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REVIEW ARTICLE

Cinnamon: Potential Role in the Prevention of Insulin Resistance, Metabolic Syndrome, and Type 2 Diabetes

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Abstract

Metabolic syndrome is associated with insulin resistance, elevated glucose and lipids, inflammation, decreased antioxidant activity, increased weight gain, and increased glycation of proteins. Cinnamon has been shown to improve all of these variables in *in vitro*, animal, and/or human studies. In addition, cinnamon has been shown to alleviate factors associated with Alzheimer's disease by blocking and reversing tau formation *in vitro* and in ischemic stroke by blocking cell swelling. *In vitro* studies also show that components of cinnamon control angiogenesis associated with the proliferation of cancer cells. Human studies involving control subjects and subjects with metabolic syndrome, type 2 diabetes mellitus, and polycystic ovary syndrome all show beneficial effects of whole cinnamon and/or aqueous extracts of cinnamon on glucose, insulin, insulin sensitivity, lipids, antioxidant status, blood pressure, lean body mass, and gastric emptying. However, not all studies have shown positive effects of cinnamon, and type and amount of cinnamon, as well as the type of subjects and drugs subjects are taking, are likely to affect the response to cinnamon. In summary, components of cinnamon may be important in the alleviation and prevention of the signs and symptoms of metabolic syndrome, type 2 diabetes, and cardiovascular and related diseases.

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Introduction

Common cinnamon (*Cinnamomum verum, C. zeylanicum*) and cassia (*C. aromaticum*) have a long history of uses as spices, flavoring agents, preservatives, and pharmacological agents. A review of the safety and efficacy of cinnamon on antioxidant activity, *Heliobacter pylori* infection, activation of olfactory cortex and brain, oral candidiasis in human immunodeficiency virus, and chronic salmonellosis has been published.[1] In addition, several studies have examined the effects of cinnamon on glucose, insulin, and lipid metabolism associated with metabolic syndrome, which are the focus of this review. This review is an update of previous reviews.[2,3]

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Abbreviations: (apoB48) apolipoprotein B48, (AD) Alzheimer's disease, (CD36) cluster of differentiation 36, (CE) cinnamon extract, (FRAP) ferric-reducing antioxidant power, (GLP-1) glucagon-like peptide-1, (HFD) high fructose diet, (IL) interleukin, (IR) insulin receptor, (IRS1) IR substrate-1, (MDA) malondyaldehyde, (MTP) microsomal triglyceride transfer protein, (MW) molecular weight, (NO) nitric oxide, (PCOS) polycystic ovary syndrome, (PI3K) phosphoinositide 3-kinase, (RBP4) retinol-binding protein 4, (SREBP) sterol regulatory element-binding protein, (T2DM) type 2 diabetes mellitus, (TNF) tumor necrosis factor, (VEGF) vascular endothelial growth factor, (VEGFR) VEGF receptor

Keywords: cardiovascular diseases, cinnamon, diabetes, insulin sensitivity, metabolic syndrome

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In 1990, we reported that compounds found in cinnamon have insulin-potentiating properties and may be involved in the alleviation of the signs and symptoms of diabetes and cardiovascular diseases related to insulin resistance and metabolic syndrome.[4] Furthermore, when compared to herbs, spices, and medicinal extracts for insulin-like or insulin-potentiating activity in an *in vitro* model,[5] aqueous cinnamon extracts (CE) potentiated insulin activity more than 20-fold, higher than any other compound tested at comparable dilutions. The effects of adding more of the aqueous extract of cinnamon appear similar to adding more insulin. This is important from a human health standpoint because it results in increased insulin sensitivity and less insulin is required to have larger insulin effects. People with metabolic syndrome have adequate amounts of insulin but the insulin is not efficient. Components of cinnamon make insulin more efficient.

Anderson and colleagues[6] demonstrated that the *in vitro* insulin-potentiating activity found in cinnamon is present in the aqueous fraction. The aqueous extract of "spent cinnamon" (product that is left when cinnamon oil is removed) in which many of the organic components found in cinnamon, including cinnamaldehyde, are largely removed has basically the same *in vitro* insulin-potentiating activity as extracts from the cinnamon before the cinnamon oil is removed. In addition, cinnamon oil and its major components, including cinnamaldehyde, cinnamic acid, eugenol, and coumarin, have no *in vitro* insulin-enhancing activity in epididymal fat cells.[6] The structure of a class of water-soluble cinnamon polyphenol compounds that display insulin-potentiating, antioxidant, and related activities is shown in **Figure 1**. These are type A polyphenols. Several of these have been isolated from cinnamon, and the most abundant ones are trimers with a molecular weight (MW) of 864 and a tetramer with a molecular weight of 1152 daltons.[6] The two major trimers can be converted to two other trimers with the same molecular weight (unpublished observation). The activities of a purified trimer[7–10] and tetramer[10] have been documented.

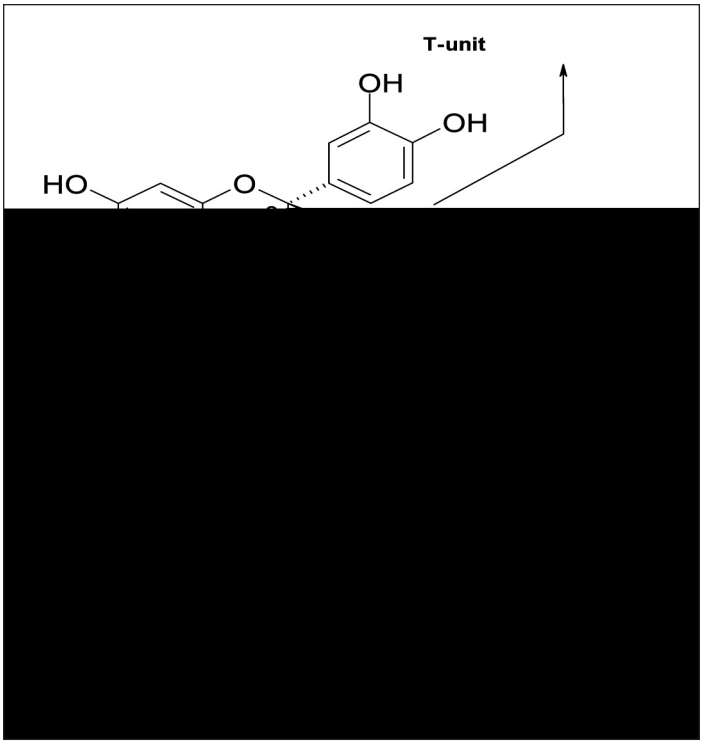

Figure 1. Structure of a class of water-soluble cinnamon polyphenol compounds that display insulin-potentiating and antioxidant activities. One tetramer and four type A trimers have been isolated from cinnamon and all were shown to have *in vitro* insulin-potentiating activity.[6]

Insulin resistance is a core defect in obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome. Cinnamon extract-treated rats have significantly higher glucose infusion rates compared with controls.[11] The insulin-stimulated insulin receptor (IR) β and IR substrate-1 (IRS1) tyrosine phosphorylation levels and IRS1/phosphoinositide 3-kinase (PI3K) in skeletal muscle of chow diet-fed rats are enhanced by CE. It was also demonstrated[12] that CE improves glucose utilization in normal male rats fed a high fructose diet (HFD). The decreased glucose infusion rate in HFD-fed rats (60% of normal controls) was improved by CE to the level of controls, and the improving effects of CE on the glucose infusion rates of HFD-fed rats were blocked by *N*-monomethyl-L-arginine (an inhibitor of nitric oxide, NO). The decreased muscular insulin-stimulated IRβ and IRS1 tyrosine phosphorylation levels and IRS1 associated with PI3K in HFD-fed rats are also improved significantly by CE. These data suggest that CE prevents the development of insulin resistance, at least in part by enhancing insulin signaling and possibly via the NO pathway in skeletal muscle. An aqueous extract of cinnamon has also been shown to improve insulin sensitivity in humans.[13]

The glucose transporter, GLUT4, facilitates the transport of glucose across plasma membranes into skeletal muscle and adipocytes. Previous studies reported that CE increases glucose uptake and GLUT4 expression in 3T3-L1 adipose cells. It has been observed[14] that a water extract of cinnamon (Cinnulin PF®) reduced blood glucose, plasma insulin, and soluble cluster of differentiation 36 (CD36), which is reported as a novel marker of insulin resistance.[15] Cinnamon extracts also inhibited retinol-binding protein 4 (RBP4), a novel adipokine that contributes to insulin resistance in plasma and adipose tissues.[16] Retinol-binding

protein 4 is increased in the serum of insulin-resistant humans and rodents and mediates insulin resistance in muscle and increases glucose production in liver.[17,18] Plasma RBP4 levels are inversely correlated with the expression of GLUT4 in adipose tissue.[17,18] Cinnamon extract consumption also appears to regulate glucose uptake-related genes, such as Glut1, Glut4, glycogen synthesis 1, and glycogen synthase kinase 3β mRNA expression in adipose tissue.[14]

Growing evidence suggests a strong link between systemic inflammation and T2DM and that elevated inflammatory cytokines may contribute to insulin resistance.[14] Tristetraprolin is an anti-inflammatory protein and a potential therapeutic target for the treatment of inflammation-related diseases. Tristetraprolin gene expression is reduced in the adipose tissue of obese subjects with metabolic syndrome.[19] It has been reported that tristetraprolin may offer partial protection against the development of insulin resistance and diabetes.[20] Cinnamon extract rapidly induces the expression of tristetraprolin mRNA levels in 3T3-L1 adipocytes.[20] The proinflammatory cytokine, tumor necrosis factor (TNF)-α, which is a link among obesity, insulin resistance, and metabolic syndrome, stimulates the overproduction of intestinal apolipoprotein B48 (apoB48)-containing lipoproteins.[8,21] *In vivo* oral treatment with Cinnulin PF inhibits the postprandial overproduction of apoB48-containing lipoproteins and serum triglyceride levels in rats and hamsters. In *ex vivo* [35] S-labeling studies, CE inhibited the oversecretion of apoB48 induced by TNF-α-treated enterocytes into the medium. Cinnamon extract treatment decreases the mRNA expression of the inflammatory factors [interleukin (IL)1β, IL6, and TNF-α]; improves the mRNA expression of IR, IRS1, IRS2, PI3K, and Akt1; inhibits CD36, microsomal triglyceride transfer protein (MTP), and phosphatase and tensin homolog; and enhances impaired sterol regulatory element-binding protein (SREBP)-1c expression in TNF-α-treated enterocytes.[22] That study[22] suggested that CE helps prevent the elevation of circulating triglyceride-rich lipoproteins with significant effects on intestinal insulin resistance. Accumulating evidence indicates that dyslipidemia is associated with insulin-resistant states resulting from the overproduction of both intestinal and hepatic triglyceride-rich lipoproteins and the delay of their hepatic clearance. Cinnamon extract reduces inflammation-related dyslipidemia and decreases risk factors associated with cardiovascular diseases.

It is well known that HFDs not only induce systemic insulin resistance, but also induce an enhanced inflammatory state.[21,23] The inflammatory factors may be at least one mechanism that leads to the overproduction of apoB48-containing lipoproteins,[21] which may be particularly atherogenic. We presented[24] both *in vivo* and *ex vivo* evidence that acute oral Cinnulin PF inhibits increases in postprandial triglycerides and the overproduction of apoB48-containing lipoproteins in fructose-fed, insulin-resistant rats. Cinnamon extract inhibits the secretion of apoB48 in enterocytes isolated from fructose-fed hamsters, enhances the impaired mRNA expression of intestinal insulin signaling, and downregulates the overexpression of MTP and SREBP-1c mRNA levels. Cinnamon extract also improves the postprandial overproduction of intestinal apoB48-containing lipoproteins by ameliorating intestinal insulin resistance and may be beneficial in the control of lipid metabolism.

Several phenolic compounds found in cinnamon, such as catechin, epicatechin, procyanidin B2, and phenol polymers, all showed significant inhibitory effects on the formation of advanced glycation end products. Their antiglycation activities are not only brought about by their antioxidant activities, but are also related to the trapping abilities of reactive carbonyl species.[25] That study demonstrated that proanthocyanidins can effectively scavenge reactive carbonyl species, inhibit the formation of advanced glycation end products, and, therefore, have the potential to be developed as agents to alleviate diabetic complications.[25]

Vascular endothelial growth factor is a mitogenic and angiogenic factor involved in tumor progression, in collateral vessel formation in ischemic tissues, and in inflammation, as well as in the development of diabetic retinopathy.[26] Vascular endothelial growth factor is also a key mediator of adipogenesis in obesity and insulin resistance.[27] Vascular endothelial growth factor is one of the most critical factors that induce angiogenesis and has thus become an attractive target for antiangiogenesis treatment. However, most current anti-VEGF agents often cause side effects and therefore cannot be recommended for long-term use. Identification of naturally occurring VEGF inhibitors derived from foods would be one alternative approach to control with an advantage of anticipated safety. Cinnamon extract inhibits VEGF-induced endothelial cell proliferation, migration, and tube formation

in vitro, sprouts formation from aortic ring *ex vivo*, and tumor-induced blood vessel formation *in vivo*.[10] While cinnamaldehyde, a component associated with the aroma of CE, has little effect on VEGF receptor (VEGFR) kinase activity, high-performance liquid chromatography-purified components of CE, procyanidin type A trimer (MW 864) and a tetramer (MW 1152), inhibit the kinase activity of purified VEGFR and VEGFR signaling pathways. These data suggest that procyanidin oligomers are active components in CE that inhibit angiogenesis. Taken together, this study revealed novel activity in cinnamon and identified a natural inhibitor of VEGF signaling that could potentially be useful in cancer prevention and/or treatment.[10]

Extracellular plaques related to β-amyloid (Aß) and intracellular neurofibrillary tangles of tau are the hallmarks of Alzheimer's disease (AD).[28] The incidence of AD is increased with insulin resistance, and Alzheimer's disease is now often referred to as type 3 diabetes.[29] The belief has emerged that tangles are formed as downstream events in relation to amyloid formation and thus are possibly the central pathology of this neurodegenerative process.[30] Thus, it is possible that agents capable of preventing tau aggregation may be key in the development of new AD therapies. An aqueous extract of Ceylon cinnamon (*C. zeylanicum*) was found to inhibit tau aggregation and filament formation, hallmarks of AD.[9] The extract can also promote complete disassembly of recombinant tau filaments and cause substantial alteration of the morphology of paired helical filaments isolated from the brain of a person who died of Alzheimer's disease. An A-linked proanthocyanidin trimer molecule was purified from the cinnamon extract and shown to contain a significant proportion of inhibitory activity. A large portion of the remainder of the inhibitory activity could be attributed to cinnamaldehyde. Cinnamon extract and type A polymers, but not cinnamaldehyde, also blocked cell swelling in an *in vitro* model of ischemic stroke.[31] These studies suggest that compounds endogenous to cinnamon may be beneficial to Alzheimer's disease and/or stroke and may lead to the discovery of other potential therapeutics.

Clinical Trials

Following the initial study of Khan and colleagues[32] reporting statistically and clinically significant effects of cinnamon on glucose and lipid metabolism of people with T2DM, there have been several studies involving whole cinnamon or aqueous cinnamon extracts on healthy normal subjects with a mean lean body mass less than 25, subjects with metabolic syndrome, subjects with T2DM, and women with polycystic ovary syndrome (PCOS), which is also associated with insulin resistance (**Table 1**).

There have been five studies involving cinnamon effects on healthy, normal subjects with normal glucose tolerance (**Table 1**). Four of the studies reported beneficial effects of cinnamon,[33–36] and a related study, designed to determine the absorption and excretion of oxalate from cinnamon and turmeric, reported no effects on fasting glucose but also no effects on oxalate absorption and excretion.[37] While the oxalate content of cinnamon is high, it is insoluble and is absorbed very poorly.

Seven lean healthy male volunteers, aged 26 ± 1 year, with a body mass index of 24.5 ± 0.3 kg/m2, underwent three oral glucose tolerance tests supplemented with a 5-gram placebo, 5-grams of cinnamon, or 5 grams of cinnamon taken 12 hours before the oral glucose tolerance test in a randomized crossover design.[33] Cinnamon ingestion reduced total plasma glucose responses to oral glucose ingestion, as well as improving insulin sensitivity. Cinnamon effects were significant when taken with the glucose solution, and effects were still significant if cinnamon was taken 12 hours before the glucose.[33] In a follow-up study by the same group, 8 healthy male volunteers underwent two 14-day interventions involving cinnamon or placebo supplementation, 3 g/day, compared with a 5-gram cinnamon bolus in the earlier study.[34] Cinnamon ingestion reduced the glucose response to an oral glucose challenge on days 1 and 14. Cinnamon ingestion also reduced insulin responses to glucose on day 14, as well as improving insulin sensitivity on day 14. The addition of cinnamon (6 grams) to rice pudding significantly delayed gastric emptying and lowered the postprandial glucose response in 14 healthy subjects in a crossover trial.[35] Reductions in postprandial blood glucose concentrations were much more noticeable and pronounced than lowering of the gastric-emptying rate. In a follow-up study involving 15 subjects, 1 and 3 grams of cinnamon had no significant effects on gastric-emptying rate, satiety, glucose, glucose-dependent insulinotropic polypeptide, or ghrelin response. However, the insulin response at 60 minutes and the area under the curve were significantly lower after the ingestion of rice pudding with 3 grams of cinnamon. The change in the glucagon-like peptide-1 (GLP-1) response and the change in the

maximum concentration were both significantly higher after the ingestion of rice pudding with 3 grams but not with 1 gram cinnamon. The ingestion of 3 grams of cinnamon with rice pudding reduced postprandial serum insulin and increased GLP-1 concentrations without significantly affecting blood glucose, glucose-dependent insulinotropic polypeptide, ghrelin concentrations, satiety, or gastric-emptying rate in healthy subjects. The combined results of the two studies indicate a relationship between the amount of cinnamon consumed and the decrease in glucose and insulin concentrations and related effects.[35,36]

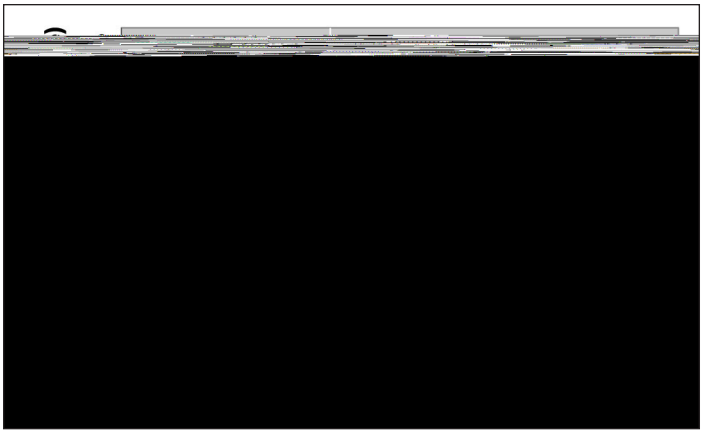

Figure 2. Beneficial effects of an aqueous extract of cinnamon on glucose, blood pressure, percent body fat, and lean mass of subjects with metabolic syndrome.[38] FBG, fasting blood glucose; SBP, systolic blood pressure.

In a study involving 22 subjects with metabolic syndrome, subjects were divided into two groups and given either 500 mg/day of an aqueous extract of cinnamon (Cinnulin PF, Integrity Nutraceuticals, Spring Hill, TN) or a placebo for 12 weeks. Subjects in the group receiving capsules containing the aqueous extract of cinnamon displayed decreased fasting blood glucose, decreased systolic blood pressure, and increased lean mass compared with the placebo group. There was also significantly decreased body fat in the cinnamon-treated group (**Figure 2**).[38]

Roussel and associates[39] found a significant positive correlation between plasma glucose levels and plasma malondyaldehyde (MDA), a measure of lipid peroxidation, in people with metabolic syndrome. Oxidative stress plays an important role in the development of diabetes and cardiovascular diseases.[40] The improvement of impaired fasting glucose as a result of cinnamon was correlated with the antioxidant effects of cinnamon supplementation assessed by plasma MDA, sulfhydryl groups, and plasma antioxidant status evaluated using ferric-reducing antioxidant power (FRAP).[39] A significant positive correlation between plasma glucose levels and plasma MDA confirmed a previous study showing that plasma glucose levels played a role in determining oxidative status.[41] In subjects with metabolic syndrome, plasma MDA levels were reduced by the aqueous extract of cinnamon, indicating decreased lipid peroxidation, whereas plasma sulfhydryl groups were increased, indicating a protection of antioxidant sulfhydryl groups against oxidation.[39] In the group receiving cinnamon, plasma sulfhydryl groups were increased after 12 weeks of supplementation, suggesting that cinnamon acts in protecting both lipids and proteins against oxidation. In parallel, the FRAP, which is a measure of the total antioxidant capacity of plasma, was increased, thereby providing a contributory factor to the protective effects of cinnamon supplementation.[39]

In addition to the initial study of Khan and colleagues[32] demonstrating that cinnamon improves blood glucose, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol in people with T2DM, Mang and associates[42] also reported decreased fasting glucose in subjects with T2DM consuming 3 g/day of an aqueous extract of cinnamon. Stoecker and colleagues[43] also reported decreased fasting and postprandial glucose due to CE (CinSulin, Tang-An, Beijing, China) in a trial involving 137 patients being treated for T2DM (**Table 1**). Crawford[44] reported that cinnamon lowered hemoglobin A1c (HbA1c 0.83%) compared with usual care alone (0.37%) in a study involving 109 patients with T2DM. Subjects in the treatment group had a baseline HbA1c of 8.47 ± 1.8% and 8.28 ± 1.3 in the control group. The study attempted to replicate conditions found in primary care, where patients often have medication, diet, and lifestyle changes. There were no restrictions on participation other than pregnancy, age younger than 18 years, or cinnamon allergy. The authors noted in the discussion of the study that a reduction in HbA1c from 7.9 to 7% lowers the risk of macrovascular disease 16%, retinopathy 17–21%, and nephropathy 24–33%[45]; thus, a drop of 0.83% observed in their study might be expected to yield similar reductions in morbidity.[44] Fairman and Curtiss[46] evaluated the study of Crawford[44] and concluded that the effects of supplemental cinnamon on HbA1c values were only slightly less than the placebo-adjusted reductions reported for two popular drugs, sitagliptin and saxagliptin, used in

the treatment of T2DM. However, cinnamon is without known side effects and can be used to treat more than 25 times as many patients for the same amount of money.[46]

Blevins and colleagues[47] also measured HbA1c in 43 subjects with T2DM but did not observe improvements in HbA1c due to cinnamon. However, the HbA1c levels were 7.2 and 7.1% at the onset of the study, which are near the goal levels for HbA1c, and values would not be expected to decrease further, as subjects were in good control at the onset of the study. Suppapitiporn and associates[48] also reported no significant effects on HbA1c; however, the proportion of patients achieving HbA1c <7 was greater (35% vs 15%) in the group receiving cinnamon compared to the control group.

Polycystic ovary syndrome is one of the most common endocrinopathies among women of child-bearing age, affecting 5–10% of the population.[13] Insulin resistance and compensatory hyperinsulinemia are present in 50–70% of the women with PCOS and may be as high as 95% in overweight women. Excess insulin secretion may also be implicated in the increased metabolic and cardiovascular risks reported in this disorder. Because insulin-sensitizing agents such as chromium and troglitazone showed beneficial effects in the treatment of PCOS, it was postulated that the insulin-potentiating, water-soluble polyphenol compounds found in cinnamon may also be beneficial for women with PCOS.[13] During an 8-week treatment period, an oral cinnamon extract (Cinnulin PF, 1 g/day) resulted in a significant reduction in fasting glucose, as well as in insulin resistance. Oral glucose tolerance tests also showed a 21% reduction in mean glucose and an increase in Matsuda's insulin sensitivity index. The cinnamon extract improved insulin resistance in women with PCOS to that of age-matched control women.

Five other studies reported no significant effects of cinnamon (**Table 1**). The majority of studies not reporting beneficial effects of cinnamon or the aqueous extract of cinnamon involved subjects taking adequate amounts of glucose-lowering drugs to control blood glucose and maintain normal HbA1c levels; based on these studies, a meta-analysis reported no effects of additional cinnamon.[49] However, if subjects are taking adequate amounts of glucose-lowering drugs at the onset and throughout the study, it is not surprising that a nutraceutical does not have additional effects. Similarly, additional amounts of glucose-lowering drugs would also likely not show significant additional effects if glucose-related variables are well controlled. One study that did not report beneficial effects involved adolescents with type 1 DM, who would not be expected to respond to cinnamon.[50] In all of the human studies involving cinnamon or aqueous extracts of cinnamon, there have been no reported adverse effects and subjects with the poorest glycemic control appeared to benefit the most.[3]

Summary

In summary, cinnamon and components of cinnamon have been shown to have beneficial effects on essentially all of the factors associated with metabolic syndrome, including insulin sensitivity, glucose, lipids, antioxidants, inflammation, blood pressure, and body weight. In addition, factors associated with related diseases, including Alzheimer's disease, stroke, and cancer, have also been shown to be improved by cinnamon and its components in *in vitro* studies.

Table 1.
Summary of Human Studies Involving Cinnamon or Its Components

Year/reference	# of subjects/ type/time	Significant effects	Cinnamon/medications	Comments
2003/Khan *et al.*[32]	60/T2DM/40 days	Decreased fasting glucose, cholesterol, triglycerides and low-density lipoprotein; increased high-density lipoprotein	*Cinnamomum cassia* (1, 3, and 6 g/day)/sulfonylurea drugs	Similar effects with 1–6 g cinnamon, significant effects even after 20 days of washout
2006/Ziegenfuss *et al.*[38]	22/metabolic syndrome/42 days	Decreased fasting glucose, systolic blood pressure, % body fat, increased lean body mass	Cinnamon extract (Cinnulin PF, 500 mg/day)/no known medications	No medications for glucose

Continued →

Table 1. Continued

Year/reference	# of subjects/ type/time	Significant effects	Cinnamon/medications	Comments
2006/Suppapitiporn *et al.*[48]	60/T2DM/72 days	No significant effects	*C. cassia* (1.5 g/day)/ metformin or sulfonylurea	Number of subjects with decreases in HbA1c was more than double in the cinnamon group but decreases were not significant (35% vs 15%)
2006/Mang *et al.*[42]	79/T2DM/120 days	Decreased fasting glucose	Aqueous cinnamon extract powder (3 g/day)/oral antidiabetics or diet, no insulin	Decrease in plasma glucose correlated significantly with initial baseline glucose
2006/Vanschoonbeek *et al.*[51]	25/post-menopausal with T2DM/42 days	No significant effects	*C. cassia* (1.5 g/day)/sulfonylurea derivatives with or without metformin derivatives	Subjects under good glucose control, 7.4 ± 0.3 or better
2007/Solomon & Blannin[33]	7/healthy, lean (BMI 24.5 ± 0.3) young (26 ± 10), male/12 hours	Decreased total plasma glucose response; improved oral glucose tolerance and insulin sensitivity	*C. cassia* (5 g with glucose)/ none	Response in healthy normal subjects after 12 hours and if given simultaneously with glucose tolerance test
2007/Wang *et al.*[13]	15/polycystic ovary syndrome/48 days	Increased insulin sensitivity	Cinnamon extract (Cinnulin PF, 1 g/day)/no oral hypoglycemic or insulin-sensitizing drugs	Insulin sensitivity in women with PCOS improved to levels of women without PCOS
2007/Blevins *et al.*[47]	43/T2DM/3 months	No significant effects	*C. cassia* (1 g/day)/several, including 75% taking metformin, 33% taking thiazoledinedione, and 50% taking hydroxymethylglutaryl-coenzyme A reductase inhibitors	Subjects were taking several drugs and mean BMI was over 32
2007/Hlebowicz *et al.*[35]	14/healthy normal, BMI 22.6 ± 2.2/ simultaneously with food	Reduced postprandial glucose and decreased gastric-emptying rate	Cinnamon (6 g with test meal)/no known medications	Decreases in glucose could only be partly explained by gastric-emptying rate
2007/Altschuler *et al.*[50]	72/adolescents with type 1 diabetes	No significant effects	Cinnamon (1 g/day)/insulin	Cinnamon is not a replacement for insulin
2008/Tang *et al.*[37]	11/healthy normal/4 weeks	No significant effects	Cinnamon (3 g)/no known medications	Study was designed to study oxalate excretion. No postprandial measurements.
2009/Roussel *et al.*[39]	22/impaired fasting glucose/12 weeks	Improved fasting glucose and antioxidant variables	Cinnamon extract (Cinnulin PF, 500 mg/day)/no known medications for glucose	Improvements in antioxidants related to decreases in fasting glucose
2009/Solomon and Blannin[34]	8/healthy normal/14 days	Improved glucose tolerance and insulin sensitivity	*C. cassia* (3 g/day)/none	Cinnamon effects lost when cinnamon discontinued
2009/Hlebowicz *et al.*[36]	15/healthy normal/ simultaneously with food	3 g reduced postprandial insulin and increased GLP-1	Cinnamon (1 and 3 g with test meal)/no known medications	Dose response with cinnamon with the two studies
2009/Crawford[44]	109/T2DM; HbA1c >7.0/90 days	Decreased HbA1c	Cinnamon (1 g/day)/insulin and/or varied medications	Patients were a cross section of people treated for T2DM
2010/Stoecker *et al.*[43]	137/T2DM/2 months	Decreased fasting and postprandial glucose	Cinnamon extract (CinSulin, 500 mg/day)/insulin and/or varied medications	Patients were a cross section of people treated for T2DM

[a] BMI, body mass index; HbA1c, hemoglobin A1c.

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