogeneity of results. However, the sample sizes of the two studies were powered adequately. John *et al,* (2003) did not reported different outcomes on BMI, blood pressure, serum lipid profiles and HbA1c levels compared with Dans *et al,* (2007).

John *et al,* (2003) reported the results of first RCT of efficacy of *Momordica* as an oral hypoglycemic agent among Indian type 2 diabetic patients. In his trial, a total of 50 type 2 diabetic patients with fasting plasma glucose (FPG) of 140 – 200mg/dl or post prandial plasma glucose (PPS) of 200 – 300 mg/dl were randomized to receive either *Momordica* tablets (*Momordica charantia* - 6g dried powdered fresh whole fruit) or placebo (6g riboflavin) for a period of 2 to 4 weeks. As the tablets were dissimilar, the investigator could not be blinded in this trial and this is a limitation of the study. The mean values of FPG and PPS after two and four weeks of *Momordica* supplementation did not demonstrate any significant changes.

Furthermore, this study suggests that there could be many reasons for the insignificant changes in blood glucose levels, such as bitter melon may not have hypoglycemic effect, larger quantity of the drug may have to be ingested and drying the fruit or actual making of the tablets may have affected the efficacy of bitter melon. Therefore this study concluded that dried whole fruit of bitter melon has no blood sugar lowering effect, when administered at the specific dose. Even though the sample size calculation and randomization procedures were clearly illustrated in this study, blinding and placebo effects (due to riboflavin) are not adequately explained. None of the patients reported any side effects or gastrointestinal disturbances due to *Momordica* supplementation in this study.

Dans *et al,* (2007) reported the second randomized, double blind, placebo controlled trial to determine the efficacy and safety of *Momordica* as an adjunct to standard therapy of newly diagnosed type 2 diabetes mellitus. A total of 40 patients (15 males and 25 females) over 18 years old, diagnosed with type 2 diabetes mellitus, taking only oral hypoglycemic agents and HbA1c between 7% - 9% (sub optimal glycemic control) were recruited for this trial and randomized to consume either *Momordica charantia* (extract) or placebo capsules. The intervention group received 3g of *Momordica* (2 capsules of *Momordica charantia* three times

per day after meals) and the control group received placebo at the same dose for 3 months period. The primary outcome of this trial is to measure the changes in HbA1c and the secondary outcome includes changes in fasting blood sugar, serum cholesterol, blood pressure and body weight.

The results of this study (Dans *et al,* 2007) suggest that the HbA1c in both the intervention and control group showed a statistically insignificant rise with a mean change of -0.28% and -0.50% respectively. Also there was no significant effect on mean fasting plasma glucose, total cholesterol and BMI. Gastro intestinal complaints such as diarrhea, epigastric pain and gastroenteritis were the most common reported adverse events in this study.

Table 2.1 – The baseline characteristics of the study population in selected RCTs of *Momordica* and type 2 diabetes mellitus.

Variable	John *et al*, (2003)			Dans *et al*, (2007)	
Treatment	*Momordica*		Placebo	*Momordica*	Placebo
N	n = 26		n = 24	n = 20	n = 20
Men	7		9	7	8
Women	19		15	13	12
Ethnicity	Ethnicity not noted but recruitment was from India			Philippines	
Mean Age (years)	52.3 ± 10.9 52.2 ± 6.2	Males Females	57.6 ± 7.6 50.9 ± 10.8	58.7 ± 9.81	59.76 ± 10.04
Baseline mean FPG (mmol/l)	8.25 ± 1.47 14.54 ± 1.80*		8.56 ± 1.37 13.95 ± 1.61*	8.40 ± 2.24	8.14 ± 2.36
Baseline mean SBP (mmHg)		___		132.5 ± 11.18	133.0 ± 11.74
Baseline mean DBP (mmHg)		___		80.5 ± 9.44	77.8 ± 18.75
Baseline Body Mass Index (kgm^{-2})		___		26.37 ± 4.75	26.00 ± 3.94
Baseline mean total cholesterol (mmol/l)		___		5.25 ± 1.46	5.08 ± 1.09
Baselines mean HbA1c (%)		___		7.92 ± 0.59	8.07 ± 0.77

Data presented as means ± SD; N corresponds to the number of participants at beginning;* Baseline post prandial plasma glucose Level; FPG – Fasting Plasma Glucose; SBP – Systolic blood pressure; DBP – Diastolic blood pressure

Table 2.2 - Summation of methodologies used in the selected RCTs of *Momordica* and type 2 diabetes studies.

Methodology	John *et al*, (2003)	Dans *et al*, (2007)
Study design	Randomized, placebo controlled trial	Randomized, Double-blind placebo controlled trial
Type of *Momordica* used	Dried powdered fresh whole fruit	*Momordica* extract
Dose of *Momordica*	6g per day	3g per day
Study duration	2 to 4 weeks	3 months
Inclusion	Type 2 diabetes mellitus, Patients with fasting plasma glucose of 140 – 200 mg/dl or post prandial plasma glucose of 200 – 300 mg/dl	At least 18 years old, Type 2 diabetes mellitus and sub optimal glycaemic control of HbA1c of 7% - 9%,
Exclusion	Type 1 diabetes, Patients with fasting plasma glucose of > 200 mg/dl or post prandial plasma glucose of > 300 mg/dl, diabetic related complications, pregnant women and patients on insulin treatment	Evidence of hepatic dysfunction, known plant allergic, severe chronic or acute illness, pregnancy and lactation and inability to attend follow up clinics
Conclusion	6g of dried whole *Momordica* powder per day for 4 weeks did not demonstrate any significant effect on FPG	3g of *Momordica* extract for 3 months did not suggest any anti-diabetic effects

2.3.4 Case control studies of *Momordica* and diabetes

To date there are only two randomized controlled clinical trials which have evaluated the effect of *Momordica*, and both have reported no promising effects on glycaemic control. The clinical studies carried out so far have some several important limitations; small sample size which may not adequately powered, short intervention periods, poor blinding and not controlled. However, the hypoglycemic effect documented from previous case control or non randomized trials demonstrated that *Momordica* has the ability to control glycated hemoglobin (HbA1c) (Rosales & Fernando, 2001; Srivastava *et al,* 1993; Leathedale *et al,* 1981) and fasting plasma glucose (Ahmed *et al,* 1999; Srivastava *et al,* 1993; Welhinda *et al,* 1986; Baldwa *et al,* 1977). Table 2.3 shows the design, sample and intervention of these case control studies of diabetes and *Momordica.*

Rosales and Fernando, (2001) investigated the effect of bitter melon tea among type 2 diabetic patients with suboptimal glycemic control. A total of 27 patients were randomly assigned to receive either bitter melon tea (n=14) or commercial (lipton) tea (n=13) for 12 weeks with a cross over at 12 weeks. Bitter melon tea was prepared by using dried fruits with 650ml of boiled water and brewed for additional 5 minutes. Each patient was advised to drink one glass (200ml) of either bitter melon tea or lipton tea after each major meal. Patients who took bitter melon tea showed a significant reduction (- 0.63%, P = 0.005) in their HbA1c. The mean decrease in fasting plasma glucose was found to be insignificant (-2.96mg/dl; p=0.403). Further more the observed changes in HbA1c and FPG during lipton tea (control) usage were not statistically significant. It was concluded that bitter melon may be a useful dietary adjunct in the management of type 2 diabetes mellitus.

Ahmad *et al,* (1999) investigated the effect of aqueous suspension of bitter melon pulp on fasting and postprandial serum glucose levels in 100 type 2 diabetic patients for 2 days. The effect at one hour after bitter melon administration and then two hours after 75g oral glucose tolerance test (OGTT) was evaluated. The results of this study revealed that on the second day, mean fasting blood glucose after bitter melon extract supplementation was (131mg/dl), significantly different from first day mean fasting glucose level (152mg/dl) without bitter melon extract ($p<0.001$). Similarly the mean 2-hour blood glucose (after 75g OGTT) was also reduced from 257mg/dl to 222mg/dl after bitter melon extract supplementation. However, the author did not explain how the dose of bitter melon extract was administered in this study.

Srivastava *et al,* (1993) conducted a case series study to find out the effect of aqueous bitter melon and dried bitter melon powder on blood glucose levels in 12 type 2 diabetic patients. Seven of these patients received aqueous extract of 100g chopped bitter melon fruit and five of these patients received 5g of dried fruit powder three times per day for 3 weeks. Patients who received aqueous extract showed a significant reduction in their mean blood glucose (56%) and HbA1c levels (8.37% to 6.95%; $p<0.01$). This is a poorly designed study without any baseline description of patient's characteristics, statistical analysis, study duration and sample size.

Welhinda *et al,* (1986) conducted a case series, non-randomized, open label crossover trial involving 18 patients with newly diagnosed type 2 diabetes mellitus. Patients treated with 100ml of bitter melon juice 30 minutes before glucose loading for glucose tolerance test (GTT) shows moderate significant improvement in GTT compared to patients treated with distilled water as control. No adverse effects were reported in this study. This study was not randomised or blinded, also the crossover design, preparation method of bitter melon juice and patients characteristics were not well established in this trial.

Leatherdale *et al,* (1981) examined the effect of bitter melon juice and fried bitter melon fruit on blood sugar levels in nine Asian diabetic outpatients (6 men and 3 women). All patients underwent three 50g oral glucose tolerance tests (OGTT); a standard test, a test with 50ml bitter melon juice and a test after 8-11 weeks of taking 230g fried bitter melon fruit daily. The standard test and the test with added bitter melon juice were performed after 7 to 10 days and blood glucose and HbA1c levels were measured.

The oral glucose tolerance test (OGTT) carried out after the period of 230g of fried fruit and juice ingestion revealed a mean decrease in glucose levels of approximately 6% and 12% respectively after one hour. In addition, consuming fried bitter melon for 8-11 weeks significantly reduced HbA1c levels (8%) compared to standard test. This study has some areas of methodological weaknesses, including a lack of controls, failure to describe patient's baseline characteristics, and inadequate explanation of statistical methods, and therefore firm conclusions cannot be drawn from this study.

Table 2.3 – Summary of case controlled studies of *Momordica* and diabetes mellitus

Study	Design	Sample	Duration	Intervention	Results
Rosales & Fernando 2001	Open label, cross over, clinical trial	N=27; type 2 diabetes mellitus, treated with only oral hypoglycemic agents, age 40 - 70 years, HbA1c between 7.1% - 9.5%.	24 weeks	Bitter melon tea (200ml after each meals) and commercially available lipton tea for controls	Significant reduction of HbA1c of 0.63% ($P<0.05$)
Ahmed *et al* 1999	Case series	N=100; type 2 diabetes	2 days	Aqueous suspension of bitter melon pulp (dose not given)	Significant reduction in post prandial glucose and fasting plasma glucose ($P<0.05$)
Srivastava *et al* 1993	Case series	N=12; type 2 diabetes	21 days	Aqueous extract of 100g of chopped bitter melon per day & 5g of dried bitter melon powder 3 times per day	aqueous extract reduced blood glucose and HbA1c significantly.
Welhinda *et al* 1986	Case series	N=18; newly diagnosed type 2 diabetes		100ml of bitter melon juice 30 minutes before OGTT. Control group treated with distilled water.	Moderate improvement in glucose tolerance
Leatherdale *et al* 1981	Case series	N=9 (6 men and 3 women); Asian diabetic patients	8-11 weeks	50ml of bitter melon juice & 230g of fried bitter melon fruit every day	Fried bitter melon significantly reduces HbA1c
Baldwa *et al* 1977	Case series; controlled clinical trial	N=14; type 1& type 2 diabetic patients and healthy volunteers		Bitter melon extract (purified protein extract)	Decreases serum glucose levels.

Baldwa *et al,* (1977) investigated the effects of bitter melon extract on blood sugar levels in patients with diabetes. A total of 19 patients were recruited including 14 type 1 or type 2 diabetic patients and 5 healthy volunteers. Nine of these diabetic patients were treated with vegetable insulin (purified protein extract of *Momordica*) injected subcutaneously and rest of them (5 diabetic and 5 healthy volunteers) was treated with a placebo injection for a short-term period. The mean serum glucose level was decreased in patients treated with vegetable insulin (6 type-1 and 3 type-2 patients) after 12 hours (a 28% drop). In contrast, a mean serum glucose decrease about 5% was observed in placebo group.

Even though the result of this study shows potential effects, once again there was no appropriate statistical analysis and the study was not randomized, blinded or controlled. The placebo injection of this study is unspecified, and patients who received treatment (vegetable insulin) had a substantially different baseline serum glucose concentration from placebo group (295mg/dl and 210 mg/dl respectively). Inclusion of both type-1 and type-2 diabetic patients also remains unclear, because these diseases have different etiologies and mechanism of actions.

2.3.5 Discussion and conclusion

To date there are no large-scale adequately designed prospective randomized controlled trials that have been carried out to investigate the safety, adverse effects and dosage of *Momordica* for patients with diabetes mellitus. Human trials carried out so far did not claim any serious side effects due to *Momordica* supplementation. Gastrointestinal complications such as diarrhea, epigastric pain and cholecystolithiasis were the most common reported events after *Momordica* supplementation in human intervention trial (Tiwari, 2007; Dan *et al,* 2007). Two children were reported with hypoglycemic coma after the supplementation of bitter melon tea (Basch *et al,* 2003). Different *in vivo* animal studies have shown an increase in phosphatase and gamma glutamyl transferase in rats; hypotension, elevated serum cholesterol and nonesterified fatty acids in dogs; and uterine bleeding in pregnant mice after *Momordica* supplementation (Dan *et al,* 2007). Consumption of bitter melon tea shows abdominal cramps, soft stools, increased frequency of bowel movement and some skin infections among diabetic patients (Rosales & Fernando, 2001).

A recent review of the efficacy and safety of *Momordica* suggests that *Momordica* may have additive effects when taken with other glucose lowering agents (Basch *et al,* 2003). To date there are no studies that have been carried out to find out the effective dose of *Momordica* for

diabetes management. A range of different administration methods of *Momordica* such as purified protein extract (Baldwa *et al,* 1977), capsules (Dan *et al,* 2007), dried powder (Srivastava *et al,* 1993), juice (Welhinda *et al,* 1986), fried fruit (Leatherdale *et al,* 1981) and aqueous extract (Baldwa *et al,* 1977; Srivastava *et al,* 1993) have been used to treat diabetes mellitus in these case series and controlled clinical trials. None of these studies provide evidence of a safe dosage of *Momordica* for diabetes mellitus. However, normal dosage of capsulized dried powder range from 3 – 15 g per day was suggested in one study (Dey *et al,* 2002). As this was quite a large dose, so in order to avoid taking too many capsules, a standardized extract may be used with dosages of 100 – 200mg, three times per day (Day *et al,* 2002).

In summary, even though *Momordica* is widely used as an effective herbal dietary supplement for blood glucose control, its safety and efficacy needs to be further evaluated by well defined, randomized controlled clinical studies. Furthermore, preparation of standardized dietary supplements of *Momordica* is important to be investigated in future studies. Although *Momordica* is less likely to have the drawbacks of conventional drugs, the potential for herb-drug interaction should be kept in mind for patients also receiving conventional anti-diabetic medications. As a result, *Momordica* cannot be routinely recommended as an effective herbal dietary supplement for the management of diabetes.

2.4 Therapeutic effect of *Gymnema* in the management of Diabetes Mellitus

2.4.1 Introduction

Gymnema, belonging to the Asclepediaceae family, is a large woody highly branched climber, found in India and tropical Africa (Saxena & Vikram, 2004). There are different spices of *Gymnema* such as; *Gymnema sylvestre*, *Gymnema inodorum* and *Gymnema yunnanese.* It is thought to repair or regenerate the pancreatic cells in animals which play an important role in production and secretion of insulin (Ananthan *et al,* 2004; Shimizu *et al,* 2001). *Gymnema sylvestre* and *Gymnema inodorum* have been known to be effective for some chronic conditions including diabetes mellitus, rheumatic arthritis and gout (Shimizu *et al,* 2001). The leaves of *Gymnema* have also been used for stomach ailments, constipation, water retention and liver diseases (Joffe & Freed, 2001). *Gymnema* is regarded as one of the plants with potent anti-diabetic properties (Kanetkar *et al,* 2007). In general, the secondary plant metabolites have a complex and unique structure and their production is often enhanced by biotic and abiotic stress conditions, similarly gymnemic acid exhibits a potent inhibitory effect on diabetes (Li Ahmed *et al,* 2009) and appears to improve glycemic control (Nahas & Mohar, 2009).

***Gymnema* leafs**

Most of the previous studies focused on leaf extracts of *Gymnema* when trying to evaluate the active components of the plant (Saxena & Vikram, 2004; Kanetkar *et al,* 2007; Nahas & Mohar, 2009; Leach, 2007; Yeh *et al,* 2003; Grover *et al,* 2002). Studies indicate that this plant contains several important active substances that could lower blood sugar and lipid levels such as, gymnemic acids, conduritol-A, gurmarin and triterpene glycosides (Saxena & Vikram, 2004; Ramkumar *et al,* 2005; Wei *et al,* 2008; Xie *et al,* 2003). A number of *in vitro* and *in-vivo* animal studies have demonstrated the mechanism of hypoglycaemic action of this plant. The anti-diabetic array of molecules has been identified as a group of closely related gymnemic acids after isolation and purification from the leaves of *Gymnema Sylvestre* (Lie *et al*, 1992; Devasagayam, 2007). The aqueous ethanolic extracts of the *Gymnema* leaves provide two potentially active fractions, one containing conduritol-A (an acid soluble polyol-polyhydroxy cyclic compound), and the other containing a mixture of gymnemic acids (acid soluble triterpenoid saponins) designated GS3 and GS4 (Persaud *et al,* 1999). Conduritol-A has been reported to have stimulatory effects on basal insulin secretion through an undefined mechanism in animals (Billington *et al,* 1994). The gymnemic acid 4 (GS4) isolated from *Gymnema sylvestre* (GS) leaves has shown anti-

hyperglycemic, glucose uptake inhibitory and gut glycosidase inhibitory effects (Kimura, 2006). In addition; GS-1, GS-2, GS-3 and GS-5 do not show any of these effects. *In vivo* studies also suggest that *Gymnema yunnanense* extract could be used as an effective anti-hyperglycaemic and body weight reducing agent (Xie *et al,* 2003).

The atomic arrangements of gymnemic acid molecules are similar to that of glucose molecules (Kanetkat *et al,* 2007), and these molecules fill the receptor locations on the taste buds thereby preventing its activation by sugar molecules present in the food, thereby curbing the sugar craving. Similarly, gymnemic acid molecules fill the receptor location in the absorptive external layers of the intestine thereby preventing the sugar molecules absorption by the intestine, which results in low blood glucose levels (Kanerkar *et al,* 2007; Porchezhian & Dobriyal, 2003; Sahu *et al,* 1996). **Figure 2.2** shows the molecular structure of gymnemic acid and glucose inhibition mechanism in intestinal wall.

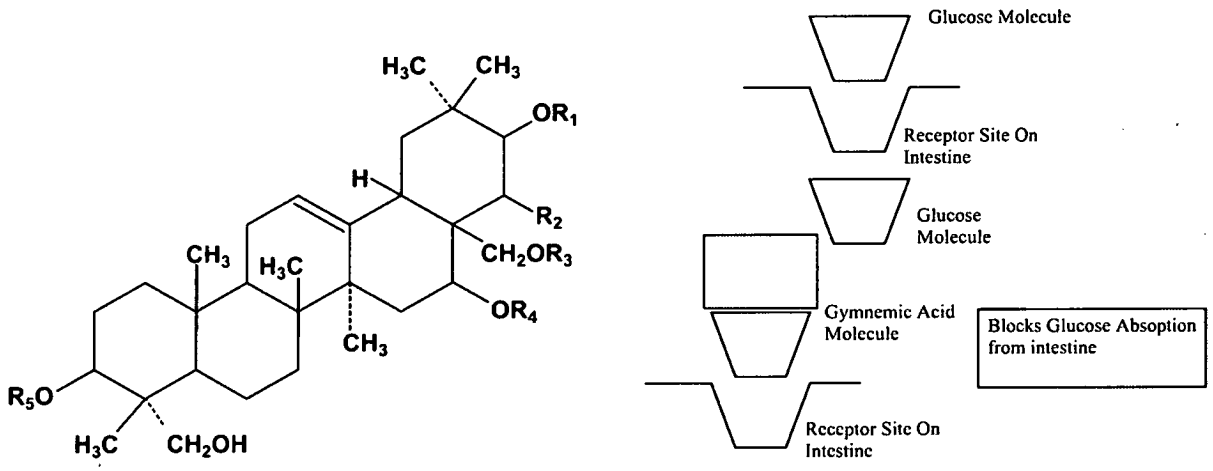


Figure 2.2 – Basic molecular structure of gymnemic acid and schematic representation of competitive inhibition of receptor on intestine by gymnemic acid - source: Kanetkar *et al,* (2007)

Persuat *et al,* (1999) investigated the effects of GS4 on beta cell lines and on isolated islets of langerhans in rat models. The results of this study demonstrated that GS4 caused a dose related (0mg/ml, 0.125mg/ml, 0.25mg/ml and 0.5mg/ml) increase in insulin release from beta cell lines in the absence of any other stimulus. Similarly Shimizu *et al,* (2001) evaluated the pharmacological activity of the four components from *Gymnema inodorum* leaf extracts (GiA-1, GiA-2, GiA-5 and GiA-7) and confirmed an inhibitory effect on glucose absorption in intestinal tract. *Gymnema* has also demonstrated improvements in glycogen synthesis, glycolysis,

gluconeogenesis and hepatic and muscle glucose uptake in animal studies (Shanmugasundaram *et al,* 1983).

In an experimental *in vivo* animal study, oral administration of *Gymnema* leaf ethanolic extracts (GLEt) at a dose of 50, 100 and 200mg/kg of body weight for 30 days, suggested a significant decrease in plasma glucose levels in the group received 200mg of GLEt/kg body weight (Ananthan *et al,* 2004). Plasma insulin also significantly reduced after GLEt administration. This study further demonstrated that the ethanolic extract of *Gymnema* possess antioxidant activity mainly in the liver and kidney tissues (Ananthan *et al,* 2004).

Another study carried out by Ananthan *et al,* (2003a, 2003b) reveals that, GLEt significantly reduces the serum and tissue lipids in diabetic rats. GLEt has also shown beneficial effects on plasma insulin levels and these findings further strengthen the observation that naturally occurring plant extract compounds show antidiabetic effects. The possible mechanism by which GLEt brings about it's antidiabetic action may be due to potentiating pancreatic secretion of insulin from beta cells or due to enhanced transport of blood glucose to peripheral tissues (Ananthan *et al,* 2003a; Ananthan *et al,* 2003b).

2.4.2 Methods

Figure 2.3 shows the inclusion and exclusion of studies in the selection criteria. A total of 67 articles were identified, of these only 3 articles met the inclusion criteria for human intervention trials of *Gymnema* and diabetes mellitus (Baskaran *et al,* 1990; Shanmugasundaram *et al,* 1990; Joffe & Freed. 2001).

Out of these 67 articles, 58 were excluded either due to duplication, they were *in-vivo* animal studies, *in-vitro* studies, not published in English language, did not have an abstracts or author's name and did not include adequate methodology/intervention method (Figure 2.3). Another 6 articles were excluded because they were reviews of *Gymnema* (Saxena & Vikram. 2004; Kanetkar *et al,* 2007; Nahas & Mohar. 2009; Leach. 2007; Yeh *et al,* 2003; Cefalu *et al,* 2008). Finally 3 non-randomized trials of *Gymnema* and diabetes mellitus and was included for further review and analysis (Baskaran *et al,* 1990; Shanmugasundaram *et al,* 1990; Joffe & Freed. 2001) (Figure 2.3).

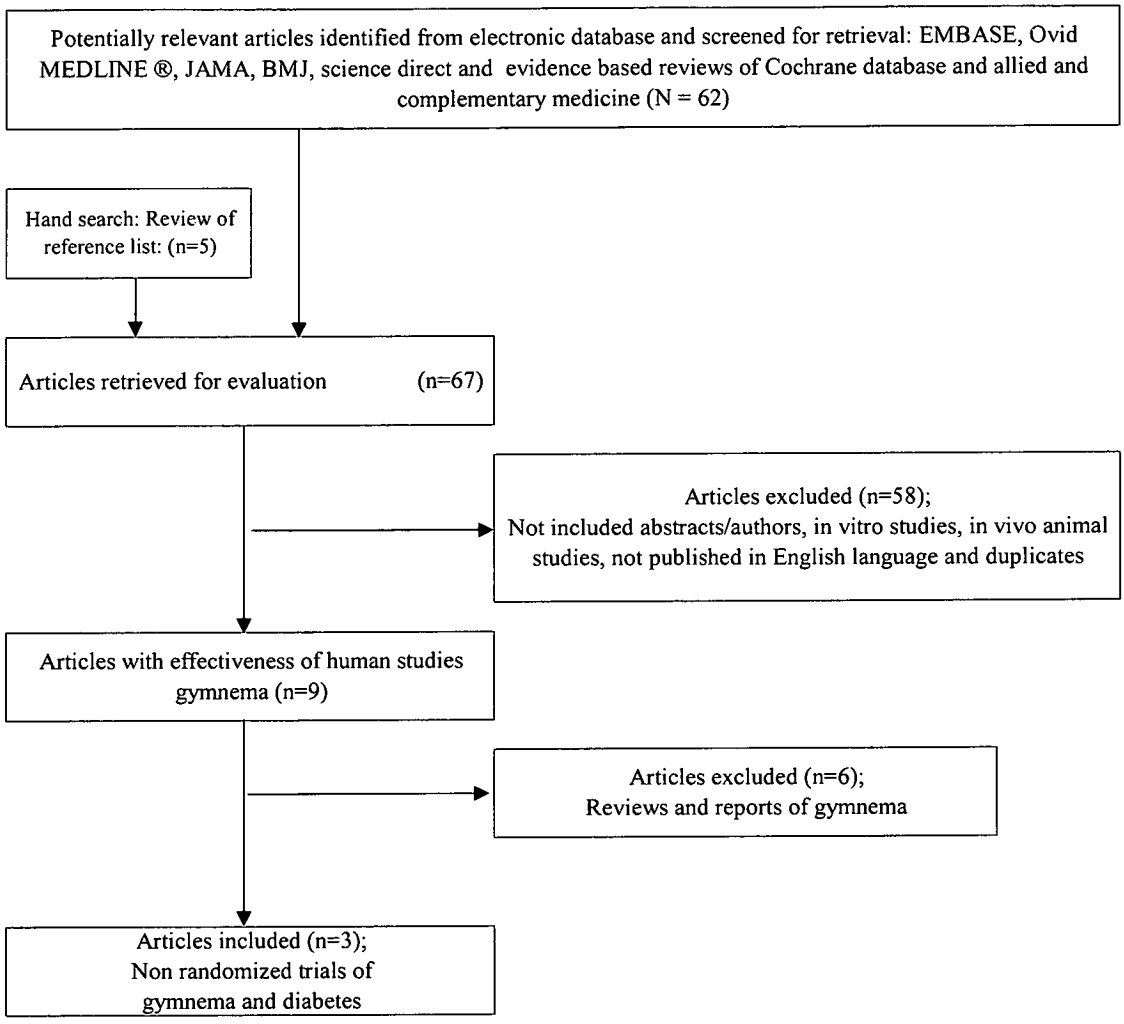


Figure 2.3 - Systematic review of *Gymnema* and diabetes mellitus. n = number of articles, RCT - randomized control trials. A total of 67 articles were identified, of these only 3 articles met the inclusion criteria for human intervention trials of *Gymnema* and diabetes mellitus

2.4.3 Results

Baskaran *et al,* (1990) reported the results of the first non randomised, open label, parallel design trial to investigate the effect of GS4 extract of *Gymnema sylvestre* (GS) on HbA1c and plasma glucose concentration among diabetic patients. Forty seven patients with type 2 diabetes were assigned to receive either GS extract, GS4 400mg/day (n=22) as a supplement to conventional oral hypoglycaemic agents or to receive conventional oral hypoglycaemic agents (n=25) for a period of 18 to 20 months (Table 2.4). Results of this study revealed that fasting blood glucose and HbA1c were significantly reduced compared to baseline (P<0.001) after 18-20 months, and none of these reductions were observed in patients receiving conventional therapy alone. The mean HbA1c decreased from a baseline of 11.9% to 8.34% (P<0.001) in

patients who received the GS4 extract. Fasting and post-prandial serum insulin levels were significantly increased (P<0.01) and serum cholesterol, triglycerides and phospholipids levels were significantly reduced among patients treated with GS4 extract. Therefore, this study concluded that GS extract could be used as an effective oral anti-diabetic agent for both hypoglycaemic and hypolipidaemic effects.

In an attempt to replicate the study, Shanmugasundaram *et al,* (1990) from the same investigator group of Baskaran *et al,* (1990), examined the similar effects of GS4 extract (400mg/day) along with insulin therapy among 27 type-1 diabetic patients compared with 37 controls receiving insulin only. This was also a non randomised, open label, parallel design study conducted for 2-30 months period. It was noticed that insulin dosage had to be reduced by approximately 25% after 6-8 months and by approximately 50% after 26-30 months following GS4 administration. Significant reductions in HbA1c, fasting blood glucose and blood cholesterol levels were also observed in the GS4 administered group compared to controls (Table 2.4).

Recently, Joffe & Freed (2001) conducted a non randomised, non controlled, open label, study to investigate the acute effects of supplementing the diet with GS to reduce HbA1c and complications of diabetes mellitus. Sixty five patients with type1 and type2 diabetes mellitus, having HbA1c >7.8% were treated with GS, 800mg/day (1x400mg tablet, twice daily) for 90 days. Results of this study demonstrated that GS lowered mean daily pre-prandial glucose and 2-hour postprandial plasma glucose concentrations by 11% and 13% respectively. The HbA1c dropped significantly from 8.8% - 8.2% (0.6% decrease) after 90 days of GS supplementation (Table 2.4).

Table 2.4 - Summary of randomized controlled clinical trials of *Gymnema* and diabetes mellitus

Study	Design	Sample	Duration	Intervention	Results
Baskaran *et al.* 1990	Non-randomised, open label, 2 group, parallel design.	N=47 ; diagnosed type 2 diabetes, treated with conventional oral hypoglycemic agents.	18 - 20 months	Intervention: treated with GS extract-400mg/day + oral hypoglycemic agents for 18-22 months (n=22). Control: treated with only oral hypoglycemic agents (n=25).	Significant improvement (P<0.05) in HbA1c, fasting blood glucose, glycosylated protein, conventional medication, urine glucose and increased insulin compared to baseline. No side effects were reported.
Shanmugasundaram *et al.* 1990	Non-randomised, open label, 2 group, parallel design.	N=64; type 1 diabetes mellitus, treated with insulin.	2 - 30 months	Intervention: treated with GS extract - 400mg/day + insulin for 2-30 months (n=27). Control: treated with only insulin for 2-30 months (n=25).	Significant improvement (P<0.05) in HbA1c, fasting blood glucose, glycosylated protein, insulin requirements and urine glucose compared to baseline. No side effects were reported.
Joffe & Freed.2001	Non randomised, non control, 1 group, parallel design.	N=65; type 2 and type 1 diabetes, treated with orl hypoglycemic agents and insulin.	90 days	Supplementing the diet with GS extract, 800mg/day for 90 days.	Lowers mean daily 2hours post-prandial and pre-prandial glucose concentrations. Significant reduction in HbA1c also noticed after 90 days (P<0.05).

2.4.4 Discussion and conclusion

The two studies conducted by Baskaran *et al,* (1990) and Shanmugasundaram *et al,* (1990) were from the same investigator group from India, and both studies examined the effect of a 400mg/day dose of GS extract among type1 and type2 diabetic patients on different occasions. Both studies showed improvements in HbA1c and blood glucose levels due to long term supplementation of *Gymnema* extract. This study was performed with Indian diabetic patients with poor glycemic control (HbA1c~11.9%), and may not be valid for people of other ethnic origins because of the different genetic and lifestyle backgrounds. Further, it is not clear whether less than 400mg/day of GS would also be beneficial for a long term supplementation and whether it was effective for patients from other ethnic origins? A randomized, placebo controlled, double blind eight week trial of 60 overweight subjects demonstrated that, a combination of hydroxycitric acid, niacin bound chromium and *Gymnema sylvestre* extract facilitated a significant reduction in body weight and BMI, and promoted healthy blood lipid profiles (Preuss *et al,* 2004). This is the first well defined RCT investigating the effect of *Gymnema* extract in combination with other therapies on body weight. Therefore the observed reduction in body weight might improve glucose tolerance via increase insulin sensitivity and control blood glucose or HbA1c effectively.

Joffe & Freed (2001), demonstrated that 800mg/day of *Gymnema sylvestre* (GS) extract showed a significant reduction in HbA1c for both in type 1 and type 2 diabetic patients. The etiological background of type1 and type2 diabetes is different, and thus it remains unclear why the investigator included both type 1 and type 2 diabetic patients in one group and treated them with 800mg of GS extract, even though it has been shown that 400mg of GS extract showed significant improvements on HbA1c in the previous human studies (Baskaran *et al,* 1990; Shanmugasundaram *et al,* 1990). The reduction in fasting blood glucose levels and HbA1c in the above mentioned studies are further supported by two small non randomized, open label trials of patients with diabetes, of which 6 – 10g of *Gymnema* leaf extract were administered for 15 – 21 days (Balasubramanium *et al,* 1988; Khare *et al,* 1983).

Evidence from previous *in-vitro* and *in-vivo* animal studies has demonstrated the following;

1. Insulin releasing action of gymnemic acid may contribute to the anti-hyperglycaemic effects (Sugihara *et al,* 2000).
2. Components of *Gymnema* inhibit the increase in the blood glucose by interfering with the intestinal glucose absorption process (Shimizu *et al,* 1997).

3. The active compound of conduritol-A could have an effect on regulating the metabolism of blood lipids, free radical scavenging and enhancing the antioxidant ability (Wei *et al,* 2008).
4. *Gymnema* extract may prove to be of clinical importance in improving the management of diabetes by body weight reduction (Xie *et al,* 2003).
5. Phytochemicals present in *Gymnema* may play an important role in suppressing the elevated lipid profiles in diabetes and may be useful for the prevention and or early treatment of diabetes associated hyperlipidaemia (Ramkumar *et al,* 2008a).
6. *Gymnema* may also be useful for the control, management and prevention of oxidative stress associated with diabetes (Ramkumar *et al,* 2008b).
7. Stimulatory effects of GS4 on insulin release in mainly due to increasing beta cell permeability (Persaud *et al,* 1999).

However, when it comes to safety and tolerability of *Gymnema* in human studies, it is generally regarded as safe and with no side effects although it is recommended that it should be avoided during pregnancy (Joffe & Freed, 2001). Historically, it has been documented that *Gymnema* can safely been taken for years (Talbot, 2003). Human studies carried out so far have not claimed any serious side effects due to *Gymnema* supplementation. *Gymnema* may enhance the blood glucose lowering effects of insulin and hypoglycemic agents, potentially causing hypoglycemia (Khare *et al,* 1983). Thus, extra care should be taken in monitoring blood sugar levels. *Gymnema* is possibly effective in reducing total cholesterol and triglycerides in diabetic patients (Baskaran *et al,* 1990). Further, in human studies, the most common dose of *Gymnema* administered for blood glucose control ranged from 400mg to 800mg per day for 2 to 30 months in the form of water soluble *Gymnema* acidic fractions. To date no studies have been carried out to find out the effectiveness of different doses of *Gymnema* for diabetes mellitus.

In summary, using the Joanna Briggs institute critical appraisal of evidence of effectiveness tool (Guyatt *et al,* 1993; Persis *et al,* 2004), the earlier two human studies of *Gymnema* (Baskaran *et al,* 1990; Shanmugasundaram *et al,* 1990) had an appraisal score of only 3/11, meaning that both studies had a high level of bias (Leach *et al,* 2007). Therefore, given that no clinical trials of *Gymnema* were of good quality, statistical pooling of results was not appropriate. Furthermore, this systematic review has only been supported by small number of non randomized and open label trials (narrative review), further investigation into the clinical effect of *Gymnema* in the management of diabetes mellitus is urgently needed.

2.5 Therapeutic effect of *Ginseng* in the management of Diabetes Mellitus

This section does not include an extensive systematic review of *Ginseng* and diabetes. However, the active compounds and theoretical mechanism of action of *Ginseng* (section 2.5.1) and results from previously published and widely reported human intervention trials (section 2.5.2) were reported in this review.

Ginseng is a well-known medicinal plant used in traditional oriental medicine. In recent decades, *Ginseng* root has gained popularity as a dietary supplement in the United States (Xie *et al,* 2005). Despite a lack of medical evidence to support its therapeutic efficacy, the use of *Ginseng* has increased considerably. In recent decades, *Ginseng* root has gained popularity as a dietary supplement and has also been commonly used in oriental medicine to treat diabetes-like conditions (Xie *et al,* 2005). *Ginseng* extracts have long been used in traditional Chinese medicine to restore and enhance well being (Volger et al, 1999). *Ginseng* comprises a number of different species, which belong to the same plant family Aaraliaceae. The most commonly used Korean, Asian and Chinese *Ginseng* belongs to genus panax *Ginseng* (Volger *et al,* 1999).

***Ginseng* berry and root**

The therapeutic potency of *Ginseng* mainly relies on its geographical locality, dosage, processing and type of diabetes. *Panax Ginseng* (Chinese or Korean *Ginseng*) is the most commonly used therapeutic *Ginseng* has the highest anti-diabetic therapeutic potency (Hui *et al,* 2009). *Ginseng* is widely available as an over the counter food supplement nowadays. Modern therapeutic claims refer to vitality, immune function, cancer, cardiovascular disease and diabetes, and these claims are mostly based on uncontrolled or non randomized clinical studies (Banz *et al,* 2007; Buetnner *et al,* 2007; Coleman *et al,* 2003; Volger *et al,* 1999; Vuksan *et al,* 2000b; Vuksan *et al,* 2001; Xie *et al,* 2005; Yeh *et al,* 2003). Previous studies demonstrated that both *Ginseng* root and berry possess anti-diabetic activity (Vuksan *et al,* 2001). However, the anti-hyperglycaemic effect of *Ginseng* root and berry is still unclear. *In vivo* animal studies demonstrates that compared to *Ginseng* root, *Ginseng* berry exhibits more potent anti-hyperglycemic activity and shows marked anti-obesity effects in rat models (Dey *et al,* 2003).

Ginsenosides, the active component of *Ginseng*, exerts antidiabetic effects (Hwang *et al,* 2009). *Panax Ginseng* is a well-known medicinal herb native to China and Korea, and has been used as a herbal remedy in eastern Asia for thousands of years (Xie *et al,* 2003). However, there is different evidence of *Ginseng* efficacy between traditional Chinese medicine (TCM), modern pharmacological experiments and clinical trials (Xiang *et al,* 2008). In TCM, *Ginseng* is a highly valued herb and has been applied to a variety of pathological conditions and illnesses such as hypodynamia, anorexia, shortness of breath, palpitation, insomnia, impotence, hemorrhage and diabetes (Xiang *et al,* 2008).

2.5.1 Active compounds and therapeutic effects of *Ginseng*

Ginseng extracts made from root, rootlet, berry and leaf of Panax quinquefolium (American *Ginseng*) and Panax *Ginseng* (Asian *Ginseng*), are shown for anti-hyperglycemia, insulin sensitization, islet protection, anti-obesity and anti-oxidation in many studies (Yin *et al,* 2008). *Ginseng*-specific saponins (ginsenosides) are considered as the major bioactive compounds for the metabolic activities of *Ginseng* (Yin *et al,* 2008).

The evidence from *in-vitro* and *in-vivo* animal studies suggest that the hypoglycemic effect of *Ginseng* is mainly achieved by increasing insulin secretion, enhancing glucose uptake by adipose and muscle tissues, inhibiting glucose absorption from the intestine and inhibiting glucose production from heptocytes (Hui *et al,* 2009). *Ginseng* has been reported to ameliorate hyperglycemia in experimental and clinical studies; however, its detailed mechanism of action remains unclear (Lee *et al,* 2009). The Korean *Ginseng* showed improved insulin sensitivity and significantly preserved glucose tolerance in *in-vivo* animal studies (Kim *et al,* 2008; Lee *et al,* 2009). The heat-processed Korean *Ginseng,* has a long history as a herbal remedy for anti-diabetic effect (Kim *et al,* 2008).

Antioxidants have been considered as a useful remedy in diabetes therapeutics, and thus, herbal dietary supplements with antioxidant properties may play a major role in treating diabetes (Xie *et al,* 2009). However, the anti-diabetic effect of American *Ginseng* may not be linked to its antioxidant actions (Xie *et al,* 2009). Therefore, the mechanisms of *Ginseng's* antioxidant effects on reducing high blood glucose levels remain unclear.

Animal studies suggest that the hypoglycemic effects of malonyl-ginsenosides (MGR) extracted from roots of *Panax Ginseng* may be prescribed as an adjunct to drug treatment for controlling

diabetes mellitus (Liu *et al,* 2009). Furthermore, *Ginseng* possesses anti-diabetic and anti-obesity activities and may prove to be of clinical importance in improving the management of type 2 diabetes (Chen *et al,* 2008b). Recent studies have revealed that beta-cell dysfunction is an important factor in developing type 2 diabetes (Park *et al,* 2008). Beta-cell dysfunction is related to impairment of the insulin/IGF-1 signaling cascade through insulin receptor substrate-2 (IRS2). The induction of IRS2 in beta-cells plays an important role in potentiating beta-cell function and mass (Park *et al,* 2008) and *Ginseng* could be used for this purpose.

Furthermore, the results of several *in-vivo* animal studies indicated that some *Ginseng* fractions stimulated insulin release, especially glucose-induced insulin release from pancreatic islets and thereby lowered the blood glucose level (Kimura *et al,* 1981). The active compounds of *Ginseng* include ginsenoside-Rb1 and -Rg1 decreased the insulin content of islet to an undetectable level (Waki *et al,* 1982). Ginsenoside Rh2 has an ability to improve insulin sensitivity and it seems suitable to use ginsenoside Rh2 as an adjuvant therapy for diabetic patients and/or the subjects wishing to increase insulin sensitivity (Lee *et al,* 2006; Lee *et al,* 2007).

Animal studies further suggests that *Ginseng* radix can improve hyperglycaemia possibly by blocking intestinal glucose absorption and inhibiting hepatic glucose-6-phosphatase activity (Chung *et al,* 2001). In addition, *Ginseng* exerts its antilipolytic effect through a signalling pathway different from that of insulin (Wang *et al,* 2006).

2.5.2 Widely reported human intervention studies of *Ginseng* and diabetes mellitus

Zhang *et al,* (2007) demonstrated that routine western medicine treatment combined with panax quinquefolius saponin (PQS) showed superiority in lowering fasting plasma glucose (FPG), could significantly decrease the levels of total cholesterol and LDL-cholesterol, and might improve the beta-cell function in patients of coronary heart disease (CHD) with blood glucose abnormalities (BGA). It showed no effect on insulin sensitivity of patients (Zhang *et al,* 2007). The objective of this study was to investigate the effect of PQS on blood glucose, blood lipid and insulin sensitivity in patients with CHD with BGA. A total of 84 patients of CHD with BGA, namely CHD patients with impaired fasting glucose (IFG), or impaired glucose tolerance (IGT), or type 2 diabetes mellitus (T2DM), were randomly assigned to the PQS group (43 cases) and the control group (41 cases), and all were treated with routine Western medicine in this human intervention study (Zhang *et al,* 2007).

Recently, a placebo-controlled, double-blind, cross-over study was conducted to investigate the effects of chronic ingestion of Panax *Ginseng* on HbA1c, fasting plasma insulin, fasting plasma glucose and postprandial response in healthy volunteers (Reay *et al,* 2009). Results of this study suggested that chronic use of Panax *Ginseng* by non-diabetic individuals will have little long-term effect on glucose regulation. It was also found that Panax *Ginseng* had no effect on any gluco-regulatory parameter investigated in this study (Reay *et al,* 2009). The anti diabetic effect of panax *Ginseng* appears to be superior compared to other varieties (Chen *et al,* 2008a).

Sotaniemi *et al,* (1995) investigated the effect of *Ginseng* on newly diagnosed non-insulin-dependent diabetes mellitus (NIDDM) patients. In this double-blind placebo-controlled study, 36 NIDDM patients were treated for 8 weeks with *Ginseng* (100 or 200 mg) or placebo. The results of this study demonstrated that *Ginseng* therapy reduced fasting blood glucose (FBG) and body weight. The 200-mg dose of *Ginseng* improved glycated haemoglobin of the diabetic patients. Therefore, *Ginseng* may be a useful therapeutic adjunct in the management of NIDDM (Sotaniemi *et al,* 1995).

The short-term clinical effect of American *Ginseng* (*Panax quinquefolius L*) on postprandial glycaemia (PPG) was examined in humans (Vuksan *et al,* 2000). On 4 separate occasions, 10 non-diabetic subjects and 9 subjects with type 2 diabetes mellitus were randomly assigned to receive either 3g of *Ginseng* or placebo capsules (either 40 minutes before or together with a 25-g oral glucose challenge). The results of this study demonstrated that, in non-diabetic subjects, no differences were found in postprandial glycaemia between placebo and *Ginseng* when administered together with the glucose challenge. When *Ginseng* was taken 40 minutes before the glucose challenge, a significant reduction in postprandial glycaemia was observed. In subjects with type 2 diabetes mellitus, the same was true whether capsules were taken before or together with the glucose challenge ($P<.05$). Therefore, American *Ginseng*s attenuated postprandial glycaemia in both study groups (Vuksan *et al,* 2000).

In an attempt to investigate further reduction in postprandial glycaemia (PPG), Vuksan *et al* (2000b) investigated whether further reductions can be achieved with escalation of dose and time of American *Ginseng* supplementation. A total of 10 type 2 diabetic patients were randomly administered 0 g (placebo) or 3g, 6g, or 9g ground American *Ginseng* root in capsules at 120, 80, 40, or 0 min before a 25-g oral glucose challenge. The results of this study demonstrates that, American *Ginseng* reduced PPG irrespective of dose and time of

administration. No more than 3 g American *Ginseng* was required at any time in relation to the challenge to achieve reductions (Vuksan *et al,* 2000b).

Vuksan *et al,* (2001) further demonstrated that even less than 3g of American *Ginseng* might be beneficial in controlling postprandial glucose levels in healthy subjects. The objective of this study was to investigate the dosing and timing effects of American *Ginseng* on postprandial glycaemia (PPG). In a random crossover design, 12 healthy subjects received 16 treatments: 0g (placebo), 1g, 2g, or 3g American *Ginseng* at 40, 20, 10, or 0 min before a 25-g oral glucose challenge. This study concluded that American *Ginseng* reduced postprandial glycaemia in subjects without diabetes, and reductions were time dependent but not dose dependent (Vuksan *et al,* 2001).

Furthermore, recently Vuksan *et al,* (2008) conducted a randomized, double blind, placebo controlled cross over study to assess *Ginseng* on long-term outcomes in type 2 diabetes. The objective of this study was to assess the clinical anti-diabetic efficacy and safety of 12 weeks of supplementation with a Korean Red *Ginseng* (KRG). A total of 19 participants with well-controlled type 2 diabetes (HbA1c < 6.5%) treated with KRG (rootlets) 6g per day for 12 weeks. The study outcomes included measures of HbA1c, fasting- and 75-g oral glucose tolerance test [OGTT], plasma glucose [PG], plasma insulin [PI], and insulin sensitivity index [ISI] indices. Results of this study revealed that the selected KRG treatment decreased 75 g-OGTT-PG indices by 8-11% and fasting-PI and 75 g-OGTT-PI indices by 33-38% and increased fasting-ISI and 75 g-OGTT-ISI by 33%, compared with placebo ($P<0.05$). The clinical efficacy as assessed by HbA1c was not demonstrated in this study. However, the 12 weeks of KRG supplementation maintained good glycaemia control and improved PG and PI regulation safely beyond usual therapy in people with well-controlled type 2 diabetes (Vuksan *et al,* 2008).

2.5.3 Discussion and conclusion

Even though the anti diabetic potency of *Ginseng* has been demonstrated by a range of animal and human trials, the widespread use of *Ginseng* as herbal dietary supplement warrants more rigorous investigations to assess its efficacy and safety. The reported side-effects from previous human studies of *Ginseng* at different doses given include; insomnia, diarrhea, vaginal bleeding, breast pain, severe headache and schizophrenia (Kiefer. 2003). The recommended dosage of *Ginseng* application is 1–3 g of root or 200–600 mg of extract (Vuksan *et al,* 2000).

As there are different *Ginseng* spices (American *Ginseng*, Chinese *Ginseng*, and Asian *Ginseng*), not all *Ginseng* species may be equal in their effects (Sievenpiper *et al,* 2003). Therefore, the effect of inter-spices variation in components on safety and efficacy must be explored further. In addition, future research should be identifying the active components of *Ginseng* to provide a basis for standardization that allows for the development of specific indications. In the absence of standardization of *Ginseng* dose or species, practitioners should warn their patients about the potentially variable effects of *Ginseng.*

2.6 Therapeutic effect of *Cinnamomum* in the management of Diabetes mellitus

2.6.1 Introduction

Cinnamomum (known as cinnamon) has a long history as an anti-diabetic spice, although studies involving cinnamon supplementation in diabetic patients have produced contrasting results. However, several animal and human studies have illustrated anti-hyperglycemic properties of cinnamon. This chapter systematically appraises the previously published randomized controlled trials of cinnamon in the management of type 2 diabetes mellitus.

Cinnamon is one of the oldest herbs used in naturopathic medicine, cited in Chinese medical books 4000 years ago (Qin *et al,* 2003). It has a range of historical uses in different cultures, including: the treatment of diabetes, rheumatism, certain menstrual disorders, diarrhea and gastrointestinal problems such as irritable bowel syndrome, dysbiosis, abdominal cramps and indigestion (Leung & Foster. 1996; Solgar. 2006). Most people are familiar with cinnamon. It has had a long history of use both as a spice and as a medicine and has a sweet pungent taste. Cinnamon trees normally grow in tropical countries like India, Sri Lanka, China, Madagascar and the Caribbean. It has been widely used in folk medicine for its hypothetical anti-diabetic effects. Interest in this spice has increased since the discovery of its insulin potentiating properties (Khan *et al,* 1990).

Cinnamon seems to be highly bioactive (Broadhurst *et al,* 2000), appearing to mimic the effect of insulin through increased glucose uptake in adipocytes and skeletal muscle (Qin *et al,* 2003; Roffey *et al,* 2006). Initial findings provided some strong scientific evidence that cinnamon reduces fasting plasma glucose (FPG) and plasma lipids (Khan *et al,* 2003). However, subsequent studies have reported conflicting results, questioning whether cinnamon can reduce fasting plasma glucose and clouding it's potential as a natural remedy for diabetes.

Conventional diabetes medications have a number of drawbacks and limitations (Chitturi and George. 2002; Rendell and Kirchain. 2002) such as weight gain, hepatic and renal impairment (British Medical Association. 2007), and bone loss (Schwartz and Sellmeyer. 2007). However, lifestyle interventions focusing on diet or dietary supplements, weight management and physical

activity could delay incidence of type 2 diabetes in high-risk individuals (Tuomilehto *et al,* 2001; Knowler *et al,* 2002; Lindström *et al,* 2003; Bazzano *et al,* 2005; Laatikainen *et al,* 2007).

Several *in vitro* and animal studies have indicated that cinnamon may mimic the effects of insulin and thus may improve glucose utilization (Broadhurst *et al,* 2000; Mang *et al,* 2006). *In vitro* studies have shown that cinnamon enhances glucose uptake by activating insulin receptor kinase activity (Jarvill *et al,* 2001). Extracts of cinnamon enhance the activity of insulin; mainly the water soluble polyphenolic polymers found in cinnamon may function as antioxidants and potentate insulin action, and may be beneficial in the control of glucose intolerance and diabetes (Anderson *et al,* 2003). Long term use of cinnamon bark may also provide beneficial effects to control blood glucose in diabetic conditions (Onderoglu *et al,* 1999).

As diabetes, metabolic syndrome and heart disease continue to be growing health concerns, it is important to systematically evaluate the anti-hyperglycaemic, hypolipidaemic or blood pressure lowering properties of cinnamon, and appraise its validity as an effective anti-diabetic dietary supplement.

2.6.2 The active compounds and mechanism of action at cellular level

This section discusses the anti diabetic potential of cinnamon in relation to its active compounds and proposed mechanism of action at cellular level. The results and methodologies administered in several *in vivo* animal studies are also discussed and compared in this section.

There are two types of cinnamon – *Cinnamomum verum (zeylanicum)* and *Cinnamomum cassia* (Chinese cinnamon) (World Health Organization. 1999[a]). Cassia is the type most commonly sold as a spice, with reportedly greater insulin-stimulating properties (Verspohl *et al,* 2005; Chase and McQueen. 2007). It is postulated that *C. cassia* and cinnamon extract (CE) are more effective than *C. zeylanicum* or bark in animal studies (Verspohl *et al,* 2005). However, similar insulin-enhancing effects from cinnamon of differing geographical sources and commercial preparation have been illustrated (Anderson *et al,* 2004), and powdered bark has resulted in the most significant results to date (Khan *et al,* 2003) although limited information is provided regarding the cinnamon preparation used.

Cinnamon contains three main active components of cinnamaldehyde, cinnamyl acetate, and cinnamyl alcohol, as well a wide range of other volatile substances which also show blood sugar

lowering effects (Subash *et al,* 2007). The medicinal effect of cinnamon has been attributed by Subash *et al* (2007), to it active volatile compounds of eugenol and cinnamaldehyde and 60-80% of the volatile compounds are mainly from cinnamaldehyde. Another active ingredient identified in cinnamon that could trigger the activity of insulin is the water-soluble polyphenol compound called methylhydroxy chalcone polymer (MHCP) (Jarvill *et al,* 2001). In laboratory experiments, MHCP mimics insulin, activates its receptor, and works synergistically with insulin in cells (Jarvill *et al,* 2001).

In vitro studies have shown that cinnamon enhances the activity of insulin. Water soluble polyphenol polymers found in cinnamon may function as antioxidants, potentiate insulin action, and may be beneficial in the control of glucose intolerance in diabetes (Andersan *et al,* 2004). Water soluble cinnamon extract and purified cinnamon polyphenols with doubly linked procyanidin type-A polymers display insulin like activity (Andersan *et al,* 2004; Cao *et al,* 2007)

2.6.3 The proposed active compounds of cinnamon and mechanism of action

2.6.3.1 Insulin action and the etiology of insulin resistance

Type 2 diabetes is characterized by diminished cellular response to insulin through defects in the insulin signaling pathway resulting in decreased glycogen synthesis and elevated blood glucose. Insulin enables glucose uptake by stimulating translocation of a glucose transporter (GLUT4) to the cell membrane (Kansaki. 2006), although the exact mechanisms behind this are still being investigated. Bogan *et al,* (2003) and Yu *et al,* (2007) suggested the dissociation of a tethering protein (TUG) to allow translocation of GLUT4, whereas others (Bryant *et al,* 2002; Watson *et al,* 2004; Kansaki, 2006) indicate a cellular re-distribution of GLUT4 including, but not exclusive to, TUG dissociation. Insulin resistance has been attributed to decreased GLUT4 activity, caused by inhibited insulin-receptor substrate (IRS)-1 tyrosine phosphorylation, which results in reduced phosphatidyl-inositol-3-kinase activity (Petersen and Shulman. 2006). The active components of cinnamon appear to override this disturbance, stimulating GLUT4 activity and enabling cellular glucose uptake (Jarvill-Taylor *et al,* 2001; Kannappan *et al,* 2006; Kim *et al,* 2006[b]; Roffey *et al,* 2006; Cao *et al,* 2007). Figure 4.1 shows how normal insulin action is affected during insulin resistance.

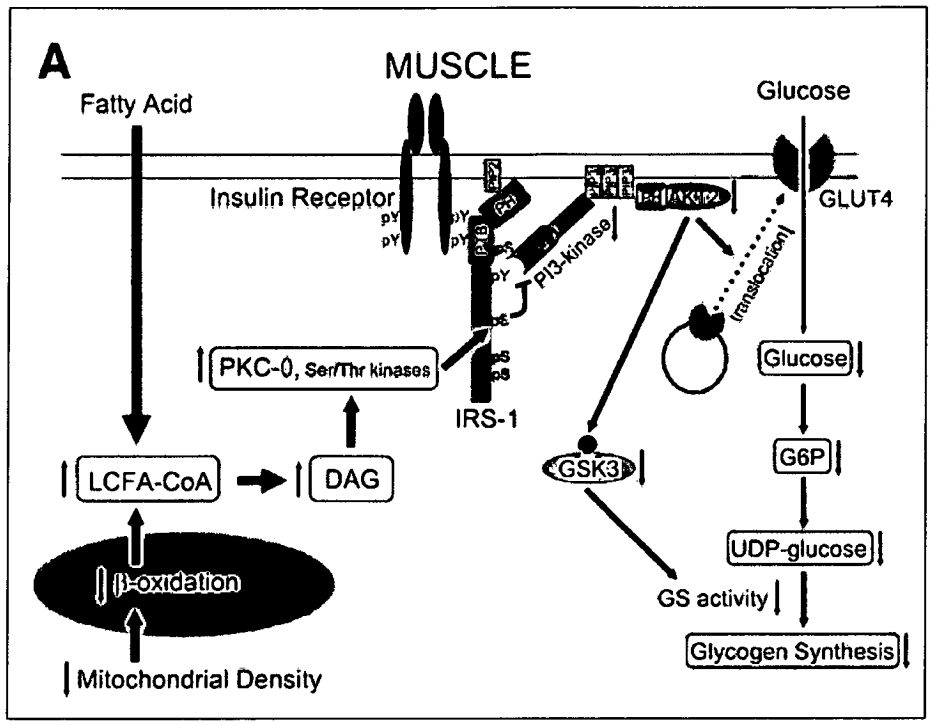


Figure 2.4 Diagram illustrating how normal insulin action is affected during insulin resistance (Morino *et al,* 2006).
Due to increases in intracellular fat, protein kinases (PKC-0) are activated and inhibit insulin-induced PI3-kinase activity at the insulin receptor (IRS-1), resulting in reduced AKT2 activity. This in turn fails to activate GLUT4 translocation and reduces cellular glucose uptake, as shown on the right hand side of the diagram. Reduced AKT2 also diminishes glycogen synthetase kinase-3 (GSK3) activity, reducing glycogen synthesis.

2.6.3.2 Cinnamon action in conjunction with insulin

Cinnamon also seems to work in conjunction with insulin, although there appears to be a negative feedback mechanism or limiting factor which curbs cellular glucose uptake (Cao *et al,* 2007), as inhibitory results have been noted with cinnamon treatment in conjunction with 50nM insulin in adipocytes (Roffey *et al,* 2006). The researchers postulated that the glucose uptake pathways used by cinnamon are the same as in insulin-mediated uptake, although this may relate only to muscle tissue, as a supplementary mechanism in adipocytes has been suggested (Pinent *et al,* 2004).

2.6.3.3 Proposed active components of cinnamon

Anderson *et al,* (2004) proposed that cinnamon's most active ingredients are A-type doubly linked procyanidin oligomers of the flavonoid catechins/epicatechins. This suggestion is supported by the insulin-like effects of procyanidins illustrating increased glucose uptake in diabetic rats via the same mechanism as insulin, and potentially by an additional mechanism in adipose tissue (Pinent *et al,* 2004). Anti-hyperglycaemic activity through varying mechanisms

has been illustrated in a number of other flavonoids (Kao *et al,* 2000; Shimizu *et al,* 2000; Waltner-Law *et al,* 2002; Kim *et al,* 2003; Al-Awwadi *et al,* 2004). In a recent human study, Ziegenfuss *et al,* (2006) used a cinnamon supplement containing these proposed active polymers and induced a significant reduction in fasting plasma glucose (FPG) ($p < 0.01$), although population size was small and the equivalence of 10g of cinnamon was used.

In the same year, Kim *et al,* (2006[b]) extracted, purified and screened hydroxycinnamic acids in an attempt to identify the active components of cinnamon. A naphthalenemethyl ester of 3,4-dihydroxyhydrocinnamic acid showed the highest glucose transport activity *in vitro,* and subsequently increased glucose transport through translocation of GLUT4 and enhancement of insulin receptor (IR) ß and IR substrate-1 phosphorylation in adipocytes.

2.6.3.4 Proposed cellular activity of cinnamon

Results from several *in vitro* experiments (Imparl-Radosevich *et al,* 1998; Jarvill-Taylor *et al,* 2001; Anderson *et al,* 2004) supported the proposal that cinnamon polyphenols mimic insulin action via a number of different mechanisms, and report multiple active fractions of cinnamon. Imparl-Radosevich *et al,* (1998) illustrated insulin receptor activation with cinnamon extract in rat adipocytes through increasing insulin receptor phosphorylation and decreasing inactivating protein tyrosine phosphatase (PTP-1), overcoming insulin resistance. Although Qin *et al,* (2003) reported no increase in skeletal protein, higher levels of GLUT4 and IR ß protein were measured with immuno-blotting after treatment with various cinnamon fractions in mouse extracts (Cao *et al,* 2007) (figure 2.5), and Jarvill-Taylor *et al,* (2001) reported increased glycogen synthase with decreased glycogen synthase kinase-3 ß activity, resulting in increased glycogen synthesis. All of these actions are recognized insulin responses, decreasing glucose levels through increased cellular utilization and conversion to glycogen.

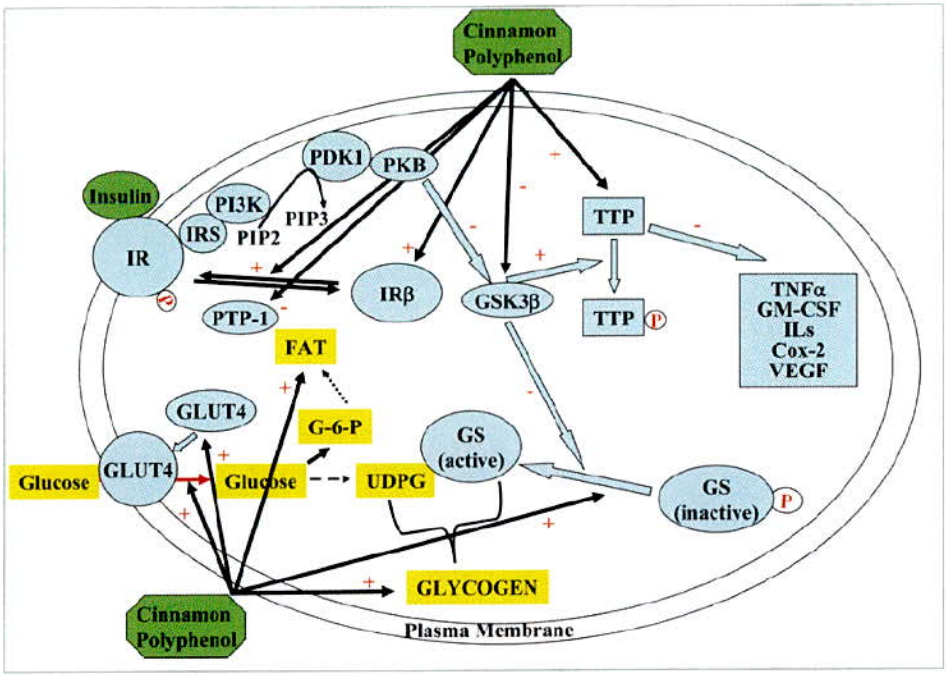


Figure 2.5 A model illustrating proposed cinnamon actions (1-6) in the insulin signal transduction pathway (Cao *et al,* 2007).
Cinnamon polyphenols (CP): (1) activate insulin receptors (IR) by increasing tyrosine phosphorylation activity and decreasing phosphatase activity; (2) increase the amount of insulin receptor-3 and GLUT4 proteins; (3) increase glycogen synthase activity and glycogen accumulation; (4) decrease glycogen synthetase (GS) kinase-3 3 (GSK33) activity; (5) increase the amount of tristetraprolin (TTP) protein; (6) may increase the activity of TTP by decreasing its phosphorylation through inhibition of GSK3JI activity. Insulin receptor substrate (IRS), 1-phosphatidyilnositol 3-kinase (P13K), phosphatidylinositol 4,5-bisphosphate (PIP2), phosphatidylinositol-3 4,5-trisphosphate (PIP3), protein tyrosine phosphatase-1 (PTP-1), phosphatidy-inositol-dependent protein kinase 1 (PDK1), glucose 6-phosphate (G-6-P), protein kinase B (PKB), uridine diphosphoglucose (UDPG), granulocyte-macrophage colony-stimulating factor (GM-CSF), cyclooxygenase-2 (Cox2), vascular endothelial growth factor (VEGF), ("+" represents positive effect and "-" represents negative effect). Source: Cao *et al,* (2007).

Yu *et al,* (2007) proposed that cytokine inflammation disrupts the action of TUG in fat and muscle cells, decreasing GLUT4 translocation to the cell membrane and reducing insulin action, and Lebrun and Van Obberghen (2008) hypothesized that suppression of cytokine signaling (SOCS) proteins affects insulin signaling through inhibition of tyrosine phosphorylation. Cao *et al,* (2007) illustrated increased levels of the anti-inflammatory protein tristetraprolin with cinnamon treatment, which reduces pro-inflammatory cytokine synthesis in adipose tissue and is normally induced by insulin. From these proposed mechanisms it may be concluded that anti-oxidant fractions in cinnamon (Halvorsen *et al,* 2006) could increase glucose utilization by overriding the effects of inflammation present in insulin resistance (Dandona *et al,* 2004; Anderson. 2008). This may enable GLUT4 translocation by superseding cellular inflammation, and enhance glucose uptake. This hypothesis is dependant upon the active components of cinnamon increasing glucose utilization in the presence of insulin resistance, which has already been illustrated (Qin *et al,* 2003; Wang *et al,* 2007).

Several animal trials (Verspohl *et al,* 2005; Kannappan *et al,* 2006; Kim *et al,* 2006[a]; Preuss *et al,* 2006) illustrated less significant results in the absence of elevated blood glucose. From these findings it is postulated that, as hyperglycaemia and insulin resistance are generally present together (Whincup *et al,* 2005; Abdul-Ghani *et al,* 2006; Abdul Ghani *et al,* 2008), if the active components of cinnamon share common pathways with insulin, there may greater opportunity for glucose uptake via cinnamon-activated GLUT4 translocation and enhanced insulin receptor activity during insulin resistance. Hyperglycaemia induces inflammation which may reduce insulin action, but be overridden via the anti-oxidant components of a cinnamon procyanidin (Cao *et al,* 2008). Thus it is concluded that the level of obesity-activated insulin resistance may affect cinnamon efficacy, offering a possible explanation as to why higher FPG levels have elicited a more significant effect, even with lower cinnamon doses.

GLUT4 is the main insulin responsive glucose transporter and is located primarily in muscle cells and adipocytes. In normal muscle cells and adipocytes GLUT4 is recycled between the plasma membrane and intracellular storage pools. According to Shepherd and Kahn (1999), in the presence of insulin or another stimulus (like cinnamon polyphenols), the equilibrium of this recycling process of is altered to favor the translocation (regulated movement) of GLUT4 from intracellular storage vesicles to the plasma membrane and, in the case of muscles, to the transverse tubules as well. The net effect is a rise in the maximal velocity of glucose transport into the cells (Gould and Holman. 1993; Pessin and Saltiel. 2000) (Figure 2.6). The active compounds and overall mechanism of action of cinnamon is shown in Figure 2.9.

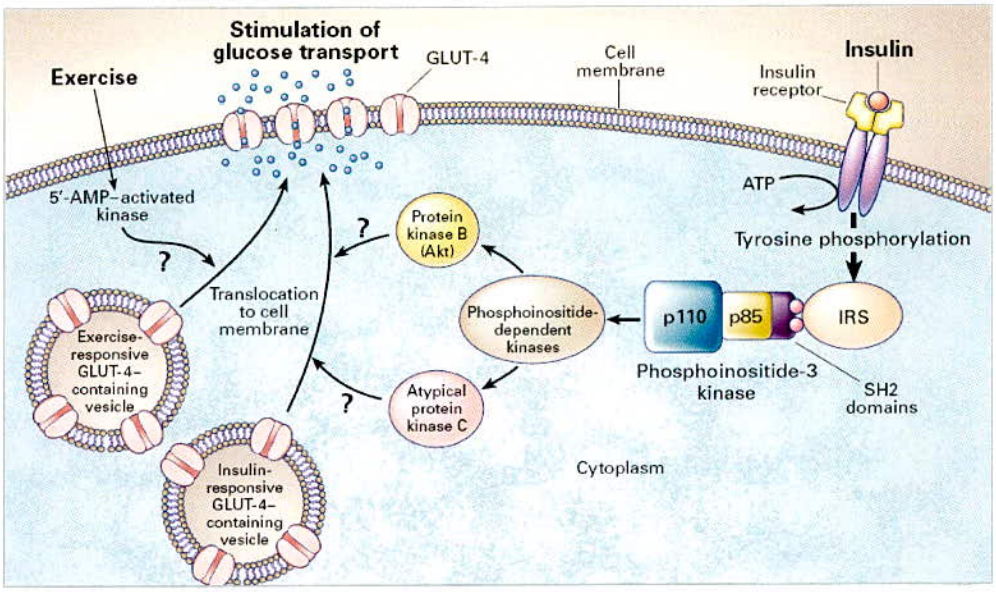


Figure 2.6 – Insulin signaling pathway that regulate glucose metabolism in Muscle Cells and Adipocytes (source: Shepherd and Kahn, 1999).
GLUT-4 is stored in intracellular vesicles. Insulin binds to its receptor in the plasma membrane, resulting in phosphorylation of the receptor and insulin-receptor substrates such as the IRS molecules. These substrates form complexes with docking proteins such as phosphoinositide-3 kinase at its 85-kd subunit (p85) by means of SH2 (Scr homology region 2) domains. Then p85 is constitutively bound to the catalytic subunit (p110). Activation of phosphoinositide-3 kinase is a major pathway in the mediation of insulin-stimulated glucose transport and metabolism. It activates phosphoinositide-dependent kinases that participate in the activation of protein kinase B (also known as Akt) and typical forms of protein kinase C (PKC). Exercise stimulates glucose transport by pathways that are independent of phosphoinositide-3 kinase and that may involve 5'-AMP–activated kinase.

2.6.3.5 Proposed anti hyperglycemic mechanism of cinnamon

Procyanidins have been reported to have varying anti-hyperglycaemic actions (Kao *et al,* 2000; Shimizu *et al,* 2000; Waltner-Law *et al,* 2002; Kim *et al,* 2003) and studies have offered varying hypotheses for the action of cinnamon. It has been proposed that at least some of the mechanisms of procyanidin-stimulated glucose uptake are via the same cellular pathways as insulin.

Some *in-vivo* animal studies report higher insulin levels with cinnamon supplementation (Kim *et al,* 2006[a]; Babu *et al,* 2007) and postulate that this may be a result of stimulation of the pancreatic beta cells; Verspohl *et al,* (2005) compared it to the anti-diabetic drug glibenclamide which stimulates insulin secretion (Geng *et al,* 2007). However, other animal studies report reduced insulin levels (Kannappan *et al,* 2006; Preuss *et al,* 2006). Whether these studies illustrate, respectively, evidence of an insulin-sparing effect or lower insulin secretion following reductions in blood glucose, little is to be gained in extrapolating these contradictory effects in animals across to human subjects, especially as differing methods may have incurred the cretin

effect and affected insulin measures (Abdul-Ghani *et al,* 2006). Human studies reveal little change in plasma insulin (Vanschoonbeek *et al,* 2006; Solomon and Blannin, 2007; Wang *et al,* 2007), possibly indicating that cinnamon effects are limited to plasma glucose. However, Vanschoonbeek *et al,* (2006) failed to produce a significant change in FPG and the remaining studies measured insulin with an oral glucose tolerance test (OGTT), so enduring effects upon insulin secretion once hyperglycaemia has been reduced are yet to be studied.

Cinnamon also appears to reduce hyperglycaemia and inflammation through delayed gastric emptying (Hlebowicz *et al,* 2007), reducing excess post-prandial triglycerides and glucose which induce cellular inflammation through increased C-reactive protein and cytokines (Monnier *et al,* 2006; O'Keefe *et al,* 2008). Suppressed glucose absorption (Kwon *et al,* 2007) and significant reductions in glycosidase activity (Kim *et al,* 2006[a]) have also been reported, which would reduce circulating glucose and create an anti-diabetic effect (Scheen. 2003). These actions may have contributed to the reduced plasma glucose reported following OGTTs (Solomon and Blannin. 2007; Wang *et al,* 2007), and may be due to the presence of catechin polymers in cinnamon (Shimizu *et al,* 2000; Anderson *et al,* 2004) or inhibition of intestinal ATP-ase (Kreydiyyeh *et al,* 2000). In comparison to other flavonoids, epicatechins have illustrated the highest inhibitory action with sodium-independent facilitated glucose uptake (Chen *et al,* 2007). Increased glycogen synthesis has also been reported (Cao *et al,* 2007), an action replicated by the epicatechin gallates (Waltner-Law *et al,* 2002). Figure 2.7, shows flavonoid inhibition of glucose absorption in small intestine and cinnamon compounds are also thought to slow down glucose absorption in a similar way.

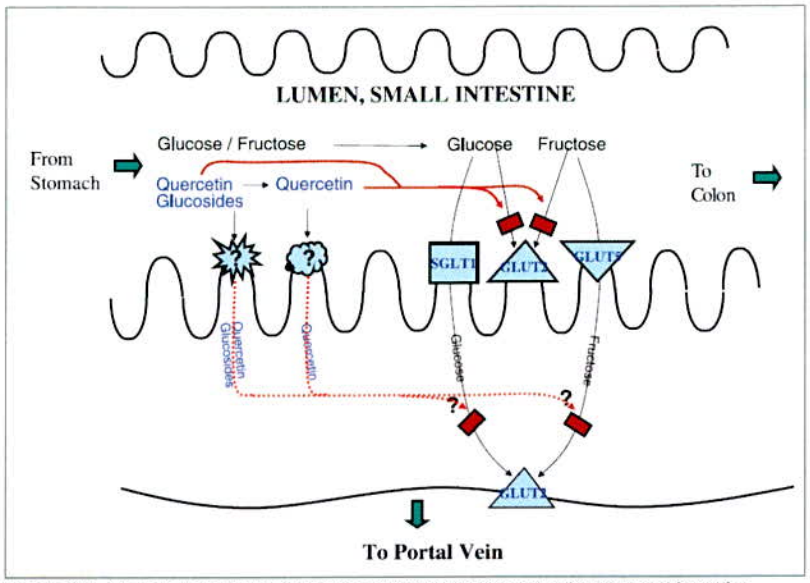


Figure 2.7 - Model of flavonoid inhibition of glucose absorption in the small intestine. Glucose is normally transported to the portal vein by GLUT2 and SGLT1 (sodium coupled glucose transporters). This model shows flavonoid compounds blocking absorption (Kwon *et al,* 2007). Quercetin is shown in this example (Kwon *et al,* 2007), but cinnamon compounds are thought to slow glucose absorption in a similar fashion.

It is not known why glycosylated haemoglobin (HbA1c) has been largely unaffected in human studies where FPG has reduced, as Babu *et al,* (2007) illustrated a 40.2% reduction in HbA1c in rats ($p < 0.05$), and there is evidence of cinnamon reducing advanced glycation end products (Peng *et al,* 2008). There is a strong correlation between anti-oxidant capacity and the phenolic compounds such as those found in cinnamon (Matsuda *et al,* 2003; Jayaprakasha *et al,* 2006; Peng *et al,* 2008), thus it is hypothesized that cinnamon may promote glycation-lowering, longer term benefits for diabetic patients (Dandona *et al,* 2004; Monnier *et al,* 2006). If cinnamon reduces post-prandial hyperlipidaemia and hyperglycaemia through delayed gastric emptying (Hlebowicz *et al,* 2007) and reduced absorption (Kreydiyyeh *et al,* 2000), it has potential to lower risk factors for diabetes, metabolic syndrome and heart disease, regardless of cinnamatic adipose or skeletal muscle activity (Festa *et al,* 2004; Abdul-Ghani *et al,* 2006). Figure 2.8 shows the overall possible potential cinnamon mechanism in the body.

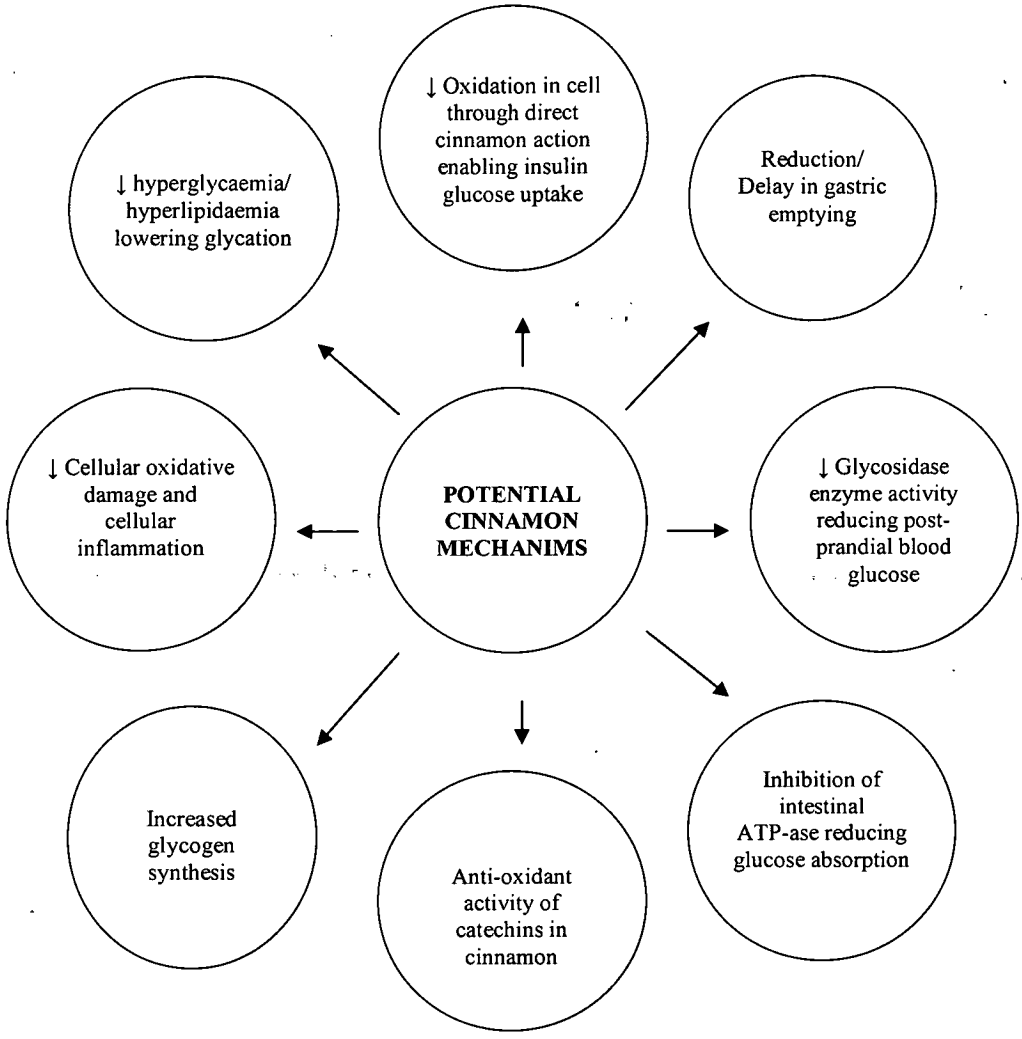
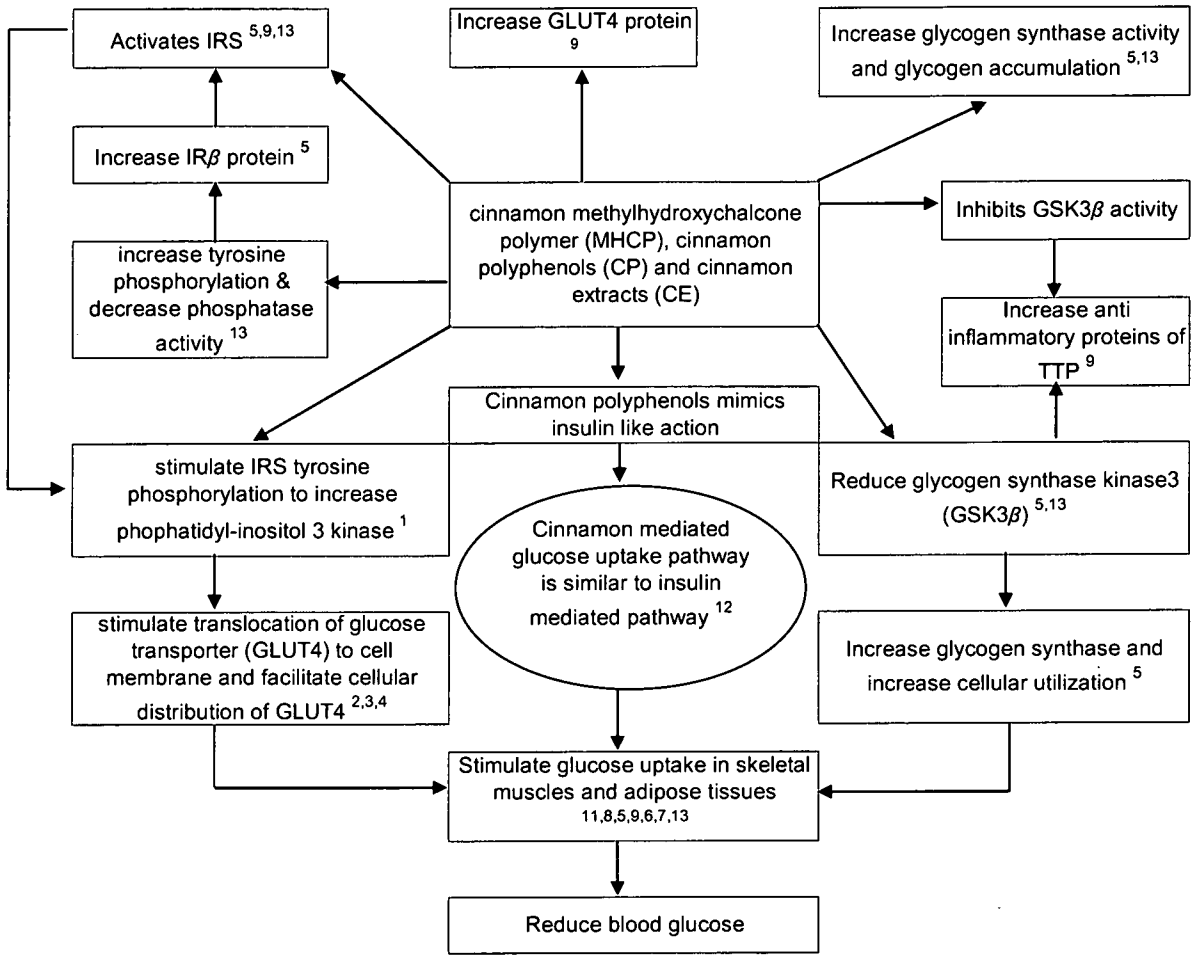


Figure 2.8 – The potential anti hyperglycaemic mechanism of cinnamon in the body.
The suggested mechanisms were based on the evidence from previous *in vitro* and *in vivo* intervention trials



[1]Petersen & Shulman (2006); [2]Kansaki *et al* (2006); [3]Bryant *et al.* (2002); [4]Watson *et al.* (2004); [5]Jarvill-Taylor *et al.* (2004); [6]kannappan *et al.* (2006); [7]Kim *et al.* (2006); [8]Roffey *et al.* (2006); [9]Cao *et al.* (2007); [10]Anderson *et al.* (2004); [11]Qin *et al.* (2003); [12]Pinnet *et al.* (2004); [13]Imparl-radosevich *et al* .(1998)

Figure 2.9 – The summary of active compounds and mechanism of action of cinnamon based on the evidence from *in vitro* and *in vivo* studies

2.6.4 Evidence from some *in vitro* and *in vivo* animal studies

During the last decade, *in vitro* studies revealed that the cinnamon extract mimics the effect of insulin, which potentate's insulin action in the body (Bradhurst *et al,* 2000). Several *in vitro* and *in vivo* animal studies have reported strong insulin like or insulin potentiating effects after cinnamon administration. The summary of methodologies and results of *in vitro* and *in vivo* animal studies are shown in Table 2.5.

Although human studies have shown no dose dependant effect (Khan *et al,* 2003), several *in vivo* animal studies have illustrated dose dependant FPG reductions (Kannappan *et al,* 2006; Kim *et al,* 2006[a]; Babu *et al,* 2007). Significant decreases are also reported in HbA1c% (Kannappan *et al,* 2006; Preuss *et al,* 2006; Babu *et al,* 2007), plasma insulin (Kannappan *et al,* 2006; Kim *et al,* 2006[a]; Preuss *et al,* 2006), triglycerides, total and LDL cholesterol (Kannappan *et al,* 2006; Kim *et al,* 2006[a]; Babu *et al,* 2007), and increases in HDL (Kim *et al,* 2006[a]; Babu *et al,* 2007). Other animal studies report enhanced insulin signaling and increased glucose uptake with cinnamon in a dose dependant manner (Qin *et al,* 2003), and *in vitro* results illustrate reduced plasma glucose and increased insulin in response to glucose load (Verspohl *et al,* 2005). Kim *et al,* (2006[a]) reported a higher rate of glucose disposal which returned blood glucose levels in diabetic mice to normal, also illustrating that disaccharide conversion into glucose in the highest dose cinnamon group was significantly decreased in various parts of the small intestine ($p < 0.01$ to $p < 0.001$) (Table 2.5)

Table 2.5 - Summary of methodologies and results of some identified previous *in vitro* and *in vivo* animal studies of cinnamon and glycaemic control.

Study information	Qin et al (2003)	Verspohl et al (2005)	Kannapan et al(2006)	Kim et al (2006)	Preuss et al (2006)	Babu et al (2007)
In vitro/iv vivo	*in vivo*	*in vivo & in vitro*	*in vivo*	*in vivo*	*in vivo*	*in vivo*
Methodology	3 groups of 6 rats Saline control 30mg/kg cinnamon; 300mg/kg cinnamon; wgt. 145 – 160g	Various controls used wgt. 250 – 350g	4 groups of 6 rats 2 controls (normal/diabetic) wgt. 150 – 170g	4 groups of 10 rats plus control group wgt. 150 – 170g	4 groups of 6 rats plus control wgt. 150 – 200g	7 groups of 6 rats plus placebo, diabetic and glibenclamide controls
Type of cinnamon	Cinnamon extract	C. cassia bark, C. cassia and C. zeylanicum extracts	C. zeylanicum extract	C. cassia extract	C. burmannii extract	C. zeylanicum bark
Cinnamon dose	30mg/kg 300mg/kg	Bark 85.7mg/kg, C. cassia extract 5.29mg/kg, z. extract 5.96mg/kg	0.2ml/day (diabetic rats) 2ml/day (diabetic rats) 0.2ml/day (non-diabetic rats) 2ml/day (non-diabetic rats)	50mg/kg cinnamon 100mg/kg cinnamon 150mg/kg cinnamon 200mg/kg cinnamon	1% solution, 2% solution, 4% solution and 8% solution	20mg/kg BW (non diabetic rats); diabetic rats 5mg/kg, 10mg/kg and 20mg/kg BW.
Study duration	3 weeks	GTT and *in vitro* cells	60 days	2, 4 and 6 weeks	3 - 4 weeks	45 days
Plasma measures	FBG, Plasma Insulin Plasma FFA Muscle protein content (IR-ß, IRS-1, PI 3-kinase	FBG Plasma insulin Cellular insulin secretion	FBG, HbA1c% Plasma insulin, FFA, triglycerides, total cholesterol, HOMA-IR	FBG, Plasma insulin, FFA, triglycerides, total cholesterol, HDL	SBP, FBG, Plasma insulin[a], HbA1c, FFA, HDL, triglycerides, total cholesterol	Plasma glucose, HbA1c%, Plasma insulin, HDL, triglycerides, total cholesterol, glycogen
Results	No effect on FBG or plasma FFA. ↑ amount/activity of IR-ß*, IRS-1**, PI 3-kinase**	C. cassia superior to C. zeylanicum. FBG ↓* (with glucose load) Plasma insulin ↑* *In vitro* Insulin secretion ↑	Glucose*, insulin*, HbA1c%*, HOMA-IR* and plasma lipids* ↓ in diabetic rats, especially in 2ml/day CE rats	Dose dependant results. For 200mg/kg group: FBG ↓ *** Plasma insulin ↑*, HDL ↑*, triglycerides ↓**	SBP ↓ Plasma glucose, HbA1c% and plasma lipids - no significant effect	In diabetic rats: ↑ liver glycogen*, insulin*, And HDL*. ↓ glucose*, HbA1c%* (40.2%), total cholesterol* and triglycerides*

Data presented as means ± SD; C - *cinnamomum*; CE - cinnamon extract; FBG - fasting blood glucose; FFA - free fatty acids; GTT - glucose tolerance test, HbA1c - glycosylated haemoglobin; HDL - high density lipoprotein; HOMA-IR - homeostasis model insulin resistance index; IR-ß - insulin receptor; IRS-1 - insulin receptor substrate; PI - phosphatidylinositol; SBP - systolic blood pressure; wgt - weight; z - zeylanicum; [a] Changes in plasma insulin documented but unclear in original paper. * $P<0.05$; ** $P<0.01$; *** $P<0.001$

Animal experiments have shown similar effects when comparing aqueous cinnamon extract to whole cinnamon spice, supporting the hypothesis of Preuss *et al,* (2006) that the bioactivity relating to insulin activity is present in the water soluble fraction of cinnamon. It is feasible that some animal and human studies have used preparations with low levels of the active component, possibly explaining why animal studies using higher doses (20mg – 200mg per kg body weight) have resulted in greater blood glucose reduction (Verspohl *et al,* 2005; Kim *et al,* 2006[a]); although these studies used different cinnamon preparations, a high enough dose may have contained adequate levels of the active components. However, although animal studies illustrate promising anti-diabetic properties, proof that cinnamon can reduce blood glucose levels in humans remains to be established.

Subash *et al,* (2007) conducted a randomized control study to investigate the hypoglycaemic and hypolipidemic effects of cinnamaldehyde (*Cinnamonum zeylanicum*) in streptozotocin (STZ) induced diabetic rats. Cinnamaldehyde was administered at different doses (5, 10 and 20mg/kg body weight) for 45 days to STZ induced male diabetic rats. The findings of this study showed that oral administration of cinnamaldehyde produced a significant antihyperglycemic effect and lowered glycosylated haemoglobin (HbA1c) level, total cholesterol and triglyceride levels and, at the same time, increased HDL cholesterol in STZ induced diabetic rats. The plasma glucose concentration was significantly ($p<0.05$) decreased in a dose dependent manner compared to the control. Results of this study revealed the potential of cinnamaldehyde for use as a natural oral anti diabetic agent, with both hypoglycaemic and hypolipidemic effects.

Cao *et al,* (2007) reported the novel findings that cinnamon extract and polyphenols exhibit the potential to increase the amount of insulin receptor (IRβ) protein, tristetraprolin (TTP) protein and glulcose transporter 4 (GLUT4) proteins in mouse 3T3-L1 adiposytes. The objective of this study was to investigate the effects of cinnamon extract and cinnamon polyphenols on the regulation of IRβ, GLUT 4 and TTP proteins in mouse 3T3-L1 adipocytes. These three proteins are involved in the insulin signalling transduction pathway that functions in insulin receptor substrate activation, insulin regulated glucose transport and anti inflammatory responses respectively. Cell cultures of mouse 3T3-L1 adipocytes were used in this study to investigate the effect of cinnamon polyphenols. The result of this study revealed that cinnamon polyphenols activate insulin receptors by increasing their tyrosine phosphorylation activity and decreasing phosphatase activity that inactivates the insulin receptor. This is achieved by cinnamon polyphenols increasing the glycogen synthase activity and glycogen accumulation, insulin receptor protein and GLUT 4 proteins.

Anderson *et al,* (2004) evaluated the effect of the cinnamon extract on the insulin action in aroused rats and analysed possible changes in insulin signalling occurring in skeletal muscles. After 3 weeks of this trial, cinnamon extract treated rats showed a significantly higher glucose infusion rate compared with controls. The results of this study suggest that the cinnamon extract would improve insulin action via increasing glucose uptake *in vivo*, at least in part through enhancing the insulin signalling pathway in skeletal muscles.

Jarvill *et al,* (2001) investigate the ability of methylhydroxychalcone polymer (MHCP) to stimulate insulin like responses in 3T3-L1 adipocytes. The 3T3-L1 cells are routinely used in the signalling studies and are regarded as demonstrating all of the features of adipocytes. Result of this study demonstrate that MHCP is fully capable of mimicking insulin. Thus, the MHCP can be used as another tool in studying the pathways leading to glucose uptake and glycogen synthesis. Because MHCP can work alone, it may function as a therapeutic agent for use with insulin resistant cells.

2.6.5 Methods

Figure 2.10 shows that a total of 317 articles were identified, of these only 4 articles met the strict inclusion criteria for randomized controlled trials of cinnamon and type 2 diabetes mellitus.

2.6.5.1 Inclusion and exclusion criteria

Out of the 317 articles, 305 were excluded either because they were duplicates, *in vivo* animal studies, *in vitro* laboratory studies, not published in English language, did not have an abstracts or author's name or did not include a proper controlled intervention. From the remaining studies (n=12) of human intervention trials of cinnamon, 8 studies were excluded as reviews of cinnamon and diabetes, studies with cinnamon and pre/non diabetes, RCT for type 1, and gestational diabetes mellitus. Finally 4 RCTs of cinnamon and type 2 diabetes mellitus was chosen for further review.

2.6.5.2 Data extraction and analysis

Data from 4 randomized controlled trials (RCTs) were included in the review and appraised in terms of participant numbers, population characteristics, RCT methodology, data analysis and results in order to explore the hypothesis that cinnamon may improve glycaemic control and blood cholesterol levels in type 2 diabetic patients.

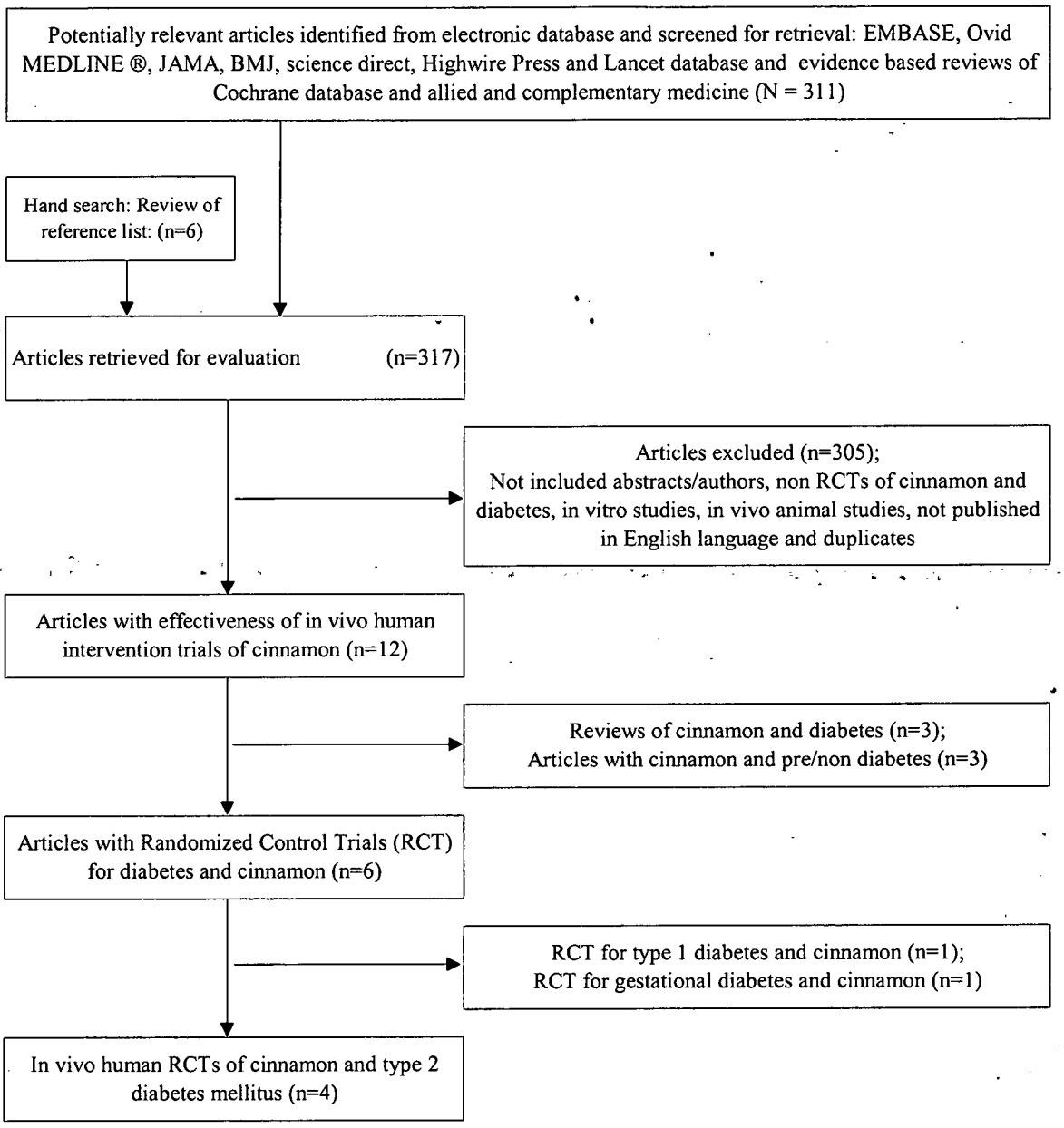


Figure 2.10 - Systematic review of cinnamon and type 2 diabetes mellitus. n = number of articles, RCT - randomized control trials. A total of 317 articles were identified, of these only 4 articles met the strict inclusion criteria for RCT for cinnamon and type 2 diabetes mellitus

2.6.6 Results

Four randomized, placebo controlled trials on patients with type 2 diabetes mellitus were included in this review. These studies together consisted of a total of 205 patients who were followed up for a period of between 5.7 to 16 weeks. Two RCTs had a duration of less than 6 weeks (Vanchonbeek *et al,*2006; Khan *et al*; 2003) and two studies were of more than 12 weeks duration (Blevins *et al,* 2007; Mang *et al,* 2006). Three of these RCTs were prospective, randomized, double-blind, placebo-controlled clinical trials (Khan *et al,* 2003; Mang *et al,* 2006; Blevins *et al,* 2007) and one was a prospective, placebo-controlled clinical trial (Vanschoonbeek *et al,* 2006). In all four clinical trials the same cinnamon genus of *Cinnamomum cassia* was administered and the dose ranged from one to six grams per day. Three studies provided powder filled cinnamon capsules in the intervention group compared with either wheat flour filled placebo capsules in the control group (n=3) (Khan *et al,* 2003; Vanschoonbeek *et al,* 2006; Blevins *et al,* 2007) or aqueous extract filled cinnamon capsules in the intervention group (n=1) (Mang *et al,* 2006) (Table 2.7). All four RCTs analysed the effect of cinnamon on blood lipid profiles and plasma glucose concentration and three RCTs analysed the effect on HbA1c levels (Table 2.8).

Table 2.6 gives the baseline characteristics of the 4 RCTs. Age, years since diagnosis and BMI were similar across all studies and therefore less likely to be factors contributing to different results. Vanschoonbeek *et al,* (2006) suggested that the study outcome may have been affected by the fact that the study was restricted to menopausal females. All other trials included both genders, and there were no apparent gender-related sub-groups in these studies. There were differences in ethnicity which may have contributed to the heterogeneity of results, although Blevins *et al,* (2007) included different ethnicities with no sub-groups appearing. However, population size may have been too small to investigate this. Khan *et al,* (2003) did not report or measure changes in BMI, waist circumference and HbA1c levels.

Khan *et al,* (2003) and Mang *et al,* (2006) appear to have exerted minimal control over diet, and reported significant reduction in fasting plasma glucose concentration, whereas studies utilizing three day food diaries (Blevins *et al,* 2007) and standardized pre oral glucose tolerance test (OGTT) meals (Vanschoonbeek *et al,* 2006) illustrated no significant effect on blood glucose levels (Table 2.7).

Cinnamon efficacy may be affected by the type of diabetes medication used. In the study by Khan *et al,* (2003) all patients were treated with sulphonylureas, whereas in the other 3 RCTs patients

were treated with metformin, sulphonylureas and/or thiazolidinediones (Table 2.7). The additional use of anti-hypertensive and dyslipidaemia medications were reported in two RCTs (Blevins *et al,* 2007; Mang *et al,* 2006), but Vanchoonbeek *et al,* (2006) did not reported the use of anti hypertensives or statins nor their potential effects as a result of the dose.

Khan *et al,* (2003) reported the results of a first human intervention trial on cinnamon supplementation for type 2 diabetes mellitus in Pakistan. This trial was designed to evaluate whether cinnamon improved blood glucose and serum lipid levels in people with type 2 diabetes mellitus. People with type 2 diabetes mellitus were included in the trial if they were, aged >40 years, not on insulin therapy, patients using only sulphonylurea drugs who were not taking medicine for other health conditions and fasting blood glucose levels between 7.8 and 22.2 mmol/l (140 – 400mg/dl). This study was conducted for 60 days and included a 20 day wash out period. A total of 60 individuals; 30 men and 30 women with type 2 diabetes mellitus, were divided randomly into six equal groups. The cinnamon group were given 1g, 3g or 6g of cinnamon in capsules per day and the placebo group were given 1g, 3g and 6g of wheat flour capsules per day for a 40 day period. *Cinnamon cassia* powder was used to prepare capsules; each capsule contained either 500mg of cinnamon or wheat flour. Patients who were assigned to cinnamon groups (group 1, 2 and 3) consumed either two 500mg (1g) capsules of cinnamon, six 500mg (3g) capsules of cinnamon and 12 500mg (6g) capsules of cinnamon per day. Patients assigned to placebo group (groups 4, 5 and 6) were given placebo capsules of wheat flour (1g, 3g and 6g respectively) for 40 days. On days 0, 20, 40 and 60, fasting blood samples were collected from subjects and plasma glucose concentration, triglycerides, HDL, LDL and total cholesterol levels were measured.

The results of this study demonstrated that the addition of 1, 3 and 6g of cinnamon led to a significant decrease ($p<0.05$) in serum glucose levels after 40 days, and a decrease of serum glucose ranging from 18 – 29%. The baseline plasma glucose concentration was found to be 13.7mmol/l and 12.0mmol/l in both placebo and cinnamon groups respectively (Table 2.6). The consumption of cinnamon also led to a time dependent decrease in serum triglyceride levels for all amounts of cinnamon tested after 40 days (with a wash out period) ranging from 23 – 30%. Significant ($p<0.05$) decreases in serum cholesterol levels in all three cinnamon groups were observed and no changes were noted in the respective placebo group which ranging from 13 – 26%. A decrease in LDL cholesterol levels were also significant ($p<0.05$) in the 3g and 6g groups after 40 days with a decrease of 10 – 24%. However, there were no significant changes in HDL in the subjects

consuming 1 or 6g of cinnamon for 40 days (for more details of results, study outcomes and comparisons see Tables 2.6 – 2.9).

In an attempt to repeat Khan's study, a group of Dutch researchers performed a similar study to investigate the proposed health benefits of cinnamon use in postmenopausal women with diabetes. This was the second clinical trial carried out by Vanschoonbeek *et al,* and published in 2006. This study assessed the effects of 2 and 6 weeks of cinnamon supplementation on fasting glucose, insulin and HbA1c, indices of oral glucose tolerance and whole body insulin sensitivity, and fasting blood lipid profiles. A total of 25 postmenopausal women diagnosed with type 2 diabetes mellitus were selected to participate in these 2 to 6 weeks of prospective, double blind, placebo control study. Postmenopausal women treated only with oral anti diabetic drugs of sulphonylurea, metformin, thiazolidinediones and combined therapies were included in this trial.

All subjects were assigned to either a control (n=13) and cinnamon group (n=12), matched for age, BMI, years since diagnosis with diabetes, fasting plasma glucose concentration and type of medication received (stratified random sampling). Participants were instructed to take either 1500mg of cinnamon or placebo (wheat flour) capsules every day for 6 weeks (three 500mg capsules per day with breakfast, lunch and dinner). Insulin sensitivity and oral glucose tolerance were analysed at baseline and after 2^{nd} and 6^{th} weeks of cinnamon supplementation.

The results of this study failed to detect any effect on plasma glucose level, insulin sensitivity and blood lipid profiles in postmenopausal diabetic women. There were no time and treatment interactions for whole body insulin sensitivity or oral glucose tolerance (Table 2.9). The blood lipid profiles and HbA1c measurements did not change after cinnamon supplementation. This study concluded that cinnamon supplementation (1.5g per day) did not improve fasting plasma glucose, oral glucose tolerance, blood lipid profiles and whole body insulin sensitivity measures in postmenopausal women with type 2 diabetes mellitus.

A publication from a German group of scientists reported that cinnamon had a positive effect in controlling type 2 diabetes mellitus. This was a prospective, randomized, placebo controlled trial carried out by Mang *et al,* (2006) investigating the effects of the daily intake of an aqueous cinnamon extract *(cinnamomum cassia)* over 4 months on HbA1c, fasting plasma glucose and serum lipids in type 2 German diabetic patients. A total of 65 type 2 diabetic patients were randomly assigned to take either cinnamon extract (3g) or placebo capsules three times per day for

4 months period. One cinnamon capsule contained 112mg of the aqueous cinnamon extract, corresponding to 1g of cinnamon.

The results of this study revealed that fasting plasma glucose for the cinnamon group was significantly reduced after the intervention period compared with baseline, and the mean percentage difference in glucose concentrations were 10.3±13.2% for the cinnamon group and 3.37±14.2% for the placebo group (p=0.046). The patients who had the highest blood sugar readings at the start of the trial experienced the greatest reductions. There were no changes regarding the lipid profiles after the intervention compared with baseline in this study. The decrease in plasma glucose concentrations in this study was not sufficient to induce an improvement of the lipoprotein concentration. The conclusion of this study suggests that cinnamon extract (corresponding to 3g cinnamon powder per day) seemed to have a moderate effect in reducing fasting plasma glucose concentration but not on HbA1c and serum lipid measurements.

More recently Blevins *et al,* (2007) conducted a clinical trial in USA and suggested that cinnamon cannot be generally recommended for the treatment of type 2 diabetes mellitus in an American population. This was a prospective, double blind, placebo controlled trial which investigated the effects of cinnamon on glucose and lipid levels in subjects with type 2 diabetes mellitus. A total of 58 subjects were randomly (stratified by gender) assigned to receive either 1g per day of cinnamon powder (*cinnamon cassia*) or placebo (wheat flour) for 3 months. Subjects were instructed to ingest one capsule (500mg) with breakfast and one with dinner. The results of this study demonstrated that there were no significant differences between the cinnamon and placebo groups for any measure comparing baseline to 3 months (Table 4.2). Further this study concluded that cinnamon taken at a dose of 1 gram daily for 3 months did not explain any significant reductions in fasting glucose, lipids, HbA1c and plasma insulin levels.

Table 2.6 – The baseline characteristics of the study population in 4 RCTs of cinnamon and type 2 diabetes mellitus.

Variable	Khan *et al*, 2003		Mang *et al*, 2006		Vanschoonbeek *et al*, 2006		Blevins *et al*, 2007	
Treatment	Cinnamon	Placebo	Cinnamon	Placebo	Cinnamon	Placebo	Cinnamon	Placebo
N	n = 30	n = 30	n = 33	n = 32	n = 13	n = 12	n = 28	n = 30
Men %	50%	50%	63.6%	71.9%	0%		Not known	
Women %	50%	50%	36.4%	28.1%	100%		Not known	
Ethnicity	Ethnicity not noted but recruitment was from Pakistan		German		Ethnicity not noted but recruitment was from Maastricht, The Netherlands		68% Caucasian 16% Native American 7% African American 4% Hispanic 2% Asian 3% unknown	
Time since diagnosis (mean) of diabetes (y)	7.10 ± 3.29	6.73 ± 2.32	7.1 ± 6.2	6.8 ± 4.7	7.6 ± 1.4	7.1 ± 1.6	-	
Baseline FPG (mmol/L) [a]	12 ± 1.43	13.76 ± 1.40	9.26 ± 2.26	8.66 ± 1.47	8.37 ± 0.59	8.28 ± 0.33	7.38 ± 0.51	8.04 ± 0.57
Mean age (y)	52 ± 5.85	52 ± 6.87	62.8 ± 8.37	63.7± 7.17	62 ± 2	64 ± 2	63.6	58
Mean height (m)	-		1.72 ± 0.09	1.73 ± 0 07	1.67 ± 0.02	1.65 ± 0 02	-	
Mean weight (kg)	-		88.5 ± 19.1	89.9 ± 14.1	85.4 ± 3.6	82.2 ± 4.0	-	
Mean BMI (kg/m²)	-		29.6 ± 4.64	30.1 ± 5.22	30.7 ± 1.1	30.1 ± 1.4	32.5 ± 1.7	32.0 ± 1.5
Mean waist circumference (cm)	-		100.5± 15.0	102.7± 11.2	-		-	

Data presented as means ± SD; N corresponds to the number of participants for which data was available upon completion of each study [a] as no dose-response relationship was found between 1g, 3g and 6g in the study by Khan *et al*, (2003). There is no significant difference in mean FPG, age, BMI and waist circumference at baseline between the cinnamon and placebo groups in all 4 RCTs. BMI – Body Mass Index; FPG – Fasting Plasma Glucose.

Table 2.7 - Comparison of RCT methodologies of selected cinnamon and type 2 diabetes mellitus.

Variable	Khan *et al*, 2003	Mang *et al*, 2006	Vanschoonbeek *et al*, 2006	Blevins *et al*, 2007
Study design	Single-blind randomized placebo controlled trial	Double-blind randomized placebo controlled trial	Double-blind randomized placebo controlled trial	Double-blind randomized placebo controlled trial
Matched pairs	Matched for age	Not matched	Matched for age, BMI, years since diagnosis, baseline FBG and medication	Stratified by gender and randomized
Type of cinnamon used	*C. cassia* powder	*C. cassia* aqueous extract	*C. cassia* powder	*C. cassia* powder
Dose of cinnamon	1g, 3g and 6g	3g	1.5g	1g
Study duration	40 days intervention 20 days washout	4 months	6 weeks	3 months
Dietary control	None mentioned other than participants consumed usual diet	None mentioned	2 day food diary Pre-OGTT exercise control and standardized meal pre-OGTT	Diet monitored with a 3 day food diary
Diabetes medication taken by participants	All sulphonylureas	27.7% metformin, 12.3% sulphonylureas, 4.6% glinides, 1.5% glitazones, 30.8% combination therapy, 23.1% diet	Sulphonylureas with metformin (n=14), metformin (n=3), thiazolidinediones with/without metformin (n=6), diet only (n=4)	¾ metformin, Over $^1/_3$ thiazolidinedione ½ hydroxymethylglutaryl-CoA reductase inhibitor. Diet only: 23% (cinnamon group), 9% placebo group
Other medication	No other medications taken	49.2% anti-hypertensive medication 20% dyslipidaemia medication	None reported	55% cinnamon group and 48% placebo group took dyslipidaemia medication

Table 2.8 – The results of baseline and post intervention serum glucose, HbA1c and Blood lipid profiles of the selected 4 RCTs of cinnamon and type 2 diabetes mellitus.

	Intervention		Fasting serum glucose (mmol/l)		Fasting serum lipid profiles (mmol/l)								HbA1c (%)	
					Total cholesterol		HDL		LDL		Triglycerides			
			Baseline Mean ± SD	After intervention Mean ± SD	Base line Mean ± SD	After intervention Mean ± SD	base line Mean ± SD	After intervention Mean ± SD	base line Mean ± SD	After intervention Mean ± SD	base line Mean ± SD	After intervention Mean ± SD	base line Mean ± SD	After intervention Mean ± SD
Khan *et al* (2003)	Placebo	1g	12.2±1.0	[a]12.4±1.1*	4.58±0.28	[a]4.58±0.31*	—	—	2.30±0.22	[a]2.20±0.22*	2.31±0.32	[a]2.50±0.30*	—	—
		3g	12.4±1.0	[a]12.7±1.0*	4.81±0.30	[a]5.04±0.31*	—	—	2.56±0.25	[a]2.66±0.27*	2.38±0.29	[a]2.39±0.28*	—	—
		6g	16.7±1.4	[a]16.8±1.7*	5.51±0.41	[a]5.66±0.43*	—	—	3.03±0.31	[a]3.28±0.34*	2.55±0.34	[a]2.52±0.40*	—	—
	Intervention	1g	11.6±1.7	[a]8.7±1.6*	4.91±0.23	[a]4.32±0.27*	—	—	2.66±0.12	[a]2.48±0.10*	2.25±0.35	[a]1.57±0.21*	—	—
		3g	11.4±1.2	[a]9.4±1.1*	5.51±0.29	[a]4.09±0.26*	—	—	2.77±0.18	[a]2.04±0.19*	2.75±0.30	[a]2.01±0.36*	—	—
		6g	13.0±1.4	[a]9.2±1.5*	5.30±0.22	[a]4.65±0.24*	—	—	2.87±0.18	[a]2.59±0.16*	2.48±0.39	[a]1.91±0.30*	—	—
	Placebo (1g + 3g + 6g)		13.77±1.13	13.97±1.23	4.97±0.33	5.09±0.35	—	—	2.63±0.26	2.71±0.27	2.41±0.32	2.47±0.33	—	—
	Intervention (1g + 3g + 6g)		12.0±1.43	9.1±1.40	5.24±0.25	4.35±0.26	—	—	2.77±0.16	2.37±0.15	2.49±0.35	1.83±0.29	—	—
Mang (2006)	Placebo		8.66±1.47	8.31±1.62	5.25±0.79	5.17±0.75	1.34±0.31	1.33±0.30	3.59±0.69	3.60±0.64	1.66±0.78	1.73±0.70	6.71±0.73	6.68±0.70
	Intervention		9.26±2.26	8.15±1.65†	5.38±0.89	5.29±0.89	1.44±0.49	1.46±0.52	3.48±0.71	3.52±0.75	1.96±1.65	1.81±1.58	6.86±1.00	6.83±0.83
Vans (2006)	Placebo		8.28±0.33	8.07±0.36	4.91±0.30	4.66±0.31	1.29±0.11	1.29±0.09	3.04±0.25	2.77±0.24	1.28±0.14	1.32±0.18	7.1±0.2	7.2±0.2
	Intervention		8.37±0.64	7.91±0.71	5.05±0.15	4.81±0.19	1.42±0.09	1.41±0.09	3.06±0.15	2.85±0.16	1.25±0.17	1.20±0.13	7.4±0.3	7.5±0.3
Blevins (2007)	Placebo‡		8.04	8.02	4.56	4.63	-2.2	—	2.72	2.79	1.76	1.58	7.1	7.2
	Intervention‡		7.38	6.84	4.4	4.38	1.13	1.11	2.62	2.67	1.49	1.39	7.2	7.4

All data shown above are mean+SD; [a] mean±SD after 40 days of intervention; * P<0.05 shows that there is a significant reduction in mean fasting serum glucose, total cholesterol, LDL cholesterol and serum triglyceride levels in the cinnamon group compared to placebo group after intervention; † P<0.05 shows that the fasting serum glucose level was significantly reduced in the cinnamon group compared to placebo after intervention; ‡ data presented as only means. __ shows data not measured or presented in publications. HbA1c – glycated haemoglobin levels. Blevins *et al,* (2007), Vanschoonbeek *et al,* (2006) and Mang *et al,* (2006) studies demonstrated that there is no significance difference (P<0.05) in HbA1c and serum lipid profiles in the cinnamon group compared to placebo group after intervention.

Table 2.9 – The main results and clinical outcomes measured in the 4 RCTs of cinnamon and type 2 diabetes mellitus

Results	Khan *et al*, 2003	Mang *et al*, 2006	Vanschoonbeek *et al*, 2006	Blevins *et al*, 2007
FBG (mmol/L)	↓ by 2.9mmol/L[1g]* ↓ by 2mmol/L [3g]* ↓ by 3.8mmol/L [6g]*	↓ by 1.11mmol/L *v baseline* $p < 0.001$ v placebo $p < 0.038$	↓ by 0.46mmol/L $p > 0.05$	↓ by 0.54mmol/L ($p = 0.38$)
HbA1c (%)	-	No significant effect	↑ by 0.1%	No significant effect
Total cholesterol (mmol/L)	↓ by 0.59mmol/L [1g]* ↓ by 1.42mmol/L [3g]* ↓ by 0.65mmol/L [6g]*	No significant effect	No significant effect	No significant effect
LDL (mmol/L)	↓ by 0.18mmol/L [1g]* ↓ by 0.73mmol/L [3g]* ↓ by 0.28mmol/L [6g]*	No significant effect	No significant effect	No significant effect
HDL (mmol/L)	No significant effect in 1g and 6g. 3g dose significant but unknown	No significant effect	No significant effect	No significant effect
Triglycerides (mmol/L)	↓ by 0.68mmol/L [1g]* ↓ by 0.74mmol/L [3g]* ↓ by 0.57mmol/L [6g]*	No significant effect	No significant effect	No significant effect
Plasma insulin (pmol/L)	-	-	No significant effect	No significant effect
HOMA-IR	-	-	No significant effect	-
ISIcomp	-	-	No significant effect	-
OGIS	-	-	No significant effect	-

Data presented as means and SD; – indicates not measured; FBG - fasting blood glucose; HbA1c - glycosylated haemoglobin; HDL - high density Lipoprotein; HOMA-IR – homeostasis model insulin resistance index; ISIcomp - whole body insulin sensitivity; LDL - low density Lipoprotein; OGIS - whole body insulin sensitivity; * $P < 0.05$shows that there is a significant reduction in mean fasting serum glucose, total cholesterol, LDL cholesterol and serum triglyceride levels in the cinnamon group compared to placebo group after intervention; ↓ shows reduced by and ↑ shows increased by.

2.6.6.1 Correlations between baseline and post intervention blood glucose levels

The changes in fasting plasma glucose (FPG) at baseline and post intervention are shown in Figure 2.11. Data from studies by Khan *et al,* (2003) and Mang *et al,* (2006), indicated that the elevated baseline FPG is likely to have contributed to the significant results (Figure 2.11 and Table 2.12). Mang *et al,* (2006) illustrated a statistically significant relationship and strong causality between mean baseline FPG and reduction in FPG ($r = 0.685$; $P < 0.001$). Data plots from the Type 2 diabetic studies appear to show a correlation, although this becomes less apparent as baseline FPG reduce. Despite a lower baseline FBG, Blevins *et al,* (2007) reported a slightly greater reduction compared with Vanschoonbeek *et al,* (2006), although duration of treatment was greater, suggesting that this may also contribute to efficacy, as cinnamon dosage was also lower.

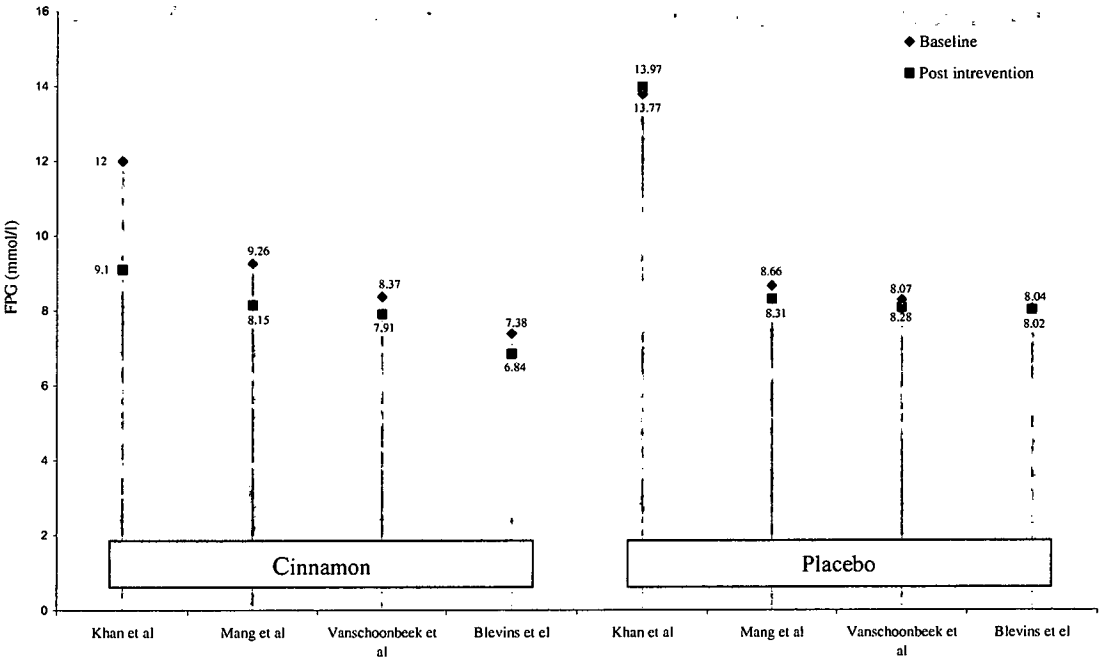


Figure 2.11 – Changes in mean fasting plasma glucose (FPG) levels at baseline and post intervention in the selected 4 RCTs of cinnamon and type 2 diabetes mellitus. A significant (P<0.05) reduction in FPG was reported in Khan *et al*, (2003) study, this may be due to elevated FPG levels (poor control) at the baseline.

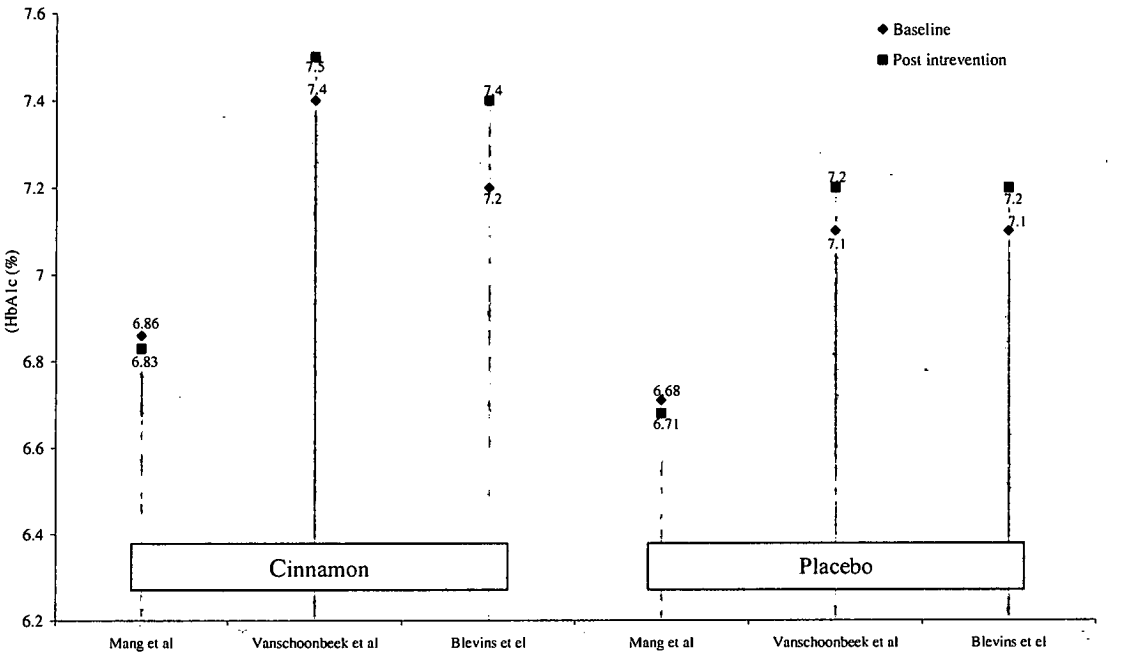


Figure 2.12 – Changes in mean HbA1c% at baseline and post intervention in the selected 4 RCTs of cinnamon and type 2 diabetes mellitus. A significant reduction in HbA1c was NOT reported in the above three RCTs, this may be because all patients had a good control of HbA1c (~ 7%) at baseline.

There were no significant changes in HbA1c between the cinnamon groups compared with the placebo groups in all three RCTs reported (Figure 2.12). Khan *et al,* (2003) did not report the HbA1c data in his study. The range of baseline HbA1c in these studies was found to be 6.8% to 7.4% and suggest patients with fairly good control of blood sugar levels.

2.6.7 Discussion and conclusion

Khan's study (Khan *et al,* 2003) has some unusual features. The most important is that there was no evidence of a dose response at the different levels of cinnamon doses 1g, 3g and 6g tested. This lack of dose related effect in this study suggests that any of the doses employed in the study may lower serum levels of blood glucose and certain lipoproteins. It is not clear whether even less than 1g of cinnamon per day would also be beneficial. The patient's withdrawals were not reported in this study and also no compliance data was provided. The consumption of 6g of cinnamon (12 capsules) per day may have been problematic. However the results of this study, which was performed with Pakistani diabetic patients, may not be valid for western population because of the different genetic and lifestyle background. The results also reveal that the baseline mean fasting plasma glucose levels of the study population ranged from 11.4mmol/l – 16.7mmol/l, and such poor control of diabetes and high fasting serum glucose concentrations are

unusual in western populations (Mang *et al,* 2006). The mean triglyceride levels were high in both placebo and cinnamon group (2.41mmol/l and 2.49mmol/l respectively) compared to other studies (Table 2.8).

The clinical measurements of body mass index (BMI), waist circumference, dietary influence on plasma glucose and glycosylated haemoglobin levels (HbA1c) were not published by Khan *et al,* (2003). Furthermore it remains unclear why potential changes in HbA1c were not measured in this study. Because HbA1c remains the most important long term predictor of complications in both type 1 and type 2 diabetes mellitus, the effect of any intervention on HbA1c is critical in determining its clinical usefulness (Justin *et al,* 2007). HbA1c reflects long-term glycemic control and is a more accurate and stable measure than fasting blood glucose levels (Goldstein *et al,* 2003). It reflects the patients control over a 3 month period and is relatively stable. It has less measurement error than fasting plasma glucose (Rohlfing *et al,* 2002). Glycosylated hemoglobin is at the center of the clinical management of hyperglycemia in people with diabetes (Rohlfing *et al,* 2002).

In Khan *et al's.* (2003) study, there were no improvements in plasma glucose or lipid profiles in the placebo group, and compared to other studies this too is unusual (Table 2.8). From the statistical point of view, there was no power analysis documented for the sample size calculations. Compared with Khan's study (2003), Vanschoonbeek's study (2006) used different indices such as oral glucose tolerance, HbA1c and whole body insulin sensitivity. These did not show any significance association with cinnamon supplementation. Differences in patient outcome between these two studies may be attributed to the inclusion of overweight postmenopausal women and the type of medication that was used by the patients. Although Khan *et al,* (2003) selected subjects using only sulfonylurea derivatives; Vanschoonbeek *et al,* (2006) selected a group of patients using a range of oral anti diabetic drugs like metformin, sulfonylurea and thiazolidinediones.

Dietary food intake records were reported by Vanschoonbeek *et al,* (2006) but energy intake and macronutrient composition of diets did not differ between placebo and cinnamon groups. The baseline mean fasting plasma glucose concentration in both placebo and cinnamon group is less compared to other studies (Table 2.8). This study has several other important limitations as well. The duration of the study is 2 to 6 weeks and perhaps this shorter duration could contribute to a false negative result in HbA1c measurements. Because the lifespan of red blood cells is 120

days, it is believed that at least a minimum of 3 months (90 days) is a sufficient time to demonstrate an effect of cinnamon on HbA1c levels (Justin *et al,* 2007). Therefore it remains unclear why the authors chose 6 weeks for the study duration. Again no power analysis was documented for the sample size calculations. However this study reported different clinical outcomes of insulin resistance index and whole body insulin sensitivity compared to other studies.

The study by Mang *et al,* (2006) was a well designed randomized control trial, which measured the potential clinical measurements of fasting plasma glucose, HbA1c, blood lipid profiles, BMI and waist circumference. This is the first study that evaluated the effect of an aqueous cinnamon extract on fasting plasma glucose and HbA1c levels in western type 2 diabetes patients. The mean baseline HbA1c of 6.8% in this study demonstrates that the patients included in this study were well controlled for diabetes. The ADA (2005) guidelines for HbA1c suggest that, normal or near normal glycaemia with an HbA1c <7% should be achieved for type 2 diabetic patients. Therefore it remains unclear that why the author included well controlled diabetic patients in this study rather than poorly controlled patients (> 7% of HbA1c). It may be that this was the reason as to why no significant association was observed in HbA1c after cinnamon supplementation.

The main limitations in the study by Blevin *et al,* (2007) could be attributed to inadequately powered sample size and may be due to a lack of cinnamon dosage. Further, the mean baseline HbA1c of 7.1% and inclusion of subjects with HbA1c > 6% suggest that patients were near normal glycemia (HbAc < 7%) with fairly good control of blood glucose levels.

HbA1c (%) is one of the primary indicators used in diabetes studies and is increasingly used to assess hyperglycaemia through the level of glycated proteins (Rohlfing *et al,* 2002; Gavin *et al,* 2003), diabetic complications and overall morbidity (Brewer *et al,* 2008; Cederholm *et al,* 2008). Despite a known relationship ($r = 0.90$) between plasma glucose and HbA1c% (Nathan *et al,* 2007), there are genetic differences in glycation, so if cinnamon reduces FPG, the effect upon HbA1c% may be less direct in some individuals (Snieder *et al,* 2001). This may explain the reduction in FPG but not in HbA1c% reported by Mang *et al,* (2006), although duration is considered to have been adequate to expect some reduction, especially when it is estimated that newer erythrocytes may contribute approximately 50% to HbA1c values, in comparison with 10% from older erythrocytes (Rohlfing *et al,* 2002).

Additionally, although HbA1c% increases gradually among patients with uncontrolled diabetes (American Diabetes Association, 2006), the relationship between FPG and HbA1c% is not always entirely linear, and a highly statistically significant inverse correlation (r = -0.66, p < 0.01) has been illustrated between glycation percentage and average erythrocyte life span of 120 days: higher glycation increases cell turnover and may not accurately convey the degree of hyperglycemia (Virtue *et al,* 2004). Therefore, blood glucose remains a key parameter which can be used to determine cinnamon efficacy (Kilpatrick *et al,* 2007). Although association between these measures differs depending upon genetic factors and glycaemic control of the population, it is expected that studies reporting no significant reductions in FPG (Vanschoonbeek *et al,* 2006; Blevins *et al,* 2007) would not find changes in HbA1c%. It has been illustrated that intensively-treated diabetes display lower mean plasma glucose concentrations in relation to HbA1c% (Kilpatrick *et al,* 2007), which may explain why Altschuler *et al,* (2007) reported no change in HbA1c%, due to the Type 1 diabetic participants in this study receiving exogenous insulin therapy to reduce blood glucose. However, HbA1c levels in this study were not particularly low (8.4 ± 1.3 in cinnamon group) (Saydah *et al,* 2004). None of the studies mentioned if the aroma associated with cinnamon and placebo were similar which could have affected the adequacy of double blinding.

2.6.8 RCT of cinnamon in other diabetic studies

2.6.8.1 RCT of Cinnamon and Gestational diabetes mellitus

Graham *et al,* (2007) carried out a pilot randomized, double blind, placebo controlled trial to determine the effect of cinnamon supplementation on glycemic control among gestational diabetes patients in the USA. A total of 51 patients with gestational diabetes (diagnosed between 24 and 32 weeks gestation) were supplemented with either 1g of cinnamon or placebo (bran cereal) per day for 6 weeks period. The total insulin requirements were assessed among these patients weekly. Result of this study demonstrated a trend towards decreased insulin requirement for gestational diabetics treated with cinnamon supplements (9.3 U/kg cinnamon vs 12.0 U/kg placebo) but the association was not significant.

2.6.8.2 RCT of Cinnamon on gastric emptying and satiety

Hlebowizc *et al,* (2007) in Sweden showed that using cinnamon as a functional ingredient may lead to slower emptying of the stomach and reduce postprandial blood glucose rise in healthy subjects. Fourteen healthy subjects were included in a cross over study and treated with 300g rice pudding or 300g rice pudding and 6g of cinnamon. The gastric emptying rate was measured

by using standardised real time ultrasonography as the percentage change in the antral cross sectional area measured at 15 to 90 minutes after the ingestion of test meal. All subjects were examined after an 8 hour fast. The results of this study demonstrates that ingestion of rice pudding with 6g cinnamon resulted in a significantly delayed gastric emptying rate and lowered postprandial blood glucose response ($p<0.05$) in healthy subjects. Moreover, this study suggested that further investigation of the effect of cinnamon on insulin resistance and gastric emptying rate in patients with type 2 diabetes mellitus is needed.

2.6.9 RCTs of cinnamon and non diabetic (health individuals) studies

To date, three non-diabetic human studies have been reported on the effect of cinnamon on plasma glucose concentration. These includes a study on pre-diabetic subjects with metabolic syndrome (Ziegenfuss *et al,* 2006), one study with insulin-resistant subjects (Wang *et al,* 2006) and a third involving lean, healthy volunteers undergoing an OGTT (Soloman and Blanin. 2007). All these studies reported reductions in plasma glucose following OGTT with cinnamon supplementation, although studies are likely to be underpowered, and population characteristics and methodology are dissimilar. Table 2.10 summarizes the methodologies and results of the three studies.

Characteristics between non-diabetic studies were heterogeneous, but did not differ between intra-study intervention and control groups, although participants in the Ziegenfuss *et al,* (2006) study were matched. Age and BMI in the study by Solomon and Blannin. (2007) are considerably lower than those of the diabetic subjects, and cinnamon efficacy was tested through OGTT-induced glucose elevation and subsequent glucose clearance. Solomon and Blannin. (2007) and Ziegenfuss *et al,* (2006) used higher cinnamon doses, and, despite lower baseline FBG, reported reductions in FBG, suggesting a possible inverse relationship between baseline FBG and therapeutic cinnamon dose.

Solomon and Blannin. (2007) controlled dietary intake prior to OGTTs, and illustrated a significant 13% reduction ($p < 0.05$) in plasma glucose response and improved insulin sensitivity index ($p < 0.05$) versus placebo using 5g of cinnamon. Ziegenfuss *et al,* (2006) included food diary analysis in a 12 week intervention, reporting an 8.4% FPG reduction ($p < 0.01$) in patients with metabolic syndrome. Wang *et al,* (2007) illustrated FPG reduction of 16.9% ($p < 0.03$) against baseline FBG, although the control group also reduced FPG by 7.7% following 8 weeks with 1g cinnamon daily. A mean 20.9% reduction in plasma glucose

following OGTT ($p < 0.03$) in the cinnamon group is reported, but no OGTT results are included for the control group, reducing the significance of these results. However, improvements in insulin resistance and sensitivity in the cinnamon group became similar to those in a separate control group without insulin resistance ($p < 0.17$).

Table 2.10 – The summary of population characteristics, methodologies and results of cinnamon studies with non-diabetic participants

Study information	Ziegenfuss *et al*, [N = 22]	Solomon and Blannin, [N = 7]	Wang *et al*, [N = 15]
Type of trial	Double-blind, randomized, placebo-controlled trial	Double-blind, randomized crossover trial	Double-blind, randomized, placebo controlled trial
Age (y)	46.0 ± 9.7	26 ± 1.0	31.1 ± 2.0
Gender (M/F)	11 Males and 11 Females.	Male	Female
BMI (kg/m²)	33.2 ± 9.3	24.5 ± 0.3	28.8 ± 1.3
Baseline FBG (mmol/L)	6.46 ± 0.71	4.9 pre-OGTT	5.32 ± n/k
Ethnicity	American	British	American
Matched pairs	Matched for age, FBG, SBP and physical activity habits	n/a	Not matched but did not differ for BMI, FBG, insulin, QUICKI, HOMA-IR or insulin sensitivity index
Methodology	Cinnamon supplements or placebo given to insulin resistant participants. Changes in FBG, lipids, BP and anthropometric measures assessed	Healthy subjects underwent 3 OGTTs: 1 placebo, 1 cinnamon (cin), 1 cinnamon 12 hours before (cin12pre). AUC and insulin sensitivity measured	Cinnamon supplements or placebo given to insulin resistance women. FBG, AUC and insulin sensitivity assessed before and after OGTT
Supplement and dose	10g (equivalent) Cinnulin PF® a CE of *Cinnamomum* bermannii	5g Cassia powder capsules	1g Cassia extract
Study duration	12 weeks	After OGTT and OGTT (cin12pre)	8 weeks
Dietary control	3 day food diary analyzed by a licensed, registered dietician using commercially vailable software	2 day food diary Diet replicated prior to each OGTT. Subjects asked to refrain from alcohol, caffeine, cinnamon products and exercise 48 hours before each OGTT	Advised not to modify diet or exercise habits
Measures taken	Weight, height, BMI, body fat %, lean mass (kg), BP, FBG, total cholesterol, LDL, VLDL, HDL, triacylglycerol, kCals and food intake	Plasma glucose Serum insulin Insulin sensitivity	Insulin sensitivity Insulin resistance FBG OGTT plasma glucose
Significant results in cinnamon group compared with placebo group Wang et al, [26] compare with baseline	FBG ↓ 8.4% $p < 0.01$ 116.3 ± 12.8mg/dL [pre] - 106.5 ± 20.1mg/dL [post] SBP ↓ 3.8% $p < 0.001$ 133 ± 14 mmHg dL [pre] - 128 ± 18 mmHg [post] Lean tissue ↑ 1.1% $p < 0.002$ 53.7 ± 11.8 kg [pre] – 54.3 ± 18 11.8 kg [post]	AUC (mmol/12h) ↓ 12.9% in cin $p < 0.05$ 674.7 ± 39.3 [pre] – 584.4 ± 37.5 [post] AUC (mmol/12h) ↓ 10% in cin12pre $p < 0.05$ 674.7± 39.3 [pre] – 603.8 ± 35.6 [post] Insulin sensitivity index measures also improved: 4.74 ± 0.69 [pre] – 7.96 ± 1.29 [post] ISI cin12pre ($p < 0.05$) 4.74 ± 0.69 [pre] – 8.26 ± 1.46 [post]	FBG ↓ 16.9% $p < 0.03$ 95.83 mg/dL [pre] – 79.67mg/dL [post] AUC ↓ 20.9% $p < 0.03$ 144.88 mg/dL/min [pre] - 114.54 mg/dL/min [post] QUICKI ↑ 7.7% $p < 0.03$ 0.35 [pre] – 0.38 [post] HOMA-IR ↓ 44.5% $p < 0.03$ 2.57 [pre] – 1.43 [post]

Data presented as means ± SD. Age and BMI means are for study population. Baseline FBG shown is for cinnamon groups in each study. AUC; plasma glucose post oral glucose tolerance test, BP; blood pressure, CE; cinnamon extract, FBG; fasting blood glucose, h; hours, kCals; calories, LDL; low density lipoprotein, HDL; high density lipoprotein, OGTT; oral glucose tolerance test, OGTT(cin12pre); CE 12 hours prior to OGTT, QUICKI; insulin sensitivity index, HOMA-IR; eostasis model insulin resistance index, SBP; systolic blood pressure, VLDL; very low density protein.

2.6.10 Safety and Adverse effects of cinnamon

Adverse effects of cinnamon supplementation were not reported in human intervention trials at the doses given (Mang *et al,* 2006; Khan *et al,* 2003; Vanschoonbeek *et al,* 2006; Belvins *et al,* 2007). Recently cinnamon has been granted GRAS (Generally Recognized As Safe) status by the United States Food and Drug Administration (USFDA) (Tim *et al,* 2006). Caution in using cinnamon is warranted in patient's known to be allergic to it. No such dose related adverse effects or interaction from cinnamon have been reported in the previous studies at the doses given.

Hypoglycemia is an expected effect when cinnamon is used in combination with anti diabetic drugs; therefore, care should be taken to monitor blood glucose levels when beginning supplementation of cinnamon. It's possible that if the treatment is given to a pregnant woman sometimes it might harm the unborn child. Therefore cinnamon should not be taken during pregnancy or lactation (Solgar. 2006). Women who plan to become pregnant also should avoid taking cinnamon supplements.

Only a few cases were reported with contact stomatitis for cinnamon (Hlebowicz *et al,* 2007). Contact stomatitis describes an inflammatory reaction of the oral mucosa by contact with irritants of cinnamon. Cinnamon flavoring agents like cinnamic aldehyde, cinnamic acid, and cinnamon oil are known to act on the mucosa as irritants or sensitizers (Endo & Rees. 2006). The effect of contact stomatitis could be minimized if people consume cinnamon capsules. Products containing cinnamon have been linked to skin irritation and sensitization, mucous membrane irritation and stomatitis (Alternative Therapies. 2007).

It was reported in German, that some people develop bronchial constriction or skin rash after exposure to cinnamon (Blumenthal *et al,* 1998). Therefore anyone with known allergy to cinnamon should avoid taking it. According to the German Commission, cinnamon is not recommended for use by pregnant women (Blumenthal *et al,* 1998), because it might harm the unborn baby.

2.6.11 Cinnamon interaction with diabetes medication

Although participants in diabetic studies have used different medications, no intra-group differences were identified, despite the most impressive cinnamon results achieved by participants taking only sulphonylureas (Khan *et al,* 2003). Sulphonylureas increase insulin

secretion and have been shown to reduce HbA1c% more other diabetic medications (Monami *et al,* 2008). Although HbA1c% was not measured by Khan *et al,* (2003), baseline FBG was the highest of all studies reviewed and the ethnicity of participants indicates greater risk of insulin resistance (Whincup *et al,* 2005). This may indicate that sulphonylurea effectiveness may have been reduced in the presence of insulin resistance (illustrated by elevated FBG levels), enabling cinnamon to lower blood glucose using the pathways normally activated by insulin (Jarvill-Taylor *et al,* 2001). Higher insulin resistance is associated with increased BMI and central adiposity (Festa *et al,* 2004; Reaven *et al,* 2004), but measures were not taken in the aforementioned study to support this theory.

Biguanides such as Metformin decrease gluconeogenesis (Hundal *et al,* 2000) and alpha-glucosidase inhibitors modify starch digestion, both decreasing blood glucose levels. Insulin resistance may reduce in conjunction with lower glucose levels (Gavin *et al,* 2003), enabling some insulin activity and reducing the opportunity for cinnamon to share cellular pathways (Pinent *et al,* 2004; Roffey *et al,* 2006). Thiazolidinediones sensitize hepatic and muscle cells to accept insulin more readily, also limiting cinnamon potential if glucose uptake pathways are shared (Rangwala and Lazar. 2004). It may be hypothesized that these drug actions in combination with cinnamon have contributed to the contrasting results between studies, although considering the combination of drug therapies used in trials reporting significant and insignificant results and lack of intra-group classifications, this seems unlikely. Further research is required to quantify the effect of drug therapy upon insulin resistance, impaired glucose tolerance and impaired fasting glucose levels, the parameters which are likely to affect cinnamon activity.

2.6.12 General Conclusion and Future Directions

The anti diabetic or glucose lowering potential of *Momordica* is still not clear. However, studies suggested that *Momordica* could be used as an effective dietary supplement for the management of diabetes and/or metabolic syndromes (Cefalu & Wang. 2008). Even though some uncontrolled trials of *Momordica* demonstrated significant or moderate improvements in glucose tolerance (Rosales & Fernando. 2001; Ahmed *et al,* 1999; Srivastava *et al,* 1993; Leatherdal *et al,* 1981; Baldwa *et al,* 1977), to date, there is not enough evidence from well defined RCTs to support the use of *Momordica*. It should be noted that stimulating insulin release is probably less desirable than improving insulin sensitivity (Nahas & Moher. 2009). At present, it would be premature to consider *Momordica* an evidence-based treatment for diabetes. Therefore, further research is warranted to assess the safety, dosage and tolerability of *Momordica* on glycaemic control before it can be routinely recommended as an effective supplement for diabetes mellitus.

The studies of *Gymnema* and diabetes carried out to date were poorly designed non randomized or un controlled, open label trials and have several important limitations such as small sample size which is not adequately powered, no blinding, not controlled and lacking information about dosage. Hence, further clinical trials of *Gymnema* are important to evaluate the efficacy, safety, dosage and tolerability. This could be achieved through a well designed randomized, and placebo controlled double blind clinical trial with an adequately powered sample size. Therefore, it would be early to actively recommend use of *Gymnema* to treat either blood glucose or other risk factors as evidence based treatment for diabetes.

Studies have shown that *Ginseng* and its components attenuate hyperglycemia in two ways, the first through enhancing pancreatic beta-cell function and the other through reducing insulin resistance. This leads us to believe that *Ginseng* may have benefits for both type I and type II diabetes (Luo & Luo. 2008). *Ginseng's* widespread traditional use merits further study, particularly in patients originating from cultures with a long history of traditional use. Therefore, *Ginseng* is a dietary supplement that may hold promising effects in glycaemic control, and future properly designed, adequately powered, randomized control trials evaluating the safety, dose and tolerability of *Ginseng* on HbA1c, plasma glucose and lipid profiles are of paramount importance. Furthermore, the majority of the previously reported human intervention studies of *Ginseng* and diabetes are from a single investigator group led by Vuksan (2000 – 2008).

Ginseng and *Momordica* are the most popular hypoglycemic herbs used in Chinese medicine to treat diabetes mellitus (Hui *et al,* 2009). The efficacy of these hypoglycemic herbs appears to be achieved by increasing insulin secretion, enhancing glucose uptake by adipose and muscle tissues, inhibiting glucose absorption from intestine and inhibiting glucose production from heptocytes (Hui *et al,* 2009).

Although evidence from animals and human studies supports the therapeutic activities of *Ginseng, Gymnema and Momordica*, multi-center large-scale clinical trials have not been conducted so far to evaluate the long term efficacy and safety of these herbal medicines (Yin *et al,* 2008). Therefore, due to the lack of sufficient evidence from clinical studies of *Momordica, Gymnema and Ginseng* discussed in this chapter, it may be premature to actively recommend use of any particular herb to treat either glucose or other risk factors associated with diabetes (Cefalu *et al,* 2008). There is very limited scientific evidence for the effects of herbs and spices on diabetes mellitus. More research (well defined RCTs) is warranted, particularly examining the effects of chronic consumption patterns (Tapsell *et al,* 2006).

Prior to 2006, even though the quality of the studies were low, there were a substantial number of human intervention trials published on the anti-diabetic efficacy of *Momordica* (6 trials), *Gymnema* (3 trials), and *Ginseng* (5 trials). As a result of this review, it would be difficult to recommend any of these herbs for clinical routine use, since the majority of the studies had low methodological quality and the benefit has not been conformed by large trials of high quality. As there is a potential benefit of herbal dietary supplements for diabetes, it will become increasingly important to evaluate the efficacy of these supplements. However, in general the clinical trials conducted so far have several important limitations, mainly;

(1) The sample size was generally small.

(2) Methodological weakness in terms of randomization, sample size and blinding.

If a trial is not blinded, there may be a possibility of performance or detection bias. Methodologically less rigorous trials show significantly larger intervention effects than trials that are more rigorous (Moher. 1998; Schulz. 1995). Although the herbal supplements evaluated in this review generally appeared to be safe, it might be premature to conclude on the safety of using herbal dietary supplements in diabetic patients as adverse effects may not be sufficiently reported.

Finally, the methodological quality of randomized controlled trials (RCTs) of herbal dietary supplements for diabetes mellitus needs to be improved, and the following aspects should be addressed in the future studies;

(1) Detailed reporting of the methods used to generate allocation sequence and allocation concealment.

(2) Sufficient application of double blinding with the use of appropriate placebo.

(3) Adequately powered sample size.

(4) Clear description of withdrawals or dropouts during the trial and use of intention to treat analysis method.

(5) Reporting the clinically important outcome measures from long term follow-ups.

The small number of clinical trials, low study numbers and conflicting results do not allow a definitive conclusion to be drawn regarding the efficacy of cinnamon as an effective dietary supplement for diabetes. However, the studies do indicate that cinnamon might possess anti-hyperglycaemic properties and may be able to reduce blood glucose through different mechanisms as discussed in sections 2.6.2 and 2.6.3.

The clinical studies of cinnamon and glycaemic control carried out so far have some important limitations; inadequately powered studies with small sample sizes, lack of verification of double blinding and lack of inclusion of clinical measurements like insulin sensitivity measures and dietary interventions. In addition, participation in these clinical trials was limited to specific demographic or ethnic characteristics in specific populations which may not representative of the overall patient population with type 2 diabetes mellitus due to cultural dietary differences. Of the 4 studies, two were conducted in Europe (Vanchoonbeak *et al,* 2006; Mang *et al,* 2006), one in USA (Blevins *et al,* 2007) and one in Pakistan (Khan *et al,* 2003). The inclusion of representative patient population of type 2 diabetes mellitus from multi ethnic population is important to verify the role of cinnamon in diabetes control.

Patients who have diabetes mellitus are at risk of developing metabolic syndrome and cardiovascular disease in future (NCEP. 2001). Therefore dietary supplements that can modulate glucose homeostasis and potentially improve lipid parameters would be desirable, particularly for patients with elevated blood lipid profiles. These patients could benefit from a low risk, inexpensive, diet based intervention (diet supplement) aimed at normalising their blood glucose and lipid profiles. Cinnamon is a dietary supplement that may hold promise in this regard and in

future well defined, adequately powered, randomized controlled trials evaluating the effect of cinnamon on HbA1c, plasma glucose concentration and serum lipids is paramount important. This could be introduced as a cost effective dietary supplementation model for patients with impaired glucose tolerance or diabetes in NHS.

At present, it would be early to consider cinnamon as an evidence based treatment for either people with diabetes or high cholesterol. To date, there have only been four randomized controlled trials investigating the effects of cinnamon supplementation on plasma glucose concentrations and blood lipids in patients with type 2 diabetes mellitus. The UK Diabetes Association *(www.diabetes.org.uk)* has also suggested that further studies are warranted in relation to diabetes and cinnamon supplementation before any firm conclusions.

Further research is warranted to assess the effects of cinnamon supplementation on glucose tolerance, blood pressure and blood lipid profiles. So far there are no studies associated to find out the efficacy of cinnamon supplementation on HbA1c, serum lipid levels and blood pressure among patients diagnosed with type 2 diabetes mellitus in the UK. Interestingly, prior to 2006, although the anti-diabetic potency of cinnamon had been shown to be effective in numerous *in-vitro* and *in-vivo* animal studies, there was very limited data on human intervention trials to support the clinical efficacy of cinnamon in diabetes management. Only one published human study of cinnamon and diabetes (Khan *et al,* 2003) was accessible before 2006. This study had several important limitations such as poor blinding and short study duration and important study outcomes were not reported. Therefore, based on the view of conducting primary research for the first time in the UK among a multi ethnic western population, cinnamon was chosen and an RCT was performed to evaluate the anti-diabetic potential of cinnamon among type 2 diabetic patients (see chapter 4).

2.6.13 Limitations

The methodology used for this literature review was confined to English language articles. An extensive systematic review was not conducted for *Ginseng;* however most of the recent human intervention trials on *Ginseng* and diabetes were included in this review. The researcher is unaware of any bias within this review. It is hoped that the methodology illustrates no selection bias, although the available literature search was confined to English language articles. Variations in population characteristics and methodology between cinnamon and diabetes (human trials) make comparisons problematic; therefore the diabetic studies are reviewed in

depth to enable analysis of homogeneous trials (cinnamon and type 2 diabetes) with greater external validity. This review did not include a very recently published (September/2009) RCT of cinnamon and diabetes (Crawford. 2009), as this thesis has been submitted in October 2009. Other human intervention trials such as the effect of cinnamon in type 1 diabetes, gestational diabetes, gastric emptying time and effect of cinnamon on non diabetic patients were discussed in section 2.6.8.

CHAPTER 3

THE PREVALENCE AND USE OF DIETARY SUPPLEMENTS AND OTHER COMPLEMENTARY AND ALTERNATIVE MEDICAL (CAM) THERAPIES BY INDIVIDUALS WITH FEATURES OF METABOLIC SYNDROME

A Survey Study

3.1 Introduction

There is considerable debate around the definition of Complementary and Alternative Medicine (CAM), definitions varying over time (Lorenc *et al*, 2009). CAM therapies consist of a number of different treatment options, and the use of dietary supplements is one of the main approaches that falls into this category (for definitions of CAM see section 3.2.5). This study examined the level of use of dietary and herbal supplements independently from other CAM therapies to obtain in-depth information on individuals with features of metabolic syndrome either diagnosed with self reported diabetes, hypertension, hyper-cholesterolaemia or obesity (section 3.3.8). This survey was conducted as a stepping stone, prior to the randomized controlled trial (RCT) of cinnamon and diabetes (chapter 4) in order to investigate the acceptability or willingness to take different dietary supplements or herbal supplements by individuals with specific health conditions, in particular those with features of metabolic syndrome (defined in section 3.2.4.4). Therefore, based on the results of this survey, the feasibility of using herbal dietary supplements could be evaluated prior to conducting the RCT. This chapter comprises of methodology (section 3.2), results (section 3.3), discussion (section 3.4), limitations (section 3.5) and conclusion and future directions (section 3.6) of a questionnaire based study.

A recent survey conducted in Switzerland demonstrated that patients with type 1 diabetes were more likely to use CAM especially herbal supplements of cinnamon, homeopathy, magnesium and some special beverages to improve general well being and ameliorate glucose homeostasis (Scheidegger *et al,* 2009). The use of herbal supplements by older British people is increasing, and the use of these supplements frequently involves the several herbs (Canter & Ernst, 2004). More than 10% of the adults in England take herbal supplements and this is associated with age, gender, ethnicity and social class (Harrison *et al*, 2004). Furthermore, the evidence base to support some popular herbal dietary supplements is weak and thus large well deigned RCTs are needed to quantify the value of herbal supplements for health and well being (Harrison *et al*, 2004)

Within the last decade there has been a dramatic increase in the sale and use of CAM especially herbal dietary supplements by individuals within the UK (Ritchie, 2007). Furthermore the rise in the use of dietary supplements or CAM by the UK population can be attributed to several factors, including promotion via health programmes, a greater use of CAM and herbal supplements, particularly by patients with different health conditions, increased media publicity,

a change in public attitude and training of more CAM as a result of the increased availability of courses (Ritchie, 2007).

CAM has increasingly become a focus of public health attention and discussion. Yet there is no single universally accepted definition of CAM (O'Connor *et al,* 1997). It consists of a wide range of often disparate approaches to health, illness and wellbeing. Use of CAM is substantial in the UK (Ernst & White, 2000). Previous studies suggests that people who use CAM, do so because they hold beliefs about health, treatment and illness which are congruent with CAM, have chronic health problems, and are disillusioned with the experience and outcomes from conventional medicine (Ernst, 2000; Thomas & Coleman, 2004; Hanssen *et al,* 2005; Millar, 1997).

The Cochrane collaboration has defined CAM as follows (Zollman & Vickers, 1999), "CAM is a broad domain of healing resources that encompasses all health system modalities and practices and their accompanying theories and beliefs, other than those intrinsic to the politically dominant heath system of a particular society or culture in a given historical period". CAM includes all such practices and ideas self-defined by their users as preventing or treating illness or promoting health and well being. Therefore boundaries within CAM and between the CAM domain and that of the dominant system are not always sharp or fixed (Zollman & Vickers, 1999; Bishop, 2005).

Currently substantial numbers of people are turning to CAM. It is very popular, with recent population based estimates of yearly adult use in the UK of 20% to 28% (Lorenc *et al,* 2009). The prevalence of the CAM use in the general population in the USA increased from 34% in 1990 to 39% in 1997 (Bishop, 2005; Eisenberg *et al,* 1998) and remained stable from 1997 to 2002. In the UK, 46% of the population can be expected to use one or more CAM therapies in their life time (Thomas *et al,* 2001; Bishop, 2005). The prevalence of CAM use in north east of Scotland increased from 29% in 1993 to 41% in 1999, and among these CAM therapies the use of aromatherapy, acupuncture and reflexology increased significantly during this time period (Emslie *et al,* 2002).

The dietary or herbal supplements are different from other CAM therapies because their effectiveness can be evaluated using standard pharmacological approaches the same way as standard pharmaceuticals (Levin *et al,* 1997). According to the study by Bishop (2005), it is

difficult to make comparisons across surveys of CAM use as they employ different definitions of CAM. For example, Thomas & Coleman, (2004) investigated the use of 23 practitioner based CAM forms, whereas Eisenberg, (1998) investigated the use of 16 different CAM approaches. Therefore, understanding why people use dietary supplements or CAM has a number of broader implications in terms of theory development and understanding the relationships between health and treatment beliefs and behaviours. The research to date focussed on associations between CAM use and demographic characteristics, health beliefs and treatment beliefs and individuals' own reasons for using CAM. However the findings across studies are not always consistent (Bishop, 2005; Hori *et al*, 2008).

The area of interest of this current study was to compare the prevalence and pattern of use of different dietary supplements and other CAM therapies by individuals with self reported features of Metabolic Syndrome (MS). The metabolic syndrome (see section 3.2.4.3) is a condition that promotes insulin resistance and increases the risk of cardiovascular events (Ford *et al*, 2002; Grundy, 1998). The characteristics of the metabolic syndrome include atherogenic dyslipidaemia, insulin resistance, hypertension and abnormal obesity (Panagiotakos *et al*, 2004). Therefore each abnormality promotes atherosclerosis independently, but when clustered together, these metabolic disorders are increasingly atherogenic and enhance the risk of cardiovascular mortality and morbidity (Grundy, 1999). Individuals with insulin resistance or diabetes mellitus, elevated blood pressure, obesity, hypercholesterolemia have a high risk of developing metabolic syndrome in the future and recently considerable attention is paid to this metabolic syndrome.

As a result, individuals with specific health conditions, like features of metabolic syndrome may use range of dietary and herbal supplements and other complementary and alternative approaches in order to improve their health status. This could result in decreased GP visits, hospitalisations and reduced prescribed drug usage for the specified health conditions; if they are successful in reducing the potential associated risk factors.

3.1.1 Objectives

The objective of this study was to;

1. Determine whether individuals with self reported features of metabolic syndrome were more likely to use different dietary supplements of herbs, vitamins and minerals and other CAM therapies compared with individuals without self reported features of metabolic syndrome.

2. Evaluate the level of use and acceptability of dietary supplements especially herbal supplements by individuals with self reported medical conditions of diabetes and features of metabolic syndrome.

3. Provide preliminary and exploratory data for future studies by identifying practices and/or products for further investigation.

3.2 Methodology

3.2.1 Study design

The study protocol was approved by the Faculty of Health and Human Sciences research ethics committee, Thames Valley University (TVU) (FREC31/Feb07) (Appendix 3.1). This study adopts a quantitative research approach using a questionnaire-based survey. A semi-structured questionnaire (Appendix 3.2) was used to obtain information about the prevalence and level of use of different dietary supplements and complementary and alternative medical therapies. This survey uses convenience sampling to obtain information from staff and students at TVU.

3.2.2 Study population

The study population consisted of students, academic and non academic staff members registered with Thames Valley University (TVU), UK. The study was carried out between 01 June 2007 to 30 March 2008 at the different sites of the university including Reading, Ealing and Slough campuses of TVU. Thames Valley University is one of the largest universities in London consisting approximately 45,000 part time and full time students from different ethnic background and diverse in their socio demographic status. The study sample included a broad cross section of TVU staff and students. Subjects were recruited entirely on a voluntary basis, and no one was asked to participate in this study against his or her will.

3.2.3 Sample size and recruitment

The names and contact details of the academic and non academic staff members (n=150) were randomly chosen (by using random list of staff extension numbers) from Thames Valley University (TVU) intranet (*www.intranet.tvu.ac.uk*) and the questionnaires along with information sheets (Appendix 3.3), consent forms (Appendix 3.4) and return envelopes were sent via university's internal post. Staff members representing all faculties of Professional studies, Health and Human Sciences, Arts, Technology and the Graduate school were included.

Undergraduate and postgraduate students (n=150) from same faculties were randomly contacted at all TVU campus sites at Paragon house, St Mary's road, Reading and Slough and asked to complete the questionnaires. In order to increase the response rate, an online questionnaire was also developed by using survey monkey website (www.surveymonkey.com), and the web link was distributed to the same staff and students by email. *(http://www.surveymonkey.com/s.aspx?sm=n88u09ssMVLHXjjB4yD8GA_3d_3d).* Responses were coded and sorted in text file on the website. Data retrieval was protected by username and

password access, and data files were transferred into SPSS for statistical analysis. Therefore, a total of 300 individuals were invited to participate in this study. Of these, 210 individuals completed the questionnaires (giving a 70% response rate). Of the 210 respondents, 37% (n=78) completed and returned questionnaires by post, while 63% (n=132) of the respondents completed the questionnaires online.

3.2.4 Conduct of the study

The self-administered semi-structured questionnaire consisted of 37 questions and was used to collect relevant information for this study and included some open-ended questions (Appendix 3.2). The draft questionnaire was piloted on 5 staff members of the university and some minor alterations were made prior to formally undertaking the survey. The questions was designed to collect information on; socio-demographic characteristics of the individuals, self reported health conditions of individuals, use of dietary supplements and use of CAM therapies. The questionnaire took an average of 15 minutes to complete.

3.2.4.1 Defining demographic characteristics

The socio-demographic data collection in the study included, age, gender, ethnicity, educational level and household income. Five age categories were created; 25 – 34, 35 – 44, 45 – 54, 55 – 64 and ≥65 years. According to the census (Census, 2001), sixteen ethnic categories were defined: White British, White Irish, Other White, White and Black Caribbean mixed, White and Black African mixed, White and Asian mixed, other mixed background, Asian or Asian British Indian, Asian or Asian British Pakistani, Asian or Asian British Bangladeshi, other Asian background, Black or Black British Caribbean, Black or Black British African, other black background and Chinese. Five levels of education were used: secondary, college, university, postgraduate and others. Household income was categorized as £0 – 9,999, £10,000 – 14,999, £15,000 – 19,999, £20,000 – 29,000, £30,000 – 39,000, £40,000 and above.

3.2.4.2 Self reported health condition of the respondents

The questionnaire also included questions about individuals' medical conditions (self reported medical conditions) including; diabetes mellitus, hypertension, hyper-cholesterolaemia and obesity, all of which contribute to metabolic syndrome. Furthermore, subjects also reported their family history of chronic diseases such as diabetes, hypertension, hypercholesterolaemia and obesity.

3.2.4.3 Definition of metabolic syndrome

Metabolic syndrome, also known as insulin resistance syndrome, is a metabolic abnormality associated with dyslipidemia and increased secretion of Very Low Density Lipoprotein (VLDL) particles, and is marked by increased plasma triglycerides (TG), hypertension, abdominal obesity, low levels of High Density Lipoprotein (HDL) and Impaired Glucose Tolerance (IGT) (Hurst, 2002).

According to the Third Report of the National Cholesterol Education Programme (NCEP) Adult Treatment Panel (NCEP, 2001), the combination of abdominal obesity, type 2 diabetes mellitus, hyperlipidemia and hypertension have become characteristic of the condition known as Metabolic Syndrome. According to NCEP, (2001), diagnosis of Metabolic Syndrome is made when three or more of the following criteria's are present:

- Abdominal obesity consisting of a waist circumference greater than 40 inch (102 cm) for men or more than 35 inch (88cm) for women
- Triglyceride levels more than 150 mg/dL (1.7 mmol/l); HDL levels less than 40mg/dL (1 mmol/l) in men or less than 50mg/dL (1.3 mmol/l) in women,
- Blood Pressure $\geq$130/85mmHg and
- Fasting plasma glucose levels $\geq$100mg/dL ($\geq$ 6.1 mmol/l).

3.2.4.4 Define features of metabolic syndrome

The diagnosis of chronic medical conditions such as diabetes mellitus, high blood pressure, high blood cholesterol and obesity in this study was based on self report and self perception of respondents. Therefore, the diagnosis of "features of metabolic syndrome" was defined by any individuals having at least one self reported condition of diabetes or hypertension or hyper-cholesterol or obesity. Finally, two categories were created for cross tabulation analysis; Individuals with features of metabolic syndrome and individuals without features of metabolic syndrome.

3.2.5 Definition of CAM

The US National Centre for Complementary and Alternative Medicine (NCCAM) defines Complementary and Alternative Medicine as a "group of diverse medical and health care systems, practices and products that are not presently considered to be part of conventional medicine (Hori *et al,* 2008; NCCAM, 2008; *http://nccam.nih.gov*). CAM therapies have been classified broadly into five main categories (Table 3.1).

Table 3.1 – NCCAM classification of CAM therapies (source: Hori *et al*, 2008)

1 Whole medical systems	Homeopathic medicine, naturopathic medicine, chiropractic, traditional Chinese medicine, Ayurvedic etc.
2 Mind-body interventions	Meditation, Prayer, mental healing, art, dance, music therapy etc.
3 Biologically based therapies	Herbs, vitamins, dietary supplements, health foods, aromatherapy etc.
4 Manipulative and body based methods	Chiropractic or osteopathic manipulation, massage etc.
5 Energy therapies (Biofield therapies and bioelectomagnetic based therapies)	Reiki, Qi gong, therapeutic touch, electromagnetic fields etc.

The Complementary and Alternative Medicine (CAM) categories included in this study (questionnaire) were chosen from NCCAM classification and other previous CAM studies (Nachtigal *et al,* 2005; Egede *et al*, 2002; Hori *et al*, 2008; Tindle *et al*, 2005). The questionnaire was further refined to include or exclude some additional CAM categories that may be important or unimportant in the university setting in UK. For example in Japan, kampo (traditional Japanese herbal medicine) is widely practiced alongside conventional medicine. However, kampo is not widely practiced in UK and it was excluded in the study. What constitutes CAM however is culturally dependent (Hori *et al,* 2008). Therefore, this questionnaire consisted of widely used CAM therapies in UK.

Based on the objective of this study and to obtain more in-depth information about the level of use of dietary supplements by individuals with features of metabolic syndrome, the biological based therapies (see Table 3.1) of herbal supplements, vitamins, minerals and other dietary supplements are presented independently from other CAM therapies in the questionnaire (Appendix 3.2). Similarly the results on the level of use of dietary supplements (apart from other CAM therapies) are presented in sections 3.3.3 to 3.3.10.

The use of various dietary supplements and CAM therapies were identified by using the following questions in the questionnaire (Appendix 3.2);

- The use of dietary supplements and CAM therapies in the past 12 months
- The different types of dietary supplements and CAM used by participants
- Whether the supplementation therapies were perceived as being helpful
- Average amount spent per month on dietary supplements
- Whether the intake of dietary supplements or CAM was discussed with the GP

- Whether the supplements recommended to the participants, if so by whom?
- Place of purchase of dietary supplements

3.2.6 Inclusion and Exclusion criteria

Inclusion criteria

1. Staff or a student registered with TVU.
2. Age over 25 years.

Exclusion criteria

1. Individuals who refused or unable to provide informed consent.
2. Staff or students who were not registered with TVU.

Note - The use of any conventional over the counter medicines including non-herbal pain medicines such as paracetamol, ibuprofen, non-herbal; laxatives and any other over the counter medicines that did not meet the criteria for being a dietary supplements or complementary therapy were excluded from the analysis.

3.2.7 Data Analysis

Statistical analysis was performed by using SPSS statistical software (version 15.0). This questionnaire was developed by bearing in mind requirements for cross tabulation and reporting. Cross tabulation yielded information about any correlations between dietary supplementation practices and socio-demographic and other dietary or CAM variables. Chi square test was employed to test whether any correlations reached statistical significance.

Descriptive statistical analysis was performed, and data are reported as mean, percentages and frequency tables. Missing values were entered appropriately on SPSS. Percentages calculated are based on respondents answering one or more options for a specific question (therefore, overall % in some tables seems more than 100%). Two different methods of statistical analyses were performed in this study. Firstly, the proportion was estimated for individuals with features of metabolic syndrome by demographic characteristics and other variables. Secondly, individuals with features of metabolic syndrome were compared to individuals without features of metabolic syndrome by using cross tabulation/Chi square statistics. Results mentioned and discussed as 'significant' are statistically significant at the $P<0.05$ level at 95% confidence interval.

3.3 Results

3.3.1 Socio-demographic characteristics of the participants

Of the three hundred questionnaires administered in this study, a total of 210 individuals completed and returned the questionnaires (an overall response rate of 70%). The socio-demographic characteristics of the individuals are presented in Table 3.2. A total of 65% (n=136) were females and 35% (n=74) were males. The majority of the respondents were in the age range of 25 to 35 years (31%; n=65). The majority (83%) being under 54 years of age. Fifty five percent were academic and non-academic staff, 24% were from Faculty of Arts, 23% from Faculty of Professional studies and 21% from Faculty of Health and Human Sciences. Respondents self identified their ethnic origin, 39% (n=82) from White, 36% (n=75) from Black or Black British origins and approximately 16% (n=33) from Asian or Asian British. Approximately 54% (n=112) already had received university education and majority (21.6%) with an income of £30,000 - £40,000 per year.

3.3.2 Individuals with features of metabolic syndrome (MS)

The main features of metabolic syndrome include: insulin resistance or diabetes mellitus, hypertension or high blood pressure, abnormal blood cholesterol levels and overweight or obesity (defined in section 3.2.4.4). Table 3.3 shows the self reported percentages of these features; diabetes (5%), hypertension (5.9%), high blood cholesterol (9.9%) and obesity (20.3%). The frequency of respondents reporting family history of diabetes (13.5%), hypertension (24.6%), blood cholesterol (15%) and obesity (23.7%) (Table 3.3). Approximately 30% (n=60) of individuals had at least one self reported condition of either diabetes or hypertension or high cholesterol or obesity and were therefore defined as "having features of metabolic syndrome (MS)" (Figure 3.1).

Table 3.2 – Socio-demographic characteristics of the study respondents [N=210].

Demographic Characteristics		n	%
Sex (n=210)	Male	74	35.2
	Female	136	64.8
Age (n=210)	25 - 34 years	65	31.0
	35 - 44 years	62	29.5
	45 - 54 years	47	22.9
	55 - 64 years	33	15.7
	65+ years	3	1.4
Ethnicity (n=210)	**White (n=82)**	**82**	**39.0**
	White British	59	28.1
	White Irish	10	4.8
	Other White Background	13	6.2
	Mixed (n=19)	**19**	**9.0**
	White and Black Caribbean	5	2.4
	White and Black African	8	3.8
	White and Asian	3	1.4
	Other Mixed Background	3	1.4
	Asian or Asian British (n=33)	**33**	**15.7**
	Indian	21	10.0
	Pakistani	5	2.4
	Bangladeshi	1	0.5
	Other Asian Background	6	2.9
	Black or Black British (n=75)	**75**	**35.7**
	Caribbean	27	12.9
	African	35	16.7
	Other Black Background	13	6.2
	Chinese (n=1)	1	0.5
Education (n=206)	Secondary	8	3.9
	College	41	19.9
	University	112	54.4
	Postgraduate	45	21.8
Annual income (n=199)	£ 0 - 9,999	14	7.0
	10,000 - 14,000	33	16.6
	15,000 - 19,000	32	16.1
	20,000 - 29,000	38	19.1
	30,000 - 39,000	43	21.6
	40,000 and above	39	19.6
Faculty belongs to (n=206)	Arts	50	24.3
	Professional studies	48	23.3
	Health & Human Sciences	44	21.3
	Technology	34	16.5
	Graduate School	6	2.9
	Others	24	11.6
Occupation (n=207)	Undergraduate	66	31.9
	Postgraduate	27	13.0
	Academic staff	52	25.1
	Non academic staff	62	30.0

Table 3.3 – The family history and self reported health conditions of the study participants [N=210].

Family History	%	n
Diabetes	13.5	28
Hypertension	24.6	51
High blood cholesterol	15.0	31
Obesity	23.7	49
None of the above	50.7	105

Answered questions (n=207)

Self reported health condition	%	n
Diabetes	5.0%	10
Hypertension	5.9%	12
High blood cholesterol	9.9%	20
Obesity	20.3%	41
None of the above	70.3%	142

Answered questions (n=202)

Figure 3.1 shows that, among individuals with features of metabolic syndrome (n=60), 68.3% (n=41) had only one self reported health condition of either diabetes or hypertension or high blood cholesterol or obesity, while 25.3% (n=15) and 6.7% (n=4) had two and three or four self reported conditions respectively.

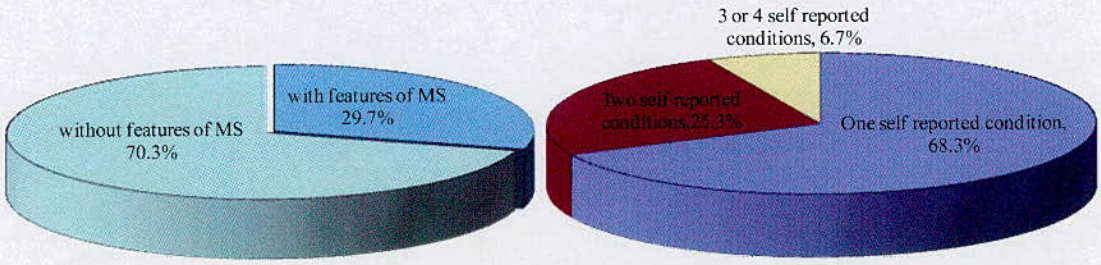


Figure 3.1 – Self reported health conditions of individuals with (70.3%) and without (29.7%) features of metabolic syndrome. Among individuals with features of metabolic syndrome (n=60), majority of them (68.3%, n=41) have one self reported condition of either diabetes or hypertension or hyper cholesterol or obesity.

3.3.3 Level of use of Dietary Supplements

Individuals who reported that they used different diet supplements currently or in the past 12 months are presented in Table 3.4. Thirty two percent of individuals (n=66) were currently using or had used dietary supplements in the past 12 months. Approximately 28% (n=57) of the respondents were currently using diet supplements, while 27% (n=55) had used these in the past 12 months. The majority of the respondents had not used dietary supplements in the past 12 months (n=140, 68%).

Table 3.4 – Level of use of dietary supplements by individuals

Dietary supplements	n	%
Using currently or have used within the past 12 months	66	32.0
Using currently	57	27.7
Have used within the past 12 months	55	26.7
Never used in the past 12 months	140	68.0

Data presented as n (%); Answered question (n=206)

The survey asked individuals to list different types of dietary supplements they used or had used in last 12 months including different vitamins, minerals, herbs and other health foods, and the level of use of different dietary supplements. These are shown in Figure 3.2. The five most common dietary supplements used by the individuals currently or in the past 12 months were found to be; multi vitamins (38%; n=25), fish oils (35%; n=23), calcium (26%; n=17), different herbal supplements (24%; n=16) and omega 3 oils (24%; n=16). Approximately 23% of the respondents reported that they used other types of supplements not specifically listed in the questionnaire, these included cod liver oils, primrose oil and soya milk.

3.3.4 Sources of recommendation and place of purchase

Among individuals who were using or had used diet supplements in the past 12 months (n=66), the majority of them (62%; n=41) did not discuss it with their General Practitioners (GP's) (Table 3.5). The survey asked individuals "whether they were recommended to take dietary supplements", 59% (n=39) reported that they were recommended to take diet supplements. Of these 39 individuals who were recommended to take dietary supplements, the majority of them were recommended by GP's (41%; n=16), friends or relatives (38%; n=15) and dieticians (31%; n=12). Very few were recommended by CAM practitioners/providers (2.5%; n=1). The sources of recommendation for the use of dietary supplements are summarized in Figure 3.3.

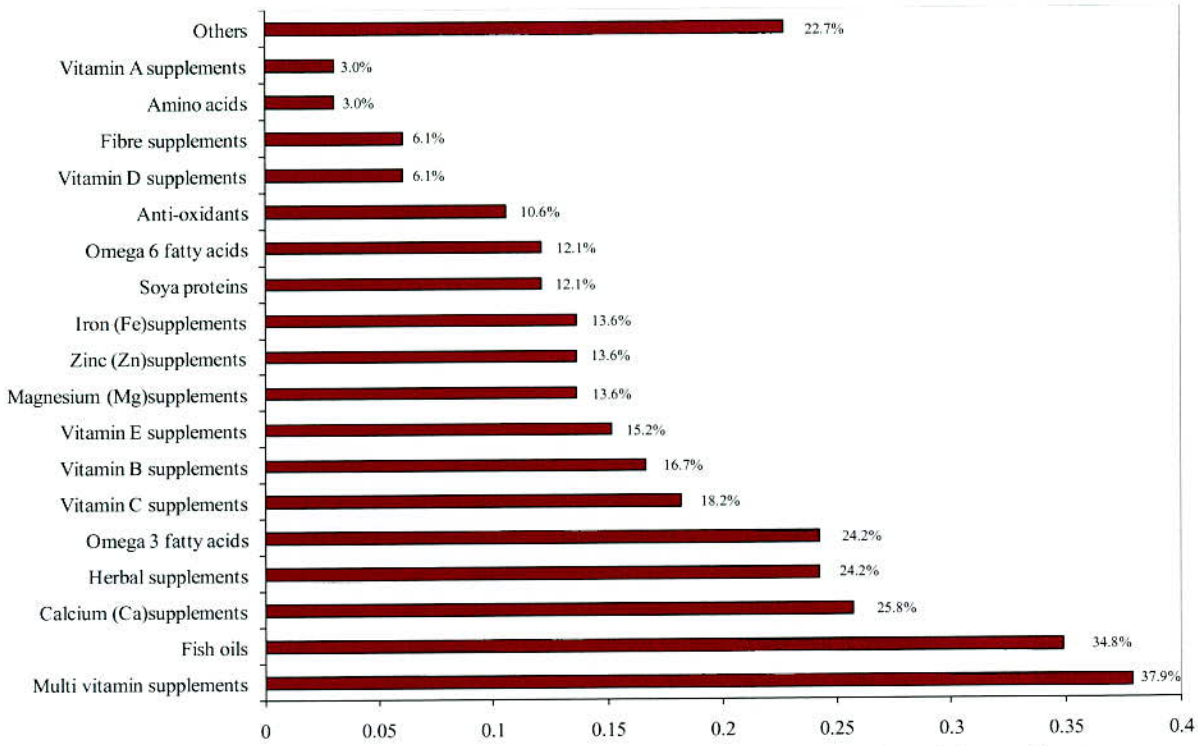


Figure 3.2 – Level of use of dietary supplements; currently or in the past 12 months by participants Data presented as % based on the answered question of N=66.

Table 3.5 – Participants ability to discuss with GP and recommendation of dietary supplements

Recommendation of diet supplements	n	%
Discussed with GP	25	37.8
Not discussed with GP	41	62.2
Recommended to take diet supplements	39	59.1
Not recommended to take diet supplements	27	40.9

Data presented as n (%); Answered question = 66

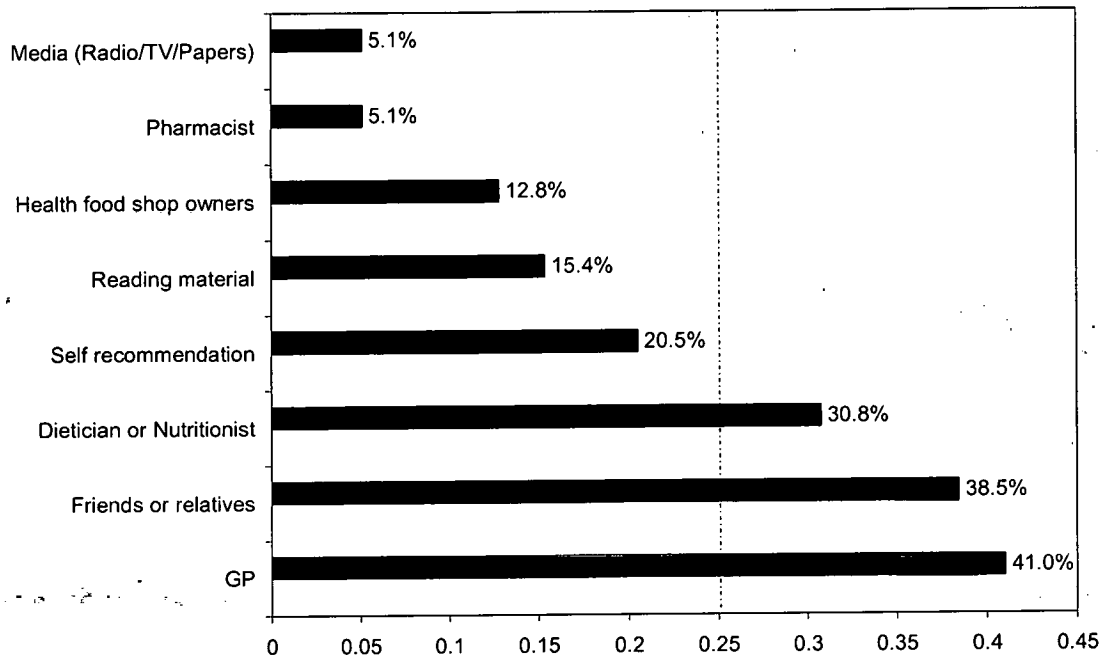


Figure 3.3 – Sources of recommendation for the use of dietary supplements; Data presented as % based on the answered question of n=29.

The places of purchase for dietary supplements can be seen in Figure 3.4. Over 30% of individuals purchased their dietary supplements from supermarkets (36%), pharmacies (36%) and health food shops (33%), while others purchased them from dieticians (5%), mail order (6.9%) or prepared their own supplements or own products (14%). Very few purchased their dietary supplements from CAM providers/practitioners (7%; n=1).

Those individuals who did not consume any dietary supplements (n=140) were asked, "whether there are any specific reasons why they did not consume supplements either currently or in the past 12 months" (Figure 3.5). Majority of the respondents reported "I am healthy" (28%; n=39), "not necessary" (26.4%, n=37) and "no reason" (12%, n=17). The rest of the subjects did not consume supplements for a wide variety of reasons, including "don't believe them", "don't like to", "expensive", "happy with the current treatment from GP", "takes enough medicine already", "They don't work" etc.

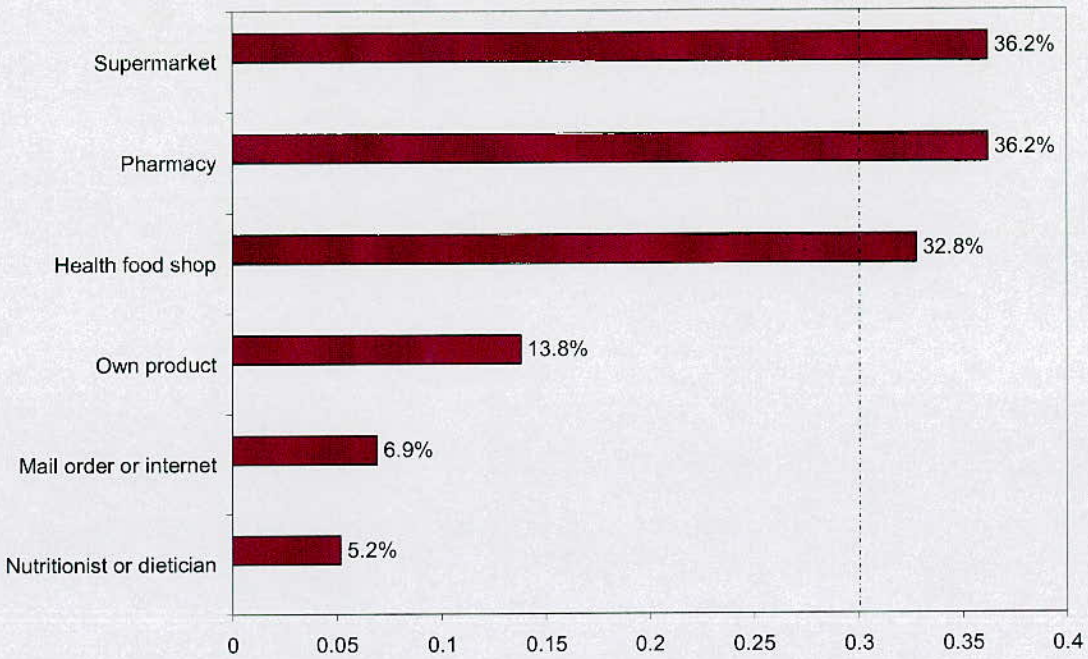


Figure 3.4 – The places of purchase of dietary supplements by participants; Data presented as % based on the answered question of n=58.

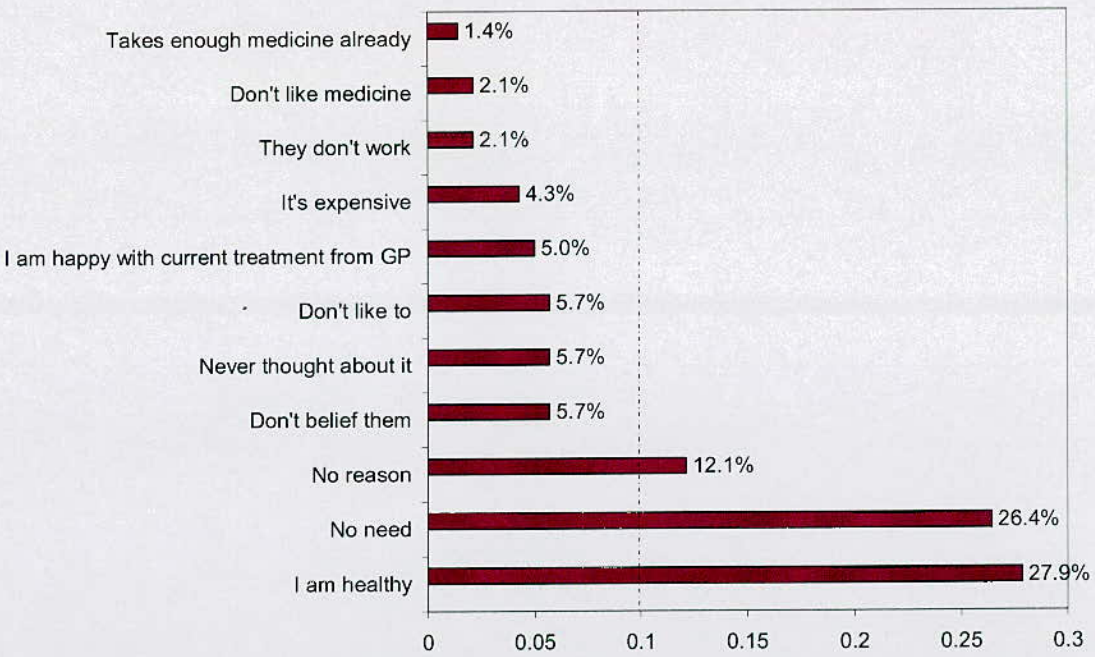


Figure 3.5 – The reasons for not taking dietary supplements by participants; Data presented as % based on the answered question n=140.

3.3.5 Frequency of use and cost of supplements

The frequency of use and buying power of dietary supplements are shown in Table 3.6. Of the 62 individuals who answered the question about how helpful they felt the dietary supplements were, 58 (93%) reported that they thought were moderately helpful. The majority of the individuals had been using these supplements for less than one year (42%, n=26). More than 50% of the individuals bought supplements less than once a month.

Table 3.6 – The buying power, duration of use and helpfulness of the dietary supplements

	%	n
How helpful (n=62)		
Not helpful at all	0.0	0
Less helpful	6.5	4
Moderately helpful	46.8	29
Very helpful	32.3	20
Extremely helpful	14.5	9
Average buying power (n=66)		
Less than 1 time per month	51.5	34
1 to 2 times per month	33.3	22
2 to 4 times per month	13.6	9
More than 4 times per month	1.5	1
How long been using (n=62)		
Less than 1 year	41.9	26
1 - 2 years	29.0	18
2 - 4 years	8.1	5
4 - 6 years	6.5	4
More than 6 years	14.5	9

Data presented as n (%);

The average expenditure to prepare or purchase supplements by individuals who were using or have used dietary supplements currently or in the past 12 months was found to be £15.88 per month with a range of £4.00 to £28.00

3.3.6 Association between socio-demographic characteristics and features of metabolic syndrome

Data on demographic characteristics of respondents with or without features of metabolic syndrome are shown in Table 3.7. Individuals with features of metabolic syndrome tended to be older; young individuals were less likely to have features of MS compared with older individuals ($P<0.01$). Individuals with higher education levels of university or postgraduate

degrees were more likely to have features of metabolic syndrome compared with individuals with secondary school education (P=0.027). Gender, ethnicity and income status of the individuals did not show any significant associations with features of metabolic syndrome.

Table 3.7 – The relationship between Socio-demographic characteristics and features of MS [N=210]

Demographic Characteristics		Respondents with Features of MS		Respondent without Features of MS		p
		n	%	n	%	
Sex (n=210)	Male	22	36.7	52	34.7	
	Female	38	63.3	98	65.3	0.452
Age (n=210)	25 - 34 years	9	15.0	56	37.3	
	35 - 44 years	14	23.3	48	32.0	
	45 - 54 years	20	33.3	27	18.0	
	55 - 64 years	16	26.7	17	11.3	
	65+ years	1	1.7	2	1.3	**0.001***
Ethnicity (n=210)	White	19	31.7	63	42.0	
	Mixed	4	6.7	15	10.0	
	Asia/Asian British	11	18.3	22	14.7	
	Black/Black British	26	43.3	49	32.7	
	Chinese	0	0.0	1	0.7	0.429
Education (n=206)	Secondary	4	0.7	4	2.7	
	College	5	8.8	36	24.2	
	University	31	54.4	81	54.4	
	Postgraduate	17	29.8	28	18.8	**0.027***
Annual income £ (n=199)	0 - 9,999	0	0.0	14	10.1	
	10,000 - 14,000	12	20.0	21	15.1	
	15,000 - 19,000	9	15.0	23	16.5	
	20,000 - 29,000	14	23.3	24	17.3	
	30,000 - 39,000	14	23.3	29	20.9	
	40,000 and above	11	18.3	28	20.1	0.173
Faculty belongs to (n=206)	Arts	11	18.3	39	26.7	
	Professional studies	15	25.0	33	22.6	
	Health & Human Sciences	9	15.0	35	24.0	
	Technology	15	25.0	19	13.0	
	Graduate School	3	5.0	3	2.1	
	Others	7	11.7	17	11.6	0.162

Data presented as n (%); MS – Metabolic Syndrome; * P<0.05 shows that there is a significant association between age and educational status of the respondents with features of MS. Individuals with features of MS tended to be older and having higher educational levels.

3.3.7 Association between demographic characteristics and individuals taking dietary supplements

Data on demographic characteristics of respondents taking dietary supplements are shown in Table 3.8. Individuals taking dietary supplements currently or in the past 12 months tended to be significantly older, and young individuals were less likely to use dietary supplements (P<0.003). There were no significant associations between the level of use of dietary supplements and gender, ethnicity, educational status and income levels.

Table 3.8 – The relationship between socio demographic characteristics and use of dietary supplements, N=210

Socio demographic Characteristics		Respondents not taking any dietary supplements		Respondent taking dietary supplement current/past 12 months		Total N (%)	*p*
		n	%	n	%		
Sex	Male	53	38	18	27	71 (34)	
	Female	87	62	48	73	135 (66)	
		140	100	66	100	206 (100)	0.159
Age	25 - 34 years	54	39	9	16	63 (31)	
	35 - 44 years	40	29	22	33	62 (30)	
	45 - 54 years	29	20	17	25	46 (22)	
	55 - 64 years	16	11	16	24	32 (15)	
	65+ years	1	1	2	2	3 (2)	
		140	100	66	100	206 (100)	***0.003****
Ethnicity	White	58	41	21	32	79 (38)	
	Mixed	13	9	5	8	18 (9)	
	Asia/Asian British	23	16	10	15	33 (16)	
	Black/Black British	45	33	30	45	75 (36)	
	Chinese	1	1	0	0	1 (1)	
		140	100	66	100	206 (100)	*0.415*
Education	Secondary	5	4	3	5	8 (4)	
	College	27	19	14	22	41 (20)	
	University	80	58	30	47	110 (54)	
	Postgraduate	27	19	17	26	44 (22)	
		139	100	64	100	203 (100)	*0.529*
Annual income (£)	0 - 9,999	12	10	2	3	14 (8)	
	10,000 - 14,000	20	15	13	21	33 (17)	
	15,000 - 19,000	24	18	8	13	32 (16)	
	20,000 - 29,000	23	17	15	23	38 (19)	
	30,000 - 39,000	27	20	15	23	42 (21)	
	40,000 and above	27	20	11	17	38 (19)	
		133	100	64	100	197 (100)	*0.427*

Data presented as n (%) based on number of completed questions; * P=0.003 shows that individuals taking dietary supplements currently or in the past 12 months tended to be significantly older. N=total number of samples.

3.3.8 Association between self reported medical conditions and use of dietary and herbal supplements

The relationship between self reported medical conditions of diabetes, hypertension, hypercholesterolaemia and obesity and use of dietary and herbal supplements are presented in Table 3.9. Individuals with diabetes mellitus were significantly more likely to use dietary supplements (P<0.001), especially herbal supplements (P<0.001) than individuals without having diabetes mellitus. Similarly, individuals reporting hyper-cholesterol and obesity were more likely (P<0.05) to use dietary supplements, but not herbal supplements.

Table 3.9 – The relationship between self reported medical conditions and use of dietary and herbal Supplements [N=210].

Self reported health conditions	Respondents taking dietary supplements current/past 12 months (n=65)	Respondents not taking dietary supplements (n=133)	P
Diabetes mellitus	10 (15%)	0 (0%)	< 0.001*
Hypertension	7 (11%)	5 (4%)	0.063
Hyper-cholesterol	14 (22%)	6 (4%)	0.001*
Obesity	23 (35%)	18 (13%)	0.001*
	Use of herbal supplements (n=16)	**Not using herbal supplements (n=182)**	**P**
Diabetes mellitus	9 (56%)	1 (1%)	< 0.001$^{\beta}$
Hypertension	4 (25%)	8 (4%)	0.01$^{\beta}$
Hyper-cholesterol	4 (25%)	16 (9%)	0.062
Obesity	5 (31%)	36 (20%)	0.332

Data presented as n (%); * P<0.05 shows that individuals with diabetes mellitus, hyper cholesterol and obesity were more likely to use dietary supplements. $^{\beta}$P<0.05 shows that individuals with diabetes and hypertension were more likely to use herbal supplements.

3.3.9 Association between family history and features of metabolic syndrome

Table 3.10 shows the relationship between the family history and individuals' features of metabolic syndrome. Those individuals with family history of either diabetes or hypertension or high blood cholesterol or obesity were significantly more likely to have features of metabolic syndrome (P<0.01).

Table 3.10 – Relationship between family history and features of Metabolic Syndrome [N=210].

Family History	Respondents with Features of MS (n=60)		Respondents without Features of MS (n=146)		p
	n	%	n	%	
Having family history of Diabetes Mellitus	15	25.0	13	8.9	0.003*
Having family history of Hypertension	22	36.7	29	19.9	0.01*
Having family history of hyper-cholesterol	17	28.3	14	9.6	0.001*
Having family history of Obesity	30	50.0	19	13.0	<0.001*

Data presented as n (%) based on the answered questions; MS – metabolic syndrome, * P<0.05shows that individuals with family history of either diabetes or hypertension or high blood cholesterol or obesity were significantly more likely to have features of metabolic syndrome.

3.3.10 Association between intake of dietary supplements and features of metabolic syndrome

Table 3.11 shows the use of the different dietary supplements of vitamins, minerals, herbs and other health foods reported by individuals with and without features of metabolic syndrome. Although numbers were small, individuals with features of MS were significantly more likely to use vitamin E, multi-vitamins, calcium, herbal supplements, high fibre and antioxidant rich foods, soya proteins and fish oils than their counterparts without features of MS ($p<0.05$). There was no significant association between the use of other dietary supplements and features of MS. Furthermore, individuals with features of MS were significantly more likely to use dietary supplements currently or in the past 12 months compared to persons without features of MS ($P<0.001$) (Table 3.11). Out of the 66 individuals who reported using dietary supplements currently or in the past 12 months, the majority of them (n=31; 47%) were using 3 or more types of supplements currently or within the last 12 months. Furthermore individuals with features of MS were significantly more likely to use 3 or more types of dietary supplements compared with individuals without features of MS ($P=0.037$) (Table 3.11). In contrast individuals with features of MS were less likely to use only one or two different types of supplements compared to persons without features of MS ($P>0.05$).

Table 3.11 – The relationship betweens intake of different dietary supplements and features of MS [N=210].

Diet supplements	Respondents with Features of MS (n=60)		Respondent without Features of MS (n=146)		p
	n	%	n	%	
Vitamin B	6	10.0	5	3.4	0.063
Vitamin A	1	1.7	1	0.7	0.499
Vitamin C	6	10.0	6	4.1	0.098
Vitamin D	2	3.3	2	1.4	0.332
Vitamin E	8	13.3	2	1.4	$^{\phi}$**0.001**
Multi vitamins	12	20.0	13	8.9	$^{\phi}$**0.027**
Calcium [Ca]	10	16.7	7	4.8	$^{\phi}$**0.008**
Magnesium [Mg]	4	6.7	5	3.4	0.247
Zinc [Zn]	4	6.7	5	3.4	0.247
Iron [Fe]	4	6.7	5	3.4	0.247
Herbal supplements	9	15.0	7	4.8	$^{\phi}$**0.017**
Antioxidants	6	10.0	1	0.7	$^{\phi}$**0.003**
High fiber foods / supplements	4	6.7	0	0.0	$^{\phi}$**0.007**
Amino acids	0	0.0	2	1.4	0.503
Soya proteins	5	8.3	3	2.1	$^{\phi}$**0.048**
Fish oils	11	18.3	12	8.2	$^{\phi}$**0.035**
Omega 3 oils	8	13.3	8	5.5	0.056
Omega 6 oils	5	8.3	3	2.1	$^{\phi}$**0.048**
Level of intake of diet supplements					
Using currently or in the last 12 months	34	56.7	32	21.9	
Not using any diet supplements	26	43.3	114	78.1	**<0.001**$^{\beta}$
Number of different supplements used by individuals (n=66) †					
One type of supplement	8	23.5	11	34.4	
Two types of diet supplements	5	14.7	11	34.4	
Three or more than three types of diet supplements	21	61.8	10	31.3	**0.037**^{a}

Data presented as n (%). MS – metabolic syndrome, † respondents with and without features of metabolic syndrome n=34 and n=32 respectively, $^{\phi}$ P <0.05 shows that individuals with features of MS were significantly more likely to use vitamin E, multi-vitamins, calcium, herbal supplements, high fibre and antioxidant rich foods, soya proteins and fish oils than their counterparts without features of MS. ^{B} P<0.001 shows that individuals with features of MS were significantly more likely to use dietary supplements currently or in the past 12 months. ^{a} P=0.37 shows that individuals with features of MS were significantly more likely to use 3 or more types of dietary supplements.

Similarly individuals with features of MS were significantly less likely to report or discuss the use of dietary supplements with their general practitioner (P=0.043) (Table 3.12). Although majority of the respondents were recommended to take supplements (n=39; 59%) there was no significant relationship between the two groups of individuals with or without features of MS (Table 3.12).

Table 3.12 – Subjects intention to discuss the intake of dietary supplements with GP [N=66]

Pattern of use of supplements	Respondents with Features of MS (n=33)		Respondents without Features of MS (n=33)		p
	n	%	n	%	
Discuss the use of supplements with GP †					
Discussed with GP	9	26.5	16	50.0	
Not discussed with GP	25	73.5	16	50.0	**0.043***
Sources of recommendation					
Recommended to take dietary supplements	21	63.6	18	54.5	
Not recommended to take dietary supplements	12	36.4	15	45.5	0.309

Data presented as n (%); MS – metabolic syndrome, * P=0.043 shows that individuals with features of MS were significantly less likely to report or discuss the use of dietary supplements with their general practitioner. † respondents with and without features of metabolic Syndrome was found to be n=34 and n=32 respectively.

3.3.11 The level of use of Complementary and Alternative therapies apart from dietary supplements.

The survey asked the individuals about the use of different types of other CAM therapies (apart from dietary supplements). Respondents who reported using different CAM approaches either currently or in the past 12 months are presented in Table 3.13. Approximately 40% (n=76) of individuals were currently using or had used CAM in the past 12 months, with 20% (n=37) of individuals being current users of CAM. A majority of the individuals (60%, n=116) never used CAM therapies in the past 12 months.

Table 3.13 – The level of use of CAM therapies (apart from dietary supplements) by participants [N=192].

CAM therapy	n	%
Using currently or have used within the past 12 months	76	39.6
Using currently $^{\phi}$	37	19.7
Have used within the past 12 months	40	20.8
Never used in the past 12 months	116	60.4

Data presented as n (%); % calculated based on the answered questions N=192; $^{\phi}$ % calculated based on the answered question of N=188.

The survey also asked individuals to list different types of CAM approaches they were using currently or had used in the past 12 months. The level of use of different CAM approaches is shown in Figure 3.6. The five most common CAM approaches used by the individuals currently or in the past 12 months (n=76) were found to be massage therapy (42.1%, n=32), acupuncture (26.3%, n=26), yoga (26.3%, n=20) aromatherapy (21.1%, n=16) and reflexology (19.7%, n=15). The average expenditure on CAM per month was found to be £37.20 with a range of £5.00 to £75.00 per month.

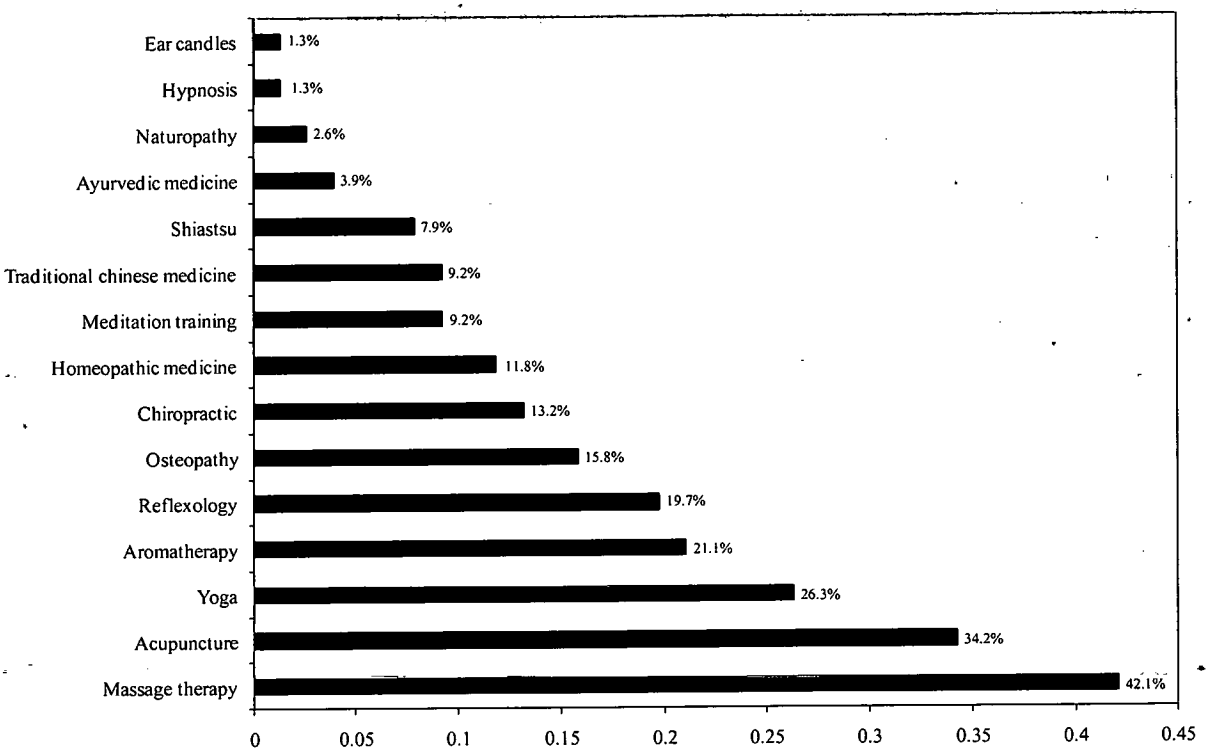


Figure 3.6 – The level of use of different CAM therapies apart from dietary and herbal supplements; currently or in the past 12 months. Data presented as % based on the answered question of N=76.

3.3.12 Association between use of CAM therapies (excluding dietary supplements) and features of metabolic syndrome

Table 3.14 details on the use of different types of CAM therapies by individuals with or without features of metabolic syndrome. Individuals with features of MS were more likely to use massage therapy (P<0.001) and aromatherapy (P=0.045) than their counterparts without features of MS and no significant difference for other types of CAM approaches. However in general, individuals with features of MS are more likely to use CAM therapies currently or in the past 12 months compared to persons without features of MS (P=0.003). In agreement with reporting the use of dietary supplements to their GP, individuals with features of MS were significantly less likely to report or discuss the use of different CAM therapies with their General Practitioner (P=0.006) (Table 3.14). Out of the 76 individuals who reported to use CAM approaches currently or in the past 12 months, the majority of them (n=14; 26%) were using 3 or more types of CAM approaches currently or in the last 12 months. Furthermore, individuals with features of MS were more likely to use 3 or more types of CAM than individuals without features of MS (P=0.033) (Table 3.14).

Table 3.14 – The relationship betweens intake of different CAM therapies (apart from dietary supplements and herbal remedies) and features of MS [N=192].

CAM Therapy	Respondents with Features of MS (n=54)		Respondent without Features of MS (n=138)		p
	n	%	n	%	
Acupuncture	4	7.4	22	15.9	0.089
Shiatsu	3	5.6	3	2.2	0.219
Chiropractic	5	9.3	5	3.6	0.114
Massage therapy	18	33.3	14	10.1	**<0.001***
Reflexology	4	7.4	11	8.0	0.581
Aromatherapy	8	14.8	8	5.8	**0.045***
Meditation training	3	5.6	4	2.9	0.309
Yoga	8	14.8	12	8.7	0.162
Naturopathy	1	1.9	1	0.7	0.484
Ayurvedic medicine	1	1.9	2	1.4	0.631
Osteopathy	2	3.7	10	7.2	0.292
Homeopathy	3	5.6	6	4.3	0.488
Hypnosis	0	0.0	1	0.7	0.719
Traditional Chinese medicine	2	307.0	5	306.0	0.634
Use of CAM (n=192) [†]					
currently or in the past 12 months	30	56.6	46	33.1	**0.003**[μ]
Discuss the use of CAM with GP (n=61) [β]					
Discussed with General Practitioner	4	16.0	18	50.0	**0.006**[a]
Use of one or more CAM therapies					
Have used only CAM therapy	5	9.3	11	8.0	
Have used two CAM Therapies	11	20.4	16	11.6	
Have used three or more CAM therapies	14	25.9	19	13.8	
Never used any Cam therapies	24	44.4	92	66.7	**0.033**[‡]

Data presented as n (%); MS – metabolic syndrome, * P<0.05 shows that individuals with features of MS were more likely to use massage therapy (P<0.001) and aromatherapy (P=0.045) than their counterparts without features of MS. [μ] P=0.003 shows that individuals with features of MS are more likely to use CAM therapies currently or in the past 12 months compared to persons without features of MS. [a] P=0.006 shows that individuals with features of MS were significantly less likely to report or discuss the use of different CAM therapies with their General Practitioner. [‡] P=0.033 shows that individuals with features of MS were more likely to use 3 or more types of CAM than individuals without features of MS. [†] respondents with and without features of metabolic syndrome n=53 and n=139 respectively; [β] respondents with and without features of metabolic syndrome n=25 and n=36 respectively.

3.3.13 Association between demographic characteristics and use of CAM therapies

The relationship between socio demographic characteristics and use of CAM currently or in the past 12 months is given in Table 3.15. Similar to the use of dietary supplements, individuals using CAM currently or in the past 12 months tended to be older, and younger individuals were less likely to use CAM therapies (P=0.046). There were no significant associations between the use of CAM and other demographic characteristics of gender, ethnicity, educational status or income levels.

Table 3.15 – The relationship between socio demographic characteristics and use of CAM therapies [N=192].

Socio demographic Characteristics		Respondents not taking any CAM therapies		Respondents taking CAM therapies current/past 12 months		Total N (%)	*p*
		n	%	n	%		
Sex	Male	50	36	13	25	63 (33)	
	Female	90	64	39	75	129 (67)	
		140	100	52	100	192 (100)	0.171
Age	25 - 34 years	46	33	12	23	58 (30)	
	35 - 44 years	48	34	12	23	60 (32)	
	45 - 54 years	29	21	13	25	42 (21)	
	55 - 64 years	15	11	14	27	29 (15)	
	65+ years	2	1	1	2	3 (2)	
		140	100	52	100	192 (100)	***0.046****
Ethnicity	White	50	36	24	46	74 (39)	
	Mixed	14	10	2	4	16 (8)	
	Asia/Asian British	22	16	8	15	30 (15)	
	Black/Black British	53	37	18	35	71 (37)	
	Chinese	1	1	0	0	1 (1)	
		140	100	52	100	192 (100)	*0.513*
Education	Secondary	5	4	2	4	7 (4)	
	College	30	22	11	22	41 (22)	
	University	76	54	25	49	101 (53)	
	Postgraduate	27	20	13	25	40 (21)	
		138	100	51	100	189 (100)	*0.830*
Annual income (£)	0 - 9,999	8	6	4	8	12 (6)	
	10,000 - 14,000	25	19	7	13	32 (17)	
	15,000 - 19,000	22	17	5	10	27 (15)	
	20,000 - 29,000	24	18	12	23	36 (20)	
	30,000 - 39,000	26	20	13	25	39 (21)	
	40,000 and above	27	20	11	21	38 (21)	
		132	100	52	100	184 (100)	*0.697*

Data presented as n (%) based on number of completed questions; * P=0.046 shows that individuals using CAM currently or in the past 12 months tended to be older, and younger individuals were less likely to use CAM therapies. N=total number of samples.

3.4 Discussion

The National Centre for Complementary and Alternative Medicine (NCCAM) defines CAM as those healthcare and medical practices that are not currently an integral part of conventional medicine (Egede *et al,* 2002; NCCAM, 2008). CAM is most widely used term in this area, but there is considerable debate around its definition (Ernst *et al,* 1995). The definition used here is any health improving technique outside of the mainstream of conventional medicine, where conventional medical treatments are those intrinsic to the politically dominant health system of a particular society or culture (Anon, 1997)

The estimates of CAM use in this study differ considerably from those of Eisenberg *et al,* (1998) but closely approximate those from other studies using data from the medical expenditure panel surveys (Astin, 1998). There are two possible reasons for these differences. One reason is the heterogeneity of CAM practices, which means that estimates of CAM use will change depending on what is included or excluded in the definition of CAM in this study. The second reason is the convenience sampling of staff and students from a university population in this study. This approach may have increased the proportion of individuals of higher educational or socioeconomic status, who have been shown to have higher usage of CAM or dietary supplements in this study.

Although dietary/nutritional counselling and lifestyle modification are essential components in the routine management of metabolic syndrome and diabetes care, it is important to recognize that such advice were obtained from dieticians and GP's (Figure 3.3) in this study. Approximately 31% and 41% of the respondents use dietary supplements based on the recommendations of dieticians and general practitioners. In contrast, very few subjects were recommended to take dietary supplements by CAM providers (2%; n=1). The NCCAM definition of CAM (NCCAM, 2008), implies that dietary/nutritional advice and lifestyle diets provided by CAM practitioners differ from conventional nutritional/dietary recommendations endorsed by dieticians or physicians. Examples of nutritional advice and lifestyle diets offered by CAM practitioners include ayurvedic diets, naturopathic, nutrition/diets, and orthomolecular therapies such as magnesium, melatonin, or megadoses of vitamins (NCCAM, 2008). In addition, special diets, such as those proposed by Drs. Atkins, Ornish, Pritikin, and Weil, also qualify as CAM lifestyle nutrition/diets (NCCAM, 2008). Nutritional advice and lifestyle diets offered by CAM practitioners are similar to the advice provided by dieticians and physicians (Bausell *et al,* 2001). In addition, it is currently unknown whether additional nutritional advice

and lifestyle diets by CAM practitioners conflict with conventional dietary recommendations. Therefore, due to these reasons of potential disparities in dietary advice by CAM practitioners and dieticians, the questions about the level of use of dietary supplements are presented independently from other CAM therapies in the questionnaire (Appendix 3.2).

Surveys conducted in various developed countries have shown that personnel use of dietary supplements is becoming widespread and increasingly popular (Block *et al,* 2007; Hori *et al,* 2008; Kirk *et al,* 1999). However, little is known about dietary supplementation practices (particularly the use of herbs) among those suffering from diabetes, hypertension, hypercholesterolaemia or obesity (features of metabolic syndrome).

This study explored the use of dietary supplements and other CAM therapies amongst staff and students at Thames Valley University (TVU), London, UK. Approximately 32% (n=66) of those questioned were using or had used different dietary supplements currently or in the last 12 months (Table 3.4). Among those, more than 20% of the respondents were using multi vitamins, fish oils, calcium supplements, herbal remedies or omega 3 oils as dietary supplements. This was also found by the national diet and nutrition survey, which suggested that the most commonly used dietary supplements among British adults were multivitamins, cod-liver oil, vitamin C and vitamin B complex (Gregory *et al,* 1990).

This study specifically examined whether individuals with features of metabolic syndrome were more likely to use dietary supplements or CAM therapies than those individuals without features of metabolic syndrome. Interestingly, individuals with features of metabolic syndrome were significantly more likely to use different dietary supplements especially herbal remedies, multi vitamins, vitamin E, antioxidants, calcium, soya proteins, fish oils and fibre supplements than individuals without features of metabolic syndrome (Table 3.11). Furthermore, subjects with features of metabolic syndrome were significantly more likely to use three or more different types of dietary supplements compared with their counterparts (Table 3.11). Particularly, individuals with self reported condition of diabetes mellitus were significantly more likely to use dietary supplements or herbal remedies than individuals without diabetes mellitus (Table 3.9). One explanation for this is that individuals with at least one or more self reported medical condition (in this case features of metabolic syndrome) may have had less success in treating their own health problems and their continued problems may have prompted them to seek alternative dietary supplements or CAM. Other studies have also shown that patients suffering

from chronic diseases have a higher use of alternative therapies than those who do not have chronic diseases (Tindle *et al*, 2005; Barnes *et al*, 2002; Fleming *et al*, 2007; Kaboli *et al,* 2001; Rao *et al*, 1999; Chenot *et al*, 2007; Kajiyama *el al*, 2006). Furthermore, Egede *et al,* (2000) demonstrated that individuals with diabetes were twice as likely to use CAM as the general population without chronic medical conditions.

People who are concerned about their dietary intake, quality of food, presence of chemicals in food and generally the effect of diet on health condition may use different dietary supplements (Marakis, 2006; Hori *et al*, 2008). People who use supplements tend to hold the belief that the quality of the food supply has deteriorated over the past decades (Marakis, 2006). They tend to see food processing as a depletion process, which destroys the natural nutritional properties of foods (Marakis, 2006). From this stand point supplementation could be their attempt to restore the natural balance of intake of food nutrients, especially individuals with chronic health conditions. This may be the reason why people with features of metabolic syndrome were significantly more likely to use required dietary supplements of multi vitamins, herbal supplements, calcium, anti oxidants, fibre supplements, soya proteins and fish oils than their counter parts. It is interesting to note that there is a significant association between the use of herbal supplements by respondents with features of metabolic syndrome and diabetes (Table 3.10). However, the use of different types of herbal supplements was not reported in this study.

Previous studies of systematic reviews and Meta analysis suggested that calcium or vitamin D supplementation play an important role to reduce risk factors associated with metabolic syndrome and diabetes mellitus (Peterlik & Cross, 2009; Hjelmesaeth *et al,* 2009; Yamaguchi & Sugimoto, 2008; Pittas *et al,* 2007; Peterlik & Cross, 2005). The amount of antioxidant (especially from fruits and vegetables) plays an important role in reducing risk factors linked with many health conditions. Ford *et al,* (2003) suggested that adults with metabolic syndrome have suboptimal concentrations of several antioxidants, which may partially explain their increased risk of diabetes and cardiovascular disease.

Similarly, different observational, animal and human studies support a role for soya protein in the improvement of glycaemic control in type 2 diabetes (Gobert *et al*, 2009). Furthermore, the role of fibre supplements in the management of diabetes or metabolic syndrome was well established in many studies (Isharwal *et al*, 2009; Astrup, 2008; Ventura *et al,* 2008; Esposito *et al*, 2007; Weickert & Pfeiffer, 2008; Bo *et al*, 2006; Wagh & Stone, 2004). The results of our

study also demonstrated that individuals with risk of metabolic syndrome are more likely to take fibre supplements than their counterparts. It is accepted that viscous and gel forming properties of soluble dietary fibre inhibits macronutrient absorption, reduce postprandial glucose response, beneficially influence certain blood lipids and ultimately improve factors associated with metabolic syndrome (Esposito *et al*, 2007). Bran has been shown to be very popular fibre supplement in a recent random population survey of Australians, and up to 1/5 of women and 1/8 of men regularly add bran to their diets (Marakis, 2006).

Previous studies have also confirmed the beneficial effects of fish oil administration on the metabolic syndrome or diabetes mellitus (Martin-de-Santa *et al*, 2009; Gani, 2008; Oh & Lanier, 2007; Alexander *et al*, 2006). The health effects of these oils include reduction of cardiovascular risk and lipid lowering actions.

Furthermore, the results of this study demonstrated that individuals with features of metabolic syndrome were more likely to be older and with higher educational status compared with individuals not having features of metabolic syndrome (Table 3.7). This may be because individuals with higher educational background and older age are more likely to be sedentary workers and this could lead to increased risk of having features of metabolic syndrome because of less physical activity.

This study further demonstrates that older subjects were more likely to use dietary supplements and other CAM approaches than younger subjects (Table 3.8), and this is consistent with previously published findings (Tindle *et al,* 2002; Wiles and Rosenberg, 2001; Conboy *et al*, 2005; Fukuda *et al*, 2006; Al-windi, 2004). Individuals with features of metabolic syndrome were more likely to be older (Table 3.8). Individuals with higher educational status did not show any significant associations with diet supplements or CAM use. However, the associations between higher education and CAM use have been reported in a range of UK based studies (Thomas and Coleman, 2004; Harris *et al,* 2003; Rees *et al,* 2000; Furnham & Beard, 1995).

In addition, a US survey (Astin, 1998), found that while education was associated with CAM use, income was not, suggesting that income cannot be the only explanation. Educational status could be important in increasing people's awareness of and ability to seek out information about dietary supplements and CAM. However, the results of our study did not demonstrate any association between educational status or income and use of dietary supplements (Table 3.8).

This is probably due to small sample size in our study (n=210) compared to Astin, (1998) study (n= 1035).

The educational status of the respondents has been associated with CAM use in a wide range of studies and such consistency warrants the conclusion that education indeed has a role in CAM use (Harris *et al*, 2003). The association between CAM use and education can be explained in terms of higher education, being associated with having a higher income enabling people being able to afford to pay for any dietary supplements or CAM therapies. A Canadian population based study suggested that females, those who are younger to middle aged, affluent and more educated were more likely to use CAM (Statistics Canada, 1996).

Individuals with features of metabolic syndrome (MS) were significantly less likely to report discussing the use of different dietary supplements and CAM with their General Practitioner (GP) (Table 3.12 and 3.14). In agreement with Shakeel *et al,* (2009) a large number of patients take CAM for a variety of reasons, but most do not inform their physicians. This is because people may be frightened to report the use of CAM therapies, as GPs may ask them to stop taking CAM therapies because of their potentially adverse effects or interactions with regular medications. Interaction between CAM use and prescription medicine is possible and there are many reports in the literature of interactions, adverse effects and even fatalities associated with CAM use (Heck *et al,* 2000; Myers, 2002). Furthermore, Canter & Ernst, (2004) suggested that the concomitant use of several herbal supplements is poorly reported to doctors and may place older British people at risk of negative herb-drug interaction. Therefore this issue needs to be addressed by educating the general public or patients to discuss the use of dietary supplements and CAM with their GP (Shakeel *et al*, 2009). Additionally GP's need to regularly start asking their patients whether they are taking any dietary supplements or CAM. Therefore it would be more appropriate that health care providers and GPs acknowledge the use of dietary supplements (including herbs) and CAM, and learn to discuss CAM use with their patients.

Generally, of those who reported using different CAM therapies (excluding dietary supplements), respondents with features of metabolic syndrome were more likely to use massage therapy and aromatherapy compared to individuals without features of metabolic syndrome (Table 3.14). Furthermore, individuals with features of metabolic syndrome had used three or more CAM therapies compared with those without such features. The estimates of CAM use in this study (40%) differs considerably from those of Egede *et al,* (2002) and

Eisenberg *et al,* (1993), who reported 34% among US adults. There are different possible reasons for these changes. One reason could be the heterogeneity of CAM practices (NCCAM, 2008; National Institute of Health Office of Alternative Medicine, 1997), which means that estimates of CAM use will change depending on what is included or excluded in the definition of CAM in different countries (like USA and UK). The other reason is the difference in target population across studies (USA vs. UK).

Previous studies also demonstrate that lifestyle and dietary modifications, spiritual healing, herbal remedies, massage and meditation were the most frequently used CAM treatments among individuals with diabetes mellitus (Eisenberg *et al,* 1993; Eisenberg *et al,* 1998; Elder *et al,* 1997; Burg *et al,* 1998; Egede *et al,* 2002). However, in general within the UK the most popular type of CAM is herbal medicine, probably because of their association with plant products (House of Lords Committee on Science and Technology, 2000). However, in our study homeopathy is not widely used, this may be due to our purposive sample selection (not a representative sample). Furthermore, a BBC survey of CAM use in UK suggested that consumers spent approximately £1.6 x 10^9/year on CAM (Ernst & White, 2000) and estimated that expenditure on CAM will increase by 50% every 5 years (Thomas *et al,* 2001). Therefore, according to the projected UK population in 2009 (Census, 2001), the average expenditure on CAM in the UK will be approximately £4.50/person/month, irrespective of age. In our study the approximate expenditure on dietary supplements and CAM was found to be £16 and £37 per person per month (among adults > 25 years old) respectively.

3.5 Limitations

There are some limitations to this study. Despite a good response rate of 70%, a major limitation is the small number of individuals who took part in this study. This study investigated a population of individuals attached to the university and is therefore not representative of the general population. Individuals were also asked to fill a questionnaire and to recall the use of dietary supplements and CAM therapies in the past 12 months therefore they may have been subjected to recall bias.

The self reported or perceived medical conditions of diabetes, hypertension, hyper-cholesterol and obesity could be a limitation in this survey. However, previous studies have shown that self reports are reliable for the diagnosis of diabetes and other chronic diseases (Stein *et al,* 1993; Bowlin *et al,* 1996; Egede *et al,* 2002). The ambiguous definition of CAM is one of the main

limitations, which allows for estimates that are dependent on the inclusion and exclusion criteria used to define CAM. This limitation may interfere with the ability of researcher to compare findings across studies.

Obesity was defined based on self reported information, and a consistent observation is that individuals have a tendency to underestimate their weight (Krassas *et al*, 2003). Therefore self-report bias had consequences for the accuracy of a screen for overweight and obesity in this study. Even though self-reports will remain an important health surveillance tool it should not be relied on exclusively to detect weight problems. Alvar-ez-Torices *et al,* (1993), in an effort to evaluate the usefulness of self-reported measures of height and weight, found that the prevalence of obesity based on measured weight and height was 1.8 times that of self-reported values in men and 2.5 times that of self-reported values in women.

3.6 Conclusion and future directions

Individuals with features of metabolic syndrome were more likely to use dietary supplements, especially herbal supplements, fish oils, multivitamins, fibre, anti oxidants, soya proteins and CAM (massage and aromatherapy) than individuals without features of metabolic syndrome. Likewise, respondents with self reported health condition of diabetes were more likely to use dietary supplements of herbal remedies than their counterparts. This is not surprising because earlier studies have linked increased CAM use with the presence of chronic as opposed to acute or life threatening medical conditions (Astin, 1998; Eisenberg *et al*, 1993; Egede *et al,* 2002).

There is a substantial increase in the use of dietary supplements and CAM within the UK. There is evidence that increasing numbers of individuals in the UK use one or more CAM approaches or dietary supplements for the treatment of common medical conditions (Ritchie, 2007). Individuals who are more likely to use dietary supplements or herbal supplements tend to wish to have a choice in their health care. An attraction of CAM and the use of dietary supplements is that they are perceived by some individuals to be safe and traditional. Such persons may be more reluctant to use drugs or medicines. These individuals may be dissatisfied or disappointed with previous experiences of drugs or medicines. Therefore, the potential to self-medicate with a range of dietary supplements may be an important public health issue. Finally, public opinion has a profound affect on the use of CAM and dietary or herbal supplements (Ritchie, 2007). As a result of increased awareness and availably of information about CAM and dietary

supplements, the use of supplements has changed over the last decade and is likely to increase (Kirk *et al*, 1999; Ritchie, 2007).

As metabolic syndrome or diabetes mellitus is a chronic debilitating medical condition, there are two important areas for future research. Firstly, there is an urgent need to use rigorous research designs to establish the efficacy of several dietary supplements or herbal remedies that are currently being used by individuals with diabetes or metabolic syndrome. Secondly, future studies must determine the effectiveness of herbal remedies or diet supplements used in typical clinical situations and the effect of these herbal supplements should be assessed by quality randomized controlled clinical trials.

This study suggested that introducing dietary or herbal supplements or investigating the efficacy of herbal supplements for individuals with features of metabolic syndrome is acceptable and feasible. Because individuals with features or risk of metabolic syndrome are more likely to use herbal supplements than individuals without features of metabolic syndrome. Therefore, based on the results of this survey and systematic reviews of dietary supplements (chapter 2), cinnamon was chosen and the effect of dietary supplement of cinnamon on glycaemic control, blood pressure and serum lipid profiles was evaluated by using a randomized controlled clinical trial (chapter 4).

CHAPTER 4

EFFECT OF DIETARY INTERVENTION OF CINNAMON ON HbA1c, BLOOD PRESSURE AND SERUM LIPIDS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

A Randomized, Placebo controlled, Double blind Clinical Trial - RCT

4.1 Introduction

Cinnamon is widely used as spice and studies has suggested that it may have useful pharmacological effects in the treatment of diabetes (Khan *et al*, 2003; Mang *et al,* 2006). A detailed systematic review of therapeutic effect of cinnamon and diabetes mellitus was evidently explained in chapter 2 (section 2.6). Recent studies reported that cinnamon does not seem to improve glycated haemoglobin (HbA1c) and serum lipid profiles in type 2 (Blevins *et al,* 2007; Vanschoonbeek *et al,* 2006) and type 1 diabetic patients (Altschuler *et al,* 2007). Our previously published systematic review of cinnamon and diabetes (Kirkham *et al,* 2009) and Meta analysis (Baker *et al,* 2008) also demonstrated that cinnamon does not appear to improve blood glucose and lipid parameters in type 1 or 2 diabetic patients. In contrast, studies in people with pre diabetes or metabolic syndrome or insulin resistance revealed that cinnamon has the potential to improve glucose tolerance and insulin sensitivity (Solomon and Blanin, 2007; Ziegenfuss *et al,* 2006).

The glucose lowering potential and pharmacological mechanisms of cinnamon has already been explained in section 2.6. In the last few years nutritional research on diabetes has improved well in terms of both number of studies produced and quality of methodologies employed. Therefore, it is now possible to attempt to identify new evidence on effectiveness of cinnamon supplementation for the management of type 2 diabetes mellitus. Therefore it is possible to reduce the risk factors associated with diabetes by means of well defined randomized controlled clinical trials among patients diagnosed with type 2 diabetes mellitus (Geode *et al,* 2008; UK Prospective Diabetes Study, 1995). This will provide a new emphasis on managing type 2 diabetes mellitus in combination with effective dietary supplementation of cinnamon, and this might limit the dramatic increase in the incidence of type 2 diabetes expected in next few years.

To date there have been few quality randomized controlled clinical trials reported regarding the use of cinnamon in type 2 diabetes mellitus. These trials are heterogeneous with differences reported including; in the concurrent anti diabetic medication, the cinnamon dose administered, duration of the trial, the number and type of participants included, baseline blood glucose and BMI and ethnicity of participants (section 2.6.6). These studies have had contradictory results. Diabetes UK (a charity supporting people with diabetes) has also suggested that further studies on cinnamon and diabetes are important before recommending cinnamon to patients *(www.diabetes.org.uk).*

Given the different sources of evidence from preclinical and clinical evidence of cinnamon (section 2.6) and the results of survey (chapter 3) showed that people with diabetes take various natural health products. Therefore, there is a need to determine the safety, efficacy and pharmacological activity of the cinnamon. Based on the previous evidence from *in vitro* and *in vivo* studies, it was postulated that consumption of cinnamon would lead to improved glucose and blood lipids *in vivo*. Therefore, this study was designed to determine whether there is a glucose lowering response of cinnamon on clinical variables associated with diabetes and cardiovascular diseases in people with type 2 diabetes.

4.1.1 Objectives

1. To evaluate whether dietary supplementation of cinnamon has the potential to improve glycaemic control, blood pressure and serum lipid profiles in poorly controlled type 2 diabetes patients without evidence of micro or macro vascular complications.
2. To determine the effect of cinnamon on body weight or BMI and waist circumference of the type 2 diabetes patients.
3. To verify the effect of daily energy intake (dietary analysis) on blood glucose and blood lipid profiles of the diabetic patients.

4.1.2 Hypothesis

The null hypothesis [H_0] of this trial is "there will be **no** significant improvement in glycaemic control, blood pressure, serum lipid profiles and body weight or waist circumference following the cinnamon intervention compared to placebo group"

The alternative hypothesis [H_1] of this trial is "there is a significant improvement in glycaemic control, blood pressure, serum lipid profiles and body weight or waist circumference following the cinnamon intervention compared to placebo group"

4.1.3 Research questions

This randomized controlled clinical trial will address the following research questions;

1. Could the intervention be used to treat other forms of chronic diseases such as Cardio Vascular Diseases (CVD), metabolic syndrome, hypertension and obesity?
2. Is cinnamon supplementation feasible (tolerance) or would the intervention be appropriate for use among patients with diabetes mellitus?
3. To investigate the success in achieving the predefined end points (out comes) of HbA1c, blood pressure, serum lipid profiles and anthropometrics by end of the intervention.

4.2 Methodology

This section describes study design, randomization of samples, data collection and analysis that are relevant to more than one of the experiments presented in this chapter.

4.2.1 Ethical approval

Ethical concerns are unique, especially for randomized controlled trials. The study protocol was approved by the Brent Medical Ethics Committee of the Northwick Park Hospital, London, UK (ref: 07/H0717/47) (Appendix 4.1). The study was carried out within Brent NHS, UK between October 2007 and January 2009. Patient information sheets (Appendix 4.2) were given to all potential subjects. Written informed consent (Appendix 4.3) was obtained from all subjects who were aware that as volunteers they were free to withdraw from the study or intervention at any time.

Consolidated standards of reporting trials (CONSORT)

According to the International Committee of Medical Journal Editors (ICMJE) (Salley *et al,* 2008; Clinical trial registration: a statement from the ICMJE, 2007) and CONSORT guidelines, this study was registered with clinicaltrials.gov (NCT00846898) (Appendix 4.4). CONSORT statement reports the minimum list of essential items, which authors should consider when reporting the results of randomized controlled trials (RCT) (Salley *et al,* 2008) and CONSORT has been endorsed by the ICMJE. Therefore very high standards have been maintained in reporting the results of this RCT, especially the methodology and results of this study were reported according to the CONSORT guidelines.

4.2.2 Study design and rationale

This study included 12 weeks of randomized, placebo controlled, double blind clinical trial with two parallel groups. This randomized controlled trial is used to examine the effect of cinnamon on particular outcomes such as glycaemic control, lipid profiles and blood pressure levels of type 2 diabetic patients. The randomized controlled trial is one of the simplest but most powerful tools of research. In essence, the randomized controlled trial is a study in which people are allocated at random to receive one of several clinical interventions (Jadad, 1998), and some consider randomized controlled trials to be the best of all research designs or the most powerful tool in modern clinical research (Nystrom *et al,* 1993). This method is widely considered the most reliable form of scientific evidence because it is the best known study design to eliminate

the variety of biases that regularly compromise the validity of the trial or research (John, 2003; David *et al,* 1982).

The main purpose of using a placebo-controlled group in this study was to allow discrimination of patient outcomes (for example, changes in symptom, signs etc) caused by the test treatment from outcomes caused by other factors such as natural progression of the disease (Fredric, 1986). The placebo control group experience tells us what would have happened to diabetes patients if they had not received the test treatment or cinnamon or if they had received a normal treatment known to be effective. The treatment and control groups should be similar with regard to all baseline measurements and parameters and on treatment variables that could influence outcome, except for the study treatment (John, 2003). Therefore to predict outcome measures with adequate accuracy the placebo control group is essential in this study.

4.2.3 Sample size

The size of the expected effect of the intervention is the main determinant of the sample size necessary to conduct a successful randomized control trial (Harald *et al,* 2004). Obtaining statistically significant differences between two samples is less problematic if large differences are expected. However, the smaller the expected effect of the intervention, the larger the sample size needed to be able to conclude, with enough power, that the differences are unlikely to be due to chance (Harald *et al,* 2004). For example, in this study we assumed that we wish to study two groups of patients who will undergo different interventions, one of which was a new intervention (cinnamon).

It was expected to observe a decrease in the primary outcome of HbA1c by at least 0.5% with the cinnamon treatment in order to be able to detect this difference with a probability (power) of 80%, a total of 64 patients (32 per arm) was estimated (Rosner, 2000). Normally the sample size required to achieve power in a study is inversely proportional to the treatment effect (Rosner, 2000). Due to financial constraints and time limitations, we managed to recruit a total of 58 patients for this study. In the beginning, we suspected the sample size might not be enough to prove the hypothesis, however a survey of 71 randomized controlled trials showed that most of these trials were too small (insufficient power) to detect important clinical outcome (Freiman *et al,* 1978) and thus inadequately powered sample size is one of the main limitation in RCTs.

4.2.4 Subjects

Patients included in this study were; 18 years of age or older, diagnosed with type 2 diabetes on two consecutive fasting glucose measurements of greater than 7mmol/L, a HbA1c $\geq$ 7% and treated with oral hypoglycemic agents. Exclusion criteria included patients treated with insulin therapy, pregnant and/or lactating women, patients already taking cinnamon or other herbal supplements with the potential use to control blood glucose levels, patients with acute health conditions such as cardiovascular disease, liver disease, kidney disease and cancer. Patients that were unable to read or understand the consent form and/or the information sheet in English were also excluded. Participants that changed their medication during the study or were diagnosed with other medical conditions would be withdrawn from the study.

4.2.5 Recruitment

Subjects were recruited from three different community NHS diabetes centers in NHS Brent - Monks park health centre, Willesden health centre and Wembley health centre. Patients were normally referred by their general practitioners (GP's) to dieticians for diet and lifestyle counseling at these community diabetes clinics as part of their regular diabetes care (standard care). Therefore dieticians at these sites were responsible for making initial contact with patients and identifying suitable patients for the study based on strict inclusion criterias. Patients who were eligible and showed interest were then referred by the dietician to the investigator. All patients were seen by dieticians at diabetes clinics and received at least two sessions of diet and lifestyle advice during the study period as per standard care. Patients who are eligible and missed the appointment with the dietician in diabetes clinics were contacted by sending an invitation letter (Appendix 4.5) and return slips (Appendix 4.6) with patient information sheet. Subjects were also given phone numbers and email addresses of the investigator and instructed to call with any questions or concerns. All patients were recruited entirely on a voluntary basis, and no one was asked to participate in this study against his or her will and was able to withdraw from the study at any time. The recruitment and randomization procedures of samples are shown in Figure 4.1.

After agreeing for randomization and obtaining written informed consent from patients, their respective GP's were informed (Appendix 4.7) about their participation in this clinical trial. The list of details of GPs surgeries in Brent was obtained from NHS Brent. Appointment letters were send to patients informing them of the clinic date, place and time (Appendix 4.8). The details of

the patients (name or hospital number) were then entered onto a computer and a randomization list was prepared by using random numbers and randomizations of patients were carried out.

4.2.6 Randomization

The randomization procedure gives the randomized controlled trial its strength. Random allocation means that all participants have the same chance of being allocated to each of the study groups (two arms) (Altman, 1991). Therefore the random allocation of participants in our study assures that the characteristics of the subjects are as likely to be similar as possible across the two groups at the start of the study or baseline.

Randomization in this study was computer generated, with allocation concealment by a central office (university) with allocations kept in a locked, unreadable computer file that the investigator can access only after the characteristics of an enrolled participant are entered, and sequentially numbered.

Initially 68 patients expressed interest in this study; however only 58 of them agreed to randomization and provided informed consent. Therefore a total of 58 patients were randomly assigned to placebo (n=28) and cinnamon (n=30) groups (Figure 4.1). Of these patients, 55 completed the study.Two patients in the placebo group were asked to withdraw at week 7 and week 9 due to adjustments in their dose of anti diabetic medications. One patient in the cinnamon group was asked to withdraw at week 9, as he started taking other alternative therapies (yoga) which may be effective and act as a confounder. Patients who withdrew (n=3), their remaining data were assigned (i.e., week 0 values were used at week 12) by using a "Last Observation Carried Forward method" (LOCF) for the final analysis. To encourage participation and reduce drop out rates, a £10.00 book voucher was given to each participant at the end of the 12 weeks trial period.

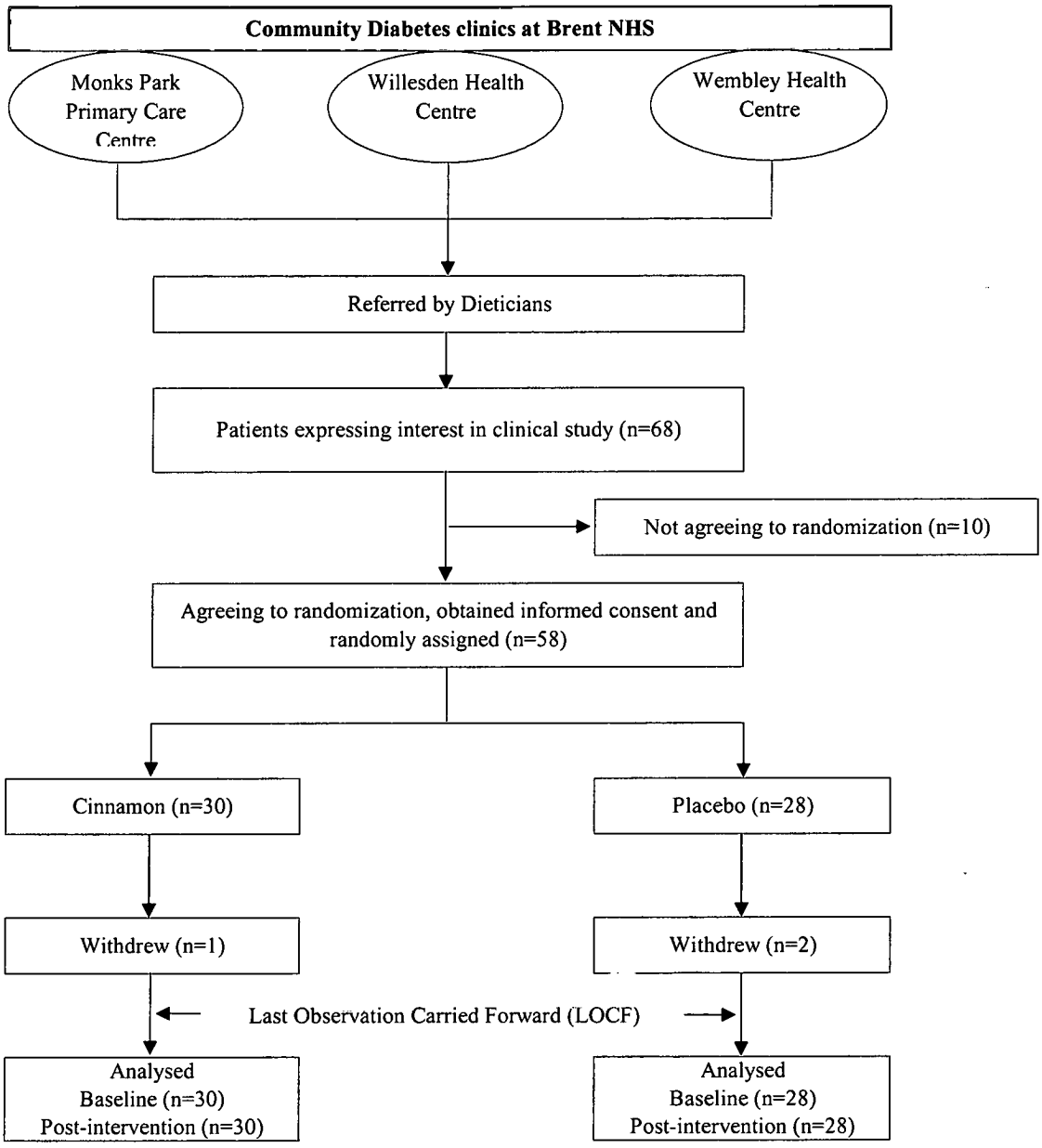


Figure 4.1 – Recruitment and randomization of participants for RCT based on CONSORT guidelines

4.2.7 Double blinding

Double blinding of this trial was ensured by use of matching colour, size and smell of placebo and cinnamon. Capsules were packaged in non transparent black plastic bottles and coded appropriately. To ensure that characteristic cinnamon smell was present with the placebo capsules, cinnamon powder was placed under the lid of the placebo bottles. The investigator received sealed bottles of capsules (A and B) for distribution and was unaware which were

active and which was placebo until the end of the trial. Compliance was monitored by capsule count at week 6 and week 12. Finally a post intervention compliance questionnaire (Appendix 4.9) was used to collect information pertaining to compliance with capsule counts, tolerability and safety. To make sure that the study was properly double blinded, the patients were asked post intervention (questionnaire) whether they were aware of the type of capsule they were taking; the majority of patients (80%) stated they were taking cinnamon, 16% said they had no idea and 4% said they were taking placebo.

4.2.8 Side effects

The cinnamon used in this study did not cause any reported side effects, however one patient in the placebo group reported mild gastric pain for 2 days. Subjects did not report any changes in their hypertensive or dyslipidaemia medications and usual physical activity levels during the course of the study. This was recorded by the investigator while meeting the patients at week 6 and week 12.

4.2.9 Intervention programme

Each subject was instructed to take 2g (500mg x 4 capsules) of either starch filled placebo capsules or cinnamon powder *(cinnamomum cassia)* every day for 12 weeks. Subjects in the cinnamon group were supplied with 12 weeks of cinnamon capsules. The 2g dose of cinnamon was spread over the day as 500mg (1 capsule) after breakfast, 1000mg (2 capsules) after lunch and 500mg (1 capsule) after dinner. The subjects were instructed to take the capsules immediately after the meals or with the meals.

Similarly, subjects in the placebo group supplied with starch filled placebo capsules for a 12 week period. The 2g doses of starch capsules were spread over the day as 500mg (1 capsule) after breakfast, 1000mg (2 capsules) after lunch and 500mg (1 capsule) after dinner. These subjects were also instructed to take the placebo capsules immediately after the meals or with the meals.

The specific cinnamon capsules (500mg) were supplied by Holland and Barrett, Pharmaceutical Company, UK. The cinnamon capsule is 100% certified natural herb (Ref: HBL14020NB) by Holland and Barrett Pharmaceutical Company. The pure cinnamon (*Cinnamomum cassia*) was ground finely and put into transparent capsules. The ingredients of cinnamon capsule includes; cinnamon bark powder, capsule shell (hydroxypropyl methylcellulose) and anti-caking agents of

silicone dioxide, magnesium stearate and stearic acid. The placebo capsules were also supplied by Holland and Barrett, UK. Clear transparent placebo capsules were filled with chocolate colour starch powder to match the colour and size of cinnamon capsules. The capsule shell (hydroxypropyl methylcellulose) and anti-caking agents in the placebo capsules were also similar to cinnamon capsules. Furthermore, both the cinnamon and placebo capsules did not contain any traces of lactose, soya, gluten, wheat or yeast. No impurities or traces were mixed with the capsules during synthesis, formulation and production procedures. The quality and purity of both cinnamon and placebo capsules were finally certified by the manufacturer.

Each capsule contained 500mg of either cinnamon powder or starch and packaged in non-transparent black bottles containing 56 capsules (4 capsules per day for 2 weeks) and prepared for distribution to the subjects. At the time of enrolment, patients were given 6 weeks supply of cinnamon or placebo (3 bottles or 3 x 56 capsules). When subjects completed the capsules after the first 6 weeks, they were given the 4^{th}, 5^{th} and 6^{th} bottles of capsules. Compliance was monitored by capsule count which was done at week 6 and week 12 and compliance was considered excellent when all capsules were consumed. During the study period, participants were asked to maintain a patient record card (Appendix 4.10) with details of the trial they are in, and they were requested to carry it at all times and record any effects they think could be related to their treatment. Figure 4.2 describes the overall RCT procedures followed the study.

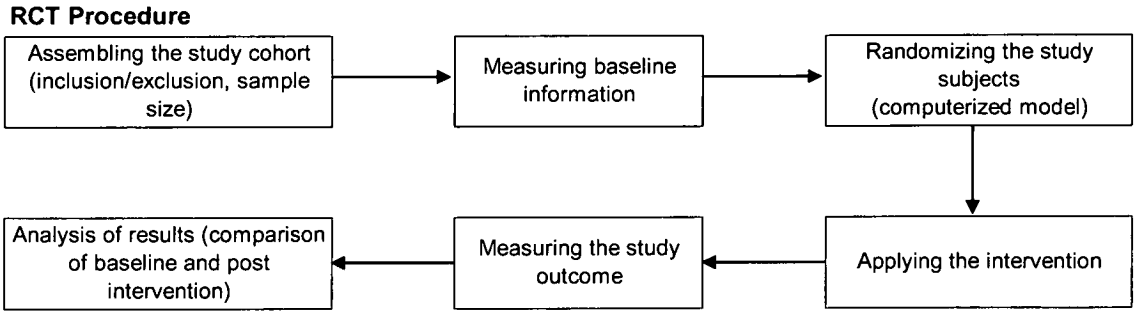


Figure 4.2 – The procedures of RCTs of cinnamon and type 2 diabetes mellitus

4.2.10 Data collection

4.2.10.1 General questionnaire

At the baseline (week 0), all participants were requested to complete a structured questionnaire (Appendix 4.11) reporting socio demographic characteristics (such as sex, age, ethnicity, religion, marital status, education and family income) and lifestyle characteristics (such as smoking habits, consumption of alcohol, physical activity and dietary habits). Participants also answered questions regarding time since diagnosis of diabetes, family history, type of treatment for diabetes, other diagnosed medical conditions (such as hypertension and dyslipidaemia) and related treatment options.

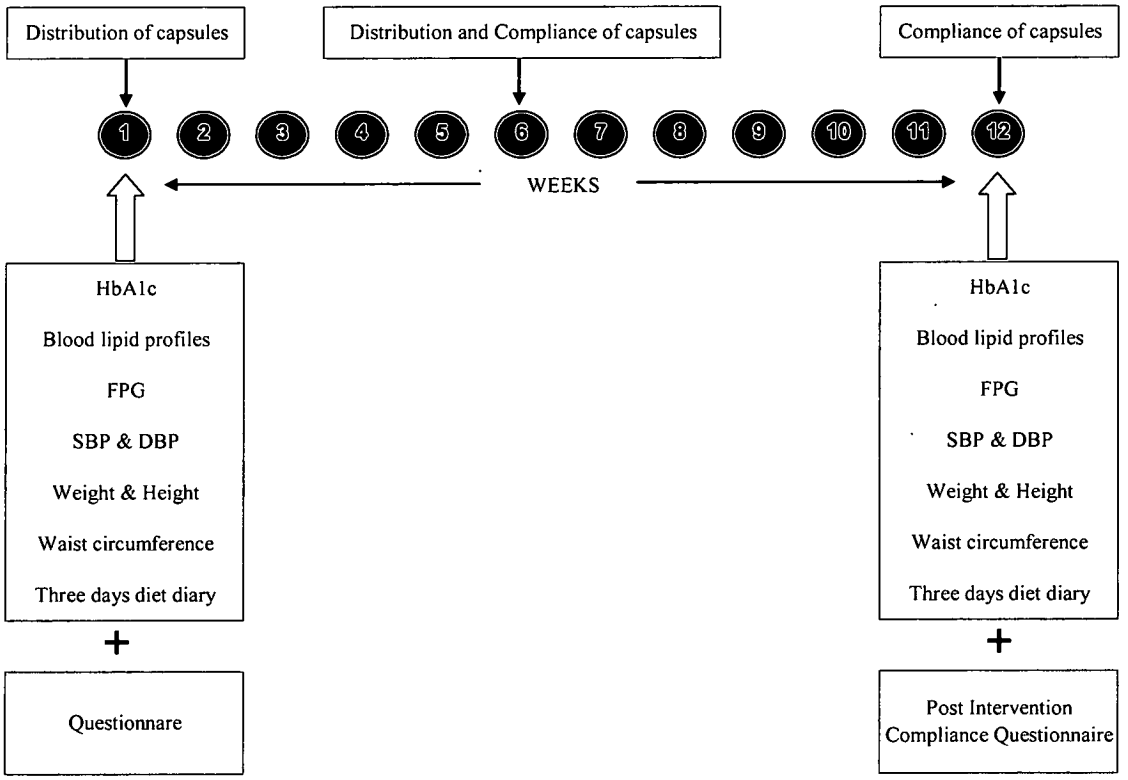


Figure 4.3 – Data collection and distribution of cinnamon capsules at baseline and after intervention during the 12 weeks intervention period

4.2.10.2 Anthropometrics

The detailed data collection procedures were shown in Figure 4.3. Anthropometrics of height, weight and waist circumference was measured at baseline (week 0) and after intervention (week 12). Anthropometrics measurements of this RCT includes,

1. Weight
2. Height

3. Waist circumference
4. Body mass index (BMI)

Height was measured while the subject stood erect and bare footed on a stadiometer with a movable headpiece. The headpiece was levelled with skull vault and height was recorded to the nearest 0.5cm. Weight was measured by using a calibrated electronic balanced beam scale (TANITA body composition analyser TBF-300) with light clothes and no shoes, and the weight was recorded to the nearest 100g (0.1kg). Waist circumference was measured at the level of the umbilicus to the nearest 0.5cm while the subject stood erect with relaxed abdominal muscles, arms at the side and feet together. This measurement was taken at the end of normal respiration. All measurements were taken with a flexible, non-stretchable tape in close contact with the skin. Same investigator measured the waist circumference.

The waist circumference is a common measure used to assess abdominal fat content. The presence of excess body fat in the abdomen, when out of proportion to total body fat, is considered an independent predictor of risk factors and ailments associated with obesity (NCEP ATP 111, 2001). Therefore men are at risk who has a waist circumference of greater than 102cm (40 inches). Women are at risk who has a waist circumference of greater than 88cm (35 inches) (NCEP ATP 111, 2001).

Body mass index (BMI) is a simple index of weight for height, which is commonly used to classify underweight, overweight and obesity in adults. BMI is defined as the weight in kilograms divides by the square of the height in meters (kg/m^2).

Table 4.1 shows the international classification of adult underweight, overweight and obesity according to BMI based on World Health Organisation (WHO) recommendations (WHO, 1995; WHO, 2004[abc]; WHO, 2000[a]). According to WHO guidelines, BMI values are age-independent and the same for both sexes. However, BMI may not correspond to the same degree of fatness in different populations due, in part, to different body proportions. The health risks associated with increasing BMI are continuous and the interpretation of BMI grading in relation to risk may differ for different populations.

Table 4.1 - International classification of adult obesity based on body mass index categories

Classification	BMI (kg/m^2)	
	Principal cut-off points	**Additional cut-off points**
Underweight	<18.50	< 18.50
Severe thinness	<16.00	< 16.00
Moderate thinness	16.00 – 16.99	16.00 – 16.99
Mild thinness	17.00 – 18.49	17.00 – 18.49
Normal range	18.50 – 24.99	18.50 – 22.99
		23.00 – 24.99
Overweight	≥ 25.00	≥ 25.00
Pre obese	25.00 – 29.99	25.00 – 27.49
		27.50 – 29.99
Obese	≥ 30.00	≥ 30.00
Obese class I	30.00 – 34.99	30.00 – 32.49
		32.50 – 34.99
Obese class II	35.00 – 39.99	35.00 – 37.49
		37.50 – 39.99
Obese class III	≥ 40.00	≥ 40.00

Source: The BMI categories are adapted from WHO, 2000[a] and WHO, 2004[abc] guidelines

4.2.10.3 Blood Pressure measurements

The systolic blood pressure (SBP) and diastolic blood pressure (DBP) was measured by the investigator at baseline (week 0) and after intervention (week 12). Blood pressure was measured three times on the left arm with the subject in a sitting position and was measured a second time, after 5 minutes of rest. The average of the last two measurements was used to characterize the blood pressure of the participants.

SBP and DBP were measured by stethoscope auscultation of the vascular wall motion sound using a sphygmomanometer (MDF 740 professional pulse/time stethoscope). The pressure cuff (Tycos TR-2 hand aneroid) was placed approximately in the middle of the left upper arm bicep. After putting the cuff in place, air was pumped into the entire system with the valve closed (the pressure was raised by inflating the cuff to 30 mmHg above the systolic blood pressure as estimated by palpation) and the stethoscope was placed gently over the artery at the point of maximal pulsation. Then the pressure was reduced at approximately 2-3 mmHg per second. The point at which repetitive, clear tapping sounds first appear for at least two consecutive beats

gave the systolic blood pressure. The point where the repetitive sounds finally disappeared gave the diastolic blood pressure.

Hypertension was defined based on a systolic blood pressure (SBP) of at least 140 mmHg or above, a diastolic blood pressure (DBP) of at least 90 mmHg or above or both (American Diabetes Association, 2004[ac]; Martha *et al,* 1993). The SBP is the maximum pressure in an artery at the moment when the heart is beating and pumping blood, DBP is the lowest pressure in an artery in the moments between beats when the heart is resting.

4.2.10.4 Blood glucose measurements

The HbA1c levels and fasting plasma glucose (FPG) concentration were measured as part of patient's regular diabetes checks (standard care) in community diabetes clinics attached to Brent NHS. The blood test results were obtained from NHS clinical records at baseline (week 0) and after 12 weeks.

4.2.10.5 Blood lipid parameters measurements

The fasting blood lipid measurements total cholesterol, triglycerides, HDL cholesterol (high density lipoprotein) and LDL cholesterol (low density lipoprotein) levels were measured as part of patients regular diabetes checks (standard care) in community diabetes clinics at Brent NHS. The blood test results were obtained from NHS clinical records at baseline (week 0) and after 12 weeks. According to the American Diabetes Association guidelines for dyslipidemia management (American Diabetes Association, 2004[ab]), the target LDL cholesterol levels for adults with diabetes are < 2.6 mmol/l, HDL cholesterol levels are > 1.02 mmol/l and triglycerides are < 1.7 mmol/l in both men and women.

The American Diabetes Association (2002[ab], 2004[abcd], 2005, 2006) and World Health Organization (1995, 1999[ab], 2004[abc], 2000[ab], 2005,) guidelines have been used to internationally define the cut off points of glycaemic indicators (HbA1c and FPG), serum lipid profiles (triglycerides, LDL, HDL and total cholesterols) and blood pressure (SBP and DBP) measurements in this thesis as both guidelines are similar and widely used in medical research.

4.2.10.6 Dietary Assessments

The subjects were requested to complete a 3 day diet diary (which included two weekdays and one weekend day) at baseline and after intervention (week 12), which was used to analyse total

energy intake including total carbohydrates (starch and sugars), proteins and fats (saturated fats, mono and poly unsaturated fats and trans fats). All patients were instructed clearly about how to maintain the three day diet diary (Appendix 4.12; Appendix 4.13). Individuals have been reported to eat 20% more on weekend days than week days (De-Castro, 1991) therefore participants were asked to include 2 week days and one weekend day in order to gain an accurate view of average intake. To enhance accuracy of the food records, all subjects received instructions during or before baseline testing on how to accurately estimate portion sizes and this advice was reinforced during each visit (week 6). Volunteers were given verbal and written instructions on completing food diaries and reminded of the importance of recording portion sizes and cooking methods. Volunteers were asked to keep packaging of foods consumed as much as possible, so that the exact nutritional information could be recorded. Subjects also instructed to bring their diet diaries (Appendix 4.13) every clinical visit. At week 0 and week 12, diet diaries were collected and the total energy intake was calculated by using diet plan 6 (Forestfield Software Diet plan 6 windows version) (Appendix 4.14). Food composition tables were also used to calculate the nutrient intake of some foods which were not included in the software. The means of dietary variables are reported as percentage of total energy intake (% TEI). Finally the total energy intake at baseline and after intervention was compared with the Diabetes UK recommendations (Diabetes UK, 2003; Diabetes UK, 2007). Compliance with the diet diary was monitored by individual discussions at each clinical visit.

4.2.11 Study outcomes

Primary outcome:

1. Changes in glycated haemoglobin (HbA1c) level of at least 0.5% reduction.

Secondary outcomes:

1. Changes in fasting plasma glucose concentration.
2. Changes in serum lipid profile measurements (including total serum cholesterol, LDL, HDL, and triglycerides).
3. Changes in systolic and diastolic blood pressures.

Additional outcomes:

1. Changes in body mass index, waist circumference and body weight.
2. Monitor the total intake of calories and macronutrients (carbohydrates, fats, proteins and fibres) to exclude dietary influences on primary and secondary study outcomes.

4.2.12 Statistical Analysis

All data were entered manually onto a data entry sheet (Appendix 4.15 – 4.17) and transferred to SPSS. The following techniques were used to describe the data and test the hypothesis.

4.2.12.1 Frequency distributions

Frequency distributions (histograms) were used to describe the distribution of values. There are two main ways in which a distribution can deviate from normal (Field, 2000),

1. lack of symmetry (called skewness)
2. pointyness (called kurtosis)

Therefore, in a normal distribution the values of skew and kurtosis are 0 (i.e. the distribution is neither too pointy, nor too flat, and is perfectly symmetrical). If a distribution has values of skew or kurtosis above or below 0 then this indicates a deviation from normal.

4.2.12.2 Testing whether a distribution is normal

Kolmogorov-Smirnov (K-S) tests were performed to compare the scores in the sample to a normally distributed set of scores with a same mean and standard deviation (Field, 2005). If the test is not significant ($P > 0.05$) it suggests that the distribution of the sample is not significantly different from a normal distribution (i.e. it is a normal distribution). If, however, the test is significant ($P < 0.05$) then the distribution is significantly different from normal distribution (i.e. it is a non normal distribution).

4.2.12.3 Testing differences between means

4.2.12.3.1 Parametric tests – Independent sample *T* test and Paired sample *T* test

This is the simplest form of statistical test that can be done with only one independent variable that is manipulated in only two ways with only one outcome is measured (Field, 2005). For example; in this study, the effect of cinnamon/placebo (independent variables) on the primary outcome of HbA1c levels (dependent variable) before and after the study was compared. Therefore, the *T* test was appropriate. There are, in fact, two different *T* tests and it depends on whether the independent variable was manipulated using the same participant or different participants (Field, 2005; Rosnow and Rosenthal, 2005; Wright, 2002; Howell, 2002).

- Independent sample *T* test – is used when there are two experimental conditions and different participants were assigned to each condition (for example, HbA1c measurements at baseline or after intervention in cinnamon and placebo group)
- Paired sample or dependent *T* test – is used when there are two experimental conditions and the same participants took part in both conditions of the experiment (for example, HbA1c measurements at baseline and after intervention in cinnamon or placebo group)

Both the independent and dependent *T* tests are parametric tests assume normal distribution of the data. Therefore the following assumptions were used when using this test,

1. Data were from normally distributed population
2. Data were measured at least at the interval level (baseline vs post intervention).
3. Variances in (independent T test) these populations were roughly equal (homogeneity of variance assumed)
4. Scores were independent (because they come from different people)

Based on K-S test results, parametric tests of an independent sample *T* test and paired sample *T* tests were performed to compare the difference in means between groups and within groups respectively (if samples were normally distributed). Levene's test was performed to test the assumption of homogeneity of variance. Therefore, if Levene's test is significant at $P < 0.05$, the null hypothesis is incorrect and that the variances are significantly different and therefore the assumption of homogeneity of variance has been violated. If Levene's test is non significant ($P > 0.05$), the null hypothesis is correct and the variances were not significantly different and assumption of homogeneity of variance can be assumed (Field, 2005; Wright, 2002).

For example, the K-S tests for the outcome of systolic blood pressure during baseline suggest a normal distribution ($P > 0.05$) (Figure 4.4). Furthermore, SPSS also produces a normal Q-Q plot for systolic blood pressure specified (Figure 4.4). The normal Q-Q chart plots the values expected if the distribution were normal (expected values) against the values actually seen in the data set (observed values). Therefore, if the data were normally distributed, then the observed values (the dots on the chart) should fall exactly along the straight line. Any deviation of the dots from the line represents a deviation from normality. Figure 4.4 demonstrate the normal distribution curve of baseline systolic blood pressure and Normal Q-Q plot. In contrast, Figure 4.5 revealed that the baseline HbA1c level of the samples was not normally distributed in both frequency table (curve distribution) and Q-Q plot.

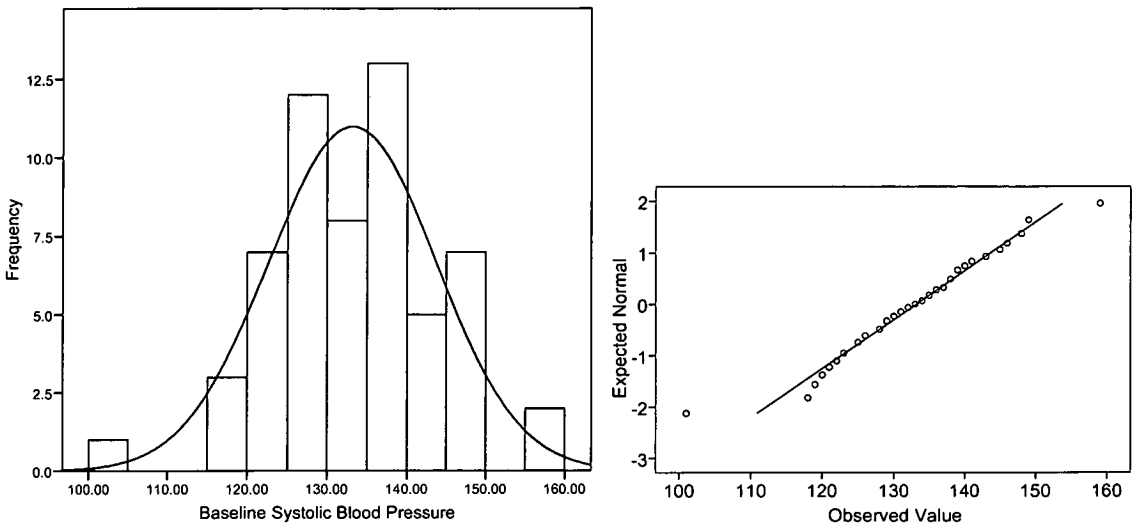


Figure 4.4 – The normal distribution curve and Q-Q plot of baseline systolic blood pressure (SBP)

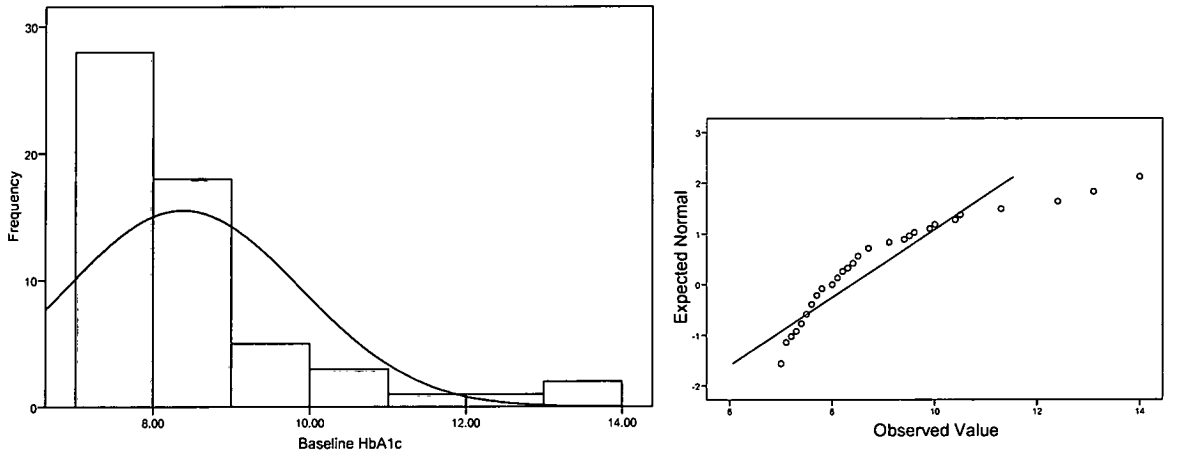


Figure 4.5 – The non-normal distribution curve and Q-Q plot of baseline HbA1c of the study population

4.2.12.3.2 Non parametric tests - Mann-Whitney test and Wilcoxon signed rank test

Non parametric tests were performed in this study if samples were not normally distributed (homogeneity of variance not assumed). The non parametric test of Wilcoxon's signed-rank test was carried out to calculate the difference in means at the baseline and after intervention (intra group) in both control and intervention groups. The Mann-Whitney test was used to compare means of two independent conditions between control and intervention groups (inter group) (Field, 2005; Wright, 2002). For example, the K-S tests for the primary outcome of HbA1c during baseline suggest a non normal distribution (Figure 4.5).

In our study the following variables are not normally distributed and a non parametric tests were performed to compare the means of plasma triglycerides, fasting plasma glucose concentration, diastolic blood pressure, body mass index, percentage of protein intake, percentage of carbohydrate intake, percentage of fat intake, percentage of sodium intake, percentage of fibre intake and total kcal of protein intake. All other variables were found to be normally distributed and parametric t tests were performed.

Non parametric tests are sometimes known as assumption free tests because they make fewer assumptions about the type of data on which they can be used (Field, 2000).The Mann-Whitney test compares two conditions when different participants take part in each condition and the resulting data are not normally distributed or violate an assumption of the independent *T* test (Field, 2000). In contrast, the Wilcoxon signed rank test compares two conditions when the same participants take part in each condition and the resulting data are not normally distributed or violate an assumption of the dependent *T* test (Field, 2000).

4.2.12.4 Confidence interval

Confidence interval is a different approach to assessing the accuracy of the sample mean as an estimate of the mean in the population is to calculate boundaries within which the true value of the mean will fall (Field, 2000). The basic idea behind confidence intervals is to construct a range of values with in which the population value probably falls.

4.2.12.5 Intent to treat (ITT) analysis

An "intent to treat" (ITT) analysis and last observation carried forward (LOCF) strategies were used in this study to avoid the effects of drop outs (Parkash *et al,* 2008; Hollis & Campbell, 1999). A method to correct for differential dropout rates between patients from one arm of the study and another is to analyse data by intent to treat – that is, data is analysed in the way patients were randomized, regardless of whether or not they received the intended intervention (Harald *et al,* 2004). The intent to treat correction is a form of protection against bias and strengthens the conclusions of a study (Jadad, 1998; Fisher *et al,* 1990).

4.2.12.6 Last observation carried forward (LOCF) method

The LOCF method was used in this study for the final analysis. The LOCF is probably the most widely used technique in drug trials and has gained the seal of approval from the food and drug administration (Norman and Streiner, 2003). There are various analytical strategies for

addressing missing data in clinical trials which are utilized in reporting study results and one of the most commonly used analytical method is LOCF (Parkash *et al,* 2008). When a person drops put of a study, the last recorded value is carried forward to full fill in the blanks (Norman and Streiner, 2003). The logic is that this is conservative, operating against the hypothesis that people will get better over time. The LOCF approach further assumes that subjects responses would have been constant from the last observed value, to the end point of the trial (Lane, 2008).

4.2.12.7 Analysis of covariance (ANCOVA)

ANCOVA was used to measure covariates. Covariates are used to control for the influence they have on the dependant variable by including them in a regression model. Therefore it can be seen what effect an independent variable (cinnamon/placebo) has after the effect of the covariates (for example age, BMI, body weight). As such we control for the covariate. The *b* value in ANCOVA analysis represents the positive and negative relationships of the effect of covariates. The main reason for including covariates in ANOVA is, to reduce with in group error variance and elimination of confounding variables (there may be unmeasured variables that confound the results of the study). Simple linear regression and correlation coefficient (r) analysis was also used to measure difference between two variables (Field, 2005).

4.2.12.8 Descriptive statistics

Descriptive statistics were used to analyse mean, median, standard deviation and range. The data from questionnaires were coded by using pre developed categories. The data was then entered in to SPSS for tabulations of results. Descriptive and Frequency tables for socio demographic and lifestyle characteristics of the participants were analysed accordingly.

4.3 Results

4.3.1 The general socio demographic and lifestyle characteristics of the study population

4.3.1.1 Socio demographic characteristics of the participants

The socio demographic characteristics of participant's are presented in Table 4.2. In our study 45% were men and 55% were women. The random allocation of males and females in both cinnamon and placebo groups were found to be similar. The mean age of the diabetic patients in this study was 54.9 $\pm$ 11.1 with a range of 33 – 78 years. With regards to ethnic composition it was very heterogeneous. The majority of patients were Asian British (57%, n=33), which includes British Indians (n=19), British Pakistanis (n=9) and other Asian British (n=5). The second largest group was Black British (26%, n=15), which included Black British African (n=2), Black British Caribbean (n=14) and other Black British (n=1). Seventeen percent (n=10) of the patients were White British or Irish or other Whites (British Whites, n=5; Irish, n=1 and other Whites, n=4).

The educational status of the participants revealed that most patients had not achieved a higher educational qualification. Approximately 52% completed elementary or secondary education, while others completed college (23%, n=13) and University (25%, n=14) qualifications. Majority of the patients are Christians (44%, n=25), while others are Hindus (30%), Muslims (23%) and Sikhs (3%). The data split by marital status show that, 69% (n=40) were married, 14% (n=8) were single, 9% (n=5) were divorced, 5% (n=3) were widowed and 3% (n=2) were living together as couples. Finally the household annual family income (after tax) of the participants suggested that majority of the patients (57%, n=30) earned less than £20,000 per annum as family income. Further the socio demographic characteristics were found to be similar in both cinnamon and placebo groups (Table 4.2).

Table 4.2 - Socio-demographic characteristics of the participants in cinnamon and placebo groups [N=58]

Socio-demographic Characteristics	Cinnamon (n=30)	Placebo (n=28)	N (%)
Age (yrs) †	54.90 ± 10.14	54.43 ± 12.53	
Sex †			
Males	11 (37%)	15 (54%)	26 (45%)
Females	19 (63%)	13 (46%)	32 (55%)
Ethnicity †			
White (British/Irish/Others)	6 (20%)	4 (14%)	10 (17%)
Asian British (Indians/Pakistani/Bangladeshi/Others)	17 (57%)	16 (57%)	33 (57%)
Black British (African/Caribbean/others)	7 (23%)	8 (29%)	15 (26%)
Religion* †			
Christian	13 (43%)	12 (44%)	25 (44%)
Hindu	12 (40%)	5 (19%)	17 (30%)
Muslim	4 (13%)	9 (33%)	13 (23%)
Sikh	1 (3%)	1 (4%)	2 (3%)
Educational status* †			
Elementary	3 (10%)	3 (11%)	6 (10%)
Secondary	15 (52%)	9 (32%)	24 (42%)
College	5 (17%)	8 (29%)	13 (23%)
University	6 (21%)	8 (29%)	14 (25%)
Annual family income †			
< £ 10,000	7 (23%)	5 (18%)	12 (21%)
£ 10,000 - £ 14,999	6 (20%)	5 (18%)	11 (19%)
£ 15,000 - £ 19,999	3 (10%)	7 (25%)	10 (17%)
£ 20,000 - £ 29,999	5 (17%)	7 (25%)	12 (20%)
£ 30,000 - £ 39,999	2 (7%)	3 (11%)	5 (9%)
≥ £ 40,000	7 (23%)	1 (4%)	8 (14%)
	30 (100%)	28 (100%)	58 (100%)

Data presented as n (%); N – total number of participants; n – number of participants in cinnamon or placebo group;
* answered question n=57; † P > 0.05 shows that there is no significant differences in sex, ethnicity, religion, educational status and family income of the participants at baseline between the cinnamon and placebo groups.

4.3.1.2 Lifestyle characteristics of the participants

The lifestyle characteristics of the participants including smoking habits, alcohol consumption, physical activity and dietary habits are shown in Table 4.3. When patients were asked about their habits of alcohol consumption, forty percent (n=23) reported that they currently consumed alcohol. Majority of the participants drank alcohol occasionally or during special events (74%, n=17) and consumed less than one standard drink (35%, n=8). Others drank less than once a week (9%, n=2), 1 to 2 days per week (9%, n=2), 3 to 4 days per week (4%, n=1) and daily (4%, n=1). The smoking habits of the participants showed that most patients had never smoked (91%, n=52). Further 6% (n=3) of the participants smoke daily while others used to smoke (3%, n=2).

The physical activity behaviour of the participant's demonstrated that the patients did not undertake regular physical activities. Fifty two percent (n=29) of the participants reported that they did not walk much, and 43% (n=24) reported that they walked quite a lot. Further, the intensity of physical activity reported by participants was only moderate (31%, n=18) or light (37%, n=21). The majority of patients reported that compared with last year they were doing the same level of exercise this year (42%, n=22) (Table 4.3). When patients were asked about their current type of diet, most ate a mixed diet with meat (75%, n=43), vegetarians eating dairy (16%), vegetarians eating fish and dairy (4%) and vegans (5%). Furthermore, a majority of the patients reported consuming a good portion size of fruits and vegetables every day; one to two portions (44%) and three to five portions (40%). Furthermore, the different lifestyle characteristics of the participants were found to be similar in both cinnamon and placebo groups (Table 4.3).

Table 4.3 - Lifestyle characteristics of the participants in cinnamon and placebo groups [N=58]

Lifestyle Characteristics	Cinnamon (n=30)	Placebo (n=28)	N (%)
Alcohol consumption* †			
Yes	13 (45%)	10 (36%)	23 (40%)
No	16 (55%)	18 (64%)	34 (60%)
Habits of smoking* †			
Never smoked	26 (90%)	26 (93%)	52 (91%)
I used to smoke	2 (7%)	0 (0%)	2 (3%)
I smoke daily	1 (3%)	2 (7%)	3 (6%)
Type of activity normally engaged in β †			
I am usually sitting and do not walk about much	15 (54%)	14 (50%)	29 (52%)
I stand and walk about quite a lot	12 (43%)	12 (43%)	24 (43%)
I usually lift or carry light loads or have to climb stairs or hills often	1 (4%)	1 (4%)	2 (3%)
I do heavy works or carry heavy loads often	0 (0%)	1(4%)	1 (2%)
Compared with last year; activity this year* †			
More physical activity	8 (28%)	8 (29%)	16 (28%)
About the same	14 (48%)	10 (36%)	24 (42%)
Less physical activity	7 (24%)	10 (36%)	17 (30%)
Level of exercise* †			
Hardly any	6 (21%)	10 (36%)	16 (28%)
Light	13 (45%)	8 (29%)	21 (37%)
Moderate	10 (34%)	8 (29%)	18 (31%)
Heavy	0 (0%)	2 (7%)	2 (4%)
Type of diet* †			
Vegan	1 (3%)	2 (7%)	3 (5%)
Vegetarian/dairy	6 (21%)	3 (11%)	9 (16%)
Vegetarian/eat fish and dairy	1(3%)	1(4%)	2 (4%)
Mixed diet	21(72%)	22 (79%)	43 (75%)
Intake of fruits and vegetables* †			
None	2 (7%)	2 (7%)	4 (7%)
one - two portions	13 (45%)	12 (43%)	25 (44%)
Three - five portions	10 (34%)	13 (46%)	23 (40%)
More than five portions	4 (14%)	1 (4%)	5 (7%)
	29 (100%)	28 (100%)	57 (100%)

Data presented as n (%); N – total number of participants; n – number of participants in cinnamon or placebo group; * answered question n=57; β answered question n=56; † P > 0.05 shows that there is no significant differences in consumption of alcohol, smoking habits, type of physical activity and dietary intake of fruits and vegetables of the participants between the cinnamon and placebo groups at baseline.

4.3.1.3 Family history, treatment and other diagnosed medical conditions

The family history, other diagnosed medical conditions (other than diabetes) and related treatments are presented in Table 4.4. All diabetic patients were treated with either metformin or sulphonylureas or both. Seventy six percent (n=44) of those were treated only with metformin, 12% (n=7) were treated with only sulphonylureas and 12% (n=7) were treated with both metformin and sulphonylureas. Reported diagnosed medical conditions of hypertension and dyslipidaemia at baseline was 29% (n=17) and 15% (n=9) respectively. A total of 24% (n=14) of the subjects had both medical conditions while 31% (n=18) had neither condition. Of the subjects 22% (n=13), 21% (n=12) and 12% (n=7) were taking anti-hypertensive drugs, statins and both anti-hypertensives and statins for their medical condition respectively. The majority of the patients 45% (n=26) were only taking anti diabetic drugs and not anti-hypertensives or statins (Table 4.4).

Figure 4.6 shows that about 72% (n=41) of the respondents have a family history of diabetes; while 53%, 12% and 37% of them had a family history of hypertension, dyslipidaemia and obesity respectively. Further, most patients (40%, n=23) had a family history of two diagnosed medical conditions of hypertension or dyslipidaemia or diabetes (Table 4.4).

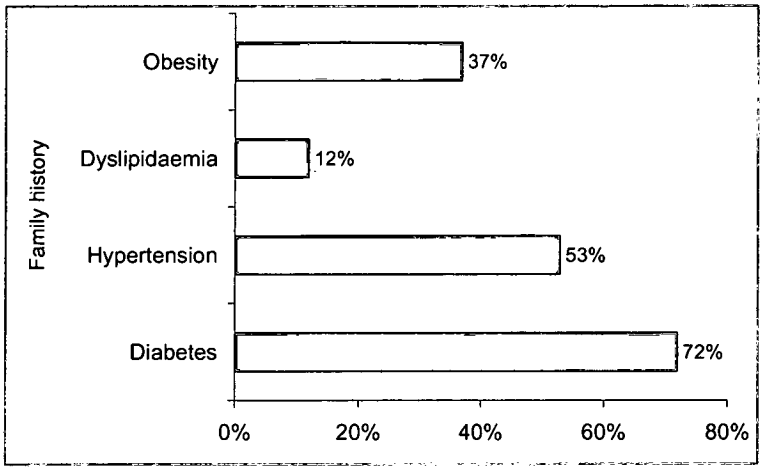


Figure 4.6 – The reported family history of diabetes, hypertension, dyslipidaemia and obesity of the study participants [n=58]. Percentage calculated base on the total sample of N=58.

Table 4.4 - Family history and other diagnosed medical conditions of the study participants [N=58]

Family history/medical conditions	Cinnamon (n=30)	Placebo (n=28)	N (%)
Diagnosed medical conditions of hypertension or dyslipidaemia*			
Hypertension	6 (20%)	11 (39%)	17 (29.3%)
Dyslipidaemia	7 (23%)	2 (7%)	9 (15.5%)
Both hypertension & dyslipidaemia	7 (23%)	7 (25%)	14 (24.1%)
None	10 (33%)	8 (29%)	18 (31.1%)
Type of medication/drugs*			
Antihypertensives only	4 (13%)	9 (32%)	13 (22.4%)
Statins only	8 (27%)	4 (14%)	12 (20.7%)
Both antihypertensives & Statins	5 (17%)	2 (7%)	7 (12.1%)
None	13 (43%)	13 (46%)	26 (44.8%)
Type of anti-diabetic medication/drugs*			
Metformin	24 (80%)	20 (71%)	44 (75.8%)
Sulphonylureas	2 (7%)	5 (18%)	7 (12.1%)
Metformin + Sulphonylureas	4 (13%)	3 (11%)	7 (12.1%)
Family history of diabetes or hypertension or dyslipidaemia*			
No family history	4 (13%)	4 (14%)	8 (14%)
Family history of one medical condition	6 (20%)	10 (36%)	16 (28%)
Family history of two medical conditions	13 (43%)	10 (36%)	23 (40%)
Family history of all three medical conditions	7 (23%)	4 (14%)	11 (18%)
	30 (100%)	28 (100%)	58 (100%)

Data presented as n (%); N – total number of participants; n – number of participants in cinnamon or placebo group; * P > 0.05 shows that there is no significant differences in the type of medications of antihypertensives, statins, metformin and sulphonylureas and other diagnosed medical conditions of hypertension and dyslipidaemia between the cinnamon and placebo groups at baseline.

4.3.1.4 Baseline characteristics of the study population

The baseline characteristics of the study population including blood biochemical analysis, anthropometrics and calorie intake are presented in Table 4.5. There were no significant differences in age, anthropometrics (BMI, waist circumference and body weight), blood glucose (HbA1c% and FPG), systolic and diastolic blood pressures, total energy intake and blood lipid profiles (HDL, LDL, triglycerides and total cholesterol) between the cinnamon and placebo groups at baseline. (For more detail see sections 4.3.2 to 4.3.6).

Table 4.5 – The baseline characteristics of anthropometrics and bio chemical measurements of the study participants [N=58]

Baseline Characteristics	Cinnamon (n=30)	Placebo (n=28)	P
Age (yrs)	54.90 ± 10.14	54.43 ± 12.53	0.877
Body weight (kg)	87.60 ± 17.51	87.53 ± 20.24	0.989
BMI (kgm^{-2})	33.36 ± 4.20	32.13 ± 8.31	0.150
Waist circumference (cm)	106.3 ± 11.8	105.0 ± 13.4	0.704
HbA1c (%)	8.22 ± 1.16	8.55 ± 1.82	0.809
FPG (mmol/L)	8.82 ± 3.45	8.77 ± 2.59	0.641
HDL Cholesterol (mmol/L)	1.18 ± 0.29	1.16 ± 0.19	0.764
LDL Cholesterol (mmol/L)	2.47 ± 0.96	2.27 ± 0.75	0.284
Triglycerides (mmol/L)	1.65 ± 0.93	1.48 ± 1.04	0.427
Total Cholesterol (mmol/L)	4.31 ± 1.07	4.10 ± 0.87	0.420
SBP (mmHg)	132.57 ± 8.66	134.50 ± 10.92	0.654
DBP (mmHg)	85.17 ± 6.45	86.78 ± 8.82	0.473
Total energy intake (kcal/day)	1862 ± 270	1844 ± 228	0.776

Data presented as mean ± SD; n – number of participants in cinnamon or placebo group ; FPG – fasting plasma glucose; HDL – high density lipoprotein; LDL – low density lipoprotein, SBP – systolic blood pressure; DBP – diastolic blood pressure; BMI – body mass index; P > 0.05 values shows that there is no significant differences in anthropometrics (body weight, BMI and waist circumference) and biochemical measurements (HbAic, FPG, SBP, DBP, triglycerides, HDL, LDL and total cholesterols) between the cinnamon and placebo groups at baseline.

4.3.1.5 Tolerability and compliance of cinnamon capsules

The tolerability and compliance of cinnamon and placebo capsules are presented in Table 4.6. The tolerability of the capsules was considered as excellent if the score was > 80%. Approximately 67% (n=39) and 29% (n=17) of respondents reported that the tolerability of capsules was excellent and good respectively. The number of capsules remaining after the 12 weeks of intervention period was calculated and found to be similar in both cinnamon and placebo groups, this further strengthened the tolerability of capsules. The time since diagnosis of diabetes among the patients also found to be similar in both groups of approximately 6 years (p=0.946).

Table 4.6 – The tolerability and compliance issues associated with cinnamon and placebo capsules during the intervention period [N=58].

Tolerability and compliance	Cinnamon (n=30)	Placebo (n=28)	P
Time since diagnosis of type 2 diabetes (years)	5.76 ± 4.93	5.84 ± 4.23	0.946
Number of capsules remaining (capsule count after 12 weeks)	1.50 ± 1.52	1.75 ± 2.03	0.596
Tolerability scores *			
Excellent (>80%)	21 (70%)	18 (64%)	39 (67%)‡
Good (65% - 80%)	8 (27%)	9 (32%)	17 (29%)‡
Acceptable (50% - 65%)	1 (3%)	1 (4%)	2 (4%)‡
	30 (100%)	28 (100%)	58 (100%)

Data presented as n (%) and mean ± SD; n – number of participants in cinnamon or placebo group; ‡ data of total sample N (%); P > 0.05 values shows there is no significant differences in time since diagnosis of type 2 diabetes mellitus and number of remaining capsules after intervention between the cinnamon and placebo group. * The tolerability scores (excellent or good or acceptable) were calculated from post intervention questionnaire at the end of intervention.

4.3.2 Anthropometric indicators of BMI, waist circumference and body weight of the study population

The prevalence of obesity based on BMI categories of the study participants at baseline (before the intake of cinnamon or placebo capsules) are presented in Figure 4.7. According to the WHO guidelines for the management of body mass index (WHO, 2000[a]; WHO, 2004[abc]), at baseline 69% (n=40) of the respondents were obese, among them 50% (n=20) were obese class I category, 40% (n=16) were obese class II and 10% (n=4) were obese class III category. Only 3% (n=2) of the subjects were found to be of normal body weight, while 28% (n=16) of the respondents are pre-obese or overweight with a BMI of 25 – 29.99 (Figure 4.7). A total of forty patients (69%) showed reduction in BMI after 12 weeks of intervention, among them 27 from cinnamon and 13 from placebo groups.

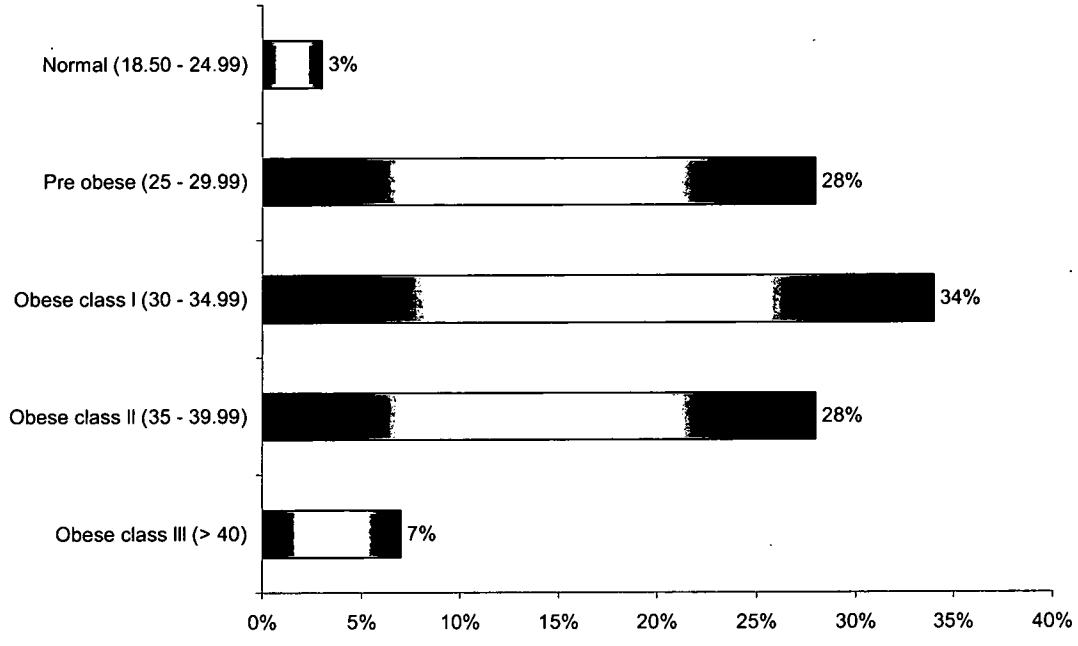


Figure 4.7 – The prevalence of obesity based on BMI categories of the study participants; Data presented as % based on the total sample of N=58.

The prevalence of central obesity based on waist circumference categories of both male and female participants at the beginning of the study are presented in Figure 4.8. According to the National Cholesterol Education Program (NCEP, 2001) guidelines for the management of waist circumference, at the beginning of the study (baseline) 91% (n=29) of the female participants had waist circumference of 88cm or more and 81% (n=21) of the male participants had waist circumference of 102 cm or more, and defined as centrally obese. Only 9% (n=3) of females and

19% (n=5) of males had desirable waist circumference at the start of study (Figure 4.8). A total of forty patients showed reduction in waist circumference during the study period, among them 26 from cinnamon and 14 from placebo groups. The frequency of achieving waist circumference below the upper normal limit (for males $\leq$ 102 cm; females $\leq$ 88 cm) after 12 weeks of intervention was evaluated. There was one male patient and two female patients in the cinnamon group who achieved desirable waist circumference. Furthermore, 5 males and 3 females achieved required waist circumference in the placebo group.

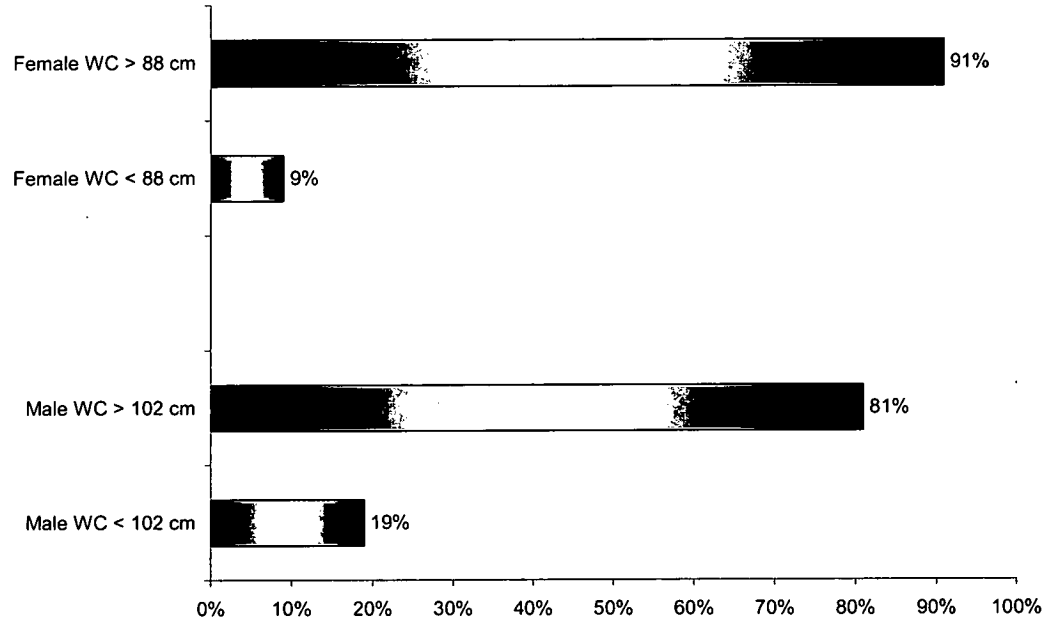


Figure 4.8 – The prevalence of central obesity based on waist circumference categories of both male (n=26) and female (n=32) participants at the beginning of the study; Data presented as %, [N=58].

4.3.2.1 Effect of cinnamon on body mass index (BMI) of the participants

The mean±SD, confidence interval and range of BMI of the participants are presented in Table 4.7. Similarly the effects of cinnamon or placebo on BMI at baseline and post intervention are presented in Table 4.8 and Figure 4.9.

The mean body mass index (BMI) of the diabetic individuals of the cinnamon and placebo groups at baseline were found to be similar (33.36 kgm^{-2} and 32.13 kgm^{-2} respectively; P=0.150) and ranged from 20.54 – 64.78 kgm^{-2} (Table 4.7, Table 4.8). The mean BMI in both cinnamon and placebo groups had dropped to 32.30 kgm^{-2} and 31.94 kgm^{-2} respectively after 12 weeks of intervention. Patients treated with cinnamon showed a significant drop of 3.2% (from 33.36 kgm^{-2} to 32.30 kgm^{-2}; P<0.001) of BMI compared with baseline. Patients treated with placebo

also showed 0.6% drop in their BMI (from 32.13 kgm^{-2} to 31.94 kgm^{-2}; P=0.478). Based on intend to treat analysis, the mean post intervention BMI among patients in the cinnamon group was not significantly different from that in the placebo group (32.30 vs 31.94, P=0.418). The mean change (Δ) in BMI was also not statistically significant between cinnamon and placebo groups (cinnamon Δ BMI -1.06, placebo Δ BMI -0.19; P=0.478). (Table 4.8 and Figure 4.9).

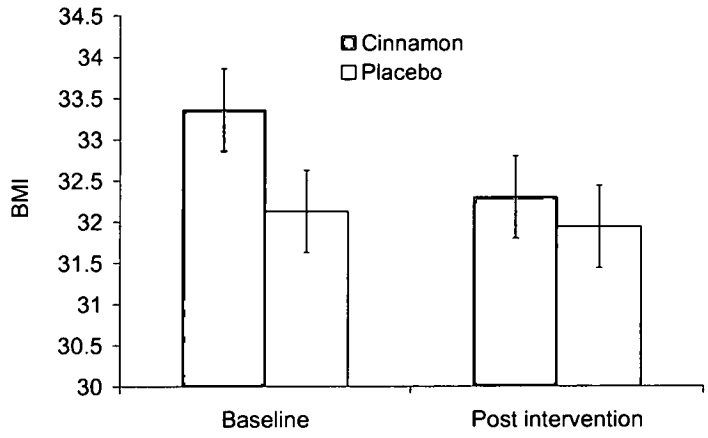


Figure 4.9 – The changes in BMI between cinnamon (n=30, shaded bars) and placebo (n=28, white bars) groups at baseline and post intervention. Data presented as changes in mean BMI. Patients treated with cinnamon showed a significant reduction (P<0.05) in BMI at post intervention compared to baseline [N=58].

To demonstrate the potential effect of diet or total energy intake as a covariate (other variable) on changes in BMI, the hypothesis that the changes in BMI in the cinnamon group did not relate to the changes in total energy intake by using ANCOVA with total energy intake as covariates was tested (for more details about dietary intervention - see section 5.3.6). The P value for total energy intake (P=0.338), indicate that there was no possible influence of the change in total energy intake on BMI. The *b* values from the ANCOVA for the covariates of total energy intake (*b*=0.001) revealed that, when all other variables being controlled or equal and if changes in total energy intake increases by one unit, then the changes in BMI should increase by 0.001 units, which is nearly no change.

4.3.2.2 Effect of cinnamon on waist circumference of the participants

The mean±SD, confidence interval and range of waist circumference of the participants are presented in Table 4.7. Similarly the effects of cinnamon or placebo on waist circumference at baseline and post intervention are presented in Table 4.8 and Figure 4.10.

At baseline, the mean waist circumference (WC) of the diabetic individuals of the cinnamon and placebo groups was 106.36 cm and 105.09 cm respectively (P=0.704) and ranging from 79 – 134 cm (Table 4.7, Table 4.8). After 12 weeks of intervention, the mean WC in both cinnamon

and placebo groups had dropped to 103.94 cm and 104.48 cm respectively. Patients treated with cinnamon showed a significant drop of 2.3% (from 106.36 cm to 103.94 cm; P < 0.001) of WC compared with baseline. Patients treated with placebo also showed 0.6% drop in their WC (from 105.09 cm to 104.48 cm). Based on intend to treat analysis, the mean post intervention waist circumference among patients in the cinnamon group was not significantly different from that in the placebo group (103.94 vs 104.48, P=0.860). The mean change in waist circumference was also not statistically significant between cinnamon and placebo groups (cinnamon Δ WC -2.42, placebo Δ WC -0.61; P=0.354) (Table 4.8 and Figure 4.10).

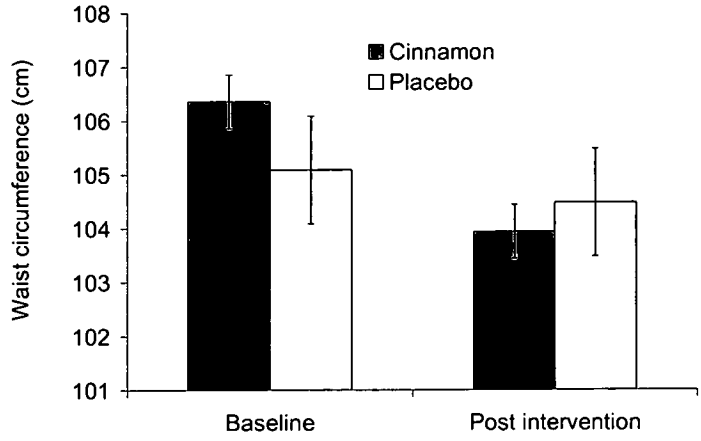


Figure 4.10 – The changes in waist circumference between cinnamon (n=30, shaded bars) and placebo (n=28, white bars) groups at baseline and post intervention. Data presented as changes in mean waist circumference. Patients treated with cinnamon showed a significant reduction (P<0.05) in waist circumference at post intervention compared to baseline.

The test of ANCOVA demonstrates that there were no possible influence of the change in total energy intake on the improvement of waist circumference (b=0.003, P=0.106) when all other variables are controlled.

4.3.2.3 Effect of cinnamon on body weight of the participants

The mean±SD, confidence interval and range of body weight of the participants are given in Table 4.7. Similarly the effects of cinnamon or placebo on body weight at baseline and post intervention are presented in Table 4.8 and Figure 4.11.

At baseline, the mean body weight of the diabetic individuals of the cinnamon and placebo groups were 87.6 kg and 87.5 kg respectively (P=0.989) and ranging from 56 – 148.1 kg (Table 4.7, Table 4.8). After the 12 weeks intervention of cinnamon and placebo, the mean body weight in both cinnamon and placebo groups had dropped to 87.7 kg and 87.02 kg respectively. Patients treated with cinnamon showed a significant drop of 3.3% (from 87.6 kg to 84.7 kg; P<0.001) in

weight compared with baseline. Patients in the placebo group also showed a 0.6% drop in their body weight, however this reduction was not significant compared with baseline (from 87.52 kg to 87.02 kg; P=0.183). Based on intend to treat analysis, the mean post intervention body weight among patients in the cinnamon group was not significantly different from that in the placebo group (84.70 vs 87.02, P=0.618). The mean change in body weight was also not statistically significant between cinnamon and placebo groups (cinnamon Δ weight -2.9, placebo Δ weight -0.5; P=0.183). (Table 4.8 and Figure 4.11)

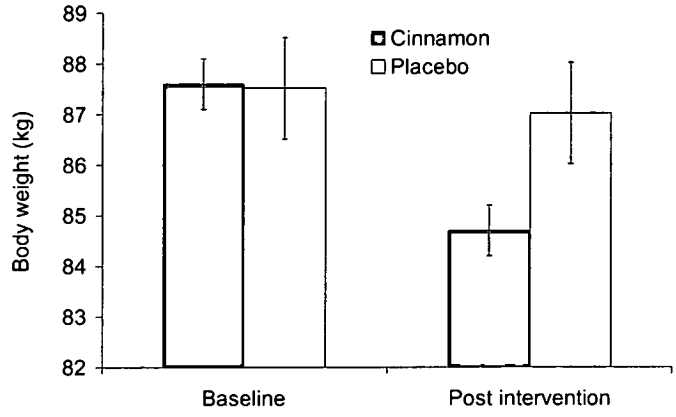


Figure 4.11 – The changes in body weight between cinnamon (n=30, shaded bars) and placebo (n=28, white bars) groups at baseline and post intervention. Data presented as changes in mean body weight. Patients treated with cinnamon showed a significant reduction (P<0.05) in body weight at post intervention compared to baseline.

Similar to changes in BMI, a total of forty patients (69%) showed reduction in body weight after 12 weeks of intervention, among them 27 from cinnamon and 13 from placebo groups.

To demonstrate the potential effect of diet or total energy intake as a covariate on changes in body weight, the hypothesis that the changes in body weight in the cinnamon group did not relate to the changes in total energy intake by using ANCOVA with total energy intake as covariates was tested (for more details about dietary intervention - see section 5.3.6). The P value for total energy intake (P=0.186), indicate that there was no possible influence of the change in total energy intake on the improvement of body weight. The *b* values from the ANCOVA for the covariates of total energy intake (*b*=0.002) revealed that, when all other variables being controlled or equal and if changes in total energy intake increases by one unit, then the changes in body weight should increase by 0.002 units or nearly no change.

Table 4.7 – The mean, confidence interval (CI) and range of anthropometric measurements at baseline and post intervention in cinnamon and placebo groups [N=58].

Anthropometrics		Treatment	n	mean ± SD	95% CI for mean	minimum	maximum
BW (kg)	Baseline	Cinnamon	30	87.6 ± 17.5	81.1 - 94.1	62.6	128.2
		Placebo	28	87.5 ± 20.2	79.7 - 95.3	56.0	148.1
		Total	58	87.6 ± 18.7	82.6 - 92.4	56.0	148.1
	12 weeks	Cinnamon	30	84.7 ± 16.4	78.5 - 90.8	59.8	125.5
		Placebo	28	87.0 ± 18.8	79.7 - 94.3	56.3	141.0
		Total	58	85.8 ± 17.5	81.2 - 90.4	56.3	141.0
WC (cm)	Baseline	Cinnamon	30	106.3 ± 11.8	101.9 - 110.8	83.0	134.0
		Placebo	28	105.0 ± 13.4	99.8 - 110.2	79.0	128.0
		Total	58	105.7 ± 12.5	102.4 - 109.0	79.0	134.0
	12 weeks	Cinnamon	30	103.9 ± 10.8	99.9 - 107.9	86.0	129.6
		Placebo	28	104.4 ± 12.8	99.5 - 109.4	78.5	129.0
		Total	58	104.2 ± 11.7	101.1 - 107.2	78.5	129.6
BMI	Baseline	Cinnamon	30	33.36 ± 4.19	31.79 - 34.92	25.50	44.30
		Placebo	28	32.13 ± 8.30	28.90 - 35.35	20.54	64.78
		Total	58	32.76 ± 6.48	31.06 - 34.47	20.54	64.78
	12 weeks	Cinnamon	30	32.30 ± 3.87	30.86 - 33.75	24.98	41.68
		Placebo	28	31.94 ± 7.76	28.93 - 34.95	20.65	61.67
		Total	58	32.13 ± 6.01	30.55 - 33.71	20.65	61.67

Data presented as mean ± SD, 95% confidence interval and range (minimum – maximum). n=number of participants. BW-body weight, WC-waist circumference, BMI-body mass index.

Table 4.8 - Effect of cinnamon on body weight, waist circumference and BMI at baseline and post intervention [N=58].

Anthropometrics	Cinnamon (n=30)	Placebo (n=28)	*P* value	*T*
Body weight (kg)				
Baseline	87.60 ± 17.51	87.52 ± 20.24	0.989	0.014
Post-intervention	84.70 ± 16.43	87.02 ± 18.88	0.618	-0.502
Difference	- 2.90 ± 2.33 †	- 0.50 ± 1.92		
Waist circumference (cm)				
Baseline	106.36 ± 11.89	105.09 ± 13.40	0.704	0.381
Post-intervention	103.94 ± 10.80	104.48 ± 12.85	0.860	-0.177
Difference	- 2.42 ± 2.01 †	- 0.61 ± 3.40		
BMI (kgm^{-2})				
Baseline	33.36 ± 4.20	32.13 ± 8.30	0.150	* -1.439
Post-intervention	32.30 ± 3.87	31.94 ± 7.76	0.418	* -0.809
Difference	- 1.06 ± 0.80 †	- 0.19 ± 0.75		

Data presented as mean ± SD; * *z* values of data; † P < 0.001 shows that body weight, BMI and waist circumference were significantly reduced at post intervention compared to baseline in the cinnamon group. The differences in BW, BMI and WC (baseline vs post intervention) between the cinnamon and placebo groups are not significant (P>0.05).

4.3.3 Glycaemic indicators of HbA1c and fasting plasma glucose of the study population

The glycaemic indicators HbA1c and fasting plasma glucose (FPG) of the participants at the beginning of the study are presented in Table 4.9. Patients included in this study had HbA1c ≥ 7% (poor glycaemic control) at baseline. Sixty five percent (n=38) of the subjects had HbA1c between 7% - 8.5%, 21% (n=12) had an HbA1c between 8.5% - 10% and only 14% (n=8) of the respondents had an elevated HbA1c of ≥ 10% at the baseline. The baseline HbA1c was ranging from 7% - 14%. However, there were no significant differences between HbA1c categories at baseline in both cinnamon and placebo groups (Table 4.9).

Table 4.9 – Glycaemic indicators of HbA1c and FPG of the study participants at baseline [N=58].

Blood Glucose	Cinnamon n (%)	Placebo n (%)	N (%)
HbA1c: 7% - 8.5%†	21 (70%)	17 (61%)	38 (65%)
HbA1c: 8.5% - 10%†	6 (20%)	6 (21%)	12 (21%)
HbA1c: ≥ 10%†	3 (10%)	5 (18%)	8 (14%)
	30 (100%)	28 (100%)	58 (100%)
FPG: ≤ 7.2 mmol/l†	10 (33%)	8 (29%)	18 (31%)
FPG: 7.2 - 9.99 mmol/l†	14 (47%)	11 (39%)	25 (43%)
FPG: 10 - 13.99 mmol/l†	3 (10%)	8 (29%)	11 (19%)
FPG: > 14 mmol/l†	3 (10%)	1 (4%)	4 (7%)
	30 (100%)	28 (100%)	58 (100%)

Data presented as n (%); N – total number of participants; n – number of participants in cinnamon or placebo group; † P > 0.05 shows that there is no significant differences in HbA1c and FPG between the cinnamon and placebo group at baseline. ADA (2004[ad]) recommends for adults with diabetes should maintain HbA1c < 7% and FPG 5.0 - 7.2 mmol/l.

Similarly, according to the ADA guidelines (American Diabetes Association, 2004[ad]) for the management of plasma glucose levels, at baseline approximately 31% (n=18) of the subjects had good control of FPG (≤ 7.2 mmol/l). Further 7% (n=4) of the subjects had very high FPG levels of ≥ 14 mmol/L compared to others with elevated FPG of 7.2 – 9.99 mmol/l (43%, n=25) and 10 – 13.99 mmol/l (19%, n=11). At baseline the FPG ranged from 4.2 – 18.4 mmol/l, but there was no significant difference in FPG categories at baseline for both cinnamon and placebo groups (Table 4.9)

The post intervention and baseline HbA1c and FPG of the participants are compared in Table 4.10. Overall, 22 (73%) subjects in the cinnamon group and 9 (32%) subjects in the placebo group showed reduction in their post intervention mean HbA1c compared to baseline. Similarly, 18 (60%) subjects in the cinnamon group and 11 (39%) subjects in the placebo group showed

reduction in their mean FPG during the 12 weeks of intervention period. Approximately 38% (n=22) and 29% (n=17) of the subjects showed higher post intervention HbA1c and FPG respectively compared to baseline, where as 9% (n=5) and 21% (n=12) showed no changes in HbA1c and FPG respectively during the intervention period (Table 4.10).

Among patients with elevated plasma glucose levels (had HbA1c of > 7% or FPG > 7.2 mmol/l), the frequency of achieving HbA1c and FPG below the upper normal limits (HbA1c of ≤ 7% and FPG ≤ 7.2 mmol/l) after 12 weeks of intervention was evaluated. There were 20% (n=6) respondents in the cinnamon group versus 7% (n=2) in the placebo group achieved HbA1c levels below 7%. Furthermore 13% (n=4) respondents in the cinnamon group versus 7% (n=2) in the placebo group achieved FPG levels below 7.2 mmol/l at the end of 12 weeks intervention.

Table - 4.10 - Comparison of post intervention (PI) and baseline (BL) glycaemic indicators of HbA1c and FPG during the intervention period [N=58].

Blood glucose	Cinnamon (n=30)	Placebo (n=28)	N (58)
PI HbA1c < BL HbA1c	22 (73%)	9 (32%)	31 (53%)
PI HbA1c > BL HbA1c	6 (20%)	16 (57%)	22 (38%)
PI HbA1c = BL HbA1c	2 (7%)	3 (11%)	5 (9%)
	30 (100%)	28 (100%)	58 (100%)
PI FPG < BL FPG	18 (60%)	11 (39%)	29 (50%)
PI FPG > BL FPG	9 (30%)	8 (29%)	17 (29%)
PI FPG = BL FPG	3 (10%)	9 (32%)	12 (21%)
	30 (100%)	28 (100%)	58 (100%)

Data presented as n (%); N – total number of participants; n – number of participants in cinnamon or placebo group. FPG – fasting plasma glucose.

4.3.3.1 Effect of cinnamon on Fasting plasma glucose (FPG) of the participants

The mean±SD, confidence interval and range of FPG of the participants are presented in Table 4.11. Similarly the effects of cinnamon or placebo on FPG at baseline and post intervention are presented in Table 4.12 and Figure 4.12. The FPG values at baseline indicate the FPG of diabetic individuals prior to the start of the RCT.

The mean FPG levels of the diabetic individuals of the cinnamon and placebo groups at baseline were found to be 8.82 mmol/L and 8.77 mmol/L respectively (P=0.641) (Table 4.12). When patients treated with cinnamon and placebo for 12 weeks, the mean FPG in both cinnamon and placebo groups had dropped from 8.82 mmol/L to 8.04 mmol/L and from 8.77 mmol/L to 8.74

mmol/L respectively. Further more, patients treated with cinnamon demonstrated a significant drop of 8.8% of FPG compared with baseline (from 8.82 mmol/L to 8.04 mmol/L; P=0.047). Patients in the placebo group also showed a 0.3% drop in their FPG, however compared with baseline this is not significant (from 8.77 mmol/L to 8.74 mmol/L; P=0.888). Based on intend to treat analysis, the mean final FPG among patients in the cinnamon group was not significantly different from that in the placebo group (8.04 vs 8.74, P=0.318). The mean change in FPG was also not statistically significant between cinnamon and placebo groups (cinnamon Δ FPG -0.78, placebo Δ FPG -0.03; P=0.888). (Table 4.12 and Figure 4.12).

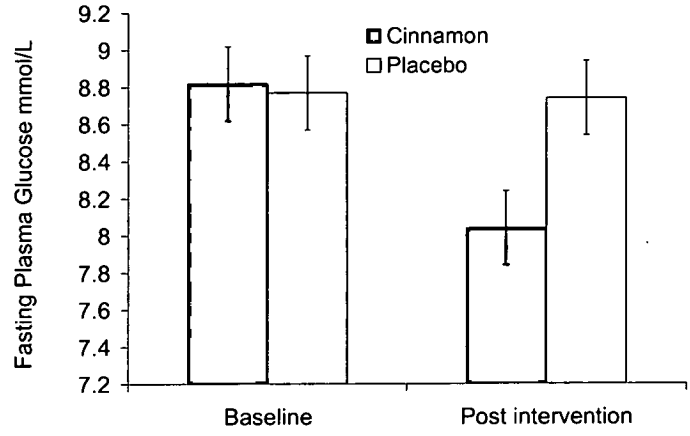


Figure 4.12 – The changes in fasting plasma glucose between cinnamon (n=30, shaded bars) and placebo (n=28, white bars) groups at baseline and post intervention. Data presented as changes in mean FPG. Patients treated with cinnamon showed a significant reduction in FPG at post intervention compared to baseline. No changes in placebo groups.

4.3.3.2 Effect of cinnamon on Glycated haemoglobin (HbA1c) of the participants

The mean±SD, confidence interval and range of HbA1c of the participants are presented in Table 4.11. A comparison between the cinnamon and placebo groups on HbA1c at baseline and after intervention is presented in Table 4.12 and Figure 4.13.

At baseline, the mean HbA1c levels of the diabetic individuals of the cinnamon and placebo groups were 8.22% and 8.55% respectively (P=0.809) (Table 4.12). In patients who were treated with cinnamon for 12 weeks, the mean HbA1c was significantly reduced by 4.3% (from 8.22% to 7.86%; P=0.002) compared to baseline. Where as, the mean HbA1c had slightly increased by 1.4% in the placebo group compared to baseline and this increase was not statistically significant (from 8.55% to 8.68%; P=0.492). Based on intend to treat analysis, the mean final HbA1c among patients in the cinnamon group was significantly different from that in the placebo group (7.86% vs 8.68%, P=0.029). Change was not observed in the placebo group after 12 weeks ((P=0.492) versus baseline. The mean change in HbA1c was also statistically

significant between cinnamon and placebo groups (cinnamon Δ HbA1c -0.36, placebo Δ HbA1c +0.12; P=0.002). (Table 4.12 and Figure 4.13).

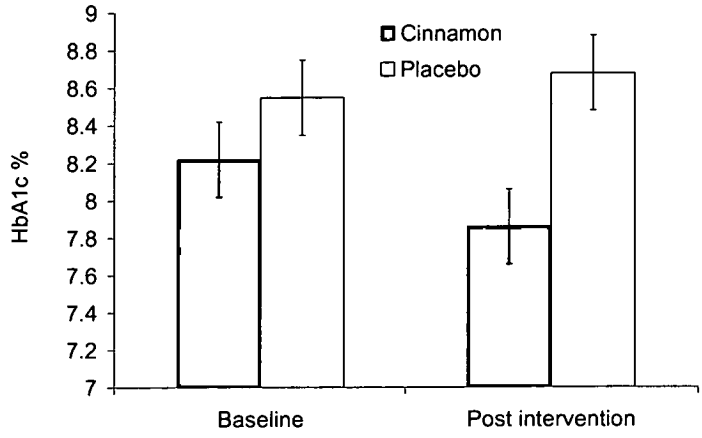


Figure 4.13 – The changes in HbA1c between cinnamon (n=30, shaded bars) and placebo (n=28, white bars) groups at baseline and post intervention. Data presented as changes in mean HbA1c. Patients treated with cinnamon showed a significant reduction in HbA1c at post intervention. The changes in HbA1c (baseline Vs post intervention) in the cinnamon group is significantly different from the changes in HbA1c in placebo group

To demonstrate the possible effect of covariates (other variables) on changes in HbA1c, the hypothesis that the changes in HbA1c in the cinnamon group did not relate to the changes in body weight and total energy intake by using ANCOVA with body weight and total energy intake as covariates was tested. The P values for body weight (P=0.383) and total energy intake (P=0.791), indicate that there was no possible influence of the change in body weight and total energy intake on the improvement of HbA1c. The *b* values from the ANCOVA for the covariates of body weight change (*b*=-0.232) and total energy intake (*b*=0.000) revealed that, when all other variables being controlled or equal and if changes in body weight and total energy intake increases by one unit, then the changes in HbA1c should decrease by 0.232 units and 0.000 (no change) respectively. Therefore, it is apparent that the changes in body weight and total calorie intake did not contribute to the changes in HbA1c levels positively. Further more, there was a slightly positive correlation between the increase of age and baseline HbA1c among subjects (r = 0.031; P = 0.819).

Table 4.11 - The mean, confidence interval (CI) and range of glycaemic indicators of HbA1c and FPG at baseline and post intervention in cinnamon and placebo groups [N=58].

Blood glucose		Treatment	n	mean ± SD	95% CI for mean	minimum	maximum
HbA1c (%)	Baseline	Cinnamon	30	8.22 ± 1.10	7.80 - 8.63	7.0	11.3
		Placebo	28	8.55 ± 1.82	7.84 - 9.26	7.0	14.0
		Total	58	8.38 ± 1.49	7.98 - 8.77	7.0	14.0
	12 weeks	Cinnamon	30	7.86 ± 1.42	7.33 - 8.39	6.2	13.0
		Placebo	28	8.68 ± 1.83	7.97 - 9.39	6.4	13.4
		Total	58	8.25 ± 1.67	7.81 - 8.69	6.2	13.4
FPG (mmol/L)	Baseline	Cinnamon	30	8.82 ± 3.45	7.53 - 10.11	4.5	18.4
		Placebo	28	8.77 ± 2.59	7.76 - 9.78	4.2	14.7
		Total	58	8.80 ± 3.04	8.00 - 9.60	4.2	18.4
	12 weeks	Cinnamon	30	8.04 ± 3.10	6.88 - 9.20	4.4	18.9
		Placebo	28	8.74 ± 3.11	7.53 - 9.95	3.6	15.6
		Total	58	8.38 ± 3.10	7.56 - 9.19	3.6	18.9

Data presented as mean ± SD, 95% confidence interval and range (minimum – maximum). n=number of participants. HbA1c – glycated haemoglobin, FPG – fasting plasma glucose.

Table 4.12 - Effect of cinnamon on HbA1c and fasting plasma glucose at baseline and post intervention [N=58].

Blood glucose level	Cinnamon (n=30)	Placebo (n=28)	*P* value	*Z*
HbA1c (%)				
Baseline	8.22 ± 1.16	8.55 ± 1.82	0.809	-0.240
Post-intervention	7.86 ± 1.42	8.68 ± 1.83	0.029*	-2.180
Difference	- 0.36 ± 0.90 †	0.12 ± 0.82		
FPG (mmol L^{-1})				
Baseline	8.82 ± 3.45	8.77 ± 2.59	0.641	-0.467
Post-intervention	8.04 ± 3.10	8.74 ± 3.11	0.318	-0.996
Difference	- 0.78 ± 1.86 β	- 0.03 ± 1.82		

Data presented as mean ± SD; * *z* values of data; † P = 0.002 shows that HbA1c was significantly reduced at post intervention compared to baseline in the cinnamon group. β P=0.047 shows that FPG was significantly reduced at post intervention compared to baseline in the cinnamon group. The mean changes in HbA1c (cinnamon) was significantly differ from mean changes in HbA1c in placebo group (cinnamon Δ HbA1c -0.36, placebo Δ HbA1c +0.12; P=0.002). * P=0.029 shows that there is a significant difference in HbA1c at post intervention between the cinnamon and placebo groups.

4.3.4 Serum lipid profile indicators of HDL cholesterol, LDL cholesterol, serum triglycerides and serum total cholesterol of the study population

According to the ADA (American Diabetes Association, 2004[b]) standards of medical care guidelines for the dyslipidaemia management, the serum lipid profile indicators of serum triglycerides, HDL cholesterol and LDL cholesterols levels of the participants at the beginning of the study are presented in Table 4.13.

At the beginning of the study, approximately 67% (n=39) of the subjects had a good control of serum triglycerides of $\leq$ 1.7 mmol/l, ranging from 0.83 – 5.53 mmol/l. Further more, 68% (n=39) and 60% (n=34) of the participants had a good control of HDL ($\geq$ 1.02 mmol/l) and LDL ($\leq$ 2.6 mmol/l) cholesterols respectively (Table 4.13). At baseline, the HDL and LDL cholesterol levels ranged from 0.64 – 1.87 mmol/l and 0.86 – 4.84 mmol/l correspondingly. Overall, 14 (48%) subjects in the cinnamon group and 12 (44%) subjects in the placebo group demonstrated reduction in their mean LDL cholesterol compared to baseline. Whereas 17 (56%) subjects in the cinnamon group and 10 (35%) subjects in the placebo group showed increased HDL cholesterol levels compared to baseline during the 12 weeks of study period. Furthermore, 31% (n=9) and 39% (n=11) of the respondents in the cinnamon group achieved desirable LDL cholesterol ($\leq$ 2.6mmol/l) and HDL cholesterol ($\geq$ 1.02 mmol/l) levels during the 12 weeks of intervention period.

Among patients with dyslipidaemia or elevated serum cholesterol levels (had serum triglycerides > 1.7 mmol/l or HDL < 1.02 mmol/l or LDL > 2.6 mol/l), the frequency of achieving serum lipid profiles below the upper normal limit (serum triglycerides of $\leq$ 1.7 mmol/l or HDL of $\geq$ 1.02 mmol/l or LDL $\leq$ 2.6 mol/l) after 12 weeks of intervention was evaluated. Ten percent (n=3) respondents in the cinnamon group versus 4% (n=1) in the placebo group achieved TG levels below 1.7 mmol/l. Overall, 19 (63%) subjects in the cinnamon group and 15 (53%) subjects in the placebo group showed reduction in their mean serum triglyceride levels during the intervention period.

Table 4.13 – Serum lipid profile indicators of serum triglycerides, HDL and LDL cholesterols of the study participants at baseline [N=58].

Blood pressure	Cinnamon n (%)	Placebo n (%)	N (%)
Serum triglycerides (TG)			
≤ 1.7 mmol/l	19 (63)	20 (71)	39 (67)
> 1.7 mmol/l	11 (37)	8 (29)	19 (33)
	30 (100)	28 (100) †	58 (100)
HDL Cholesterol			
< 1.02 mmol/l	10 (33)	9 (32)	19 (32)
≥ 1.02 mmol/l	20 (67)	19 (68)	39 (68)
	30 (100)	28 (100) †	58 (100)
LDL cholesterol			
≤ 2.6 mmol/l	15 (52)	19 (70)	34 (60)
> 2.6 mmol/l	14 (48)	8 (30)	32 (40)
	29 (100)	27 (100) †	56 (100)

Data presented as n (%) at baseline; N – total number of participants; n – number of participants in cinnamon or placebo group; † P > 0.05shows there is no significant differences in serum triglycerides, HDL and LDL cholesterol levels among participants in cinnamon and placebo groups at baseline. Recommendations are based on ADA (2004[b]) guidelines for dyslipidemia management in adults with diabetes TG ≤ 1.7 mmol/l, HDL > 1.02 mmol/l and LDL ≤ 2.6 mmol/l.

4.3.4.1 Effect of cinnamon on serum HDL cholesterol

The mean±SD, confidence intervals and range of serum lipid profiles of HDL cholesterol, LDL cholesterol, serum triglycerides, total cholesterol and HDL ratio of the participants are presented in Table 4.14. Similarly the effects of cinnamon or placebo on HDL, LDL, serum triglycerides and total cholesterol levels at baseline and post intervention are given in Table 4.15.

At baseline, the mean fasting serum HDL cholesterol in both cinnamon and placebo groups were 1.18 mmol/L and 1.16 mmol/L respectively and found to be similar (P=0.764) (Table 4.15). For patients treated with cinnamon for 12 weeks, the mean HDL cholesterol levels were increased by 2.5% (from 1.18 mmol/L to 1.21 mmol/L; P=0.257). In contrast the mean HDL cholesterol had dropped by 1.7% (from 1.16 mmol/L to 1.14 mmol/L; P=0.485) in patients treated with placebo. Based on intent to treat analysis, the mean post intervention HDL among patients in the cinnamon group was not significantly different from that in the placebo group (1.21 mmol/l vs 1.14 mmol/l, P=0.360). The mean change in HDL cholesterol was also not statistically significant between cinnamon and placebo groups (cinnamon Δ HDL +0.03, placebo Δ HDL -0.02; P=0.257) (Table 4.15 and Figure 4.14).

Patients treated with cinnamon exhibited a slight increase in HDL levels; it was shown that the increase in HDL in the cinnamon group was not related to the changes in HbA1c, body weight or total energy intake by using analysis of covariance (ANCOVA) with HbA1c, body weight and total energy intake as covariates. The P values for HbA1c (P=0.579), body weight (P=0.089) and total energy intake (P=0.550), indicated that there was no possible significant influence of the changes in HbA1c, body weight and total energy intake on the improvement of HDL cholesterol during the 12 weeks study period. The *b* values from the ANCOVA for the covariates of changes in HbA1c (*b*=0.012), body weight (*b*= - 0.003) and total energy intake (*b*= 5.57) revealed that, with other variables being controlled or equal and if changes in HbA1c increased by one unit, then the changes in HDL cholesterol would increase by 0.012. Likewise, if changes in body weight increased by one unit then the changes in HDL cholesterol would decrease by 0.003 units. Similarly, if changes in energy intake increased by one unit then the HDL cholesterol should increase by 5.57 units. However, these associations were not significant (P>0.05) and as a result, there is no possible influence of body weight or HbA1c or total calorie intake on changes in HDL cholesterol levels.

4.3.4.2 Effect of cinnamon on serum LDL cholesterol

The mean fasting serum LDL cholesterol levels of the diabetic individuals of the cinnamon and placebo groups at baseline were found to be 2.47 mmol/L and 2.27 mmol/L respectively (P=0.284) (Table 4.15, Figure 4.14). During the 12 weeks of intervention period, the mean serum LDL cholesterol levels in both cinnamon and placebo groups increased to 2.52 mmol/L, and 2.34 mmol/L respectively. Furthermore, patients treated with cinnamon showed 1.6% increase in their LDL cholesterol (from 2.47 mmol/l to 2.52 mmol/l; P=0.740) compared with 3.1% increase (from 2.27 mmol/l to 2.34 mmol/l; P=0.351) among patients treated with placebo. Based on intention to treat analysis, the mean post intervention LDL cholesterol levels among patients in the cinnamon group was not significantly different from that in the placebo group (2.52 mmol/l vs 2.34 mmol/l, P=0.648). The mean change in LDL was also not statistically significant between cinnamon and placebo groups (cinnamon Δ LDL +0.04, placebo Δ HDL +0.07; P=0.740). (Table 4.15 and Figure 4.14).

Analysis of covariance (ANCOVA) was also performed to test the influence of changes in HbA1c or total calorie intake of body weight on changes in LDL cholesterol levels. The changes in LDL cholesterol levels in the cinnamon group during the 12 weeks of intervention period did not suggest any significant (P > 0.05) correlation or possible influences with changes in HbA1c

(r=-0.136, b=-0.037), body weight (r=-0.218, b= 0.009) and total energy intake (r =-0.199, b= 3.67).

4.3.4.3 Effect of cinnamon on serum triglycerides

At baseline, the mean fasting serum triglyceride (TG) levels of the diabetic individuals of the cinnamon and placebo groups were 1.65 mmol/L and 1.48 mmol/L respectively (P=0.427) and ranged from 0.81 – 5.53 mmol/L (Table 4.15). When patients were treated with cinnamon for 12 weeks, the mean serum triglyceride levels had decreased to 1.60 mmol/L, while in the placebo group the serum triglyceride levels was increased to 1.66 mmol/L. Further, patients treated with cinnamon showed 3% reduction in their serum triglycerides (from 1.65 mmol/l to 1.60 mmol/l; P=0.509) compared with 12% increase (from 1.48 mmol/l to 1.66 mmol/l; P=0.136) among patients treated with placebo. Based on intention to treat analysis, the mean post intervention serum triglyceride among patients in the cinnamon group was not significantly different from that in the placebo group (1.60 mmol/l vs 1.66 mmol/l, P=0.774). The mean change in serum TG was also not statistically significant between cinnamon and placebo groups (cinnamon Δ TG -0.05, placebo Δ TG +0.18; P=0.509) (Table 4.15 and Figure 4.14).

According to the analysis of ANCOVA, the changes in serum triglycerides in the cinnamon group during the study period did not demonstrate a significant correlation (P>0.05) or possible influences with changes in HbA1c (r= -0.195, b=0.064), body weight (r=-0.353, b= 0.026) and total energy intake (r = -0.236, b= 4.30).

4.3.4.4 Effect of cinnamon on serum total cholesterol

At baseline, the mean fasting total cholesterol levels of the diabetic individuals of the cinnamon and placebo groups were found to be similar (4.31 mmol/L and 4.10 mmol/L respectively; P=0.420) and ranging from 2.5 – 6.8 mmol/L (Table 4.14, Table 4.15). The mean total cholesterol levels in both cinnamon and placebo groups were increased to 4.34 mmol/L and 4.25 mmol/L when patients treated with cinnamon and placebo for 12 weeks respectively. Furthermore, patients treated with cinnamon showed 0.7% increase in their serum total cholesterol (from 4.31 mmol/l to 4.34 mmol/l; P=0.844) compared with 3.7% increase (from 4.10 mmol/l to 4.25 mmol/l; P=0.154) among patients treated with placebo. Based on intention to treat analysis, the mean post intervention serum total cholesterol levels among patients in the cinnamon group was not significantly different from that in the placebo group (4.34 mmol/l vs 4.25 mmol/l; P=0.743). The mean change in serum TC was also not statistically significant

between cinnamon and placebo groups (cinnamon Δ TC +0.03, placebo Δ TC +0.15; P=0.844). (Table 4.15 and Figure 4.14).

The changes in total cholesterol levels in the cinnamon group during the intervention period did not demonstrate a significant correlation or possible influence with changes with HbA1c (r= -0.074, b=0.056), body weight (r=-0.339, b= -0.011) and total energy intake (r = -0.205, b= -3.92).

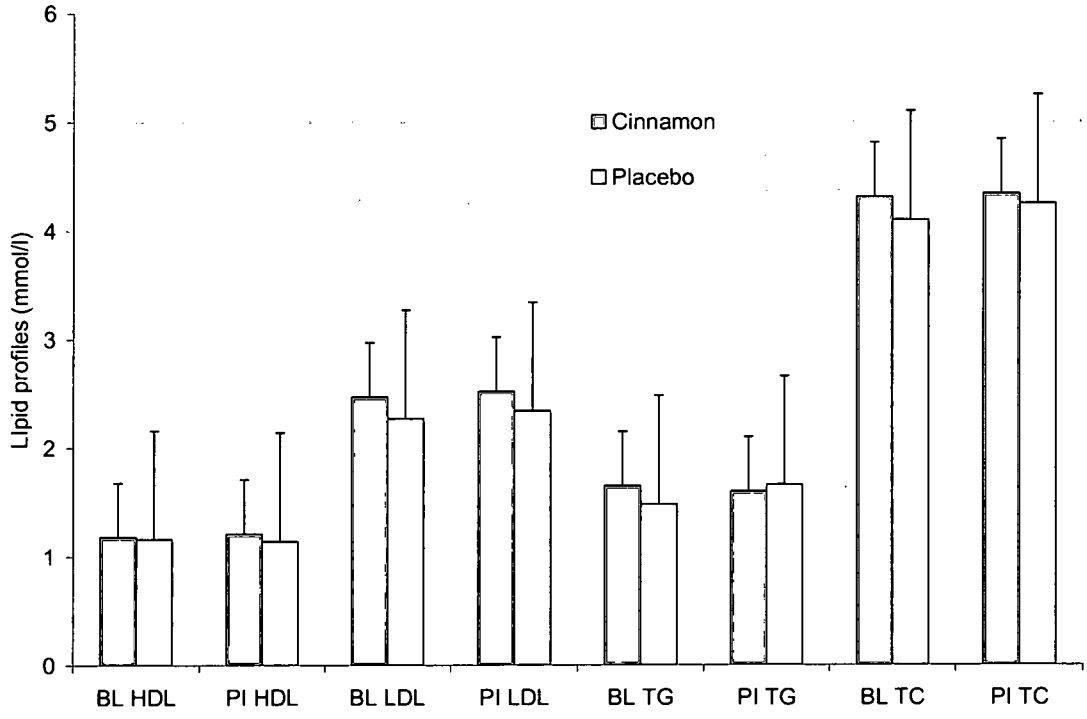


Figure 4.14 – The changes in serum triglycerides, HDL, LDL and total cholesterol levels between cinnamon (n=30, shaded bars) and placebo (n=28, white bars) groups at baseline (BL) and post intervention (PI). Data presented as changes in mean serum lipid profiles. Patients treated with cinnamon did not show a significant reduction in serum lipid profiles at post intervention compared to baseline. Similarly, the changes in serum lipid profiles (baseline Vs post intervention) in the cinnamon group are not significantly different from the changes in lipid profiles in placebo.

4.3.4.5 Effect of cinnamon on HDL ratio (HDLR)

The mean HDLR levels of the diabetic individuals of the cinnamon and placebo groups were found to be similar at baseline (3.83 and 3.63 respectively; P=0.534), and ranging from 2.14 – 6.28 (Table 4.14; Table 4.15). For patients treated with cinnamon or placebo for 12 weeks, the mean HLDR in both cinnamon and placebo groups were increased to 3.87 and 3.82 respectively. Further, patients treated with cinnamon showed 1% increase in their HDLR (from 3.83 to 3.87; P=0.789) compared with 5.2% (from 3.63 to 3.82; P=0.067) increase among patients treated with placebo. Based on intention to treat analysis, the mean post intervention HDLR among patients in the cinnamon group was not significantly different from that in the placebo group (3.87 vs 3.82, P=0.885). The mean change in HDLR was also not statistically significant between cinnamon and placebo groups (cinnamon Δ HDLR +0.04, placebo Δ HDLR +0.19; P=0.844) (Table 4.15 and Figure 4.15).

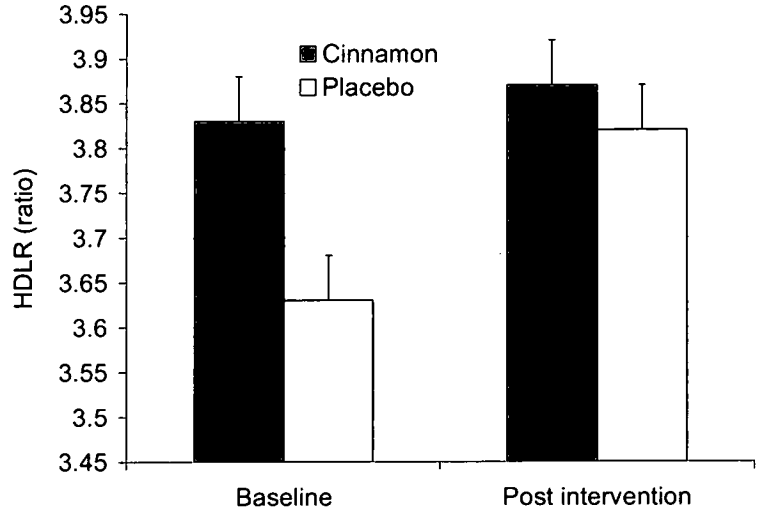


Figure 4.15 – The changes in HDLR ratio between cinnamon (n=30, shaded bars) and placebo (n=28, white bars) groups at baseline and post intervention. Data presented as changes in mean HDLR. Patients treated with cinnamon did not show any significant reduction in HDLR at post intervention.

Table 4.14 - The mean, confidence interval (CI) and range of serum lipid profiles of triglycerides, HDL, LDL and total cholesterol at baseline and post intervention in cinnamon and placebo groups [N=58].

Plasma lipid profiles		Treatment	n	Mean ± SD	95% CI for mean	Minimum	Maximum
HDL (mmol/L)	Baseline	Cinnamon	30	1.18 ± 0.29	1.06 – 1.28	0.64	1.87
		Placebo	28	1.16 ± 0.19	1.08 – 1.23	0.79	1.49
		Total	58	1.17 ± 0.25	1.10 – 1.23	0.64	1.87
	12 weeks	Cinnamon	30	1.21 ± 0.31	1.08 – 1.32	0.63	2.14
		Placebo	28	1.14 ± 0.21	1.05 – 1.22	0.79	1.68
		Total	58	1.17 ± 0.27	1.10 – 1.24	0.63	2.14
LDL (mmol/L)	Baseline	Cinnamon	29	2.47 ± 0.96	2.11 – 2.83	0.86	4.84
		Placebo	27	2.27 ± 0.75	1.93 – 2.52	1.21	4.48
		Total	56	2.34 ± 0.85	2.12 – 2.58	0.86	4.84
	12 weeks	Cinnamon	29	2.52 ± 1.00	2.06 – 2.85	0.77	5.46
		Placebo	25	2.34 ± 0.78	2.01 – 2.66	1.21	4.47
		Total	54	2.43 ± 0.91	2.15 – 2.65	0.77	5.46
Triglycerides (mmol/L)	Baseline	Cinnamon	30	1.65 ± 0.93	1.28 – 1.97	0.58	4.8
		Placebo	28	1.48 ± 1.04	1.11 – 1.91	0.51	5.53
		Total	58	1.57 ± 0.97	1.32 – 1.83	0.81	5.53
	12 weeks	Cinnamon	29	1.60 ± 0.83	1.28 – 1.91	0.49	3.56
		Placebo	27	1.66 ± 0.16	1.20 – 2.12	0.51	4.85
		Total	56	1.63 ± 0.99	1.36 – 1.89	0.49	4.85
Total Cholesterol (mmol/L)	Baseline	Cinnamon	30	4.31 ± 1.07	3.91 – 4.71	2.5	6.8
		Placebo	28	4.10 ± 0.87	3.76 – 4.44	2.8	5.9
		Total	58	4.21 ± 0.97	3.95 – 4.47	2.5	6.8
	12 weeks	Cinnamon	30	4.34 ± 1.09	3.93 – 4.75	2.5	7.9
		Placebo	28	4.25 ± 1.05	3.84 – 4.66	2.8	7.1
		Total	58	4.30 ± 1.06	4.02 – 4.58	2.5	7.9
HDLR	Baseline	Cinnamon	30	3.83 ± 1.00	3.42 – 4.17	2.14	5.87
		Placebo	28	3.63 ± 0.94	3.25 – 4.01	2.3	6.28
		Total	58	3.73 ± 0.98	3.46 – 3.98	2.14	6.28
	12 weeks	Cinnamon	29	3.87 ± 1.09	3.45 – 4.28	2.11	6.17
		Placebo	27	3.82 ± 1.08	3.39 – 4.25	2.31	6.02
		Total	56	3.84 ± 1.08	3.55 – 4.13	2.11	6.17

Data presented as mean ± SD, 95% confidence interval and range (minimum – maximum). n=number of participants. LDL – low density lipoprotein, HDL – high density lipoprotein, HDLR – high density lipoprotein ratio.

Table 4.15 - Effect of cinnamon on serum triglycerides, HDL, LDL and total cholesterol levels at baseline and post intervention [N=58].

Blood lipid profiles	Cinnamon (n=30)	Placebo (n=28)	*P* value	*T*
HDL (mmol L-1)				
Baseline	1.18 ± 0.29	1.16 ± 0.19	0.764	0.302
Post-intervention	1.21 ± 0.31	1.14 ± 0.21	0.360	0.923
Difference	0.03 ± 0.13	- 0.02 ± 1.13		
LDL (mmol L^{-1})				
Baseline	2.47 ± 0.96	2.27 ± 0.75	0.284	1.082
Post-intervention	2.52 ± 1.00	2.34 ± 0.78	0.648	0.459
Difference	0.04 ± 0.72	0.07 ± 0.35		
Triglycerides (mmol L^{-1})				
Baseline	1.65 ± 0.93	1.48 ± 1.04	0.427	* -0.794
Post-intervention	1.60 ± 0.83	1.66 ± 1.16	0.774	* -0.287
Difference	- 0.05 ± 0.45	0.18 ± 0.53		
Total cholesterol (mmol L^{-1})				
Baseline	4.31 ± 1.07	4.10 ± 0.87	0.420	0.812
Post-intervention	4.34 ± 1.09	4.25 ± 1.05	0.743	0.329
Difference	0.03 ± 0.82	0.15 ± 0.52		
HDLR				
Baseline	3.83 ± 1.00	3.63 ± 0.99	0.534	0.625
Post-intervention	3.87 ± 1.09	3.82 ± 1.08	0.885	0.146
Difference	0.04 ± 0.79	0.19 ± 0.53		

Data presented as mean ± SD; * *z* values of data; The mean changes in serum triglycerides, HDLR, HDL, LDL and total cholesterol levels in the cinnamon group was not significantly differ from mean changes of serum lipid profiles in placebo group ($P > 0.05$).

4.3.5 Systolic and diastolic blood pressure of the study population

According to the ADA (American Diabetes Association, 2004[c]; Martha *et al,* 1993) guidelines for hypertension management in adults with diabetes, the systolic and diastolic blood pressures of the participants are presented in Table 4.16. At the beginning of the study, approximately 24% (n=14) of the subjects had elevated systolic blood pressure (SBP ≥ 140 mmHg) levels. Forty percent (n=23) of the subjects had elevated diastolic blood pressure (≥ 90 mmHg). However, the systolic and diastolic blood pressures found to be similar at baseline (Table 4.16).

Table 4.16 – Systolic and diastolic blood pressure of the study participants at baseline [N=58].

Blood pressure	Cinnamon n (%)	Placebo n (%)	N (%)
Systolic blood pressure			
< 140 mmHg †	24 (80%)	20 (71%)	44 (76%)
≥ 140 mmHg †	6 (20%)	8 (29%)	14 (24%)
	30 (100%)	28 (100%)	58 (100%)
Diastolic blood pressure			
< 90 mmHg †	19 (63%)	16 (57%)	35 (60%)
≥ 90 mmHg †	11 (37%)	12 (43%)	23 (40%)
	30 (100%)	28 (100%)	58 (100%)

Data presented as n (%) at baseline; N – total number of participants; n – number of participants in cinnamon or placebo group; † P > 0.05 shows that there is no significant differences in the systolic and diastolic blood pressure measurements between the cinnamon and placebo groups at baseline. Blood pressure defined based on the ADA (2004[c]) guidelines for hypertension management in adults with diabetes SBP ≥ 140 mmHg and DBP ≥ 90 mmHg.

The post intervention and baseline blood pressure of the participants are compared in Table 4.17. Overall, 27 (90%) subjects in the cinnamon group and 14 (50%) subjects in the placebo group showed reduction in their mean SBP compared to baseline. Similarly, 26 (87%) subjects in the cinnamon group and 15 (54%) subjects in the placebo group showed reduction in their mean DBP during the 12 weeks of intervention period. Approximately 21% (n=12) of the subjects showed higher post intervention systolic and diastolic blood pressure values compared to baseline, where as 9% (n=5) showed no changes in SBP and DBP during the intervention period (Table 4.17). Most importantly, none of the patients reported with changes in blood pressure medication during the intervention period.

Among patients with hypertension (had SBP of ≥ 140 mmHg or DBP of ≥ 90 mmHg or both at baseline), the frequency of achieving systolic blood pressure (SBP) and diastolic blood pressure

(DBP) below the upper normal limit (SBP of <140 mmHg and DBP of < 90 mmHg or both) after 12 weeks of intervention was evaluated. There were 10% (n=3) of respondents in the cinnamon group versus 7% (n=2) in the placebo group who achieved SBP levels below 140 mmHg. Furthermore 28% (n=8) of respondents in the cinnamon group versus 11% (n=3) in the placebo group achieved DBP levels below 90 mmHg at the end of the 12 week intervention.

Table - 4.17 - Comparison of post intervention (PI) and baseline (BL) measurements of systolic and diastolic blood pressures during the intervention period [N=58].

Blood pressure	Cinnamon (n=30)	Placebo (n=28)	N (58)
PI SBP < BL SBP	27 (90%)	14 (50%)	41 (71%)
PI SBP > BL SBP	2 (7%)	10 (36%)	12 (21%)
PI SBP = BL SBP	1 (3%)	4 (14%)	5 (9%)
	30 (100%)	28 (100%)	58 (100%)
PI DBP < BL DBP	26 (87%)	15 (54%)	41 (71%)
PI DBP > BL DBP	3 (10%)	9 (32%)	12 (21%)
PI DBP = BL DBP	1 (3%)	4 (14%)	5 (9%)
	30 (100%)	28 (100%)	58 (100%)

Data presented as n (%); N – total number of participants; n – number of participants in cinnamon or placebo group; SBP - Systolic Blood Pressure; DBP - Diastolic Blood Pressure

4.3.5.1 Effect of cinnamon on systolic blood pressure of the participants

The mean±SD, confidence intervals and range of systolic and diastolic blood pressures of the participants are presented in Table 4.18. Similarly the effects of cinnamon or placebo on systolic and diastolic blood pressure of the participants at baseline and post intervention are shown in Table 4.19.

At baseline, the mean SBP of the diabetic individuals of the cinnamon and placebo groups were similar and found to be 132.57 mmHg and 134.5 mmHg respectively (P=0.654) and ranging from 101 - 159 mmol/L (Table 4.18, Table 4.19). After 12 weeks, subjects in the cinnamon group showed a significant reduction of approximately 3% in their SBP (from 133 mmHg to 129 mmHg; P<0.001) compared to baseline. In contrast, the SBP of the subjects in the placebo group had barely increased by 0.7% (from 134 mmHg to 135 mmHg; P=0.571) compared with baseline. Based on intention to treat analysis, the mean post intervention SBP among patients in the cinnamon group was significantly different from that in the placebo group (129 mmHg vs 135 mmHg, P=0.011). The mean change in SBP was also statistically significant between

cinnamon and placebo groups (cinnamon Δ SBP -4 mmHg, placebo Δ SBP +1 mmHg; P=0.571). (Table 4.19 and Figure 4.16).

The hypothesis that the decrease in SBP in the cinnamon group was not influenced by the changes in HbA1c, body weight and total energy intake was tested by using analysis of covariance (ANCOVA) with HbA1c, body weight and total energy intake as covariates. The P values for HbA1c (P=0.591), body weight (P=0.348) and total energy intake (P=0.568), signifying that there were no possible influence of the changes in body weight or HbA1c or total energy intake on SBP. The *b* values from the ANCOVA for the covariates of changes in HbA1c (b=0.360), body weight (*b*=0.967) and total energy intake (*b*=0.002) reveals that, when other variables being controlled or equal and if changes in HbA1c, body weight and total energy intake increases by one unit, then the changes in SBP should increase by 0.36 units, 0.967 units and 0.002 units respectively.

Furthermore, changes in systolic blood pressure in the cinnamon group showed a mild positive correlation with changes in blood lipid profiles of total cholesterol (r=0.071), LDL cholesterol (r=0.136) and triglycerides (r=0.002), HbA1c (r=0.028), total calorie intake (r=0.150), body weight (r=0.225) and BMI (r=0.241), however this correlation was not statistically significant (P>0.05).

4.3.5.2 Effect of cinnamon on diastolic blood pressure (DBP)

At baseline, the mean DBP levels of the diabetic individuals of the cinnamon and placebo groups were similar (85.17 mmHg and 86.78 mmHg respectively; P=0.473) and ranged from 70 - 105 mmol/L (Table 4.18, Table 4.19). After 12 weeks, subjects in both cinnamon and placebo groups decreased their DBP by 4.7% (from 85 mmHg to 81 mmHg; P<0.001) and 1.1% (from 87 mmHg to 86 mmHg; P=0.365) respectively. The decrease in DBP was more prominent in the cinnamon group compared to baseline (p<0.001). Based on intention to treat analysis, the mean post intervention DBP among patients in the cinnamon group was significantly different from that in the placebo group (81 mmHg vs 86 mmHg, P=0.008). The mean change in DBP was also statistically significant between cinnamon and placebo groups (cinnamon Δ DBP - 4 mmHg, placebo Δ DBP - 1 mmHg; P=0.571) (Table 4.19 and Figure 4.16).

The hypothesis that the decrease in DBP in the cinnamon group was not related to the changes in HbA1c, body weight and total energy intake was tested by using analysis of covariance (ANCOVA) with body weight and total energy intake as covariates. The P values for HbA1c

(b=-0.304, P=0.649), body weight (*b*=1.02, P=0.243) and total energy intake (*b*=0.002, P=0.531), indicating that there were no possible influence of the change in HbA1c, body weight and total energy intake on DBP of the participants. The changes in salt intake as covariate also demonstrates that there were no likely influence of the salt intake on the improvement of DBP (P=0.345, b=0.000, r=-0.07).

Furthermore, changes in diastolic blood pressure in the cinnamon group showed a moderate positive correlation with changes in HbA1c (r=0.33), LDL cholesterol (r=0.022), body weight (r=0.147) and BMI (r=0.106); and showed slightly negative correlation with changes in HDL cholesterol (r= -0.167), TG (r= -0.194), total cholesterol (r= -0.054) and waist circumference (r= - 0.042). However these correlations did not suggest any statistically significant (P>0.05) relationship.

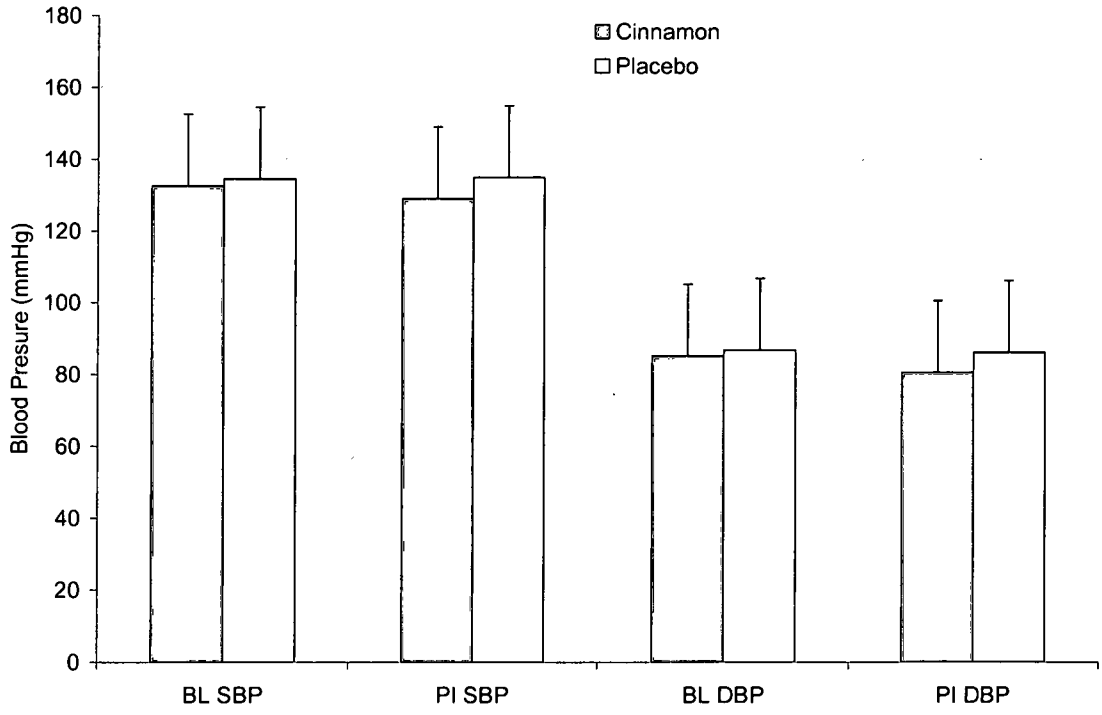


Figure 4.16 – The changes in systolic and diastolic blood pressures between cinnamon (n=30, shaded bars) and placebo (n=28, white bars) groups at baseline (BL) and post intervention (PI). Data presented as changes in mean blood pressure. Patients treated with cinnamon showed a significant reduction in systolic and diastolic blood pressures at post intervention. Similarly, the changes in SBP and DBP (baseline Vs post intervention) in the cinnamon group were significantly different from the changes in SBP and DBP in placebo group.

Table 4.18 - The mean, confidence interval (CI) and range of systolic and diastolic blood pressures at baseline and post intervention in cinnamon and placebo groups [N=58].

Blood glucose		Treatment	n	mean ± SD	95% CI for mean	minimum	maximum
SBP (mmHg)	Baseline	Cinnamon	30	132.5 + 8.66	129 - 136	119	149
		Placebo	28	134.5 + 10.92	129 - 139	101	159
		Total	58	133.1 + 10.53	130 - 136	101	159
	12 weeks	Cinnamon	30	128.97 + 7.98	126 - 132	117	144
		Placebo	28	134.93 + 9.27	131 - 139	123	158
		Total	58	131.84 + 9.07	129 - 134	117	158
DBP (mmHg)	Baseline	Cinnamon	30	85.17 + 6.45	83 - 88	70	96
		Placebo	28	86.78 + 8.82	83 - 90	71	105
		Total	58	85.95 + 7.66	84 - 88	70	105
	12 weeks	Cinnamon	30	80.60 + 5.80	78 - 83	68	91
		Placebo	28	86.14 + 8.08	83 - 89	71	98
		Total	58	83.28 + 7.48	81 - 85	68	98

Data presented as mean ± SD, 95% confidence interval and range (minimum – maximum). n=number of participants
SBP - Systolic blood pressure; DBP - Diastolic blood pressure.

Table 4.19 - Effect of cinnamon on systolic and diastolic blood pressure levels at baseline and post intervention [N=58].

Blood pressure	Cinnamon (n=30)	Placebo (n=28)	*P* value	*T*
SBP (mmHg)				
Baseline	132.57 ± 8.66	134.50 ± 10.92	0.654	-0.450
Post-intervention	128.97 ± 7.98	134.93 ± 9.27	0.011 $^{\beta}$	-2.629
Difference	- 3.6 ± 1.77 †	0.43 ± 3.95		
DBP (mmHg)				
Baseline	85.17 ± 6.45	86.78 ± 8.82	0.473	* -0.718
Post-intervention	80.60 ± 5.80	86.14 ± 8.08	0.008 $^{\delta}$	* -2.667
Difference	- 4.57 ± 4.25 †	- 0.64 ± 4.32		

Data presented as mean ± SD; SBP - Systolic blood pressure; DBP - Diastolic blood pressure; * *z* values of data;
† P = 0.001 shows that SBP and DBP were significantly reduced at post intervention compared to baseline in the cinnamon group. The mean changes in SBD and DBP in the cinnamon group was significantly differing from mean changes in SBP and DBP in placebo group. $^{\beta}$ P = 0.011 shows that there is a significant differences in the post intervention SBP between the cinnamon and placebo groups. $^{\delta}$ P = 0.088 shows that there is a significant differences in the post intervention DBP between the cinnamon and placebo groups.

4.3.6 Dietary analysis of average total daily energy intake from carbohydrates, fats and proteins

The average daily total energy intake of carbohydrates, fats and proteins from the three day diet diary at baseline and post intervention was analyzed, compared and reported according to the current recommendations of the American Diabetic Association (ADA) and Diabetes UK guidelines of standards in nutrition principles and recommendations for type 2 diabetes mellitus (Nutrition Sub-Committee of the British Diabetic Association Professional Advisory Committee. 1992; Nutrition Sub-Committee of the British Diabetic Association Professional Advisory Committee, 2003; Ha and Lean, 1998; Franz *et al,* 2002; Diabetes and Nutrition Study Group of the European Association, 2000; American Diabetic Association Position Statement, 2002[b]; American Diabetic Association Position statement, 2004[d]).

The total energy intake (%) of carbohydrates, fats and proteins of the participants in both cinnamon and placebo groups at baseline are presented in Figure 4.17. As per the standard care, patients completing the intervention programme (n=58) were seen by dietician at diabetes clinics and received two sessions of diet and lifestyle advice. At the beginning of the study, the average daily total energy intake from carbohydrates, fats and proteins were found to be 48%, 38% and 14% respectively among the participants. The total energy intake from carbohydrate (48%) includes energy contribution from starch (36%) and sugars (12%). Similarly total energy from fats (38%) includes energy contribution from saturated fatty acids (SFA – 10%), poly unsaturated fatty acids (PUFA – 8%), mono unsaturated fatty acids (MUFA – 11%), trans fatty acids (TFA – 0.5%) and other un-identified (un–id) fats of 8.5%. Figure 4.18 shows the energy contributions from starch, sugar, SFA, PUFA, MUFA, TFA at the beginning of the study.

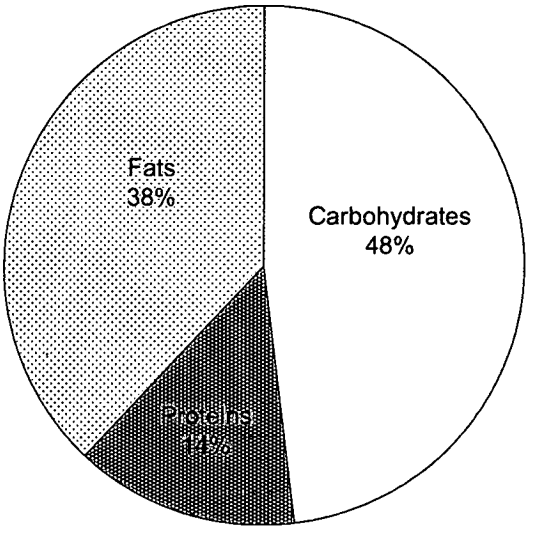


Figure 4.17 – The total energy intake (%) of carbohydrates, fats and proteins of the study participants in both cinnamon (n=30) and placebo (n=28) groups at baseline [N=58].

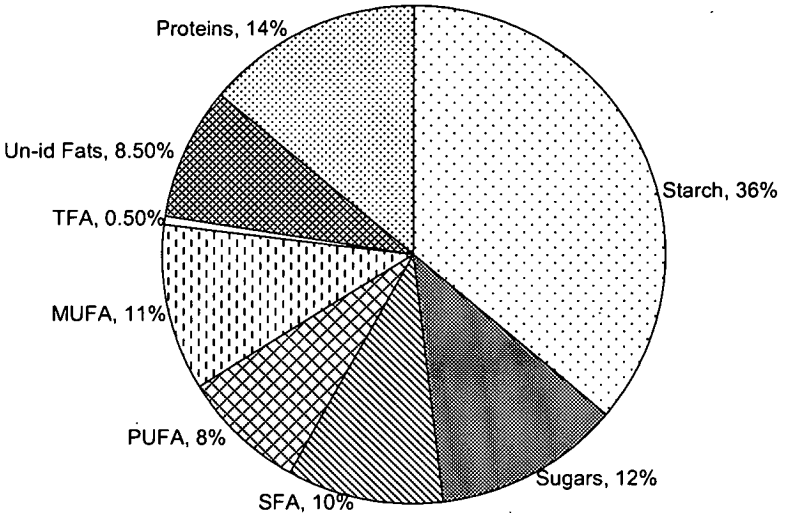


Figure 4.18 – The total energy intake of starch, sugars, poly unsaturated fatty acids (PUFA), mono unsaturated fatty acids (MUFA), saturated fatty acids (SFA), trans fatty acids (TFA) and proteins of the study participants in both cinnamon (n=30) and placebo (n=28) at baseline [N=58].

The average daily baseline energy intake of the study participants in both cinnamon and placebo groups were compared with the ADA and Diabetes, UK recommendations on dietary composition for diabetes management (Nutrition Sub-Committee of the British Diabetic Association Professional Advisory Committee, 1992, 2003; American Diabetes Association Position statement, 2004[d]; 2002[b]), and presented in Table 4.20. The average intakes of carbohydrates, SFA, PUFA, MUFA and salt were found to be with in the recommended

limitations at baseline in both groups. The mean fat intake (38%) was slightly higher than the recommended limit of 35% and mean protein intake was little lower (14%) than the normal recommendation of 15 – 20% (Table 4.20).

Table 4.20 - Comparison of average baseline energy intake of the study participants [N=58] with ADA. (2002[b], 2004[d]) and Diabetes UK. (2003) recommendations of average daily energy intake.

Macro Nutrients	% of energy intake	
	Average baseline energy intake (per day)	ADA and Diabetes UK recommendations †
Carbohydrates	48%	45 - 60%
Fats	38%	< 35%
Proteins	14%	15 – 20% or < 1g per kg body weight
Saturated and trans fats	10%	< 10%
Poly unsaturated fats	8%	< 10%
Mono unsaturated fats	11%	10 - 20%
Salts	4.4g	≤ 6g / day
Fiber	6g	no recommendation

The post intervention and baseline total energy intake of the participants are compared in Table 4.21. Sixteen subjects (53%) in the cinnamon group and 13 (46%) subjects in the placebo group showed a reduction in their mean daily total energy intake post intervention compared to baseline. In contrast, 12 (40%) subjects in the cinnamon group and 14 (50%) subjects in the placebo group showed an increase in their mean daily total energy intake at post intervention compared to baseline. An overall 5% (n=3) of the subjects consumed the same amount of energy at baseline and post intervention (Table 4.21).

Table - 4.21 - Comparison of post intervention (PI) and baseline (BL) total energy intake during the intervention period [N=58].

Total energy intake	Cinnamon (n=30)	Placebo (n=28)	N (58)
PI TEI < BL TEI	16 (53%)	13 (46%)	29 (50%)
PI TEI > BL TEI	12 (40%)	14 (50%)	26 (45%)
PI TEI = BL TEI	2 (7%)	1 (4%)	3 (5%)
	30 (100%)	28 (100%)	58 (100%)

Data presented as n (%); N – total number of participants; n – number of participants in cinnamon or placebo group ; TEI - Total Energy Intake.

4.3.6.1 The average daily total energy intake at baseline and post intervention

The mean±SD, confidence intervals and range of total calorie intake of the participants are presented in Table 4.23. Similarly the effects of cinnamon or placebo on total calorie intake of the participants at baseline and post intervention are presented in Table 4.24.

The average daily total energy intake (TEI) of the diabetic individuals of the cinnamon and placebo groups at baseline were found to be similar (1863 kcal/day vs 1844 kcal/day; P=0.776) and ranging from 1314 – 2535 kcal/day (Table 4.23 and Table 4.24). In patients treated with cinnamon, the mean TEI had dropped by 2.5% (from 1863 kcal to 1818 kcal/day; P=0.247) at post intervention compared to baseline. Furthermore, patients in the placebo group did not demonstrate any changes in their TEI at post intervention compared with baseline (from 1844 kcal/day to 1843 kcal/day; P=0.365). Based on intend to treat analysis, the mean post intervention TEI among patients in the cinnamon group was not significantly different from that in the placebo group (1818 kcal vs 1843 kcal/day; P=0.658). The mean change in TE was also not statistically significant between cinnamon and placebo groups (cinnamon Δ TE – 45 kcal/day, placebo Δ TE -1 kcal/day; P=0.658). (Table 4.24 and Figure 4.19).

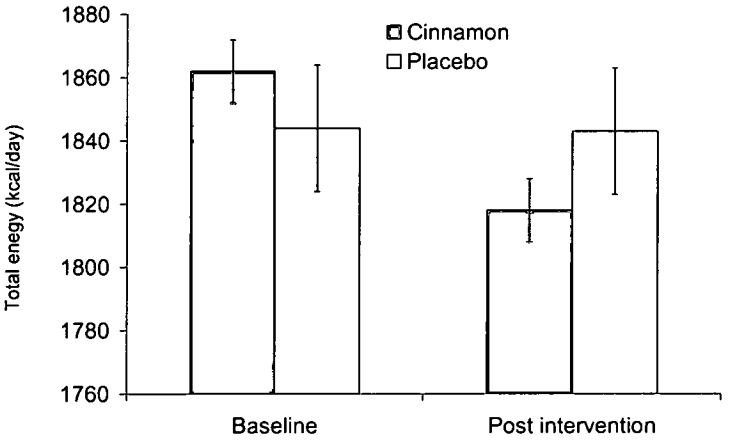


Figure 4.19 – The changes in total energy intake (TEI) between cinnamon (n=30, shaded bars) and placebo (n=28, white bars) groups at baseline and post intervention. Data presented as changes in mean TEI. The TEI found to be similar in both cinnamon and placebo groups at baseline and post intervention.

4.3.6.2 Dietary intake of total carbohydrates at baseline and post intervention

The mean±SD, confidence intervals and range of % total carbohydrates, % sugar and % starch intake of the participants are presented in Table 4.23 and Table 4.25. Similarly the effects of cinnamon or placebo on % total carbohydrates (% sugar + % starch) of the participants at baseline and post intervention are presented in Table 4.26.

At baseline, the mean % total energy (TE) intake of carbohydrates of the cinnamon and placebo groups were similar (47.6% vs 47% respectively; P=0.460) and ranging from 33.2% – 68.5% (Table 4.23, Table 4.26). Post intervention, subjects in the cinnamon group decreased their % TE from carbohydrates by 0.8% (from 47.66% to 47.27%; P=0.936), whereas the % TE from carbohydrates was increased by 3.3% (from 47.02 to 48.59%; P=0.209) among subjects in placebo group. Based on intention to treat analysis, the mean post intervention % TE intake of carbohydrates among patients in the cinnamon group was not significantly different from that in the placebo group (47.27% vs 48.59%; P=0.549). (Table 4.26 and Figure 4.20).

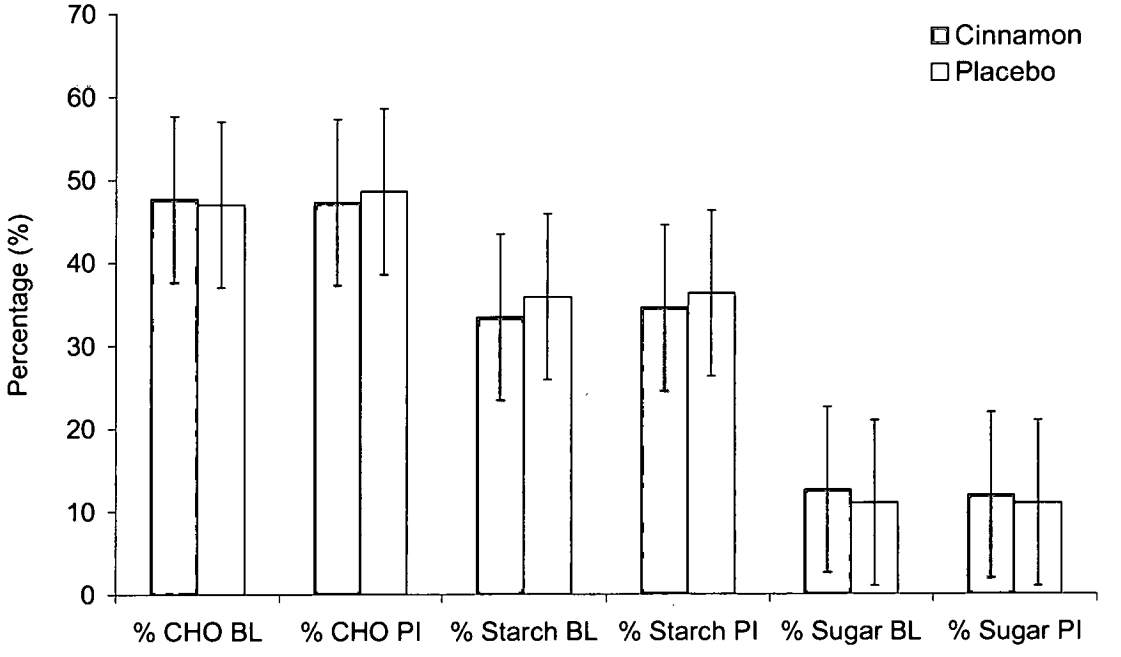


Figure 4.20 – The changes in % carbohydrate (CHO), starch and sugar intake between cinnamon (n=30, shaded bars) and placebo (n=28, white bars) groups at baseline (BL) and post intervention (PI). Data presented as changes in %. The total intake of carbohydrates, starch and sugars found to be similar at baseline and post intervention in both cinnamon and placebo groups.

Overall, 12 (40%) subjects in the cinnamon group and 10 (36%) subjects in the placebo group showed reduction in their % TE of carbohydrates at post intervention compared to baseline. Furthermore at baseline, the % TE from starch was found to be similar in both cinnamon and placebo groups (33.44% and 35.89% respectively; P=0.125), and ranged from 22.8% - 55% at baseline (Table 4.25 and Table 4.26). After 12 weeks of intervention, % TE from starch was slightly increased by 3.35% (from 33.44% to 34.54%) and 1% (from 35.89% to 36.28%) in both cinnamon and placebo groups respectively. Based on intention to treat analysis, the mean post intervention % TE intake of starch among patients in the cinnamon group was not significantly

different from that in the placebo group (33.54% vs 36.28; P=0.349) (Table 4.26 and Figure 4.20). In general, 8 (27%) subjects in the cinnamon group and 13 (46%) subjects in the placebo group showed a reduction in their % TE of starch intake during the 12 weeks of intervention period.

Likewise, % TE of sugar was found to be similar in both cinnamon and placebo groups at baseline (12.58% vs 10.99%; P=0.066) and ranging from 4.3 – 21.3% (Table 4.25 and Table 4.26). There was no significant difference in % TE of sugars between cinnamon and placebo groups after the intervention (11.93% vs 10.98%; P=0.323). Fifteen (50%) subjects in the cinnamon group and 11 (39%) subjects in the placebo group reduced their % TE from sugar (Table 4.26 and Figure 4.20) during the study period.

4.3.6.3 Dietary intake of total fats at baseline and post intervention

The mean±SD, confidence intervals and range of % total fats, % PUFA, % MUFA, % SFA and % TFA intake of the participants are presented in Table 4.23 and Table 4.27. Similarly the effects of cinnamon or placebo on % total fats (% PUFA + % MUFA + % SFA + % TFA) of the participants at baseline and post intervention are presented in Table 4.28.

The mean % TE intake from fats of the diabetic individuals of the cinnamon and placebo groups was similar at baseline (38.03% vs 38.31%; P=0.619) and ranging from 21.6% to 56.2% (Table 4.23, Table 4.28). After 12 weeks of intervention, the mean % TE from fats in both cinnamon and placebo groups were 37.82% and 37.27% respectively. Based on intention to treat analysis, the mean post intervention % TE from fats among patients in the cinnamon group was not significantly different from that in the placebo group (37.82% vs 37.27%; P=0.446). The mean change in % TE from fats was also not statistically significant between cinnamon and placebo groups (cinnamon Δ % TE from fats -0.21%, placebo Δ % TE from fats -1.04%; P=0.451) (Table 4.28 and Figure 4.21). Approximately, 15 (50%) subjects in the cinnamon group and 15 (54%) subjects in the placebo group showed reduction in their % TE from fats during the study period compared to baseline.

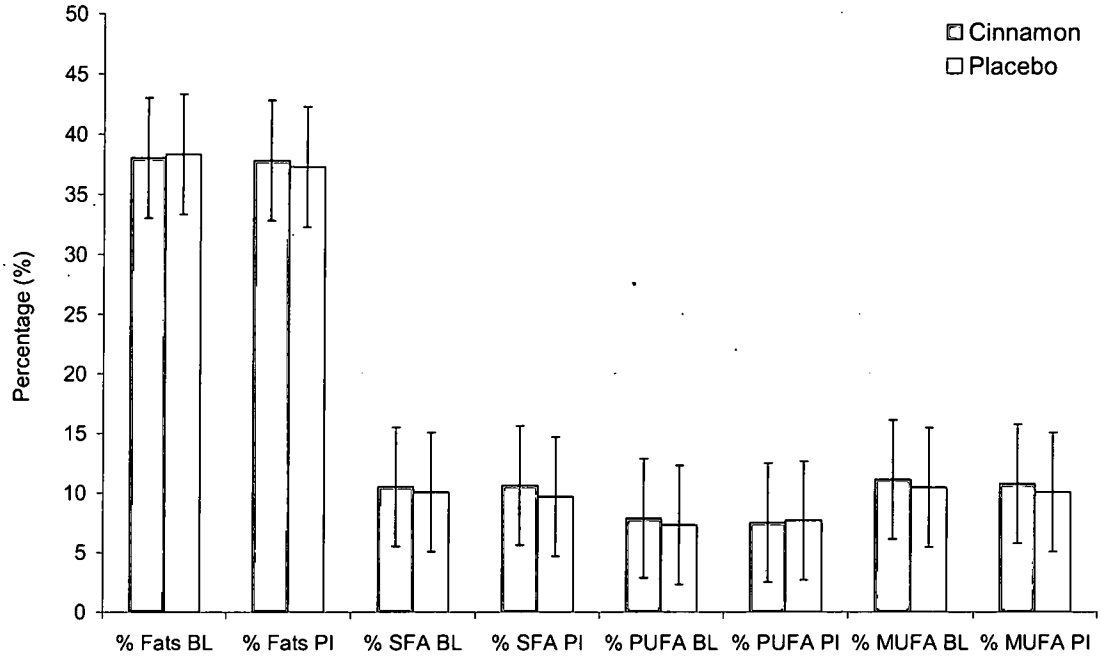


Figure 4.21 – The changes (%) in total fat, saturated fat (SFA), poly and mono unsaturated fat (PUFA and MUFA) intakes between cinnamon (n=30, shaded bars) and placebo (n=28, white bars) groups at baseline (BL) and post intervention (PI). Data presented as changes in %. The intake of SFA, MUFA and PUFA found to be similar at baseline and post intervention in both cinnamon and placebo groups.

Furthermore, at baseline the % TE from SFA was similar in both cinnamon and placebo groups (10.52% vs 10.09%; P=0.695) and ranged from 1.3% to 19.7% (Table 4.27 and Table 4.28). Post intervention, % TE from SFA was slightly increased by 1.3% (from 10.52% to 10.66%; P=0.807) in the cinnamon group and decreased by 3.9% (from 10.09% to 9.7%; P=0.620) in the placebo group. Based on intention to treat analysis, The mean post intervention % TE intake of SFA among patients in the cinnamon group was not significantly different from that in the placebo group (10.66% vs 9.7%; P=0.454) (Table 4.28 and Figure 4.21). Overall, 14 (46%) subjects in the cinnamon group and 12 (43%) subjects in the placebo group showed a reduction in their % TE of SFA intake during the study period.

In the same way, the mean % TE intake from poly unsaturated fatty acids (PUFA) of the cinnamon and placebo groups were similar at baseline (7.88% vs 7.33% respectively; P=0.462) and ranged from 3.2% to 14.1% (Table 4.27, Table 4.28). After 12 weeks of intervention, subjects in cinnamon group decreased their % TE from PUFA by 4.6% (from 7.88% to 7.52%; P=0.610), whereas the % TE from PUFA was increased by 4.9% (from 7.33% to 7.69%; P=0.523) among subjects in placebo group. Based on intent to treat analysis, the mean post intervention % TE intake from PUFA among patients in the cinnamon group was not

significantly different from that in the placebo group (7.52% vs 7.69%; P=0.815). (Table 4.28 and Figure 4.21). Overall, 15 (50%) subjects in the cinnamon group and 12 (43%) subjects in the placebo group demonstrated reduction in their % TE from PUFA intake.

Further, the % TE from mono unsaturated fatty acids (MUFA) was found to be similar in both cinnamon and placebo groups at baseline (11.145 vs 10.49%; 0.464; P=0.464) and ranged from 3.4% to 17.1% (Table 4.27, Table 4.28). Subjects in both cinnamon and placebo group showed reduction in their % TE from MUFA of 3.2% and 3.6% respectively (cinnamon: from 11.14% to 10.78%: P=0.554; placebo: from 10.49% to 10.11%: P=0.353). Based on intention to treat analysis, there was no significant difference in % TE from MUFA between cinnamon and placebo groups after the 12 weeks of intervention (10.78% vs 10.11%; P=0.457) (Table 4.28, Figure 4.21). In particular, 15 (30%) subjects in the cinnamon group and 12 (43%) subjects in the placebo group proved reduction in their % TE from MUFA during the 12 weeks study period.

The % TE form trans fatty acids (TFA) was also found to be similar in both cinnamon and placebo groups at baseline (0.44% vs 0.59%; P=0.110) and there was no significant difference in % TE from TFA between cinnamon and placebo groups after the 12 weeks of intervention (0.29% vs 0.45%; P=0.054) (Table 4.27 and Table 4.28).

4.3.6.4 Dietary intake of total proteins at baseline and post intervention

The mean±SD, confidence intervals and range of % total energy intake from protein are presented in Table 4.23. Similarly the effects of cinnamon or placebo on % total protein of the participants at baseline and post intervention are presented in Table 4.26.

At baseline, the mean % TE from protein intake of the diabetic individuals of the cinnamon and placebo groups were 13.92% and 14.69% respectively (P=0.283) (Table 4.26). The % TE from protein ranged from 9.5% - 20.6% at baseline (Table 4.23). After 12 weeks of intervention, the mean % TE of protein was dropped by 2.7% in the cinnamon group (from 13.92% to 13.55%; P=0.270) and 4% in the placebo group (from 14.69% to 14.10%; P=0.158). Based on intent to treat analysis, the mean post intervention % TE from protein among patients in the cinnamon group was not significantly different from that in the placebo group (13.55% vs 14.10%; P=0.575) (Table 4.26, Figure 4.22). Overall, 17 (57%) subjects in the cinnamon group and 17

(61%) subjects in the placebo group showed reduction in their % TE from protein intake during the 12 weeks of intervention.

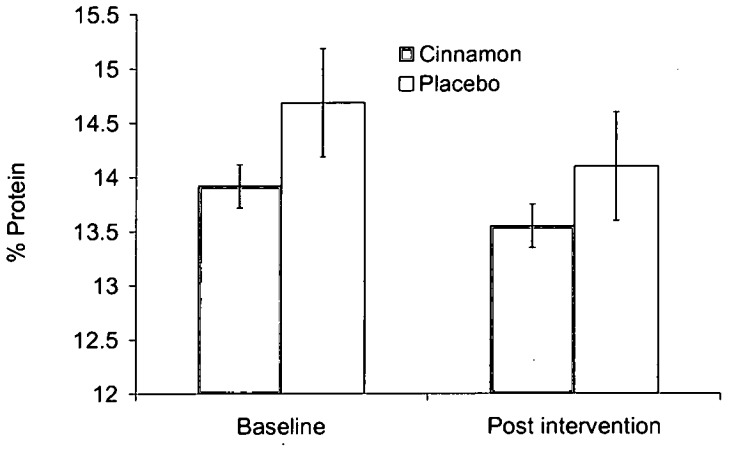


Figure 4.22 – The changes in % protein intake between cinnamon (n=30, shaded bars) and placebo (n=28, white bars) groups at baseline and post intervention. Data presented as changes in %. The total intake of proteins found to be similar at baseline and post intervention in both cinnamon and placebo groups.

4.3.6.5 Dietary intake of Salt and fiber at baseline and post intervention

The mean±SD, confidence intervals and range of average daily intake of salt and fiber are presented in Table 4.24. Similarly the effects of cinnamon or placebo on salt and fiber intake of the participants at baseline and post intervention are presented in Table 4.30.

The average intake of sodium (salt) at baseline was similar in both cinnamon and placebo groups (4312 mg/day vs 4497 mg/day; P=0.523) and ranged from 1299 to 8265 mg/day (Table 4.29 and Table 4.30). At post intervention, the mean salt intake was reduced by approximately 2 % in cinnamon group (from 4312 to 4242 mg/day; P=0.524) and increased almost by 4% in placebo group (from 4497 to 4678 mg/day: P=0.424). Based on intention to treat analysis, the mean post intervention salt intake of the participants in the cinnamon group was not significantly different from that in the placebo group (4242 vs 4678 mg/day: P=0.513) (Table 4.30, Figure 4.23). Overall, 17 (57%) subjects in the cinnamon group and 12 (43%) subjects in the placebo group showed reduction in their mean salt intake during the 12 weeks of intervention.

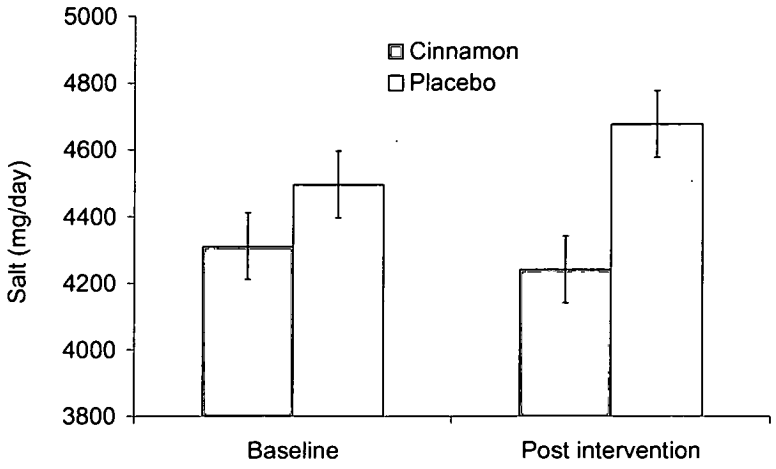


Figure 4.23 – The changes in salt intake between cinnamon (n=30, shaded bars) and placebo (n=28, white bars) groups at baseline and post intervention. Data presented as mean changes in salt. The total intake of salts found to be similar at baseline and post intervention in both cinnamon and placebo groups.

A similar trend was observed for fiber intake, and there was no significant difference in average fiber intake at baseline between cinnamon and placebo groups (6.15 g/day vs 6.13 g/day; P=0.498). At baseline the amount of fiber intake was ranging from 2.8 to 12.5 g/day (Table 4.29 and Table 4.30). At post intervention, patients treated with cinnamon and placebo did not demonstrate any improvements in fiber intake compared to baseline (cinnamon: from 6.15 to 6.14: P=0.596; placebo: from 6.13 to 6.28: P=0.427). Based on intention to treat analysis, the mean post intervention fiber intake of the participants in the cinnamon group was not significantly different from that in the placebo group (6.14 vs 6.28: P=0.528) (Table 4.30, Figure 4.24). Overall, 10 (33%) subjects in the cinnamon group and 10 (36%) subjects in the placebo group showed reduction in their mean fiber intake during the 12 weeks study period.

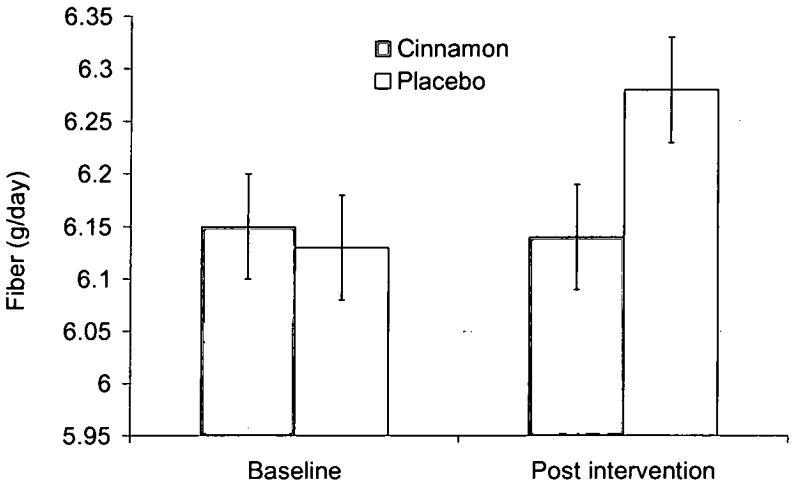


Figure 4.24 – The changes in fiber intake between cinnamon (n=30, shaded bars) and placebo (n=28, white bars) groups at baseline and post intervention. Data presented as mean changes in fiber. The total intake of fiber found to be similar at baseline and post intervention in both cinnamon and placebo groups.

4.3.6.6 Comparison of three days total energy intake of subjects

The % total energy intake of total carbohydrates, fats and proteins of the participants at baseline in both cinnamon and placebo groups are compared with ADA and Diabetes UK guidelines and presented in Table 4.22.

With reference to the ADA and Diabetes, UK (Nutrition Sub-Committee of the British Diabetic Association Professional Advisory Committee, 1990 & 2003; American Diabetes Association Position statement, 2004) recommendations of dietary composition for diabetes management, the majority of the subjects (60%; n=35) were consuming recommended amounts of energy from total carbohydrates of 45 – 60% at baseline, and there were no significant different between cinnamon and placebo group. Furthermore, only 28% (n= 16) and 41% (n=24) of the respondents were consuming recommended levels of energy from fats and proteins respectively.

Table 4.22 - Comparison of % total energy intake of total carbohydrates, fats and proteins of the participants at baseline with ADA and Diabetes UK recommendations of total energy intakes [N=58].

Total Energy Intake	Cinnamon n (%)	Placebo n (%)	N (%)
Total Carbohydrates			
< 45%	8 (27)	12 (43)	20 (34)
45 - 60% $^{\beta}$	21 (70)	14 (50)	35 (60)
> 60%	1(3)	2 (7)	3 (5)
	30 (100)	28 (100) †	58 (100)
Total Fats			
≤ 35% $^{\beta}$	12 (40)	4 (14)	16 (28)
> 35%	18 (60)	24 (86)	42 (72)
	30 (100)	28 (100) †	58 (100)
Total Proteins			
< 15%	19 (63)	13 (46)	32 (55)
15 - 20% $^{\beta}$	11 (37)	13 (46)	24 (41)
> 20%	0	2 (8)	2 (3)
	30 (100)	28 (100) †	58 (100)
PUFA			
≤ 10% $^{\beta}$	21(70)	24 (86)	45 (78)
> 10%	9 (30)	4 (14)	13 (22)
	30 (100)	28 (100) †	58 (100)
SFA + TFA			
≤ 10% $^{\beta}$	15 (50)	12 (43)	27 (47)
> 10%	15 (50)	16 (57)	31 (53)
	30 (100)	28 (100) †	58 (100)
MUFA			
< 10%	10 (33)	13 (46)	23 (40)
10 - 20% $^{\beta}$	20 (67)	15 (54)	35 (60)
> 20%	0	0	0
	30 (100)	28 (100) †	58 (100)
Salt			
≤ 6g/day $^{\beta}$	25 (83)	24 (86)	49 (84)
> 6g/day	5 (17)	4 (14)	9 (16)
	30 (100)	28 (100) †	58 (100)

Data presented as n (%) at baseline; N – total number of participants; n – number of participants in cinnamon or placebo group; † P > 0.05 compared to cinnamon group (not significant); $^{\beta}$ ADA and Diabetes UK recommendations for dietary management in adults with diabetes - carbohydrates 45 - 60%; Fats ≤ 35%; Proteins 15 - 20%; PUFA ≤ 10%; MUFA 10 - 20%; SFA+TFA ≤ 10% and salt ≤ 6g/day.

Approximately 78% (n=45) of the respondents were taking recommended levels of less than 10% poly unsaturated fatty acids (PUFA), and levels f intake was found to be similar in both cinnamon and placebo groups. However, when considering the non beneficial fats of saturated and trans fatty acids, majority of the subjects (53%, n=31) were consuming more than the recommended limits of 10% from saturated and trans fatty acids. About 84% (n=49) and 60% (n=35) of the subjects were taking recommended amount of salt and mono unsaturated fatty

acids (MUFA) respectively, and this was found to be similar in both cinnamon and placebo groups at baseline.

Table 4.23 – The mean, confidence interval (CI) and range of total calorie intakes of carbohydrates, proteins and fats at baseline and post intervention in cinnamon and placebo groups [N=58].

Total calorie intake		Treatment	n	mean ± SD	95% CI for mean	minimum	maximum
Total calorie intake (kcal/day)	Baseline	Cinnamon	30	1863 ± 269.9	1761.9 - 1963.6	1314	2268
		Placebo	28	1844 ± 228.5	1755.4 - 1932.5	1530	2535
		Total	58	1854 ± 248.6	1788.3 - 1919.1	1314	2535
	12 weeks	Cinnamon	30	1818 ± 192.1	1746.4 - 1889.9	1386	2123
		Placebo	28	1843 ± 235.2	1751.9 - 1934.4	1520	2376
		Total	58	1830 ± 212.5	1774.3 - 1886.1	1386	2376
% Total calories from Carbohydrates (% kcal/day)	Baseline	Cinnamon	30	47.66 ± 7.18	44.97 - 50.33	33.2	64.6
		Placebo	28	47.02 ± 6.97	44.31 - 49.72	38.3	68.5
		Total	58	47.34 ± 7.02	45.50 - 49.19	33.2	68.5
	12 weeks	Cinnamon	30	47.27 ± 9.49	43.72 - 50.81	16.3	64.3
		Placebo	28	48.59 ± 6.03	46.25 - 50.93	38.3	61.0
		Total	58	47.90 ± 7.97	45.81 - 50.00	16.3	64.3
% Total calories from Proteins (% kcal/day)	Baseline	Cinnamon	30	13.92 ± 3.19	12.72 - 15.11	9.5	19.9
		Placebo	28	14.69 ± 2.73	13.63 - 15.75	9.9	20.6
		Total	58	14.29 ± 2.98	13.51 - 15.08	9.5	20.6
	12 weeks	Cinnamon	30	13.55 ± 2.76	12.52 - 14.58	8.3	21.4
		Placebo	28	14.10 ± 2.92	12.96 - 15.23	10.2	22.3
		Total	58	13.81 ± 2.83	13.07 - 14.56	8.3	22.3
% Total calories from Fats (% kcal/day)	Baseline	Cinnamon	30	38.03 ± 6.65	35.54 - 40.51	23.6	56.2
		Placebo	28	38.31 ± 5.85	36.04 - 40.58	21.6	46.3
		Total	58	38.16 ± 6.22	36.52 - 39.80	21.6	56.2
	12 weeks	Cinnamon	30	37.82 ± 7.17	35.14 - 40.50	22.7	49.1
		Placebo	28	37.27 ± 5.42	35.17 - 39.38	28.6	49.6
		Total	58	37.55 ± 6.34	35.89 - 39.22	22.7	49.6

Data presented as mean ± SD, 95% confidence interval and range (minimum – maximum). n=number of participants.

Table 4.24 - Effect of cinnamon on total calorie intakes of carbohydrates, fats and proteins at baseline and post intervention [N=58].

Total energy intake (kcal/day)	Cinnamon (n=30)	Placebo (n=28)	*P* value	*T*
Total calories (kcal/day)				
Baseline	1863 ± 269.96	1844 ± 228.25	0.776	0.285
Post-intervention	1818 ± 192.17	1843 ± 235.24	0.658	-0.445
Difference	- 45 ± 207.04	- 1 ± 186.87		
Carbohydrates (kcal/day)				
Baseline	884 ± 170.66	870 ± 185.23	0.755	0.314
Post-intervention	874 ± 136.30	898 ± 169.78	0.551	-0.599
Difference	- 10 ± 179.93	28 ± 185.65		
Proteins (kcal/day)				
Baseline	258 ± 64.05	270 ± 58.31	0.363	* -0.911
Post-intervention	247 ± 61.88	258 ± 51.18	0.388	* -0.864
Difference	- 11 ± 73.99	- 12 ± 65.82		
Fats (kcal/day)				
Baseline	711 ± 170.97	703 ± 127.69	0.835	0.209
Post-intervention	691 ± 159.49	687 ± 129.25	0.905	0.120
Difference	- 20 ± 126.26	- 16 ± 110.44		

Data presented as mean ± SD; * *z* values of data; The mean differences in total calories, carbohydrates, fats and protein intakes in the cinnamon group was not significantly differ from mean changes of placebo group (P > 0.05). Similarly, the baseline and post intervention total calories, carbohydrates, fats and protein intakes were found to be similar in both cinnamon and placebo groups.

Table 4.25 – The mean, confidence interval (CI) and range of % starch and sugar intake at baseline and post intervention in cinnamon and placebo groups [N=58].

% calories from starch and sugars		Treatment	n	mean ± SD	95% CI for mean	minimum	maximum
% Calories from Starch (% kcal/day)	Baseline	Cinnamon	30	33.44 ± 5.65	31.33 - 35.55	23.7	46.5
		Placebo	28	35.89 ± 6.30	33.44 - 38.33	22.8	55.0
		Total	58	34.62 ± 6.05	33.03 - 36.21	22.8	55.0
	12 weeks	Cinnamon	30	34.54 ± 6.89	31.97 - 37.12	16.6	49.7
		Placebo	28	36.28 ± 6.97	33.56 - 38.97	22.6	46.1
		Total	58	35.37 ± 6.92	33.55 - 37.19	16.6	49.7
% Calories from Sugars (% kcal/day)	Baseline	Cinnamon	30	12.58 ± 3.79	11.16 - 14.00	4.7	18.4
		Placebo	28	10.99 ± 4.12	9.38 - 12.59	4.3	21.3
		Total	58	11.81 ± 4.00	10.76 - 12.86	4.3	21.3
	12 weeks	Cinnamon	30	11.93 ± 4.52	10.24 - 13.62	4.4	23.3
		Placebo	28	10.98 ± 4.73	9.14 - 12.82	4.3	23.8
		Total	58	11.47 ± 4.61	10.26 - 12.68	4.3	23.8

Data presented as mean ± SD, 95% confidence interval and range (minimum – maximum). n=number of participants.

Table 4.26 - Effect of cinnamon on total carbohydrate and protein intake at baseline and post intervention [N=58].

Total carbohydrates (% kcal/day)	Cinnamon (n=30)	Placebo (n=28)	*P* value	*T*
% Total carbohydrates (% kcal/day)				
Baseline	47.66 ± 7.18	47.02 ± 6.97	0.460	* -0.739
Post-intervention	47.27 ± 9.49	48.59 ± 6.03	0.549	* -0.599
Difference	- 0.39 ± 8.90	1.57 ± 7.26		
% Starch (% kcal/day)				
Baseline	33.44 ± 5.65	35.89 ± 6.30	0.125	-1.557
Post-intervention	34.54 ± 6.89	36.28 ± 6.97	0.349	-0.945
Difference	1.10 ± 6.28	0.37 ± 6.82		
% Sugar (% kcal/day)				
Baseline	12.58 ± 3.97	10.99 ± 4.12	0.066	* -1.837
Post-intervention	11.93 ± 4.52	10.98 ± 4.73	0.323	* -0.988
Difference	- 0.65 ± 4.11	- 0.01 ± 4.26		
% Proteins (% kcal/day)				
Baseline	13.92 ± 3.19	14.69 ± 2.73	0.283	* -1.074
Post-intervention	13.55 ± 2.76	14.10 ± 2.92	0.575	* -0.56
Difference	- 0.37 ± 3.46	- 0.59 ± 3.39		

Data presented as mean ± SD; * *z* values of data; The mean differences in % total carbohydrates, % starch, % sugar and % protein intake in the cinnamon group was not significantly differ from mean changes of in placebo group ($P > 0.05$). Similarly, the baseline and post intervention % total calories, starch, sugar and proteins were found to be similar in both cinnamon and placebo groups

Table 4.27 – The mean, confidence interval (CI) and range of % calorie intake from fats at baseline and post intervention in cinnamon and placebo groups [N=58].

% calories from SFA, PUFA, MUFA and TFA		Treatment	n	mean ± SD	95% CI for mean	minimum	maximum
% calories from Saturated Fatty Acids (SFA) (% kcal/day)	Baseline	Cinnamon	30	10.52 ± 4.41	8.87 - 12.17	1.3	19.7
		Placebo	28	10.09 ± 3.93	8.56 - 11.61	2.7	17.8
		Total	58	10.31 ± 4.15	9.22 - 11.41	1.3	19.7
	12 weeks	Cinnamon	30	10.66 ± 4.99	8.80 - 12.53	2.5	22.4
		Placebo	28	9.70 ± 4.68	7.89 - 11.52	2.5	18.1
		Total	58	10.20 ± 4.82	8.93 - 11.47	2.5	22.4
% calories from Poly Unsaturated Fatty Acids (PUFA) (% kcal/day)	Baseline	Cinnamon	30	7.88 ± 2.89	6.80 - 8.96	3.6	13.8
		Placebo	28	7.33 ± 2.68	6.29 - 8.37	3.2	14.1
		Total	58	7.61 ± 2.78	6.88 - 8.34	3.2	14.1
	12 weeks	Cinnamon	30	7.52 ± 2.97	6.40 - 8.63	2.5	14.0
		Placebo	28	7.69 ± 2.72	6.63 - 8.75	2.7	13.7
		Total	58	7.60 ± 2.83	6.86 - 8.35	2.5	14.0
% calories from Mono Unsaturated Fatty Acids (MUFA) (% kcal/day)	Baseline	Cinnamon	30	11.14 ± 3.30	9.91 - 12.38	3.4	15.7
		Placebo	28	10.49 ± 3.45	9.15 - 11.83	3.8	17.1
		Total	58	10.83 ± 3.36	9.94 - 11.71	3.4	17.1
	12 weeks	Cinnamon	30	10.78 ± 3.58	9.44 - 12.12	4.1	17.6
		Placebo	28	10.10 ± 3.30	8.82 - 11.38	4.3	15.5
		Total	58	10.45 ± 3.43	9.55 - 11.36	4.1	17.6
% calories from Trans Fatty Acids (TFA) (% kcal/day)	Baseline	Cinnamon	30	0.44 ± 0.60	0.20 - 0.65	0.0	3.1
		Placebo	28	0.59 ± 0.62	0.34 - 0.82	0.0	3.2
		Total	58	0.50 ± 0.61	0.34 - 0.66	0.0	3.2
	12 weeks	Cinnamon	30	0.29 ± 0.43	0.13 - 0.45	0.0	2.0
		Placebo	28	0.45 ± 0.44	0.27 - 0.61	0.0	2.0
		Total	58	0.36 ± 0.44	0.25 - 0.48	0.0	2.0

Data presented as mean ± SD, 95% confidence interval and range (minimum – maximum). n=number of participants.

Table 4.28 - Effect of cinnamon on total fat (%) intake at baseline and post intervention [N=58].

% Total Fats (% kcal/day)	Cinnamon (n=30)	Placebo (n=28)	*P* value	*T*
Baseline	38.03 ± 6.65	38.31 ± 5.85	0.619	* -0.498
Post-intervention	37.82 ± 7.17	37.27 ± 5.42	0.446	* -0.763
Difference	- 0.21 ± 6.95	- 1.04 ± 6.22		
SFA (% kcal/day)				
Baseline	10.52 ± 4.41	10.09 ± 3.93	0.695	0.394
Post-intervention	10.66 ± 4.99	9.70 ± 4.68	0.454	0.754
Difference	0.14 ± 3.10	- 0.39 ± 4.07		
PUFA (% kcal/day)				
Baseline	7.88 ± 2.89	7.33 ± 2.68	0.462	0.741
Post-intervention	7.52 ± 2.97	7.69 ± 2.72	0.815	-0.235
Difference	- 0.36 ± 3.81	0.36 ± 2.95		
MUFA (% kcal/day)				
Baseline	11.14 ± 3.30	10.49 ± 3.45	0.464	0.737
Post-intervention	10.78 ± 3.58	10.11 ± 3.30	0.457	0.749
Difference	- 0.36 ± 3.29	- 0.38 ± 2.16		
Trans fats (% kcal/day)				
Baseline	0.44 ± 0.60	0.59 ± 0.62	0.110	* -1.598
Post-intervention	0.29 ± 0.43	0.45 ± 0.44	0.054	* -1.927
Difference	- 0.15 ± 0.16	- 0.14 ± 0.11		

Data presented as mean ± SD; * *z* values of data; The mean differences in SFA, MUFA, PUFA and trans fatty acid levels in the cinnamon group was not significantly differ from mean differences of placebo group ($P > 0.05$).

Table 4.29 – The mean, confidence interval (CI) and range of sodium and fiber intake at baseline and post intervention in cinnamon and placebo groups [N=58].

Intake of Salt and Fibre		Treatment	n	mean ± SD	95% CI for mean	minimum	maximum
Sodium intake (mg/day)	Baseline	Cinnamon	30	4312 ± 1793	3642 - 4981	1299	8106
		Placebo	28	4497 ± 1425	3944 - 5049	1832	8265
		Total	58	4401 ± 1614	3976 - 4826	1299	8265
	12 weeks	Cinnamon	30	4242 ± 1486	3687 - 4797	1094	8008
		Placebo	28	4678 ± 1861	3180 - 6175	1832	8351
		Total	58	4452 ± 2870	3698 - 5207	1094	8351
Fibre intake (g/day)	Baseline	Cinnamon	30	6.15 ± 1.66	5.53 - 6.77	4.4	11.1
		Placebo	28	6.13 ± 2.26	5.24 - 7.00	2.8	12.5
		Total	58	6.14 ± 1.96	5.62 - 6.65	2.8	12.5
	12 weeks	Cinnamon	30	6.14 ± 2.52	5.19 - 7.08	2.8	11.7
		Placebo	28	6.28 ± 2.17	5.43 - 7.12	3.6	11.7
		Total	58	6.20 ± 2.34	5.59 - 6.82	2.8	11.7

Data presented as mean ± SD, 95% confidence interval and range (minimum – maximum). n=number of participants.

Table 4.30 - Effect of cinnamon on total sodium and fiber intake at baseline and post intervention [N=58].

Sodium & Fibre intake	Cinnamon (n=30)	Placebo (n=28)	*P* value	*T*
Sodium (mg/day				
Baseline	4312 ± 1793	4497 ± 1425	0.523	* -0.638
Post-intervention	4242 ± 1486	4678 ± 1861	0.513	* -0.654
Difference	- 69 ± 1749	181 ± 3447		
Fibre (g/day)				
Baseline	6.15 ± 1.66	6.13 ± 2.26	0.498	* -0.678
Post-intervention	6.14 ± 2.52	6.28 ± 2.17	0.528	* -0.631
Difference	- 0.01 ± 2.44	0.16 ± 2.36		

Data presented as mean ± SD; * *z* values of data; The mean differences in sodium and fiber levels in the cinnamon group was not significantly different from mean changes of sodium and fiber levels in the placebo group (P > 0.05).

4.4 Discussion

The glucose lowering potency of cinnamon has long been recognised, and over the past few years different clinical trials have demonstrated conflicting results related to the anti-diabetic effects of cinnamon (Khan *et al,* 2003; Altschuler *et al,* 2007; Mang *et al,* 2006, Blevins *et al,* 2007; Vanschoonbeek *et al,* 2006). This is the first clinical trial in the UK studying multi ethnic groups and has confirmed the beneficial effects of cinnamon on HbA1c for poorly controlled type 2 diabetes patients with HbA1c $\geq$ 7%. In addition, it has demonstrated for the first time, an improvement in blood pressure expressed by the significant decrease in both systolic and diastolic blood pressures.

4.4.1 The socio demographic and lifestyle characteristics of the participants

The socio demographic characteristics such as age, gender, ethnicity, religion, educational status and family income of the participants were similar for both cinnamon and placebo groups. Therefore, the effects of socio demographic factors on the study outcomes were minimal. The majority of the subjects are females, Asian British and Christians, and had an annual income of less than £10,000 with secondary school educational status. Most importantly, the patients recruited in this study provide a wide ethnic (White, Irish, Pakistani, Indian, Bangladeshi, African and Caribbean) and religious (Christian, Hindu, Muslim and Sikh) diversity.

Vanschoonbeek *et al,* (2006) suggested that the single female gender of their study may have affected their study outcome, but all other studies have included both genders. There were no apparent gender-related sub-groups to suggest this influence on gender. Although a multi ethnic patient population was included in this study, there are differences in ethnicity in other studies which may have contributed to the heterogeneity of results. For example, Blevins *et al,* (2007) included different ethnicities with no sub-groups appearing. The ethnicity of the subjects were not reported in the studies conducted by Khan *et al,* (2003), Mang *et al,* (2006) and Vanschoonbeek *et al,* (2006), even though subjects were recruited from Pakistan, German and Netherlands respectively.

The lifestyle characteristics such as habits of smoking, alcohol consumption, level of physical activity and dietary intake of the subjects in this study was found to be similar in both the cinnamon and placebo groups. This was due to the recruitment procedure. Patients recruited for this trial were referred to a dietician to receive at least two sessions of diet and lifestyle counselling. The majority of the subjects were non smokers (91%), did not consume alcohol

(60%), and ate a mixed diet (75%) with considerable portions of fruits and vegetables. The total energy intake of the participants at the beginning of the study was found to be similar in both groups (cinnamon: 1863 kcal/day; placebo: 1844 kcal/day) and less than the recommended total calorie intake of diabetic patients (< 2000kcal/day). This may be because, patients in this study received at least two sessions of diet/lifestyle advice from dieticians.

Even though subjects received lifestyle counselling from the dietician, the physical activity behaviour of the patients was not convincing. The majority of the participants were involved in moderate or light exercise (96%), and 72% of the subjects were involved in same level of exercise or less compared to last year. However, patients may always over report their exercise habits. Other studies all have discrepancy with respect to dietary and physical activity control, and to the type of drug the patients were taking. For example, the publications from Mang *et al,* (2006) and Khan *et al,* (2003) fail to describe dietary or exercise control during their intervention. These are factors that can markedly influence glycaemic control and insulin sensitivity (Barnard & Wen, 1994), and care must be taken in comparing such findings. A recent RCT showed no effect of 1.5g/day of cinnamon in postmenopausal diabetic patients (Vanschoonbeek *et al,* 2006). This had a superior study design to the studies of Khan *et al,* (2003) and Mang *et al,* (2006) with strict pharmaceutical, dietary and exercise restrictions, but included only female subjects and used a relatively low dose, which may possibly account for the null findings (Soloman, 2007).

4.4.2 The study design

This study adopts a randomized, placebo controlled, double blind clinical trial. The simple random assignment of subjects to either cinnamon or placebo groups with equal probabilities of allocation was ensured by the computer generated randomization list. The choice of starch flour as a placebo was shown to have no effect on glucose responses, nor could volunteers distinguish it from the cinnamon capsules. The encapsulation of cinnamon and placebo capsules are similar and made from gelatine and plant based gelling substance (modified form of starch and cellulose).

To ensure double blinding, the non transparent cinnamon and placebo bottles were prepared by another researcher and labelled as A and B. The author, who gave the supplements to subjects, was blinded until the end of the trial. The subjects were also blinded as the appearance was similar and the characteristic cinnamon smell (cinnamon powder) was placed under the lid of the

placebo bottles. The colour, shape and size of cinnamon and placebo capsules were identical. Also, at post intervention approximately 80% (n=43) of the subjects reported that they were taking cinnamon and 17% (n=9) reported they did not know which capsule they were taking. Double blinding of this trail was therefore appropriate. The anti-diabetic potential of *Cinnamomum cassia* is likely to be superior (Versphol *et al,* 2005) and therefore a 2g dose of *cinnamomum cassia* powder was chosen to be administered for 12 weeks in this study. The dose for this study was based on the previously demonstrated benefit of 1 to 6g/day (Khan *et al,* 2003). Compliance or side effects due to cinnamon consumption were not reported during the study period.

The primary outcome of this study was to measure changes in HbA1c before and after the intervention, because HbA1c remains the most important long term predictor of complications in both type 1 and type 2 diabetes and the effect of any intervention on HbA1c is critical in determining its clinical usefulness (Altschuler *et al,* 2007). The HbA1c levels, already planned as part of subjects standard diabetes care within their NHS diabetes consultation, were obtained from medical records at the time of enrolment (baseline) and 12 weeks later (post intervention). The previous studies (Altschuler *et al,* 2006) and the NHS UK standard care procedures for diabetes management suggested that 12 weeks of study duration is good enough to show the effect of cinnamon on the primary outcome of HbA1c levels.

The sample size of this study demonstrated that a total of 64 subjects (32 per arm) would be sufficient to have power of 80% to detect a reduction in HbA1c at 3 months of 0.5, based on an SD of 0.7 for change in HbA1c (primary outcome) over three months and type 1 error of 5%. Though, due to limited time, the cost of trial, the sample size was restricted to 58 subjects. However, 58 subjects were sufficient to demonstrate an effect and also pointed out that these results were consistent with other recent observations (Mang *et al,* 2006). Other studies did not demonstrate any significant reduction in HbA1c, and this may be attributed due to underpowered sample size (Mang *et al,* 2006; Blevins *et al,* 2007) and possibly reporting false negative and false positive outcomes, respectively (Greenhalgh, 2001).

The stratification of samples by age or gender or duration of diabetes was not included in this study. However, at baseline the gender and age of the respondents were found to be similar in both cinnamon and placebo groups. Although previous studies were randomized controlled trials, none provide details of how randomization took place. Only Vanschoonbeek *et al,* (2006)

matched pairs by all characteristics, and Blevins *et al,* (2007) stratified only by gender. Although variation between control and intervention groups in all studies is statistically insignificant, systematic bias may have been inadvertently present by not matching subjects taking differing diabetes medications, although no apparent sub-groups were discussed (Mang *et al,* 2006; Blevins *et al,* 2007).

Khan *et al,* (2003) failed to verify whether their study was double blind, and the recognizable cinnamon aroma may have created potential detection bias in all previous studies. There appears to be no performance bias, and exclusions and withdrawals were reported appropriately with the exception of Khan *et al,* (2003), who reported none. Mang *et al,* (2006) failed to report which group their withdrawals came from, although both arms remained evenly distributed. Diabetes medications may vary and affect cinnamon efficacy, although no previous studies reported the occurrence of sub-groups due to differing medication. Hypertensive and lipid-lowering medication constitute a further heterogeneous factor, although there is no known interaction between these medications and the action of cinnamon (World Health Organization, 1999[b]). Therefore at this time it is hypothesized that non-diabetic medications are not a factor in the contrasting results reported in this study.

The mean age, BMI and years since diagnosis of diabetes in our study was similar compared to other studies (Khan *et al,* 2003; Mang *et al,* 2006; Vanschoonbeek *et al,* 2006, Blevins *et al,* 2007; Altschuler *et al,* 2007), and therefore less likely to be heterogeneous factors contributing to the different results. Although the number of years since diagnosis of diabetes among subjects were similar for cinnamon and placebo groups (5.76 ± 4.93 and 5.83 ± 4.23 respectively), a higher standard deviation in this study indicates that the data points tend to be spread out over a large range of 1 – 15 years. Therefore, the mean diabetes duration might not represent the true value. Stratified sampling method based on diabetes duration might eliminate this bias.

An intention to treat analysis method was adopted in this study. Only Blevins *et al,* (2007) and Altschuler *et al,* (2007) confirm data analysis on an intention to treat basis. This is more significant for Mang *et al,* (2006), as although the numbers of groups (cinnamon and placebo) in each study remained balanced, how withdrawals and exclusions affected control and intervention groups is not reported, and data is not analyzed on an intention to treat basis. The remaining studies (Khan et al, 2003; Vanschoonbeek et al, 2006) failed to comment on their statistical analysis based on intention to treat analysis.

4.4.3 Changes in glycaemic indicators of HbA1c and FPG

The mean baseline HbA1c (cinnamon 8.22%; placebo 8.55%) of this study shows that patients had elevated glycaemic levels. Subjects with poor glycaemic control of HbA1c of $\geq$ 7% were recruited in this study and this may have been the reason why subjects treated with cinnamon showed a significant reduction of 4.4% in their HbA1c compared to the placebo group. Other studies have not shown any significant reduction in HbA1c (Mang *et al,* 2003; Blevins *et al,* 2007; Vanschoonbeek et al, 2006), because the baseline HbA1c in these studies were found to be normal or near normal, ranged from 6.7% to 7.1% (Figure 4.25).

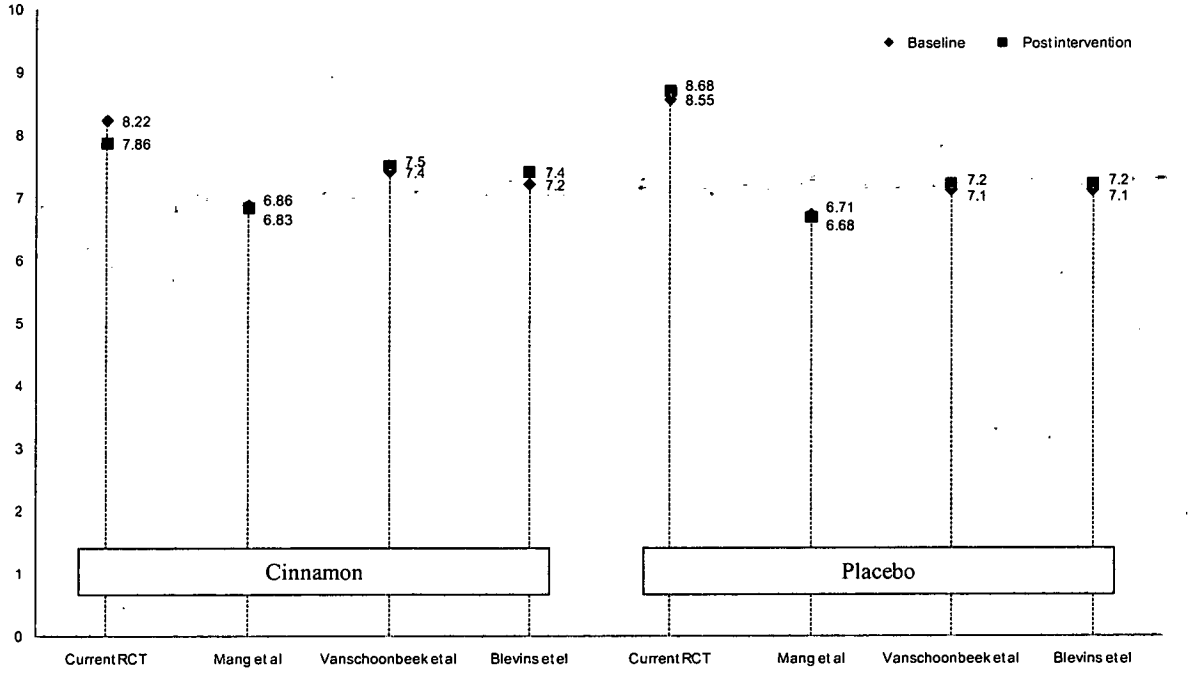


Figure 4.25 – Comparison of the mean HbA1c of current RCT with previous randomized controlled trials. Data presented as mean HbA1c; our current RCT shows higher baseline HbA1c levels in both cinnamon and placebo groups compared to previous RCTs of Mang's, Vanschoonbeek's and Blevin's studies.

According to the current guidelines recommended for the treatment of diabetes, normal or near normal glycaemia with an HbA1c of < 7% should be achieved (American Diabetes Association, 2005, 2006). This suggests that in well controlled type 2 diabetic patients (controlled HbA1c of < 7%) the effects of cinnamon on HbA1c may be minimalised. The other possible explanation for the positive results in this study could be due to the 2g dose of cinnamon and none of the previous studies administered 2g of cinnamon for 12 weeks of duration.

In agreement with Blevins *et al,* (2007) and Vanschoonbeek *et al,* (2006), but in contrast with Khan *et al,* (2003) and Mang *et al,* (2006), significant changes in FPG were not observed in our study. This suggests that improvements in FPG are found with higher baseline (pre-trial) values, i.e. with poor glycaemic control. The discrepancies between studies may therefore become clear by looking at the baseline FPG values of the cinnamon group (Figure 4.26): Khan *et al,* (2003) – 12 mmol/l; Mang *et al,* (2006) – 9.26 mmol/l; Vancschoonbeek *et al,* (2006) – 8.37 mmol/l; Blevins *et al,* (2007) – 7.38 mmol/l; Current RCT – 8.82 mmol/l. No changes in FPG were found in our current RCT data or Blevin's data or Vanschoonbeek's data (Figure 4.26)

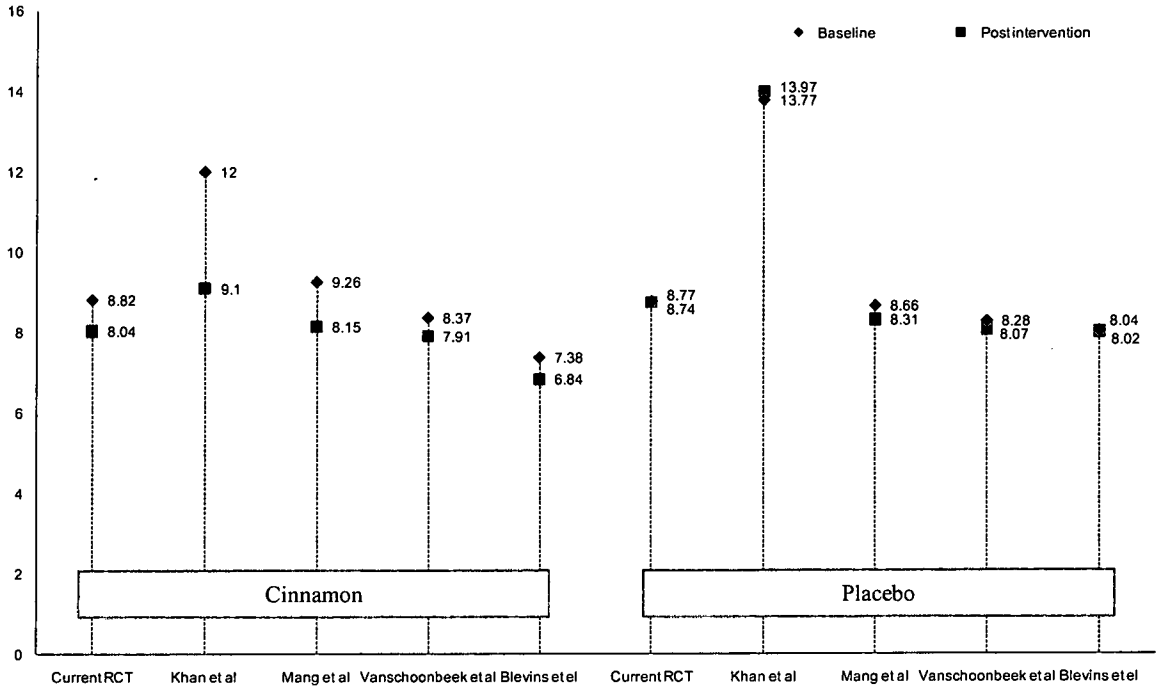


Figure 4.26 – Comparison of the mean fasting plasma glucose (FPG) of current RCT with previous randomized controlled trials. Data presented as mean FPG (mmol/l); Khans study shows elevated FPG levels of ≥ 12mmol/l at baseline in both cinnamon and placebo groups compared to other studies.

Khan *et al,* (2003) and Mang *et al,* (2006) demonstrated a significant reduction in FPG in the cinnamon group, and this may have been because of the elevated FPG levels at baseline in cinnamon group (12 mmol/l and 9.26 mmol/l respectively) (Figure 4.26). The baseline FPG in our study (cinnamon – 8.82 mmol/l and placebo - 8.77 mmol/l) suggested that, subjects had near normal FPG at baseline and this may be the reason why a significant reduction was not obtained in FPG in the cinnamon group. A similar trend was observed in other studies (Vanschoonbeek *et al,* 2006; Blevins *et al,* 2007) (Figure 4.26). According to the American Diabetes Association guidelines for glycaemic control (ADA, 2005), pre-prandial blood glucose levels should be

maintained between 5.0 – 7.2 mmol/l. Since the HbA1c test reflects mean glycaemia over the proceeding 2 to 3 months, measurement approximately every three months is requires determining whether a patient's metabolic control has been reached and maintained with in the target range (Sacks *et al,* 2002). Therefore measuring HbA1c is more stable indicator of glycemic level than measuring FPG (American Diabetes Association, 2005).

Several human studies have investigated the effect of cinnamon upon blood glucose, but sample sizes have been small and results are varied. The first study (Khan *et al,* 2003) reported statistically and clinically significant reductions in FPG (18-29%) with 1, 3 and 6g of cinnamon, although comparable results have not been reproduced. A second study reduced FPG by 10.3% with 3g of cinnamon, and illustrated a strong correlation ($p < 0.001$) between higher baseline FPG and FPG reduction (Mang *et al,* 2006) and no significant changes in HbA1c% was observed. A small randomized crossover trial involving 7 non-diabetic subjects reported a 13% reduction in FPG and improved insulin sensitivity ($p < 0.05$) following an oral glucose tolerance test (OGTT) with 5g of cinnamon versus placebo (Solomon and Blannin, 2007). A randomized placebo controlled trial with 15 insulin resistant women illustrated significant reductions in insulin resistance, FPG and post-OGTT FPG ($p < 0.03$) in the cinnamon group (Wang *et al,* 2007), although FPG in the control group also decreased. Another study involving 22 pre-diabetic subjects diagnosed with metabolic syndrome reported a reduction of 8.4% FPG ($p < 0.01$) with 10g of cinnamon for 12 weeks in a placebo-controlled, double blind study (Ziegenfuss *et al,* 2006).

Vanschoonbeek *et al,* (2006) reported 1.5g of cinnamon supplementation for 6 weeks did not improve HbA1c or glucose tolerance in post menopausal type 2 diabetic patients. The reasons for the negative results in this study could be due to inadequate study duration or inclusion of only postmenopausal women in this study. At least 90 days are required to see the effect of cinnamon on HbA1c (Altschuler *et al,* 2007). Whether differences in hormone balance affect the potential interaction between cinnamon supplementation and glucose control is unknown among postmenopausal women in this study. Mang *et al,* (2006) revealed that cinnamon extract showed moderate effects in reducing FPG but not on HbA1c. The mean baseline HbA1c of 6.8% suggests that for type 2 diabetes patients with good glycemic control, the effect of cinnamon in lowering HbA1c is rather weak. Administration of cinnamon extract instead of cinnamon powder may also be a contributory factor for the false negative results in this study. Therefore

the effects of cinnamon on blood glucose levels differ by population (ethnicity), their habitual diet, BMI, baseline glucose levels and dose of cinnamon (Blevins *et al,* 2007).

As a result, based on the results of our current RCT, it is most likely that the therapeutic dose of cinnamon may depend upon the subjects' baseline HbA1c or FPG, rather than there being a significant dose-dependant effect. Ziegenfuss *et al,* (2006) reported an 8.4% reduction in FPG in subjects with mean baseline FPG of 6.46 mmol/L and treated with 10g of cinnamon daily for 12 weeks. This illustrates that even higher cinnamon doses can bring about a significant reduction in blood glucose ($p < 0.01$) in subjects with lower baseline FPG, and suggests a possible relationship between baseline FPG or HbA1c, dose of cinnamon and % reduction in glycaemic levels which might be tested in future studies. However, the tolerability and compliance of high dose of cinnamon along with anti diabetic medication might be questionable and needs to be studied further.

Also different methodologies used in *in-vivo* animal studies presenting significant results support this hypothesis, as elevated glucose load and higher cinnamon dosage against bodyweight in comparison to human studies are commonly used. When comparing cinnamon powder (Vanschoonbeek *et al,* 2006; Kannappan *et al,* 2007) or cinnamon extract (Kim *et al,* 2006[a]; Mang *et al,* 2006), cinnamon dosage in rats was 6.6 times higher than in human studies. The equivalent human dosage if applying the measure per bodyweight administered by Kannappan *et al,* (2007) would be approximately 17g cinnamon/day rather than the 1.5g used by Vanschoonbeek *et al,* (2006). Less effect upon glucose levels is seen in animal studies without glucose challenge (Babu *et al,* 2007), and greater results reported with elevated glucose load (Verspohl *et al,* 2005; Kannappan *et al,* 2006; Kim *et al,* 2006[a]; Preuss *et al,* 2006), supporting the hypothesis that the efficacy of cinnamon is dependant upon the level of hyperglycaemia. Consequently, in diabetic studies reporting significant reduction in FPG, it remains unclear whether cinnamatic effects are due to the dosage or duration of study or baseline glycemic levels, and further studies are warranted to address these issues.

In addition, the literature suggests that cinnamon can directly up regulate insulin receptor autophosphorylation and inhibit phosphatase action and glycogen synthase kinase-3β (GSK - 3β) activity *in vitro* (Imparl-Radosevich *et al,* 1998). Therefore, the effect of cinnamon on insulin sensitivity may be through acting directly on aspects of the insulin signalling cascade

that are directly associated with insulin resistance and type 2 diabetes (Saltiel & Kahn, 2001; Eldar-Finkelman & Krebs, 1997; Cline *et al,* 1999; Soloman, 2007).

Clinical measurement of FPG is more consistent and reproducible than postprandial glucose (PPG), because there are more variables in the latter, such as timing and carbohydrate load (Barr *et al,* 2002). Likewise, FPG may be easier to control with medication than PPG. The variables of food intake and exercise, for example, are much less of a factor at night preceding measurement of the FPG, and this may enable a more consistent pattern of values for FPG (Barr *et al,* 2002). However, the roles of FPG and PPG continue to be debated (Erlinger *et al,* 2001). Because the FPG and pre-meal glucose levels are reflected in the PPG, it seems most practical to routinely control pre-meal glucose first, since it will likewise lower post-meal glucose levels, as well (Erlinger *et al,* 2001; Barr *et al,* 2002). Therefore, with the evidence suggesting cinnamon may reduces gastric emptying (Hlebowizc *et al,* 2007), this may reduces postprandial glucose (PPG) and HbA1c levels in type 2 diabetic patients.

4.4.4 Changes in systolic and diastolic blood pressures

The baseline SBP (cinnamon 132.5 mmHg: placebo 134.4 mmHg) and DBP (cinnamon 85.2 mmHg: placebo 86.8 mmHg) in our current RCT demonstrates that majority of the patients had elevated or upper normal blood pressure levels, but not with hypertension. According to the current guidelines recommended for the treatment of diabetes, normal or near normal blood pressure with a SBP of < 130 mmHg and DBP of < 80 mmHg should be achieved (American Diabetes Association, 2005, 2004[c]). In agreement with Ziegenfuss *et al,* (2006), findings, our study also suggested that cinnamon significantly reduces systolic blood pressure compared to placebo group. However, in contrast with Ziegenfuss *et al* (2006), a significant reduction in diastolic blood pressure was observed in the cinnamon group compared to placebo in this current RCT. This may be because of the vasodilation effect of cinnamon or the baseline DBP of this study was found to be higher than Ziegenfuss *et al,* (2006) study (Figure 4.27).

Furthermore, this demonstrates that improvements in systolic and diastolic blood pressures are found with higher baseline values, i.e. with poor blood pressure control. The discrepancies between studies may therefore become clear by looking at the baseline SBP and DBP of the cinnamon group in Figure 4.27. This suggests that in patients with poor control of blood pressure, the effects of cinnamon on blood pressure may be higher. None of the previous human studies reported the beneficial effects of cinnamon on blood pressure levels.

Ziegenfuss *et al,* (2006) reported the beneficial effect of the water soluble cinnamon extract on body composition and features of metabolic syndrome, and showed that supplementation of cinnamon extract (10g/day) significantly reduces systolic blood pressure from 133 mmHg to 128 mmHg in cinnamon group compared to placebo (Figure 4.27) . Ravindran *et al,* (2003) recently demonstrated in his book that, cinnamon (cinnamaldehyde) produced a hypotensive effect mainly due to peripheral vasodilation in dogs. Animal studies have also proposed that addition of dietary cinnamon consistently reduced systolic blood pressure levels in experimental rat models (Preuss *et al,* 2006). However, the detail mechanism of cinnamon on blood pressure on human needs to be studied further.

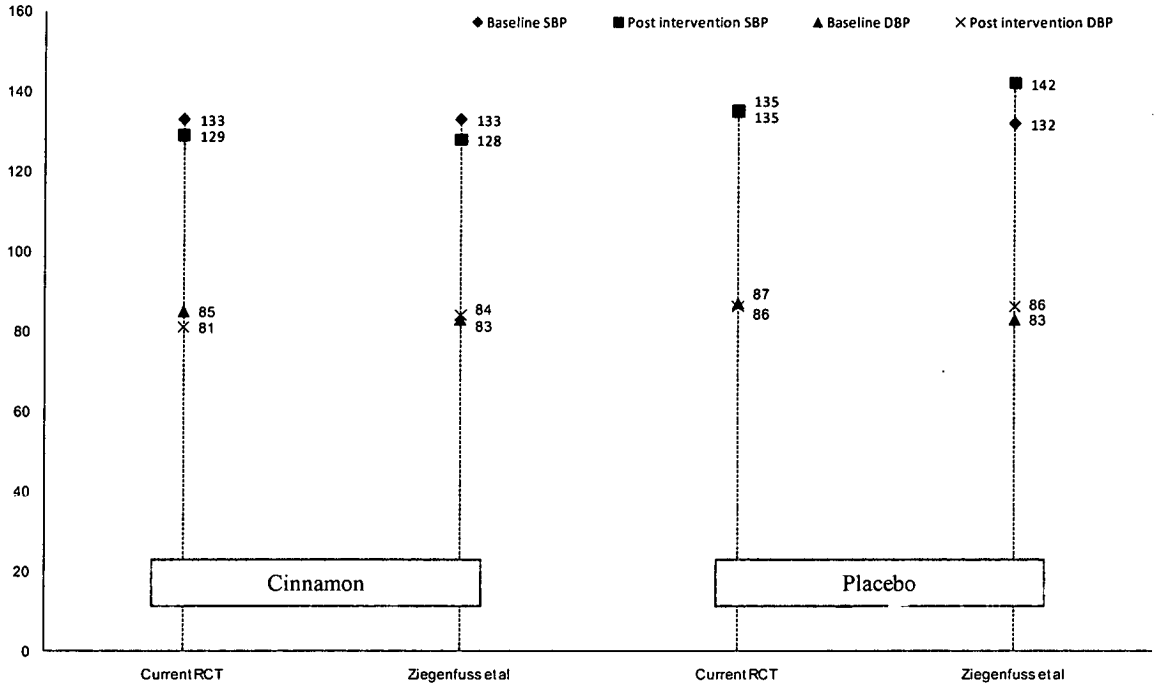


Figure 4.27 – Comparison of the mean systolic and diastolic blood pressure (SBP and DBP) of current RCT with previous randomized controlled trial. Data presented as mean SBP and DBP (mmHg); the current RCT and Ziegenfuss *et al,* (2006) studies shows a similar baseline SBP and DBP in both cinnamon and placebo groups.

The use of antihypertensives or statins was similar for both cinnamon and placebo groups in the current RCT. Similarly there was no significant effect of salt or total energy intake on blood pressure levels (P>0.05). Therefore, it was suspected that cinnamon independently associated with reduction of systolic and diastolic blood pressure levels, however the dose and type of antihypertensive drugs used by the subjects are unknown in our stduy, and this may have an impact on the blood pressure levels of the type 2 diabetic subjects. Many commonly ingested nutrients or dietary elements known to augment insulin resistance are also associated with elevated blood pressure, for example fatty acids (Appel *et al,* 1993; Kraegen *et al,* 1991) and

sugars (Yudkin, 1988; Israel *et al,* 1983). In contrast, dietary factors generally accepted to enhance insulin sensitivity such as soluble fibers (Zein *et al,* 1990; Gondal *et al,* 1996) and Chromium (Preuss *et al,* 1995; Mertz, 1993) are associated with lower blood pressure. In confirmation of the correlation between glucose or insulin metabolism and blood pressure regulation, certain drugs, such as metformin (Verma *et al,* 1994) and exercise (Reaven *et al,* 1998), which all augment insulin sensitivity, are also recognized to lower blood pressure. All this indirectly suggests that perturbed glucose/insulin metabolism is directly or indirectly involved, at least to some extent, in some forms of hypertension (Preuss *et al,* 2006). Consequently, further studies might necessary to proof the efficacy of cinnamon on systolic and diastolic blood pressure levels among diabetic patients who take similar dose or type of anti hypertensive drugs.

4.4.5 Changes in serum lipid profiles of total cholesterol, serum triglycerides, HDL and LDL cholesterols

According to the current guidelines recommended for the dyslipidaemia management in type 2 diabetes patients, normal or near normal serum lipid levels with a LDL cholesterol < 2.6 mmol/l, HDL cholesterol > 1.02 mmol/l and serum triglycerides < 1.7 mmol/l should be achieved (American Diabetes Association. 2005, 2004[b]). In our current RCT, the baseline LDL cholesterol (cinnamon 2.47 mmol/l; placebo 2.27 mmol/l), HDL cholesterol (cinnamon 1.18 mmol/l; placebo 1.16 mmol/l) and serum triglycerides (cinnamon 1.65 mmol/l: placebo 1.48 mmol/l) demonstrates that patients had well controlled or normal serum lipid profiles at the beginning of the study (baseline). This further confirms that patients with good control of serum lipid profiles, the effect of cinnamon on serum lipid profiles is always minimum. Therefore, in agreement with Mang *et al,* (2003), Vanschoonbeek *et al,* (2006) and Blevins *et al,* (2007), and in contrast with Khan *et al,* (2003), the results of our current RCT demonstrated that patients treated with cinnamon did not show any significant reduction in their serum lipid parameters of serum triglycerides, HDL and LDL cholesterols (Figure 4.28; Figure 4.29). Even though Khan *et al* (2003) reported a significant reduction in total cholesterol, LDL cholesterol land serum triglycerides in his study.

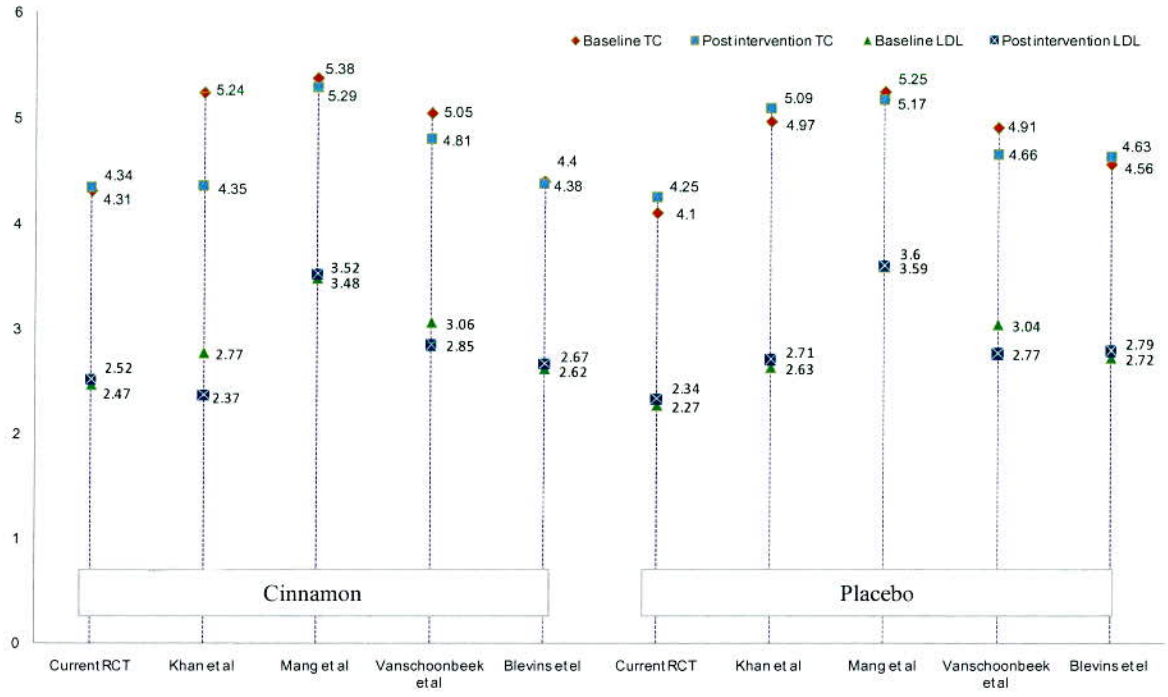


Figure 4.28 – Comparison of the mean LDL and total cholesterol (TC) levels of current RCT with previous randomized controlled trials. Data presented as mean cholesterol levels (mmol/l); the current RCT and Blevins study shows a similar baseline total cholesterol levels in the cinnamon group; Khan's, Mang's and Vanschoonbeek's studies shows similar total cholesterol at baseline (≥ 5 mmol/l) in cinnamon group; the mean LDL cholesterol is ≤ 2.6 mmol/l at baseline in cinnamon group in this current RCT and Blevin's study.

Khan *et al,* (2003) showed elevated baseline lipid parameters of total cholesterol, LDL and triglyceride levels (Figure 4.28; Figure 4.29) in his study and concluded that cinnamon significantly reduces mean serum triglycerides (23 – 30%), LDL cholesterol (7 – 27%) and total cholesterol (12 – 26%) compared to placebo group. In contrast, Mang *et al,* (2006) and Vanschoonbeek *et al,* (2006) studies did not reported any significant reductions in the lipid profiles, even though their patients had elevated LDL and total cholesterol levels at baseline (Figure 4.28; Figure 4.29). This may be because of the use of cinnamon extract instead of cinnamon powder in Mang's study and inclusion of single gender of postmenopausal women or 6 weeks of study duration or less number of samples (n=25) in Vanschoonbeek's study.

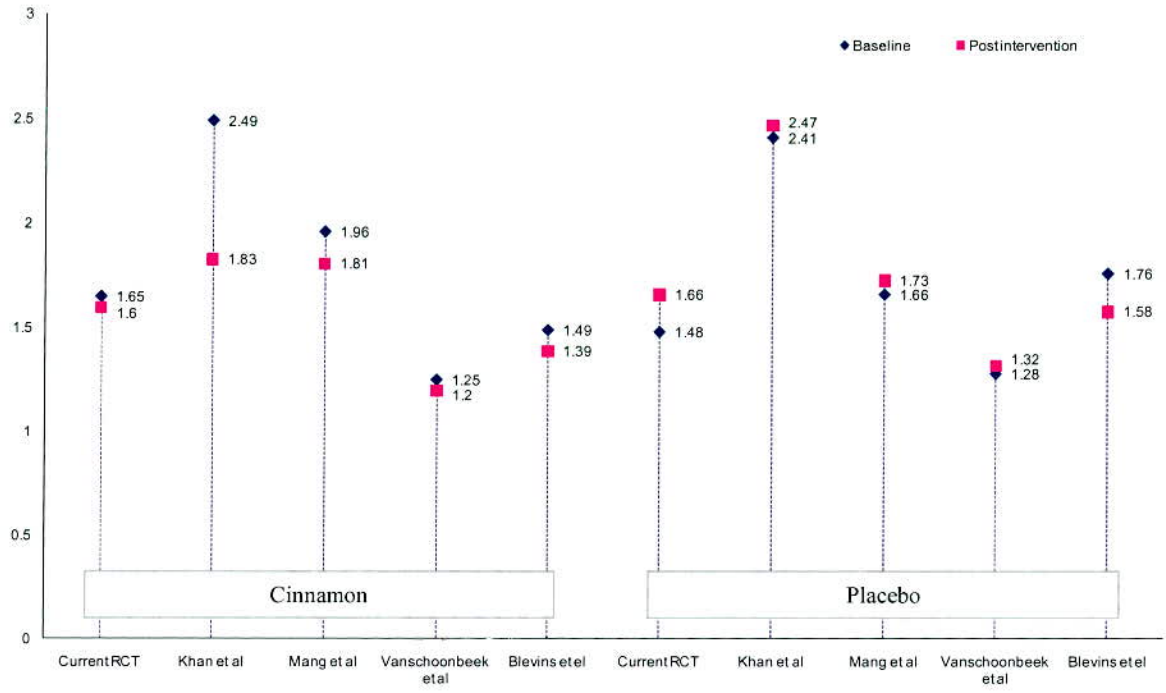


Figure 4.29 – Comparison of the mean serum triglyceride levels of current RCT with previous randomized controlled trials. Data presented as mean serum triglyceride (mmol/l);; the current RCT, Vanschoonbeek's study and Blevins study shows a good control of baseline serum triglyceride levels in the cinnamon group (≤ 1.7 mmol/l); Khans and Mangs studies shows elevated serum triglycerides at baseline (≥ 1,7 mmol/l) in the cinnamon group.

Normally, insulin resistance leads to the over production of very low density lipoproteins (VLDL) and to reduce lipoprotein lipase activity, thereby resulting in dyslipidaemia (Ruotolo and Howard, 2002; Simsolo *et al,* 1992). Therefore, attainment of better glycemic control may improve the blood lipid profiles (Krentz, 2003; Steinmetz, 2003). Obviously, the significant reduction in HbA1c levels in our study might sufficient to induce an improvement of the lipoprotein concentration. Also subjects with poor lipoprotein levels may benefit more from cinnamon intake. One of the other reasons may be, roughly, 21% of our subjects were taking statins and about 12% were taking both antihypertensives and statins, whereas these medicines were not taken by subjects or reported in Khan *et al,* (2003) study. Furthermore, still its unclear why Khan *et al,* (2003) did not provide data on non diabetic drugs (antihypertensives or statins) and other data of diet, BMI, ethnic mix and HbA1c precluding further comparison of our studies.

4.4.6 Changes in total energy intake including total carbohydrates, fats and proteins

The current RCT demonstrates there were no significant changes regarding the total energy intake (calories from macro nutrients) after the intervention compared with baseline in both groups. A similar result of no changes in total daily energy intake has been previously reported (Ziegenfuss *et al,* 2006). The baseline energy intake in this current RCT (cinnamon 1863 kcal/day; placebo 1844 kcal/day) is approximately similar to the baseline energy intake of Ziegenfuss study (cinnamon 1741 kcal/day: placebo 1706 kcal/day) (Figure 4.30). None of the previous studies reported the dietary data, although Blevin *et al,* (2007) included a three days food journal in his study; however he did not report the results of his data.

In accordance with Ziegenfuss *et al,* (2006), no significant difference in amount of carbohydrate (%) intake compared to baseline in both cinnamon and placebo groups. The nutrition subcommittee of the diabetes care UK. (2003) and American Diabetes Association, (2004[d], 2002[b]) guidelines of carbohydrate intake suggest that, patient with diabetes should limit their total carbohydrate intake by 45 – 60% of the total energy intake (Figure 4.31).

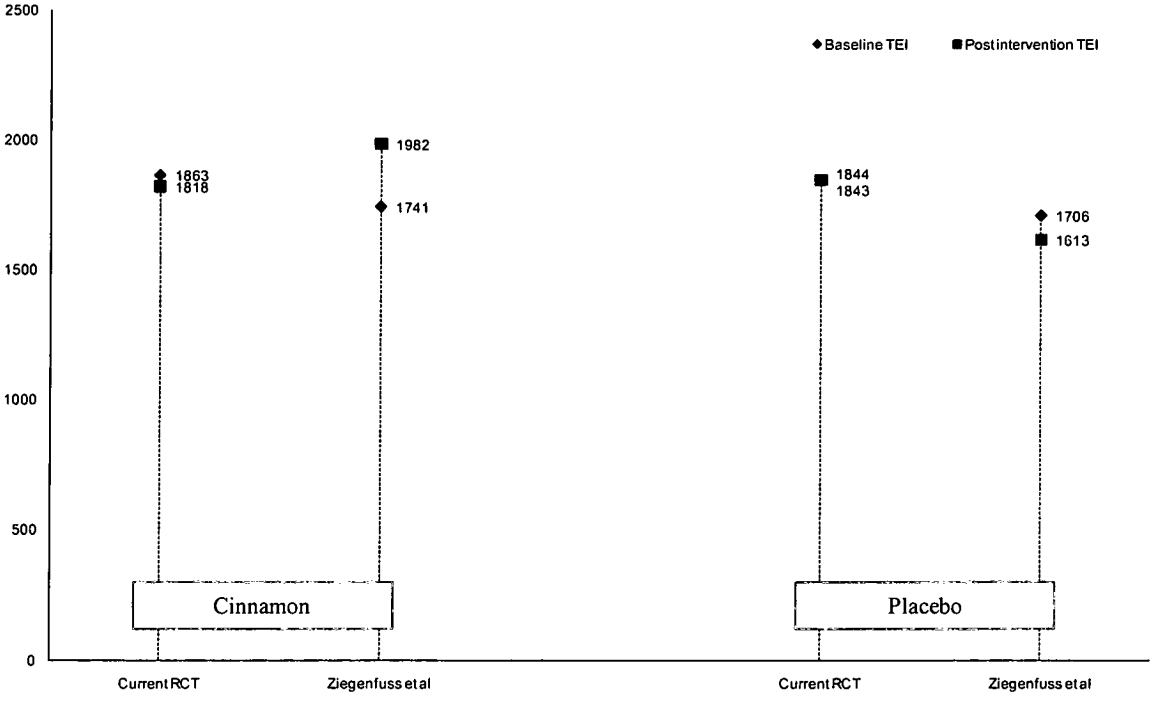


Figure 4.30 – Comparison of the mean total energy intake of current RCT with previous randomized controlled trial. Data presented as mean total energy intake (kcal/day); the current RCT and Ziegenfuss study shows that the total energy intake at baseline was found to be less than the recommended calories of 2000 kcal/day in both cinnamon and placebo groups.

The mean total carbohydrate intake at baseline in this study found to be approximately 47% and with in the recommended carbohydrate load and this might be the reason this study did not found any significant difference in carbohydrate intake before and after intervention. Also according to the diabetes standard care practices at Brent NHS, all patients received diet and lifestyle advice from a dietician. Therefore it might be possible that the glucose and blood pressure lowering effects in this study is not due to the changes in dietary intake and it may be due to the cinnamon effect.

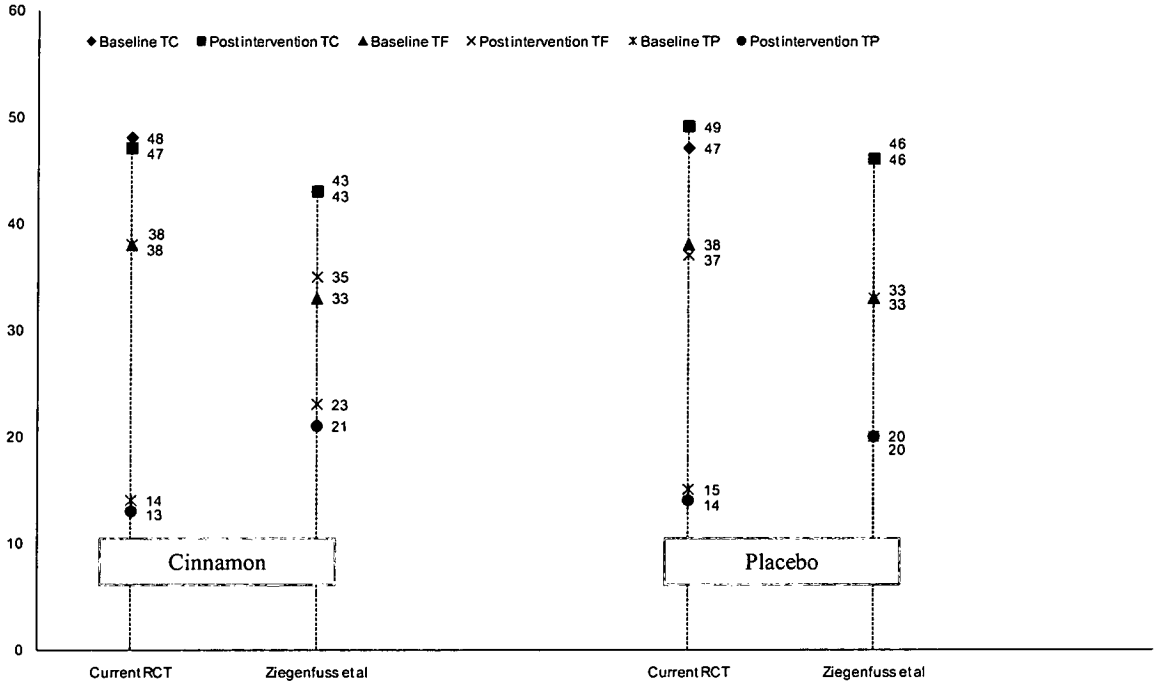


Figure 4.31 – Comparison of the mean % total energy intakes from total carbohydrates (TC), total fats (TF) and total proteins (TP) of current RCT with previous randomized controlled trial. Data presented as % total energy intake; the current RCT shows that the TC intake and TP intake at baseline were with in the recommended limits of 45 – 60% and 15 – 20% respectively in both cinnamon and placebo groups; The TF intake at baseline was slightly higher than the recommended limit of < 35% in this study.

The total intake of proteins, saturated fatty acids (SFA), mono and poly unsaturated fatty acids (MUFA and PUFA) in this study were found to be with in the recommended allowances. According to the Nutrition Subcommittee of the Diabetes Care UK, (2003), greater flexibility in the proportions of energy should be derived from carbohydrates and mono unsaturated fats. MUFA are promoted as the main source of dietary fat because of their lower susceptibility to lipid peroxidation and consequent lower atherogenic potential (Kratz *et al,* 2002). Moreover, provided that energy intake is controlled, the use of MUFA instead of carbohydrate as a replacement for saturated fat cause an increase as opposed to a decrease in HDL cholesterol and affect the serum lipid profiles (Grag, 1998). The protein intake should be restricted (15-20%) in

diabetic patients; however the role of dietary protein restriction in the management of diabetic nephropathy is still uncertain (Pedrini *et al,* 1996). A recent Cochrane review concluded that protein reduction appeared to slow the rate of progression of renal failure in diabetic patients (Waugh and Robertson, 2001).

In agreement with Ziegenfuss *et al,* (2006), the average salt intake at baseline was found to be around 4.4g/day in this current RCT (which is 0.5g higher compared to Ziegenfuss *et al, 2006*) and no significant differences in salt intake was observed in both cinnamon and placebo groups compared to baseline. Furthermore, the baseline salt intake was within the recommended limits of $\leq$ 6g/day (Nutrition Subcommittee of Diabetes Care, UK. 2003). Salt restriction from a daily intake of 12g to 6g daily results in a drop in systolic or diastolic blood pressure (SBP/DBP) of about 2.5 to 3 mmHg (Arauz-Pacheco *et al,* 2002), and possibly more in hypertensive patients with type 2 diabetes in whom it also potentiates the effect of some anti hypertensive drugs (Houlihan *et al,* 2002; Feldstein, 2002). As the salt intake was found to be similar at baseline and after intervention (both groups) in our study, its clear that there was no salt restriction among our subjects and the anticipated drop in blood pressure might be purely due to the cinnamon effect.

Cinnamon did not contribute to caloric intake (Khan *et al,* 2003). Normally changes in dietary intake has a significant likelihood of influencing study outcome (Gannon *et al,* 2003), and must be controlled to reduce the impact of independent variables. It appears that in type 2 diabetic studies, the tighter the dietary control the less significant the results were obtained (Solomon and Blannin, 2007). Consenting participants who have shown an interest in a naturopathic approach to blood glucose control may inadvertently make dietary changes which affect blood glucose levels (Bazzano *et al,* 2005; McAuley and Mann, 2006), so dietary intake or total energy intake is an important independent variable to be controlled, without which rigorous evaluation of cinnamon efficacy is unattainable. Most human trials administered cinnamon with meals, which potentially maximized the effects of delayed gastric emptying and reduced glucose absorption, limiting postprandial hyperglycaemia and protein glycation (O'Keefe *et al,* 2008).

Many factors affect the glycaemic response to foods. The amount of carbohydrates in meals or snacks has much greater influence on glycaemia than the source or type (Franz *et al,* 2002), and, although carbohydrates restriction is no longer part of diabetes management, for most patients the total carbohydrate intake remains an important consideration in order to optimize glycaemic

control (Ha and Lean, 1998). In recent years attempts have been made to devise a more meaningful way of quantifying the glycaemic effect of different foods by means of glycaemic index (GI). Different methods of food processing or preparation can make large difference to the GI (Wolver, 1997; Bjorck *et al,* 2000). Also the GI of a specific food can be influenced by the other foods in a mixed meal, and there is limited information on the GI's of different food combinations and some of this is based on theoretical calculations (Frost and Dornhorst, 2000). Therefore, this might be a limiting factor when analyzing the three days diet diary in our study, because most male patients failed to provide details about the food processing and preparation methods in their diet diary and this might affect the Glycaemic index or load of the diet. Glycemic index or load and carbohydrate consumption are probably not associated with insulin sensitivity and insulin secretion (Liese *et al,* 2006). Generally low glycemic index food that reduces postprandial hyperglycemia is recommended, but it is not clear whether it prevents diabetes (Janket *et al,* 2003; Meyer *et al,* 2000; Colditz *et al,* 1992). Furthermore, majority of the subjects in our study were obese (70%), and they might under report their three days diet intake, however this is one of the inevitable limitation in this three days diet analysis method. Furthermore the average calorie intake at baseline and after intervention in both cinnamon and placebo groups were less than 2000kcal/day, which were not likely to be the true amounts consumed or under reported values.

In addition to the argument of implications, the glycaemic index of an individual food or a mixed meal may be influenced by what was eaten at the preceding meal (Hettiiarachchi *et al,* 2001: Axelson *et al,* 1999) and foods with similar GI may have different insulinaemic indices (Axelson *et al,* 1999). Despite these various problems, there is evidence that diets based on foods with low GI can improve glycaemic control, insulin resistance and lipid profiles (Wolver, 1997; Frost and Dornhorst, 2000), though the evidence has been disputed (Coulston and Reaven, 1997) and the debate still continues (Miller *et al,* 1997; Reaven *et al,* 1997).

The prevalence of type 2 diabetes, obesity and hypertension is greater in people of South Asian, Caribbean and West African origin than in the white population of the UK (Cappuccio *et al,* 1997). The principles of dietary management in respect to diabetes are no different for ethnic minorities than for any other population, but they do have to be applied in a way which is culturally appropriate for patients. One of the most difficult tasks in our study may have been the fact that dieticians might not be familiar with customs, food habits and cooking practices of

different ethnic groups. These can be diversity within a particular ethnic group, and even sometimes within a single family.

One of the other problems with our study was that during the month of Ramadan season, practising Muslims abstain from food and liquids between dawn and sunset, and commonly eating one large evening meal after sunset and a light meal before dawn. As we reported earlier, approximately 23% (n=13) of our subjects were Muslims, and two patients were treated with cinnamon and placebo during the Ramadan fasting season. The content of the meal, as well as the timing, may change during Ramadan (Akram, 1999; Burden, 2001), the blood glucose levels might have been affected by this. For example, sweets taken in Ramadan, *Khir* (rice pudding) and vermicelli are sugary and may require alterations in drug dosage (Qureshi, 2002). Furthermore, in our study some Hindu women engaged in partial fasting in which only certain foods such as fruits and milk are eaten on one day (Fridays) each week. Similarly, among the 44% (n=25) of the Christians, three subjects (cinnamon=1; placebo=2) were recruited during the Christmas season (November to January 2008/09), therefore the quantity and quality of the meals may different from average three days diet diary; however these limitations are unavoidable and acceptable.

4.4.7 Changes in anthropometrics

Subjects in the cinnamon group did not illustrate any significant reduction in their body weight or waist circumference or BMI compared to placebo group, however a significant intra group reduction was observed in the cinnamon group compared to baseline ($P<0.001$). Previous studies has shown cinnamon extract can activate glycogen synthase, stimulate glucose uptake and inhibit glycogen synthase kinase 3β (Broadhurast *et al,* 2000; Andersan *et al,* 2004; Jarvil-Tayler *et al,* 2001). Collectively, these effects, combined with the slight decrease in total energy intake, may have led to the observed decrease in lean mass or fat mass in the cinnamon group. Cinnamon also has antioxidant effects (Shan *et al,* 2005; Blomhoff, 2004; Chrysohoou *et al,* 2006), and very recently Chrysohoou *et al,* (2006) reported an inverse relationship between body fat and antioxidant capacity, even after controlling for smoking, physical activity, dietary habits, blood pressure, glucose levels and lipid concentrations. It is therefore possible that the observed improvements in FPG as well as plasma antioxidant status might be responsible, at least in part, for cinnamons beneficial effect on body weight or waist circumference or BMI. Therefore further research on beneficial effects of cinnamon on body composition is paramount important before recommending cinnamon as an alternative method to lose weight.

4.4.8 Cinnamon interaction with diabetes medication

In this study, subjects took antihyperglycaemic drugs; metformin, sulphonylureas or both (76%, 12% and 12% respectively). The different pharmacological effects of these drugs will affect the blood glucose lowering capacity. Although participants in previous diabetic studies have used different medications, no intra-group differences were identified, despite the most notable cinnamon results achieved by participants taking only sulphonylureas (Khan *et al,* 2003). Sulphonylureas increase insulin secretion and have been shown to reduce HbA1c more compared to other diabetic medications (Monami *et al,* 2008). Although HbA1c was not measured by Khan *et al,* (2003), baseline FPG was the highest of all studies reviewed. The ethnicity of participants indicates greater risk of insulin resistance (Whincup *et al,* 2005). This may suggest that sulphonylurea effectiveness may have been reduced in the presence of insulin resistance (illustrated by elevated FPG levels), enabling cinnamon to lower blood glucose using the pathways normally activated by insulin (Jarvill-Taylor *et al,* 2001). Insulin resistance is normally associated with increased BMI and central adiposity (Festa *et al,* 2004; Reaven *et al,* 2004), but measures were not taken in the aforementioned study to support this theory.

Metformin decreases gluconeogenesis (Hundal *et al,* 2000) and alpha-glucosidase inhibitors modify starch digestion, both decreasing blood glucose levels. Insulin resistance may reduce in conjunction with lower glucose levels (Gavin *et al,* 2003), enabling some insulin activity and reducing the opportunity for cinnamon to share cellular pathways (Pinent *et al,* 2004; Roffey *et al,* 2006). Therefore it may be hypothesized that these drug actions in combination with cinnamon supplementation have contributed to the differences in results between the studies, although considering the combination of drug therapies used in trials reporting significant and insignificant results and lack of intra-group classifications, this seems unlikely. As a result, further research is required to quantify the effect of different type and dose of anti-diabetic drugs (including antihypertensive and statins) upon insulin resistance, and we suspect these parameters are more likely to affect cinnamon activity.

Although insulin sensitivity improved following oral glucose tolerance test (OGTT) (Solomon and Blannin, 2007; Wang *et al,* 2007), plasma insulin in diabetic human studies has remained unchanged (Vanschoonbeek *et al,* 2006; Blevins *et al,* 2007). Therefore the blood glucose lowering effect of cinnamon may not through increased insulin secretion but via gastrointestinal mechanisms through delaying gastric emptying and glucose absorption, through improved cellular uptake and factors such as timing cinnamon supplementation with meals may have a

significant effect upon cinnamon's glucose lowering ability. As a result, it is suggested that insulin parameters are measured in future studies to ascertain changes in insulin sensitivity and secretion following blood glucose reduction.

It appears that both cinnamon extract and powder are effective, though the level of bioactive ingredients in the preparation is the important factor. It is hypothesized that studies reporting insignificant results did not provide a large enough amount of the bioactive cinnamon components required to affect the associated baseline FPG or HbA1c. Based upon more recent studies, it appears that clarification of the bioactive components is progressing (Ziegenfuss *et al,* 2006), and continued analysis to determine the most active constituents of cinnamon will increase the likelihood of positive results in future studies.

It has emerged that at a certain dose, cinnamon is able to lower blood glucose, but whether there is a lasting therapeutic effect upon insulin resistance and sensitivity, with promise to improve the pathophysiology of diabetes requires further investigation. If there is an association between cinnamon efficacy and baseline FPG or HbA1c levels, or if cellular cinnamon-activated glucose uptake is limited in the presence of insulin, it may be hypothesized that anti-hyperglycaemic benefits are through delayed gastric emptying (Hlebowicz *et al,* 2007) and reduced glucose absorption (Kim *et al,* 2006[b]) in subjects with lower blood glucose levels or less insulin resistance.

Generally, dietary supplementation of cinnamon may have greater use in countries where orthodox treatment is less effective in controlling hyperglycaemia or as an initial treatment for newly diagnosed diabetics with elevated blood glucose levels or impaired glucose tolerance (IGT). As significant results have been limited to specific and relatively small patient populations, larger studies are required to detect statistically significant reductions in FPG or HbA1c following cinnamon supplementation (Baker *et al,* 2008), particularly within a Westernized diabetic population where blood glucose levels are lower (Saydah *et al,* 2004). In a meta-analysis of diabetic trials to date, Baker *et al,* (2008) suggested a sample size in excess of 100 participants may be required. As this meta analysis included the significant results from the study by Khan *et al,* (2003), if the correlation between baseline FPG and cinnamon efficacy is correct, it is likely that an even larger sample size will be required to produce statistically and clinically significant effects within a Westernized community with lower baseline blood glucose levels. However, this may enable relative and absolute risk reductions to be expressed, potentially confirming the external validity of cinnamon use in the community.

4.5 Conclusion

For the first time in UK, a significant reduction in HbA1c and systolic and diastolic blood pressures after cinnamon intervention in diabetic patients has been demonstrated. This may be because majority of our patients were British Indian or Pakistani (57%) and had elevated baseline HbA1c (> 7%) and higher blood pressure levels (poor control). The effect of cinnamon might vary depending on the ethnicity of patients and baseline blood measurements and may require further investigation.

So far, the small number of clinical trials reported, with smaller sample sizes and conflicting results do not allow a definitive conclusion to be drawn regarding the efficacy of cinnamon as an alternative treatment for diabetes along with normal medication. However, cinnamon appears to possess anti-hyperglycaemic properties able to reduce blood glucose through the mechanisms discussed in chapter 04.

Although insulin sensitivity improved following OGTTs (Solomon and Blannin. 2007; Wang *et al,* 2007), plasma insulin in diabetic human studies has remained unchanged (Vanschoonbeek *et al,* 2006; Blevins *et al,* 2007). Therefore, we suspect that where blood glucose was reduced by cinnamon, this was not through increased insulin secretion but via gastrointestinal mechanisms through delaying gastric emptying and glucose absorption, and through improved cellular uptake, and those factors such as timing cinnamon supplementation with meals may have a significant effect upon cinnamon's glucose lowering ability. As a result, it is suggested that insulin parameters are measured in future studies to ascertain changes in insulin sensitivity and secretion following blood glucose reduction.

It appears that both cinnamon extract and powder are effective, though the level of bioactive ingredients in the preparation is the important factor. It is hypothesized that studies reporting insignificant results did not supplement with a sufficient amount of the bioactive cinnamon components required to affect the associated baseline FPG or HbA1c. Based upon more recent studies, it appears that clarification of the bioactive components is progressing (Ziegenfuss *et al,* 2006), and continued analysis to determine the most active constituents of cinnamon will increase the likelihood of positive results in future studies.

It emerged that at a certain dose relation to baseline glycaemic levels, cinnamon is able to lower blood glucose, but whether there is a lasting therapeutic effect upon insulin resistance and

sensitivity, with promise to improve the pathophysiology of diabetes, remains to be discovered. If there is an association between cinnamon efficacy and baseline FPG or HbA1c levels, or if cellular cinnamon-activated glucose uptake is limited in the presence of insulin, it may be hypothesized that anti-hyperglycaemic benefits are through delayed gastric emptying (Hlebowicz *et al,* 2007) and reduced glucose absorption (Kim *et al,* 2006[b]) in subjects with lower blood glucose levels or less insulin resistance. Cinnamon may have greater use in countries where orthodox treatment is less effective in controlling hyperglycaemia or as an initial treatment for newly diagnosed diabetics with elevated blood glucose levels or impaired glucose tolerance (IGT).

As significant results have been limited to specific and relatively small patient populations, larger studies are required to detect statistically significant reductions in FPG or HbA1c following cinnamon supplementation (Baker *et al,* 2008), particularly within a Westernized diabetic population where blood glucose levels are lower (Saydah *et al,* 2004). In a meta-analysis of diabetic trials to date, Baker *et al,* (2008) suggested a sample size in excess of 100 participants may be required. As this Meta analysis included the significant results from the study by Khan *et al,* (2003), if the correlation between baseline FPG and cinnamon efficacy is correct, it is likely that an even larger sample size will be required to produce statistically and clinically significant effects within a Westernized community with lower baseline blood glucose levels. However, this may enable relative and absolute risk reductions to be expressed, potentially confirming the external validity of cinnamon use in the community

In summary, the administration of cinnamon (2g/day for 12 weeks) along with regular medications for type 2 diabetes with an HbA1c of $\geq$ 7%, significantly reduced HbA1c, SBP and DBP compared to a placebo group. The dose of cinnamon administered in our study was safe and well tolerated over the 12 weeks of treatment. Cinnamon could be potentially be used in addition to current standard care for treating patients with type 2 diabetes. The sustainability and durability of the effect of cinnamon has not been tested nor has its long term tolerability and safety both of which will need to be determined. Trials longer than 12 weeks will need to be conducted. However the short term effects of the use of cinnamon for patients with type 2 diabetes looks very promising.

CHAPTER 5

REFLECTION AND GENERAL CONCLUSION OF THE THESIS

5 Reflections on the Thesis

The researcher's reflections on the experience of the process of carrying out this research project, especially, the strength and weaknesses of the RCT of cinnamon (chapter 4) and challenges involved in creating the RCT study design and conducting the RCT are discussed in this section.

5.1 Strengths of RCT

In recent years the RCT has been described as the "gold standard" research design as it minimizes the possibility of bias being introduced. However, the potential for bias to exist within an RCT remains a very real possibility. The randomized control trial is regarded by many as the optimum quantitative methodology for obtaining reliable information about a treatment or the effect of an intervention (Richardson, 2000). Moreover, the RCT holds a superior status over other research methods as the 'gold standard' of evidence on which to base decisions about health care (Black, 2006). The strength of this RCT involves strict application of standardized procedures to reduce systematic bias and eliminate erroneous conclusions (Hicks, 1998). The control group in this study was useful in several ways, including, random sampling, inclusion/exclusion criteria, use of a comparison group, subject matching across groups, manipulation of the independent variable (cinnamon), double blinding procedures, the use of precise measurement tools and the application of standardized statistical tests.

The investigator/researcher had experience in assessing clinical measurements of body anthropometrics and was appropriately trained in measuring blood pressure of the participants. In general, this study includes the following important strengths;

1. Detailed reporting of the methods used to generate random allocation sequence.
2. Sufficient application of double blinding with the use of appropriate placebo.
3. Adequately powered sample size.
4. Clear description of withdrawals or dropouts during the trial and use of intention to treat analysis method.
5. Reporting the clinically important outcome measures of HbA1c, FPG, serum lipid profiles, blood pressure, influence of total energy intake/dietary analysis and body mass index.
6. The results were reported based on the CONSORT (Consolidated standards of reporting trials) method.

The excellent acceptability and tolerability of cinnamon supplements and minimum drop out rate was the main success in our current RCT. Acceptability refers to the preference that person might show towards a particular treatment approach. It is essential to examine patient's preference for empowering patient's decision making and choice in relation to treatments (Say and Thompson, 2003). The concept of acceptability of cinnamon supplements was specifically measured during the study, and suggested that acceptability and tolerability was excellent. Furthermore, dropout rate is often described as a reliable indicator of treatment acceptability (Ehlers *et al,* 2005). Ninety-five percent of the patients successfully completed the trial without any major complaints.

A number of possible reasons could account for the very low dropout rate (5%) observed in our current RCT. Firstly, during the baseline visit potential participants were made aware of the fact that they would be contributing data towards the researcher's doctoral thesis. Participants maintained an awareness of this throughout the intervention period, regularly asking the researcher about the progress with the doctoral programme. Individuals may have experienced a sense of obligation to remain within the trial as they received input form the researcher and dieticians under the standard care for diabetes at NHS Brent. Furthermore, this trial was conducted with consent according to the research ethics and participants were told they could withdraw at any time from the clinical trial.

Secondly, the researcher made every effort to ensure that baseline and post intervention clinical data sets were complete wherever possible. This clinical trial included a relatively small number of patients. This had the advantage that it was easier to keep in touch with patients and monitor their progress. As patients had their majority of contact with the researcher, rather than a team of people, they seemed reluctant to let the researcher down by cancelling sessions or failing to complete the post intervention measurements or study. Irregular attendance at clinical sessions may negatively impact upon the progress made during intervention trials (Tarrier *et al,* 2000).

Furthermore, another strong-point of the present study (RCT) was the expert supervision provided by academics, consultants, specialist doctors and dieticians involved in the development and evaluation of the target interventions. It was necessary to receive adequate training and supervision when conducting clinical trials especially in an NHS setting.

5.2 Limitations of RCT

Despite the strengths of this RCT study design there are some important limitations that may jeopardize the internal and external validity of this study. The simple random sampling technique of this study relies on the development of explicit criteria prior to initiation of the study. Subjects were not stratified by age or gender or type of anti diabetic medication or time since diagnosis of diabetes. However, at baseline there were no significant difference between gender and age between the two groups. All subjects in this study were treated with anti-diabetic medications of both sulfonylurea and metformin, and these medications have different pharmacological effects. Therefore, it may have been more appropriate to recruit patients who were treated only with metformin or sulfonylurea drugs or to stratify subjects based on the type of drugs they use – this bias could be addressed in future studies. Metformin is probably the initial oral hypoglycaemic drug of choice in people with type 2 diabetes who need more than just a dietary management, because weight gain is less common than with sulphonylureas, as the incidence of hypoglycaemia is only slightly greater than in those treated by diet alone (UK prospective diabetes study group, 1998).

In future research, it would be important to incorporate a larger sample size to be better able to detect important areas of significance. Randomization could then be stratified according to important factors such as; age, sex, duration of diabetes and type of anti-diabetic drugs used by patients. However, under the logistical and financial resources constraints of the current RCT, the completion of this trial does however provide the justification for further investigation. This RCT did not include appropriate wash out period after intervention. Therefore, in future studies it would be suitable to incorporate washout period after intervention

A total of 68 patients expressed their interest in this RCT, and a most of those patients approached opted to take part in the study (n=58; 85% of those invited to participate). There may be number of reasons for patients deciding not to opt-in, such as; the status of the investigator as doctoral research student, the chance of being allocated to the placebo group and the prospect of being involved in a research trial despite anonymity being assured. Difficulty in recruiting subjects to participate in a clinical trial is, however, remarkably common.

The attrition rate was fairly comparable for both cinnamon and placebo groups. Two individuals dropped out from placebo and one individual from cinnamon group. The last observation carried forward method (LOCF) was used, where the last observed response for each measure was entered in to the analysis. Unfortunately, in the present study (RCT), it

was not possible to obtain complete post intervention data sets from individuals that dropped out (n=3), although attempts were made. The LOCF methods was used but there is generally no consensus on whether this is an acceptable strategy for handling missing data (Hollis and Campbell, 1999). There are more sophisticated techniques available for handling missing data but they require assumptions about the missing data mechanisms that could not have been provided in this trial. However, future research could benefit from clearly documenting a strategy for handling missing data prior to commencing the study.

The participant's attendance rate might be impacted upon treatment adherence. At times repeated cancellations of baseline or post intervention appointments by patients generated protracted gaps between sessions and the necessity to review certain aspects of the intervention. This resulted in minor deviations from the trial protocols due to factors beyond the researchers' control. For example, during the Ramadan season, two Muslim patients cancelled their appointments in 12^{th} week and completed the study in 13^{th} week (more than 12 weeks); therefore an extra cinnamon and placebo capsules were provided during this period in consultation with the specialist doctors. Due to the religious reason, clinicians were not allowed to inject needles (for sample collection) during the fasting period of Ramadan and the post intervention data (blood samples) was collected at week 13 for the above two subjects. All other patients completed the clinical trial/data collection at week 12 and the compliance of capsules was very good. The number of capsules remaining after intervention (12 weeks) was found to be less than 2 in both cinnamon and placebo groups.

One of the other problems with our RCT was, as part of the study falls during the Ramadan and Christmas seasons (2008), the content and timing of the meal during this festive season may change the blood glucose levels of the participants. Furthermore, when reporting the three day diet diary, the quantity and quality of the meals may change during the festive seasons, and result in reporting higher or lower total energy intake. However, these limitations are unavoidable and acceptable. Also majority of the subjects in our study were obese (70%), and we suspect reporting bias in their three day diet diaries (under reporting of total energy intake).

The research was introduced to potential participants as a trial to compare two treatments (cinnamon/placebo) for the management of type 2 diabetes. This may have generated expectations in those participants allocated to the placebo group that they would experience some improvements in FPG measurements. This expectation could generate a placebo effect, driven by the individual's anticipation that the treatment will have a particular effect (Stewart-Williams and Podd, 2004). The placebo effect may be influenced by different

factors such as a patient's motivation, a patients perception of the cinnamon intervention and therapeutic rapport. However, this has not always found to be the case in RCTs (Hammersley *et al,* 1998). What was interesting was that most patients were asking the researcher for additional cinnamon capsules for themselves and their friends after the 12 weeks of intervention period. More noticeably patients treated with placebo were also asking for extra capsules suggesting that the blinding of this trial was effective and patients were highly motivated. However, the extra capsules of cinnamon were not given to patients until the end of study period (January 2009).

Almost all subjects failed to give information pertaining to the type and dose of statins and antihypertensive drugs they were currently taking in this trial, and this data is not reported in our study. The duration of this study might be not be long enough to investigate the long term safety, tolerability and efficacy of cinnamon on glycaemic control. Therefore in future, trials may need to address these issues.

Although *Cinnamon cassia* species was administered in this study, the precise consideration of purity of cinnamon, chemical composition or active ingredients and potency of derivatives of cinnamon may be grossly influenced by the age of the cinnamon plant, the geographical location, the season of harvest, the method of drying and crude preparation etc. (Yeh *et al,* 2003; Goldman, 2001). Therefore future studies needs to address these issues.

5.3 Challenges involved in creating the study design and conducting the RCT

The most significant challenge in this study was to obtain ethical approval and make appropriate links with NHS Brent and the community diabetes clinics at Wembley, Willesden and Monks Park Health Centers attached to NHS Brent. This was required in order to set up the study sites and clinics prior to ethical approval. The investigator (author) obtained an honorary contract through NHS Brent research governance process, which provided management approval for research studies involving the use of any NHS resources, such as staff, facilities, NHS patients, patient data and patient samples. After obtaining an honorary contract from NHS Brent, a substantial amount of time was required to organize regular meetings with the research governance office for Brent NHS, dieticians and diabetes specialist doctors/consultants prior to commencing the clinical trial and to ensure the study could be operationalised. Considering the ethical issues related with this study, it was decided that the patients should be initially approached and identified by dieticians at the diabetes and weight management clinics from the above mentioned Health Care Centers, and eligible patients meeting the inclusion and exclusion criteria referred to the investigator. This inevitably caused some delays. Subsequently, the NHS ethics application was made in

February 2007 and the ethical approval for this study was obtained in October 2007. The research ethics committee approval safeguards the rights, safety, dignity and well being of people participating in research in the NHS.

One of the other major constraints in this study was its logistics and financial limitations. Due to this, time was needed to make appropriate links with pharmaceutical companies and requests for a donation of cinnamon and placebo capsules according to the specifications of the study protocol. Finally Holland & Barrett Pharmaceuticals agreed to donate the cinnamon and placebo capsules and non transparent plastic bottles for this clinical trial. Lamberts Heath Care Ltd donated equipment for measuring blood pressure and weight/ height. The supplements were received in February 2008. This study was carried out independently (by the investigator) at TVU and the suppliers of the capsules were not involved in conducting the trial, the analysis or interpretation of the data.

Delays in this clinical trial were also due to identifying, approaching and recruiting diabetic patients based on the strict inclusion criteria from above mentioned diabetes clinics. The average recruitment rate was 1 to 2 patients per week, and it took nearly one year to recruit 58 patients for this study. At the beginning, according to the power sample size calculations, it was anticipated to recruit 64 subjects for this study, however due to financial constraints and time the recruitment was stopped on 30 October 2008 and the final patient completed the trial on 30 January 2009. Finally, in order to encourage participants to complete the intervention period of 12 weeks, each subject received £10.00 worth of book token vouchers at the end of trial period.

5.4 Recommendations and future investigations

The recent rise in obesity and diabetes prevalence demonstrates the urgent need for effective therapies. The large diabetes intervention studies in the USA, Finland, China and Japan (Kosaka *et al,* 2005; Orchard *et al,* 2005; Pan *et al,* 1997; Lindstrom *et al,* 1993) have generated convincing evidence that lifestyle alteration via diet and increased physical activity is a powerful therapeutic tool. However systematic reviews of herbal dietary supplements (chapter 2) did not provide sufficient evidence to draw definite conclusions about the efficacy of different herbal dietary supplements of *Momordica, Ginseng* and *Gymnema* for diabetes management, even though they appear to be safe (Yeh *et al,* 2003). In addition the Department of Health Statistics shows that the recommended levels of physical activity are only achieved by 29% of the population in the UK (Health survey for England. 2005; British Heart Foundation health promotion research group. 2006). Therefore, randomized controlled clinical trials, with adequately powered sample size reporting

clinically important outcomes are important to demonstrate the long term efficacy of herbal dietary supplements.

As a result, future investigations could be designed or achieved through the following ways; In Chapter 2, even though the anti diabetic potency of *Momordica, Gymnema* and *Ginseng* have been shown in range of animal and human trials, the widespread use of these herbal dietary supplements warrants more rigorous investigations to assess its efficacy, tolerability and safety. Therefore, the methodological quality of randomized controlled trials (RCTs) evaluating the efficacy of such herbal dietary supplements of *Momordica, Gymnema* and *Ginseng* for diabetes management needs to be improved. The following aspects should be addressed in the future studies. (1) inclusion of appropriate study outcomes (for example HbA1c), (2) adequately powered sample size with appropriate study durations, (3) detailed reporting of the methods used to generate allocation sequence and allocation concealment (4) sufficient application of double blinding with the use of matching placebo; (5) clear description of withdrawals or dropouts during the trial and use of intention to treat analysis method and (6) investigate the long term efficacy, safety and tolerability of *Momordica, Ginseng* and *Gymnema* on different blood parameters of glycaemic control, serum lipids and anthropometrics of type 2 diabetic patients.

Chapter 3 provides evidence that people with diabetes were more likely to use dietary supplements and CAM. As a result, in future studies must designed to investigate how dietary supplements and CAM use relate to various health related behaviors, race and gender and whether there are differences between people who use only dietary supplements/CAM or only conventional medicine, and those who use both. Furthermore, using rigorous research designs to establish the efficacy of several herbal dietary supplements that are currently being used by individuals with diabetes or metabolic syndrome, especially in multi ethnic populations is important. Standardized instruments are required in order to provide results of dietary supplements that can be compared over time and between different countries. Future studies must be designed to determine the effectiveness of different herbal dietary supplements used in various clinical situations and the effect of these herbal supplements should be assessed by well defined randomized controlled clinical trials.

In chapter 4; as the short term efficacy, safety and tolerability of cinnamon on HbA1c and blood pressure is demonstrated in our study, the long term efficacy of cinnamon on glycaemic control (including HbA1c and FPG) needs to be studied among patients with poor glycaemic control ($\geq$ HbA1c 7%) with suitable washout period. Also, it would be more appropriate to compare the long term effect of cinnamon on HbA1c and FPG among patients

with poor glycaemic control (controlled by drugs) and patients with good glycaemic control (controlled by diet and exercise alone). In agreement with Blevins *et al,* (2007) and Mang *et al,* (2006), and in contrast with Khan *et al,* (2003); our study did not demonstrate any positive effects on serum lipid profiles with cinnamon administration. For that reason, it might be more suitable to investigate the long term efficacy and tolerability of cinnamon on serum lipid profiles of HDL cholesterol, LDL cholesterol, serum triglycerides and total cholesterol levels among type 2 diabetic patients with adequately powered sample and suitable wash out periods. From lessons learnt, it may be important to recruit diabetic patients with a clinically poor control of serum lipid profiles (elevated blood cholesterol level).

None of the previous human trials investigated the effect of cinnamon on blood pressure levels. Our study is the first to demonstrate the short term positive effect of cinnamon on systolic and diastolic blood pressures among type 2 diabetic patients. However, the long term effect of cinnamon on blood pressure is unknown. Thus, further trials (RCT) investigating the long term efficacy of cinnamon on systolic and diastolic blood pressures among patients with poorly controlled (elevated blood pressure of $\geq$ 135/85mmHg) or well controlled systolic and diastolic blood pressure is of paramount importance.

Finally, long term cinnamon efficacy trials (RCT) should be conducted to determine how specific variables such as diet, ethnicity, BMI or adiposity, different cinnamon doses and concurrent medication affect cinnamon responsiveness. Until then, cinnamon cannot be generally recommended as a long term alternative addition for use in people with type 2 diabetes mellitus.

5.5 General Conclusions

The central aim of this thesis was to evaluate whether dietary supplementation of cinnamon has the potential to improve glycaemic control, serum lipid profiles and blood pressure among patients with type 2 diabetes mellitus. The results of this study indicated that cinnamon significantly improves glycaemic control (HbA1c) and blood pressure in diabetic patients. The recruitment strategy in this study generated a diverse sample with people from a range of cultural or ethnic, social and economic backgrounds, to address criticisms of previous trials and generate a representative clinical sample.

The Randomized Controlled clinical Trial (RCT) adopted in this thesis was ground-breaking primary research in UK. This research attempted to find a way to manage type 2 diabetes mellitus by using effective dietary intervention along with conventional medications. The setting and focus of the RCT was novel, specifically focusing on a community based, multi-ethnic patient population with poorly controlled type 2 diabetes in the UK.

This research is original in that it uses a consistent, fully articulated dietary approach (cinnamon) to manage glycaemic control. To improve the reporting of this RCT CONSORT (CONsolidated Standards of Reporting Trials) guidelines were followed. This research has also provided a sound basis for further research, and demonstrated that further research in this area is warranted.

The systematic review of dietary supplements revealed that cinnamon could not be used as an effective dietary supplement for glycaemic control. Data obtained from survey study has given interesting and important insights and suggested that the people with diabetes or features of metabolic syndrome were more likely to use dietary herbal supplements than people without diabetes or features of metabolic syndrome.

The innovative findings of this PhD project adds new information to current literature and research directions investigating effect of herbal dietary interventions for the management of diabetes mellitus. This thesis has made a significant contribution towards elucidating underlying mechanisms on how cinnamon improves glycamic indicators (HbA1c) and blood pressure (SBP and DBP) among people with type 2 diabetes mellitus. It demonstrates that dietary supplementation of 2g of cinnamon for 12 weeks significantly reduced glycated haemoglobin, systolic and diastolic blood pressures among poorly controlled type 2 diabetic patients with an HbA1c of $\geq$ 7%. Furthermore, cinnamon could be considered as an effective dietary approach to regulate blood glucose and blood pressure levels along with regular medications in short term period.

In conclusion, there is an immense need for large, long term, well designed dietary interventions considering all ages, genders and ethnic groups in order to make an informed decision about future dietary supplements for people with diabetes mellitus.

5.6 Dissemination of thesis

The appropriate dissemination of results of this thesis is an important part of the research process. The obvious route to inform the research community is publication through scientific journals and conferences. During the course of this research, the results were actively disseminated to the medical professionals, dieticians and other related research communities in the form of conference, publications and lunch time presentations.

Especially, for the RCT of cinnamon and diabetes (chapter 4); the study progress, patients' compliance and preliminary results of the RCT was discussed at monthly meetings (lunch time presentation) with the diabetes specialist consultant, diabetic specialist doctors and nurses at Jeffrey Kelson Diabetes Centre, Central Middlesex Hospital, London and necessary amendments to the study design made as a result. Furthermore, the results of this RCT were also disseminated to Department of Dietetics, British Nutrition Society, Diabetes UK and Research and Development office, NHS Brent, at quarterly meetings. Manuscripts will be prepared for further publication on completion of this PhD. Attempts have been made to disseminate the results of the RCT to study participants and other potential patients by organizing focus groups discussion and distributing leaflets at the diabetes clinics.

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APPENDIX

REVIEW ARTICLE

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The potential of cinnamon to reduce blood glucose levels in patients with type 2 diabetes and insulin resistance

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Aim: Cinnamon has a long history as an antidiabetic spice, but trials involving cinnamon supplementation have produced contrasting results. The aim of this review was to examine the results of randomized controlled clinical trials of cinnamon and evaluate the therapeutic potential amongst patients with diabetes and insulin-resistant patients, particularly the ability to reduce blood glucose levels and inhibit protein glycation.

Methods: A systematic electronic literature search using the medical subject headings 'cinnamon' and 'blood glucose' was carried out to include randomized, placebo-controlled *in vivo* clinical trials using *Cinnamomum verum* or *Cinnamomum cassia* conducted between January 2003 and July 2008.

Results: Five type 2 diabetic and three non-diabetic studies (total N = 311) were eligible. Two of the diabetic studies illustrated significant fasting blood glucose (FBG) reductions of 18–29% and 10.3% ($p < 0.05$), supported by one non-diabetic trial reporting an 8.4% FBG reduction ($p < 0.01$) vs. placebo, and another illustrating significant reductions in glucose response using oral glucose tolerance tests ($p < 0.05$). Three diabetic studies reported no significant results.

Conclusions: Whilst definitive conclusions cannot be drawn regarding the use of cinnamon as an antidiabetic therapy, it does possess antihyperglycaemic properties and potential to reduce postprandial blood glucose levels. Further research is required to confirm a possible correlation between baseline FBG and blood glucose reduction and to assess the potential to reduce pathogenic diabetic complications with cinnamon supplementation.

Keywords: cinnamon, diabetes, glucose, glycaemic control, insulin sensitivity
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Introduction

Cinnamon is one of the oldest spices used in naturopathic medicine, cited in Chinese books 4000 years ago [1] and traditionally used in Ayurvedic and Chinese medicine to treat diabetes [2]. Interest in this spice has increased since the discovery of its insulin potentiating properties [3] and initial findings illustrating cinnamon's ability to reduce fasting blood glucose (FBG) and plasma lipids [4]. However, subsequent studies have reported conflicting results, questioning the hypothesis that cinnamon can reduce FBG and clouding the potential of a natural remedy for diabetes. Type 2 diabetes is characterized by diminished cellular response to insulin through defects in the insulin signalling pathway resulting in decreased glycogen synthesis and elevated blood glucose. It is proposed that reduced glucose uptake occurs as a result of defects in insulin receptor (IR) binding and cellular phosphorylation [5].

Anderson *et al.* [6] proposed that cinnamon's most active ingredients are A-type doubly linked procyanidin oligomers of the flavonoid catechins/epicatechins. This suggestion is supported by the insulin-like effects of procyanidins illustrating increased glucose uptake in diabetic rats via the same mechanism as insulin, and potentially by an additional mechanism in adipose tissue [7]. Kim *et al.* [8] extracted, purified and screened hydroxycinnamic acids in an attempt to identify the active components of *Cinnamomum cassia*. A naphthalenemethyl ester of 3,4-dihydroxyhydrocinnamic acid showed the highest glucose transport activity *in vitro*, and subsequently increased glucose transport through GLUT4 translocation and enhancement of IR ß and IR substrate-1 phosphorylation in adipocytes. Procyanidins have been reported to have varying antihyperglycaemic actions [9–12] and studies have offered varying hypotheses for the action of cinnamon. It has been proposed that at least some of the mechanisms of procyanidin-stimulated glucose uptake are via the same cellular pathways as insulin.

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Proposed Cellular Activity of Cinnamon

Results from several *in vitro* experiments [5,6,13] support the proposal that cinnamon polyphenols mimic insulin action through a number of different mechanisms, and report multiple active fractions of cinnamon. Imparl-Radosevich *et al.* [13] illustrated insulin receptor activation with cinnamon extract in rat adipocytes through increasing insulin receptor phosphorylation and decreasing inactivating protein tyrosine phosphatase (PTP-1), overcoming insulin resistance. Cao *et al.* [14] reported higher levels of GLUT4 and IR ß protein, measured with immuno-blotting after treatment with various *C. cassia* fractions in mouse extracts, and Jarvill-Taylor *et al.* [5] reported increased glycogen synthase with decreased glycogen synthase kinase-3 ß activity, resulting in increased glycogen synthesis. All of these actions are recognized insulin responses, decreasing glucose levels through increased cellular utilization and conversion to glycogen.

Yu *et al.* [15] proposed that cytokine inflammation disrupts the action of TUG in fat and muscle cells, decreasing GLUT4 translocation to the cell membrane and reducing insulin action, and Lobrun and Van Obberghen [16] hypothesized that suppressor of cytokine signalling (SOCS) proteins affect insulin signalling through inhibition of tyrosine phosphorylation. Cao *et al.* [14] illustrated increased levels of anti-inflammatory protein tristetraprolin, which reduces proinflammatory cytokine synthesis in adipose tissue and is normally induced by insulin. From these proposed mechanisms, it is suggested that antioxidant fractions in cinnamon could increase glucose utilization by overriding the inflammatory effects present in insulin resistance [17,18]. This may enable GLUT4 translocation by superseding cellular inflammation, and enhance glucose uptake. This hypothesis is dependant upon the active components of cinnamon increasing glucose utilization in the presence of insulin resistance, which has already been illustrated [1,19].

Potential Antihyperglycaemic Mechanisms of Cinnamon

Cinnamon also appears to reduce hyperglycaemia and inflammation through delayed gastric emptying [20], reducing excess postprandial glucose and triglycerides which induce cellular inflammation through increased C-reactive protein and cytokines [21,22]. Flavonoid-suppressed glucose absorption [23] and significant reductions in glycosidase activity [24] with aqueous extracts of *C. cassia* have also been reported, which would reduce circulating glucose and create an antidiabetic effect [25]. These actions may have contributed to the reduced plasma glucose following oral glucose tolerance tests (OGTTs) [19,26], and may be because of the presence of catechin polymers in cinnamon [6,10] or inhibition of intestinal ATP-ase reducing intestinal glucose absorption [27]. In comparison with other flavonoids, epicatechins have illustrated the highest inhibitory action with sodium-independent facilitated glucose uptake [28]. Increased glycogen synthesis has also been reported [14], an action replicated by the epicatechin gallates [11]. However, much of this *in vitro* and animal research may be less relevant when applied to the human *in vivo* population, so our literature search was focused as discussed in the following methodology.

Methods

A systematic electronic literature search was carried out to identify and analyse all relevant literature providing information regarding the antihyperglycaemic effects of cinnamon. To be included in this review, *in vivo* clinical trials had to be randomized, placebo-controlled and conducted between January 2003 and July 2008. Using these criteria, a search of the following databases was conducted:

- All EBM reviews – Cochrane Database of Systematic Reviews, ACP Journal Club, DARE, CCTR, CMR, HTA and NHSEED, Allied and Complementary Medicine
- EMBASE and Ovid MEDLINE(R)
- JAMA, BMJ, Highwire Press and Lancet databases January 2003 to July 2008.

Medical subject headings used for searching were 'cinnamon' and 'blood glucose'. Trials which did not include

cinnamon studied in isolation or those reporting on other properties of cinnamon were excluded. The literature search was confined to English language articles, but bias was limited where possible, as results from any non-English studies where enough information was available are included in the review [29]. Data from all relevant articles were analysed in detail for participant numbers, population characteristics, methodology, data analysis and results to test the hypothesis that cinnamon may reduce blood glucose, and consider the external validity for the diabetic and insulin-resistant population. Reviews and meta-analyses were also evaluated.

Results

Eight studies (total N = 311) investigating the effect of cinnamon on blood glucose were found. All studies except for one used *C. cassia*: Ziegenfuss *et al.* [30] used a supplement called Cinnulin PF made from *C. burmannii* of the *verum* genus [31] on patients with prediabetes and metabolic syndrome. Five randomized, placebo-controlled trials (two single blind, three double blind) investigate the effect of varying amounts of cinnamon (1–6 g) on plasma glucose in patients with type 2 diabetes [4,29,32–34]; non-diabetic trials used insulin-resistant adults [19], patients with metabolic syndrome [30], and healthy participants [26].

One study involving patients with type 1 diabetes was found, but this study was excluded from systematic review because of differences in methodology and disease etiology. Altschuler *et al.* [35] recruited type 1 diabetic teenagers on insulin therapy, and did not measure blood glucose levels. Differences in disease pathology also make the results less applicable to those with type 2 diabetes and insulin resistance. This study showed no significant effects on HbA_{1c}, although it reported a 39% increase in hypoglycaemic episodes ($p < 0.17$).

Results of the studies on type 2 diabetic patients are summarized in table 3. Khan *et al.* [4] report statistically significant and clinically marked reductions ($p < 0.05$) in FBG (18–29%), total cholesterol (12–26%), low-density lipoprotein (7–27%) and triglycerides (23–30%) with 1–6 g cinnamon. Mang *et al.* [34] report a 10.3% mean reduction in FBG vs. control group (3.37% reduction) following 3 g cinnamon ($p < 0.038$) and illustrate a strong correlation ($r = 0.685$, $p < 0.001$) between baseline and FBG reduction. However, existing literature reviews and a meta-analysis of randomized controlled trials on subjects with diabetes conclude that cinnamon does not significantly reduce FBG or plasma lipids [36,37] and that further research is required [38]. This is supported by other studies illustrating insignificant effects with 1.5 g [29,32] and 1 g of cinnamon [33], although a trend in reduction of either HbA_{1c} or FBG vs. placebo is noted.

Table 4 summarizes the methodologies, measures taken and results of trials using non-diabetic patients. Studies involving subjects with metabolic syndrome (N = 22), insulin-resistant subjects (N = 15), and lean, healthy volunteers undergoing an OGTT (N = 7) all report reductions in FBG or plasma glucose following OGTT with cinnamon supplementation, although studies are likely to be underpowered, and population characteristics and methodology are dissimilar. Solomon and Blannin [26] controlled dietary intake prior to OGTTs, and illustrate a significant 13% reduction ($p < 0.05$) in plasma glucose response and improved insulin sensitivity index ($p < 0.05$) vs. placebo using 5 g of cinnamon. Ziegenfuss *et al.* [30] included food diary analysis in a 12-week intervention, reporting an 8.4% FBG reduction ($p < 0.01$) in patients with metabolic syndrome. Wang *et al.* [19] illustrates FBG reduction of 16.9% ($p < 0.03$) against baseline FBG, although the control group also reduced FBG by 7.7% following 8 weeks with 1 g cinnamon daily. A mean 20.9% reduction in mean glucose levels ($AUC_{glucose}$/120 min) following glucose load ($p < 0.03$) in the cinnamon group is reported, but no OGTT results are included for the control group, reducing the significance of these results. However, improvements in insulin resistance and sensitivity in the cinnamon group became similar to those in a separate control group without insulin resistance ($p < 0.17$).

Discussion

The small number of clinical trials, low population numbers and conflicting results do not allow a definitive conclusion to be drawn regarding the efficacy of *C. cassia* or *C. burmannii* as a treatment for diabetes. However, it is concluded that there are a number of potential mechanisms that might enable cinnamon to reduce hyperglycaemia, and also several factors that appear to affect its efficacy. Differences in research methodologies include variations in baseline FBG, diabetes medication, study duration, dietary control and type of cinnamon used.

Population Characteristics

Age, years since diagnosis and body mass indexes (BMIs) are similar across all participants with type 2 diabetes, and therefore less likely to be heterogeneous factors contributing to contrasting results (table 1).

Table 1 Summation of population characteristics in cinnamon studies involving participants with type 2 diabetes

Variable	Khan *et al.* 2003, *N* = 60		Mang *et al.* 2006, *N* = 65		Vanschoonbeek *et al.* 2006, *N* = 25		Blevins *et al.* 2007, *N* = 37		Suppapitiporn *et al.* 2006, *N* = 60	
Population numbers in each study arm	Cinnamon	Placebo	Cinnamon	Placebo	Cinnamon	Placebo	Cinnamon	Placebo	Cinnamon	Placebo
	n = 30	*n* = 30	*n* = 33	*n* = 32	*n* = 13	*n* = 12	*n* = 29	*n* = 28	Not known	
Men %	50%	50%	63.6%	71.9%	0%		49%		Not known	
Women %	50%	50%	36.4%	28.1%	100%		51%		Not known	
Ethnicity	Ethnicity not noted but recruitment was from Pakistan		German		Ethnicity not noted but recruitment was from Maastrict, The Netherlands		68% Caucasian, 16% Native American, 7% African American, 4% Hispanic, 2% Asian, 3% unknown		Not known	
Time since diagnosis (mean) of diabetes (y)	7.10 ± 3.29	6.70 ± 2.32	7.1 ± 6.2	6.8 ± 4.7	7.6 ± 1.4	7.1 ± 1.6	—		Not known	
Baseline FBG (mmol/L)*	12 ± 1.43	13.76 ± 1.40	9.26 ± 2.26	8.66 ± 1.47	8.37 ± 0.59	8.28 ± 0.33	7.38 ± 0.51	8.04 ± 0.57	8.37 ± 0.59	
Average age (y)	52 ± 5.85	52 ± 6.87	62.8 ± 8.37	63.7 ± 7.17	62 ± 2	64 ± 2	63.6	58	Not known	
Height (m)	—	—	1.72 ± 0.09	1.73 ± 0.07	1.67 ± 0.02	1.65 ± 0.02	—	—	Not known	
Weight (kg)	—	—	88.5 ± 19.1	89.9 ± 14.1	85.4 ± 3.6	82.2 ± 4.0	—	—	Not known	
BMI (kg/m^2)	—	—	29.6 ± 4.64	30.1 ± 5.22	30.7 ± 1.1	30.1 ± 1.4	32.5 ± 1.7	32.0 ± 1.5	Not known	
Waist circumference (cm)	—	—	100.5 ± 15.0	102.7 ± 11.2	—	—	—	—	—	

Data are means ± standard deviation. *N*, correspondes to the number of participants for which data were available upon completion of each study.
BMI, body mass index; cm, centimetres; kg, kilograms; m, metres; m^2, metres squared; y, years.
*As no dose–response relationship was found between 1, 3 and 6 g in the study by Khan *et al.* [4] population characteristics of each subgroup in this trial are combined here.

Table 2 Summation of methodology used in studies involving patients with type 2 diabetes

Variable	Khan *et al.* 2003, $N = 60$	Mang *et al.* 2006, $N = 65$	Vanschoonbeek *et al.* 2006, $N = 25$	Blevins *et al.* 2007, $N = 57$	Suppapitiporn *et al.* 2006, $N = 60$
Type of trial	Single-blind, randomized, placebo-controlled trial	Double-blind, randomized, placebo-controlled trial	Double-blind, randomized, placebo-controlled trial	Double-blind, randomized, placebo-controlled trial	Single-blind, randomized, placebo-controlled trial
Matched pairs	Matched for age	Not matched	Matched for age, BMI, years since diagnosis, baseline FBG and medication	Stratified by gender and randomized	Not known
Type of cinnamon used	*C. cassia* powder	*C. cassia* aqueous extract	*C. cassia* powder	*C. cassia* powder	*C. cassia* powder
Dose used	1, 3 and 6 g	3 g	1.5 g	1 g	1.5 g
Study duration	40 days intervention 20 days wash-out	4 months	6 weeks	3 months	12 weeks
Dietary control	None mentioned other than participants consumed usual diet	None mentioned	2-day food diary; pre-OGTT exercise control and standardized meal pre-OGTT	Diet monitored with a 3-day food diary	Not known
Diabetes medication taken by participants*	All sulphonylureas	27.7% metformin, 12.3% sulphonylureas,4.6% glinides, 1.5% glitazones, 30.8% combination therapy, 23.1% diet	Sulphonylureas with metformin ($n = 14$, 56%), metformin ($n = 3$, 12%), thiazolidinediones with/without metformin ($n = 6$, 24%), diet only ($n = 4$, 16%)	~ $\frac{3}{4}$ metformin (75%), > $\frac{1}{2}$ thiazolidinedione (33%) $\frac{1}{2}$ hydroxymethylglutaryl-CoA reductase inhibitor (60%). Diet only: 23% (cinnamon group), 9% placebo group	Sulphonylureas or metformin
Other medication	No other medications taken	49.2% antihypertensive medication 20% dyslipidaemia medication	None reported	55% cinnamon group and 48% placebo group took lipid lowering medication	Not known

Data are means ± standard deviation. *N* corresponds to the number of participants for which data were available upon completion of each study.
*For consistency and easy reference, the numbers of patients taking different types of medication have also been illustrated as percentages, although Vanschoonbeek *et al.* [32] originally note this information only in patient numbers, and Blevins *et al.* [33] illustrate the fractions only.

Table 3 Important outcomes in cinnamon studies involving subjects with type 2 diabetes

Results	Khan *et al.* 2003 1, 3 and 6 g	Mang *et al.* 2006, 3g	Vanschoonbeek *et al.* 2006, 1.5g	Blevins *et al.* 2007, 1g	Suppapitiporn *et al.* 2006, 1.5g
FBG (mmol/L)	↓ by 2.9 mmol/L [1 g] ↓ by 2 mmol/L [3 g] ↓ by 3.8 mmol/L [6 g] All $p < 0.05$	↓ by 1.11 mmol/L v baseline $p < 0.001$ v placebo $p < 0.039$	↓ by 0.46 mmol/L $p > 0.05$	↓ by 0.54 mmol/L ($p = 0.38$)	No significant effect
HbA_{1c}	–	No significant effect	↑ by 0.1%	No significant effect	↓ by 0.38%; $p > 0.05$
Total cholesterol (mmol/L)	↓ by 0.59 mmol/L [1 g] ↓ by 1.42 mmol/L [3 g] ↓ by 0.65 mmol/L [6 g] All $p < 0.05$	No significant effect	No significant effect	No significant effect	No significant effect
LDL (mmol/L)	↓ by 0.18 mmol/L [1 g] ↓ by 0.73 mmol/L [3 g] ↓ by 0.28 mmol/L [6 g] All $p < 0.05$	No significant effect	No significant effect	No significant effect	No significant effect
HDL (mmol/L)	No significant effect in 1 and 6 g; 3 g dose significant but unknown	No significant effect	No significant effect	No significant effect	No significant effect
Triglycerides (mmol/L)	↓ by 0.68 mmol/L [1 g] ↓ by 0.74 mmol/L [3 g] ↓ by 0.57 mmol/L [6 g] All $p < 0.05$	No significant effect	No significant effect	No significant effect	No significant effect
Plasma insulin (pmol/L)	—	—	No significant effect	No significant effect	—
HOMA-IR	—	—	No significant effect	—	—
ISIcomp	—	—	No significant effect	—	—
OGIS	—	—	No significant effect	—	—

Data are means ± standard deviation. – indicates not measured.
FBG, fasting blood glucose; HbA1c, glycosylated haemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostasis model insulin resistance index; ISIcomp, whole body insulin sensitivity; LDL, low-density lipoprotein; OGIS, whole body insulin sensitivity.

Vanschoonbeek *et al.* [32] suggest that the single gender of their study may have affected the outcome, but three other trials involving type 2 diabetic patients included both genders, and there are no apparent gender-related subgroups to support this hypothesis. There are differences in ethnicity which may have contributed to the heterogeneity of results, and Blevins *et al.* [33] conclude that cinnamon effects differ by population when comparing their study to that of Khan *et al.* [4], although despite typically higher HbA_{1c} in some of the ethnicities in this study [39,40], no ethnic intragroups are noted. However, population size may have been too small to illustrate this. Several reviews suggest that ethnicity may contribute to contrasting results in diabetic studies [36–38], illustrating a need for further research to test this hypothesis. Apart from ethnicity, the strongest variable likely to have contributed to the difference in results of type 2 diabetic trials is baseline FBG, which ranges from 7.38 to 12 mmol/L in cinnamon groups.

Khan *et al.* [4] report neither BMI nor waist circumference, despite known differences between Western and Asian populations [41,42] and strong correlation ($p < 0.01$) between BMI and plasma glucose [43]. However, although adiposity is a strong predictor of type 2 diabetes ($p = 0.0002$) [44], and relationships between BMI and waist circumference, and hyperglycaemia and hyperlipidaemia exist [45], no association between these measures and cinnamon efficacy is evident in studies which include anthropometric values, as contrasting results are noted with similar BMI measurements [32–34]. However, these studies mostly report an average BMI < 31, reducing the likelihood of a noticeable association. Cinnamon appears to have an additive effect upon insulin in fat but not muscle cells when insulin resistance is not present [7], which may have contributed to the results of the Khan *et al.* [4] study, considering differences in adiposity between populations [46]. However, because of the absence of insulin measures and anthropometric data, and a known association between increased adiposity and insulin resistance [47], a clear hypothesis cannot be reached. It is suggested that there may be a complex relationship between cinnamon efficacy and levels of adiposity and insulin resistance.

Characteristics between non-diabetic studies are heterogeneous, but do not differ between intrastudy intervention and control groups, and participants in the Ziegenfuss *et al.* [30] study were matched. Age and BMI in the study by Solomon and Blannin [26] are considerably lower than those of the diabetic subjects, and cinnamon efficacy is tested through OGTT-induced glucose elevation and subsequent glucose clearance.

Type and Amount of Cinnamon Used

Although Ziegenfuss *et al.* [30] used a concentrated supplement made from *C. burmannii*, *C. verum* remains otherwise untested in clinical trials. Supplement preparation may have influenced the outcome of several studies, as cinnamon contains a number of active agents with varying antihyperglycaemic actions [6,8], and although it is proposed that the active components appear in both aqueous extract and powdered bark [6,48], information regarding the concentration of these components in the *C. cassia* and *C. burmannii* used remains largely unknown. Some studies may have used preparations with low levels of the active components, and with cellular bioavailability of cinnamon in the nanomolar range, low physiological concentrations create a challenge for research methodologies and accurate deductions. This may explain why animal studies using higher doses have resulted in greater blood glucose reduction [48]. Animal studies presenting significant results have commonly used higher cinnamon dosage against body weight in comparison with human studies. For example, the equivalent human dosage if applying the measure per body weight administered by Kannappan *et al.* [49] to rats would be 17.08 g cinnamon/day rather than the 1.5 g used by Vanschoonbeek *et al.* [32].

It appears that both cinnamon extract and powder are effective, the level of bioactive ingredients in the preparation a more important factor. Based upon the results of the diabetic studies reviewed, it is possible that the therapeutic dose of cinnamon may depend upon the subjects' baseline FBG, rather than there being a significant dose-dependant effect. However, Ziegenfuss *et al.* [30] report an 8.4% FBG reduction in subjects with a mean baseline FBG of 6.46 mmol/L ingesting 10 g of cinnamon daily for 12 weeks, illustrating that a higher cinnamon dose can bring about a significant reduction in blood glucose ($p < 0.01$) in subjects with lower baseline FBG. Although this suggests a possible relationship between baseline FBG, FBG reduction and therapeutic cinnamon dose, the 16.9% FBG reduction Wang *et al.* [19] report using insulin-resistant subjects with a mean baseline FBG of 5.32 mmol/L ingesting 1 g of cinnamon daily for 90 days suggests otherwise. However, the placebo group also illustrated significant FBG reductions ($p < 0.03$), potentially reducing causality. Correlations between these variables might be tested using regression analysis.

Table 4 Summation of population characteristics, methodology and results of cinnamon studies with non-diabetic participants

Study information	Ziegenfuss *et al.* 2006. *N* = 22	Solomon and Blannin 2006. *N* = 7	Wang *et al.* 2007. *N* = 15
Type of trial	Double-blind, randomized, placebo-controlled trial	Double-blind, randomized, crossover trial	Double-blind, randomized, placebo-controlled trial
Age (y)	46.0 ± 9.7	26 ± 1.0	31.1 ± 2.0
Gender (M/F)	11 M, 11 F; mated gender in each group	Male	Female
BMI (kg/m^2)	33.2 ± 0.3	24.5 ± 0.3	28.8 ± 1.3
Baseline FBG (mmol/L)	6.46 ± 0.71	4.9 pre OGTT	5.32 ± n.k
Ethnicity	American	British	American
Matched pairs	Matched for age, FBG, SBP and physical activity habits	nil	Not matched but did not differ for BMI, FBG, insulin, QUICKI, HOMA-IR or insulin sensitivity index
Methodology	Cinnamon supplements or placebo given to insulin-resistant participants; changes in FBG, lipids, BP and anthropometric measures assessed	Healthy subjects underwent three OGTTs: one placebo, one cinnamon (cin), one cinnamon 12 h before i.cin 12 pre); AUC and insulin sensitivity measured	Cinnamon supplements or placebo given to insulin resistance women; FBG, AUC and insulin sensitivity assessed before and after OGTT
Supplement and dose	10 g (equivalent) Cinnulin PF a* CE of *Cinnamomum burmanni*	5 g Cassia powder capsules	1 g Cassia extract
Study duration	12 weeks	After OGTT and OGTT (cin 12pre)	8 weeks
Dietary control	3-day food diary analyzed by a licensed, registered dietitian using commercially available software	2-day food diary; diet replicated prior to each OGTT; subjects asked to refrain from alcohol, caffeine, cinnamon products and exercise 48 h before each OGTT	Advised not to modify diet or exercise habits
Measures taken	Weight, height, BMI, body fat %, leanmass (kg), BP, FBG, total cholesterol, LDL, VLDL, HDL, triacylglycerol, kCals and food intake	Plasma glucose, serum insulin; insulin sensitivity	Insulin sensitivity, insulin resistance, FBG, OGTT, plasma glucose
Significant results in cinnamon group compared with placebo group [26,30], or baseline [19]	FBG ↓ 8.4% $p < 0.01$	AUC (mmol/l2 h) ↓ 12.9% in cin $p < 0.05$	FBG ↓ 16.9% $p < 0.03$
	116.7 ± 12.8 mg/dl. [pre] – 106.5 ± 20.1 mg/dl. [post]	674.7 ± 39.3 [pre] –584.4 ± 37.5 [post]	95.93 mg/dl. [pre] –79.67 mg/dl. [post]
	SBP ↓ 3.8% $p < 0.001$	AUC (mmol/12 h) ↓ 10% in cin12pre $p < 0.05$	AUC ↓ 20.9% $p < 0.03$
	123 ± 14 mmHg [pre] –129 ± 18 mmHg [post]	674.7 ± 39.3 [pre] –603.8 ± 35.6 [post]	144.88 mg/dL/min [pre] –114.54 mg/dL/min [post]
	Lean tissue ↑ 1.1% $p < 0.002$	Insulin sensitivity index measures also improved:	QUICKI ↑ 7.7% $p < 0.03$ 0.35 [pre] –0.38 [post]
	53.7 ± 11.9 kg [pre] –54.3 ± 18 11.8 kg [post]	ISI Matsuda on $p < 0.05$)	HOMA-IR ↓ 44.5% $p < 0.03$ 2.57 [pre] –1.43 [post]
	FBG ↓ 8.4% $p < 0.01$	4.74 ± 0.69 [pre] –7.95 ± 1.29 [post]	
		ISI Matsuda cin12pre ($p < 0.05$)	
		4.74 ± 0.69 [pre] –8.26 ± 1.46 [post]	

Data are means ± standard deviation. Age and BMI means are for study population. Baseline FBG shown is for cinnamon groups in each study.
AUC, plasma glucose post oral glucose tolerance test; BP, blood pressure;
CE, cinnamon extract; FBG, fasting blood glucose; h, hours; kCals, calories; LDL, low-density lipoprotein; HDL, high-density lipoprotein; OGTT, oral glucose tolerance test; OGTT (cin) 2pre), OGTT 12 h prior to OGTT; QUICKI, insulin sensitivity index; HOMA-IR, homeostasis model insulin resistance index; SBP, systolic blood pressure; VLDL, very low density lipoprotein.
*Cinnulin is made from cinnamon powder; it contains at least 1% doubly-linked polyphenol type-A polymers, highly bioactive components of cinnamon.

Table 5 Association between mean baseline FBG and reduction in FBG

Study and cinnamon dose	Baseline FBG (mmol/L)	End FBG (mmol/L)	Reduction in FBG (mmol/L)	% reduction in FBG	Duration of study
Khan *et al.* 2003, 1, 3, and 6 g*	12	9.1	2.90	↓ 24%	40 days
Mang *et al.* 2006, 3 g	9.26	8.15	1.11	↓ 11.9%	4 months
Vanschoonbeek *et al.* 2006, 1.5 g	8.37	7.91	0.46	↓ 5.49%	6 weeks
Blevins *et al.* 2007, 1 g	7.38	6.84	0.54	↓ 7.3%	3 months
Ziegenfuss *et al.* 2006, 10 g	6.46	5.91	0.55	↓ 8.4%	12 weeks
Wang *et al.* 2007, 1 g	5.32	4.42	0.90	↓ 16.9%	90 days

Measures are average baseline fasting blood glucose (FBG) of cinnamon groups.
*Khan *et al.* [4] examined three different cinnamon doses; as no dose–dependant relationship was found between 1 and 6 g cinnamon, the baseline FBG levels and FBG reductions are combined to create an average. No FBG results are available for Suppapitiporn *et al.* [29].

although consideration must be given to the metabolic differences between diabetic and insulin-resistant subjects.

Association Between Baseline FBG and Reduction in FBG

Corresponding with the conclusion reached by Mang *et al.* [34] ($r = 0.685$; $p < 0.001$), in trials involving patients with type 2 diabetes, there may be a correlation between mean baseline FBG and FBG reduction, indicating that elevated baseline FBG in the study by Khan *et al.* [4] is likely to have contributed to the significant results (table 5). Data from studies involving patients with type 2 diabetes appear to support this proposed correlation, although this becomes less apparent as baseline FBG reduces; despite a lower baseline FBG, Blevins *et al.* [33] report a slightly greater reduction than Vanschoonbeek *et al.* [32], although duration was greater, suggesting that this may also contribute to efficacy, as cinnamon dosage was lower. This hypothesis is supported by data from non-diabetic studies as both Wang *et al.* [19] and Ziegenfuss *et al.* [30] illustrate lower average baseline FBG yet report greater reductions; duration of both studies was approximately 3 months, but the variance in dosage supports the proposition that efficacy is not dose-dependant, although the bioavailability and level of active components in each cinnamon supplement also requires consideration.

It is postulated that higher glucose levels caused by insulin resistance create cellular inflammation, potentiating insulin resistance and reducing insulin action [47,50,51], but cinnamon may be able to override this and activate glucose uptake. Hence, in the presence of insulin resistance the pathways normally utilized by insulin are available for cinnamatic activity. Potential to reduce hyperglycaemia with cinnamon may be greater when insulin functionality is low, as a natural cut-off point for cellular glucose uptake has been suggested [52]. Thus, it is concluded that the level of obesity-activated insulin resistance may affect cinnamon efficacy, offering a possible explanation as to why higher FBG levels have elicited a more significant effect, even with lower cinnamon doses. Less effect upon glucose levels is also seen in animal studies without glucose challenge [53], and greater results reported with elevated glucose load [24,48,49], supporting the theory that the efficacy of cinnamon may be dependant upon the level of hyperglycaemia. However, although animal studies illustrate promising antidiabetic properties, proof that cinnamon can reduce blood glucose levels in humans remains to be established.

HbA_{1c}

Although association between plasma glucose and glycosylated haemoglobin (HbA_{1c}) differ depending upon genetic factors and glycaemic control of the population, it is expected that studies reporting no significant reductions in FBG [32,33] would not find changes in HbA_{1c}. However, it is not known why HbA_{1c} has been largely unaffected in human studies where FBG has reduced, as Babu *et al.* [53] illustrated a 40.2% reduction in HbA_{1c} in rats ($p < 0.05$), and there is evidence of cinnamon compounds showing antioxidant and radical scavenging activities [54], and reducing advanced glycation end products [55]. HbA_{1c} is increasingly used to assess hyperglycaemia through the level of glycated proteins [56,57], contributing to diabetic complications and overall morbidity [58,59]. Despite a known relationship ($r = 0.90$) between plasma glucose and HbA_{1c} [60], there are genetic differences in glycation, so if cinnamon reduces FBG, the effect upon HbA_{1c} may be less direct in some individuals [61]. This may explain the reduction in FBG but not in HbA_{1c} reported by Mang *et al.* [34], although duration is considered to have been adequate

to expect some reduction especially when it is estimated that newer erythrocytes may contribute approximately 50% to HbA_{1c} values, in comparison with 10% from older erythrocytes [56]. The post-study HbA1c data of the study by Vanschoonbeek *et al.* [32] is therefore less valid.

In addition, although HbA_{1c} increases in diabetic patients [62], the relationship between FBG and HbA_{1c} is not always entirely linear, and a highly statistically significant inverse association ($r = -0.66$, $p < 0.01$) has been illustrated between glycation percentage and average erythrocyte life span of 120 days: higher glycation increases cell turnover and may not accurately convey the degree of hyperglycaemia [63]. In addition, the relationship between mean plasma glucose and HbA_{1c} differs depending upon glycaemic control, so blood glucose remains a key parameter to determine cinnamon efficacy [64]. It has been illustrated that intensively treated patients with diabetes display lower mean plasma glucose concentrations in relation to HbA_{1c} [64]; this may explain why Altschuler *et al.* [35] report no change in HbA_{1c}, because of the patients with type 1 diabetes in this study receiving exogenous insulin therapy to reduce blood glucose. It is proposed that if plasma glucose is reduced for a long enough period, HbA_{1c} will also reduce.

Cinnamon Interaction With Diabetes Medication and Other Drugs

Although participants in diabetic studies have used different medications, no intragroup differences are identified, despite the most impressive cinnamon results achieved by participants taking only sulphonylureas [4]. Sulphonylureas increase insulin secretion and have been shown to reduce HbA_{1c} more other diabetic medications [65]. Although HbA_{1c} was not measured by Khan *et al.* [4], baseline FBG was the highest of all studies reviewed and the ethnicity of participants indicates greater risk of insulin resistance [66]. This may indicate that sulphonylurea effectiveness could have been reduced in the presence of insulin resistance (illustrated by elevated FBG levels), enabling cinnamon to lower blood glucose using the pathways normally activated by insulin [5]. Higher insulin resistance is associated with increased BMI and central adiposity [57,67], but measures were not taken in the aforementioned study to support this theory.

Biguanides such as metformin decrease gluconeogenesis [68] and alpha-glucosidase inhibitors modify starch digestion, both decreasing blood glucose levels. Insulin resistance may reduce in conjunction with lower glucose levels [57], enabling some insulin activity and reducing the opportunity for cinnamon to share cellular pathways [7,52]. Thiazolidinediones sensitize hepatic and muscle cells to accept insulin more readily, also limiting cinnamon potential if glucose uptake pathways are shared [69]. It may be hypothesized that these drug actions in combination with cinnamon have contributed to the contrasting results between studies, although considering the combination of drug therapies used in trials reporting significant and insignificant results, and lack of intragroup classifications, this seems less likely. Further research is required to quantify the effect of drug therapy upon insulin resistance, impaired glucose tolerance and impaired fasting glucose levels, the parameters which are likely to affect cinnamon activity. Hypertensive and lipid-lowering medications constitute a further heterogeneous factor which may have affected study outcomes, although differing results were reported in studies where participants took these drugs, and no subgroups were noted.

Dietary Analysis in Cinnamon Studies

Dietary intake has a significant likelihood of influencing study outcome [70], and must be controlled to reduce the impact of independent variables. It appears that in studies involving participants with type 2 diabetes, the tighter the dietary control the less significant the results were; however, non-diabetic trials report significant results ($p < 0.01$) with an analysed food diary [30], or with food intake replicated prior to OGTT [26]. Most trials administered cinnamon with meals, which potentially maximized the effects of delayed gastric emptying and reduced glucose absorption, limiting postprandial hyperglycaemia and protein glycation [22]. However, this is not illustrated when comparing results between trials.

Duration of Studies

It appears that there may be a stronger correlation between baseline FBG and cinnamon efficacy rather than duration, considering the insignificant results reported by Blevins *et al.* [33] over a 3-month period. As considerable blood glucose reductions have been illustrated following cinnamon intake with glucose load [19,26], this suggests an immediate therapeutic effect, and with no FBG measures taken or reported in less than the 20 days of Khan *et al.* [4] in diabetic studies reporting significant results, it remains unknown whether cinnamatic effects are because of the most recent dose, one single dose, or a shorter duration than that tested. The postintervention wash-out of Khan

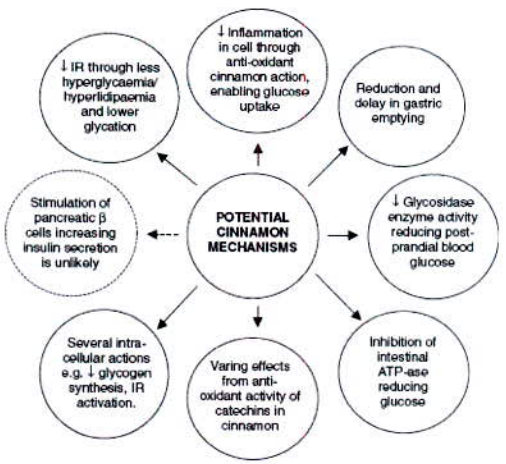

Fig. 1 Potential antihyperglycaemic actions of cinnamon.

et al. [4] illustrated that a cinnamatic effect continues postsupplementation, although effectiveness reduces; gradual blood glucose increase without cinnamon and no changes in the placebo group supports the theory that cinnamon possesses antihyperglycaemic properties.

Conclusion

Although insulin sensitivity improved following OGTTs [19,26], plasma insulin in diabetic human studies has remained unchanged [32,33]. Therefore, it is deducted that where blood glucose was reduced by cinnamon, this was not through increased insulin secretion but through gastrointestinal mechanisms reducing gastric emptying and glucose absorption, and through improved cellular uptake and glucose utilization, and that factors such as timing cinnamon supplementation with meals may have a significant effect upon cinnamon's glucose lowering ability. It appears that at a certain dose, possibly relative to baseline FBG, cinnamon is able to lower blood glucose, but whether there is a lasting therapeutic effect upon insulin resistance and sensitivity, with promise to improve the pathophysiology of type 2 diabetes, remains to be discovered. If there is an association between cinnamon efficacy and baseline FBG levels, or if cellular cinnamon-activated glucose uptake is limited in the presence of insulin, it may be hypothesized that antihyperglycaemic benefits are through delayed gastric emptying [20] and reduced glucose absorption [24] in subjects with lower blood glucose levels or less insulin resistance. It is suggested that HbA_{1c} and insulin parameters are measured in future studies to ascertain changes in glycosylated haemoglobin, insulin sensitivity and insulin secretion following blood glucose reduction, to determine the potential longer term effects of cinnamon use.

Early studies report promising results in subjects with type 2 diabetes, but it may be erroneous to apply the results achieved by Khan *et al.* [4] to the general diabetic population when factors such as elevated baseline FBG, BMI and adiposity levels could have a considerable effect upon cinnamon efficacy. As significant results have been limited to specific and relatively small patient populations, more research with larger subject numbers is required to detect statistically significant FBG reductions following cinnamon supplementation. In a meta-analysis of diabetic trials to date, Baker *et al.* [37] suggest a sample size in excess of 1000 participants. As this analysis included the significant results from Khan *et al.* [4], if the correlation between baseline FBG and cinnamon efficacy is correct, it is likely that an even larger sample size will be required to produce statistically significant results within a Westernized diabetic population with lower blood glucose levels [71].

However, such research may provide clinically effective results, and enable relative and absolute risk reductions to be expressed, potentially confirming the external validity of cinnamon use in the community.

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ABSTRACT

Abstracts from the Developing Research Strategies Conference, March 2007, Northampton, UK

Available online 3 June 2008

This conference, held in collaboration with the Southampton Complementary Medicine Research Unit on 29th–30th March 2007 at the University of Northampton, was aimed at individuals and research groups interested in the methodological and political development of complementary and alternative medicine research. The aim of the conference was to enable the development of the CAM research community and provide opportunities for researchers to present ideas and work in progress.

Oral presentations

Invited lecture: maximizing or minimizing non-specific effects in clinical trials

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In medicine there is still a strong demand that any treatment offered to patients should have more effect than a mere placebo. To ensure this, the randomised placebo controlled study has become the standard tool to evaluate new treatments.

The aim of such a study is to subtract the non-specific effect from the total effect of a treatment, thus demonstrating the specific part of the overall treatment effect. The size of this specific treatment effect is strongly influenced by the size of the non-specific effect, a fact that is often ignored. The size of the non-specific effect itself depends on various determinants (treatment and setting, patient, physician, and patient–physician interaction) that have an impact on the outcome through a number of mechanisms (such as expectations and conditioning). Studies on conventional pain treatment and acupuncture treatment studies have shown that patient expectations could have an impact on the treatment outcome. It might well be that the answer to the question – which treatment is the most effective? – may vary between health care settings and, as, e.g., expectations or interaction styles might change, over time. The narrow interpretation of study results accepts only the so-called specific effects as relevant for decisions which treatments are best for a patient. It neglects the benefits from unspecific factors and is therefore not adequate for all situations.

Efforts are needed to develop reliable and valid, yet simple tools for measuring factors such as patient expectations in clinical settings.

A pilot randomised controlled trial of individualised homeopathy in children with severe asthma

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We will present a report on provisional results from a pilot randomised control trial of individualised homeopathy in children with severe asthma. We used a pragmatic design to preserve the homeopathic approach as a complex intervention. Recruitment to the trial was difficult and we gathered children from multiple sites within Bristol. For some families who were randomised to the standard arm they withdrew early on in order to pursue homeopathic treatment immediately rather than waiting the 16-week study period. Our impression of the trial at this time was that the complexity of the illness itself provides a dimension to running a trial that is challenging. This and provisional results will be discussed at the Conference.

With reference to the design of trials in the future, we will also review the complementary and alternative

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medicine programme that has developed within the Bristol area within the past 5 years and our hope for future developments.

Acupuncture in the treatment of schizophrenia

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In psychology, research on acupuncture in the treatment of disorders like depression and also insomnia has received increased attention both in and outside of China.

After having conducted extensive reviews in the field of e.g., acupuncture and schizophrenia, acupuncture and insomnia and fMRI results on acupuncture, the authors of this abstract have planned a thorough study of acupuncture in the treatment of a less investigated disorder; schizophrenia.

In the current presentation, relevant results from our reviews will be discussed. Moreover, a discussion on acupuncture research methods in schizophrenic patients would be highly welcomed and also relevant to other researchers, doing or planning experiments in patient groups.

The choice of good control groups and design is essential, not only for the reliability and validity of the results, but also to make acupuncture research taken more seriously and to make it more accepted and conclusive, both in the East and in the West, in the future.

Nutritional medicine and lifestyle modifications (NMLM) to improve Hba1c level in patients recently diagnosed with type 2 diabetes mellitus

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Objective: To investigate whether dietary supplementation of fenugreek and cinnamon combined with lifestyle modification programme has the potential to improve HbA1c and serum lipids in patients recently diagnosed with type 2 Diabetes mellitus.

Methods: This proposed study is a randomised, parallel design, 4 arm pilot efficacy trial. A total of 60 patients recently diagnosed with type 2 diabetes mellitus, age over 30 years and treated only with oral anti diabetics or diet will randomly assigned to one of the four treatment arms; a control group, a Lifestyle Modification (LM) group, a LM and cinnamon group and a LM and fenugreek group.

Subjects in the control group will receive usual care of diabetes. Subjects in LM group will receive an intensive face to face diet and exercise counselling from nutritionist in addition to usual care. Subjects in LM cinnamon and LM fenugreek groups will receive the same treatment as those in LM group, but in addition they will receive a dietary supplementation of 4.5 g of cinnamon and 6 g of fenugreek per day for 6 months respectively.

A structured questionnaire will also be used to gather information on socio-demographic and lifestyle characteristics of the participants. The primary outcome of this study is change in HbA1c level. Secondary outcome measures include changes in glucose tolerance and changes in blood lipid profiles.

Conclusion: The hypothesis is that the three interventions may significantly improve HbA1c levels with greater changes expected in LM cinnamon and fenugreek groups.

Space, place and complementary therapy within hospice care

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There is a small but increasing amount of research into the perceptions and experiences of complementary therapy (CT) users and providers within hospice care. However, no CT research has yet utilised the concepts of space, place and therapeutic landscapes as a means of framing questions about the perceptions and experiences of people using and providing CTs within hospice care and how CT may contribute towards the creation of a holistic care environment.

Hospice day-care patients, medical/nursing staff and CT therapists will be invited to participate in the study which uses photo-elicitation interviews (PEIs), whereby photographs are taken by the participants to record spaces and places within the hospice setting that they perceive to be particularly therapeutic, or that conversely create negative feelings. These will then be used to illustrate and inform the discussion of such phenomena while exploring therapeutic landscapes within the hospice. In-depth qualitative interviews, postcard diaries and observation will also be utilised to explore the perceptions and experiences of those using and providing CTs within a hospice environment.

This study aims to explore CT's contribution towards the creation of a therapeutic landscape and healing environment, while exploring ideas that the integration of CTs into healthcare settings can also be seen in terms of how CT practice 'fits' into the physical and psychological environment – its place in a geography of care – and how this may contribute towards creating a holistic care landscape.

Acupuncture for irritable bowel syndrome: a pilot randomised controlled trial

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Background: The evidence on acupuncture for irritable bowel syndrome (IBS) is inconclusive. However many patients with IBS are self-referring for acupuncture. Therefore it is in the public interest to know whether acupuncture is effective or not. The aim of this study was to explore feasibility and design criteria for a larger-scale and more definitive trial.

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9 February 2007

Mr Raj Akilen
Tutorial Assistant/Research Student
CCHIM
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Walpole House

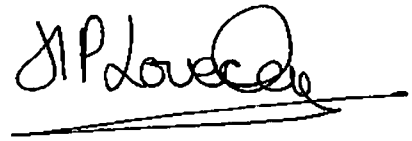
Dear Raj

Re: Application for Ethical Approval No. FREC31/Feb07

Thank you for your application for approval. The Committee considered your application at the meeting held on 6 February and approved the research without major amendment.

The Committee must be informed of any changes to the research proposal or methodology as this may entail the need for additional review. A report on the progress/completion of the research is required in 12 months or on completion of the research, whichever is the sooner. The Committee wish you well with the research and look forward to your report.

Yours sincerely



Heather Loveday
Principal Lecturer (Research)
Chair of the Faculty Research Review Committee

Copy: Prof. Nicky Robinson, Dr Amalia Tsiami

Confidential Questionnaire

We are very interested in identifying the level of use of dietary supplements by staff and students attached to TVU with the age of 25+. We should, therefore, be very grateful if you would complete this questionnaire which asks some general socio-demographic and use of diet supplements questions. The answers to all those questions will of course be kept strictly confidential and you do not have to put your name in this questionnaire.

Please read and answer each question carefully. Your complete and honest answers will help us in this research project. It's important that you try to answer all the questions.

This questionnaire is designed to complete in 5 to 10 minutes

Nutritional Medicine
Centre for Complementary Health and Integrated Medicine CCHIM
Faculty of Health and Human Sciences
Thames Valley University
2007

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Use Dietary Supplements and Other Complementary Approaches to Health

Tick boxes which apply to you or write in space as prompted

Socio Demographic Characteristics

1 Are you?

- Male ☐
- Female ☐

2 How old are you?

- 25 - 34 years ☐
- 35 - 44 years ☐
- 45 - 54 years ☐
- 55 - 64 years ☐
- 65 + years ☐

3 Which Faculty you belongs to?

- Faculty of Professional Studies (low, management, computing, tourism, hospitality, business service industries etc) ☐
- Faculty of Health and Human Sciences (science, midwifery etc) ☐
- Faculty of Arts (music and performance, media, arts and design, etc) ☐
- Faculty of Technology (computer etc) ☐
- The Graduate school ☐
- Any others (please specify)..... ☐

4 Are you?

- Undergraduate student ☐
- Postgraduate student ☐
- Academic staff/lecturer ☐
- Non academic staff/Administration ☐
- Other (please specify)..... ☐

5 What type of highest educational establishment you have attended or are you attending?

- Secondary ☐
- College ☐
- University ☐
- Post graduate ☐
- Other type (specify) ☐ .....

6 Please indicate the ethnic group to which you feel you belong to

White

- British ☐
- Irish ☐
- Any other white background, please specify ☐ .....

Mixed

- White and Black Caribbean ☐
- White and Black African ☐
- White and Asian ☐
- Any other mixed background, please specify ☐ .....

Asian or Asian British

- Indian ☐
- Pakistani ☐
- Bangladeshi ☐
- Any other Asian background, please specify ☐ .....

Black or Black British

- Caribbean ☐
- African ☐
- Any other Black background, please specify ☐ .....

Chinese or other ethnic group

- Chinese ☐
- Any other ethnic group, please specify ☐ .....

7 Would you please tell us which group below best describes your family (household) income after tax (i.e. take home pay). Please include any allowances, benefits and pensions you receive.

- £ 0 to £ 9,999 ☐
- £ 10,000 to £ 14,999 ☐
- £ 15,000 to £ 19,999 ☐
- £ 20,000 to £ 29,999 ☐
- £ 30,000 to £ 39,999 ☐
- £ 40,000 and above ☐

General Health Status

8 Do you have a family history (mother or father or brother or sister) for any of the following conditions? (please mark one or more boxes appropriately)

- Diabetes mellitus ☐
- Hypertension / high blood pressure ☐
- High blood cholesterol ☐
- Overweight / obesity ☐
- None of the above ☐

9 Which member(s) of the family does this affect

Father ☐ Sister ☐ Other ☐ .....
Mother ☐ Brother ☐ (specify)

10 Do you have any one of the following conditions? (please mark one or more boxes appropriately)

- Diabetes mellitus ☐
- Hypertension / high blood pressure ☐
- High blood cholesterol ☐
- Overweight / obese ☐
- None of the above diseases ☐

11 If you have any above conditions (Q 10), please give details of when these were diagnosed?

.....
.....
.....

Use of Dietary Supplements for Health

12 Have you taken dietary supplements in the last 12 months?

- Yes ☐
- No ☐

13 Are you taking dietary supplements currently?

- Yes ☐
- No ☐

(if your answer is **no for question 12 and 13**; please **go to question 23** and beyond)

14 If you are **currently** using dietary supplements, how helpful was this?

- Not helpful at all ☐
- Less helpful ☐
- Moderately helpful ☐
- Very helpful ☐
- Extremely helpful ☐

15 On average how many times per month do you buy dietary supplements?

- Less than 1 time per month ☐
- 1 to 2 times per month ☐
- 2 to 4 times per month ☐
- More than 4 times per month ☐

16 For how long have you been using these dietary supplements for your health condition?

- Less than 1 year ☐
- 1 to 2 years ☐
- 2 to 4 years ☐
- 4 to 6 years ☐
- More than 6 years ☐

17 On average how much do you spend per month on purchasing dietary supplements?
.....£ per month

18 Have you discussed the use of dietary supplements with your GP or physician?
Yes ☐
No ☐

19 Were you recommended to take nutritional or dietary supplements?
Yes ☐
No ☐

20 If yes, who recommended you to take dietary supplements?
Friends or relatives ☐
Self recommendation ☐
GP ☐
Pharmacist ☐
Reading material ☐
Dietician or Nutritionist ☐
Media (Radio/TV/Papers) ☐
Health food shop owners ☐
CAM providers /clinicians ☐
Other (please specify) ☐ .....

21 Where do you normally purchase your food or dietary supplements?
Pharmacy ☐
Health food shop ☐
Own product ☐
Mail order or internet ☐
Nutritionist or dietician ☐
Supermarket ☐
CAM providers /clinicians ☐
other (please specify) ☐ .....

22 Please list the dietary supplements that you take for your health condition?
(please mark one or more boxes appropriately).

	Currently	Previous 12 months
Vitamin B supplements	☐	☐
Vitamin A supplements	☐	☐
Vitamin C supplements	☐	☐
Vitamin D supplements	☐	☐
Vitamin E supplements	☐	☐
Multi vitamin supplements	☐	☐
Calcium (Ca) supplements	☐	☐
Chromium (Cr) supplements	☐	☐
Magnesium (Mg) supplements	☐	☐
Zinc (Zn) supplements	☐	☐
Iron (Fe) supplements	☐	☐
Herbal supplements	☐	☐
Fiber supplements	☐	☐
Amino acids	☐	☐
Soya proteins	☐	☐
Fish oils	☐	☐
Omega 3 supplements	☐	☐
Omega 6 supplements	☐	☐
Any other supplements (please specify)	☐	☐
.....	.....	.....
.....	.....	.....
.....	.....	.....
.....	.....	.....

23 If you are **not using** any dietary supplements (question **12 and 13**), why you think it is unnecessary?

- I am happy with current treatment from GP ☐
- No need ☐
- It's expensive ☐
- Take enough medicine already ☐
- They don't work ☐
- No reason ☐
- I am healthy ☐
- Don't believe them ☐
- Fear ☐
- Don't like to ☐
- Advised not to take ☐
- Don't like medicine ☐
- Never thought about it ☐
- other reason (please specify) ☐ .....

Use of Complementary and Alternative Medical (CAM) Approaches to Health

24 The following, What type of Complementary and Alternative Medical (CAM) therapy have you received or are currently receiving? (please mark one or more boxes appropriately)

Acupuncture	☐	Chiropractic	☐
Shiatsu	☐	Folk remedies	☐
Massage therapy	☐	Kinesiology	☐
Traditional Chinese Medicine	☐	Reflexology	☐
Bio feedback	☐	Aromatherapy	☐
Meditation training	☐	Energy healing	☐
Yoga	☐	Naturopathy	☐
Ayurvedic medicine	☐	Osteopathy	☐
Homeopathic medicine	☐	Spiritual healing	☐
Hypnosis	☐	None of the above	☐
		Other (please specify) ☐	

25 Have you received any CAM therapies in the last 12 months?

Yes ☐ No ☐

26 Are you taking any CAM therapies currently?

Yes ☐ No ☐

If yes, which?

.....

.....

(if your answer is **no for question 25 and 26**; please **go to question number 37**)

27 If you have used more than one CAM therapies (above) please give details which is better?

.....

.....

.....

28 Why did you use the CAM therapy(ies)? (give your reasons)

.....

.....

29 How helpful was the above CAM therapy?

Not helpful at all	☐	Very helpful	☐
Less helpful	☐	Extremely helpful	☐
Moderately helpful	☐		

30 Were you recommended to take CAM therapy?

Yes ☐

No ☐

31 if yes, Who recommended you to take CAM therapy?

- Friends or relatives ☐
- Self recommendation ☐
- GP ☐
- Pharmacist ☐
- Reading material ☐
- CAM therapist ☐
- Media (Radio/TV/Papers) ☐
- Health food shop owners ☐
- Other (please specify) ☐ .....

32 If you have bought any CAM supplements, where do you normally purchase them?

- Pharmacy ☐
- Health food shop ☐
- Own product ☐
- Mail order or internet ☐
- CAM clinics ☐
- Supermarket ☐
- other (please specify) ☐ .....

33 How much on average are you spending to purchase or prepare CAM supplements per month?

.....£ per month.

34 Have you discussed the use of CAM with your GP or physician?

- Yes ☐
- No ☐

35 Do you think that uses of CAM therapy will positively contributing to your health?

- Yes ☐
- No ☐

36 For how long you been using CAM therapy for your health?

- Less than 1 year ☐
- 1 to 2 years ☐
- 2 to 4 years ☐
- 4 to 6 years ☐
- More than 6 years ☐

37 If you are **not using** any complementary and alternative medical therapies (as question **20**), why you think it's not necessary?

- I am happy with current treatment from GP ☐
- No need ☐
- It's expensive ☐
- Takes enough medicine already ☐
- They don't work ☐
- No reason ☐
- I am healthy ☐
- Don't believe them ☐
- Fear ☐
- Don't like to ☐
- Advised not to take ☐
- Don't like medicine ☐
- Never thought about it ☐
- others (please specify) ☐ .....

If you prefer please give us your name and contact details, we may contact you in future

Name ..... TP .....

Address .....

Please check that you have answered all the questions that apply to you. All information will keep strictly confidential in accordance with data protection procedures.

Thank you very much for your help. We are grateful for the trouble you have taken.

PARTICIPANT INFORMATION SHEET

The Prevalence and Use of Nutritional Supplements

You are being invited to complete the attached questionnaire and as such take part in a research study. Before you complete the questionnaire it's important for you to understand why the research is being done. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. All information will be kept strictly confidential. Thank you for reading this.

1. What is the purpose of the study?
The aim of this study is to determine the prevalence and pattern of use of nutritional supplements by staff and students at TVU. We are interested in looking at the different factors predicting the level of use of nutritional supplements.

2. Why have I been sent this questionnaire?
The offer to take part in this research study is for all staff and students at TVU who are over the age of 25 years. This study forms part of my PhD. After you have completed the questionnaire you will be able to book a free nutritional consultation in the new Complementary Medicine Centre in Ealing.

3. Do I have to complete the questionnaire?
It is up to you to decide whether or not to complete the questionnaire. Taking part in this research is entirely voluntary. If you do decide to return the questionnaire, it will be presumed that in doing so you are confirming you have read this information sheet, and that you are giving consent for the information you provide to be used in confidence for the purpose of this study. Additionally, you may omit to answer any question contained in the questionnaire. The questionnaire will not have any personal identifier such as your name and address and we will assure anonymity. All information will be kept strictly confidential.

4. What will I be asked to do if I take part?
If you are a TVU registered staff or student and age of 25+ you are fully eligible to take part in this study. You have two choices. Simply go to the News & Events section of the TVU's Centre for Complementary Healthcare and Integrated Medicine (CCHIM) website at www.cchim.com and go to Research section and then either:

- ✓ Complete the 'questionnaire for the Prevalence and Use of Nutritional Supplements' online and pressing the 'submit' button once you have finished.

OR

- ✓ Print a copy of the questionnaire, complete it by hand and then return it to us either via post (or internal post) to the researcher at the address (in page 2) or by fax on 020 8280 5308 or by email.

5. What will happen to the results of the research study?

From the results of this study it is hoped that it will be possible to identify the level of use of nutritional supplements. We will write a report and publish the results of this study in academic journals and results will be delivered as conference papers and as part of a PhD qualification. We will not use your name or any other information that might identify you in the report or publication. The report will be available by the autumn.

6. Who is organising and funding the research?

The research study is being supported by the Centre for Complementary Healthcare and Integrated Medicine (CCHIM) at Thames Valley University. The research is supervised by Prof.N.Robinson and Dr.A.Tsiami.

7. Who has reviewed the study?

The study has been reviewed by members of staff of the Faculty of Health and Human Sciences. Additionally, the study has been reviewed by the Faculty of Health and Human Sciences Research Review Committee, Thames Valley University who raised no objections on ethical grounds.

8. Will my take part in this study be kept confidential?

The fact that you have returned a questionnaire will not be disclosed outside of the study. All of the information collected about you from the questionnaire will be kept strictly confidential and will be labelled in such a way that will enable you to be identified or recognised from it. To safeguard your anonymity, the questionnaire does not ask for your name.

9. Contact for Further Information

Raj.Akilen – Principle investigator
MPhil/PhD student,
Nutritional Medicine – CCHIM,
Faculty of Health and Human Sciences,
Thames Valley University,
Walpole House,
18-22 Bond Street,
Ealing, W5 5AA.

Telephone : 020 82094147
Facsimile: : 020 8280 5308
e-mail : raj.akilen@tvu.ac.uk
Website : www.cchim.com

Thank you for taking the time to read this information sheet. If you decide to take part in the study you will be given a copy of the information sheet and a signed consent form for you to keep.

Thank you in advance for your participation in this study.

THAMES VALLEY UNIVERSITY
Faculty of Health and Human Sciences
Faculty Research Ethics Committee

CONSENT FORM

Title of Project: The Prevalence and Use of Nutritional Supplements

Name of Lead Investigators: Raj.Akilen
Dr.Amalia Tsiami
Prof.Nicola Robinson

Please initial box

1. I confirm that I have read and understand the information sheet dated November 03 (version 1) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. ☐

3. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
.....	.....	.....
Name of Person taking consent (If different from researcher)	Date	Signature
.....	.....	.....
Researcher	Date	Signature
.....	.....	.....

Brent Medical Ethics Committee
Room 007, Level 5, L Block
Northwick Park Hospital
Watford Road
Harrow
Middlesex
HA1 3UJ

Telephone: 020 8869 3805
Facsimile: 020 8869 5222

23 October 2007

Dr Amalia Tsiami
Senior lecturer - Nutritional Medicine
Thames Valley University
Walpole House,
18-22 Bond Street,
Ealing, London.
W5 5AA

Dear Dr Tsiami

Full title of study: **Effect of Cinnamon on HbA1c and Serum Lipids in Type 2 Diabetes Mellitus**
REC reference number: **07/H0717/47**

Thank you for your letter of 10 October 2007, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Ethical review of research sites

The favourable opinion applies to the research sites listed on the attached form.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Application		03 July 2007
Investigator CV		01 June 2007
Protocol	1.0	10 April 2007
Covering Letter		02 July 2007

Letter from Sponsor	Brent PCT	21 June 2007
Peer Review	Dr David Lawrence	28 June 2007
Peer Review	Dr Sushma Sharma	
Peer Review	Dr Sushma Sharma	28 June 2007
Statistician Comments		26 September 2007
Questionnaire	1.0	10 April 2007
Advertisement	1.0	10 April 2007
Letter of invitation to participant	2.0	15 August 2007
GP/Consultant Information Sheets	2.0	15 August 2007
Participant Information Sheet	4.0	15 August 2007
Participant Consent Form	4.0	15 August 2007
Response to Request for Further Information		10 October 2007
Brent PCT contract - Mr Akilen		16 January 2007
3-day food diary	1.0	15 August 2007
Instructions for keeping 3-day food record	1.0	15 August 2007
Letter of Indemnity - TVU		27 June 2007
TVU - Evidence of Insurance		17 August 2006
Rajadurai Akilen		01 June 2007
CV for Professor Nicola Robinson		01 June 2007
CV for Ms Farhat Hamid	1	08 August 2007

R&D approval

All researchers and research collaborators who will be participating in the research at NHS sites should apply for R&D approval from the relevant care organisation, if they have not yet done so. R&D approval is required, whether or not the study is exempt from SSA. You should advise researchers and local collaborators accordingly.

Guidance on applying for R&D approval is available from http://www.rdforum.nhs.uk/rdform.htm.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

Here you will find links to the following

a) Providing feedback. You are invited to give your view of the service that you have received from the National Research Ethics Service on the application procedure. If you wish to make your views known please use the feedback form available on the website https://www.nationalres.org.uk/AppForm/Modules/Feedback/EthicalReview.aspx.
b) Progress Reports. Please refer to the attached Standard conditions of approval by Research Ethics Committees.

c) Safety Reports. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
d) Amendments. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
e) End of Study/Project. Please refer to the attached Standard conditions of approval by Research Ethics Committees.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nationalres.org.uk .

07/H0717/47	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Dr Bernie Colaço
Chair

Email: Mona.Shah@nwlh.nhs.uk

Enclosures: *Standard approval conditions - SL-AC2 for other studies*
Site approval form

Copy to: Prof Nicola Robinson

Brent Medical Ethics Committee

LIST OF SITES WITH A FAVOURABLE ETHICAL OPINION

For all studies requiring site-specific assessment, this form is issued by the main REC to the Chief Investigator and sponsor with the favourable opinion letter and following subsequent notifications from site assessors. For issue 2 onwards, all sites with a favourable opinion are listed, adding the new sites approved.

REC reference number:	07/H0717/47	**Issue number:**	0	**Date of issue:**	23 October 2007
Chief Investigator:	Dr Amalia Tsiami				
Full title of study:	Effect of Cinnamon on HbA1c and Serum Lipids in Type 2 Diabetes Mellitus				

This study was given a favourable ethical opinion by Brent Medical Ethics Committee on 22 October 2007. The favourable opinion is extended to each of the sites listed below. The research may commence at each NHS site when management approval from the relevant NHS care organisation has been confirmed.

Principal Investigator	*Post*	*Research site*	*Site assessor*	*Date of favourable opinion for this site*	*Notes* (1)
Mr Akilen Rajadurai	PhD research student, Thames Valley University and Research Assistant - R & D office, Brent tPCT.	Brent teaching Primary Care Trust (tPCT)	Brent Medical Ethics Committee	23/10/2007	

Approved by the Chair on behalf of the REC:

..... (Signature of Chair/Co-ordinator)
(delete as applicable)

..... (Name)

(1) The notes column may be used by the main REC to record the early closure or withdrawal of a site (where notified by the Chief Investigator or sponsor), the suspension of termination of the favourable opinion for an individual site, or any other relevant development. The date should be recorded.

PARTICIPANT INFORMATION SHEET

Effect of Cinnamon on Glycated Haemoglobin (HbA1c) and Serum Lipids in Type 2 Diabetes Mellitus

You are being invited to take part in a research project. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

1. What is the purpose of the study?

Our study aimed at examining the effects of cinnamon supplementation on blood glucose and blood cholesterol levels in diabetes patients in addition to their usual day to day care. We will study 64 patients who have been diagnosed with type 2 diabetes mellitus and age over 18 years. 32 of these patients will be looked after in normal way (usual care) for 12 weeks. The other 32 patients will be receiving cinnamon supplementation for 12 weeks. Extra help in lifestyle modification counselling will be given by dieticians for all patients. At the end of the study (after 12 weeks) we will be able to determine whether dietary supplementation of cinnamon lowers blood glucose and blood cholesterol measurements in addition to your usual day to day treatment.

What is glycated haemoglobin (HbA1c)?

In the blood stream are the red blood cells, which are made of a molecule, haemoglobin. Glucose sticks to the haemoglobin to make a 'glycosylated haemoglobin' molecule, called haemoglobin A1C or HbA1c. The more glucose in the blood, the more haemoglobin A1c or HbA1c will be present in the blood. By measuring the HbA1c it can tell us how high your blood glucose has been on average over the last 8-12 weeks.

2. Why have I been chosen?

We are asking you to take part in this study because you have been diagnosed with type 2 diabetes mellitus. If you are a type 2 diabetes patient, age over 18 years with a stable blood sugar level and using oral anti diabetic drugs (not taking insulin therapy) or diet you are fully eligible to take part in this study.

3. Do I have to take part?

No, It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep (and be asked to sign a consent form) and you are free to withdraw from this study at any time without giving any reason.

If you decide to take part in this study, it's important that you should continue your normal diabetes medication (drug or diet) while you are taking cinnamon supplements. Your routine diabetes medication will not be changed or affected during the study period.

4. What will happen to me if I take part?

Once you agreed to take part in this study, you will be required to attend minimum of 3 sessions of lifestyle counselling programme with dietician. This is part of your routine diabetic care that you would normally receive in this clinic. This visit will normally take place in mornings, and during the first and third sessions (week 0 and week 12) you will be asked to

come with 12 to 14 hours of fasting (you having had nothing to eat and drink except water) and approximately 40-50ml (7 teaspoons) of blood will be collected by a nurse to measure your HbA1c, blood glucose and blood cholesterol levels. Also the dietician will measure your bogy weight, height, waist circumference, blood pressure and diet intake during every sessions (week 0, week 6 and week 12).

4.1 Patient recruitment:
If you volunteer to participate in this study, we will arrange to meet you and we will give you more information about the study and ask you to sign a consent form. Then in order to assess whether you are eligible to join the study we will ask you some questions. If you are not eligible for the study we will notify you before the next visit is due. The purpose of the induction programme is to ensure that you are suitable to take part in the study.

4.2 Patient randomization and treatment plan:
There are two different treatment regimens will be used to compare in the trials. A minimum of total of 64 patients with diabetes mellitus will be recruited and randomly allocated in to 2 groups, and each group consist minimum of 32 patients.

- Group 1 : Placebo control group
- Group 2 : Cinnamon group

Sometimes we don't know which way of treating patients is best. To find out, we need to make comparisons between the different treatments. We put people into 2 different groups and give each group different treatment. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly). The results are then compared. Once you have been recruited for this study, your details will be entered into a secure computer programme which decides which treatment plan (group) you receive for the rest of the trial. The treatment plan each persons going to receive will be decided by the computer by chance only (random allocation). Scientifically, this is the best way of making sure that the groups receiving each treatment are similar. We are going to compare two different groups in our trial.

The participants in the study will be assigned at random, that is, by a method of chance (like a flip of a coin), to one of two groups. You will have a 1 in 2 chance of being in the group that receives placebo and 1in 2 chance of being in the group that receives cinnamon capsules. Neither you nor your dietician will know which group you are in. However, in the case of an emergency the code can be broken.

This is a placebo-controlled study. That means you will be assigned by chance (like a flip of a coin) to a group of people who receive either cinnamon capsules or placebo capsules. A placebo is an inactive substance, like a starch flour capsule. In this study you have a 1 in 2 (50%) chance of receiving the placebo and a 1 in 2 (50%) chance of receiving cinnamon capsules. If you receive placebo, it is possible that your diabetic condition may not improve well. Your condition will be carefully monitored through out the study period.

What is placebo control group?

If you are randomly allocated to this group, you will be receiving a treatment similar to the treatment you would normally receive from your respective NHS or primary care trust for 12 weeks. In addition you will be receiving 2g placebo capsules (starch flour) per day for 12 weeks period. The 2g dose of placebo will be spread over the day as 500mg (1 capsule) after breakfast, 1000mg (2 capsules) after lunch and 500mg (1 capsule) after dinner respectively. You will be instructed to take the capsules immediately after the meals.

What is cinnamon group?

If you are randomly allocated to this group, you will be receiving a treatment similar to the treatment you would normally receive from your respective NHS or primary care trust for 12 weeks. In addition you will be receiving 2g cinnamon capsules per day for 12 weeks period. The 2g dose of cinnamon will be spread over the day as 500mg (1 capsule) after breakfast, 1000mg (2 capsules) after lunch and 500mg (1 capsule) after dinner respectively. You will be instructed to take the capsules immediately after the meals.

In this study, you will be receiving prepackaged amounts of capsules containing either placebo or cinnamon. During the study period, you will be asked to maintain a patient record card with details of the trial you are in, and you will be asked to carry it at all times.

4.3 General diet and lifestyle modification:

A dietician will also gives a general lifestyle counselling for all participants tailored to each subject, 3 sessions (week 0, week 6 and week12) during the study period. The advice will be taken account of the individual's personnel and cultural preferences, beliefs and lifestyle, and must respect the individual's wishes and willingness to change.

We will explain you the reasons for the advice by taking your medical history and we will give you a general diet and exercise prescription accordingly. Also we will ask you to complete a comprehensive 3-days food diary during the study period for this we will give you weight approximation diagrams to measure your appropriate diet intake. Instructions for keeping 3 days diet diary will be given by the dietician during the sessions. Diet and exercise advice will be given by a dietician after considering your 3 days food diary. At the end of every session, goals will be set for the next visit.

4.4 General questionnaire:

During the initial stage you will be asked to complete a simple questionnaire, which includes a general socio demographic and lifestyle questions like age, income level, education, ethnicity, level of physical activity, habits of smoking and consumption of alcohol etc. This questionnaire is designed to take about 10 minutes to complete.

5. Will I be told the results of all the tests?

We will let you know the results of all of the tests that may have an impact on your future health. During the study visits and sessions you will discuss the results of this study with the researcher.

6. What are the possible disadvantages and risks of taking part?

There is no potential adverse or side effects reported with cinnamon supplementation. Caution in using cinnamon is warranted in patient's known to be allergic to it. Supplementation of cinnamon may cause diarrhea and flatulence effects due to it's fiber content. Lowering of blood glucose level (hypoglycemia) is an expected effect; therefore, care should be taken to monitor blood glucose levels when beginning supplementation of cinnamon. It's important that the cinnamon intake should not exceed more than 2g per day during the study period (12 weeks).

It's possible that if the treatment is given to a pregnant woman sometimes it might harm the unborn child. Therefore pregnant women must not take part in this study; neither should women who plan to become pregnant during the study period. Any woman who finds that she has become pregnant while taking part in the project should immediately tell her researcher and doctor.

7. What are the possible benefits of taking part?
We hope that all the treatments will help you. However, this cannot be guaranteed. The information we get from this study may help us to treat future patients with type 2 diabetes mellitus better.

Possible benefits from entering the study is that you will be getting 3 sessions of general lifestyle counselling with a dietician and also see your doctor. Also you could improve your lifestyle characteristics through a self management programme, which may result to reduce other risk factors of diabetes mellitus like over weight, blood pressure and blood cholesterol levels in future.

8. What if new information becomes available?
Sometimes during the course of a research project, new information becomes available about the treatment procedure or supplementation that is being studied. If this happens, your researcher will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw, your researcher will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

9. What happens when the research study stops?
The treatment will not be available after the research finishes; but as a member of this study, you could contact and receive lifestyle counselling with dietician after the study period.

10. What if something goes wrong?
We do not anticipate that anything should go wrong. The dieticians will available in normal working hours at Brent PCT and may be contacted at anytime if you encounter any difficulties.

11. Will my taking part in this project be kept confidential?
If you agreed to participate in this study your consent form will be kept in a confidential locked file by the principle researcher. All the information you give us will be kept in confidential files only to study personnel and will only be used for research purpose.

All information, which is collected, about you during the course of the research will be kept strictly confidential. Any information about you, which is given out, will have your name and address removed so that you cannot be recognised from it.

12. What will happen to the results of the research project?
Results of this study will be published in nutrition and medical journals and presented at conferences. We will provide you with a report of the research results on completion of the study, which we expect to be at the end of July 2008.

13. Who is organising and funding the research?
The research study is being supported by the Centre for Complementary Healthcare and Integrated Medicine (CCHIM), Thames Valley University (TVU) and Brent teaching Primary Care Trust, and funded by the Faculty of Health and Human Sciences, TVU.

14. Who has reviewed the project?
The study has been reviewed by members of staff of the Faculty of Health and Human Sciences, TVU and Research Degrees Committee of Thames Valley University. Additionally, the study has been reviewed by the Brent Research Ethics Committee, who raised no objections on ethical grounds.

15. Will your GP be informed that you are taking part in the study?
Yes, once you have been recruited for this study we will inform your GP about your participation in this study.

16. What do I do now?
All you need to do is to complete and return the enclosed return slip to the freepost address shown above telling us whether or not you are willing to take part in this study.

17. Contact for further information

Dr. Amalia.Tsiami – Chief Investigator
Faculty of Health and Human Science
Thames Valley University (TVU),
Paragon House,
Boston Manor Road,
Brentford, TW8 9GA.

Telephone : (0)20 8209 4422
Facsimile : (0)20 8280 5308
e-mail : amalia.tsiami@tvu.ac.uk
Website : www.cchim.com

Thank you for taking the time to read this information sheet. If you decide to take part in the study you will be given a copy of the information sheet and a signed consent form for you to keep.

If you are able to help we will contact you and we can answer any questions you may have and, if you wish, we can arrange a time for you to come and meet us to discuss the study further.

Centre Number :
Study Number :
Patient identification number for this trial:

CONSENT FORM

Effect of Cinnamon on HbA1c and Serum Lipids in Type 2 Diabetes Mellitus

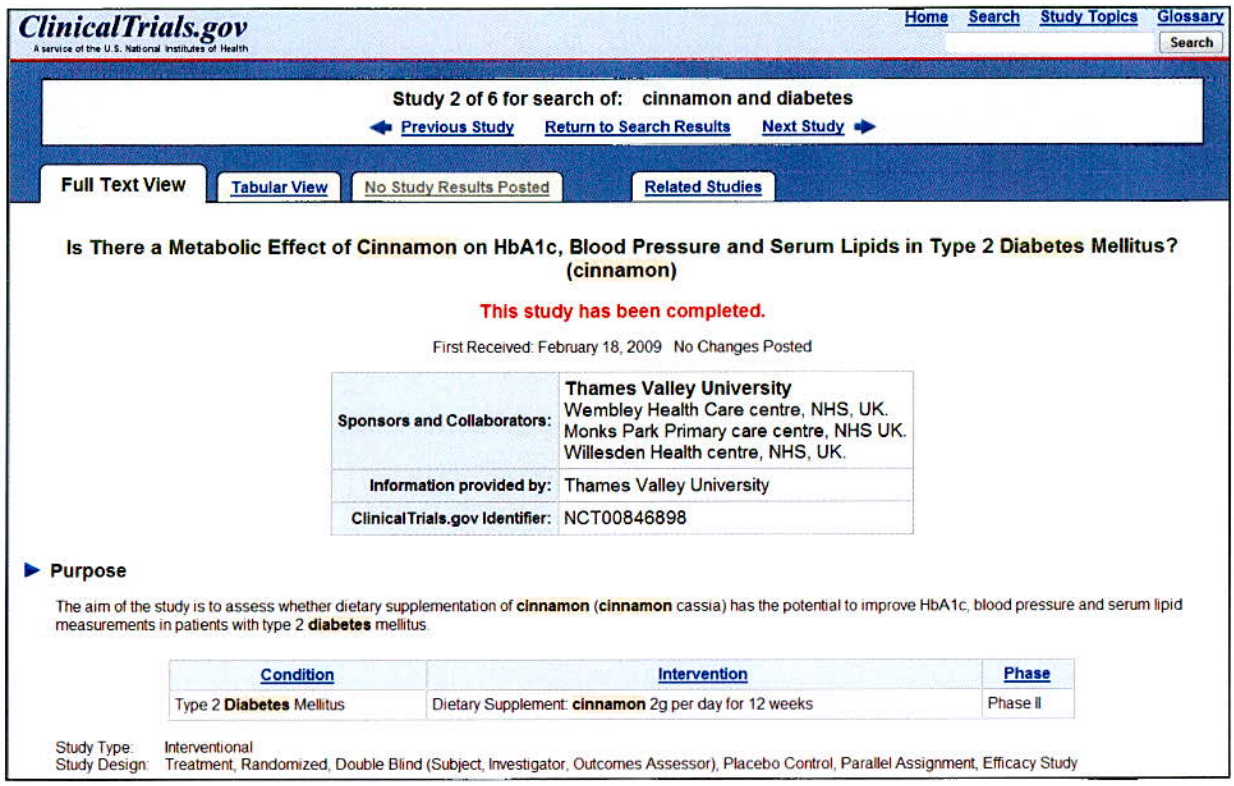
Name of Researcher :

If you agree with each sentence below, please initial the box.

1	I confirm that I have read and understood the information sheet **(ver 2.0, 22/11/05)** for the above study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily.	☐
2	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving ant reason, without my medical care or legal rights being affected.	☐
3	I understand that relevant sections of any of my medical notes and data collected during the study, may be looked at by responsible individuals from TVU or from regulatory authorities or from the NHS trust, where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.	☐
4	I agree to my GP being informed of my participation in the study.	☐
5	I agree to take part in the above study.	☐

..... Name of patient	..... Date	..... Signature
..... Name of person taking consent (if different from researcher)	..... Date	..... Signature
..... Researcher	..... Date	..... Signature

When completed, 1 for patient; 1 for researcher site file; 1 (original) to be kept in medical records.



ClinicalTrials.gov
A service of the U.S. National Institutes of Health

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Study 2 of 6 for search of: cinnamon and diabetes
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Is There a Metabolic Effect of Cinnamon on HbA1c, Blood Pressure and Serum Lipids in Type 2 Diabetes Mellitus? (cinnamon)

This study has been completed.

First Received: February 18, 2009 No Changes Posted

Sponsors and Collaborators:	**Thames Valley University** Wembley Health Care centre, NHS, UK. Monks Park Primary care centre, NHS UK. Willesden Health centre, NHS, UK.
Information provided by:	Thames Valley University
ClinicalTrials.gov Identifier:	NCT00846898

Purpose

The aim of the study is to assess whether dietary supplementation of **cinnamon** (**cinnamon** cassia) has the potential to improve HbA1c, blood pressure and serum lipid measurements in patients with type 2 **diabetes** mellitus.

Condition	Intervention	Phase
Type 2 **Diabetes** Mellitus	Dietary Supplement: **cinnamon** 2g per day for 12 weeks	Phase II

Study Type: Interventional
Study Design: Treatment, Randomized, Double Blind (Subject, Investigator, Outcomes Assessor), Placebo Control, Parallel Assignment, Efficacy Study

Have you been diagnosed with
Type 2 Diabetes and over the age of 18?

If you have been diagnosed with type 2 Diabetes Mellitus and over 18 years, you might be eligible to take part in our study.

We are now recruiting patients for our study to investigate whether supplementing your diet with cinnamon has the potential to improve your blood glucose and blood cholesterol levels. This will be in addition to your usual care for your diabetes.

If you are interested in taking part or have any question about the study we will be happy to either talk with you directly or post you a copy of the patient information sheet. Alternatively you can download the information sheet and study details at our website *www.cchim.com*. Take time to read through the information sheet and share it with your family and GP if you wish. At first sight it may look like a lot to read, but we want to explain exactly what taking part in the study will involve.

If you would like to take part in this study, contact us or please print out the reply slip and send it back to our study centre free post address.

For further information please contact our Chief investigator,

Dr. Amalia Tsiami
Centre for Complementary Health and Integrated Medicine (CCHIM),
Faculty of Health & Human Sciences, Thames Valley University,
Paragon House, 4th Floor,
Brentford, TW8 9GA.
Telephone : 020 8209 4422 or 020 8209 4172 or 020 8209 4147.
Facsimile : 020 8280 5308
e-mail : amalia.tsiami@tvu.ac.uk
Website : www.cchim.com

STUDY - RETURN SLIP

Name .....

Address .....

.....

.....

Post code .....

Would you like to meet one of our staff member to discuss about this study?

Yes ☐ No ☐

Would you be interested in finding out more about this study?

Yes ☐ No ☐

If No please state why?

.....

.....

.....

.....

If yes, please complete the details below,

Day time telephone number .....

Evening telephone number .....

Best time to ring?

Morning ☐ Afternoon ☐ Evening ☐

Thank you very much for your time.

Please return this slip to,

CCHIM, Faculty of Health and Human Science,

Thames valley University,

Freepost.....

Paragon house, 4th Floor,

Bostan Manor Road,

Brentford, TW8 9GA.

Dear Dr,

Effect of Cinnamon on HbA1c and Serum Lipids in Type 2 Diabetes Mellitus

We are currently conducting a randomised controlled trial to investigate whether dietary supplementation of cinnamon has the potential to improve HbA1c, plasma glucose and serum lipids in patients diagnosed with type 2 diabetes mellitus?

It is a 12 weeks study co-ordinated by the Centre for Complementary Health and Integrated Medicine (CCHIM), Thames Valley University and The Research and Development Office, Brent teaching Primary Care Trust. We aimed to recruit minimum of 72 patients who have been diagnosed with type 2 diabetes mellitus, aged over 18 years and treated with oral anti-diabetic drugs or diet only. The participation will entirely be voluntary basis. The research protocol will take place entirely at Brent tPCT. All patients will be seen in the Brent tPCT.

Your patients have agreed to participate in the above randomised trial. The patient information sheet is enclosed for your records. If you have any questions please contact the chief investigator on the below address.

Your help in recruiting patients for this study is greatly appreciated.

Thanking you.

Dr. Amalia Tsiami
Chief Investigator,
Centre for Complementary Healthcare and Integrated Medicine (CCHIM)
Faculty of Health & Human Sciences
Thames Valley University,
Paragon House
Boston Manor Road
Brentford, TW8 9GA, London.
Telephone: (0)20 8209 4422; Facsimile: (0)20 8280 5308
e-mail: amalia.tsiami@tvu.ac.uk
Website: www.cchim.com

Diabetes and Cinnamon Research Programme

Dear ……..,

The purpose of this letter is to invite you to attend Diabetes and Cinnamon supplementation programme,

On : ……..

At : Monks Park Primary care Centre
Monks Park,
Wembley,
HA9 6JE
(Tel: 020 8453 5900)

If you have any questions about the appointment date and time please contact me on 07832110357 or raj.akilen@tvu.ac.uk . Please come by 12 - 14 hours fasting for a blood test and it would be better to bring something to eat soon after your fasting blood test.

I hope to see you on ……..

Many Thanks

Sincerely,

……..

Raj.Akilen
PhD Research student
Diabetes & Cinnamon Research Programme,
Wembley, Willesden and Monks park health care centres,
email: raj.akilen@tvu.ac.uk
mobile: 07832110357

Post Intervention Compliance Questionnaire

1 Were you aware of the type of capsule you were taking?

Cinnamon ☐

Placebo ☐

No idea/I don't know/cannot tell exactly ☐

2 Please state the number of remaining or unused capsules after intervention.

After 6 weeks ☐

After 12 weeks ☐

3 Can you state the tolerability and safety (scores) of the capsules during the study period?

Excellent (>80%) ☐

Good (65% - 80%) ☐

Acceptable (50% - 65%) ☐

Poor (<50%) ☐

4 If the tolerability is poor or acceptable or if there are any side effects please state the reason below?

.....

.....

.....

.....

Centre for Complementary Healthcare and Integrated Medicine (CCHIM), Faculty of Health & Human Sciences,
THAMES VALLEY UNIVERSITY, Boston Manor Road, Brentford, TW8 9GA

Patient Record Card

Effect of Cinnamon on HbA1c and Serum Lipids in Type 2 Diabetes Mellitus

Ref No	
Date	
First Language	
Date of Birth	
NHS No	
Gp's name	
Post code	

We are asking you to take part in this study because you might be in the group of recently been diagnosed with type 2 diabetes mellitus and you might be able to reduce the risk factors of diabetes naturally in future.

I authorize the information contained with in this record card to be used for the research purpose and analysis only.

Please bring this card every time when you visit the clinic. Your details to be completed with your GP or nutritionist.

A dietician will give you frequent face to face general diet and lifestyle advice tailored to persons individually. This individually designed programme is planned to meet each persons needs and interests and implemented taking into account the educational level of the persons.

The first study visit will be planned 1-2 weeks after your recruitment. There after, visits will be planned end of 5-6 weeks and 10^{th} to 11^{th} weeks. At the end of every visit, diet and activity goals will be set for the next visit. During every visit with the dietician the goals will be evaluated, and new goals will be set, if necessary.

Desirable targets for management of diabetes

HbA_{c1}	less than 6.5%
Fasting plasma glucose	less than or equal to 6.0 mmol/l
Serum cholesterol	less than 5.0 mmol/l
HDL	more than 1.0 mmol/l
LDL	less than 2.6mmol/l
Blood pressure	lessthan 140/80 mmHg
Triglycerides	less than 2.3 mmol/l

Date of visit: .....

Treatment change
Goals for Treatment issues discussed:

Diabetes review check list	
Parameters	**Results**
HbA_{1c} (%)	
Fasting blood glucose/Impaired glucose	
Body weight (kg)	
Body Mass Index (BMI) (kgm^{-2})	
Waist Circumference (cm)	
Waist to Hip Ratio (WHR)	
Blood pressure (mmHg)	
Total/Serum cholesterol (mmol/l)	
Triglycerides (mmol/l)	
High Density Lipoprotein (HDL) (mmol/l)	
Low Density Lipoprotein (LDL) (mmol/l)	

Signature (Dietician): .....

Signature (Investigator): .....

Confidential Questionnaire

Ref No	
Date	

Effect of Cinnamon on HbA1c and Serum Lipids in Type 2 Diabetes Mellitus

We are interested in identifying the effects of cinnamon supplementation on blood glucose and blood cholesterol levels in patients diagnosed with type 2 diabetes mellitus. We should, therefore, be very grateful if you would complete this questionnaire which asks some general socio-demographic and lifestyle questions. The answers to all those questions will, of course be kept strictly confidential and you do not have to put your name in this questionnaire.

Please read and answer each question carefully. Your complete and honest answers will help to determine eligibility for coverage. It's important that you try to answer all the questions.

Nutritional Medicine
Centre for Complementary Health and Integrated Medicine – CCHIM
Faculty of Health and Human Sciences
Thames Valley University
2007

Tick boxes which apply to you or write in space as prompted

Socio Demographic characteristics

1 Are you?

- Male ☐
- Female ☐

2 Your Date Of Birth (DOB)?

..... Years.

3 We would like you to indicate the ethnic group to which you feel you belong to

White

- British ☐
- Irish ☐
- Any other white background, please specify ☐ .....

Mixed

- White and Black Caribbean ☐
- White and Black African ☐
- White and Asian ☐
- Any other mixed background, please specify ☐ .....

Asian or Asian British

- Indian ☐
- Pakistani ☐
- Bangladeshi ☐
- Any other Asian background, please specify ☐ .....

Black or Black British

- Caribbean ☐
- African ☐
- Any other Black background, please specify ☐ .....

Chinese or other ethnic group

- Chinese ☐
- Any other ethnic group, please specify ☐ .....

4 What is you religion?

- Christian ☐
- Hindu ☐
- Buddhist ☐
- Jewish ☐
- Muslim ☐
- Sikh ☐
- None ☐
- others (please specify) ☐ .....

5 Are you?

- Single ☐
- Living together as a couple ☐
- Married ☐
- Widowed ☐
- Divorced ☐
- Other (specify) ☐ .....

6 What type of highest school or college have you attended or are you attending?

- Elementary ☐
- Secondary ☐
- College ☐
- University ☐
- Other type (specify) ☐ .....

7 Would you please tell us which group below best describes your family (household) income after tax (i.e. take home pay). Please include any allowances, benefits and pensions you receive.

- £ 0 to £ 9,999 ☐
- £ 10,000 to £ 14,999 ☐
- £ 15,000 to £ 19,999 ☐
- £ 20,000 to £ 29,999 ☐
- £ 30,000 to £ 39,999 ☐
- £ 40,000 and above ☐

General Health Status

8 Time since diagnosis of diabetes mellitus?

..... Years.....Months.

9 Do you have any family history (mother or father or brother or sister) of the following? (please mark one or more boxes appropriately)

- Diabetes mellitus ☐
- Hypertension or high blood pressure ☐
- High blood cholesterol / hyper cholesterol ☐
- Overweight or obesity ☐
- Other diseases (please specify) ☐ .....
- None of the above ☐

10 Which member(s) of the family is this

Father ☐ Sister ☐ Others ☐ .....

Mother ☐ Brother ☐ .....

11 Do you have any one of the following condition? (please mark one or more boxes appropriately)

- Hypertension or high blood pressure ☐
- High blood cholesterol ☐
- Overweight/obese ☐
- Other diseases (please specify) ☐ .....
- None of the above diseases ☐

12 If you have any above conditions (Q 11), please give details of when these were diagnosed?

.....

.....

.....

13 What type of treatment that you are currently taking for diabetes mellitus?

Drugs only ☐
Diet only ☐
Drugs and diet ☐
Others (please specify) ☐ .....

14 If you are taking drugs to control diabetes mellitus, what type of drugs you are taking?

.....

15 Are you currently taking drugs against (please mark one or more boxes approperiately)

Hypertension ☐
High cholesterol ☐
Overweight/obesity ☐
Any heart diseases ☐
Any others (please specify) ☐ .....

Lifestyle Characteristics

16 Do you drink alcohol?

Yes ☐
No ☐

(If No, go to question number 16)

17 How often do you drink alcohol?

Daily ☐
5 to 6 days per week ☐
3 to 4 days per week ☐
1 to 2 days per week ☐
Less than once a week ☐
Occasionally/special events only ☐
Never ☐

In answering the next question (question number 14), please use the following information

One standard drink =	1/2 pint of beer or 1/2 pint of cider or 1/2 pint of larger or 1 glass of wine, martini, cinzano or 1 small glass of sherry, port or 1 measure of sprits (ouzo, raki, brandy, whisky, vodka etc)
A pint of beer, cider or larger counts as two standard drinks. A double measure of sprits counts as two standard.	

18 In a typical 7 day week, including the weekend how many standard drinks of alcohol do you drink?

- Less than 1 standard drink ☐
- 1 - 2 standard drinks ☐
- 2 - 4 standard drinks ☐
- 4 - 6 standard drinks ☐
- 6 - 8 standard drinks ☐
- More tha 8 standard drinks ☐

19 Which of the following describes you? (please tick one box only)

- I have never smoked ☐
- I used to smoke (but do not smoke at all times) ☐
- I smoke occasionally ☐
- I smoke daily ☐ (Non smokers please go to question number 20)

20 How often do you or did you smoke?

- Daily ☐
- 5 to 6 days per week ☐
- 3 to 4 days per week ☐
- 1 to 2 days per week ☐
- Less than once a week ☐
- Occasionally/special events only ☐

21 When do you smoke, how many cigarettes do you usually smoke?

- 1 to 14 cigarettes per day ☐
- 15 to 34 cigarettes per day ☐
- 35 + cigarettes per day ☐

22 If you smoke occasionally but not every day, how much on average do you smoke each week?

an average of .....cigarettes per week

23 Whether you paid work or not, which of the following best describes your work or other day time activity that you usually do?

- I am usually sitting and do not walk about much ☐
- I stand and walk about quite a lot ☐
- I usually lift or carry light loads or have to climb stairs or hills often ☐
- I do heavy work or carry heavy loads often ☐

24 Compared with this time last year, do you take part in more physical activity, the same amount or less physical activity in your leisure time? (please tick one box)

- More physical activity ☐
- About the same amount ☐
- Less physical activity ☐

25 How much exercise do you take?

- Hardly any ☐
- Light ☐
- Moderate ☐
- Heavy ☐

26 Please list types of exercise that you are regularly involved?

.....

.....

27 Please indicate your current type of diet

- Vegan ☐
- Vegetarian/eat dairy ☐
- Vegetarian/eat fish and dairy ☐
- Mixed diet with meat ☐
- others (specify) ☐ .....

28 How do you rate stress in your lifestyle?

- Very stressful ☐
- Moderately stressful ☐
- Not stressful ☐

29 How many portions of fruits and vegetables do you eat per day? (include fresh, canned, frozen fruit and fruit juices. A portion is one piece of fruit, or one serving of vegetables. A large salad counts as two portions.)

- None ☐
- One portion ☐
- Two portions ☐
- Three portions ☐
- Four portions ☐
- Five portions ☐
- More than five portions ☐

30 Do you buy special foods or nutritional supplements to control your blood sugar levels?

- Yes ☐
- No ☐

31 If yes, please give details

.....

.....

.....

Please check that you have answered all the questions that apply to you. All information will keep strickly confidential.

Thank you very much for your help. We are greatful for the trouble you have taken.

Please record your food for at least 2 weekdays and 1 weekend. Please choose days that are most like your usual eating habits.

Time of meal:

Record the time for each meal and snack.

Food information:

1. Food name or brand name
2. Cooking method, (fried, broiled, baked etc.)
3. Seasonings or sauces added
4. Restaurant name, if you eat out

Tips:

Be specific about the foods. "A glass of milk" will not be as helpful as "one cup of 2% milk". If you have a sandwich, please list all the ingredients on the sandwich and the amounts that were eaten. Don't forget about mustard, mayonnaise, etc.

Portion size:

How much you eat is as important as what you eat. Please write down the amount of your serving. Serving foods with a measuring cup will make portion sizing easier. You may also judge portion size by comparing your portion to a coffee cup or tablespoon. Please avoid using "handful" or similar words, since everyone's hands are a different size. If you are eating at a restaurant, their staff can help you with the portion size if you ask. You may use the portion size booklet to help you judge the correct portion of your foods.

Examples of how to record serving sizes:
Cups: ¼ cup of syrup
Ounces: 8 ounces of fish
Pieces: 1 slice of a 9" pie
Tablespoons or teaspoon: 3 teaspoons of jelly

Label information:

If your food has a nutrition label, you can just clip the label and attach it to your food records.

Additional Information
If you take vitamins or other supplements, please include information about frequency and dose.

Instructions for Keeping Your Three-Day Food Record

1. Record **everything** that you eat and drink for three days (2-week days and 1 Weekend) during the first week and 12th week of this study.
2. For accuracy, it is best to record each meal or snack immediately after it is eaten.
3. To help you, each day is broken down into 3 meals and a snack section, but it is most important to record the food accurately, regardless of when it was eaten. Be sure to include water, coffee, tea, soda, etc.
4. If additional space is required for the same day, continue onto the back of the page, noting clearly that it is a continuation.
5. Record **brand names**, if known.
6. If eating out, record foods eaten as accurately as possible, including the **name of the establishment** and the **specific food item ordered**.
7. Always specify **method of preparation**. Examples include: baked, boiled, fried, breaded, etc.
8. Describe all foods as fully as possible. For example: 3 oz. baked chicken thigh, no skin. (Note: 3 oz. is approximately the size of a deck of cards.)
9. List **all ingredients** for sandwiches, casseroles, and other mixed dishes.
   Example: Peanut butter sandwich – 2 pieces oat bran bread, 1½ Tbsp. chunky peanut butter. A full recipe is not required.
10. Record **exact amounts** when known. Specify weight or volume or dimensions in inches (e.g., 1 piece banana bread, 1" by 2" by 4"). Use household (standard measuring cups or spoons to estimate portions.
11. Include all **additions** to food at the table, such as salt, sugar, or milk. Record each addition on a separate line.
12. Record all **medications**, including over-the-counter medicines and **dietary supplements** (e.g., vitamins, etc.). Record brand names and amounts.

3 Day Food Diary

Ref No:	
Nutritionist/health care providers name:	

Three Day Food Diary Direction:

Choose 3 days to keep your food diary. You need to be sure to include 2 weekdays (Mon-Thurs) and 1 weekend day (Fri-Sun.) This helps to ensure that we get an accurate picture of your diet. DO NOT CHANGE YOUR EATING HABITS DURING THESE DAYS!

Complete the food diary as shown below for each day. Be as specific as possible with the type/brand of food and the amount you ate.

Be sure to include any "extras" that you may have added to the meal/food. Include all drinks, candy, water, etc.

EXAMPLE:

DAY: (1) (2) (3)

DATE:...../...../.....

Meal	Food item	Serving size	Extras - salt/paper/mayo/etc
Breakfast	frosted flakes 1 cup	1 cup	
	skim milk	skim milk 1/2 cup	
Snack	red grapes-seedless	1 cup	
Lunch	Hardee's Grilled Chicken Sandwich	1 item	bun, 1 tbsp ketchup
	french fries	small	1 packet salt
	diet coke	32 oz	
Snack			
Dinner			
Snack			
Comments			

Instructions: Talk with your Nutritionist or health care provider about how to fill out this diary

Three days Diet Diary - Day 1/Day 2/Day 3

Day	1	2	3
Meal	**Food Item**	**Serving size**	**Extras**
Breakfast			
Snack			
Lunch			
Snack			
Dinner			
Snack			

Any Comments:

Thames Valley University

FHHS

Averaged Assessment

Reg.No : 015
Surname : .....
Forenames : .....
Referred : Helen Devies - Dietician
Date of birth : 16 April 1956
Height : 1.71 m.
Body Mass Index : 33.1
Note : Three days Diet Diary - base line.
Total number of foods : 39

Assessment Date : 12 December 2008
Number of days : 3

Sex : Male
Age : 52
Weight : 96.90 kg.

Total food intake : 4.89kg
per day : 1.63kg

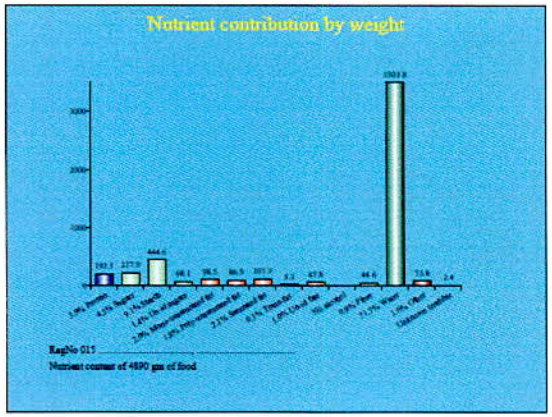
Analysis of selected nutrients :

Nutrient	Unit	Intake	per day	per 100g
Edible proportion		0.99 m	0.99	0.99
Water	g	3503.8 +	1167.9	71.7
Total Nitrogen	g	31.62	10.54	0.65
Protein	g	192.3	64.1	3.9
Fat	g	340.5	113.5	7.0
Available Carbohydrate (mse)	g	730.6	243.5	14.9
Energy (kcal)	Cal	6569	2190	134
Energy (kJ)	kJ	27543	9181	563
Starch (mse)	g	489.1	163.0	10.0
Total Sugars (mse)	g	228.8	76.3	4.7
Glucose	g	36.2 m	12.1	0.7
Fructose	g	54.3 m	18.1	1.1
Sucrose (mse)	g	83.3 m	27.8	1.7
Maltose (mse)	g	8.9 m	3.0	0.2
Lactose (mse)	g	31.6 m	10.5	0.6
Non-starch polysaccharides	g	44.6 +	14.9	0.9
Total dietary fibre (AOAC method)	g	13.3 m	4.4	0.3
Saturated fatty acids	g	101.9 m	34.0	2.1
Mono-unsaturated fatty acids	g	98.5 m	32.8	2.0
Poly-unsaturated fatty acids	g	86.9 m	29.0	1.8
Total trans fatty acids	g	5.35 m	1.78	0.11
Cholesterol	mg	589.6 m	196.5	12.1
Sodium (Na)	mg	8541 +	2847	175
Potassium (K)	mg	7659 +	2553	157
Calcium (Ca)	mg	2362 +	787	48
Magnesium (Mg)	mg	791 +	264	16
Phosphorus (P)	mg	3519 +	1173	72
Iron (Fe)	mg	38.89 +	12.96	0.80
Copper (Cu)	mg	3.53 +	1.18	0.07
Zinc (Zn)	mg	23.13 +	7.71	0.47
Chloride (Cl)	mg	12729 +	4243	260
Manganese (Mn)	mg	10.70 +	3.57	0.22

Report created 12 December 2008

Nutrient	Unit	Intake	per day	per 100g
Selenium (Se)	ug	139.2 +	46.4	2.8
Iodine (I)	ug	489.5 +	163.2	10.0
Retinol	ug	1692 m	564	35
Carotene	ug	23945 m	7982	490
Vitamin D	ug	7.20 +	2.40	0.15
Vitamin E	mg	74.09 +	24.70	1.52
Thiamin	mg	4.28 +	1.43	0.09
Riboflavin	mg	4.05 +	1.35	0.08
Niacin	mg	52.08 +	17.36	1.07
Tryptophan divided by 60	mg	38.963+	12.988	0.797
Vitamin B6	mg	3.76 +	1.25	0.08
Vitamin B12	ug	10.3 +	3.4	0.2
Total Folate	ug	792 +	264	16
Pantothenic acid, Pantothenate	mg	11.44 +	3.81	0.23
Biotin	ug	81.0 +	27.0	1.7
Vitamin C	mg	337 +	112	7

Key. For one or more contributory foods :
d: nutrient value derived or deduced
e: value estimated
+: present in significant, unknown amounts
m: missing value

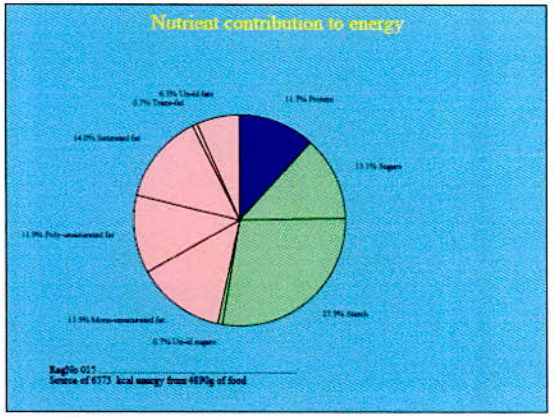


Sources of energy :

Calories from	Total	per day	per 100g	Percent	Tot(1)	Food(2)
Protein	769	256	16	11.7	15%	15%
Carbohydrate	2740	913	56	41.7	47%	50%
Fat	3065	1022	63	46.6	33%	35%
Alcohol	0	0	0	0.0	5%	
Total	6574	2191	134	100.0		

Report created 12 December 2008

NOTES 1 & 2: Columns show the percentage energy profile for the UK population as a whole. Tot (1) includes all sources of energy while Foo (2) is for food only, excluding alcohol.



Food quantities :

Src	Ref	Weight	Percent	Food or Recipe
UKN	50-846	6.0	0.1	Parsley, fresh
UKN	17-339	15.0	0.3	Vinegar
UKN	50-772	15.0	0.3	Garlic, raw
UKN	17-038	18.0	0.4	Olive oil
UKN	17-072	20.0	0.4	Jam, diabetic
UKN	17-299	20.0	0.4	Dips, sour-cream based
UKN	17-021	30.0	0.6	Margarine, soft, polyunsaturated
UKN	17-319	30.0	0.6	Mint sauce
UKN	17-516	30.0	0.6	Tomato puree
UKN	17-045	33.0	0.7	Sunflower oil
UKN	12-331	40.0	0.8	Soya, non-dairy alternative to milk, unsweetened
UKN	19-326	40.0	0.8	Meat samosas, takeaway
UKN	50-967	48.0	1.0	Strawberries, raw
UKN	13-466	50.0	1.0	Leeks, raw
MW6	1127	60.0	1.2	Orange juice concentrate, unsweetened
MW6	555	60.0	1.2	Pork sausages, chilled, grilled
UKN	11-505	60.0	1.2	Weetabix
UKN	14-272	60.0	1.2	Apple juice concentrate, unsweetened
UKN	17-123	60.0	1.2	Breadsticks
UKN	11-180	80.0	1.6	Oatcakes, homemade
UKN	12-312	80.0	1.6	Semi-skimmed milk, average
UKN	13-446	100.0	2.0	Carrots, old, raw
UKN	16-286	100.0	2.0	Fish cakes, salmon, homemade
MW6	30	120.0	2.5	Noodles, egg, boiled
MW6	33	120.0	2.5	Pasta, fresh, cheese and vegetable stuffed,
MW6	579	120.0	2.5	Chicken curry, average, takeaway
MW6	697	120.0	2.5	Seafood pasta, retail

Src	Ref	Weight	Percent	Food or Recipe
UKN	17-512	120.0	2.5	Salad cream
UKN	12-334	150.0	3.1	Cream, fresh, double
UKN	15-003	150.0	3.1	Aubergine, stuffed with vegetables, cheese
UKN	17-254	150.0	3.1	Chicken noodle soup, dried, as served
MW6	77	175.0	3.6	Sandwich, Tuna mayonnaise, white bread
UKN	11-073	200.0	4.1	Brown bread, toasted
UKN	17-160	240.0	4.9	Coffee, instant, made up with water and whole
UKN	50-782	270.0	5.5	Mixed vegetables, frozen, boiled in salted water
UKN	13-460	340.0	7.0	Tomatoes, raw
UKN	11-446	360.0	7.4	White rice, easy cook, boiled
UKN	12-380	500.0	10.2	Yogurt, low fat, fruit
UKN	50-1186	700.0	14.3	Water
	Total	4890.0	100.0	

Source of 731 g of Available Carbohydrate (mse) from 4890g of food

Src	Ref	Quantity	Percent	Food or Recipe
UKN	11-073	113.0	15.5	Brown bread, toasted
UKN	11-446	111.2	15.2	White rice, easy cook, boiled
UKN	12-380	68.5	9.4	Yogurt, low fat, fruit
UKN	11-180	50.6	6.9	Oatcakes, homemade
UKN	11-505	45.3	6.2	Weetabix
MW6	77	44.3	6.1	Sandwich, Tuna mayonnaise, white bread
UKN	17-123	43.5	6.0	Breadsticks
UKN	14-272	34.6	4.7	Apple juice concentrate, unsweetened
MW6	33	31.0	4.2	Pasta, fresh, cheese and vegetable stuffed, cooked
MW6	1127	26.9	3.7	Orange juice concentrate, unsweetened
UKN	17-512	20.0	2.7	Salad cream
UKN	50-782	17.8	2.4	Mixed vegetables, frozen, boiled in salted water
MW6	30	15.6	2.1	Noodles, egg, boiled
		108.3	14.8	Remainder

Thames Valley University
FHHS
Averaged Assessment

Reg.No : 015
Surname : .....
Forenames : .....
Referred : Helen Devies - Dietician
Date of birth : 16 April 1956
Height : 1.71 m.
Body Mass Index : 32.6
Note : Three days Diet Diary - base line.
Total number of foods : 36

Assessment Date : 12 December 2008
Number of days : 3

Sex : Male
Age : 52
Weight : 95.20 kg.

Total food intake : 4.51kg
per day : 1.50kg

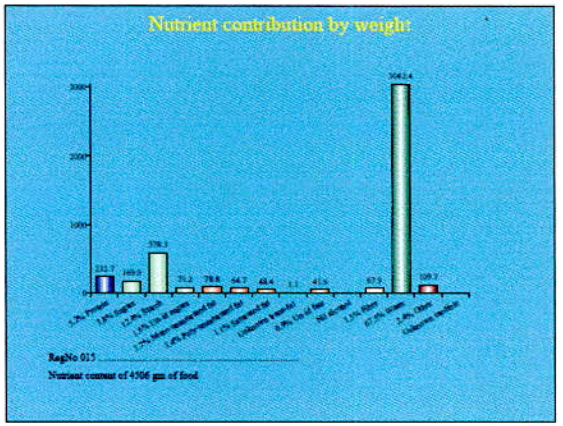
Analysis of selected nutrients :

Nutrient	Unit	Intake	per day	per 100g
Edible proportion		1.00 m	1.00	1.00
Water	g	3042.4 +	1014.1	67.5
Total Nitrogen	g	38.94	12.98	0.86
Protein	g	232.7	77.6	5.2
Fat	g	234.7	78.2	5.2
Available Carbohydrate (mse)	g	818.5 +	272.8	18.2
Energy (kcal)	Cal	6068 +	2023	135
Energy (kJ)	kJ	25566 +	8522	567
Starch (mse)	g	636.2 +	212.1	14.1
Total Sugars (mse)	g	177.4 +	59.1	3.9
Glucose	g	31.7 m	10.6	0.7
Fructose	g	50.2 m	16.7	1.1
Sucrose (mse)	g	66.6 m	22.2	1.5
Maltose (mse)	g	8.1 m	2.7	0.2
Lactose (mse)	g	2.0 m	0.7	0+
Non-starch polysaccharides	g	67.9 +	22.6	1.5
Total dietary fibre (AOAC method)	g	4.0 m	1.3	0.1
Saturated fatty acids	g	48.4 m	16.1	1.1
Mono-unsaturated fatty acids	g	78.8 m	26.3	1.7
Poly-unsaturated fatty acids	g	64.7 m	21.6	1.4
Total trans fatty acids	g	1.15 m	0.38	0.03
Cholesterol	mg	697.5 m	232.5	15.5
Sodium (Na)	mg	14318 +	4773	318
Potassium (K)	mg	7856 +	2619	174
Calcium (Ca)	mg	2209 +	736	49
Magnesium (Mg)	mg	1128 +	376	25
Phosphorus (P)	mg	4132 +	1377	92
Iron (Fe)	mg	52.97 +	17.66	1.18
Copper (Cu)	mg	4.84 +	1.61	0.11
Zinc (Zn)	mg	30.78 +	10.26	0.68
Chloride (Cl)	mg	21393 +	7131	475
Manganese (Mn)	mg	19.63 e	6.54	0.44

Report created 12 December 2008

Nutrient	Unit	Intake	per day	per 100g
Selenium (Se)	ug	129.9 +	43.3	2.9
Iodine (I)	ug	162.8 +	54.3	3.6
Retinol	ug	682 m	227	15
Carotene	ug	13578 m	4526	301
Vitamin D	ug	6.46 +	2.15	0.14
Vitamin E	mg	53.44 +	17.81	1.19
Thiamin	mg	7.81 +	2.60	0.17
Riboflavin	mg	8.72 +	2.91	0.19
Niacin	mg	87.13 +	29.04	1.93
Tryptophan divided by 60	mg	47.995+	15.998	1.065
Vitamin B6	mg	5.18 +	1.73	0.11
Vitamin B12	ug	3.5 e	1.2	0.1
Total Folate	ug	1991 +	664	44
Pantothenic acid, Pantothenate	mg	12.76 +	4.25	0.28
Biotin	ug	86.4 +	28.8	1.9
Vitamin C	mg	370 +	123	8

Key. For one or more contributory foods :
d: nutrient value derived or deduced
e: value estimated
+: present in significant, unknown amounts
m: missing value

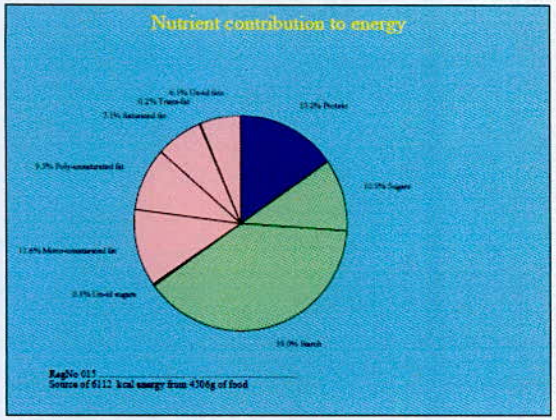


Sources of energy :

Calories from	Total	per day	per 100g	Percent	Tot(1)	Food(2)
Protein	931	310	21	15.2	15%	15%
Carbohydrate	3069	1023	68	50.2	47%	50%
Fat	2112	704	47	34.6	33%	35%
Alcohol	0	0	0	0.0	5%	
Total	6113	2038	136	100.0		

Report created 12 December 2008

NOTES 1 & 2. Columns show the percentage energy profile for the UK population as a whole. Tot (1) includes all sources of energy whi
(2) is for food only, excluding alcohol



Food quantities :

Src	Ref	Weight	Percent	Food or Recipe
UKN	50-840	9.0	0.2	Curry powder
UKN	13-801	10.0	0.2	Allspice, ground
UKN	13-832	10.0	0.2	Ginger, ground
UKN	50-772	10.0	0.2	Garlic, raw
UKN	50-842	10.0	0.2	Mint, fresh
UKN	50-846	10.0	0.2	Parsley, fresh
MW6	1226	15.0	0.3	Salt
UKN	13-817	15.0	0.3	Coriander leaves, fresh
UKN	17-021	15.0	0.3	Margarine, soft, polyunsaturated
UKN	17-339	15.0	0.3	Vinegar
UKN	50-838	15.0	0.3	Chilli powder
UKN	14-870	25.0	0.6	Almonds
UKN	13-285	30.0	0.7	Mushrooms, common, boiled in salted water
UKN	13-435	30.0	0.7	Red kidney beans, canned, re-heated, drained
UKN	17-038	33.0	0.7	Olive oil
MW6	737	40.0	0.9	Beansprouts, mung, stir-fried in blended oil
UKN	17-299	40.0	0.9	Dips, sour-cream based
MW6	387	44.0	1.0	Sunflower oil
UKN	17-517	45.0	1.0	Yeast extract
UKN	11-606	50.0	1.1	Stuffing, sage and onion
UKN	12-137	50.0	1.1	Cheese, Cheddar, English
UKN	17-123	70.0	1.6	Breadsticks
UKN	17-323	75.0	1.7	Pasta sauce, tomato based
MW6	467	80.0	1.8	Pork, leg joint, lean and fat, roast
MW6	341	100.0	2.2	Eggs, chicken, boiled
MW6	579	100.0	2.2	Chicken curry, average, takeaway
UKN	11-579	100.0	2.2	Fruit cake, wholemeal

Report created 12 December 2008

Src	Ref	Weight	Percent	Food or Recipe
MW6	74	150.0	3.3	Sandwich, Chicken salad, white bread
UKN	11-454	240.0	5.3	Spaghetti, wholemeal, raw
UKN	17-160	240.0	5.3	Coffee, instant, made up with water and whole
UKN	11-073	350.0	7.8	Brown bread, toasted
UKN	50-782	360.0	8.0	Mixed vegetables, frozen, boiled in salted water
UKN	50-856	400.0	8.9	Apples, eating, average, raw
UKN	14-298	480.0	10.7	Oranges
UKN	11-446	540.0	12.0	White rice, easy cook, boiled
UKN	50-1186	700.0	15.5	Water
	Total	4506.0	100.0	

Source of 818 g of Available Carbohydrate (mse) from 4506g of food

Src	Ref	Quantity	Percent	Food or Recipe
UKN	11-073	197.8	24.2	Brown bread, toasted
UKN	11-446	166.9	20.4	White rice, easy cook, boiled
UKN	11-454	158.9	19.4	Spaghetti, wholemeal, raw
UKN	11-579	52.4	6.4	Fruit cake, wholemeal
UKN	17-123	50.8	6.2	Breadsticks
UKN	50-856	47.2	5.8	Apples, eating, average, raw
UKN	14-298	40.8	5.0	Oranges
MW6	74	33.9	4.1	Sandwich, Chicken salad, white bread
UKN	50-782	23.8	2.9	Mixed vegetables, frozen, boiled in salted water
		46.2	5.6	Remainder

Dietplan6

Report created 12 December 2008

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Three Days Diet Diary - Data Entry Sheet

No	CAPSULE CODE	Patient Number	DOB	Sex	Age	kcal/day				% intake of macro nutrients								Others		
						kcal/day	PRO	CARBS	FATS	% protein	% Carbs	% starch	% sugars	% fats	% SFA	% poly-USFA	% mono - USFA	Na mg/day	Fiber g/day	Alcohol %
1	A	001 - Baseline																		
		001 - Post intervention																		
2	B	002 - Baseline																		
		002 - Post intervention																		
BASLINE MEAN																				
POST-INTERVENTION MEAN																				

Patient Recruitment - Data Entry Sheet

CAPSULE CODE	No	PATIENT NUMBER	ADDRESS	TP	INVESTIGATOR COMMENTS	NAME OF CLINIC	DATE	STATUS	GP
A	1	OO1							
B	2	OO2							

Patient Clinical Data Entry Sheet

No	CAPSULE CODE	Patient Number	DOB	Sex	Age	Anthropometrics						Blood test							Body fat					Start Date	End Date	Clinic
						Wt	Ht	WC	HC	SBP	DBP	HbA1c	HDL	HDLR	LDL	TG	T.CHO	FPG	Ht (m)	Ht^2	BMI	WHR	BMR			
1	A	001 - Baseline																								
		001 - Post intervention																								
2	B	002 - Baseline																								
		002 - Post intervention																								

Effect of Cinnamon on Glycated Haemoglobin (HbA1c) and Serum Lipids in Type 2 Diabetes Mellitus

Clinical Trial update

Recruitment started	Feb-08
Recruitment completed	Nov-08
Study Centers	Monks Park PCC, Wembley Health Centre and Willesden Health Centre.
Dieticians	Helen Davies, Amanda Yang and Leanne Gregory
External Supervisor	Dr.Devasenan Devendra
University Supervisors	Dr.Amalia Tsiami and Prof.Nocola Robinson
Centre Manager	Mr.Ricky Banarsee

	Total No of patients recruited	No of patients completed the trial	% completed
Capsule A	28	27	96
Capsule B	30	28	93
TOTAL	**58**	**55**	95

Information to GP's and Patients