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Review Article

The Effects of Cinnamon on Diabetes Mellitus: A narrative review

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Abstract
The increasing prevalence of diabetes mellitus is the main cause of morbidity and mortality worldwide. Despite advances in drug management of diabetes, adverse effects of drugs have made scientists look towards hypoglycemic agents of plant origin. *Cinnamon* (*Cinnamomum sp*) has been suggested to help patients with type 2 diabetes mellitus. Some randomized controlled trials that evaluate the effects of cinnamon on diabetes show conflicting results. The present review summarizes the last known abilities of cinnamon in improving complications of diabetes and constructs the theoretical mechanism by which cinnamon could tackle diabetes.
Keywords: Cinnamon, Diabetes mellitus, Lipid, Glycemic control

Introduction

Diabetes Mellitus
The term diabetes mellitus (DM) describes a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism due to defects in insulin secretion, insulin action, and/or both. The number of people worldwide with diabetes has risen from 108 million (4.7%) in 1980 to 422 million (8.5%) in 2014, a majority of whom (>90%) suffer from type 2 diabetes (T2DM) characterized by insulin resistance, hyperinsulinemia, β-cell dysfunction, and subsequent β-cell failure (1, 2). The complications of effects DM include long-term damage, dysfunction, and failure of various organs, e.g. eyes, kidneys, nerves, and heart, which can increase the overall risk of premature mortality (3). Some clinical studies conducted in recently showing potential links between herbal therapies and improved blood glucose control, which have led to an increase in diabetic people using these more 'natural' ingredients to help manage their condition (4, 5). Nowadays data shows that lots of complementary and alternative medicines (CAMs) are being used with varying successes, so that diabetic patients are 1.6 times more likely to use CAMs than non-diabetics for a host of reasons such as high-cost of medicines and strong beliefs on the effectiveness of CAMs (6, 7). Recent estimates show that over 80% of people living in developing countries depend on CAMs for treatment of various health conditions (8).

Cinnamon
Some botanical products can improve glucose metabolism and the overall condition of individuals with diabetes not only by their hypoglycemic effects but also by improving lipid metabolism, antioxidant status, and capillary function (9). A number of medicinal/culinary herbs have been reported to yield hypoglycemic effects in patients with diabetes, including bitter melon, Gymnema, Korean ginseng, onions, garlic, flaxseed meal, and specific nutrients including α-lipoic acid, biotin, carnitine, vanadium, chromium, magnesium, zinc, and vitamins B3, E, and K (10). *Cinnamomum cassia*, also known as *C. arromaticum*, Chinese cinnamon or Chinese cassia, has a long history of use in traditional medicine. It comes from the inner bark of tropical evergreen cinnamon trees (11) and contains several bioactive compounds with potential health effects. *C. cassia* L. has been known for its benefits in glucose intoler-

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ance and diabetes, antimicrobial activity and treatment of various cancer cell lines (11, 12). The average daily intake (ADI) of cinnamaldehyde permitted by The Food and Drug Administration (FDA) and World Health Organization (WHO) for an adult male is 1.25mg/kg (13). There are two varieties of cinnamon; *C. Zeylanicum* (Ceylon cinnamon) from Sri Lanka and *C. cassia* (Cassia "Chinese" Cinnamon) from either China or Indonesia (14). The bioactive compounds responsible for the putative effects are still under investigation, making it difficult to establish a clear relationship between diabetes and cinnamon. A statistical study on 295 Traditional Chinese Medicine (TCM) prescriptions shows that the bark of *C. cassia* has been used for the treatment of diabetic nephropathy since ancient times. Many original articles and meta-analyses investigating the effects of cinnamon on diabetes have documented contradictory results. Considering the popularity of cinnamon consumption in people with diabetes, the mechanisms of cinnamon effects on diabetes and its complications must be clarified.

Materials and Methods

To generate comprehensive evidence-based database for the probable underlying mechanisms of this herb affecting diabetes, studies published since 2006, were reviewed and summarized in this review. A literature search was performed to identify all randomized clinical trials (RCTs) in PubMed, Web of Science, Science Direct, and Google Scholar from January 1, 2006, through September 15, 2017, using the following search terms: Cinnamon, blood glucose, blood sugar, metabolic syndrome, diabetes, lipid profile, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), clinical trial, RCTs, humans, and English. MeSH terms "Cinnamomum" with "Cassia" were employed to explore the databases. All the studies exploring the effects of this herb were included regardless of the outcome. This study outlines the published uses of this herb to treat diseases to clarify underlying mechanisms if available.

Result

A total of 17 RCTs that evaluated cinnamon supplementation in diabetic individuals are listed in Table-1. Based on conducted studies, the possible mechanisms of cinnamon effects on diabetes are elaborated below.
One of the important issues that lead to complications in diabetes is increased blood sugar. One way to reduce the complications of diabetes is reduced blood sugar; various studies have been investigated means of improv fasting blood glucose, postprandial blood glucose, insulin secretion or insulin sensitivity. Most studies were investigating cinnamon effects on diabetes focus on its glycemic modifications. According to articles documented to date (Table-2), cinnamon can lower fasting blood sugar (FBS). The dose and duration of cinnamon supplementation in experiments varies between 0.5 to 6 gr/d and 1 to 4 month respectively. Supplementation of cinnamon with the dose of 500 mg/d for three months up to 3gr/d for four months has been found to cause a significant reduction in FBS (15, 16). Sengsuk *et al.*

Table 1. Articles included in the review

Author	Year	Study type	Subjects	Sample size		Gender	Cinnamon dose (gr)	Duration (month)	Ref
				Case	Control				
Mang *et al*.	2006	RCT	Diabetic (2)	33	32	Both	3	4	(15)
Ziegenfuss *et al*.	2006	RCT	Prediabetic	12	10	Both	0.5	3	(16)
Van-schoonbeek *et al*.	2006	RCT	Diabetic (2)	13	12	Women	1.5	1.5	(17)
Blevins *et al*.	2007	RCT	Diabetic (2)	29	28	Both	1	3	(18)
Roussel *et al*.	2009	RCT	IGT	11	11	NM	0.5	3	(19)
Crawford *et al*.	2009	RCT	Diabetic (2)	46	43	Both	1	3	(20)
Akilen *et al*.	2010	RCT	Diabetic (2)	30	28	Both	2	3	(21)
Radhia khan *et al*.	2010	RCT	Diabetic (2)	7	7	Both	1.5	1	(22)
Haghighian *et al*.	2011	RCT	Diabetic (2)	30	30	Both	1.5	2	(23)

Continue in next page

Continue of Table 1. Articles included in the review

Vafa *et al.*	2012	RCT	Diabetic (2)	22	22	Both	3	2	(24)
Lu *et al.*	2012	RCT	Diabetic (2)	23 23	20	Both	0.12 0.36	3	(25)
Hosseini *et al.*	2013	RCT	Diabetic (2)	25	25	NM	3	2	(26)
Wickenberg *et al.*	2014	RCT	IGT	9	8	Both	1	3	(27)
Lio *et al.*	2015	RCT	Over-weight Pre-dia-betic	26	26	Both	0.5(cinnamon)+0.7 (chromium& car-nosine)	4	(28)
Richard *et al.*	2015	RCT	Diabetic (2)	64	73	Both	0.5	2	(29)
Sengsuk *et al.*	2016	RCT	Diabetic (2)	49	50	Both	0.5	2	(30)
Sahib *et al.*	2016	RCT	Diabetic (2)	13	12	Both	1	3	(31)

RCT: Randomized clinical trial; **IGT:** Impaired Glucose Tolerance; **NM:** Not mention

(30) in a randomized, double-blind, placebo-controlled trial in 2016 investigated the effect of cinnamon supplementation on glucose, TG, HDL-C levels, TG/HDL-C ratio, blood pressure (BP), and estimated glomerular filtration rate (eGFR) in 99 diabetic patients. All participants received 0.5 gr/d cinnamon or placebo capsule for two months, and at the end of the study, FBS, HbA1C, TG, TG/HDL-C ratio, and BP were significantly decreased whereas HDL-C and eGFR levels were significantly increased in the cinnamon supplementation group (30). Al Jamal *et al.* (2009) studied the effects of cinnamon supplementation with a dose of 6 gr on blood glucose and lipid levels in 75 diabetic patients for one month (32). Mean value of fasting blood glucose level decreased from 210.5 mg/dl to 120.5 mg/dl, that of TG and total cholesterol from 205.5 mg/dl and 290 mg/dl to160.2 mg/dl and 215.4 mg/dl, respectively (32). On the other hand, some studies observed no significant effects of cinnamon on blood sugar. Blevins *et al.* (18) in a study of 58 patients with type 2 diabetes showed no significant changes in FBS, HbA1c and lipid profiles. The dose of cinnamon used for the study was 1 gr, and he continued supplementing for three months (18). HbA1c is increasingly being used to evaluate hyperglycemia via the levels of glycated proteins (33, 34), which contribute to diabetic complications and overall morbidity (35, 36). Results of evaluating HbA1c were inconsistent, since seven articles showed decreased HbA1c, while five articles reported no significant improvement. Despite a known relationship ($r = 0.90$) between plasma glucose and HbA1c, there are genetic differences in glycation. Hence, if cinnamon reduces FBG, the effect upon HbA1c may be less in some individuals (37), because only one third or less of the variance in HbA1c levels in nondiabetic subjects can be explained by differences in blood glucose levels (38), which may explain the reduction in FBG but not in HbA1c as reported by Lio and Mang (15, 28). Crawford *et al.* in 2009 randomized 109 type 2 diabetics (HbA1C >7.0) to a cinnamon group (1g/d) and placebo group for 90 days (20). He found that cinnamon lowered HbA1C by 0.83% compared to usual care per se (in itself) (0.37%) (20). The probable explanations for the ineffectiveness of cinnamon may be the small sample size of studies (27, 39). Another hypothetical reasoning in some RCTs that observed no improvement of cinnamon supplementation in FBS or HbA1c levels was the baseline values of these parameters. The baseline FBS level in Blevins *et al.* study, which documented no results from 1 gr cinnamon supplementation for one month (18) was 139 mg/dl while in the Sahib study (31) that used the same dose and duration, it was more than 190 mg/dl. In those studies, the same situation was true for HbA1c levels. Increasing evidence shows that insulin resistance may be the common etiological factor for the individual components of the metabolic syndrome that plays a key role in the development of diabetes (40). Mechanisms by which cinnamon or cinnamon extract supplements lower glucose, insulin, and insulin resistance are not yet completely clear, but food composition analyses, in vitro, animal, and human studies suggest some possibilities. Several steps in insulin signaling pathways are affected by cinnamon extracts. Cinnamon has demonstrated qualities that enhance glucose uptake by activating insulin receptor kinase activity, autophosphorylation of the insulin receptor, and glycogen synthase activity, in vitro and in vivo (41, 42). However, as shown in Table-2 only Richard *et al.* in 2016 with supplementation of 500 mg of water-extract of cinnamon for two months found a reduction in fasting insulin, glu-

Table 2. Studies evaluating cinnamon effects on glycemic factors

Parameters Reference	Author	FBS	HbA1C	Fasting Insulin
(15)	Mang, *et al*.	↓	NS	
(16)	Ziegenfuss *et al*.	↓		
(17)	Van-schoonbeek *et al*.	NS	NS	NS
(18)	Blevins *et al*.	NS	NS	NS
(19)	Roussel *et al*.	↓		
(20)	Crawford *et al*.		↓	
(21)	Akilen *et al*.	↓	↓	
(22)	Radhia khan *et al*.	↓		
(23)	Haghighian *et al*.	↓		
(24)	Vafa *et al*.	↓	↓	NS
(25) 120 mg	Lu *et al*.	↓	↓	
(25) 360 mg	Lu *et al*.	↓	↓	
(26)	Hosseini *et al*.	↓		
(27)	Wickenberg *et al*.	NS	NS	NS
(28)	Lio *et al*.	↓	NS	NS
(29)	Richard *et al*.	↓		↓
(30)	Sengsuk *et al*.	↓	↓	
(31)	Sahib *et al*.	↓	↓	

NS: Not Specified; **FBS**: Fasting blood sugar

cose, total cholesterol, and LDL cholesterol and enhanced insulin sensitivity in subjects with elevated blood glucose (29). Vanschoonbeek *et al*. (2006) studied 25 postmenopausal patients with type 2 diabetes, who participated in a 6-weak intervention during that they were supplemented with either cinnamon (*C. cassia*, 1.5 g/d) or a placebo for six weeks. Authors concluded that cinnamon supplementation (1.5 g/d) does not improve whole-body insulin sensitivity or oral glucose tolerance and does not modulate blood lipid profiles in postmenopausal patients with type 2 diabetes (17). Altschuler *et al*. (2007), Wickenburg *et al*. (2014), and Lio *et al*. (2015) found no significant improvement in insulin sensitivity following supplementation with cinnamon in diabetic patients too (27, 28, 43). It is noteworthy that the effect of cinnamon on blood glucose control is most likely dependent on the form of cinnamon used for patients. Furthermore, different extraction methods might affect the efficacy of cinnamon. It has been shown that the water-soluble polyphenol polymers from cinnamon could increase insulin-dependent glucose metabolism markedly in vivo as well as lead to an elevated antioxidant activity (11). The aqueous extract from cinnamon was also able to enhance insulin signaling by inhibiting protein-tyrosine phosphatase 1B, a phosphatase that negatively regulates insulin action (44). Diets with a low glycemic index (GI) and a low glycemic load diets are associated with a reduced risk of T2DM and heart disease, comparable with the reduction in risk observed with high intakes of dietary fiber and whole-grain products. Measurements of the blood glucose response two hours after eating have been shown to be a better predictor of mortality from cardiovascular disease than fasting blood glucose (45). The importance of postprandial glycemia regulation is based on the data of epidemiological studies, which have demonstrated that postprandial hyperglycemia is a predictor of diabetes and cardiovascular events (46, 47). The postprandial state can stimulate the reactive oxygen species (ROS) production leading to an oxidative stress status, a status that involves a molecular mechanism for the development of different complications associated with hyperglycemia (48, 49). Moreover, postprandial oxidative stress can be accompanied by postprandial inflammation and endothelial dysfunction as reported by Ceriello *et al*. (50). Gastric emptying, together with other factors, regulates the postprandial blood glucose response, and a reduction in the gastric emptying rate (GER) leads to a lower postprandial blood glucose concentrations. Gastrointestinal hormones, such as insulin-tropic polypeptide (GIP), glucagon-like peptide 1 (GLP-1), and ghrelin are shown to have effects on postprandial glucose, insulin secretion and gastric emptying rate (51). Research in both healthy individuals and those with T2DM have reported that cinnamon enhances glucose transport and utilization in the body, ultimately leading to improved glucose metabolism. Some cross-over RCTs have evaluated cinnamon effects on gastric emptying, intestinal hormones and postprandial glucose in healthy people. Hlebowicz *et al*. in 2007 found that intake of 6 g cinnamon with rice pudding reduces postprandial blood glucose and delays gastric emptying without affecting satiety; it also lowers the postprandial glucose response, a change that is, at least partially, explained by a delayed GER (52); the same author in 2009 studied the effect of 1 and 3 g cinnamon on GER, postprandial blood glucose, plasma concentrations of insulin and incretin hormones (glucose-dependent GIP and GLP-1), the ghrelin response, and satiety in 15 healthy subjects; finally, addition of 1 or 3 g cinnamon reduced postprandial serum insulin and increased GLP-1 concentrations without significantly affecting blood glucose, GIP, the ghrelin concentration, satiety, or GER (53), indicating that it might have the same effect on diabetic patients as well, which must clarify by studies assessing these factors. Generally, we can say that one of the major mechanisms by which cinnamon could help DM is its glucose-lowering effects found in the trails mainly through decreasing FBS and HbA1c but not insulin capacity nor sensitivity.

Lipid profile

DM produces disturbances in the lipid profiles making the cells more susceptible to lipid peroxidation (54). T2DM is associated with hyperlipidemia (elevated TG, decreased HDL and increased LDL levels) (55). Furthermore, in addition to oxidation of lipoproteins, hyperglycemia may lead to glycation and hence the formation of pro-atherogenic glycoxidation products (32, 56). The effects of cinnamon on lipid profiles are shown in Table-3, and the results of studies in this area are contradictory. Lu *et al*. in 2012 performed a randomized, double-blinded clinical study to analyze the effect of cinnamon extract on HbA1c, FBG, and lipid profiles. A total of 66 patients with T2DM were recruited and randomly divided into three groups: placebo, low-dose and high-dose groups that the two latter groups supplemented with cinnamon extract at 120 and 360 mg/d, respectively. Patients in all three groups took gliclazide throughout the three months of the study. Both HbA1c and FBS levels were significantly reduced in patients in the low- and high-dose groups. Blood TG levels were also significantly reduced in the low-dose group. Blood levels of total cholesterol, HDL cholesterol, LDL cholesterol, and liver transaminase remained unchanged in the three groups (25). On the other hand, the Khadem Haghighian *et al*. study of who 60 diabetic patients (30 case-30 control) received 1.5 gr/d cinnamon powder for 2 months, showed significant reductions in TG (32%), T-c (26%) and LDL-c (11%), but improvement in HDL-c (3%) was not significant (23). Lio *et al*. in a 4-month treatment with the dietary supplement of 500 mg cinnamon with 700 mg chromium and carnosine for 52 overweight and obese pre-diabetic patients (26 case-26 control) found decreased FPG (Fasting Plasma Glucose) compared to placebo (-0.24±0.50 vs +0.12±0.59 mmol/L, respectively), without detectable significant changes in HbA1c that was thought to be because of low base levels of HbA1c; insulin sensitivity markers, plasma insulin, plasma lipids, including TG, T-c, HDL-c and LDL-c and inflammatory markers (Adiponectin, IL-6, and protein kinase B) did not differ between treatment groups. They concluded that subjects with a higher FPG level and a milder inflammatory state at baseline benefited most from the dietary supplement (28). It has been indicated that lipid aggregation in visceral tissues such as skeletal muscles and adipose tissue can lead to insulin resistance, blood glucose elevation and consequently impairment in glucose tolerance and DM (57-59). On the other hand, insulin resistance leads to the overproduction of VLDLs and reduced lipoprotein lipase activity, thereby resulting in dyslipidemia (60). Therefore, achieving better glycemic control may improve lipid profiles (61, 62). Only three articles in this review, evaluate the effects of cinnamon on VLDL in diabetic patients; of these Mang *et al*. (15) and Ziegenfuss *et al*. (16) by supplementation with 3gr (4 months) and 0.5 gr (3 months) respectively, found no significant changes in VLDL values. Hosseini *et al*. in 2013 in a randomized double-blind intervention examined the effects of 3 gr cinnamon as capsulated powder on 50 individuals with T2DM for 2 months, After which biochemical indices of FBS (10.7 %) and lipid profiles (TG: 14.5%, total-c: 10.3%, VLDL: 15.3%) but not LDL-c improved significantly (26). Based on data available the effects of cinnamon on lipid profiles have not been confirmed as most of them found no signifi-

Table 3. studies evaluated cinnamon effects on lipid profiles.

Parameters Reference		Author	TG	T-Chol	HDL-C	LDL-C	VLDL
(15)		Mang *et al*.	NS	NS	NS	NS	NS
(16)		Ziegenfuss *et al*.	NS	NS	NS	NS	NS
(17)		Vanschoonbeek *et al*.	NS	NS	NS	NS	
(18)		Blevins *et al*.	NS	NS	NS	NS	
(21)		Akilen *et al*.	NS	NS	NS	NS	
(22)		Radhia khan *et al*.	↓	↓	NS	NS	
(23)		Haghighian *et al*.	↓	↓	NS	↓	
(24)		Vafa *et al*.	↓	NS	NS	NS	
(25)	120 mg	Lu *et al*.	↓	NS	NS	NS	
	360 mg	Lu *et al*.	NS	NS	NS	NS	
(26)		Hosseini *et al*.	↓	↓	↑	NS	↓
(27)		Wickenberg *et al*.	NS	NS	NS	NS	
(28)		Lio *et al*.	NS	NS	NS	NS	
(29)		Richard *et al*.	↓	↓	↑	↓	
(30)		Sengsuk *et al*.	↓		↑		

NS: Not Specified

cant improvement through cinnamon supplementation; an explanation for this might be the low baseline values of lipid profiles or the different type cinnamon used. Implementation a study with cinnamon supplementation on a population with T2DM, who suffer from hyperlipidemia, might be beneficial for concluding in this area of research.

Antioxidant and anti-inflammatory factors

Free radicals are mainly ROS, including superoxide free radicals, hydrogen peroxide, singlet oxygen, nitric oxide (NO) and proxy nitrite (5) that may lead to serious chronic diseases such as DM, cataract, cancer, and neurodegenerative and cardiovascular diseases (63). Oxidative stress can trigger the onset of DM by decreasing insulin sensitivity and by damaging the b-cells of the pancreas; ROS can penetrate through b-cell membranes and destroy those cells. It also plays an important role in the activation of other pathogenic pathways involved in diabetic complications including elevated polyol pathway activity, nonenzymatic glycation, advanced glycation end-products (AGE) formation, protein kinase C (PKC) activation, polyol flux, and hexosamine formation, which in turn leads to the development of micro- and macrovascular complications such as myocardial injury, retinopathy, nephropathy, and neuropathy (64). The possible mechanisms of oxidative stress in developing these complications include glucose autoxidation, decreased tissue concentration of low molecular weight antioxidants like glutathione and vitamin E, and deteriorated activation of antioxidant defense enzymes such as catalase and superoxide dismutase (SOD) (29); it also inactivates two critical anti-atherosclerotic enzymes, endothelial nitric oxide synthase, and prostacyclin synthase (65). Based on epidemiological studies, diabetic mortalities can be explained notably by an increase in vascular diseases other than hyperglycemia (66). Different molecular mechanisms associated with hyperglycemia have been identified including 1. increased glucose flux through the polyol pathway (67), 2. Formation of advanced glycation end products (AGE) (67), 3. activation of PKC (67, 68), 4. increased glucose flux through the hexosamine pathway (67), and 5.activation of the 12/15-lipoxygenase (12/15-LO) pathway (69, 70). All of these mechanisms finally lead to increase in superoxide formation; it is believed that in the onset and progression of late diabetic complication, free radicals play a major role, due to their ability to damage lipids, proteins, and DNA (71). Levels of antioxidants such as GSH (Glutathione), vitamin C, and E have been reported to be decreased in patients with diabetes, while levels of some markers of oxidative stress, e.g., oxidized low-density lipoprotein cholesterol is increased (72). Therefore, antioxidants which combat oxidative stress should be able to prevent and repair free radical-induced damage; one of the mechanisms by which cinnamon can have beneficial effects against diabetes is its antioxidant activity. Cinnamon has several compounds that have antioxidant components (12). As shown in Table-4 there are hardly any trials investigating antioxidant and anti-inflammatory effects of cinnamon on diabetic individuals. In 2016, Lio *et al.* evaluated the effects of 4-month treatment with either a 1.2 g/day dietary supplement containing 500 mg cinnamon, 700 mg chromium , and carnosine or a placebo in moderately obese or overweight pre-diabetic subjects and assessed inflammatory markers, e.g., hs-CRP (C-reactive protein), PAI-1 (Plasminogen activator inhibitor-1), and IL-6; these markers, however, did not differ between the treatment groups (28). Sahib *et al*. in 2016 using 1 gr/d cinnamon supplementation for three months found a significant reduction (10.12%) in FBS levels after 6 and 12 weeks of treatment, 10.12 %, and 17.4%, respectively. Meanwhile, glycosylated Hb values declined in the cinnamon treated group by (2.625%) and (8.25%) after 6 and 12 weeks, respectively; however, the reduction was non-significant, compared, to the baseline value. Regarding the oxidative stress markers, levels of serum glutathione showed a highly significant elevation after 12 weeks; malondialdehyde serum level decreased significantly after treatment of diabetic patients with cinnamon after 6 and 12 weeks, compared to the placebo group; however, compared to baseline value, there was a (15%) reduction only after 12 weeks of treatment which was considered highly significant change. Finally, administration of cinnamon to diabetic patients for 12 weeks resulted in an elevation of superoxide dismutase level (31). Inflammatory processes also contribute to insulin resistance (73, 74). Cao *et al.* showed that cinnamon extracts increase tristetraprolin

Table 4. Anti-oxidant and anti-inflammatory effects of cinnamon

Parameters Reference	Author	FRAP	plasma SH groups	MDA	SOD	GPx	GSH	Adiponectin	hs-CRP	PAI-1	IL-6
(19)	Roussel *et al.*	↑	↑	↓	NS	NS					
(28)	Lio *et al.*							NS	NS	NS	NS
(31)	Sahib *et al.*			↓	↑		↓				

NS: Not Specified; **FRAP:** Ferric reducing activity of plasma; **MDA:** malondialdehyde; **Gpx:** glutathione peroxidase; **GSH:** Glutathione; **PAI-1:** Plasminogen activator inhibitor-1

Table 5. Effects of cinnamon on BP

Parameters reference	Author	Blood pressure
(16)	Ziegenfuss *et al*.	↓
(21)	Akilen *et al*.	↓
(39)	Markey *et al*.	NS
(24)	Vafa *et al*.	NS
(27)	Wickenberg *et al*.	NS
(29)	Richard *et al*.	NS
(30)	Sengsuk *et al*.	↓

NS: Not Specified

(TPP) that is an anti-inflammatory protein in mice (75). Taking into account new evidence of these inflammatory effects on diabetes complication, considering cinnamon polyphenol components, it is highly recommended that its effect on diabetes complications be investigated.

BP

As indicated before, T2DM increases cardiovascular disease via hyperglycemia and diabetic atherosclerosis (76); however, effects of cinnamon on cardiovascular deceases is not widely investigated. Seven articles evaluated the effects of cinnamon on BP in diabetic individuals (Table-5). Akilen *et al*. found that mean systolic and diastolic BP (SBP and DBP) reduced significantly 12 weeks after receiving 2 gr/d cinnamon supplementation (SBP: 132.6 to 129.2 mmHg and DBP: 85.2 to 80.2 mmHg)(21). Senguc *et al*. study conducted on diabetic patients, 1 gr/d cinnamon supplementation for three months reduced plasma glucose, HbA1c, TG, TG/HDL-C ratio, and BP and increased HDL-C levels and eGFR in subjects with T2DM (30). Ziegenfuss *et al*. reported that supplementation with water-soluble cinnamon extract (Cinnulin) 500 mg/day significantly reduced FBG (-8.4%), lowered SBP (-3.8%), decreased body fat percentage and increased lean mass (+1.1%) in subjects with pre-diabetes and metabolic syndrome; all these results suggest that the inclusion of cinnamon in the diet of people with type 2 diabetes may reduce the risk factors associated with diabetes and cardiovascular diseases (16). Richard *et al*. examined the effects of a dried water extract of cinnamon in 137 subjects with type 2 diabetes, who received 0.5 gr of cinnamon for 2 months (64 cases, 73 controls) and at the end of the study, cinnamon reduced fasting insulin, glucose, total cholesterol, and LDL cholesterol and enhanced insulin sensitivity in subjects with elevated blood glucose. Whereas no significant improvement was found in systolic or diastolic BP in the cinnamon group (29), the inconsistency in results might be due to baseline BP, cholesterol status and overall condition of individuals. To assess the effects of the cinnamon on BP, factors matched between the case and control groups must be more accurate, and further works with high doses and long-term supplementation are required.

Conclusion

In this review of the anti-diabetic effects of cinnamon and probable underlying mechanisms are discussed. The multiple emerging modes of actions of cinnamon against diabetes demands in vivo experiments and clinical trials. While definitive conclusions cannot be drawn regarding the use of cinnamon as an anti-diabetic therapy probably owing to differences in the population included, dose range, dosage form, treatment duration, confounding concomitant treatments and quality of study design, it does have blood glucose lowering properties and the potential to reduce lipid profiles and oxidant and inflammatory markers. Further studies are needed on dietary factors such as cinnamon involved in the control of glucose homeostasis; hence, the prevention of diabetes complications and ameliorating especially on their anti-inflammatory and anti-oxidant properties.

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Conflict of interest

The authors declare that there is no conflict of interest.

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