A STUDY TO DETERMINE THE EFFECTS OF CINNAMON ON BLOOD GLUCOSE AND LIPID LEVELS IN PERSONS WITH TYPE-2 DIABETES

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Dedication

First and foremost, I dedicate this dissertation and doctoral degree to my Father God from whom all blessings flow. I also dedicate this dissertation to my family. To my husband Bruce; I love you and cherish your unyielding support. Your faithfulness and humor helped me persevere throughout this endeavor. To my sons Daniel and Christopher, you are my sunshine. Thank you for the endless joy you bring to my life. I am humbled and appreciative of your many sacrifices as I pursued my doctoral studies. I am indebted to my mother Mariela, thank you for all of your provision and love. To my brother Daniel and sister Monica, thank you for always being there for me. In loving memory of my grandmother Eloisa, thank you for your example, prayers and generosity. A special thanks to my friends Claudia, Ken, Marisol, Maritza, Lily, Francisca, Tonio, Alvin, and Rachel, your friendship and prayers helped sustain me through this effort. I love and cherish each of you dearly. I thank God for the blessing of having all of you in my life.
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ABSTRACT

Diabetes is the most common metabolic disease worldwide; one in twenty Americans are affected. This chronic disease can lead to a host of complications including blindness, amputations, stroke, nerve damage, heart disease and kidney failure. Many of these complications can be avoided by maintaining normal blood glucose and lipid levels. Researchers have speculated that certain spices such as cinnamon may help to normalize blood glucose and lipid levels in persons with type-2 diabetes.

The objective of this double blind, placebo-controlled study was to determine whether cinnamon improves blood glucose, triglyceride, total cholesterol, and low density lipoprotein (LDL) cholesterol levels in persons with type-2 diabetes. The population included 40 men and women diagnosed with type-2 diabetes, who had a fasting blood glucose level between 126-300 mg/dl, or a glycosylated hemoglobin (HgbA1c) level greater than 7% despite metformin treatment for glucose control. The subjects were randomly assigned to a treatment or control group. The treatment group received 1gm of the water-soluble extract of cinnamon in capsule form daily. Their fasting blood glucose, total cholesterol, triglyceride, high density lipoprotein (HDL) cholesterol, LDL cholesterol and postprandial glucose levels were measured on days 0, 20, 40, & 60 of the study. Expected outcomes included normalization of all measured blood levels, except HDL cholesterol levels, for which no significant changes were expected.

After 40 days of supplementation, fasting glucose levels were similarly decreased in both groups, an 8% decrease was found in the treatment group and a 5% decrease in the control group. Postprandial glucose levels decreased by 3% in both the treatment and
control groups. Total cholesterol levels decreased by 4% in the treatment group and by 3% in the control group. LDL cholesterol levels decreased by 12% in the treatment group and by 15% in the control group. Triglyceride levels decreased by 18% in the treatment group and increased by 7% in the control group. HDL cholesterol levels did not change over time in the treatment nor in the control group. No significant differences were found between treatment and control in any of the end points of this study.
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<td>ADA</td>
<td>American Diabetes Association</td>
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<td>ATP</td>
<td>Adenosine Triphosphate</td>
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<td>BMI</td>
<td>Body Mass Index</td>
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<td>CAM</td>
<td>Complementary Alternative Medicine</td>
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<td>CDC</td>
<td>Centers of Disease Control and Prevention</td>
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<td>FBG</td>
<td>Fasting Blood Glucose</td>
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<td>FPBG</td>
<td>Fasting Plasma Blood Glucose</td>
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<td>GLUT 4</td>
<td>Glucose Transporter-4</td>
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<td>Glucose Tolerance Test</td>
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<td>HbA1c</td>
<td>Glycosylated hemoglobin</td>
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<td>HDL</td>
<td>High density lipoproteins</td>
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<td>HIPAA</td>
<td>Health Information Protection &amp; Portability Act</td>
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<td>HOMA-IR</td>
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<td>LDL</td>
<td>Low density lipoproteins</td>
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<td>MCP-1</td>
<td>Monocyte Chemotactic Protein-1</td>
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<td>PTPases</td>
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<td>QD</td>
<td>Once daily</td>
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<tr>
<td>SAS</td>
<td>Statistical Analysis System</td>
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<td>SD</td>
<td>Standard deviation</td>
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<td>S.E.</td>
<td>Standard error</td>
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<tr>
<td>TID</td>
<td>Three times per day</td>
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<td>TTP</td>
<td>Tristertraprolin</td>
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<td>OGT</td>
<td>Oral glucose tolerance</td>
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<td>OGTT</td>
<td>Oral glucose tolerance test</td>
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<td>QUICKI</td>
<td>Quantitative insulin sensitivity check index</td>
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<td>USDA</td>
<td>United States Department of Agriculture</td>
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CHAPTER 1
INTRODUCTION

Statement of the Problem

According to the American Diabetes Association (ADA) diabetes was the seventh leading cause of death in the United States in 2006 and 7% to 8% of the United States population suffers from the complications of type-2 diabetes mellitus. More than 178,000 deaths result from the disease and its related complications (ADA, 2010).

The major complications associated with diabetes include microvascular complications (neuropathy, nephropathy, retinopathy) and macrovascular complications (cardiovascular disease, stroke, and peripheral vascular disease). In fact, people with diabetes are two to four times more likely to die from heart disease or suffer a stroke than a person without the disease (ADA, 2010). A contributing factor to the higher rates of coronary and vascular disease is the fact that person with type-2 diabetes have an increased prevalence of lipid abnormalities. Their circulating lipid levels tend to increase and elevated triglyceride and low density lipoprotein (LDL) levels are powerful risk predictors of coronary heart disease. In fact, control of serum lipids can reduce a person’s risk for cardiovascular complications by 20% to 50% (ADA, 2010; ADA, 2009; Centers for Disease Control (CDC), 2007; Deshpande, 2008).

Preliminary studies have suggested that consumption of cinnamon may help to normalize blood glucose and lipid levels in people with type-2 diabetes (Anderson et. al., 2004; Anderson et al., 1999; Broadhurst, Polansky, & Anderson, 2000; Crawford, 2009; Hlebowicz et, al., 2007; Jarvil-Taylor, Anderson, & Graves, 2001; Kim, 2006; Mang et al., 2006; Qin et al., 2003; Verspohl et. al., 2005 and Wang, Anderson & Chu, 2007).
Glycemic control helps to prevent the microvascular complications (Deshpande, 2008; Spain, 2009). The risk factors for macrovascular complications in persons with diabetes are similar to those for persons without diabetes which include hypertension, hypercholesterolemia and smoking (ADA, 2009; CDC National Diabetes Fact Sheet, 2007; Deshpande, 2008 & Spain, 2009).

As the worldwide incidence of diabetes increases (ADA, 2010), a natural product in the diet, such as cinnamon that could help to normalize plasma glucose and lipid levels would be very beneficial to persons diagnosed with type-2 diabetes mellitus, as it may help to alleviate both the microvascular and macrovascular complications associated with this disease.

Managing the complications of diabetes is quite costly. The American Diabetes Association estimates the direct and indirect medical costs attributable to diabetes mellitus was $174 billion in 2007. In 2002, the United States spent a total of $865 billion for health care, of which $160 billion was incurred by people with diabetes. Health care spending for people with diabetes is more than double what spending would be without diabetes. Clearly, efforts to delay or avoid complications would be beneficial not only to the patient, but also to the health care system (American Diabetes Association, 2010 & Cefalu, 2004).

Significance of the Study

There is no “cure” for diabetes. Both traditional and non-traditional approaches to prevent or reduce the complications of diabetes are needed. The use of “natural products” in the diet are being increasingly used by patients and health-care
professionals. In the United States, office visits to complementary alternative medical (CAM) providers now outnumber visits to primary care physicians. It is estimated that 60% of the population at large uses some type of CAM therapy and the United States population spends more than $30 billion on CAM each year (Bondurant, 2005). Patients with chronic disease such as diabetes represent a significant number of those seeking some type of complementary or alternative therapy. In fact, it is estimated that 35% to 48% of patients with diabetes use some form of CAM therapy (Bradley, 2007). Consequently, nurses need to pursue research to further the scientific basis for these alternative treatment measures.

Recent studies have purported that cinnamon may be a natural insulin sensitizer and may be a useful adjunct for glucose and lipid control in persons with diabetes (Anderson et. al., 2004; Anderson et al., 1999; Broadhurst, Polansky, & Anderson, 2000; Cao et. al., 2007; Crawford, 2009; Hlebowicz et. al., 2007; Imparl-Radosevich, et. al., 1998; Jarvil-Taylor, Anderson, & Graves, 2001; Khan et. al., 2003; Kim, 2006; Kirkham et. al., 2009; Mang et al., 2006; Qin et al., 2003; Verspohl et. al., 2005 & Wang, Anderson & Chu, 2007).

The first and only human study conducted to determine the effect of cinnamon on blood glucose and lipid levels on persons with type-2 diabetes at the outset of this dissertation research was conducted in Pakistan by Khan, Safdar, Khan, Khattak, & Anderson (2003). These investigators were the first to suggest that cinnamon may be an efficacious agent for lowering blood glucose and lipid levels in people with type-2 diabetes. Khan et. al. (2003) had very promising results and the potential beneficial effects of cinnamon were highly publicized by the media. However, since that time there
have been several new studies published related to the effect of cinnamon on blood glucose and lipid levels in a variety of patient populations with conflicting results. Some of the studies have found cinnamon to be an efficacious agent in lowering blood glucose and/or lipid levels in persons with type-2 diabetes (Crawford, 2009; Hlebowicz, et. al., 2007; Mang, et. al., 2006; Solomon & Blannin, 2007; Solomon & Blannin, 2009; and Wang, et. al., 2007); while others have not (Altschuler, et. al., 2007; Blevins, et. al., 2007; Suppapitiporn, et. al., 2006; Tang, et. al., 2008; Vanschoonbeek, et. al., 2006).

Since Khan et. al.’s (2003) publication, cinnamon has been made widely available as a dietary supplement. However, there have been few clinical trials to determine if the findings related to cinnamon efficacy on the normalization of glucose and lipid levels in persons with type-2 diabetes are reproducible utilizing this dietary supplement. If the results of Khan et. al.’s (2003) study could be reproduced, it would indeed be a significant finding, with many potential ramifications. However, the results obtained by Khan et. al. (2003) must be confirmed in additional trials before widespread use of cinnamon by persons with type-2 diabetes can be promoted as an adjunct dietary supplement for the management of diabetes mellitus.

**Purpose of the Study**

The purpose of this randomized, double-blind, placebo-controlled study was to determine whether daily consumption of 500 mg of a dietary supplement containing the aqueous extract of cinnamon will significantly lower fasting blood glucose, triglyceride, low density lipoprotein (LDL) cholesterol, total cholesterol and postprandial glucose levels of persons with type-2 diabetes who are taking Metformin for glucose control.
CHAPTER 2
LITERATURE REVIEW

There have been a number of studies exploring cinnamon as having insulin-mimetic properties (Anderson et. al., 2004; Anderson et. al., 1999; Broadhurst, Polansky, & Anderson, 2000; Cao et. al., 2007; Crawford, 2009; Hlebowicz et. al., 2007; Imparl-Radosevich, et. al., 1998; Jarvil-Taylor, Anderson, & Graves, 2001; Khan et. al., 2003; Kim, 2006; Kirkham et. al., 2009; Mang et al., 2006; Qin et al., 2003; Verspohl et. al., 2005 & Wang, Anderson & Chu, 2007). The catalyst event that prompted further study into the possible beneficial effects of cinnamon originated from a serendipitous finding by the United States Department of Agriculture (USDA) Human Nutrition Research Center. In an interview conducted by New Scientist (2003) Dr. Richard Anderson, the lead scientist of the USDA Human Nutrition Research Center stated that they were investigating the effects of common foods on blood sugar. In this investigation apple pie lowered the glucose levels of the animal specimens being studied.

They later determined that the ingredient that most likely caused this effect was cinnamon. This finding prompted further investigation on the effects of cinnamon on blood glucose and its’ possible mechanism of action. The first study related to the effect of cinnamon on blood glucose appeared in the literature in 1998 (Imparl-Radosevich, 1998). Since then several in vivo and in vitro studies have been conducted to determine the mechanism and efficacy of cinnamon as a possible means of glucose regulation. These studies are reviewed in this chapter.
Cinnamon’s Mechanism in Glucose and Lipid Regulation

Elevated glucose levels are sensed by glucose detectors in the beta-cells of the pancreas, triggering insulin secretion. Insulin binds with alpha sub-units that protrude from the outer face of the plasma membranes of cells in certain tissues, chiefly muscle and adipose tissues. In the absence of insulin, the membranes of these cells are impermeable to glucose. This binding of insulin to this protein kinase receptor on the alpha subunit activates tyrosine kinase activities in the transmembrane beta subunits that largely reside within the cytoplasm. Tyrosine kinase causes autophosphorylation by adenosine triphosphate (ATP) of the beta subunit. Subsequently, this now fully active tyrosine kinase, phosphorylates serine, threonine, and tyrosine residues on a variety of intracellular protein substrates including, protein kinases, protein phosphatases, membrane phospholipases, and guanine nucleotide-binding proteins (G proteins); the net effect is to activate some of these enzymes while inactivating others. For example, inactivation of lipase prevents the breakdown of triglycerides to fats; the inactivation of protein phosphatases prevents the dephosphorylation of tyrosine kinase; and activation of protein kinases causes phosphorylation of other proteins necessary in the insulin signaling cascade. In addition, intracellular glucose transporters called Glut 4 are activated and moved to the plasma membrane which facilitate glucose entry to the cell. Notably, some insulin actions are mimicked by diacylglycerols and protein kinase C activation (Brooks, 2010; Molina, 2010).

Another important action of insulin is prevention of fat breakdown. In adipose cells the increased supply of glucose is not used for energy. Instead, each glucose molecule is
metabolized to form two molecules of glycerol, which is used along with fatty acids to form triglycerides, the storage form of fat. The amino acids are usually obtained from the blood; however, the ultimate source is the liver. Insulin inhibits lipase, an enzyme that breaks down triglycerides and aids in the release of fatty acids into the blood stream. In the liver, insulin stimulates the synthesis or action of specific enzymes which promote the synthesis of fatty acids, amino acids, and proteins (Molina, 2010).

Some people with type-2 diabetes have a defect in their insulin signaling. Others have altered enzymatic activities, such as an increased phosphatase activity and/or seryl phosphorylation of the insulin receptor substrate by glycogen synthase kinase 3 which produce insulin resistance (Jarvil-Taylor, Anderson, & Graves, 2001). In addition, evidence suggests that people with diabetes may have increased susceptibility to oxidation of low-density lipoproteins (LDL). Oxidized LDL is processed by macrophages. These macrophages become lipid laden, and develop into foam cells which form fatty streaks along the arteries. Anderson et al. (1999) suggest that antioxidant supplementation significantly decreases susceptibility of LDL oxidation thereby, decreasing the risk of coronary artery disease (CAD).

One of the earliest events in the development of atherosclerotic lesions is the transmigration of monocytes through the blood vessel wall. These monocytes then are transformed into lipid laden foam cells, an atherosclerotic plaque then follows the formation of foam cells. Monocyte chemotactic protein-1 (MCP-1) is a cytokine responsible for the recruitment of monocytes to sites of inflammation.

Mine et al. (2006) measured serum levels of MCP-1 in healthy persons and compared them to the levels of persons diagnosed with diabetes mellitus and discovered that
MCP-1 levels were significantly higher in persons diagnosed with diabetes. They determined that MCP-1 levels correlated with poor blood glucose control. They believe that this contributes to the increased recruitment of monocytes to the vessel wall in persons with diabetes mellitus.

Imparl-Radosevich et al. (1998) characterized possible mechanisms by which cinnamon potentiates insulin’s activity. Insulin resistance may be due to a decrease in the degree of phosphorylation of the insulin receptor. It is thought that the decrease in phosphorylation is due to the action of an enzyme called protein tyrosine phosphatases (PTPases). There appears to be an increase in PTPases in type-2 diabetes, which results in impaired insulin receptor signaling. Their findings showed that cinnamon can act to inhibit a substrate of this enzyme called PTP-1, a phosphotyrosine phosphatase.

Compounds which augment the action of insulin or bypass the insulin receptor may be beneficial in developing long-term treatments for type-2 diabetes (Jarvil-Taylor, Anderson, & Graves, 2001). Cinnamon extracts have been shown to improve receptor function by activating receptor kinase and inhibiting insulin receptor phosphatase, leading to increased insulin sensitivity (Broadhurst, Polansky, & Anderson, 2000). In addition, cinnamon may also have some antioxidant effects, thereby lowering blood lipid levels (Anderson, et al. 2004).

Cao, Polansky, Blackshear, and Anderson (2007) conducted a study to determine the biochemical basis for the insulin-like effects of cinnamon on mouse adipocyte tissue. They found that cinnamon contains anti-inflammatory properties and increases the levels of important proteins involved in the insulin signal transduction pathway. They ascertain that cinnamon increases the amount of insulin receptors involved in insulin signaling.
Cinnamon also increases the amount of glucose-transporter 4 (GLUT4) available for glucose transport. In addition, they found that there was an increase in the amount of the anti-inflammatory protein, tristetraproline.

Broadherst et al. (2000) evaluated the possible effects of 49 herbs, spices, and medicinal plant extracts on insulin-dependent utilization of glucose using rat adipose tissue. Cinnamon proved to be the most effective botanical product. Anderson et al. (2004) suggest that the biologically active products of cinnamon are A type doubly linked procyanidin oligomers of catechins and/or epicatechins.

Qin et al. (2004) demonstrated that oral cinnamon extract improves the utilization of glucose in rats. In this study awaked rats were randomly divided into control and treatment groups. The control group received oral administration of saline, the treatment groups received either 30mg/kg or 300 mg/kg of the cinnamon extract for a period of three weeks.

Skeletal-muscle insulin-stimulated insulin receptor β and insulin receptor substrate-1 tyrosine phosphorylation levels and insulin receptor substrate-1, phosphoinositide 3-kinase were significantly increased in both treatment groups when compared to the control. These results suggest that glucose uptake is increased due to the enhancement of the insulin-signaling pathways in skeletal muscle.

Cao, Polansky and Anderson (2007) studied the effects of a water-soluble cinnamon extract and cinnamon polyphenols on the protein and mRNA levels of the insulin receptor, GLUT4 and tristertraprolin (TTP) in mouse adipocytes. They found that the cinnamon polyphenols increased insulin beta-receptor levels and that both cinnamon and the polyphenols increased GLUT 4 and TTP levels in mouse adipocytes. Based on these
findings, they suggest that cinnamon exhibits the potential to increase the amount of proteins involved in insulin signaling, glucose transport, and the anti-inflammatory response.

*Animal Studies to Determine the Effect of Cinnamon on Blood Glucose and Lipid Levels*

Verspohl et al. (2005) conducted a randomized, placebo-controlled study where they compared the effects of *Cinnamomum cassia* bark (85.7 mg/kg), *Cinnamomum cassia* extract (5.29 mg/kg), and *Cinnamomum zeylanicum* extracts (5.96 mg/kg) on blood glucose and insulin levels in type-2 diabetic rats. Glucose levels were significantly lower in all three of the treatment groups. However, the *cassia* extract was found to be the most efficacious of the three. In this study there was no decrease in blood glucose unless the rat was challenged in a glucose tolerance test (GTT). Insulin levels were significantly increased in all three of the treatment groups. There were no significant changes in the saline control group. They deduced that *Cinnamomum* has direct insulin stimulatory effects.

In this same study the effect of a 2g/kg glucose challenge in the absence or presence of *Cinnamomum cassia* extract (5.29 mg/kg) was compared to glibenclamide (18mg/kg) (a sulfonylurea medication used for glucose control in persons with type-2 diabetes) on plasma insulin and blood glucose. The plasma insulin levels were significantly higher in rats receiving the sulfonylurea medication and the *cassia* extract when compared to rats receiving the glucose challenge alone. However, the glibenclamide was more effective than the *cassia* extract in stimulating insulin release. The blood glucose levels were also significantly lower in the *cassia* extract and glibenclamide groups when compared to the glucose alone group. However, the glibenclamide was more effective
than the cassia extract in lowering blood glucose levels post oral glucose challenge (Vespoli et. al., 2005).

Kim et. al. (2006) studied the effect of cinnamon cassia extract at different dosages (50, 100, 150, and 200 mg/kg) for 6 weeks on blood glucose, insulin, lipids and intestinal alpha-glycosidase in type-2 diabetic animal models. These investigators found that glucose levels decreased in a dose-dependant manner (p < 0.001) with the most significant decrease in the 200 mg/kg group compared to control. They found that 200 mg/kg of the cinnamon extract significantly decreased blood glucose concentrations in mice. In addition, insulin and high density lipoprotein (HDL) levels were significantly increased and the concentration of triglyceride, total cholesterol and intestinal alpha-glycosidase activity was significantly decreased in the treatment group after 6 weeks of cinnamon administration.

Kannapan et. al. (2006) studied the effects of 8 mg/kg and 80 mg/kg of cinnamomum zeylanicum on glucose and lipid levels in fructose-fed rats. They found that the cinnamon significantly decreased glucose levels when compared to control in both treatment groups. However, 80mg/kg was more effective than 8 mg/kg of the cinnamon for glucose control. Lipid levels were significantly decreased at the higher dose and not at the lower dosage when compared to control.

Clinical Trials to Determine the Effect of Cinnamon on Blood Glucose and Lipid Levels

At the time the proposal for this dissertation research was submitted, there had been only one published clinical trial related to the effect of cinnamon on blood glucose and lipid levels. This study conducted by Khan et. al. (2003) in Pakistan had promising results and was widely publicized. This sparked an interest in the scientific community
and since that time there have been several trials investigating the effect of cinnamon on blood glucose and lipid levels. A literature search through May 2010 identified 13 clinical trials related to the effects of cinnamon on blood glucose and/or lipid levels (Altschuler et al. 2007; Blevins et al. 2007; Crawford 2009; Hlebowicz et al. 2007; Khan et al. 2003; Mang et al. 2006; Solomon & Blannin 2007; Solomon & Blannin 2009; Suppapitiporn 2006; Tang et al. 2008; Vanschoonbeek et al. 2006; Wang et al. 2007; Ziegenfuss et al. 2006).

As indicated above, the first published clinical trial was conducted by Khan et al. (2003). This study was a randomized-controlled trial of 30 men and 30 women with type-2 diabetes. These participants were divided into six groups. Groups 1, 2, and 3 consumed 1, 3, or 6 gm of cinnamon in capsule form daily respectively. Groups 4 - 6 consumed an equal number of placebo capsules daily respectively. All subjects were also on a sulfonylurea medication for glucose control. The clinical trial was conducted for 60 days and the participants consumed the cinnamon or placebo capsules for 40 days. The participants did not take the capsules during the last 20 days of the study.

On days 0, 20, 40, and 60, a fasting blood sample was obtained from each subject. Fasting glucose, triglyceride, total cholesterol, LDL (low density lipoprotein), HDL (high density lipoprotein) levels were obtained. A significant decrease in all the measured laboratory results, except in HDL cholesterol, for which cinnamon had no significant effect was found in all treatment groups.

There did not appear to be a dose response in regards to the lowering of glucose levels, because the responses to all three levels of cinnamon consumption were similar. All three cinnamon dosage groups had an 18-29% decrease in fasting glucose levels after
40 days. The fasting glucose was again measured 20 days after discontinuing the cinnamon, and they found that the glucose levels continued to be significantly lower from baseline during the washout period. All treatment groups had a 13-26% decrease in total cholesterol and a 10-24% decrease in LDL cholesterol levels. There were no significant changes in any of the placebo groups (Khan, Safdar, Khan, Khattak, & Anderson, 2003).

Wang et al. (2007) conducted a double-blind, placebo controlled trial to determine the effect of cinnamon extract on insulin resistance parameters in 15 women with polycystic ovary syndrome (PCOS). Approximately 50%-70% of women with PCOS have insulin resistance with compensatory hyperinsulinemia. In fact, it is thought that hyperinsulinemia may contribute to the development of PCOS (Azziz, 2003).

The objective of Wang et al.'s study was to determine whether cinnamon extract would improve insulin sensitivity in women with PCOS. The subjects were randomly assigned to a treatment (n=7) or control group (n=8). The treatment group received 333mg of cinnamon extract in capsule form three times per day (TID), which is equivalent to approximately 20g of whole cinnamon powder daily. The control group consumed a placebo capsule TID for a period of 8 weeks. The cinnamon capsules were provided by Integrity Nutraceuticals International (Sarasota, FL). An oral glucose tolerance test (OGTT) was obtained at baseline and at 8 weeks. Fasting venous blood samples were obtained for blood glucose and serum insulin levels, followed by ingestion of 75gm of oral glucose. Venous blood samples for glucose and insulin were then obtained at 30, 60, and 120 minutes following the ingestion of glucose. From these values the homeostasis model insulin resistance index (HOMA-IR) and the quantitative insulin sensitivity check index (QUICKI) were calculated to determine endocrine and
metabolic parameters. Glucose tolerance status was evaluated by the criteria established by the ADA (2003).

In this study, fasting glucose decreased by 16.9% in the treatment group. However, fasting glucose also decreased significantly in the placebo group. Fasting glucose decreased by 7.7% in the placebo group. Insulin sensitivity increased significantly in the treatment group as evidenced by a 7.7% increase in the QUICKI and the HOMA-IR decreased by 44.5%, both consistent with improved insulin sensitivity. There were no significant changes in the insulin sensitivity parameters in the placebo group. No adverse effects were reported in this study.

Mang et al. (2006) conducted a study in Hannover, Germany. A total of 79 subjects diagnosed with type-2 diabetes but treated with a myriad of oral hypoglycemic agents or diet (27.7% were taking metformin, 12.3% were taking sulfanylureas, 4.6% glinides, 1.5% glitazones, 30.8% were on combination treatment and 23.1% on diet therapy) were recruited and were randomly assigned to either a cinnamon extract or placebo group. The treatment group received 112 mg of the cinnamon extract three times a day (TID) with meals for a period of 4 months, which is equivalent to approximately 3gm of whole cinnamon powder daily. The aim of the study was to determine whether the cinnamon extract would improve glycosylated hemoglobin A1c, fasting plasma glucose, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides.

Fasting blood glucose levels were significantly lower in the treatment group but not in the control group when compared to baseline. The glucose levels were decreased by 10% in the treatment group and 3% in the placebo group. No significant effects were found in
the lipid levels or in the hemoglobin A1c levels. No adverse effects were reported in this study.

Ziegenfuss et al. (2006) conducted a double-blind, placebo controlled study to determine the effects of a water-soluble cinnamon extract on body composition and features of the metabolic syndrome. The cinnamon capsules (Cinnulin PF®) were provided by Integrity Nutraceuticals International (Sarasota, FL). Twenty-two subjects diagnosed with pre-diabetes and the metabolic syndrome were randomly assigned to receive a placebo or 250 mg of the cinnamon extract in capsule form twice daily, which is equivalent to 10 g of whole cinnamon powder daily. The capsules were consumed with breakfast and dinner for a period of 12 weeks. Measurements obtained at baseline included a fasting serum chemistry, body weight, body composition and blood pressure. Fasting serum chemistry, body weight and composition were then measured at the end of the 12-week period. Blood pressure measurements were obtained on week 6 and week 12.

Inclusion criteria included ages between 30 and 60 years, a fasting blood glucose between 100 mg/dL and 125 mg/dL, normal kidney and liver function tests, and willingness to maintain usual dietary and physical activity habits. Exclusion criteria included a body mass index (BMI) greater than 40, thyroid disease, hypogonadism, a history of musculoskeletal, autoimmune, or neurologic disease. Persons on anti-hyperlipidemic, thyroid, hypoglycemic, anti-hypertensive, or anticoagulant medications were also excluded from the study.

After 12 weeks of cinnamon supplementation, the treatment group decreased their systolic blood pressure by 3.8%. Fasting blood glucose was significantly lower (8.4%)
Lean body mass increased significantly by 1.1% and body fat decreased by 0.7% in the treatment group. Kidney and liver function tests were obtained at baseline and at the end of the 12-week period. There were no significant changes in these values and there were no adverse effects reported.

Crawford (2009) conducted an effectiveness trial to determine the effect of cinnamon on hemoglobin A1c (Hgb A1c) in subjects with poorly controlled type-2 diabetes mellitus. One-hundred and nine persons with type 2 diabetes were randomized to receive either usual care with management changes by their primary care physician, or usual care with management changes plus 500mg twice daily (BID) of commercially available cinnamon cassia powder capsules (Puritan’s Pride, Oakdale, NY) daily for a 3-month period. In this study Hgb A1c was lowered in both the cinnamon group and the usual care alone group. However, the cinnamon group lowered their Hgb A1c values by 0.83% compared to usual care alone lowering Hgb A1c by 0.37%. One patient in the treatment group developed a rash that resolved after discontinuing the cinnamon. No further adverse effects were identified.

Solomon and Blannin (2009) conducted a study on 8 sedentary but otherwise healthy males between the ages of 24 and 26 years. Each subject completed two 20-day interventions in a single-blind randomized cross-over design study. The first intervention was a control trial. On day 0 a fasting blood glucose sample was obtained, followed by an oral glucose tolerance test (OGTT) where each subject consumed a 75g bolus of dextrose. Blood samples were then drawn at 30, 60, 90 and 120 minutes following dextrose ingestion. This same process was repeated on days 1, 14, 16, 18, and 20. All subjects were instructed to take six placebo capsules daily following their evening meal.
during this 20-day control trial period. The control period was followed by a two-week washout period during which time each subject maintained their usual diet and activity habits.

The washout period was followed by the second intervention, which was a cinnamon trial period. The same protocol was followed during this period as the control period except 3gm of commercially available cinnamon cassia powder in capsule form (500mg capsules X 6; Everything Cinnamon, Essex, UK) was consumed daily following the evening meal on days 0 through 14; on days 15 through 20 six placebo capsules were consumed. On day 0 of the cinnamon trial period, a fasting blood glucose sample was obtained, followed by an OGTT. Blood samples were then drawn at 30, 60, 90 and 120 minutes following dextrose ingestion. This same process was repeated on days 1, 14, 16, 18, and 20 of the cinnamon trial period. Measures obtained on day 1 were compared to day 0 to determine acute effects, and measures on day 14 were compared to day 0 to determine chronic effects of cinnamon ingestion. Measures were also taken every 2 days following the discontinuation of cinnamon ingestion on day 14 to determine the time course of post-intervention recovery.

When day 1 was compared to day 0 of the cinnamon trial, glucose decreased significantly by 6.3%. When day 1 of the cinnamon trial was compared to the control trial a significant decrease in glucose of 3.9% was found. No significant changes in glucose levels were found when day 14 was compared to day 0 of the cinnamon trial nor when compared to day 14 of the control trial. Cinnamon ingestion significantly reduced the insulin response to OGTT on day 14 (27.1%), as well as improving insulin sensitivity on day 14 when compared to day 0. These effects were lost following cessation of the
cinnamon capsules.

In Solomon and Blannin’s (2009) study 3gm of cinnamon supplementation daily for 14 days resulted in a reduction of insulin and glucose responses to OGT and improved insulin sensitivity in inactive but otherwise healthy lean males. However, the effects were quickly reversed when cinnamon supplementation was discontinued. No adverse effects were reported.

Hlebowicz et al. (2007) conducted a study in Sweden to determine the effect of cinnamon on postprandial glucose, gastric emptying and satiety in healthy subjects. Fourteen healthy subjects were studied using a cross-over trial, in 2 one-day interventions. Exclusion criteria included symptoms or history of gastrointestinal disease, abdominal surgery, diabetes, connective tissue disorders, cerebrovascular disease, or endocrine disease. None of the subjects were taking any medications except for four women in the study who were taking birth control pills.

One of the factors that affect postprandial glucose levels is gastric emptying. The purpose of this study was to determine whether there is a delay in gastric emptying following cinnamon consumption. A delay in gastric emptying would theoretically also affect satiety. On exam day a fasting blood glucose was obtained on all subjects, followed by ingestion of a meal. The test meal consisted of 300 g of rice pudding mixed with 6 gm of cinnamon. The reference meal consisted of 300 gm of rice pudding. The gastric emptying rate (GER) was calculated using ultrasonography 15 minutes and 90 minutes after meal consumption. Finger prick capillary blood samples for glucose were also obtained 15, 30, 45, 60, 90 and 120 minutes after the start of the meal. Satiety was also measured during these time intervals utilizing a Likert type scale graded from 0 for
extreme hunger to 20 for extreme satiety.

Hlebowicz et. al. (2007) concluded that adding cinnamon to the diet lowers postprandial glucose concentrations and significantly delays gastric emptying. However, the effect of cinnamon on satiety was not significant. There were no adverse effects reported.

Tang, Larson & Liebman (2008) conducted a study to determine the effect of cinnamon on urinary oxalate excretion, plasma lipids and plasma glucose in healthy subjects. The objective of this study was to determine whether cinnamon or turmeric (Puritans Pride, Oakdale, NY) will increase urinary oxalate levels thereby increasing risk of kidney stones and to determine the effect on glucose and lipid levels after four weeks of cinnamon & turmeric supplementation.

In this 8-week crossover study eleven healthy subjects ages 21 to 38 underwent two four-week interventions. The subjects were randomized to receive 3g of cinnamon (n=6) or 2.8g turmeric (n=5) for 4 weeks. The subjects were instructed to take 2 capsules with breakfast, 2 with lunch and 2 with dinner. Oxalate load and fasting blood samples were obtained at baseline, week four and week eight. They concluded that oxalate levels were significantly increased with turmeric ingestion but not with cinnamon. 3gm of cinnamon or 2.8g of turmeric did not alter glucose or lipid levels in healthy non-diabetic subjects.

Vanschoonbeek et. al. (2006) conducted a study to determine the effect of cinnamon cassia powder on blood lipid profiles, insulin sensitivity and/or glucose tolerance of postmenopausal women diagnosed with type 2 diabetes. In this study, twenty-five postmenopausal women with type-2 diabetes between the ages of 60 and 66 and a BMI of 30.4 ± 0.9 kg/m² were recruited and were assigned to a treatment or control group. The
treatment group received 1.5 gm of cinnamon in capsule form daily for a period of six weeks.

Blood samples for fasting blood glucose, Hgb A1c, indices for OGT and whole body insulin sensitivity, as well as lipid profiles were obtained on day 0, week 2 and week 6 for both the treatment and placebo groups. Compliance was monitored by capsule count on week 2 and week 6.

Exclusion criteria included impaired liver or renal function, cardiovascular disease and exogenous insulin therapy. All subjects were diagnosed with type-2 diabetes and were taking oral hypoglycemic agents or were on diet therapy only (n=4) for glucose control. All subjects on medications had not had any medication modifications within 3 months of the study. Types of oral hypoglycemic agents taken included thiazolidinediones with or without metformin derivatives (n = 6); sulfanylurea derivatives with or without metformin derivatives (n=14); metformin derivatives only (n=3). Subjects were assigned to a treatment group (n=13) or placebo group (n=12), matched for age, BMI, years since diagnosis with type 2 diabetes, fasting blood glucose concentration and medications. All subjects were screened for diabetes with an OGTT.

During the experimental period, all subjects maintained their usual dietary and exercise habits and all their medications were continued, except they were asked to refrain from heavy physical exercise training and/or labor at least 3 days before the OGTT and they were asked to exclude cinnamon from their diet. Dietary food records were obtained for 2 days prior to the first OGTT. These records were used to standardize dietary intake before the rest of the OGTT. Afterwards, all subjects were fed the same standardized meal the evening before each of the OGTT trials.
Fasting blood was obtained on days 0, week 2 and week 6 followed by ingestion of 75g of glucose. Thereafter, blood samples were collected at 30, 60, 90 and 120 minutes via a catheter inserted into a dorsal hand vein. In Vanschoonbeek et al’s (2006) study, 1.5 gm of cinnamon daily did not have a significant effect on fasting blood glucose, plasma insulin concentrations, OGT, total cholesterol, LDL cholesterol, HDL cholesterol or triglyceride levels in postmenopausal women diagnosed with type 2 diabetes mellitus.

Solomon & Blannin (2007) conducted a pilot study to determine the effects of short-term cinnamon ingestion on glucose tolerance. The purpose of this study was to determine whether a single bolus ingestion of cinnamon would have an effect on glucose tolerance and insulin sensitivity and whether these effects will last 12 hours.

The study population included seven lean, healthy males ages 25 to 27 years old in England. They utilized a randomized cross-over design. Each participant completed three interventions: a control oral glucose tolerance test (OGTT_control), an OGTT supplemented with cinnamon (OGTT_cin), and an OGTT with cinnamon ingested 12 hours before the trial (OGTT_cin12hpre). Each of the three visits was separated by at least 5 days.

On test day a fasting blood sample was obtained followed by ingestion of 75g of glucose. Blood samples were then drawn at 30, 60, 90, and 120 minutes. The control group consumed a capsule containing 5g of wheat flour 12 hours prior to the OGTT_control. The cinnamon group consumed a capsule containing 5g of wheat flour 12 hours prior to the OGTT_cin and a capsule containing 5g of cinnamon at baseline, prior to the ingestion of glucose. The OGTT_cin12hpre group received 5g of cinnamon 12 hours prior to the OGTT_cin12hpre and a capsule containing 5g of wheat flour at baseline, prior to the ingestion
Plasma glucose responses were significantly decreased in OGTT<sub>cin</sub> (12.9%) and OGTT<sub>cin12hpre</sub> (10%) when compared to OGTT<sub>control</sub>. No differences were found between the two cinnamon trials. There were no significant effects on insulin responses to OGTT in any of the trials. Insulin sensitivity derived from the Matsuda test was elevated in both cinnamon trials. However, there was no significant difference in insulin sensitivity between the two cinnamon trials.

Solomon and Blannin (2007) concluded that a single bolus ingestion of 5g of cinnamon spice can reduce glucose responses to OGTT and improve insulin sensitivity in healthy individuals. This data also show that the effects of cinnamon on glucose tolerance and insulin sensitivity persist for at least 12 hours.

Altschuler et. al. (2007) conducted a study to determine the effect of cinnamon on Hgb A1c among adolescents with type 1 diabetes. Seventy-two U.S. adolescents diagnosed with type-1 diabetes between the ages of 13 and 18 were randomly assigned to either a treatment or control group. In this double-blind study, the treatment group ingested a capsule containing 1gm of cinnamon daily for 90 days; the control group ingested a placebo capsule daily for 90 days. Hgb A1c levels were drawn at baseline and at the end of the 90-day intervention. A member of the research team called each participant every 2 weeks during the study to assess adherence to the study protocol, to collect data on their insulin dosing, and possible adverse effects, including hypoglycemic episodes. One subject in the cinnamon group was withdrawn due to the development of hives and it was later determined that the subject had a family history of cinnamon allergies. There was no significant differences in final Hgb A1c, change in A1c, total
daily insulin intake or number of hypoglycemic episodes between the cinnamon and control groups. Altschuler et. al. (2007) concluded that cinnamon is not effective for improving glycemic control in adolescents with type-1 diabetes.

Blevins et. al. (2007) studied the effect of cinnamon on glucose and lipid levels in persons with non insulin-dependent type-2 diabetes. Sixty subjects diagnosed with type-2 diabetes were randomly assigned to a treatment or control group. In this double-blind study, the treatment group received 500mg of cinnamon cassia in capsule form BID with breakfast and dinner for a period of 3 months. Fasting glucose, total cholesterol, LDL, HDL, triglyceride and insulin levels were measured at baseline, 1, 2, and 3 months. Hgb A1c was measured at baseline and at 3 months. No significant differences were found in glucose, lipid levels or Hgb A1C between the treatment group and control group.

Suppapitiporn et. al. (2006) studied the anti-diabetic effect of cinnamon cassia powder in persons with type-2 diabetes. The study population included 60 subjects diagnosed with type-2 diabetes, between the ages of 30 and 70. The fasting glucose levels at baseline were between 120 and 180 mg/dl and all subjects Hgb A1c levels were greater than 7% at baseline. The mean glucose level at baseline was 154.40 ± 24.72 mg/dl. This single-blind, placebo-controlled trial was conducted in Bangkok, Thailand. Subjects were randomly assigned to a treatment or control group. All subjects were on either metformin or a sulfonylurea drug for glucose control for a period of at least 3 months.

The treatment group (n = 30) received 1.5g of cinnamon cassia powder in capsule form TID with meals for 12 weeks. The control group received a placebo capsule TID with meals for 12 weeks. Fasting blood was obtained at baseline and
at the end of the 12 week study period and evaluated for Hgb A1c and glucose levels. Renal and hepatic function were also analyzed.

Fasting glucose was significantly lower from baseline in both the treatment and control group. There was however, no statistical difference between the treatment and control group in terms of fasting glucose or Hgb A1c levels. There was no statistically significant difference between treatment and control in terms of lipid profile, renal or hepatic function. There were no adverse effects reported by the participants of this study.

A discussion, including summary tables (Tables 1 & 2) of all these clinical trials published thus far on persons with type-2 diabetes begins on page 30 of this chapter.

**Deleterious Effects of Cinnamon Consumption**

According to the World Health Organization (WHO, 1999), cinnamon is contraindicated in cases of fever of unknown origin, pregnancy, stomach or duodenal ulcers, and in patients with an allergy to cinnamon or Peru balsam. In addition, cinnamon extract markedly decreases in vitro dissolution of tetracycline hydrochloride. There is insufficient data to evaluate the carcinogenic potential of cinnamon. Additionally, available data are not sufficient for an adequate benefit/risk assessment in pregnancy. Therefore, cinnamon should not be used in pregnancy or during lactation. The safety and efficacy in children has not been established. Allergic reactions of the skin and mucosa have been reported (WHO, 1999).

Libster (2002) stated that there is one case report of a 7 year old who drank 2 ounces of cinnamon oil when challenged by a friend to do so. His symptoms included burning sensation in the mouth, chest, and stomach, double vision, dizziness, vomiting, and sleepiness. This case report was published in *Clinical Pediatrics* by Pilapil, V. (1989).
Westra et al. (1998) published a case study where a 24 year old woman who chewed five packs of cinnamon gum daily developed squamous cell carcinoma of the tongue. The woman did not chew tobacco or consume alcohol. They recommend prompt withdrawal of cinnamon products in heavy gum chewers who develop cinnamon related oral lesions.

The most common complication of cinnamon ingestion was found to be allergic reactions. Cinnamaldehyde has been identified as the leading substance responsible for allergic reactions. Allergic symptoms include urticaria, swelling of the lips and tongue, itching, burning, or blistering of the oral mucosa from the use of dental preparations containing cinnamon. These symptoms often resolve when cinnamon preparations are withdrawn (Libster, 2002; WHO, 1999; Duke, 1986; Blumenthal, 2000; & Newall et al., 1996, Dugoua et al., 2007).

Libster (2002) also suggested that cinnamon should not be used internally with tetracycline. Cinnamon bark markedly reduced the in vitro dissolution of tetracycline hydrochloride. This finding was published by DeSmet (1992) where tetracycline hydrochloride was placed in a cinnamon solution. After 30 minutes only 20% of the tetracycline remained, in contrast to 97% when only water was used. The LD$_{50}$ of cinnamon in mice is 18.48 +/- 1.8 g/kg of the crude herb (Libster, 2002). The LD$_{50}$ of the cinnamon extract is greater than 5,000 mg/kg in rats (Product Safety Laboratories, 2005).

Anderson et al. at the Beltsville Human Nutrition Research Center of the United States Department of Agriculture (USDA) has conducted extensive research on the effects of cinnamon on glucose and lipid levels. He found that the deleterious effects of cinnamon
are found largely in cinnamon oil, the fat-soluble portion of cinnamon. However, the active components of cinnamon are found in the water-soluble extract of cinnamon (Bliss, 2004). A video made available by the USDA entitled “Health Benefits of Cinnamon Extract” can be viewed at the following Web site: http://www.ars.usda.gov/is/video/vnr/cinnamon.htm. According to the United States Food and Drug Administration (USFDA, 2006), Cinnamomum, including common and cassia cinnamon are generally recognized as safe (GRAS) when used in amounts commonly found in food.

Meta Analysis

Baker et. al. (2008) conducted a meta-analysis of randomized controlled trials of cinnamon to better characterize its impact on glucose and plasma lipids. They conducted a systematic literature search through July, 2007 to identify randomized placebo-controlled trials of cinnamon that reported data on Hgb A1c, fasting blood glucose, or lipid parameters. They found five prospective randomized controlled trials (Altschuler, et. al., 2007; Blevins, et. al., 2007; Khan et. al., 2003; Mang et. al., 2006; & Vanschoonbeek, et. al. 2006).

These five clinical trials had a combined population of 282 subjects. All the studies used cinnamon cassia and doses ranged from 1g to 6g per day. Khan et. al. (2003) examined three different doses of cinnamon, the results were combined in this meta-analysis because no dose-response relationship was found between 1g and 6g of cinnamon. All but one of the studies provided cinnamon cassia in powder form except for Mang et. al’s (2006) study which provided a cinnamon extract equivalent to 3g of the cinnamon powder. All studies were conducted on adults with type-2 diabetes, except for
Altschuler et. al. (2007) who conducted their study on adolescents with type-1 diabetes. In their meta-analysis, Baker et. al. (2008) concluded that persons with type-1 or type-2 diabetes receiving cinnamon did not demonstrate statistically or clinically significant changes in Hgb A1c, fasting blood glucose, or lipid levels when comparing treatment and placebo groups in these five aggregate studies.

The median duration of these five clinical trials was 12 weeks. Baker et. al. (2008) stated that this duration of treatment is appropriate to observe clinically significant changes in fasting blood glucose and lipids. However, this is not sufficient time to evaluate changes in Hgb A1c. However, Baker et. al. (2008) stated that in fact the Hgb A1c levels increased to a greater extent in the treatment group, when compared to placebo in this meta-analysis, which may indicate that cinnamon may not have an impact on long-term glycemic control.

Baker et. al. (2008) noted limitations in their meta-analysis which included the small amount of eligible studies identified. Thus, this meta-analysis may be under-powered to detect statistically significant differences in many of the end-points. Based on the calculations conducted from the results of these studies, Baker et. al. (2008) deducted that a sample size of 1,166 - 6,853 would be needed for adequate power.

Discussion of Current Research Findings

There is clear evidence that the reduction of blood glucose and lipid levels in persons with type-2 diabetes will help to prevent macrovascular and microvascular complications (ADA, 2009 & ADA 2010). CAM offers therapies that supplement conventional medical care and interest in the use of biologically active, natural supplements is increasing in the United States. Among persons diagnosed with diabetes, it is estimated
that 35% to 48% are using some form of CAM therapy (Bradley, et. al., 2007). As health care providers, we need to be aware of CAM therapies that are beneficial based on sound empirical evidence. The results of Khan et. al’s (2003) study has prompted further scientific inquiry into the potential beneficial effects of cinnamon on glucose and lipid regulation in persons with diabetes.

As described in this literature review 12 new human studies were found related to the effect of cinnamon on glucose and/or lipid levels, since Khan et. al’s. (2003) original publication. Of these 12 studies, five were conducted on persons with type-2 diabetes (Crawford, 2009; Blevins et. al., 2007; Mang et. al., 2006; Suppapitiporn et. al., 2006; & Vanschoonbeek et. al., 2006); four were conducted on healthy adults (Hlebowicz et. al., 2007; Solomon & Blannin, 2007; Solomon & Blannin, 2009; Tang et. al., 2008); one was conducted on persons with metabolic syndrome (Ziegenfuss et. al., 2006); one was conducted on women diagnosed with polycystic ovary syndrome (Wang et. al. 2007); and one was conducted on adolescents diagnosed with type-1 diabetes (Altschuler et. al., 2007).

Including the Khan et. al (2003) study, a total of six human studies related to the effect of cinnamon on blood glucose and/or lipid levels in persons with type-2 diabetes were found in the literature through May 2010 with conflicting results. Three of these studies found cinnamon to be efficacious in lowering blood glucose or Hgb A1c in persons with type-2 diabetes (Crawford, 2009; Khan et. al., 2003; & Mang et. al., 2006). Three of these studies found no significant effect on blood glucose or lipid levels (Blevins et. al., 2007; Suppapitiporn et. al, 2006, & Vanschoonbeek et. al., 2006). Table 1 below summarizes the results of these studies. Each of these studies utilized differing
methodologies, different doses of cinnamon, and population demographics are heterogeneous all of which confound the conclusions that can be reached. Table 4 depicts the major differences of these studies. A complete table with a summary of all 13 clinical trials found published through May, 2010 related to cinnamon use and its effect on blood glucose and/or lipid levels can be found in the appendix (appendix A).
**Table 1: Summary of Randomized Controlled Trials Evaluating Cinnamon Use in Relation to Blood Glucose and Lipid Levels in Persons with Type-2 Diabetes**

<table>
<thead>
<tr>
<th>Author &amp; Journal</th>
<th>Subjects</th>
<th>Design &amp; Dosage</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Khan et. al. (2003) <em>Diabetes Care</em></td>
<td>60 (30 men &amp; 30 women) diagnosed with type-2 diabetes taking sulfonylurea drugs. Ages 52.2 +/- 6.32 years. Study conducted in Pakistan, Hayatabad Medical Complex</td>
<td>Randomly assigned into 6 equal groups. Groups 1, 2 &amp; 3 consumed 1, 3 or 6g of cinnamon cassia powder daily. Groups 4,5,6 were assigned to respective placebo groups, which consumed a corresponding # of capsules containing wheat flour. No capsules consumed after day 40. Fasting blood drawn on day 0, 40, 60 for glucose, triglyceride, total cholesterol, HDL cholesterol, &amp; LDL cholesterol levels.</td>
<td>After 40 days all three levels of cinnamon reduced the mean fasting serum glucose (18-29%), triglyceride (23-30%), LDL cholesterol (7-27%), and total cholesterol (12-26%) levels; no significant changes were noted in the placebo groups. Changes in HDL cholesterol were not significant. + Results in Type-2 DM</td>
</tr>
<tr>
<td>Suppapitiporn et. al. (2006) <em>Journal of the Medical Association of Thailand</em></td>
<td>Sixty subjects diagnosed with type-2 diabetes Age 30-70 Fasting glucose 120-180 Hgb A1C &gt; 7 Study conducted in Bangkok, Thailand</td>
<td>Single-blind, placebo-controlled trial. Subjects were randomly assigned to treatment or control group. The treatment group (n=20) received 1.5g of cinnamon cassia powder in capsule form TID with meals for 12 weeks. Fasting blood was obtained at baseline and at 12 weeks and evaluated for Hgb A1C, glucose, lipid profile, BUN, creatinine, &amp; liver function test.</td>
<td>There was no statistical difference between the treatment and control group in regards to fasting glucose, Hgb A1c or lipid profile. There was a significant increase in creatinine from baseline in the treatment group and a decrease in SGOT. No adverse effects were reported by the participants. - Results in Type-2 DM</td>
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<tr>
<th>Author &amp; Journal</th>
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<th>Design &amp; Dosage</th>
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<tr>
<td>Vanschoonbeek et al. (2006)</td>
<td>25 postmenopausal women diagnosed with type-2 diabetes. All subjects were using oral hypoglycemic agents. Age 60 - 66</td>
<td>Double-blind, placebo-controlled trial. The treatment group received 1.5 gm of cinnamon in capsule form daily for a period of six weeks. Blood samples for fasting blood glucose, HbA1c, plasma insulin, OGT, total cholesterol, LDL cholesterol, HDL cholesterol or triglyceride levels in postmenopausal women diagnosed with type 2 diabetes mellitus.</td>
<td>In this study 1.5 gm of cinnamon daily did not have a significant effect on fasting blood glucose, Hgb A1c, plasma insulin, OGT, total cholesterol, LDL cholesterol, HDL cholesterol or triglyceride levels in postmenopausal women diagnosed with type 2 diabetes mellitus.</td>
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<td>Mang et al. (2006)</td>
<td>79 subjects diagnosed with type-2 diabetes treated with an oral hypoglycemic agent or diet</td>
<td>Double-blind, placebo-controlled trial. The treatment group received 112mg of a cinnamon cassia extract three times a day (TID) with meals for a period of 4 months. The control group received a placebo capsule TID for a period of 4 months. The amount of aqueous cinnamon extract corresponded to 3g of cinnamon powder per day. Fasting blood samples were obtained at baseline and after 4 months of intervention. Compliance was monitored by capsule count and diary.</td>
<td>No adverse effects were observed and fasting blood glucose levels were significantly lower in the treatment group. However, no significant effects were found in the lipid levels or in the hemoglobin A1c levels. They concluded that cinnamon extract seems to have a moderate effect in reducing fasting plasma glucose concentrations (10.3%) in diabetic patients with poor glycemic control.</td>
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**Results in Type-2 DM in Postmenopausal Women**
<table>
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<tr>
<th>Author &amp; Journal</th>
<th>Subjects</th>
<th>Design &amp; Dosage</th>
<th>Results</th>
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<tr>
<td>Blevins et. al. (2007) <em>Diabetes Care</em></td>
<td>60 subjects diagnosed with type-2 diabetes</td>
<td>Intention to treat analysis. Double-blind, placebo-controlled trial. The treatment group received 500mg of <em>cinnamon cassia in capsule form</em> BID with breakfast and dinner for a period of 3 months. Fasting glucose, total cholesterol, LDL, HDL, triglyceride and insulin levels were measure at baseline, 1, 2, and 3 months. A1C was measured at baseline and at 3 months.</td>
<td>No significant effects found in glucose, lipid levels or Hgb A1C in the treatment group when compared to the control when analysis completed on all enrolled subjects. Negative effects were also found when the analysis was restricted to the 42 participants who completed the study.</td>
</tr>
<tr>
<td>Crawford (2009) <em>The Journal of the American Board of Family Medicine</em></td>
<td>109 subjects diagnosed with type 2 diabetes. Inclusion criteria included a HbA1C &gt; 7.0 Study conducted at Wilford Hall Medical Center, San Antonio, Texas</td>
<td>This was an effectiveness trial. Participants were randomly assigned to either usual care with management changes by their primary care physician; or usual care with management changes plus cinnamon capsules. The cinnamon group was instructed to ingest two 500 mg of <em>cinnamon cassia in capsule form daily for a period of 90 days</em>. Hgb A1C was drawn at baseline and at the end of the 90-day period for both groups.</td>
<td>Cinnamon lowered Hgb A1C 0.83% compared with usual care alone lowering Hgb A1c 0.37%</td>
</tr>
</tbody>
</table>

- Results in Type-2 DM

+ Results in Type-2 DM
Table 2: Demographics & Major Differences of Clinical Trials

<table>
<thead>
<tr>
<th>Authors/Method</th>
<th>Population</th>
<th>BMI/Length of Study/Follow-up (FU)</th>
<th>Baseline Glucose (mg/dl)</th>
<th>A1c (%)</th>
<th>Cholesterol (mg/dl)</th>
<th>Medications</th>
<th>Standardized Diet/Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blevins et. al. (2007) Double-blind, placebo-controlled</td>
<td>US men &amp; women with type-2 diabetes 68% Caucasian, 16% Native American</td>
<td>32.5±1.7 3 months FU=1, 2, 3 months</td>
<td>132.9 ± 9.3 7.2 ± 0.3 170.2 ± 8.1</td>
<td>75% Metformin; 33% Glitazones; 50% Statin drug</td>
<td>Subjects kept a food journal/500mg BID of cinnamon cassia powder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crawford (2009) Effectiveness Trial. No placebo, unblinded</td>
<td>US men &amp; women with type-2 diabetes 76% Caucasian, 16% African American</td>
<td>31.9 ± 6.4 3 months FU= day 88 called to remind of blood draw on day 90</td>
<td>Not provided 8.47 ± 1.8 Not provided</td>
<td>On a myriad of medications, including insulin. Medications could be adjusted or added during trial. Some subjects were already taking cinnamon supplements</td>
<td>No standardized diet/500mg BID of cinnamon cassia powder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Khan et. al. (2003) Double-blind, placebo-controlled</td>
<td>60 Pakistani men &amp; women with type-2 diabetes</td>
<td>BMI not reported/60 days FU= day 20, 40, 60</td>
<td>234 ± 25.2</td>
<td>100% Sulfanylureas Not on insulin, not on meds for other conditions</td>
<td>No standardized diet/1, 3 or 6mg of cinnamon cassia powder daily</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2: continued:

<table>
<thead>
<tr>
<th>Authors/Method</th>
<th>Population</th>
<th>BMI/Length of Study/Follow-up (FU)</th>
<th>Baseline Glucose (mg/dl) A1c (%)</th>
<th>Cholesterol (mg/dl)</th>
<th>Medications</th>
<th>Standardized Diet/Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mang et al. (2006)</td>
<td>65 German men &amp; women with type-2 diabetes</td>
<td>29.6± 4.6 4 months Subjects kept diary FU= 4 months</td>
<td>166.7 ± 41.0 6.86 ± 1.00</td>
<td>204.6 ± 34.4</td>
<td>Metformin 27.7%, sulfanylureas 12.3%; glinides 4.6%; glitazones 1.5%; combination therapy 30.8%, diet alone 23.1% lipid lowering medications 20%</td>
<td>No standardized diet/112 mg TID of cinnamon cassia extract equivalent to 3gm of cinnamon cassia powder daily</td>
</tr>
<tr>
<td>Suppapitporn et al. (2006)</td>
<td>60 Thai men &amp; women with type-2 diabetes</td>
<td>24.8± 1.8 3 months FU=3 months</td>
<td>154.4 ± 24.7 8.14 ± 1.10</td>
<td>196.2 ± 44.9</td>
<td>A variety of oral anti-diabetic medication, types not specified. No insulin</td>
<td>No standardized diet/1.5 gm of cinnamon cassia powder TID</td>
</tr>
<tr>
<td>Vanschoonbeek et al. (2006)</td>
<td>25 postmenopausal women with type-2 diabetes</td>
<td>30.7±1.1 6 weeks FU=week 2 &amp; 6</td>
<td>150.7 ± 10.6 7.4 ± 0.3</td>
<td>191.9 ± 5.7</td>
<td>sulfanylurea=14 thiazolidinediones= metformin=14 metformin=6 diet=4</td>
<td>Standardized meal prior to OGTT/500 mg TID of cinnamon cassia powder</td>
</tr>
</tbody>
</table>
There have been few clinical trials conducted on the effects of cinnamon on blood glucose and lipid levels in persons with type-2 diabetes. All the studies conducted thus far, have been relatively small with differing methodologies and population demographics. The results of Khan et. al.'s (2003) study has had the most efficacious results of all the clinical trials conducted thus far. This study found cinnamon to be effective in lowering blood glucose levels by 18% to 29% and lipid levels by 13% to 26%. The cinnamon treatment was equally effective in three doses: 1, 3, and 6g daily of the cinnamon cassia powder. The results of this study were further strengthened by the fact that these findings were only obtained in the treatment groups. The placebo groups glucose and lipid levels remained unchanged during the study period. Khan et. al's study did not examine the effect of cinnamon on Hgb A1c levels.

Mang et. al.'s (2006) study also demonstrated that cinnamon was efficacious in lowering blood glucose levels in persons with type-2 diabetes; however, their results were more modest. Mang et. al. (2006) reported a 10.3% reduction in FBG; however, the placebo group also had a 3.37% reduction. They utilized 112 mg of cinnamon cassia extract TID, which is equivalent to 3gm of cinnamon powder daily. The study duration was 4 months. They found no significant effect on Hgb A1c or lipid levels, although duration was adequate for an effect on Hgb A1c. The major differences between this study and Khan et. al.’s (2003) study was the following:

- Different ethnicity, the population in this study was recruited from Germany, the population in Khan et. al.’s (2003) study was recruited in Pakistan.
- The baseline mean blood glucose levels were much higher in Khan et. al.’s (2003) study (234 mg/dl compared to 166 mg/dl).
• All subjects in Khan’s study were taking sulfanylurea medications and were not taking any other drugs. The subjects in Mang et. al.’s (2006) study were on a myriad of medications including lipid lowering medications (27.7% metformin, 12.3% sulphonylureas, 4.6% glinides, 1.5% glitazones, 30.8% combination therapy, 23.1% diet, 20.1% on lipid lowering medications).

• Mang et. al. (2006) used 112mg TID of cinnamon cassia aqueous extract equivalent to 3g of cinnamon powder daily. Khan et. al. (2003) used cinnamon cassia powder, 1, 3, and 6g daily.

Crawford (2009) conducted an effectiveness trial to study the effects of 500mg BID of cinnamon powder on Hgb A1c in persons with type-2 diabetes. Hgb A1c was found to be significantly lower in the treatment group. Hgb A1c was 0.83% lower from baseline in the treatment group and 0.37% lower in the control group. The major differences of this study from Khan et. al.’s (2003) study was the following:

• There was no placebo utilized in this study. Perhaps the daily reminder of the cinnamon capsule in the treatment group may have caused a change in this group’s daily habits.

• Subjects were on a myriad of medications in this study, including insulin. Insulin was an exclusion criterion in Mang et. al.’s (2006), as well as Khan et. al.’s (2003) studies. In addition, medications were added and dosages of existing medications were adjusted in both the treatment and control groups of this study. Some subjects were already taking cinnamon supplementation.

• The ethnicity of the population of this study differed from Khan et. al’s (2003) study. This study was conducted in the United States (US); 76% of the subjects are Caucasian and 16% are African American.
Baseline glucose levels are not reported in this study. Baseline Hgb A1c was 8.47, which is relatively high. However, not as high as the likely corresponding A1c levels of Khan et. al.'s (2003) study.

Blevins et. al. (2007) studied the effect of 1g of cinnamon cassia powder on persons with type-2 diabetes and found that cinnamon did not have a significant effect on glucose, Hgb A1c or lipid levels. The major differences of this study from Khan et. al.'s (2003) study was the following:

- Baseline glucose levels are considerably lower than Khan et. al.'s (2003) study (132 mg/dl compared to 234 mg/dl).
- Baseline lipid levels are lower than Khan et. al.'s (2003) study (170 mg/dl compared to 213 mg/dl).
- The subjects in this study were taking a myriad of medications including lipid lowering medications (75% on metformin, 33% on glitazones, 50% on statins).
- Different ethnicity, this study was conducted in the US, 76% Caucasian, 16% Native American.

Vanschooonbeek et. al. (2006) conducted a study to determine the effect of 1.5gm of cinnamon cassia powder on postmenopausal women with type-2 diabetes and did not find cinnamon to have a significant effect on plasma glucose, lipids or Hgb A1c. The major differences in this study when compared to Khan et. al.’s (2003) study are the following:

- The subjects in this study were taking a myriad of medications (56% on sulfanylureas with metformin, 12% on metformin alone, 24% on thiazolinediones, 16% were not taking medications. The subjects in Khan et. al.’s (2003) study were on sulfanylurea medications only.
- Baseline glucose levels were markedly lower in this study when compared to Khan et. al.’s (2003) study (150 mg/dl compared to 234 mg/dl).
• All subjects in this study were postmenopausal women; however, there does not appear to be a gender difference in any of the published studies found.

• The subjects in this study consumed a standardized meal prior to testing, this was not a part of Khan et. al.'s (2003) methodology.

• The study length was shorter in this study when compared to Khan et. al’s (2003) study (6 weeks compared to 40 days of treatment and follow-up testing on day 60).

Suppapitiporn (2006) conducted a study to determine the effect of 1.5g TID of cinnamon cassia powder on glucose and lipid levels of persons with type 2 diabetes. This study was conducted in Thailand. Baseline glucose levels were markedly lower in this study when compared to Khan et. al.'s (2003) study (154 mg/dl compared to 234 mg/dl).

In summary, the baseline FBG subjects in Khan et. al’s. (2003) study was much higher than any other clinical study conducted thus far in persons with type-2 diabetes. Khan et. al’s (2003) study was the only study conducted where all subjects were on sulfonylurea medications for glucose control. There are many variables that could have affected the effectiveness of cinnamon on persons with type-2 diabetes in these clinical trials, which leads to the following questions. Are the differences in the results of these studies due to the differences in methodologies, variations in baseline fasting blood glucose, differences in oral anti-hyperglycemic medications, study duration, dietary control, type of cinnamon used, differences in body mass index (BMI)? All of these questions are going to require further inquiry.

As stated earlier, at the outset of this investigation Khan et. al’s (2003) study was the only human research study published on the effects of cinnamon on blood glucose and lipid levels in persons with type-2 diabetes. All the subjects in Khan et. al.’s (2003)
study were taking sulfonylurea medications for glucose control and were recruited in Pakistan. The results of their study were very promising and the purpose of this dissertation research was to determine if these effects could be reproduced in a different population.
CHAPTER 3

METHODOLOGICAL GUIDING FRAMEWORK

The hypothesis that cinnamon may help lower blood glucose and lipid levels arose from a fortuitous discovery at the USDA Human Nutrition Research Center located in Beltsville, Maryland. While testing the impact of certain foods on blood sugar levels, researchers were intrigued to find that cinnamon-flavored apple pie helped diminish blood glucose levels instead of the expected increase. Consequently, several studies have been conducted and the findings suggested that cinnamon may help to normalize blood glucose levels in persons with type-2 diabetes (Crawford, 2009; Khan et. al., 2003; Mang et. al., 2006; Solomon & Blannin, 2007; Wang et. al., 2007).

The purpose of this study was to measure the efficacy of cinnamon in lowering blood glucose and lipid levels of persons diagnosed with type-2 diabetes. Efficacy has been defined as the extent to which a specific intervention, procedure, regimen, or service produces a beneficial effect under ideal conditions (Dictionary of Epidemiology, 2008). Hence, efficacy was chosen as the methodological guiding framework for this study. The gold standard for testing efficacy of any treatment is the randomized, double-blind, placebo controlled trial. Evidence from randomized, double-blind, placebo controlled trials is also a requirement of the Food and Drug Administration approval process. Therefore, this method of inquiry was used in this study.

The Office of Technology Assessment is an advisory arm of the U.S. Congress whose basic function is to help legislators anticipate and plan for the positive and negative impacts of technological changes. This office issued a report entitled “Assessing the Efficacy and Safety of Medical Technologies” in 1978. Schlosser (2003)
asserted that for the most part, the clinical outcomes literature has adopted the definitions of efficacy research as published by the Office of Technology Assessment. This office defines efficacy in terms of four critical attributes. These critical attributes are: 1) benefit to be achieved; 2) medical problem giving rise to use of intervention, procedure, regimen or service; 3) population affected; 4) conditions of use under which the intervention, procedure, regimen or service is applied.

The most obvious critical attribute of efficacy of any technology or medical procedure is that it must provide a benefit to the recipient of care. The difficult question to answer however is: what outcomes represent benefits? Outcome criteria vary. Is the purpose of the technology in question to improve mortality and morbidity? Is it to increase life expectancy? Is it to improve psychosocial and/or physical functioning? Therefore, the definition of benefit will vary depending on the goals of the investigator and the type of technology or treatment being assessed (Office of Technology Assessment, 1978). The goal of this study is to determine whether the consumption of 500 mg of cinnamon extract daily will lower blood glucose and lipid levels of persons diagnosed with type-2 diabetes; thereby decreasing their risk for microvascular and macrovascular complications. The benefit of this study is the addition to the body of knowledge related to the efficacy of the use of cinnamon in diabetes management.

Efficacy is a relative concept; most treatments are not completely safe or efficacious. Efficacy is discussed in terms of probability and degree of benefit. A treatment or technology may be beneficial, but the value of those benefits depends on the risks involved in applying the treatment or the technology in question (Office of Technology Assessment, 1978). The Beltsville Human Nutrition Research Center has shown that the
deleterious effects of cinnamon are found largely in cinnamon oil, the fat soluble portion of cinnamon. However, the active components of cinnamon are found largely in the water-soluble extract of cinnamon (United States Department of Agriculture, n.d.). Therefore, the water-soluble components of cinnamon were utilized in this study.

The medical problem is another critical attribute of efficacy, as the efficacy of any procedure or device can only be measured in relation to the diseases or medical conditions for which it is intended and applied. The example provided by the Office of Technology Assessment (1978, pp.15) depicts this attribute by stating: “Obviously, one would not spend much time evaluating the efficacy of plaster cast applications for controlling hypertension”.

Diabetes is a disease that affects the way the body utilizes food. Persons with diabetes are at risk for developing a myriad of medical complications due to increased blood glucose levels such as blindness, amputations, stroke, nerve damage, heart disease, and kidney failure. In addition, the increased risk of cardiovascular disease in persons with type-2 diabetes has lead to more stringent goals for the management of cholesterol. Therefore, a substance in the diet that could help control glucose and lipid levels would have abundant health benefits for this patient population (ADA, 2010).

The third critical attribute of efficacy is the population affected. It is known that the effect of a medical technology or treatment varies depending on the individual treated. For example, if a study were to be conducted on an entirely male population, the results of this study could not be generalized to females because these two population types possess physiologic and other differences. How then, can we generalize a benefit to a
certain population? All generalizations applied to a specific population must be supported by valid and reliable statistical techniques and the population undergoing treatment needs to be specified when the efficacy of a medical technology or treatment is discussed (Office of Technology Assessment, 1978). Generally, type-2 diabetes is a condition that occurs in adult men and women. Therefore, adult men and women were recruited for this study. The study conducted by Khan et. al. (2003) demonstrated beneficial effects in Pakistani men and women. One of the aims of this study was to determine if those beneficial effects could be reproduced in an ethnically diverse population in Honolulu, HI.

The fourth and final critical attribute of the concept of efficacy is the conditions of use. There are many variables that can affect these conditions. Whether or not a technology or treatment proves to be efficacious partially depends on the skills, knowledge and abilities of health care personnel applying the technology or treatment. Other variables include the quality of the drugs, equipment, institutional settings, and support systems used. The benefits obtained from a drug study will be greater if correct dosages are administered at the correct times. In addition, the interaction of a drug with other drugs may affect the benefit. A situation where the healthcare provider is skillful and experienced, the medication is administered carefully, and the patient receives the best care possible is described as ideal. Not all health care providers are the most skillful and not all conditions of use are of the highest possible quality. Average conditions of use contain many variables, such as the skills of health care providers, that may differ from one hospital to another and from one application of a technology or treatment to another. "Thus, it is valuable to have an outcome measure that is not dependent on the
differing variables inherent in average conditions of use. Efficacy is this measure. By defining efficacy as benefit under ideal conditions of use, a reasonably consistent measure for that factor is introduced. No conditions of use are absolutely ideal, but, for most purposes, carefully controlled research settings can serve as a substitute for ideal circumstances” (Office of Technology Assessment, pp. 16, 1978).

The gold standard for assessing efficacy of any treatment is the randomized, double-blind, placebo-controlled trial; which is rooted in a positivist science. This is the most common type of clinical trial and is a requirement of the Food and Drug Administration (FDA) approval process. Efficacy studies are generally conducted in academic health science centers with attached hospitals or research units, by well-trained clinical investigators, are concerned with events which can be observed, the research is conducted in a stable environment, is value free and objective, is quantifiable, aims to establish causal relationships; and attempts to maximize the likelihood of a finding; and the patients under study are invariably narrowly defined. For example, the age-range of the patients is generally limited, and individuals with co-morbid conditions are usually excluded. The patients are randomized to ensure that the groups (treatment, placebo and or control) are homogenous and that differences between groups are due to the interventions and not due to bias or chance. However, if a placebo is utilized the possibility of encountering a placebo effect must always be considered. In addition, it is also very important to be able to confirm the safety and tolerability of the treatment or technology being tested. Ethical issues must also be considered (Schlosser, 2003).

Efficacy studies have high internal validity because the conditions under which efficacy research is conducted are highly controlled, thereby eliminating confounding
variables. However, efficacy research has low external validity because the researcher has a low degree of confidence in generalizing the results of the particular study to field conditions because of the difference between how efficacy studies are designed and how some therapies are conducted in the field. The structured treatment or monitoring settings which are required for efficacy trials, tends to change the way individuals conduct themselves. These changes alone may have an effect on the measured outcome. However, efficacy trials are essential if we are to know that the treatment of type-2 diabetes with cinnamon has value and is worth pursuing (Chorpita et. al., 1998; Schlosser, 2003).
CHAPTER 4

METHODOLOGY

Hypothesis

The hypothesis that cinnamon as an adjunct therapy improves insulin sensitivity was tested. We hypothesized that the consumption of 500 mg of the water-soluble extract of cinnamon daily would significantly lower postprandial glucose, fasting blood glucose and fasting blood lipid levels in persons diagnosed with type-2 diabetes who were taking metformin for glucose control. No significant difference between the placebo and control was expected in the HDL cholesterol levels.

Design

An experimental, randomized, double-blind, placebo-controlled design was utilized for this study. Forty men and women, between the ages of thirty and seventy, diagnosed with type-2 diabetes were recruited. Informed consent was obtained and a copy was given to all participants. Subjects were assigned a sequential number from 1 to 40. Integrity Nutraceuticals International (Sarasota, FL) supplied the study capsules.

Utilizing a computer-generated allocation table Tripler Medical Center Pharmacy personnel randomized the study capsule containers to treatment or control. A sequential number from 1 to 40 was assigned to each capsule container based on the computer-generated table and was displayed on the label. The investigative team did not know the capsule allocation table results. Tripler Pharmacy personnel distributed the capsule containers in a sequential manner form 1-40. The computer-generated allocation table was maintained by Tripler Pharmacy personnel in a sealed envelope to be opened only in the unlikely event of an adverse reaction and at the end of the study for data analysis.
Sample Size

A total of 40 subjects were recruited for this study. The results of Khan et al's. (2003) study were used to perform a power analysis to calculate the sample size needed for the study (appendix B). Optimal Design Software (Raudenbush, 2000) was utilized to conduct the power analysis. Sample sizes were calculated based on four assessments per person, assuming a conservative effect size variation for glucose of 0.25 utilizing Khan et al's (2003) data. Based on these calculations 12 subjects total were required for a .80 power and a 5% significance level. Power calculations were also obtained for LDL cholesterol levels utilizing an effect size of 1.0. Based on these calculations a sample size of 17 per group are needed for a .80 power and a 5% significance level for a total of 34 subjects. Since this is a longitudinal study, 40 men and women were recruited to allow for a fifteen-percent attrition.

Confirmation of Diagnostic Criteria for Entry

At the time that this study was conducted, the diagnostic criteria as defined by the ADA (ADA, 2003) of type-2 diabetes was a fasting plasma blood glucose (FPBG) test value of 126 mg/dl or above at the time of diagnosis, confirmed by a second positive FPBG test, or by an oral glucose tolerance test (OGTT) result of 200 mg/dl or above, confirmed by a second positive OGTT. Since then, the Expert Committee on the diagnosis and Classification of Diabetes Mellitus has added a Hgb A1c level ≥ 6.5% as a diagnostic criterion (ADA, 2010).

Inclusion Criteria

Inclusion criteria included age between 30 and 70 years, type-2 diabetes diagnosis, taking metformin for glucose control for at least 3 months, at a dose of at least

47
1000mg/day. Participants fasting blood glucose levels at baseline were between 126-300 mg/dl or their glycosylated hemoglobin level (Hgb A1c) was greater than 7% despite oral treatment with Metformin for glucose control.

Exclusion Criteria

Subjects on insulin therapy or on any oral hypoglycemic agent besides metformin were excluded from the study. It is unknown whether consumption of cinnamon is teratogenic; therefore, women who were pregnant or would like to become pregnant were excluded from the study. Eligible females of reproductive age who wanted to participate were asked to take a blood pregnancy test. Child-bearing age women who had not had a tubal-ligation or hysterectomy between the ages of 30 and 50 were tested for pregnancy utilizing blood samples on days 0, 20+/- 4, and 40 +/- 4 of the study. If a subject were to become pregnant during the study, they would be excluded from participation in this study. There have been documented instances of allergic reactions to cinnamon; therefore, subjects who had not had past exposure to cinnamon, or had a known allergy to cinnamon were also excluded from the study. Persons with a history of stomach or duodenal ulcers were also excluded. Cinnamon consumption lowers in vitro tetracycline levels; therefore, persons who were taking tetracycline were excluded from this study.

Persons with a body mass index (BMI) greater than 35 were also excluded, as this population is extremely insensitive to insulin and 500 mg of cinnamon will likely not be efficacious in this population. A screening tool was developed to determine subject eligibility (Appendix C).
Evaluations Before Entry

Following informed consent, a history and physical examination was performed to assess for inclusion and exclusion criteria. Fasting blood glucose, Hgb A1c, triglycerides, HDL, LDL, and total cholesterol blood levels was obtained at the Tripler Army Medical Center Outpatient Laboratory, and if the potential participant was a female of child bearing age; a pregnancy blood test was also obtained at the Tripler Army Medical Center Outpatient Laboratory.

Sampling Method

The Tripler Army Medical Center Adult Medicine Clinic and Family Practice Clinic were utilized as recruitment sites. All physicians and nurse practitioners at the Adult Medicine Clinic and the Family Practice Clinic were informed of the study and referred potential subjects to the doctoral candidate. A recruitment brochure describing the research project and participant eligibility was created and distributed to clinic physicians and nurse practitioners (see recruitment brochure in appendix D). The doctoral candidate, who is a Certified Family Nurse Practitioner was provided an office in the Adult Medicine Clinic and eligible subjects were referred to investigator for recruitment purposes. A screening tool was utilized to assess eligibility (appendix C). Potential candidates for the study were informed of the study by the researcher. If the person agreed to participate and met all inclusion and exclusion criteria, informed consent was obtained and a copy was given to all participants. The informed consent can be found in (appendix E). All subjects were informed that all data obtained would be kept confidential, research findings will only be reported as group data, their participation is voluntary, and they could withdraw at anytime. There were a total of 40 subjects.
recruited and consented for this study.

Source of Cinnamon and Placebo Capsules

Integrity Nutraceuticals International (Sarasota, FL) provided the randomized study capsules containing 250mg of a water-soluble cinnamon extract (Cinnulin PF®) for the treatment group and identical capsules containing 250 mg of bran cereal for the control group. Cinnulin PF® is a proprietary water soluble extract of Cinnamomum burmanii. The extraction process helps to filter out the possible deleterious components of whole cinnamon. This extract is standardized for the doubly-linked polyphenol type-A polymers, specifically tetramers and trimers, which are considered to be the bioactive components of cinnamon. According to the manufacturer, 500 mg of Cinnulin PF® is equivalent to approximately 10g of whole cinnamon powder (20:1 extract). (Anderson et. al., 2004, Jarvill-Taylor, 2001 & Ziegenfuss et. al., 2006). This product was assessed for safety and a certificate of analysis was provided by Integrity Nutraceuticals International and reviewed by the Institutional Review Board at Tripler Army Medical Center.

Methods

Once consent had been obtained, subjects were asked to return to obtain baseline fasting blood glucose, total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride serum levels. Following the fasting blood draw subjects were asked to consume a prescribed meal which included one serving of scrambled eggs, or one boiled egg, 2 pieces of toast, one serving of fresh fruit, and one carton of milk. A meal voucher was provided for the Tripler Cafeteria, the meal voucher was only valid for the prescribed meal.
The following tables (see tables 3 & 4) depict the sequence and procedures of the study. All subjects were assessed on days 0, 20 ± 4, 40 ± 4, and 60 ± 4 of the study. In addition, a telephone follow up assessment was conducted on days 5, 10, 15, 25, 30, 35, and 55 of the study to assess compliance and assure subjects were not experiencing any deleterious effects (see observation tool; appendix H).

**Duration, Labeling and Distribution of Therapy**

The duration of therapy was 40 days. Participants discontinued the consumption of cinnamon and placebo capsules on day 40. Subjects continued to take any prescribed medications throughout the study period. Labeling of cinnamon and placebo capsules complied with Tripler Pharmacy protocol. A Tripler Army Medical Center Pharmacist distributed all capsules.

**Dosage, Timing and Accountability of Treatment**

All participants were instructed to consume two capsules daily, one with breakfast and one with dinner. The participants in the treatment group received 250 mg of the water-soluble extract in capsule form (Cinnulin PF®) as provided by Integrity Nutraceuticals International (Sarasota, FL). The participants in the control group received identical appearing capsules containing 250 mg of bran cereal. All subjects were provided with an accountability form and they were instructed to write down the date and time that they consumed each capsule; in addition, they were asked to write down what they were looking at as they consumed the capsule. All participants were asked to bring the accountability form, along with the capsule container, with any left-over capsules to their day 20 ± 4, and their day 40 ± 4 appointment. A capsule count was performed during the day 20 ± 4 and day 40 ± 4 appointments, and the accountability form was reviewed and
placed in the subjects case report folder on those dates.
Table 3: Sequence and Procedures of Study

<table>
<thead>
<tr>
<th>Day</th>
<th>Informed consent obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td>1 14 cc of fasting blood were obtained for analysis of serum glucose, triglycerides, LDL, HDL and total cholesterol levels at the Tripler Outpatient Laboratory. In addition, 2cc of fasting blood was obtained for the USDA study group to measure effects of cinnamon on insulin, cortisol and leptin. Subjects were then asked to eat a prescribed meal and return one hour after meal for postprandial glucose levels; 6cc of blood was required for this test. 2 The Tripler Outpatient Pharmacy dispensed forty-eight 250mg capsules of cinnamon-extract to the treatment group and forty-eight placebo capsules to the control group. Both groups were informed to take two capsules daily, fill out accountability form and return for follow-up on day 20 +/-4. All subjects were instructed to bring any remaining capsules they may have and accountability form to their following appointment.</td>
</tr>
<tr>
<td>Days 5</td>
<td>Subjects were contacted by phone to assess tolerance and as a reminder to consume their capsules if no complaints of untoward effects.</td>
</tr>
<tr>
<td>Days 10 &amp; 15</td>
<td></td>
</tr>
<tr>
<td>Day 20 +/-4</td>
<td>1 All subjects were evaluated for any untoward effects</td>
</tr>
<tr>
<td></td>
<td>2 14 cc of fasting blood were obtained for analysis of serum glucose, triglycerides, LDL, HDL and total cholesterol levels at the Tripler Outpatient Laboratory. 2cc of blood was also obtained for the USDA. Subjects were then asked to eat prescribed meal and return one hour after meal for postprandial glucose; 6cc of blood was required for this test. 3 Pharmacy conducted a capsule count and documented capsule count on case report form to assess compliance. 4 The Tripler Outpatient Pharmacy dispensed forty-eight additional 250 mg capsules of cinnamon to the treatment group, and forty-eight placebo capsules to the control group. Subjects were instructed to take 2 capsules daily, fill out accountability form and return for follow-up on day 40 +/-4. They were instructed to be fasting and bring any remaining capsules they may have and accountability form to their follow-up appointment.</td>
</tr>
<tr>
<td>Days 25, 30 &amp; 35</td>
<td>Subjects were contacted by phone to assess tolerance and as a reminder to consume their capsules, if no complaints of untoward effects.</td>
</tr>
<tr>
<td>Day 40 +/-4</td>
<td>1 All subjects were evaluated for any untoward effects</td>
</tr>
<tr>
<td></td>
<td>2 14 cc of fasting blood was obtained for analysis of serum glucose, triglycerides, LDL, HDL, and total cholesterol. 2cc of blood was also obtained for USDA. Subjects were then asked to eat prescribed meal and return one hour after meal for postprandial glucose levels; 6cc of blood was required for this test. 3 Pharmacy personnel to assess compliance performed a capsule count. 4 All subjects ceased consumption of capsules on day 40 +/-4 and were instructed to return for follow-up on day 60 +/-4. 5 They were instructed to be fasting for follow-up appointment.</td>
</tr>
<tr>
<td>Day 55</td>
<td>Phone interview and reminder of final appointment</td>
</tr>
<tr>
<td>Day 60 +/-4</td>
<td>1 All subjects fasting blood were obtained for analysis of serum glucose, triglycerides, LDL, HDL, and total cholesterol at the Tripler Outpatient Laboratory to determine whether these levels continued to improve during washout period. 2cc of blood was also obtained for USDA. 2 Subjects were then asked to eat prescribed meal and return one hour after meal for postprandial glucose levels. 3 An exit physical assessment was performed.</td>
</tr>
</tbody>
</table>
Table 4: Procedural Timetable

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-1 0 5 10 15 20 25 30 35 40 55 60</td>
</tr>
<tr>
<td>Contact Information</td>
<td>X</td>
</tr>
<tr>
<td>Screening Visit</td>
<td>X</td>
</tr>
<tr>
<td>Informed Consent</td>
<td>X</td>
</tr>
<tr>
<td>Complete Physical Exam</td>
<td>X</td>
</tr>
<tr>
<td>Fasting &amp; Postprandial Laboratory Assessments</td>
<td>X X X</td>
</tr>
<tr>
<td>Obtain 48 Treatment or Placebo Capsules</td>
<td>X X</td>
</tr>
<tr>
<td>Capsule Accountability</td>
<td>X X</td>
</tr>
<tr>
<td>Telephone Follow-Up/Compliance Determination</td>
<td>X X X X</td>
</tr>
<tr>
<td>Brief Physical Exam, V/S, Weight</td>
<td>X X X</td>
</tr>
<tr>
<td>Stop Taking Capsules</td>
<td>X</td>
</tr>
</tbody>
</table>

Laboratory Analysis

The Tripler Army Medical Center Biochemistry Laboratory performed analysis of blood samples. Blood was obtained on days 0, 20 ± 4, 40 ± 4, and 60 ± 4 of the study. Values obtained included fasting blood glucose, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides. In addition, postprandial glucose levels were obtained on these same days. The critical measurements used as end-points for this study included fasting blood glucose, triglyceride, LDL, total cholesterol and postprandial glucose levels. It was hypothesized that all values would be significantly lower.

Protection of Human Participants

This study was approved by the University of Hawaii and the Tripler Army Medical Center’s Committee on Human Subjects Institutional Review Boards prior to initiation of the study. Written consent (appendix E) was obtained and a copy was given to all participants. Every participant was informed that all data obtained would be confidential,
research findings would only be reported as group data, their participation was voluntary, and they could withdraw at anytime. Data was stored in a locked cabinet in the Adult Medicine Clinic, at Tripler Army Medical Center. The participants were asked to provide their name, social security, address, and phone number on the consent form, but these identifiers did not appear on any database. The participant’s identification code was recorded on each evaluation/observation tool and consisted of a number ranging from 1 to 40.

Data was entered into an Excel spreadsheet that was password protected. In order to maintain confidentiality of the participants, only the participants’ subject identification codes were entered into the database; no person-identifiable data was entered. When the results of the study are published, no participants will be identified personally, rather data will be presented as aggregate data.

All data collected conformed to the Health Information Protection and Portability Act (HIPPA) regulations. This includes provisions for maintaining participant consent forms in a locked filing cabinet separate from data collection forms. The only person who had access to the consent forms and the data was the doctoral candidate. When the data was not in use, it was kept in locked storage.

Participants were informed that the risks of study participation included:
- Risk associated with blood sampling might include mild pain or a bruise at the site of blood draw, and feeling faint when blood is drawn for blood test. Risk of infection is slight as only sterile, one-time equipment was used.
- The major side effect of cinnamon consumption is an allergic reaction. Allergic symptoms include: pruritis, swelling of lips and tongue, rash, burning or blistering in mouth. However, the water-soluble extract was utilized for this study, which does not contain cinnamaldehyde, the compound found in the fat-soluble component of cinnamon which causes allergic reactions. In addition, cinnamon was consumed in capsule form, bypassing the oral mucosa.

- Large amounts of cinnamon may cause burning sensation in mouth, chest and stomach, double vision, dizziness vomiting, and lethargy. However, only a small amount of cinnamon was utilized in this study.

- Cinnamon may increase intestinal motility. Therefore, subjects with a history of stomach or duodenal ulcers were excluded from the study.

- It is unknown whether cinnamon is teratogenic; therefore, women who were pregnant or thought they would become pregnant during the study period were excluded from the study.

**Precautions**

Subjects were contacted via phone every 5 days to assess for any deleterious effects. A physical exam and interview were conducted on days 20 ± 4, 40 ± 4, and 60 ± 4 of the study.

**Corrective Action**

The most common deleterious effect of cinnamon is an allergic reaction. Subjects were informed to discontinue capsule consumption if any of the following symptoms occurred. If swelling of mouth or tongue occurred, subjects were instructed to present to the Tripler Emergency Room. If pruritis occurred and persisted after discontinuation of
cinnamon they would be seen by Dr. Thomas Francis, Chief of the Endocrinology Clinic, at Tripler Army Medical Center (see consent form, appendix E for research team contact information).

Large amounts of cinnamon can cause burning sensation in the mouth, chest, or stomach (Libster, 2002). Subjects were instructed to discontinue cinnamon if these symptoms occurred. If symptoms persisted after discontinuation, Dr. Thomas Francis would evaluate them. Other signs of cinnamon overdose include: double vision, vomiting, dizziness, and lethargy (Libster, 2002). If any of these symptoms occurred, subjects were informed to present to the Tripler Emergency Room. Any serious or unexpected adverse reactions would be promptly reported to the Chief, Department of Clinical Investigation at Tripler Army Medical Center and the University of Hawaii. There were no adverse effects reported in this treatment group. One person complained of nausea associated with placebo capsules.

Withdawal Criteria

Criteria for withdrawal included but was not limited to:

a. a fasting blood sugar greater than 300mg/dl at any time during the study
b. signs and symptoms of an allergic reaction to the treatment or placebo
c. subject wishing to withdraw from study
d. prescription for tetracycline obtained
e. prescription for insulin therapy obtained
f. prescription for a oral anti-hyperlycemic agent besides metformin or increase in metformin dosage
g. new prescription or adjustment of an antihyperlipidemic medication
h. pregnancy
i. hospitalization
j. any serious adverse reaction
k. if capsule count incorrect, subject may have been withdrawn from study
l. if subject was not fasting for blood samples, subject may have been withdrawn from study

There were three withdrawals in this study, which are discussed in chapter five.

**Criteria for Termination of Study**

Adverse events were not expected to occur in this study. If an adverse event had occurred, the study may have been terminated. There were no adverse events reported in this study, except for one subject in the control arm of the study reported feelings of nausea associated with capsule consumption.

**Use of Information and Publications Arising from the Study**

Information will be published in medical peer reviewed journals, adding to the body of knowledge related to diabetes management.

**Resources**

All subjects were recruited and consented by the doctoral candidate who input the laboratory orders into the Tripler Army Medical Center order-entry computer system, Dr. Thomas Francis co-signed all orders. All follow-up telephone contacts, vital signs and routine physical assessment were performed by the doctoral candidate on all subjects on days 0, 20 ± 4, 40 ± 4 and 60 ± 4 of study. The major resources utilized at Tripler Army Medical Center was the pharmacy personnel that labeled and dispensed all study capsules. Tripler Army Medical Center waived this cost. The cost of laboratory blood
work, study brochures and the cost of the prescribed breakfast on days 0, 20 ± 4, 40 ± 4 and 60 ± 4 of the study was provided by Integrity Nutraceuticals International (Sarasota, FL).
CHAPTER 5

RESULTS

Sample

A total of 40 participants diagnosed with type-2 diabetes were recruited to participate in this study. All subjects were on metformin for glucose control for at least 3 months at a dose of at least 1000 mg/day. All participants had either a fasting blood glucose level greater than 126 mg/dl or a hemoglobin A1c level greater than 7% at baseline, despite oral treatment with metformin for glucose control. Twenty-eight of the participants had a diagnosis of hyperlipidemia and were taking a statin drug for lipid control (table 9). All subjects were stable because medication had not been modified over the last 3 months.

Two subjects from the treatment group and one subject from the control group did not complete the study. Reasons for attrition included complaints of nausea associated with study capsule consumption after 3 days of treatment, this participant stated that increasing her daily pill consumption made her nauseous (control group), military orders received for change of duty station (treatment group), inability to comply with study protocol and follow-up due to time constraints (treatment group). The cinnamon capsules were well tolerated by all participants in the treatment group, no adverse effects were reported in the treatment group. Adherence was high (96%) based on capsule count and accountability forms.

Demographic Characteristics

Table 5 represents demographic characteristics of the study subjects. The mean age of the sample was 54.35 years (SD = 10.02) with a range of 36 – 67 years. The sample represented an ethnically diverse population as depicted in table 8. The majority of the
subjects were Caucasian (37.5%, n = 15), the second highest ethnic group represented were of Asian descent (27.5%, n = 11), Pacific Islanders consisted of 25% (n = 10) of the study population. There were 3 African Americans (7.5%) and one Hispanic subject in the study population (2.5%). All subjects were military healthcare beneficiaries. There were a total of 19 males (47.5%) and 21 females (52.5%) in the study population (see Table 8). The placebo and the treatment group did not differ significantly in respect to age, body mass index, sex, race, fasting plasma glucose, Hgb A1c, years since type-2 DM initial diagnosis or prescribed anti-hyperlipidemic medication at baseline. Data in the tables below are reported as means and standard deviation (SD).
Table 5: Baseline Characteristics of Study Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n = 20) Mean (SD)</th>
<th>Treatment (n = 20) Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>54.85 (10.75)</td>
<td>53.85 (9.23)</td>
</tr>
<tr>
<td>Body Mass Index (BMI)</td>
<td>31.15 (3.70)</td>
<td>31.47 (2.89)</td>
</tr>
<tr>
<td>Fasting Plasma Glucose</td>
<td>164.15 (8.77)</td>
<td>162.27 (6.12)</td>
</tr>
<tr>
<td>Fasting Hgb A1c</td>
<td>7.83 (0.24)</td>
<td>7.84 (0.25)</td>
</tr>
<tr>
<td>Fasting Cholesterol</td>
<td>179 (35.17)</td>
<td>160.1 (38.28)</td>
</tr>
<tr>
<td>Fasting LDL</td>
<td>102.3 (35.67)</td>
<td>85.4 (35.51)</td>
</tr>
<tr>
<td>Fasting Triglycerides</td>
<td>165.55 (75.17)</td>
<td>219.7 (139.5)</td>
</tr>
<tr>
<td>Fasting HDL</td>
<td>49.2* (12.93)</td>
<td>41.35* (10.17)</td>
</tr>
<tr>
<td>Postprandial Glucose</td>
<td>206 (12.42)</td>
<td>197 (12.42)</td>
</tr>
<tr>
<td>Years since Type-2 DM initial diagnosis</td>
<td>4.92 (4.82)</td>
<td>5.42 (5.85)</td>
</tr>
</tbody>
</table>

Note: Values are means and SD. * Indicate statistically significant between group difference at baseline at p < 0.05.
Table 5: Race and Gender of Study Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Treatment</th>
<th>% Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>2</td>
<td>1</td>
<td>7.5%</td>
</tr>
<tr>
<td>Asian</td>
<td>7</td>
<td>4</td>
<td>27.5%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>8</td>
<td>7</td>
<td>37.5%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0</td>
<td>1</td>
<td>2.5%</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>3</td>
<td>7</td>
<td>25.0%</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
<td>10</td>
<td>47.5%</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>10</td>
<td>52.5%</td>
</tr>
</tbody>
</table>

Note: There were not statistically significant differences between groups
**Table 7: Antihyperlipidemic Medications**

<table>
<thead>
<tr>
<th>Medication &amp; Dosage</th>
<th>Placebo</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin 5mg QD</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Simvastatin 20mg QD</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Simvastatin 40mg QD</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Simvastatin 80mg QD</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Atorvastatin 40mg QD</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Atorvastatin 80mg QD</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Pravastatin 20mg QD</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

| Total              | 15      | 13        |
| Percentage         | 37.5%   | 32.5%     |

<table>
<thead>
<tr>
<th>On no antihyperlipidemic medication</th>
<th>Placebo</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage</td>
<td>12.5%</td>
<td>17.5%</td>
</tr>
</tbody>
</table>

Note: There were not statistically significant differences between groups.
**Data Analysis**

The hypothesis of this study was that cinnamon would significantly lower fasting blood glucose, triglycerides, LDL cholesterol, total cholesterol and postprandial glucose levels. No significant change was expected in the HDL cholesterol levels. For each dependent variable fasting glucose, triglycerides, HDL cholesterol, LDL cholesterol, and postprandial glucose levels a mixed analysis of variance (ANOVA) was undertaken with group (active versus placebo) as the between subjects factor, and time (t0, t1, t2, t3) as the within subjects factor. Efficacy of cinnamon was examined as a main effect between the treatment group and the placebo group on average and at four different time points. The results are presented as the mean and standard deviation (SD). The data was analyzed by the mixed ANOVA method utilizing the statistical analysis system (SAS) program version 9.1 (Cary, NC). Differences of p-value < 0.05 were considered statistically significant.

**Glucose Levels**

The mean glucose level of all participants was 162.27 (SD = 37.67) with a range of 100 mg/dl to 250 mg/dl. The mean Hgb A1c of all participants was 7.95 (SD = 1.06) with a range of to 11.9. There were four subjects in the treatment group with baseline glucose levels less than 126 mg/dl; however, their Hgb A1c levels were greater than 7%. Thus they qualified for the study based on the Hgb A1c inclusion criteria.

Since these four subjects glucose levels were already near normal at baseline, an additional analysis was performed on glucose levels with these four subjects removed from the data (figure 2), to determine whether exclusion of these subjects would alter the effect findings of the glucose levels.
The hypothesis that cinnamon would lower blood glucose levels in persons with type-2 diabetes was tested. This hypothesis was not supported. Results of the mixed effects ANOVA on glucose levels demonstrated that neither group nor time had a significant effect on fasting blood glucose with all subjects included in the data analysis, nor with the four subjects with baseline glucose levels less than 127 mg/dl at baseline removed. Therefore, no significant difference was found between cinnamon treatment and control groups in terms of fasting glucose (figures 1 & 2).
Figure 1. Means and Standard Deviation of Fasting Glucose Levels

Note: Data are expressed as group means and (SD), no significant differences were noted between groups over time, p > 0.05

Figure 2. Means and Standard Deviation of Fasting Glucose Levels (4 subjects removed)

Note: Data are expressed as group means and (SD), no significant differences were noted between groups over time, p > 0.05
Postprandial Glucose Levels

Utilizing the mixed effects model, neither group nor time had a significant effect on postprandial blood glucose with all subjects included in the data analysis or with the four subjects with baseline fasting blood glucose levels less than 126 mg/dl removed. Therefore, no significant difference was found between cinnamon treatment and control groups in terms of postprandial glucose (figures 3 & 4).
Figure 3. Means and SD of Postprandial Glucose Levels

![Graph showing Postprandial Glucose Levels for Control and Treatment groups over days 1, 20, 40, and 60. Data are expressed as group means and (SD), no significant differences were noted between groups over time, p > 0.05.]

Note: Data are expressed as group means and (SD), no significant differences were noted between groups over time, p > 0.05

Figure 4. Means and SD of Postprandial Glucose Levels (4 subjects removed)

![Graph showing Postprandial Glucose Levels for Control and Treatment groups over days 1, 20, 40, and 60 after removing 4 subjects. Data are expressed as group means and (SD), no significant differences were noted between groups over time, p > 0.05.]

Note: Data are expressed as group means and (SD), no significant differences were noted between groups over time, p > 0.05
High Density Lipoproteins (HDL) Levels

The hypothesis that cinnamon would not have a significant effect on HDL levels was tested, utilizing the mixed effects model. There was a significant difference between the treatment and control group at baseline, on day one (p-value = 0.0468). However over time there was no significant effect on HDL levels (figure 5).

Figure 5. Means and Standard Deviation of HDL Levels

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 20</th>
<th>Day 40</th>
<th>Day 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>49* (2.73)</td>
<td>50 (2.74)</td>
<td>50 (2.74)</td>
<td>49 (2.74)</td>
</tr>
<tr>
<td>Treatment</td>
<td>41* (2.73)</td>
<td>41 (2.75)</td>
<td>43 (2.75)</td>
<td>42 (2.76)</td>
</tr>
</tbody>
</table>

Note: Data are expressed as group means and (SD). A significant difference between groups was found at baseline (p-value = 0.0468). However, no significant differences were noted between groups over time, p > 0.05
**Total Cholesterol Levels**

It was hypothesized that cinnamon would significantly lower serum cholesterol levels over time. Results of the mixed effects ANOVA demonstrated that neither group nor time had a significant effect on total cholesterol levels. Therefore, there is no significant difference between cinnamon treatment and control over time in terms of total cholesterol levels (figure 6).

**Figure 6. Means and Standard Deviation of Total Cholesterol Levels**

![Graph showing total cholesterol levels over time for control and treatment groups.](image)

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 20</th>
<th>Day 40</th>
<th>Day 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>179 (7.64)</td>
<td>170 (7.78)</td>
<td>169 (7.78)</td>
<td>170 (7.78)</td>
</tr>
<tr>
<td>Treatment</td>
<td>160 (7.64)</td>
<td>156 (7.94)</td>
<td>154 (7.94)</td>
<td>150 (8.07)</td>
</tr>
</tbody>
</table>

Note: Data are expressed as group means and (SD), no significant differences were noted between groups over time, P > 0.05
Low Density Lipoproteins (LDL) Cholesterol Levels

It was hypothesized that cinnamon would significantly lower LDL cholesterol levels over time when compared to placebo. This hypothesis was not supported. Results of the mixed effects ANOVA found that time (p-value = 0.0356) had a significant effect on LDL cholesterol levels in both the treatment and control groups. However, there were no significant between group differences over time (p-value > 0.5). See figure 7.

Figure 7. Means and Standard Deviation LDL Cholesterol Levels

<table>
<thead>
<tr>
<th>Day</th>
<th>Control</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>98 (6.17)</td>
<td>81 (6.27)</td>
</tr>
<tr>
<td>20</td>
<td>85 (6.29)</td>
<td>76 (6.54)</td>
</tr>
<tr>
<td>40</td>
<td>83 (6.39)</td>
<td>71 (6.42)</td>
</tr>
<tr>
<td>60</td>
<td>88 (6.29)</td>
<td>72 (6.53)</td>
</tr>
</tbody>
</table>

Note: Data are expressed as group means and (SD), no significant differences were noted between groups over time, p > 0.05
Triglyceride Levels

It was hypothesized the cinnamon would significantly lower triglyceride levels. Results of the mixed effects ANOVA found that neither group nor time had a significant effect on triglyceride levels. Therefore, no significant difference was found between cinnamon treatment and control in terms of triglyceride levels (figure 8).

Figure 8. Means and Standard Deviation of Triglyceride Levels

<table>
<thead>
<tr>
<th>Day</th>
<th>Treatment Mean (SD)</th>
<th>Control Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>183 (25.56)</td>
<td>150 (25.46)</td>
</tr>
<tr>
<td>Day 20</td>
<td>177 (26.11)</td>
<td>153 (25.77)</td>
</tr>
<tr>
<td>Day 40</td>
<td>169 (26.11)</td>
<td>164 (26.02)</td>
</tr>
<tr>
<td>Day 60</td>
<td>150 (26.39)</td>
<td>161 (25.77)</td>
</tr>
</tbody>
</table>

Note: Data are expressed as group means and (SD), no significant differences were noted between groups over time, p > 0.05

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**Glycosylated Hemoglobin (Hgb A1c) Levels**

Hemoglobin A1c was obtained at baseline to determine entry criteria, it was again obtained on day 60 of the study. Hgb A1c was not an end-point of this study, as 90 days is required to determine a change in Hgb A1c. Utilizing the mixed effects ANOVA, there was a significant difference in Hbg A1c over time in both groups (p-value = 0.0590). However, there was no significant difference between groups (p-value = 0.5432). Therefore, there was no significant difference between cinnamon treatment and control in terms of Hbg A1c levels (figure 9).

**Figure 9. Least Square Means Hemoglobin A1c Levels**

![Image of least square means graph showing hemoglobin A1c levels over time for control and treatment groups.](image)

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7.84 (0.25)</td>
<td>7.62 (0.25)</td>
</tr>
<tr>
<td>Treatment</td>
<td>8.04 (0.24)</td>
<td>7.83 (0.25)</td>
</tr>
</tbody>
</table>

Note: Data are expressed as group means and (SD), no significant differences were noted between groups over time, p > 0.05
Summary

A summary of the statistical analysis can be found on Table 8. There is a trend of decreasing values over time of all endpoints except for the HDL cholesterol values which did not change over time. These decreasing values were found in the treatment as well as in the control groups of all endpoints, except for the triglyceride levels. However, when the treatment values are compared to the control group values, no statistically significant differences were found. Each of the end-point results is reviewed below.
Table 8: Hematological Responses to Supplementation

<table>
<thead>
<tr>
<th></th>
<th>Treatment Group Means</th>
<th>Control Group Means</th>
<th>P-value (G x T)</th>
<th>P-value BL</th>
<th>P-value Group</th>
<th>P-value Time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fasting Glucose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>156</td>
<td>160</td>
<td>0.9855</td>
<td>0.7561</td>
<td>0.2111</td>
<td>0.6588</td>
</tr>
<tr>
<td>Day 20</td>
<td>153</td>
<td>147</td>
<td>0.4219</td>
<td>0.4840</td>
<td>0.1120</td>
<td>0.7614</td>
</tr>
<tr>
<td>Day 40</td>
<td>150</td>
<td>151</td>
<td>0.5853</td>
<td>0.5757</td>
<td>0.4260</td>
<td>0.9864</td>
</tr>
<tr>
<td>Day 60</td>
<td>154</td>
<td>158</td>
<td>0.9215</td>
<td>0.9930</td>
<td>0.4046</td>
<td>0.9684</td>
</tr>
<tr>
<td><strong>Fasting Glucose (-4 subjects)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>169</td>
<td>160</td>
<td>0.9264</td>
<td>0.4840</td>
<td>0.1120</td>
<td>0.7614</td>
</tr>
<tr>
<td>Day 20</td>
<td>161</td>
<td>147</td>
<td>0.5853</td>
<td>0.5757</td>
<td>0.4260</td>
<td>0.9864</td>
</tr>
<tr>
<td>Day 40</td>
<td>155</td>
<td>151</td>
<td>0.9215</td>
<td>0.9930</td>
<td>0.4046</td>
<td>0.9684</td>
</tr>
<tr>
<td>Day 60</td>
<td>163</td>
<td>158</td>
<td>0.9215</td>
<td>0.9930</td>
<td>0.4046</td>
<td>0.9684</td>
</tr>
<tr>
<td><strong>PP Glucose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>197</td>
<td>206</td>
<td>0.0684</td>
<td>0.0844</td>
<td>0.2974</td>
<td>0.9250</td>
</tr>
<tr>
<td>Day 20</td>
<td>201</td>
<td>210</td>
<td>0.0695</td>
<td>0.0356*</td>
<td>0.2974</td>
<td>0.8381</td>
</tr>
<tr>
<td>Day 40</td>
<td>192</td>
<td>199</td>
<td>0.0695</td>
<td>0.0356*</td>
<td>0.2974</td>
<td>0.8381</td>
</tr>
<tr>
<td>Day 60</td>
<td>205</td>
<td>209</td>
<td>0.0695</td>
<td>0.0356*</td>
<td>0.2974</td>
<td>0.8381</td>
</tr>
<tr>
<td><strong>Cholesterol</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>160</td>
<td>179</td>
<td>0.0684</td>
<td>0.0844</td>
<td>0.2974</td>
<td>0.9250</td>
</tr>
<tr>
<td>Day 20</td>
<td>156</td>
<td>170</td>
<td>0.0695</td>
<td>0.0356*</td>
<td>0.2974</td>
<td>0.8381</td>
</tr>
<tr>
<td>Day 40</td>
<td>154</td>
<td>169</td>
<td>0.0695</td>
<td>0.0356*</td>
<td>0.2974</td>
<td>0.8381</td>
</tr>
<tr>
<td>Day 60</td>
<td>150</td>
<td>170</td>
<td>0.0695</td>
<td>0.0356*</td>
<td>0.2974</td>
<td>0.8381</td>
</tr>
<tr>
<td><strong>LDL Cholesterol</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>81</td>
<td>98</td>
<td>0.0695</td>
<td>0.0652</td>
<td>0.2974</td>
<td>0.8381</td>
</tr>
<tr>
<td>Day 20</td>
<td>76</td>
<td>85</td>
<td>0.0695</td>
<td>0.0652</td>
<td>0.2974</td>
<td>0.8381</td>
</tr>
<tr>
<td>Day 40</td>
<td>71</td>
<td>83</td>
<td>0.0695</td>
<td>0.0652</td>
<td>0.2974</td>
<td>0.8381</td>
</tr>
<tr>
<td>Day 60</td>
<td>72</td>
<td>88</td>
<td>0.0695</td>
<td>0.0652</td>
<td>0.2974</td>
<td>0.8381</td>
</tr>
</tbody>
</table>

Note: Data are expressed as group means and SD, no significant differences were noted between groups over time, p > 0.05. * indicates statistically significant P-value < 0.05.

BL = baseline.
Table 8: Hematological Responses to Supplementation Continued:

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
<th>Control</th>
<th>P-value</th>
<th>P-value</th>
<th>P-value</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Group</td>
<td>Group</td>
<td>BL</td>
<td>Group</td>
<td>Time</td>
<td>(G x T)</td>
</tr>
<tr>
<td></td>
<td>Means</td>
<td>Means</td>
<td>SD</td>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>Day 0</td>
<td>41</td>
<td>3</td>
<td>49</td>
<td>3</td>
<td>0.0482*</td>
</tr>
<tr>
<td></td>
<td>Day 20</td>
<td>41</td>
<td>3</td>
<td>50</td>
<td>3</td>
<td>0.6500</td>
</tr>
<tr>
<td></td>
<td>Day 40</td>
<td>43</td>
<td>3</td>
<td>50</td>
<td>3</td>
<td>0.6914</td>
</tr>
<tr>
<td></td>
<td>Day 60</td>
<td>42</td>
<td>3</td>
<td>49</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Day 0</td>
<td>183</td>
<td>26</td>
<td>150</td>
<td>25</td>
<td>0.6489</td>
</tr>
<tr>
<td></td>
<td>Day 20</td>
<td>177</td>
<td>26</td>
<td>153</td>
<td>26</td>
<td>0.2739</td>
</tr>
<tr>
<td></td>
<td>Day 40</td>
<td>169</td>
<td>26</td>
<td>164</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 60</td>
<td>150*</td>
<td>26</td>
<td>161</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Hgb A1c</td>
<td>Day 0</td>
<td>8.04</td>
<td>0.25</td>
<td>7.84</td>
<td>0.24</td>
<td>0.5432</td>
</tr>
<tr>
<td></td>
<td>Day 60</td>
<td>7.83</td>
<td>0.25</td>
<td>7.62</td>
<td>0.25</td>
<td>0.0590*</td>
</tr>
</tbody>
</table>

Note: Data are expressed as group means and SD, no significant differences were noted between groups over time, \( \ p > 0.05 \). * indicates statistically significant p-value < 0.05. BL = baseline.

**Glucose Levels**

Glucose levels decreased by 3.85% in the treatment group with all participants included in the analysis. When the four subjects whose baseline glucose were less than 126 mg/dl at baseline were excluded from the analysis, glucose levels decreased by 8.28% in the treatment group. However, the control group also decreased by 5.62%. None of these values were found to be statistically significant.
Postprandial Glucose Levels

Postprandial glucose levels decreased by 2.54% in the treatment group with all participants included in the analysis. When the four subjects whose baseline glucose were less than 126 mg/dl at baseline were excluded from the analysis, postprandial glucose levels decreased by 3.88% in the treatment group. However, the control group also decreased by 3.4%. None of these values were found to be statistically significant.

Total Cholesterol Levels

Total cholesterol levels decreased by 3.75% in the treatment group, the control group also decreased by 5.59%. These values were not found to be statistically significant.

LDL Cholesterol Levels

LDL cholesterol levels decreased by 12.35% in the treatment group, the control group also decreased by 15.31%. These values were found to be statistically significant over time (p = 0.036). However, no significant difference was found between groups (p-value = 0.84).

Triglyceride Levels

There was a significant finding in terms of triglyceride levels. When the values obtained on day 40 were compared to baseline in the treatment group, triglyceride levels decreased by 7.65% and continued to decrease on day 60. When day 60 was compared to baseline, the triglyceride levels decreased by 18.03% (p-value = 0.0230). The control group’s triglyceride levels increased by 7.33%. However, the difference between treatment and control was not found to be statistically significant (p-value of group x time = 0.1036).
HDL Cholesterol

HDL Cholesterol levels did not change over time in the treatment nor in the control groups.

Glycosylated Hemoglobin

Hgb A1c levels decreased by 2.61% in the treatment group, the control group also decreased by 2.81%. There was no statistical difference between groups in terms of Hgb A1c.
CHAPTER 6

DISCUSSION

The purpose of this study was to determine whether a water-soluble cinnamon extract would help to normalize blood glucose and lipid levels in persons diagnosed with type-2 diabetes. The hypothesis of this study was that 250 mg BID of an aqueous cinnamon extract would be significantly more effective than a placebo in reducing total cholesterol, LDL cholesterol, triglycerides, fasting glucose and postprandial blood glucose levels in persons diagnosed with type-2 diabetes mellitus. No significant difference between the placebo and control was expected in the HDL cholesterol levels.

The results of our study do not support our hypotheses. No significant difference was found between the treatment group and control group in any of the end-points of this study. The interaction effect between group and time were not significant for any of the end-points of this study. There are a variety of factors that may have contributed to our negative results, including the type of cinnamon utilized in this study, the dosage of cinnamon, the sample size, baseline fasting glucose levels, study length, ethnicity, dietary standardization, and drug interactions. These factors will be discussed in this chapter.

There have been six clinical trials published thus far on the effects of cinnamon on blood glucose and lipid levels in persons diagnosed with type-2 diabetes with conflicting results (Blevins et. al., 2007; Crawford, 2009; Khan et. al., 2003; Mang et. al., 2006; Suppapitiporn et. al., 2006; & Vanschoonbeek et. al., 2006). The aim of this discussion is to explore the possible reasons for our findings and to illustrate the similarities and differences between our study and these clinical trials on the effects of cinnamon on blood glucose and lipid levels. This discussion will be followed by the limitations and...
strengths of this study, recommendations for further research and the researchers’ conclusions will finalize this chapter.

*Type and Dose of Cinnamon*

A proprietary cinnamon extract (Cinnulin PF®), supplied by Integrity Nutraceuticals International (Sarasota, FL) was used in this study. The dosage of the cinnamon extract employed in this study was 250 mg BID, which according to the manufacturer is equivalent to 10 g of the cinnamon cassia powder (Zeigenfuss et. al., 2006). The supplement period was 40 days in our study, the same treatment period as Khan et. al.’s (2003) study.

To date, there have been two published human studies on the effects a proprietary cinnamon extract (Cinnulin PF®, Sarastota, FL) on blood glucose and lipid levels (Wang et. al., 2007 & Zeigenfuss et. al., 2006) and another study (Mang et. al., 2006) that used a different proprietary cinnamon extract (Diabetruw®, Gütersloh, Germany). Mang et. al. (2006) utilized 112 mg TID of this cinnamon extract, which is equivalent to 3 g of the cinnamon powder daily. The remainder of the human studies published thus far on the effects of cinnamon on blood glucose and/or lipid levels have utilized the cinnamon cassia powder with varying doses. Table 11 below depicts the doses of cinnamon utilized in these studies.

Clinical trials published thus far which have utilized a cinnamon extract, have found the extract to be efficacious in lowering blood glucose levels. Wang et. al. (2007) found that the cinnamon extract significantly decreased blood glucose levels in women with PCOS. However, the dosage was higher than that utilized by our study and the population was different. Zeigenfuss et. al. (2006) utilized the same dosage of the
cinnamon extract as the dose used for our study; however, the target population included persons with metabolic syndrome. They also found significant reduction in fasting blood glucose levels.

Since the populations of both of these studies are different from our study population, it could be postulated that this might be the cause of the disparate results. Persons with type-2 diabetes will most likely have greater insulin resistance than those with metabolic syndrome or PCOS. However, the results obtained by Mang et. al. (2006) could refute this rationale. Mang et. al. (2006) utilized a cinnamon extract on persons diagnosed with type-2 diabetes, and the cinnamon extract was found to significantly decrease fasting blood glucose in this population.

As depicted in Table 9 below, some studies have utilized a cinnamon extract with significant findings, others have used the cinnamon cassia powder with significant results. Furthermore, lower and higher doses of cinnamon than the dose utilized in our study have also been found to be efficacious in previous studies. Therefore, it does not appear that the type of cinnamon nor the dose used in this study can adequately account for the lack of significance found in our study in terms of fasting blood glucose.
Table 9: Types and Dosages of Cinnamon Utilized in Previous Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of Cinnamon</th>
<th>Dosage &amp; Length of Treatment</th>
<th>Population</th>
<th>Results Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altschuler et. al. (2007)</td>
<td>Cinnamon cassia powder</td>
<td>1 g daily for 90 days</td>
<td>Adolescents diagnosed with type-1 diabetes</td>
<td>Insignificant Hgb A1c</td>
</tr>
<tr>
<td>Blevins et. al. (2007)</td>
<td>Cinnamon cassia powder</td>
<td>1 g daily for 90 days</td>
<td>Type-2 diabetes</td>
<td>Insignificant FBG, lipids, Hgb A1c</td>
</tr>
<tr>
<td>Crawford (2009)</td>
<td>Cinnamon cassia powder</td>
<td>1 g daily for 90 days</td>
<td>Type-2 diabetes</td>
<td>Significant Hgb A1c</td>
</tr>
<tr>
<td>Hlebowicz et. al. (2007)</td>
<td>Cinnamon cassia powder</td>
<td>6 g one time dose</td>
<td>Healthy participants</td>
<td>Significant PP Glucose</td>
</tr>
<tr>
<td>Khan et. al. (2003)</td>
<td>Cinnamon cassia powder</td>
<td>1, 3, &amp; 6 g daily for 40 days</td>
<td>Type-2 diabetes</td>
<td>Significant FBG, lipids</td>
</tr>
<tr>
<td>Mang et. al. (2006)</td>
<td>Aqueous cinnamon extract</td>
<td>112 mg TID equivalent to 3 g of cinnamon powder daily for 120 days</td>
<td>Type-2 diabetes</td>
<td>Significant FBG</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Insufficient Lipids, Hgb A1c</td>
</tr>
<tr>
<td>Solomon &amp; Blannin (2007)</td>
<td>Cinnamon cassia powder</td>
<td>5 g Two doses</td>
<td>Healthy participants</td>
<td>Significant PP glucose</td>
</tr>
<tr>
<td>Solomon &amp; Blannin (2009)</td>
<td>Cinnamon cassia powder</td>
<td>3 g daily for 14 days</td>
<td>Healthy participants</td>
<td>Significant PP glucose</td>
</tr>
<tr>
<td>Suppapitiporn et. al. (2006)</td>
<td>Cinnamon cassia powder</td>
<td>4.5 g daily for 90 days</td>
<td>Type-2 diabetes</td>
<td>Insignificant FBG, lipids, Hgb A1c</td>
</tr>
<tr>
<td>Tang et. al. (2008)</td>
<td>Cinnamon cassia powder</td>
<td>6 g daily for 30 days</td>
<td>Healthy participants</td>
<td>Insignificant FBG, lipids</td>
</tr>
<tr>
<td>Vanschoonbeek et. al. (2006)</td>
<td>Cinnamon cassia powder</td>
<td>1.5 g daily for 40 days</td>
<td>Type-2 diabetes in postmenopausal women</td>
<td>Insignificant FBG, lipids, Hgb A1c</td>
</tr>
<tr>
<td>Wang et. al. (2007)</td>
<td>Aqueous cinnamon extract</td>
<td>333 mg TID equivalent to 20 g of cinnamon cassia powder daily for 60 days</td>
<td>Women with PCOS</td>
<td>Significant FBG, insulin sensitivity</td>
</tr>
<tr>
<td>Zeigenfuss et. al. (2006)</td>
<td>Aqueous cinnamon extract</td>
<td>250 mg BID equivalent to 10 g of cinnamon cassia powder daily for 90 days</td>
<td>Metabolic Syndrome</td>
<td>Significant FBG, B/P, weight</td>
</tr>
</tbody>
</table>
Baseline Blood Glucose

The baseline blood glucose levels of the participants in Khan et. al.’s (2003) study were higher than in any clinical trial related to the effects of cinnamon on blood glucose and lipid levels, that have been published thus far. Khan’s study was conducted in Pakistan targeting patients with poorly controlled diabetes. The baseline blood glucose concentrations in Khan et. al’s (2003) study ranged from 205 mg/dl to 301 mg/dl. Although Hgb A1c was not measured in Khan et. al.’s (2003) study, the baseline blood glucose values of their study correlate with a Hgb A1c of approximately 8% to 10.5%. According to the ADA (2010), the target Hgb A1c should be less than 7% and the fasting blood glucose levels should be less than 126 mg/dl.

At post-intervention, the glucose levels of the participants in the treatment group of Khan et. al.’s (2003) study ranged from 157 mg/dl to 169 mg/dl. Although the reduction in glucose levels were quite significant, these post-treatment values were higher than most of the baseline values of the clinical trials published thus far related to the effects of cinnamon on blood glucose levels.

All of the published clinical trials that have had negative findings have concluded that a possible reason for the difference in their study results and those of Khan et. al.’s (2003) study is the fact that the participants in Khan et. al.’s (2003) study had higher baseline fasting blood glucose and lipid levels than the participants in their respective studies (Blevins et. al., 2006; Suppapitiporn et. al., 2006; & Vanschoonbeek, 2006).

Mang et. al. (2006) suggested that the reason why the results of their study were not as beneficial as those obtained by Khan et. al. (2003) is possibly because the use of cinnamon in well treated diabetes will only produce weak effects and persons with poor
glycemic control may benefit more from the use of cinnamon.

The baseline blood glucose values of our study ranged from 100 mg/dl to 250 mg/dl, with a mean value of 162.26 (SD = 37.67). Entry criteria for our study included a Hgb A1c > 7%, or a fasting blood glucose level between 126 and 300 mg/dl. There were four participants in the treatment group of our study who qualified due to an elevated Hgb A1c; however, their glucose levels were found to be less than 126 mg/dl at baseline.

Therefore, an additional analysis was completed with the data of these four participants deleted from the statistical analysis. Even with the deletion of the data of these four participants, no significant difference was found between treatment and control in terms of fasting blood glucose in our study. The glucose levels did trend downwards in both the treatment and control groups of our study; however, the difference between treatment and control was not significant. This could likely be due to the Hawthorne effect.

Table 10 below depicts the association between mean baseline fasting glucose and the effectiveness of the cinnamon intervention in studies conducted thus far in persons with type-2 diabetes. The mean glucose levels in our study were similar to those of Mang et. al.’s (2006) study, which may refute the rationale that the reason for the negative effects have been due to the differences in baseline fasting blood glucose.

Again, the cinnamon dose utilized in our study does not appear to be the reason for our negative effects, as the dose used in our study was higher than the dose utilized by Mang et. al. (2006), who had a similar population in terms of diagnosis and baseline fasting blood glucose. However, Mang et. al’s (2006) study was conducted in Germany; therefore, there are some differences in the demographic characteristics of the
participants in our studies. The potential differences of the effects of cinnamon on varying ethnic groups will be discussed later in this chapter.

Table 10: Between Studies Comparison of Baseline FBG and Cinnamon Effectiveness

<table>
<thead>
<tr>
<th>Study &amp; Daily Dose</th>
<th>Mean Baseline FBG</th>
<th>Significant Findings?</th>
<th>% Decrease in Post-Intervention FBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khan et. al. (2003) 1, 3, 6 g</td>
<td>234 mg/dl</td>
<td>Yes</td>
<td>24%</td>
</tr>
<tr>
<td>Crawford (2009) 1 g</td>
<td>Approximately 220 mg/dl</td>
<td>Yes</td>
<td>Approximately 8%</td>
</tr>
<tr>
<td>Mang et. al. (2006) extract equivalent to 3 g</td>
<td>166 mg/dl</td>
<td>Yes</td>
<td>10.3%</td>
</tr>
<tr>
<td>This study extract equivalent to 10 g</td>
<td>162 mg/dl</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Suppapitiporn et. al. (2006) 4.5 g</td>
<td>154 mg/dl</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Vanschoonbeek et. al. (2006) 1.5 g</td>
<td>150 mg/dl</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Blevins et. al. (2007) 1 g</td>
<td>132 mg/dl</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

Drug Interactions

It is probable that drug interactions may have affected the benefits of cinnamon in our study. Imparl-Radoevich (1998) postulated that a cinnamon extract stimulates autophosphorylation of the insulin receptor kinase domain and inhibits protein tyrosine phosphatase, thereby decreasing the inhibition of the insulin receptor activity. This therefore, leads to an increased insulin sensitivity in persons with type-2 diabetes, as the pathogenesis of type-2 diabetes leads to reduced phosphorylation of the insulin receptor (Anderson, 2007).
Verspohl et al. (2005) demonstrated that a cinnamon extract stimulates insulin secretion and lowers blood glucose levels in type-2 diabetic animal models; however, this effect is not to the same degree as sulfanylurea medications. All the participants of Khan et al.'s (2003) study were taking sulfanylurea medications for glucose control and their study demonstrated that cinnamon may potentiate the effects of sulfanylurea medications in persons with type-2 diabetes.

All participants in our study were taking Metformin for glucose control. Metformin was chosen rather than sulfanylurea medications in this study because Metformin is generally the first line agent used in the treatment of type-2 diabetes. Therefore, we proposed to determine whether the addition of a cinnamon extract supplement would be beneficial in this patient population.

It appears that Metformin and cinnamon may have similar mechanisms of action as they both increase tyrosine kinase activity of the beta sub-unit of the insulin receptor and increase GLUT-4 transport (Imparl-Radosevich, 1998; Luna, et. al., 2005; Wiernsperger & Bailey, 1999). On the other hand, sulfanylurea drugs increase pancreatic insulin secretion and since cinnamon has been found to increase insulin sensitivity it may potentiate the effects of sulfanylurea medications (Anderson, 2007).

Metformin however does not stimulate insulin secretion and tends to reduce hyperinsulinemia. Metformin is associated with weight loss, Zeigenfuss et. al. (2006) had similar findings in relation to the use of cinnamon and weight loss. Conversely, sulfanylureas are associated with weight gain and hypoglycemia (Bennett, 2009).

Participants in other clinical trials published thus far on the effects of cinnamon on blood glucose and lipid levels in persons with type-2 diabetes, have been on a wide range
of oral anti-hyperglycemic medications. Mechanisms of these oral anti-hyperglycemic medications differ. Some reduce the absorption of glucose, others such as sulfanylureas augment the secretion of insulin, and yet others, such as Metformin, improve insulin sensitivity.

All studies published thus far have not reported whether there have been any intragroup manifestations in terms of differing medications and possible drug interactions. Khan et. al. (2003) has been the only study published thus far, where all participants were taking only one class of oral antihyperglycemic medication for glucose control and were not taking any other medications for any other disease process, including antihyperlipidemic medications.

The majority of the participants in our study were on a HMG-CoA reductase inhibitor (statin) drug for lipid control. In fact, all of the studies published thus far on the effects of cinnamon on blood glucose and lipid levels in persons with type-2 diabetes included participants on antihyperlipidemic medications. Furthermore, the attainment of glucose control in and of itself may improve the lipid profile, this further confounds the conclusions that may be reached.

**Sample Size**

The largest clinical trial conducted thus far related to the effects of cinnamon on blood glucose and lipid levels was conducted by Crawford (2009). This was an effectiveness trial, no placebo group was utilized in this study and the participant’s medications were adjusted during the trial; which may limit the conclusions that were reached. There were 109 participants in this study. The next largest study with 79 participants was conducted by Mang et. al. (2006) (see Table 10).
The additional data obtained from these newer studies, however indicate that a much larger population is needed to have adequate power. In fact, Baker et. al. (2008) conducted a meta-analysis utilizing published clinical trials on the effects of cinnamon on blood glucose levels through July 2007. Based on the results of these studies, they conducted a post-hoc sample size calculation and determined that 1,166 to 6,853 participants would be required to have adequate power based on these new research findings.

**Ethnicity**

Table 11 below depicts the varying ethnic backgrounds of the populations in each of the cinnamon studies published thus far targeting persons with type-2 diabetes:
Table 11: Ethnicity of Cinnamon Study Populations of Persons with Type-2 Diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Ethnicity</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khan et. al. (2003)</td>
<td>Study conducted in Pakistan, ethnicity not noted</td>
<td>Significant</td>
</tr>
<tr>
<td>N=60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mang et. al. (2006)</td>
<td>German</td>
<td>Significant</td>
</tr>
<tr>
<td>N=79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vanschoonbeek et. al. (2006) N=25</td>
<td>Study conducted in Netherlands, ethnicity not noted</td>
<td>Insignificant</td>
</tr>
<tr>
<td>Suppapitiporn et. al. (2007) N=60</td>
<td>Study conducted in Thailand, ethnicity not noted</td>
<td>Insignificant</td>
</tr>
<tr>
<td>Blevins et. al. (2007)</td>
<td>Study conducted in US mainland 68% Caucasian, 16% Native American, 4% Hispanic, 2% Asian, 3% Unknown</td>
<td>Insignificant</td>
</tr>
<tr>
<td>N=57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crawford (2009)</td>
<td>Study conducted in US mainland Caucasian 76%, African American 16%</td>
<td>Significant</td>
</tr>
<tr>
<td>N=109</td>
<td></td>
<td></td>
</tr>
<tr>
<td>This Study</td>
<td>Study conducted in Hawaii Caucasian 38%, Asian 28%, Pacific Islander 25%, African American 7%, Hispanic 2%</td>
<td>Insignificant</td>
</tr>
<tr>
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</table>

As illustrated in Table 11, the participants of these studies have varying ethnic backgrounds; however, none of the studies have reported ethnic group differences. The most probable rationale for the lack of intergroup comparisons is due to the sample sizes of these studies; they are most likely too small to analyze intergroup ethnic data. More studies are needed to determine whether cinnamon is more efficacious in one ethnic group over another. However, based on the above table, there does not appear to be an obvious trend in effect findings in one ethnic group when compared to others.
As noted in Table 6, the ethnic mix in the treatment and placebo groups of our study were very similar. A statistical analysis was computed to determine if there was a significant between group difference based on ethnicity in this study and no significant difference was found in the analysis, although the sample size is probably too small to detect any possible differences based on ethnicity.

**Study Length**

Table 10 denotes the length of the effectiveness studies of cinnamon on blood glucose and/or lipid levels on all subjects. The study lengths ranged from 1-day interventions to determine the short-term effects of cinnamon ingestion on postprandial blood glucose levels, utilizing an oral glucose tolerance test (Hlebowicz et. al., 2007; Solomon & Blannin, 2007) to 120 days to determine longer term effects of cinnamon ingestion on blood glucose and lipid levels (Mang et. al., 2006).

The study treatment lengths of the investigations that have been conducted thus far to determine the cinnamon effects on persons with type-2 diabetes have been either 40 days, 90 days, or 120 days in duration. The treatment lengths and efficacy results of these studies are illustrated in Table 12 below.

In this study, we proposed to determine if the effects obtained by Khan et. al. (2003) could be replicated in a different population utilizing a cinnamon extract over 40 days. On day 40 ± 4, the subjects in our investigation, stopped taking the study capsules, and a blood sample was obtained on day 60, a procedure identical to Khan et. al.’s (2003)
It is not readily apparent whether study duration has an effect on the findings of cinnamon supplementation. Khan et. al. (2003) had a significant effect on day 40; while our study and Vanschoonbeek et. al. (2006) did not. However, longer trials are certainly needed to determine the effects of long-term cinnamon supplementation. None of the trials utilizing a cinnamon extract have reported adverse effects thus far. However, the longest trial utilizing the cinnamon extract has been 120 days.

Suppapitiporn et. al. (2006) obtained renal and liver function tests and reported a significant increase in creatinine levels in the treatment arm of their study; they utilized the cinnamon powder for a 90 day period. Zeigenfuss et. al. (2006) also measured liver and renal function with no significant changes in the treatment or control groups of their study utilizing a cinnamon extract for a 90 day period. Renal and liver function was not monitored in this study.

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Dietary Standardization

Glycemic control in persons with type-2 diabetes is accomplished with appropriate nutrition, exercise and oral hypoglycemic agents. Dietary management and lifestyle changes are fundamental to the effective management of type-2 diabetes. In fact, in the early stages of type-2 diabetes, glycemic control may be effectively managed with diet and lifestyle changes alone. Therefore, the outcomes of diabetes studies can be affected by the participant’s dietary habits.

As noted in Table 2, there has been a lack of dietary standardization in most of the cinnamon clinical trials conducted thus far. Vanschoonbeek, et. al’s. (2006) participants ate a standardized meal the night before the OGTT. In our study, the participants ate a standardized breakfast after the fasting blood tests on days 0, 20, 40 and 60. Postprandial glucose levels were then obtained one hour after the breakfast.

There has been a lack of dietary standardization in most of the studies published thus far on the effects of cinnamon in type-2 diabetes. This lack of standardization may be another reason for the inconsistent findings in terms of glycemic control with the use of cinnamon supplementation.

Study Limitations

This study had several limitations. First, the sample size may have been too small for adequate power. Although a power analysis was conducted based on the results of Khan et. al’s (2003) study, these results have not been replicated in subsequent studies. Based on the results of these subsequent studies, a much larger population is needed than the sample size utilized in this investigation.

Second, although Khan et. al. (2003) had significant findings after 40 days of
cinnamon cassia powder supplementation, the study length may not have been adequate for this study. Mang et. al. (2006) had significant effects after 120 days of supplementation utilizing a cinnamon extract; unfortunately, they did not obtain blood samples prior to the end of the study to determine if there was a decrease in glucose or lipid levels over an abbreviated time period. Perhaps the cinnamon extract requires more time for its effect than the cinnamon cassia powder.

Third, whenever a placebo is utilized the Hawthorne effect has to be considered. It may be possible that the intervention changed the study groups’ daily habits, which would affect the study outcomes. A decrease in the glucose and lipid values were found in both the treatment and control groups of this study although not found to be statistically significant. The decrease in values in both groups could indicate that the Hawthorne effect did occur in this study.

The treatment and placebo capsules were identical in appearance; it is unlikely that the subjects could determine whether they were in the treatment or control group based on capsule appearance. However, the treatment group may have been able to discern that they were taking cinnamon by its’ taste. Although, the taste of the encapsulated cinnamon extract is not as strong as the cinnamon powder.

While a standardized breakfast was included in the protocol on test days, a more expansive dietary standardization would have strengthened this study, as dietary intake has a significant likelihood of affecting study outcomes.

All participants of this study who had been diagnosed with hyperlipidemia were being treated with a statin drug for lipid control (37.5% in the control group and 32.5% in the treatment group). This may have confounded the lipid results, as Khan et. al. (2003)
found significantly lower lipid levels with cinnamon supplementation; however, their participants were not taking antihyperlipidemic medications.

Four participants in the treatment group of this study had a baseline fasting blood glucose level less than 126 mg/dl. Since these values fall within the normal range, further improvements in glucose levels were improbable in these participants. However, similar negative results were found when the analysis was restricted to the participants whose baseline blood glucose levels were greater than or equal to 126 mg/dl (n = 36).

**Study Strengths**

Although a more expansive dietary standardization would have strengthened this study, the standardized breakfast on test days does increase this studies strength in relation to the postprandial glucose results.

Another study strength includes the fact that all subjects were taking only one type of oral antihyperglycemic agent for glucose control, rather than a wide variety of agents. Though there were no significant findings in this study, these results may help to formulate a hypothesis for further research. It may be that cinnamon does not potentiate Metformin due to the similarities in their therapeutic pathways, while it may be a useful adjunct in persons taking sulfanylurea medications, as demonstrated by Khan et. al. (2003).

**Recommendations for Further Research**

More clinical trials are needed to determine whether cinnamon is an effective dietary adjunct in the management of type-2 diabetes. There have been few clinical trials to determine the effects of cinnamon in glycemic and lipemic control in persons with type-2 diabetes and the results of Khan et. al’s (2003) study have not been replicated thus far.
It is recommended that further animal studies be conducted first to determine possible drug interactions with cinnamon. There is a wide range of oral antihyperglycemic medications and cinnamon may potentiate the effect of one drug over another.

Only one animal study was found (Verspohl et. al., 2005) that compared cinnamon to sulfanylurea medications. However, the investigators did not examine whether cinnamon would potentiate sulfanylureas in these animal models. More studies are needed comparing the different types of oral anti-hyperglycemic medications to determine efficacy in animal models first and then in human volunteers.

More studies are also needed to determine the optimum dose of cinnamon for glucose and/or lipid control. It is difficult to compare the results of studies conducted thus far because the methodologies have varied widely. The results obtained by Khan et. al. (2003) should be replicated by including participants only on sulfanylurea medications for glucose control in future studies, utilizing a similar study design.

All the studies conducted thus far have been small and of short duration. Larger sample sizes are needed with longer treatment periods to determine the long-term effects of cinnamon. Although cinnamon is generally considered to be safe at amounts normally consumed in the diet, the long-term effects of cinnamon supplementation are not known. Future study designs should include parameters to determine whether long-term cinnamon supplementation affects kidney or liver function. Larger sample sizes will allow for determination of between group differences in the effect of cinnamon in persons of varying ethnicity’s, BMI, and drug interactions.
It is recommended that future studies include a standardized diet in the study design, as diet has a significant effect on glycemic and lipid control in persons with type-2 diabetes.

**Conclusion**

There are more than 20 million people in the United States who have diabetes (ADA, 2010). Nurses in every setting are interacting with patients who have this chronic disease. Nurses are responsible for educating patients and helping them to identify effective therapeutic management techniques, including the use of dietary supplementation.

Food-based treatments are gaining recognition and dietary supplements are readily available. Early studies of the use of cinnamon in the management of type-2 diabetes were very promising and received much media attention. However, the studies conducted thus far have had small sample sizes with conflicting results. More studies are needed before cinnamon should be recommended as a dietary adjunct in the management of type-2 diabetes.
Appendix A

Summary of Randomized Controlled Trials Evaluating Cinnamon Use in Relation to Blood Glucose and Lipid Levels
# Summary of Randomized Controlled Trials Evaluating Cinnamon Use in Relation to Blood Glucose and Lipid Levels

<table>
<thead>
<tr>
<th>Author &amp; Journal</th>
<th>Subjects</th>
<th>Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khan et. al. (2003)</td>
<td>60 (30 men &amp; 30 women) diagnosed with type-2 diabetes taking sulfonylurea drugs. Ages 52.2 +/- 6.32 years. Study conducted in Pakistan, Hayatabad Medical Complex</td>
<td>Randomly assigned into 6 equal groups. Groups 1, 2 &amp; 3 consumed 1, 3 or 6g of cinnamon. Groups 4, 5, 6 were assigned to respective placebo groups, which consumed a corresponding # of capsules containing wheat flour. No capsules consumed after day 40. Fasting blood drawn on day 0, 40, 60 for glucose, triglyceride, total cholesterol, HDL cholesterol, &amp; LDL cholesterol levels.</td>
<td>After 40 days all three levels of cinnamon reduced the mean fasting serum glucose (18-29%), triglyceride (23-30%), LDL cholesterol (7-27%), and total cholesterol (12-26%) levels; no significant changes were noted in the placebo groups. Changes in HDL cholesterol were not significant.</td>
</tr>
</tbody>
</table>

+ Results in Type-2 DM

| Suppapitiporn et. al. (2006) | Sixty subjects diagnosed with type-2 diabetes Age 30-70 Fasting glucose 120-180 Hgb A1C > 7 Study conducted in Bangkok, Thailand | Single-blind, placebo-controlled trial. Subjects were randomly assigned to treatment or control group. The treatment group (n=20) received 1.5g of cinnamon cassie powder in capsule form TID with meals for 12 weeks. Fasting blood was obtained at baseline and at 12 weeks and evaluated for Hgb A1C, glucose, lipid profile, BUN, creatinine, & liver function test. | Fasting glucose was significantly lower from baseline in both the treatment and control group. There was no statistical difference between the treatment and control group. The treatment group there was an increase from baseline of creatinine and a decrease in SGOT. No adverse effects were reported by the participants, |

- Results in Type-2 DM
<table>
<thead>
<tr>
<th>Author &amp; Journal</th>
<th>Subjects</th>
<th>Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vanschoonbeek et. al. (2006)</strong> <em>American Society for Nutrition</em></td>
<td>25 postmenopausal women diagnosed with type-2 diabetes. All subjects were using oral hypoglycemic agents. Age 60 – 66. Study conducted in the Netherlands Academic Hospital, Maastricht, Maastricht University</td>
<td>Double-blind, placebo-controlled trial. The treatment group received 1.5 gm of cinnamon in capsule form daily for a period of six weeks. Blood samples for fasting blood glucose, HbA1C, indices for OGT and whole body insulin sensitivity, as well as lipid profiles were obtained on day 0, week 2 and week 6 for both the treatment and placebo groups. Compliance was monitored by capsule count on week 2 and week 6. Fasting blood was obtained on days 0, week 2 and week 6 followed by ingestion of 75g of glucose. Thereafter, blood samples were collected at 30, 60, 90 and 120 minutes via a catheter inserted into a dorsal hand vein.</td>
<td>In this study 1.5 gm of cinnamon daily did not have a significant effect on fasting blood glucose, Hgb A1c, plasma insulin, OGT, total cholesterol, LDL cholesterol, HDL cholesterol or triglyceride levels in postmenopausal women diagnosed with type 2 diabetes mellitus.</td>
</tr>
<tr>
<td><strong>Mang et. al. (2006)</strong> <em>European Journal of Clinical Investigation</em></td>
<td>79 subjects diagnosed with type-2 diabetes treated with an oral hypoglycemic agent or diet. Study conducted in Hannover, Germany University of Hannover</td>
<td>Double-blind, placebo-controlled trial. The treatment group received 112mg of a cinnamon extract three times a day (TID) with meals for a period of 4 months. The control group received a placebo capsule TID for a period of 4 months. The amount of aqueous cinnamon extract corresponded to 3g of cinnamon powder per day. Fasting blood samples were obtained at baseline and after 4 months of intervention. Compliance was monitored by capsule count and diary.</td>
<td>No adverse effects were observed and fasting blood glucose levels were significantly lower in the treatment group. However, no significant effects were found in the lipid levels or in the hemoglobin A1c levels. They concluded that cinnamon extract seems to have a moderate effect in reducing fasting plasma glucose concentrations (10.3%) in diabetic patients with poor glycemic control.</td>
</tr>
</tbody>
</table>

- **Results in Type-2 DM in Postmenopausal Women**

+ **Results in Type-2 DM**
<table>
<thead>
<tr>
<th>Author &amp; Journal</th>
<th>Subjects</th>
<th>Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziegenfuss et. al. (2006) <em>Journal of the International Society of Sports Nutrition</em></td>
<td>22 subjects diagnosed with pre-diabetes and metabolic syndrome. Age 30-60 yrs. Study conducted in Ohio, USA.</td>
<td>Double-blind, placebo-controlled trial. Randomly assigned to treatment or control. Treatment group received 250mg of a cinnamon extract (Cinnulin PF©) in capsule form BID with breakfast and dinner for a 12-week period. Measurements obtained at baseline included fasting serum chemistry, body weight, body composition and blood pressure.</td>
<td>• Systolic blood pressure decreased by 3.8% in the treatment group. • Fasting blood glucose was significantly lower 8.4% in the treatment group. • Lean body mass was significantly increased by 1.1% in the treatment group. • Body fat decreased by 0.7% in the treatment group.</td>
</tr>
<tr>
<td>Blevins et al. (2007) <em>Diabetes Care</em></td>
<td>60 subjects diagnosed with type-2 diabetes. Study conducted at the University of Okalhoma.</td>
<td>Intention to treat analysis. Double-blind, placebo-controlled trial. The treatment group received 500mg of cinnamon in capsule form BID with breakfast and dinner for a period of 3 months. Fasting glucose, total cholesterol, LDL, HDL, triglyceride and insulin levels were measure at baseline, 1, 2, and 3 months. A1C was measured at baseline and at 3 months.</td>
<td>No significant effects found in glucose, lipid levels or Hgb A1C in the treatment group when compared to the control when analysis completed on all enrolled subjects. Negative effects were also found when the analysis was restricted to the 42 participants who completed the study.</td>
</tr>
</tbody>
</table>

+ Results in Metabolic Syndrome

- Results in Type-2 DM

101
<table>
<thead>
<tr>
<th>Author &amp; Journal</th>
<th>Subjects</th>
<th>Design</th>
<th>Results</th>
</tr>
</thead>
</table>
| Solomon & Blannin (2007) | Seven lean, healthy males. Ages 25-27 | Randomized cross-over design. Each participant completed three interventions: a control oral glucose tolerance test (OGTT<sub>control</sub>), an OGTT supplemented with cinnamon (OGTT<sub>cin</sub>) and an OGTT with cinnamon ingested 12 hours before the trial (OGTT<sub>cin12hpre</sub>). Each of the three visits was separated by at least 5 days. On test day a fasting blood sample was obtained followed by ingestion of 75g of glucose. Blood samples were then drawn at t= 30, 60, 90 and 120 minutes. The control group consumed a capsule containing 5g of wheat flour 12h prior to the OGTT<sub>control</sub>. The cinnamon group consumed a capsule containing 5g of wheat flour 12h prior to the OGTT<sub>cin</sub> and a capsule containing 5g of cinnamon at t=0 prior to the ingestion of glucose. The OGTT<sub>cin12hpre</sub> group received 5g of cinnamon 12 hours prior to the OGTT<sub>cin12hpre</sub> and a capsule containing 5g of wheat flour at t=0 prior to the ingestion of glucose. | - Plasma glucose responses were significantly decreased in OGTT<sub>cin</sub> (12.9%) and OGTT<sub>cin12hpre</sub> (10%) when compared to OGTT<sub>control</sub>. No differences were found between the two cinnamon trials.  
- There were no significant effects on insulin responses to OGTT in any of the trials.  
- Insulin sensitivity derived from the Matsuda test was elevated in both cinnamon trials. However, there was no significant difference in insulin sensitivity between the two cinnamon trials.  

They concluded that a single bolus ingestion of 5g of cinnamon spice can reduce glucose responses to OGTT and improve insulin sensitivity in healthy individuals. These changes appeared to occur independent of changes to insulin responses, depicted by the insulin secretion indices. These data also show that the effects of cinnamon on glucose tolerance and insulin sensitivity persist for 12 hours. |

**+ Results Healthy Subjects**
<table>
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<tr>
<td>Altschuler et al. (2007) <em>Diabetes Care</em></td>
<td>72 adolescents diagnosed with type 1 diabetes. Ages 13 - 18. Study conducted at Dartmouth Hitchcock Medical Center, Hanover, New Hampshire Dartmouth College</td>
<td>Double-blind, placebo-controlled design. Subjects were randomly assigned to treatment or control. The treatment group ingested a capsule containing 1gm of cinnamon daily for 90 days. The control group ingested a placebo capsule daily for 90 days. Hgb A1C levels were drawn at baseline and at the end of the 90-day intervention. A member of the research team called each participant every 2 weeks during the study to assess adherence to the study protocol, to collect data on their insulin dosing, and possible adverse effects, including hypoglycemic episodes.</td>
<td>One subject in the cinnamon arm was withdrawn due to the development of hives, it was later determined that the subject had a family history of cinnamon allergies. There was no significant differences in final A1C, change in A1C, total daily insulin intake or number of hypoglycemic episodes between the cinnamon and control groups.</td>
</tr>
<tr>
<td>Hlebowicz et al. (2007) <em>American Journal of Clinical Nutrition</em></td>
<td>Fourteen healthy subjects (8males, 6 females). Study conducted in Sweden. Dept of Medicine, Malmo University Hospital, University of Lund</td>
<td>Crossover design (2- One day interventions). On exam day a fasting blood glucose was obtained on all subjects, followed by ingestion of a meal. The test meal consisted of 300 g of rice pudding mixed with 6 gm of cinnamon. The reference meal consisted of 300 gm of rice pudding. The gastric emptying rate (GER) was calculated using ultrasonography 15 minutes and 90 minutes after meal consumption. Finger prick capillary blood samples were also obtained 15, 30, 45, 60, 90 and 120 minutes after the start of the meal. Satiety was also measured during these time intervals utilizing a Lickert type scale graded from 0 for extreme hunger to 20 for extreme satiety.</td>
<td>The addition of cinnamon to the rice pudding significantly delayed gastric emptying and lowered the postprandial glucose response. There was no significant effect on satiety. They concluded that the intake of cinnamon lowers the postprandial glucose response which could be partially explained by a delayed GER.</td>
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</table>

- Results Type-1 DM in Adolescents

+ Results Healthy Subjects
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<th>Author &amp; Journal</th>
<th>Subjects</th>
<th>Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang et al. (2007) <em>Fertility and Sterility</em></td>
<td>15 women with polycystic ovary syndrome (PCOS)</td>
<td>Double-blind placebo controlled trial where fifteen subjects were randomly assigned to a treatment or placebo group. The treatment group received 333mg of cinnamon extract in capsule form three times per day (TID) and the control group consumed a placebo capsule TID for a period of 8 weeks. An oral glucose tolerance test (OGTT) was obtained at baseline and at 8 weeks. Fasting venous blood samples were obtained for blood glucose and serum insulin levels, followed by ingestion of 75gm of oral glucose. Venous blood samples for glucose and insulin were then obtained at 30, 60, and 120 minutes following the ingestion of glucose. From these values the homeostasis model insulin resistance index (HOMA-IR) and the quantitative insulin sensitivity check index (QUICKI) were calculated to determine endocrine and metabolic parameters. Glucose tolerance status was evaluated by the criteria established by the ADA.</td>
<td>Fasting glucose decreased by 16.9% in the treatment group. Insulin sensitivity increased significantly in the treatment group as evidenced by a 7.7% increase in the QUICKI and the HOMA-IR decreased by 44.5% both consistent with improved insulin sensitivity. However, fasting glucose also decreased significantly in the placebo group. Fasting glucose decreased by 7.7% in the placebo group. There were no significant changes in the insulin sensitivity parameters in the placebo group. No adverse effects were reported in this study.</td>
</tr>
<tr>
<td>Tang et al. (2008) <em>American Journal of Clinical Nutrition</em></td>
<td>Eleven healthy human subjects Age 21-38 Study conducted in Laramie, Wyoming, University of Wyoming</td>
<td>8-week randomized crossover study (Two 4-week interventions) Ingestion of 3g cinnamon (n=6) or 2.8g turmeric (n=5) for 4 wks. 2 capsules with breakfast, 2 with lunch and 2 with dinner. Oxalate load and fasting blood samples obtained at baseline, wk 4 and wk 8</td>
<td>Oxalate levels were significantly increased with turmeric ingestion but not with cinnamon. 3gm of cinnamon or 2.8g of turmeric did not alter glucose or lipid levels in healthy non-diabetic subjects.</td>
</tr>
</tbody>
</table>

+ Results Women with PCOS

- Results Healthy Subjects
<table>
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<th>Author &amp; Journal</th>
<th>Subjects</th>
<th>Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solomon &amp; Blannin (2009). European Journal of Applied Physiology</td>
<td>Eight healthy males Age 24-26 Study conducted in England. University of Birmingham</td>
<td>Single blind randomized crossover design (Two 20-day interventions). First intervention a control trial. Fasting glucose &amp; an OGTT test obtained on days 0, 1, 14, 16, 18 &amp; 20. During the control trial all subjects consumed 6 placebo capsules following their evening meal. This was followed by a 2-week washout period. The washout period was followed by the cinnamon treatment period. The same protocol was followed during this period as during the control period except 3gm of cinnamon in capsule form was consumed following the evening meal (6 capsules).</td>
<td>Cinnamon ingestion reduced the glucose response to OGTT on day 1 and day 14 and improved insulin sensitivity on day 14. The effects were quickly reversed when cinnamon supplementation was stopped. This is different from Khan et. al's study where a significant decrease in glucose and lipid levels were found 20 days after discontinuation of the cinnamon supplements.</td>
</tr>
<tr>
<td>Crawford (2009) The Journal of the American Board of Family Medicine</td>
<td>109 subjects diagnosed with type 2 diabetes. Inclusion criteria included a HbA1C &gt; 7.0 Study conducted at Wilford Hall Medical Center, San Antonio, Texas</td>
<td>This was an effectiveness trial. Participants were randomly assigned to either usual care with management changes by their primary care physician; or usual care with management changes plus cinnamon capsules. The cinnamon group was instructed to ingest two 500 mg of cinnamon in capsule form daily for a period of 90 days. Hgb A1C was drawn at baseline and at the end of the 90-day period for both groups.</td>
<td>Cinnamon lowered Hgb A1C 0.83% compared with usual care alone lowering Hgb A1c 0.37%</td>
</tr>
</tbody>
</table>

+ Results Healthy Subjects

+ Results in Type-2 DM

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Appendix B

Power Analysis

A second power analysis was completed utilizing the data obtained from Khan et. al.'s 2003 study results. The SAS Program, version 9.1 (Cary, N.C.) was utilized to perform this power analysis. Based on this power analysis 12 total participants were required for an 80% power in regards to the glucose levels and 20 total participants were required for an 80% power in regards to the LDL levels.
Power analysis based on Glucose levels

Overall F Test for One-Way ANOVA

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**Power analysis based on LDL levels**

**Overall F Test for One-Way ANOVA**

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<td>2</td>
<td>0.85</td>
<td>0.877</td>
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<tr>
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<td>0.954</td>
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Appendix C

Screening Tool
Cinnamon Study

Follow-Up Physical Examination Day 1

Date and time of Examination – 24h clock

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<th>D</th>
<th>Y</th>
<th>Time</th>
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Date and time of Last Meal

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<th>D</th>
<th>Y</th>
<th>Time</th>
</tr>
</thead>
</table>

Were laboratory tests performed at this visit?

- [ ] Yes  [ ] No

Did patient fast for 12 hours?

- [ ] Yes  [ ] No

Was patient instructed to eat breakfast and return to lab 1 hour after beginning breakfast?

- [ ] Yes  [ ] No

Did patient receive study capsules?

- [ ] Yes**  [ ] No

(Make certain subject obtains study capsules, monitoring form and instructions provided)**

** Vital Signs **

Blood Pressure: ____ / ____ mm/Hg  Heart Rate: ____ BPM

Temperature: _______ ° F  Weight: _________ lbs.

**Brief Physical Exam**

<table>
<thead>
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<th>PHYSICAL EXAM</th>
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<th>ABNORMAL</th>
<th>DESCRIPTION OF ABNORMALITY</th>
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<tr>
<td>Muscular/Skeletal</td>
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</table>

**Laboratory Results**

Fasting Blood Glucose: _________  Triglycerides: _________  HDL Cholesterol: _______

LDL Cholesterol: _________  Total Cholesterol: _________

Postprandial Glucose: _________

**Is fasting glucose > 350?**  **Yes ☐  No ☐

** (If the patient has a fasting blood glucose > 350 discontinue from study)**

Provider Signature: __________________________

112
Was the patients' fasting glucose level > 350  Yes ☐ No ☐  
If the answer is YES discontinue patient from study

Was the capsule count zero?  Yes ☐ No ☐  
If the answer is NO consider discontinuing patient from study
Cinnamon Study

Follow-Up Physical Examination Day 20

Date and time of Examination - 24h clock

Date and time of Last Meal

Were laboratory tests performed at this visit?  

Did patient fast for 12 hours?  

Was patient instructed to eat breakfast and return to lab 1 hour after beginning breakfast?  

Capsule Count: Is count zero?  

** (If capsule count not zero, consider discontinuation from study)

Blood Pressure: mm/Hg  Heart Rate: BPM

Temperature: °F  Weight: lbs.

Brief Physical Exam:

<table>
<thead>
<tr>
<th>PHYSICAL EXAM</th>
<th>NORMAL</th>
<th>ABNORMAL</th>
<th>DESCRIPTION OF ABNORMALITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Appearance</td>
<td></td>
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<tr>
<td>Lung</td>
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<tr>
<td>Cardiovascular</td>
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<tr>
<td>Muscular/Skeletal</td>
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</tr>
</tbody>
</table>

Laboratory Results:

Fasting Blood Glucose: Triglycerides: HDL Cholesterol: 

LDL Cholesterol: Total Cholesterol: 

Postprandial Glucose: 

**Is fasting glucose > 350?  **Yes  No  

** (If the patient has a fasting blood glucose > 350 discontinue from study)

Provider Signature: 

113
Was the patients' fasting glucose level $> 350$  Yes ☐  No ☐

If the answer is YES discontinue patient from study

Was the capsule count zero?  Yes ☐  No ☐

If the answer is NO consider discontinuing patient from study
Cinnamon Study

### Follow-Up Physical Examination Day 40

<table>
<thead>
<tr>
<th>Date and time of Examination – 24h clock</th>
<th>Date and time of Last Meal</th>
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</thead>
<tbody>
<tr>
<td>M  D  Y  Time</td>
<td>M  D  Y  Time</td>
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<td></td>
</tr>
</tbody>
</table>

- Were laboratory tests performed at this visit?  □ Yes □ No
- Did patient fast for 12 hours? □ Yes □ No
- Was patient instructed to eat breakfast and return to lab 1 hour after beginning breakfast? □ Yes □ No
- Capsule Count: _____ Is count zero? □ Yes □ No

#### Medical History

- Blood Pressure: _____ / _____ mm/Hg  Heart Rate: _______ BPM
- Temperature: _______ °F  Weight: _______ lbs.

### Brief Physical Exam

<table>
<thead>
<tr>
<th>PHYSICAL EXAM</th>
<th>NORMAL</th>
<th>ABNORMAL</th>
<th>DESCRIPTION OF ABNORMALITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Appearance</td>
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<td>□</td>
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</tr>
<tr>
<td>Lung</td>
<td>□</td>
<td>□</td>
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<tr>
<td>Cardiovascular</td>
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</tr>
<tr>
<td>Muscular/Skeletal</td>
<td>□</td>
<td>□</td>
<td></td>
</tr>
</tbody>
</table>

### Laboratory Results

- Fasting Blood Glucose: _______  Triglycerides: _______  HDL Cholesterol: _______
- LDL Cholesterol: _______  Total Cholesterol: _______
- Is fasting glucose > 350?  Yes □  No □  
  
  *(If the patient has a fasting blood glucose > 350 remove from study)*

- Postprandial Glucose: _______

Provider Signature: _______

114
Was the patients' fasting glucose level > 350  

Yes ☐  No ☐

If the answer is YES discontinue patient from study
### Follow-Up Physical Examination Day 60

**Date and time of Examination – 24h clock**

<table>
<thead>
<tr>
<th>M</th>
<th>D</th>
<th>Y</th>
<th>Time</th>
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</table>

**Date and time of Last Meal**

<table>
<thead>
<tr>
<th>M</th>
<th>D</th>
<th>Y</th>
<th>Time</th>
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</thead>
</table>

- Were laboratory tests performed at this visit? [ ] Yes [ ] No
- Did patient fast for 12 hours? [ ] Yes [ ] No
- Was patient instructed to eat breakfast and return to lab 1 hour after beginning breakfast? [ ] Yes [ ] No

### Follow-Up Physical Examination Day 60 Vital Signs

- **Blood Pressure:** _______ / _______ mm/Hg
- **Heart Rate:** _______ BPM
- **Temperature:** _______ °F
- **Weight:** _______ lbs.

### Brief Physical Exam

<table>
<thead>
<tr>
<th>PHYSICAL EXAM</th>
<th>NORMAL</th>
<th>ABNORMAL</th>
<th>DESCRIPTION OF ABNORMALITY</th>
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<tbody>
<tr>
<td>General Appearance</td>
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<tr>
<td>Muscular/Skeletal</td>
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</tbody>
</table>

### Laboratory Results

- **Fasting Blood Glucose:** _______
- **Triglycerides:** _______
- **HDL Cholesterol:** _______
- **LDL Cholesterol:** _______
- **Total Cholesterol:** _______
- **Postprandial Glucose:** _______

**Completed end of study status form** [ ] Yes [ ] No

**Provider Signature:** ____________________________
Cinnamon Study

<table>
<thead>
<tr>
<th>Day</th>
<th>Provider Signature</th>
<th>Date</th>
<th>Is patient taking capsules as prescribed?</th>
<th>Has the patient experienced any adverse reactions?</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
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<td></td>
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<td>□ Yes □ No</td>
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<td>10</td>
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<td>15</td>
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<tr>
<td>55</td>
<td></td>
<td></td>
<td>□ Yes □ No</td>
<td>□ Yes □ No</td>
</tr>
</tbody>
</table>

**(If patient has experienced any adverse reaction, fill out Adverse Events Form)**

Telephone Interview Date and Comments:

__________________________________________________________________________________________________________

__________________________________________________________________________________________________________

__________________________________________________________________________________________________________

__________________________________________________________________________________________________________

__________________________________________________________________________________________________________

__________________________________________________________________________________________________________

__________________________________________________________________________________________________________

__________________________________________________________________________________________________________
Appendix D

Recruitment Brochure
Why Should I participate?

- Persons diagnosed with type-2 diabetes are more likely to have increased blood glucose and lipid levels. This greatly increases the risk for heart disease. You may benefit from this study because lowering blood glucose and lipid levels will decrease your risk for heart disease.

- For every 1% decrease in blood cholesterol levels, the risk of a heart attack decreases by 2% - 3%

- Previous studies have shown that cinnamon can decrease cholesterol by up to 28%!

How will the data be reported?

- The information obtained during this study will become a part of a grouped data base and may be used by researchers for future activities and publications. Your name will remain completely confidential and will not be included in any of the reports.

Can I withdraw from study?

- Yes, you may withdraw from the study at any time with no penalty or loss of benefit.

Who is Eligible for this Study?

- Persons between the ages of 30 and 70 years diagnosed with type-2 diabetes
- Taking metformin for glucose control with a Hgb A1C > 7 or a fasting glucose level > 126
- Must not be on insulin or any other glucose lowering medication

A STUDY TO DETERMINE EFFECTS OF CINNAMON ON BLOOD GLUCOSE & LIPID LEVELS IN PERSONS WITH TYPE-2 DIABETES

TRIPLER ARMY MEDICAL CENTER

Principal Investigator: COL Thomas B. Francis, MD Chief, Endocrinology Service

For More Information Contact: Julieta M. Rosado, APRN, Ph.D(c) Telephone: 433-4345 or 734-9292 Pager: (808) 577-2256 E-mail: jrosado@hawaii.edu CPT Tamie Kerns, MD Pager: (808) 569-9817 E-mail: tamie.l.kerns@us.army.mil
The United States Department of Agriculture (USDA) has conducted several studies that have demonstrated that cinnamon increases the activity of insulin.

In other words, it increases the ability of the insulin hormone that is circulating in your bloodstream to utilize sugar. This will improve your blood sugar levels.

In addition, these studies have found that cinnamon consumption also lowers blood cholesterol levels. It is thought that the reason for this effect is due to the antioxidant properties contained in cinnamon.

**What is the purpose of the study?**

The purpose of this study is to confirm that cinnamon consumption lowers blood glucose and lipid levels in persons diagnosed with type-2 diabetes.

**Who is conducting the study?**

COL Thomas Francis, M.D., Chief of the Endocrinology Clinic is the Principal Investigator of this study.

Co-Investigators include: Julieta Rosado APRN, Ph.D(c)
CPT Tamie Kerns, M.D.
Todd Watoaka, Pharm.D.
Mona Kurashima, APRN, BC

**How was I selected?**

You were selected because your blood glucose levels are elevated even though you are taking medications to lower the amount of glucose circulating in your bloodstream. We want to see if adding cinnamon, which is a natural product, to your diet will improve your blood glucose and lipid levels.

**Is my confidentiality protected?**

Yes, the information obtained from this study will remain completely confidential. Your name will not be included in any of the data obtained.
Appendix E

Informed Consent
VOLUNTEER AGREEMENT AFFIDAVIT
For use of this form, see AR 70-25 or AR 40-38, the proponent agency is OTSG

PRIVACY ACT OF 1974

Authority: 10 USC 3013, 44 USC 3101, and 10 USC 1071-1087.

Principle Purpose: To document voluntary participation in the Clinical Investigation and Research Program. SSN and home address will be used for identification and locating purposes.

Routine Uses: The SSN and home address will be used for identification and locating purposes. Information derived from the study will be used to document the study; implementation of medical programs; adjudication of claims; and for the mandatory reporting of medical conditions as required by law. Information may be furnished to Federal, State and local agencies.

Disclosure: The furnishing of your SSN and home address is mandatory and necessary to provide identification and to contact you if future information indicates that your health may be adversely affected. Failure to provide the information may preclude your voluntary participation in this investigational study.

PART A(1) - VOLUNTEER AFFIDAVIT

Volunteer Subjects in Approved Department of the Army Research Studies

Volunteers under the provisions of AR 40-38 and AR 70-25 are authorized all necessary medical care for injury or disease which is the proximate result of their participation in such studies.

I, ___________________________, SSN ___________________________,

having full capacity to consent and having attained my ________________ birthday, do hereby volunteer/give consent as legal representative for ___________________________ to participate in an investigational study entitled

A Study to Determine the Effects of Cinnamon on Blood Glucose and Lipid Levels in Persons with Type-2 Diabetes

under the direction of

COL Thomas B. Francis, MD, Chief of Endocrinology Clinic, Tripler Army Medical Center

conducted at Tripler Army Medical Center

(Name of Institution)

The implications of my voluntary participation/consent as legal representative; duration and purpose of the research study; the methods and means by which it is to be conducted; and the inconveniences and hazards that may reasonably be expected have been explained to me by

I have been given an opportunity to ask questions concerning this investigational study. Any such questions were answered to my full and complete satisfaction. Should any further questions arise concerning my rights/the rights of the person I represent on study-related injury, I may contact the Center Judge Advocate at

Tripler Army Medical Center, Tripler AMC, HI 96859-5000  (808) 433-5311

(Name, Address and Phone Number of Hospital (Include Area Code))

I understand that I may at any time during the course of this study revoke my consent and withdraw/have the person I represent withdrawn from the study without further penalty or loss of benefits; however, I/the person I represent may be required (military volunteer) or requested (civilian volunteer) to undergo certain examinations if, in the opinion of the attending physician, such examinations are necessary for my/the person I represent's health and well-being. My/the person I represent's refusal to participate will involve no penalty or loss of benefits to which I am/the person I represent is otherwise entitled.

(Related Study)
PARTICIPATION INFORMATION: You have been invited to participate in a clinical investigational/research study conducted at Tripler Army Medical Center. It is very important that you read and understand the following general principles that apply to all participants in our studies: (a) your participation is entirely voluntary; (b) you may withdraw from participation in this study or any part of the study at any time; refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled; (c) after you read the explanation, please feel free to ask any questions that will allow you to clearly understand the nature of the study.

NATURE OF STUDY: The purpose of this study is to see whether adding cinnamon to your diet will lower blood glucose and lipid levels in persons diagnosed with type-2 diabetes. This research is being done because there have been several studies conducted in the laboratory performed by the United States Department of Agriculture (USDA) that have shown that cinnamon helps to lower blood glucose and lipid levels. In addition, there has been a study conducted on humans which was published in Diabetes Care in December 2003 which also showed that cinnamon lowers blood glucose and lipid levels in persons diagnosed with type-2 diabetes. We would like to perform a similar study to verify this effect on a different population using a cinnamon extract.

You have been asked to participate in this study because your glucose levels are high even though you are taking medication to lower your blood glucose levels. It is hoped that adding cinnamon to your diet will help to bring your blood glucose and lipid levels to a normal range. Persons diagnosed with type-2 diabetes are more likely to have high glucose and lipid levels, which increases your risk for heart disease. You may benefit from this study because lowering blood glucose and lipid levels will decrease your risk for heart disease, and decrease complications of elevated glucose levels. A total of 40 subjects will participate in this study.

In addition, the USDA has requested a sample of your blood that will be drawn. They want to see how cinnamon affects the way insulin functions in your body. The scientists of the Agricultural Research Service of the USDA have found that the parts of cinnamon that are beneficial are the water-soluble portions of cinnamon. Lab studies have shown that the water-soluble cinnamon increases sugar metabolism in your cells. Cinnamon appears to work through insulin. The insulin of people with type-2 diabetes is not efficient; studies have shown that the water-soluble extract of cinnamon make the insulin in your body much more efficient. Furthermore, cinnamon is an antioxidant, which studies have shown is very beneficial for people with diabetes and heart disease. These studies could help to create new products for lowering blood sugar levels.

EXPECTED DURATION OF SUBJECT'S PARTICIPATION: Sixty days. See the schedule of events on pages 4 and 5.
WHAT WILL BE DONE: If you agree to participate in this study, by a random process similar to flipping a coin, you will receive water-soluble extract of cinnamon capsules or a placebo (capsules containing bran cereal). You have a 50% chance to be in any group. Neither you nor the research team will know to which group you have been assigned to until the end of the study. However, in an emergency, this information will be made available.

If you take part in this study you will be asked to take one capsule with breakfast and one capsule with dinner daily for a period of forty days. You will be asked to continue taking any prescribed medications and to eat as you normally would. In addition, you will be asked to give a blood sample eight times during this study. Vital signs and blood samples will be obtained once before you have started taking the capsules; and again 20 +/- 4 and 40 +/- 4 days after you have started taking the capsules. You will stop taking the capsules after 40 days (+4 days if needed due to scheduling).

We will ask you to give your last blood sample 20 +/- 4 days after you have stopped taking the capsules to see if cinnamon has long lasting effects. The previous study published in Diabetes Care, showed that persons taking cinnamon continued to have lower blood glucose and lipid levels even 20 days after they stopped taking the cinnamon!

You will be asked to not eat for 12 hours prior to the blood draws. Approximately 17cc (about 2 ½ teaspoons) of blood will be drawn. Then you will be asked to eat a meal and visit the Adult Medicine Clinic for an assessment and blood pressure measurement. You will be asked to return to the lab one hour after you have begun to eat and approximately 6cc (about 1 teaspoon) of blood will be drawn. We would like everyone involved in the study to eat the same amount of carbohydrates. Therefore, we will provide you with a meal voucher that you may use at the Tripler cafeteria. The meal voucher will allow you to purchase one serving of scrambled eggs or a hard boiled egg, two pieces of toast, one serving of fresh fruit, and a carton of milk. Values obtained from your blood will include: blood glucose, total cholesterol, LDL cholesterol (the bad cholesterol), HDL cholesterol (the good cholesterol), and triglycerides. Previous studies have shown that cinnamon lowers the bad cholesterol, but does not affect the good cholesterol. These tests will be performed in the Tripler Army Medical Center Outpatient Laboratory.

A member of the research team will call you every five days to remind you to take your capsules and to see how you are doing. We will also ask you to write down the date and time that you take each capsule on a form provided to you.
In addition, the USDA would also like to perform a study with the blood drawn. This will not require you to have any additional blood drawn. They will use a sample of the blood drawn as described above. We want to see how cinnamon affects the way insulin functions in your body. There are hormones that circulate in your body that have been associated with insulin resistance. We think that cinnamon inhibits these hormones. In addition, there are substances found in persons with diabetes that cause inflammation to your blood vessels, leading to high cholesterol levels. We believe that cinnamon will inhibit the substances involved in this inflammatory process. The USDA laboratory will perform these tests and measurements. See table below for a detailed description of your visits and procedures should you choose to participate in this study.

To be eligible to participate in this study, you must be between the ages of 30 and 70, diagnosed with type-2 diabetes and taking at least 1000mg of metformin daily for a period of at least 3 months for glucose control. Your fasting blood glucose level must be between 126-300 mg/dl, or a Hemoglobin A1c level greater than 7 despite oral treatment with metformin for glucose control.

You are not eligible to participate in this study if you are on insulin therapy or on any oral hypoglycemic agent besides metformin. If you are pregnant or would like to become pregnant within the next year you will be excluded from this study. If you have not had past exposure to cinnamon, or if you have a known allergy to cinnamon you can not participate in this study. Persons with a history of stomach or duodenal ulcers will also be excluded. If you are taking tetracycline or if your body mass index (BMI) is greater than 35 or if you are lactose intolerant you may not participate in this study.
| Day 0 (before taking any capsules) | 1. Go to Adult Medicine Clinic, blood pressure and assessment will be done by a research team member. (Do not eat for 12 hours before you go to the lab.)  
2. Go to outpatient lab and 17cc (about 2 ½ teaspoons) of blood will be drawn.  
3. Go to cafeteria and use meal voucher to eat breakfast.  
4. Go to Adult Medicine Clinic for a quick check-up and to pick up capsules (48 capsules will be dispensed).  
5. Return to outpatient lab 1 hour after you started eating your meal and 6cc (about 1 teaspoon) of blood will be drawn. |
<table>
<thead>
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<tbody>
<tr>
<td>Day 5</td>
<td>A research team member will call you to remind you to take your capsules and to see how you are doing.</td>
</tr>
<tr>
<td>Day 10</td>
<td>A research team member will call you to remind you to take your capsules and to see how you are doing.</td>
</tr>
<tr>
<td>Day 15</td>
<td>A research team member will call you to remind you to take your capsules and to see how you are doing. In addition, team member will remind you of your next appointment and to bring any remaining capsules you may have with you to your appointment.</td>
</tr>
</tbody>
</table>
| Day 20 +/- 4 | 1. Go to outpatient lab and 17cc (about 2 ½ teaspoons) of blood will be drawn. (Do not eat for twelve hours before you go).  
2. Go to cafeteria and use meal voucher to eat breakfast.  
3. Go to Adult Medicine Clinic, blood pressure and assessment will be done by a research team member. (Bring your pill bottle with any capsules you have remaining with you). Pick up capsules (48 capsules will be dispensed).  
4. Return to outpatient lab 1 hour after you started eating your meal and 6cc (about 1 teaspoon) of blood will be drawn. |
| Day 25 | A research team member will call you to remind you to take your capsules and to see how you are doing. |
| Day 30 | A research team member will call you to remind you to take your capsules and to see how you are doing. |
| Day 35 | A research team member will call you to remind you to take your capsules and to see how you are doing. In addition, team member will remind you of your next appointment and to bring any remaining capsules you may have with you to your appointment. |
| Day 40 +/- 4 | 1. Go to outpatient lab and 17cc (about 2 ½ teaspoons) of blood will be drawn (Do not eat for twelve hours before you go to the lab).  
2. Go to cafeteria and use meal voucher to eat breakfast.  
3. Go to Adult Medicine Clinic, blood pressure and assessment will be done by a research team member. (Bring your pill bottle with any capsules you have remaining with you).  
4. Return to outpatient lab 1 hour after you started eating your meal and 6cc (about 1 teaspoon) of blood will be drawn.  
5. STOP TAKING CAPSULES ON DAY 40 (+4 days if needed due to scheduling). |
| Day 55 | A research team member will call you to see how you are doing and will remind you of your next appointment. |
| Day 60 +/- 4 | 1. Go to outpatient lab and 17cc (about 2 ½ teaspoons) of blood will be drawn (Do not eat for twelve hours before you go to the lab).  
2. Go to cafeteria and use meal voucher to eat breakfast.  
3. Go to Adult Medicine Clinic for vital signs and assessment.  
4. Return to outpatient lab 1 hour after you started eating your meal and 6cc (about 1 teaspoon) of blood will be drawn. |
INCLUSION AND EXCLUSION CRITERIA: To be eligible to participate in this study, you must be between the ages of 30 and 70, diagnosed with type-2 diabetes and taking at least 1000mg of metformin daily for a period of at least 3 months for glucose control. Some medical tests give results in milligrams (mg) per deciliter (dL). A milligram is one-thousandth of a gram. A gram is about 1/40 of an ounce. A deciliter measures fluid volume that is 1/10 liter. A liter is a little bigger than a quart. In order for you to be able to participate, your fasting blood glucose level must be between 126-300 mg/dl, or a Hemoglobin A1c level (blood sugar indicators) greater than 7 despite oral treatment with metformin for glucose control.

You are not eligible to participate in this study if you are on insulin therapy or on any oral hypoglycemic agent besides metformin. If you are pregnant or would like to become pregnant within the next year you will be excluded from this study. If you have not had past exposure to cinnamon, or if you have a known allergy to cinnamon you can not participate in this study. Persons with a history of stomach or duodenal ulcers will also be excluded. If you are taking tetracycline or if your body mass index (BMI) is greater than 35 or if you are lactose intolerant you may not participate in this study.

REASONABLY FORESEEABLE RISKS OR DISCOMFORTS: The most common side effect of cinnamon consumption is an allergic reaction. Allergic symptoms include:

- itching
- swelling of lips and tongue
- rash
- burning or blistering in mouth

Therefore, if you have a known allergy to cinnamon or have never eaten cinnamon you should not participate in this study. The USDA has found that the part of cinnamon that causes allergic reactions are found in the fat soluble part of cinnamon and the good effects of cinnamon are found in the water soluble part of cinnamon. The water-soluble part of the cinnamon will be utilized for this study. Therefore, it is very unlikely that you will experience any of the above symptoms.

In addition, large amounts of cinnamon may cause:

- burning sensation in mouth
- burning sensation in chest
- burning sensation in stomach
- double vision
- dizziness
- vomiting
- sleepiness

However, only a small amount of cinnamon will be utilized in this study; therefore these side effects are unlikely.
Cinnamon may also increase intestinal motility. Therefore, you may experience:

- **stomach discomfort**

If you have a history of stomach or duodenal ulcers you should not participate in this study. However, you will be receiving a small amount of cinnamon. Therefore, it is unlikely that you will experience stomach discomfort.

**Risks of Blood Draws:**

We are asking you to visit the hospital four times during the study. During your visits we are asking you to have your blood drawn twice each visit. A fasting blood sample of 17cc (about 2 1/2 teaspoons) of blood will be drawn, then you will be asked to eat a meal and return to the Tripler Outpatient laboratory where an additional 5cc (about 1 teaspoon) of blood will be drawn. The **risks are minimal and are only those of having blood drawn.** Taking blood may cause some brief soreness, bleeding, and bruising where the needle enters the body, and in a few cases swelling at the site where the needle enters the body. Occasionally, a person may faint or feel faint when blood is drawn for a blood test. Risk of infection is slight since only sterile one-time equipment will be used.

There also may be other side effects or discomforts that we cannot predict. Your blood glucose and lipid levels may not improve or may worsen while participating in this study. If you are in the treatment group that receives the bran cereal placebo capsules your glucose and lipid levels may worsen or not improve. You will be provided with the results of your blood tests at the end of the 60-day period. A research team member will call you with your results. You will be informed via a letter of the results of the study when the study is completed. Additionally, we can inform you whether you were in the treatment or control group when the study is completed if you wish to know.

The study capsules must only be taken by the persons involved in the study. Keep capsules out of reach of children and persons of limited capacity to understand.

You will be contacted via phone every 5 days to remind you to take the capsules and to determine whether or not you are having any side effects related to taking the capsules. It is unlikely that you will experience any of these symptoms, but if you do experience any of the above symptoms, stop taking the capsules and contact any of the investigators or present to the Tripler Emergency Room. Contact information:

- COL Thomas B. Francis, MD, Office: (808) 433-6933, Pager: (808) 574-3168
- Julieta Rosado, RN, MSN, APRN, BC, Ph.D. (c), Office: (808) 734-9292, Pager: (808) 577-2256
- CPT Tamie Kerns, MD, Office: (808) 433-4049, Pager: (808) 569-9817
COMPENSATION FOR INJURY: Should you be injured as a direct result of participating in this research project, you will be provided medical care at Tripler Army Medical Center, at no cost to you, for that injury. You will not receive any injury compensation, only medical care. This is not a waiver or release of your legal rights. You should discuss this issue thoroughly with the principal investigator before you enroll in this study.

BENEFIT(S) TO THE SUBJECT OR TO OTHERS: This study was not designed to benefit the subject. Your participation may provide information for future people diagnosed with type-2 diabetes. You will not receive any compensation for participation in the study.
ALTERNATIVE PROCEDURES OR COURSES OF TREATMENT: You will be asked to continue taking any prescribed medications. Instead of being in this study, you may request the standard medical treatment for hyperglycemia (excess blood sugar) and hyperlipidemia (excess fat in the bloodstream) related to type-2 diabetes. The dosage of metformin which, you are receiving, may have to be increased, or your doctor may want to add another oral hypoglycemic medication to control your glucose levels. In addition, if your lipid levels are high your doctor may want to add a lipid-lowering agent to your medication regimen. You do not have to participate in this study to receive treatment for your condition. Please talk to your regular doctor about all your treatment options.

CONFIDENTIALITY: Information gained because of your participation in this study may be publicized in the medical literature, discussed as an educational model, and used generally in the furtherance of medical science. Information from this study may be used as part of a scientific publication in medical or professional journals, but you will in no way be personally identified. Complete confidentiality cannot be promised because information bearing on your health may be required to be reported to appropriate medical or command authorities.

Your medical records relating to this study may be reviewed by the Institutional Review Boards (IRB) at Tripler Army Medical Center and the University of Hawaii, the United States Department of Agriculture (USDA), Integrity Nutraceuticals International and other government agencies as part of their normal duties, and results of the study will be reported to them. The recipients will treat this information confidentially, and in the event of publication regarding this study, your identity will not be disclosed.

This research study meets the confidentiality requirements of the Health Insurance Portability and Accountability Act (HIPAA). A HIPAA Authorization form for this study will be provided to you separately, and you will be asked to sign that form.

PRECAUTIONS TO BE OBSERVED BY SUBJECT BEFORE AND FOLLOWING THE STUDY: During the course of this study, absence of pregnancy is required. It is unknown whether cinnamon may be a significant risk to the fetus if the subject (female) is pregnant or (male) has fathered a child while on treatment.

To avoid pregnancy, or fathering a child, the subject should abstain from sexual relations or practice a method of birth control. Except for surgical removal of the uterus, however, birth-control pills, IUD, or sperm-killing products are not totally effective in preventing pregnancy. The only ways to completely avoid drug-associated risk to an unborn baby are to (1) not become pregnant or (2) not receive cinnamon extract.

The subject agrees to request testing and evaluation to diagnose pregnancy before participating in this study. If the subject becomes pregnant while on study, the subject will be withdrawn from this study and referred for medical/obstetrical attention.
Although it is unknown when or if it is safe to become pregnant, or father a child after completion of treatment, it is advised that you wait a minimum of six months after stopping therapy.

**CIRCUMSTANCES UNDER WHICH YOUR PARTICIPATION MAY BE TERMINATED WITHOUT YOUR CONSENT:** (a) Health conditions or other conditions that might occur which may be dangerous or detrimental to you or your health; (b) if military contingency requires it; (c) if you become ineligible for military care as authorized by Army regulation; (d) if the safety monitor determines that continued treatment under this study may be harmful to you; (e) if your fasting blood sugar is greater than 300 at any time during the study; (f) if you show any signs or have symptoms of an allergic reaction to the treatment or placebo; (g) if you are taking tetracycline, insulin, an oral hypoglycemic agent besides metformin, or are taking an antihyperlipidemic; (h) if the capsule count is incorrect; (i) if you did not fast prior to the blood draws

**ADDITIONAL COSTS TO SUBJECT THAT MAY RESULT FROM PARTICIPATION IN STUDY:** In accordance with AR 40-38, paragraph 3-3(j)(2), daily charges for inpatient care will be waived while the volunteer is in the hospital if the volunteer would not normally enter the hospital for treatment but is requested to do so as part of a research study or as a result of adverse reaction to the drug(s) or procedure(s) used in this study. This also applies to the volunteer's extension of time in a hospital for a research study when the volunteer is already in the hospital.

**SIGNIFICANT NEW FINDINGS:** Any significant new findings developed during the course of this study that could affect your willingness to continue participation will be made available to you. The results of the research will be made available to you if you so desire. In some cases complete results may not be known for several years.

**APPROXIMATE NUMBER OF SUBJECTS INVOLVED IN THE STUDY:** 40 men and women

**DOMICILIARY CARE STATEMENT:** The extent of medical care provided, should it become necessary, is limited and will be within the scope authorized for Department of Defense (DOD) health care beneficiaries. Necessary medical care does not include domiciliary (home or nursing home) care.
FOR FURTHER INFORMATION: For questions about the study, contact the principal investigator:

COL Thomas B. Francis, MD  
Chief, Endocrinology Clinic, Tripler Army Medical Center  
Phone: (808) 433-6933

Julieta M. Rosado, RN, MSN, APRN, BC  
Associate Investigator  
Phone: (808) 734-9292 or (808) 433-5839

CPT Tamie Kerns, MD  
Associate Investigator  
Pager: (808) 569-9817

For questions about your rights as a research participant, contact the Tripler Army Medical Center’s Institutional Review Board (which is a group of people who review the research to protect your rights) at (808) 433-6709 or the University of Hawaii’s Institutional Review Board at (808) 956-5007.

For questions about research related injury, contact the Center Judge Advocate at Tripler Army Medical Center at (808) 433-5311.

IF THERE IS ANY PORTION OF THIS EXPLANATION THAT YOU DO NOT UNDERSTAND, ASK THE INVESTIGATOR BEFORE SIGNING. A COPY OF THE VOLUNTEER AGREEMENT AFFIDAVIT WILL BE PROVIDED TO YOU.
I have read the above explanation and agree to participate in the investigational study described.

If you are a female, you must read the following two (2) sections:

During the course of this study, absence of pregnancy is required. The water-soluble extract of cinnamon involved in this study may be a significant risk to me or the fetus if I am pregnant.

I do not believe that I am pregnant and I agree to prevent pregnancy during the course of this study. If there is a possibility of pregnancy (a late period and/or sexual activity without birth control), I agree to request testing and evaluation to diagnose pregnancy before participating in this study. This request, testing and evaluation will be handled with guarantees of privacy and confidentiality, and the results will be made available only to me and/or my doctor. If pregnant, I agree to withdraw from this study and seek medical attention.

I do [ ] do not [ ] (check one & initial) consent to the inclusion of this form in my outpatient medical treatment record

SIGNATURE OF VOLUNTEER

DATE

PERMANENT ADDRESS OF VOLUNTEER
Appendix F

Evaluation/Observation Tool
**Cinnamon Study**

**Screening Visit Demographics**

<table>
<thead>
<tr>
<th>Informed Consent Obtained:</th>
<th>Yes</th>
<th>(Continue with screening)</th>
</tr>
</thead>
</table>

**Date of Birth:  / / (Exclude if younger than 30 yrs)**

**Gender:**

- [ ] M
- [ ] F

**Is the patient of child bearing potential?**

- [ ] Yes
- [ ] No

If Yes, obtain blood pregnancy test.

**Pregnancy test ordered?**

- [ ] Yes
- [ ] No

If yes, obtain blood pregnancy test.

**Birth Control Method**

- [ ] IUD
- [ ] Oral Contraceptives
- [ ] Implant
- [ ] Other: __________

**Is the patient pregnant?**

- [ ] No
- [ ] Yes

(Exclude if Pregnant)

**Is the patient nursing?**

- [ ] No
- [ ] Yes

(Exclude if Nursing)

**Height in Inches:** ________

**Body Mass Index:** ________

(Refer to Body Mass Index Table, exclude if BMI > 35)

**Weight in Pounds:** ________

**Race/Ethnicity:**

- [ ] Caucasian
- [ ] African-American
- [ ] Asian
- [ ] Pacific Islander
- [ ] American-Indian
- [ ] Hispanic
- [ ] Other: __________

**Provider Signature:** ________
### Inclusion Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patient is male, or female without child-bearing potential (post-menopausal, surgically sterile) or using an approved form of birth control (intrauterine device, implantable progesterone device, oral contraceptive, or barrier method plus spermicide).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Patient is 30 years or older at the time of randomization.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. The patient has completed the informed consent process.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. The patients' BMI is 35 or less</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If all answers are **YES** patient is eligible to enter study.

### Exclusion Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is the patient pregnant?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Is the patient nursing?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If all answers are **NO** patient is eligible to enter study.
Cinnamon Study

<table>
<thead>
<tr>
<th>Screening Visit History (continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the patient have a history of type-2 diabetes? Yes [ ] No [ ]</td>
</tr>
<tr>
<td>What year was patient diagnosed with type-2 diabetes? Year [ ]</td>
</tr>
<tr>
<td>Does the patient have any medical problems besides diabetes? Yes [ ] No [ ]</td>
</tr>
<tr>
<td>List Conditions: ____________________________</td>
</tr>
<tr>
<td>____________________________</td>
</tr>
<tr>
<td>____________________________</td>
</tr>
<tr>
<td>____________________________</td>
</tr>
<tr>
<td>____________________________</td>
</tr>
<tr>
<td>____________________________</td>
</tr>
<tr>
<td>Is the patient taking metformin for glucose control? Yes [ ] No [ ]</td>
</tr>
<tr>
<td>(Exclude if patient not on metformin for glucose control)</td>
</tr>
<tr>
<td>(All volunteers should be taking metformin 1000mg/day X 3mo)</td>
</tr>
<tr>
<td>Dose &amp; Schedule: ____________________________</td>
</tr>
<tr>
<td>Is the patient taking any other medications for glucose control? Yes [ ] No [ ]</td>
</tr>
<tr>
<td>(Exclude if patient is taking any medication besides metformin for glucose control. List all medications on Prior/Concomitant Medication Form)</td>
</tr>
<tr>
<td>Is the patients' HgbA1c &gt; 7 or is their fasting glucose level &gt; 129? Yes [ ] No [ ]</td>
</tr>
<tr>
<td>(Exclude if HgbA1c less than 7 or if fasting glucose level is less than 129. Obtain Hgb A1c if results have not been obtained within 3 months)</td>
</tr>
<tr>
<td>Is the fasting glucose greater than 350? Yes [ ] No [ ]</td>
</tr>
<tr>
<td>(Exclude if fasting glucose greater than 350)</td>
</tr>
<tr>
<td>Is the patient taking tetracycline? Yes [ ] No [ ]</td>
</tr>
<tr>
<td>(Exclude if patient taking tetracycline)</td>
</tr>
<tr>
<td>Provider Signature: ____________________________</td>
</tr>
</tbody>
</table>
1. Does the patient have a history of type-2 diabetes?  

2. Is the patient taking Metformin for glucose control?  

3. Is the fasting glucose greater than 129 or is the HgbA1c greater than 7?  

If all answers are YES patient is eligible to enter study.

1. Is the patient taking tetracycline?  

2. Is the patient taking any medications for glucose control besides Metformin?  

3. Is the fasting glucose level greater than 350?  

If all answers are NO patient is eligible to enter study.
Cinnamon Study

Screening Visit History

Has patient ever consumed cinnamon? Yes ☐ No ☐
(Exclude if patient has never consumed cinnamon)

Is patient currently consuming cinnamon for glucose control? Yes ☐ No ☐
(Exclude if patient is currently consuming cinnamon for glucose control)

Is the patient allergic to cinnamon? Yes ☐ No ☐
(Exclude if patient is allergic to cinnamon)

Is the patient allergic to bran? Yes ☐ No ☐
(Exclude if patient is allergic to bran)

Does the patient have any other known allergies? Yes ☐ No ☐

List allergies: __________________________
                                          __________________________
                                          __________________________

Reaction: __________________________
                                          __________________________

Does patient have a history of stomach or duodenal ulcers? Yes ☐ No ☐
(Exclude if patient has a history of stomach or duodenal ulcers)

Is the patient lactose intolerant? Yes ☐ No ☐
(Exclude if patient is lactose intolerant)

Provider Signature: __________________________

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### Inclusion Criteria

1. Has the patient ever consumed cinnamon?

   - YES
   - NO

   If the answer is YES patient is eligible to enter study.

### Exclusion Criteria

1. Is the patient currently consuming cinnamon for glucose control?

   - YES
   - NO

2. Does the patient have a known hypersensitivity reaction to cinnamon?

   - YES
   - NO

3. Does the patient have a known hypersensitivity reaction to bran?

   - YES
   - NO

4. Does the patient have a history of stomach or duodenal ulcers?

   - YES
   - NO

5. Is the patient lactose intolerant?

   - YES
   - NO

If all answers are NO patient is eligible to enter study.
Cinnamon Study

**Screening Visit Vital Signs**

Date of Physical Exam: ___ / ___ / ___  
Blood Pressure: ___ / ___ mm/Hg

Heart Rate: ___ BPM

Temperature: ___ °F

Is the patient's temperature > 99°F? Yes ☐ No ☐

Is cause of elevated temperature known? Yes ☐ No ☐

*(Exclude if patient has a fever of unknown origin)*

<table>
<thead>
<tr>
<th>Physical Exam</th>
<th>Normal</th>
<th>Abnormal</th>
<th>Description of Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Appearance</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>Head and Neck</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>Lymph Nodes</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>Muscular/Skeletal</td>
<td>☐</td>
<td>☐</td>
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</tr>
<tr>
<td>Cardiovascular</td>
<td>☐</td>
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<td></td>
</tr>
<tr>
<td>Lungs</td>
<td>☐</td>
<td>☐</td>
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</tr>
<tr>
<td>Abdomen</td>
<td>☐</td>
<td>☐</td>
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</tr>
<tr>
<td>Neurological</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
</tbody>
</table>

Provider Signature: _______________________

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<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
</table>

Does the patient have a fever of unknown origin?

If the answer is NO patient is eligible to enter study
References


http://www.ars.usda.gov/is/pr/2004/040419.htm


http://www.who.int/medicines/library/trm/medicinalplants/monograph_volume_one.shtml


