REVIEW ARTICLE

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The potential of cinnamon to reduce blood glucose levels in patients with type 2 diabetes and insulin resistance

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Aim: Cinnamon has a long history as an antidiabetic spice, but trials involving cinnamon supplementation have produced contrasting results. The aim of this review was to examine the results of randomized controlled clinical trials of cinnamon and evaluate the therapeutic potential amongst patients with diabetes and insulin-resistant patients, particularly the ability to reduce blood glucose levels and inhibit protein glycation.
Methods: A systematic electronic literature search using the medical subject headings 'cinnamon' and 'blood glucose' was carried out to include randomized, placebo-controlled *in vivo* clinical trials using *Cinnamomum verum* or *Cinnamomum cassia* conducted between January 2003 and July 2008.
Results: Five type 2 diabetic and three non-diabetic studies (total N = 311) were eligible. Two of the diabetic studies illustrated significant fasting blood glucose (FBG) reductions of 18–29% and 10.3% ($p < 0.05$), supported by one non-diabetic trial reporting an 8.4% FBG reduction ($p < 0.01$) vs. placebo, and another illustrating significant reductions in glucose response using oral glucose tolerance tests ($p < 0.05$). Three diabetic studies reported no significant results.
Conclusions: Whilst definitive conclusions cannot be drawn regarding the use of cinnamon as an antidiabetic therapy, it does possess antihyperglycaemic properties and potential to reduce postprandial blood glucose levels. Further research is required to confirm a possible correlation between baseline FBG and blood glucose reduction and to assess the potential to reduce pathogenic diabetic complications with cinnamon supplementation.
Keywords: cinnamon, diabetes, glucose, glycaemic control, insulin sensitivity
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Introduction

Cinnamon is one of the oldest spices used in naturopathic medicine, cited in Chinese books 4000 years ago [1] and traditionally used in Ayurvedic and Chinese medicine to treat diabetes [2]. Interest in this spice has increased since the discovery of its insulin potentiating properties [3] and initial findings illustrating cinnamon's ability to reduce fasting blood glucose (FBG) and plasma lipids [4]. However, subsequent studies have reported conflicting results, questioning the hypothesis that cinnamon can reduce FBG and clouding the potential of a natural remedy for diabetes. Type 2 diabetes is characterized by diminished cellular response to insulin through defects in the insulin signalling pathway resulting in decreased glycogen synthesis and elevated blood glucose. It is proposed that reduced glucose uptake occurs as a result of defects in insulin receptor (IR) binding and cellular phosphorylation [5].

Anderson *et al.* [6] proposed that cinnamon's most active ingredients are A-type doubly linked procyanidin oligomers of the flavonoid catechins/epicatechins. This suggestion is supported by the insulin-like effects of procyanidins illustrating increased glucose uptake in

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diabetic rats via the same mechanism as insulin, and potentially by an additional mechanism in adipose tissue [7]. Kim *et al.* [8] extracted, purified and screened hydroxycinnamic acids in an attempt to identify the active components of *Cinnamomum cassia*. A naphthalenemethyl ester of 3,4-dihydroxyhydrocinnamic acid showed the highest glucose transport activity *in vitro,* and subsequently increased glucose transport through GLUT4 translocation and enhancement of IR ß and IR substrate-1 phosphorylation in adipocytes. Procyanidins have been reported to have varying antihyperglycaemic actions [9–12] and studies have offered varying hypotheses for the action of cinnamon. It has been proposed that at least some of the mechanisms of procyanidin-stimulated glucose uptake are via the same cellular pathways as insulin.

Proposed Cellular Activity of Cinnamon

Results from several *in vitro* experiments [5,6,13] support the proposal that cinnamon polyphenols mimic insulin action through a number of different mechanisms, and report multiple active fractions of cinnamon. Imparl-Radosevich *et al.* [13] illustrated insulin receptor activation with cinnamon extract in rat adipocytes through increasing insulin receptor phosphorylation and decreasing inactivating protein tyrosine phosphatase (PTP-1), overcoming insulin resistance. Cao *et al.* [14] reported higher levels of GLUT4 and IR ß protein, measured with immuno-blotting after treatment with various *C. cassia* fractions in mouse extracts, and Jarvill-Taylor *et al.* [5] reported increased glycogen synthase with decreased glycogen synthase kinase-3 ß activity, resulting in increased glycogen synthesis. All of these actions are recognized insulin responses, decreasing glucose levels through increased cellular utilization and conversion to glycogen.

Yu *et al.* [15] proposed that cytokine inflammation disrupts the action of TUG in fat and muscle cells, decreasing GLUT4 translocation to the cell membrane and reducing insulin action, and Lebrun and Van Obberghen [16] hypothesized that suppressor of cytokine signalling (SOCS) proteins affect insulin signalling through inhibition of tyrosine phosphorylation. Cao *et al.* [14] illustrated increased levels of anti-inflammatory protein tristetraprolin, which reduces proinflammatory cytokine synthesis in adipose tissue and is normally induced by insulin. From these proposed mechanisms, it is suggested that antioxidant fractions in cinnamon could increase glucose utilization by overriding the inflammatory effects present in insulin resistance [17,18]. This may enable GLUT4 translocation by superseding cellular inflammation, and enhance glucose uptake. This hypothesis is dependant upon the active components of cinnamon increasing glucose utilization in the presence of insulin resistance, which has already been illustrated [1,19].

Potential Antihyperglycaemic Mechanisms of Cinnamon

Cinnamon also appears to reduce hyperglycaemia and inflammation through delayed gastric emptying [20], reducing excess postprandial glucose and triglycerides which induce cellular inflammation through increased C-reactive protein and cytokines [21,22]. Flavonoid-suppressed glucose absorption [23] and significant reductions in glycosidase activity [24] with aqueous extracts of *C. cassia* have also been reported, which would reduce circulating glucose and create an antidiabetic effect [25]. These actions may have contributed to the reduced plasma glucose following oral glucose tolerance tests (OGTTs) [19,26], and may be because of the presence of catechin polymers in cinnamon [6,10] or inhibition of intestinal ATP-ase reducing intestinal glucose absorption [27]. In comparison with other flavonoids, epicatechins have illustrated the highest inhibitory action with sodium-independent facilitated glucose uptake [28]. Increased glycogen synthesis has also been reported [14], an action replicated by the epicatechin gallates [11]. However, much of this *in vitro* and animal research may be less relevant when applied to the human *in vivo* population, so our literature search was focused as discussed in the following methodology.

Methods

A systematic electronic literature search was carried out to identify and analyse all relevant literature providing information regarding the antihyperglycaemic effects of cinnamon. To be included in this review, *in vivo* clinical trials had to be randomized, placebo-controlled and conducted between January 2003 and July 2008. Using these criteria, a search of the following databases was conducted:

- All EBM reviews –Cochrane Database of Systematic Reviews, ACP Journal Club, DARE, CCTR, CMR, HTA and NHSEED, Allied and Complementary Medicine
- EMBASE and Ovid MEDLINE(R)
- JAMA, BMJ, Highwire Press and Lancet databases January 2003 to July 2008.

Medical subject headings used for searching were ‘cinnamon’ and ‘blood glucose’. Trials which did not include

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cinnamon studied in isolation or those reporting on other properties of cinnamon were excluded. The literature search was confined to English language articles, but bias was limited where possible, as results from any non-English studies where enough information was available are included in the review [29]. Data from all relevant articles were analysed in detail for participant numbers, population characteristics, methodology, data analysis and results to test the hypothesis that cinnamon may reduce blood glucose, and consider the external validity for the diabetic and insulin-resistant population. Reviews and meta-analyses were also evaluated.

Results

Eight studies (total N = 311) investigating the effect of cinnamon on blood glucose were found. All studies except for one used *C. cassia*; Ziegenfuss *et al.* [30] used a supplement called Cinnulin PF made from *C. burmannii* of the *verum* genus [31] on patients with prediabetes and metabolic syndrome. Five randomized, placebo-controlled trials (two single blind, three double blind) investigate the effect of varying amounts of cinnamon (1–6 g) on plasma glucose in patients with type 2 diabetes [4,29,32–34]; non-diabetic trials used insulin-resistant adults [19], patients with metabolic syndrome [30], and healthy participants [26].

One study involving patients with type 1 diabetes was found, but this study was excluded from systematic review because of differences in methodology and disease etiology. Altschuler *et al.* [35] recruited type 1 diabetic teenagers on insulin therapy, and did not measure blood glucose levels. Differences in disease pathology also make the results less applicable to those with type 2 diabetes and insulin resistance. This study showed no significant effects on HbA_{1c}, although it reported a 39% increase in hypoglycaemic episodes ($p < 0.17$).

Results of the studies on type 2 diabetic patients are summarized in table 3. Khan *et al.* [4] report statistically significant and clinically marked reductions ($p < 0.05$) in FBG (18–29%), total cholesterol (12–26%), low-density lipoprotein (7–27%) and triglycerides (23–30%) with 1–6 g cinnamon. Mang *et al.* [34] report a 10.3% mean reduction in FBG vs. control group (3.37% reduction) following 3 g cinnamon ($p < 0.038$) and illustrate a strong correlation ($r = 0.685$, $p < 0.001$) between baseline and FBG reduction. However, existing literature reviews and a meta-analysis of randomized controlled trials on subjects with diabetes conclude that cinnamon does not significantly reduce FBG or plasma lipids [36,37] and that further research is required [38]. This is supported by other studies illustrating insignificant effects with 1.5 g [29,32] and 1 g of cinnamon [33], although a trend in reduction of either HbA_{1c} or FBG vs. placebo is noted.

Table 4 summarizes the methodologies, measures taken and results of trials using non-diabetic patients. Studies involving subjects with metabolic syndrome (N = 22), insulin-resistant subjects (N = 15), and lean, healthy volunteers undergoing an OGTT (N = 7) all report reductions in FBG or plasma glucose following OGTT with cinnamon supplementation, although studies are likely to be underpowered, and population characteristics and methodology are dissimilar. Solomon and Blannin [26] controlled dietary intake prior to OGTTs, and illustrate a significant 13% reduction ($p < 0.05$) in plasma glucose response and improved insulin sensitivity index ($p < 0.05$) vs. placebo using 5 g of cinnamon. Ziegenfuss *et al.* [30] included food diary analysis in a 12-week intervention, reporting an 8.4% FBG reduction ($p < 0.01$) in patients with metabolic syndrome. Wang *et al.* [19] illustrates FBG reduction of 16.9% ($p < 0.03$) against baseline FBG, although the control group also reduced FBG by 7.7% following 8 weeks with 1 g cinnamon daily. A mean 20.9% reduction in mean glucose levels ($AUC_{glucose}$/120 min) following glucose load ($p < 0.03$) in the cinnamon group is reported, but no OGTT results are included for the control group, reducing the significance of these results. However, improvements in insulin resistance and sensitivity in the cinnamon group became similar to those in a separate control group without insulin resistance ($p < 0.17$).

Discussion

The small number of clinical trials, low population numbers and conflicting results do not allow a definitive conclusion to be drawn regarding the efficacy of *C. cassia* or *C. burmannii* as a treatment for diabetes. However, it is concluded that there are a number of potential mechanisms that might enable cinnamon to reduce hyperglycaemia, and also several factors that appear to affect its efficacy. Differences in research methodologies include variations in baseline FBG, diabetes medication, study duration, dietary control and type of cinnamon used.

Population Characteristics

Age, years since diagnosis and body mass indexes (BMIs) are similar across all participants with type 2 diabetes, and therefore less likely to be heterogeneous factors contributing to contrasting results (table 1).

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Table 1 Summation of population characteristics in cinnamon studies involving participants with type 2 diabetes

Variable	Khan *et al.* 2003, $N = 60$		Mang *et al.* 2006, $N = 65$		Vanschoonbeek *et al.* 2006, $N = 25$		Blevins *et al.* 2007, $N = 57$		Suppapitiporn *et al.* 2006, $N = 60$	
Population numbers in each study arm	Cinnamon	Placebo	Cinnamon	Placebo	Cinnamon	Placebo	Cinnamon	Placebo	Cinnamon	Placebo
	$n = 30$	$n = 30$	$n = 33$	$n = 32$	$n = 13$	$n = 12$	$n = 29$	$n = 28$	Not known	
Men %	50%	50%	63.6%	71.9%	0%		49%		Not known	
Women %	50%	50%	36.4%	28.1%	100%		51%		Not known	
Ethnicity	Ethnicity not noted but recruitment was from Pakistan		German		Ethnicity not noted but recruitment was from Maastrict, The Netherlands		68% Caucasian, 16% Native American, 7% African American, 4% Hispanic, 2% Asian, 3% unknown		Not known	
Time since diagnosis (mean) of diabetes (y)	7.10 ± 3.29	6.73 ± 2.32	7.1 ± 6.2	6.8 ± 4.7	7.6 ± 1.4	7.1 ± 1.6	—		Not known	
Baseline FBG (mmol/L)*	12 ± 1.43	13.76 ± 1.40	9.26 ± 2.26	8.66 ± 1.47	8.37 ± 0.59	8.28 ± 0.33	7.38 ± 0.51	8.04 ± 0.57	8.37 ± 0.59	
Average age (y)	52 ± 5.85	52 ± 6.87	62.8 ± 8.37	63.7 ± 7.17	62 ± 2	64 ± 2	63.6	58	Not known	
Height (m)	—		1.72 ± 0.09	1.73 ± 0 07	1.67 ± 0.02	.65 ± 0 02	—		Not known	
Weight (kg)	—		88.5 ± 19.1	89.9 ± 14.1	85.4 ± 3.6	82.2 ± 4.0	—		Not known	
BMI (kg/m^2)	—		29.6 ± 4.64	30.1 ± 5.22	30.7 ± 1.1	30.1 ± 1.4	32.5 ± 1.7	32.0 ± 1.5	Not known	
Waist circumference (cm)	—		100.5 ± 15.0	102.7 ± 11.2	—		—		—	

Data are means ± standard deviation. N corresponds to the number of participants for which data were available upon completion of each study.

BMI, body mass index; cm, centimetres; kg, kilograms; m, metres; m^2, metres squared; y, years.

*As no dose–response relationship was found between 1, 3 and 6 g in the study by Khan *et al.* [4] population characteristics of each sub-group in this trial are combined here.

Table 2 Summation of methodology used in studies involving patients with type 2 diabetes

Variable	Khan *et al.* 2003, $N = 60$	Mang *et al.* 2006, $N = 65$	Vanschoonbeek *et al.* 2006, $N = 25$	Blevins *et al.* 2007, $N = 57$	Suppapitiporn *et al.* 2006, $N = 60$
Type of trial	Single-blind, randomized, placebo-controlled trial	Double-blind, randomized, placebo-controlled trial	Double-blind, randomized, placebo-controlled trial	Double-blind, randomized, placebo-controlled trial	Single-blind, randomized, placebo-controlled trial
Matched pairs	Matched for age	Not matched	Matched for age, BMI, years since diagnosis, baseline FBG and medication	Stratified by gender and randomized	Not known
Type of cinnamon used	*C. cassia* powder	*C. cassia* aqueous extract	*C. cassia* powder	*C. cassia* powder	*C. cassia* powder
Dose used	1, 3 and 6 g	3 g	1.5 g	1 g	1.5 g
Study duration	40 days intervention 20 days wash-out	4 months	6 weeks	3 months	12 weeks
Dietary control	None mentioned other than participants consumed usual diet	None mentioned	2-day food diary; pre-OGTT exercise control and standardized meal pre-OGTT	Diet monitored with a 3-day food diary	Not known
Diabetes medication taken by participants*	All sulphonylureas	27.7% metformin, 12.3% sulphonylureas,4.6% glinides, 1.5% glitazones, 30.8% combination therapy, 23.1% diet	Sulphonylureas with metformin ($n = 14$, 56%) , metformin ($n = 3$, 12%), thiazolidinediones with/without metformin ($n = 6$, 24%), diet only ($n = 4$, 16%)	$\sim 3/4$ metformin (75%), $> 1/3$ thiazolidinedione (33%) $1/2$ hydroxymethylglutaryl-CoA reductase inhibitor (50%). Diet only: 23% (cinnamon group), 9% placebo group	Sulphonylureas or metformin
Other medication	No other medications taken	49.2% antihypertensive medication 20% dyslipidaemia medication	None reported	55% cinnamon group and 48% placebo group took lipid lowering medication	Not known

Data are means ± standard deviation. N corresponds to the number of participants for which data were available upon completion of each study.

*For consistency and easy reference, the numbers of patients taking different types of medication have also been illustrated as percentages, although Vanschoonbeek *et al.* [32] originally note this information only in patient numbers, and Blevins *et al.* [33] illustrate the fractions only.

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Table 3 Important outcomes in cinnamon studies involving subjects with type 2 diabetes

Results	Khan *et al.* 2003 1, 3 and 6 g	Mang *et al.* 2006, 3g	Vanschoonbeek *et al.* 2006, 1.5g	Blevins *et al.* 2007, 1g	Suppapitiporn *et al.* 2006, 1.5g
FBG (mmol/L)	↓ by 2.9 mmol/L [1 g] ↓ by 2 mmol/L [3 g] ↓ by 3.8 mmol/L [6 g] All $p < 0.05$	↓ by 1.11 mmol/L v baseline $p < 0.001$ v placebo $p < 0.038$	↓ by 0.46 mmol/L $p > 0.05$	↓ by 0.54 mmol/L ($p = 0.38$)	No significant effect
HbA_{1c}	–	No significant effect	↑ by 0.1%	No significant effect	↓ by 0.38%; $p > 0.05$
Total cholesterol (mmol/L)	↓ by 0.59 mmol/L [1 g] ↓ by 1.42 mmol/L [3 g] ↓ by 0.65 mmol/L [6 g] All $p < 0.05$	No significant effect	No significant effect	No significant effect	No significant effect
LDL (mmol/L)	↓ by 0.18 mmol/L [1 g] ↓ by 0.73 mmol/L [3 g] ↓ by 0.28 mmol/L [6 g] All $p < 0.05$	No significant effect	No significant effect	No significant effect	No significant effect
HDL (mmol/L)	No significant effect in 1 and 6 g; 3 g dose significant but unknown	No significant effect	No significant effect	No significant effect	No significant effect
Triglycerides (mmol/L)	↓ by 0.68 mmol/L [1 g] ↓ by 0.74 mmol/L [3 g] ↓ by 0.57 mmol/L [6 g] All $p < 0.05$	No significant effect	No significant effect	No significant effect	No significant effect
Plasma insulin (pmol/L)	—	—	No significant effect	No significant effect	—
HOMA-IR	—	—	No significant effect	—	—
ISIcomp	—	—	No significant effect	—	—
OGIS	—	—	No significant effect	—	—

Data are means ± standard deviation. –indicates not measured.

FBG, fasting blood glucose; HbA1c, glycosylated haemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostasis model insulin resistance index; ISIcomp, whole body insulin sensitivity; LDL, low-density lipoprotein; OGIS, whole body insulin sensitivity.

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Vanschoonbeek *et al.* [32] suggest that the single gender of their study may have affected the outcome, but three other trials involving type 2 diabetic patients included both genders, and there are no apparent gender-related subgroups to support this hypothesis. There are differences in ethnicity which may have contributed to the heterogeneity of results, and Blevins *et al.* [33] conclude that cinnamon effects differ by population when comparing their study to that of Khan *et al.* [4], although despite typically higher HbA_{1C} in some of the ethnicities in this study [39,40], no ethnic intragroups are noted. However, population size may have been too small to illustrate this. Several reviews suggest that ethnicity may contribute to contrasting results in diabetic studies [36–38], illustrating a need for further research to test this hypothesis. Apart from ethnicity, the strongest variable likely to have contributed to the difference in results of type 2 diabetic trials is baseline FBG, which ranges from 7.38 to 12 mmol/L in cinnamon groups.

Khan *et al.* [4] report neither BMI nor waist circumference, despite known differences between Western and Asian populations [41,42] and strong correlation ($p < 0.01$) between BMI and plasma glucose [43]. However, although adiposity is a strong predictor of type 2 diabetes ($p = 0.0002$) [44], and relationships between BMI and waist circumference, and hyperglycaemia and hyperlipidaemia exist [45], no association between these measures and cinnamon efficacy is evident in studies which include anthropometric values, as contrasting results are noted with similar BMI measurements [32–34]. However, these studies mostly report an average BMI < 31, reducing the likelihood of a noticeable association. Cinnamon appears to have an additive effect upon insulin in fat but not muscle cells when insulin resistance is not present [7], which may have contributed to the results of the Khan *et al.* [4] study, considering differences in adiposity between populations [46]. However, because of the absence of insulin measures and anthropometric data, and a known association between increased adiposity and insulin resistance [47], a clear hypothesis cannot be reached. It is suggested that there may be a complex relationship between cinnamon efficacy and levels of adiposity and insulin resistance.

Characteristics between non-diabetic studies are heterogeneous, but do not differ between intrastudy intervention and control groups, and participants in the Ziegenfuss *et al.* [30] study were matched. Age and BMI in the study by Solomon and Blannin [26] are considerably lower than those of the diabetic subjects, and cinnamon efficacy is tested through OGTT-induced glucose elevation and subsequent glucose clearance.

Type and Amount of Cinnamon Used

Although Ziegenfuss *et al.* [30] used a concentrated supplement made from *C. burmannii*, *C. verum* remains otherwise untested in clinical trials. Supplement preparation may have influenced the outcome of several studies, as cinnamon contains a number of active agents with varying antihyperglycaemic actions [6,8], and although it is proposed that the active components appear in both aqueous extract and powdered bark [6,48], information regarding the concentration of these components in the *C. cassia* and *C. burmannii* used remains largely unknown. Some studies may have used preparations with low levels of the active components, and with cellular bioavailability of cinnamon in the nanomolar range, low physiological concentrations create a challenge for research methodologies and accurate deductions. This may explain why animal studies using higher doses have resulted in greater blood glucose reduction [48]. Animal studies presenting significant results have commonly used higher cinnamon dosage against body weight in comparison with human studies. For example, the equivalent human dosage if applying the measure per body weight administered by Kannappan *et al.* [49] to rats would be 17.08 g cinnamon/day rather than the 1.5 g used by Vanschoonbeek *et al.* [32].

It appears that both cinnamon extract and powder are effective, the level of bioactive ingredients in the preparation a more important factor. Based upon the results of the diabetic studies reviewed, it is possible that the therapeutic dose of cinnamon may depend upon the subjects' baseline FBG, rather than there being a significant dose-dependant effect. However, Ziegenfuss *et al.* [30] report an 8.4% FBG reduction in subjects with a mean baseline FBG of 6.46 mmol/L ingesting 10 g of cinnamon daily for 12 weeks, illustrating that a higher cinnamon dose can bring about a significant reduction in blood glucose ($p < 0.01$) in subjects with lower baseline FBG. Although this suggests a possible relationship between baseline FBG, FBG reduction and therapeutic cinnamon dose, the 16.9% FBG reduction Wang *et al.* [19] report using insulin-resistant subjects with a mean baseline FBG of 5.32 mmol/L ingesting 1 g of cinnamon daily for 90 days suggests otherwise. However, the placebo group also illustrated significant FBG reductions ($p < 0.03$), potentially reducing causality. Correlations between these variables might be tested using regression analysis,

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Table 4 Summation of population characteristics, methodology and results of cinnamon studies with non-diabetic participants

Study information	Ziegenfuss *et al.* 2006, $N = 22$	Solomon and Blannin 2006, $N = 7$	Wang *et al.* 2007, $N = 15$
Type of trial	Double-blind, randomized, placebo-controlled trial	Double-blind, randomized, crossover trial	Double-blind, randomized, placebo-controlled trial
Age (y)	46.0 ± 9.7	26 ± 1.0	31.1 ± 2.0
Gender (M/F)	11 M, 11 F; mixed gender in each group	Male	Female
BMI (kg/m^2)	33.2 ± 9.3	24.5 ± 0.3	28.8 ± 1.3
Baseline FBG (mmol/L)	6.46 ± 0.71	4.9 pre-OGTT	5.32 ± n/k
Ethnicity	American	British	American
Matched pairs	Matched for age, FBG, SBP and physical activity habits	n/a	Not matched but did not differ for BMI, FBG, insulin, QUICKI, HOMA-IR or insulin sensitivity index
Methodology	Cinnamon supplements or placebo given to insulin-resistant participants; changes in FBG, lipids, BP and anthropometric measures assessed	Healthy subjects underwent three OGTTs: one placebo, one cinnamon (cin), one cinnamon 12 h before (cin12pre); AUC and insulin sensitivity measured	Cinnamon supplements or placebo given to insulin resistance women; FBG, AUC and insulin sensitivity assessed before and after OGTT
Supplement and dose	10 g (equivalent) Cinnulin PF®* CE of *Cinnamomum bermannii*	5 g Cassia powder capsules	1 g Cassia extract
Study duration	12 weeks	After OGTT and OGTT (cin12pre)	8 weeks
Dietary control	3-day food diary analyzed by a licensed, registered dietician using commercially available software	2-day food diary; diet replicated prior to each OGTT; subjects asked to refrain from alcohol, caffeine, cinnamon products and exercise 48 h before each OGTT	Advised not to modify diet or exercise habits
Measures taken	Weight, height, BMI, body fat %, lean mass (kg), BP, FBG, total cholesterol, LDL, VLDL, HDL, triacylglycerol, kCals and food intake	Plasma glucose; serum insulin; insulin sensitivity	Insulin sensitivity, insulin resistance, FBG, OGTT, plasma glucose
Significant results in cinnamon group compared with placebo group [26,30], or baseline [19)	FBG ↓ 8.4% $p < 0.01$	AUC (mmol/12 h) ↓ 12.9% in cin $p < 0.05$	FBG ↓ 16.9% $p < 0.03$
	116.3 ± 12.8 mg/dL [pre] −106.5 ± 20.1 mg/dL [post]	674.7 ± 39.3 [pre] −584.4 ± 37.5 [post]	95.83 mg/dL [pre] −79.67 mg/dL [post]
	SBP ↓ 3.8% $p< 0.001$	AUC (mmol/12 h) ↓ 10% in cin12pre $p < 0.05$	AUC ↓ 20.9% $p < 0.03$
	133 ± 14 mmHg [pre] −128 ± 18 mmHg [post]	674.7 ± 39.3 [pre] −603.8 ± 35.6 [post]	144.88 mg/dL/min [pre] −114.54 mg/dL/min [post]
	Lean tissue ↑ 1.1% $p < 0.002$	Insulin sensitivity index measures also improved:	QUICKI ↑ 7.7% $p < 0.03$ 0.35 [pre] −0.38 [post]
	53.7 ± 11.8 kg [pre] −54.3 ± 18 11.8 kg [post]	$ISI^{Matsuda}_{OGTT}$ cin ($p< 0.05$)	HOMA-IR ↓ 44.5% $p < 0.03$ 2.57 [pre] −1.43 [post]
	FBG ↓ 8.4% $p< 0.01$	4.74 ± 0.69 [pre] −7.96 ± 1.29 [post]	
		$ISI^{Matsuda}_{OGTT}$ cin12pre ($p < 0.05$)	
		4.74 ± 0.69 [pre] −8.26 ± 1.46 [post]	

Data are means ± standard deviation. Age and BMI means are for study population. Baseline FBG shown is for cinnamon groups in each study.

AUC, plasma glucose post oral glucose tolerance test; BP, blood pressure;

CE, cinnamon extract; FBG, fasting blood glucose; h, hours; kCals, calories; LDL, low-density lipoprotein; HDL, high-density lipoprotein; OGTT, oral glucose tolerance test; OGTT(cin12pre), CE 12 h prior to OGTT; QUICKI, insulin sensitivity index; HOMA-IR, homeostasis model insulin resistance index; SBP, systolic blood pressure; VLDL, very low density lipoprotein.

*Cinnulin is made from cinnamon powder; it contains at least 1% doubly-linked polyphenol type-A polymers, highly bioactive components of cinnamon.

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Table 5 Association between mean baseline FBG and reduction in FBG

Study and cinnamon dose	Baseline FBG (mmol/L)	End FBG (mmol/L)	Reduction in FBG (mmol/L)	% reduction in FBG	Duration of study
Khan *et al.* 2003, 1, 3, and 6 g*	12	9.1	2.90	↓ 24%	40 days
Mang *et al.* 2006, 3 g	9.26	8.15	1.11	↓ 11.9%	4 months
Vanschoonbeek *et al.* 2006, 1.5 g	8.37	7.91	0.46	↓ 5.49%	6 weeks
Blevins *et al.* 2007, 1 g	7.38	6.84	0.54	↓ 7.3%	3 months
Ziegenfuss *et al.* 2006, 10 g	6.46	5.91	0.55	↓ 8.4%	12 weeks
Wang *et al.* 2007, 1 g	5.32	4.42	0.90	↓ 16.9%	90 days

Measures are average baseline fasting blood glucose (FBG) of cinnamon groups.
*Khan *et al.* [4] examined three different cinnamon doses; as no dose–dependant relationship was found between 1 and 6 g cinnamon, the baseline FBG levels and FBG reductions are combined to create an average. No FBG results are available for Suppapitiporn *et al.* [29].

although consideration must be given to the metabolic differences between diabetic and insulin-resistant subjects.

Association Between Baseline FBG and Reduction in FBG

Corresponding with the conclusion reached by Mang *et al.* [34] ($r = 0.685$; $p < 0.001$), in trials involving patients with type 2 diabetes, there may be a correlation between mean baseline FBG and FBG reduction, indicating that elevated baseline FBG in the study by Khan *et al.* [4] is likely to have contributed to the significant results (table 5). Data from studies involving patients with type 2 diabetes appear to support this proposed correlation, although this becomes less apparent as baseline FBG reduces; despite a lower baseline FBG, Blevins *et al.* [33] report a slightly greater reduction than Vanschoonbeek *et al.* [32], although duration was greater, suggesting that this may also contribute to efficacy, as cinnamon dosage was lower. This hypothesis is supported by data from non-diabetic studies as both Wang *et al.* [19] and Ziegenfuss *et al.* [30] illustrate lower average baseline FBG yet report greater reductions; duration of both studies was approximately 3 months, but the variance in dosage supports the proposition that efficacy is not dose-dependant, although the bioavailability and level of active components in each cinnamon supplement also requires consideration.

It is postulated that higher glucose levels caused by insulin resistance create cellular inflammation, potentiating insulin resistance and reducing insulin action [47,50,51], but cinnamon may be able to override this and activate glucose uptake. Hence, in the presence of insulin resistance the pathways normally utilized by insulin are available for cinnamatic activity. Potential to reduce hyperglycaemia with cinnamon may be greater when insulin functionality is low, as a natural cut-off point for cellular glucose uptake has been suggested [52]. Thus, it is concluded that the level of obesity-activated insulin resistance may affect cinnamon efficacy, offering a possible explanation as to why higher FBG levels have elicited a more significant effect, even with lower cinnamon doses. Less effect upon glucose levels is also seen in animal studies without glucose challenge [53], and greater results reported with elevated glucose load [24,48,49], supporting the theory that the efficacy of cinnamon may be dependant upon the level of hyperglycaemia. However, although animal studies illustrate promising antidiabetic properties, proof that cinnamon can reduce blood glucose levels in humans remains to be established.

HbA_{1c}

Although association between plasma glucose and glycosylated haemoglobin (HbA_{1c}) differ depending upon genetic factors and glycaemic control of the population, it is expected that studies reporting no significant reductions in FBG [32,33] would not find changes in HbA_{1c}. However, it is not known why HbA_{1c} has been largely unaffected in human studies where FBG has reduced, as Babu *et al.* [53] illustrated a 40.2% reduction in HbA_{1c} in rats ($p < 0.05$), and there is evidence of cinnamon compounds showing antioxidant and radical scavenging activities [54], and reducing advanced glycation end products [55]. HbA_{1c} is increasingly used to assess hyperglycaemia through the level of glycated proteins [56,57], contributing to diabetic complications and overall morbidity [58,59]. Despite a known relationship ($r = 0.90$) between plasma glucose and HbA_{1c} [60], there are genetic differences in glycation, so if cinnamon reduces FBG, the effect upon HbA_{1c} may be less direct in some individuals [61]. This may explain the reduction in FBG but not in HbA_{1c} reported by Mang *et al.* [34], although duration is considered to have been adequate

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to expect some reduction especially when it is estimated that newer erythrocytes may contribute approximately 50% to HbA_{1c} values, in comparison with 10% from older erythrocytes [56]. The post-study HbA1c data of the study by Vanschoonbeek *et al.* [32] is therefore less valid.

In addition, although HbA_{1c} increases in diabetic patients [62], the relationship between FBG and HbA_{1c} is not always entirely linear, and a highly statistically significant inverse association ($r = -0.66$, $p < 0.01$) has been illustrated between glycation percentage and average erythrocyte life span of 120 days: higher glycation increases cell turnover and may not accurately convey the degree of hyperglycaemia [63]. In addition, the relationship between mean plasma glucose and HbA_{1c} differs depending upon glycaemic control, so blood glucose remains a key parameter to determine cinnamon efficacy [64]. It has been illustrated that intensively treated patients with diabetes display lower mean plasma glucose concentrations in relation to HbA_{1c} [64]; this may explain why Altschuler *et al.* [35] report no change in HbA_{1c}, because of the patients with type 1 diabetes in this study receiving exogenous insulin therapy to reduce blood glucose. It is proposed that if plasma glucose is reduced for a long enough period, HbA_{1c} will also reduce.

Cinnamon Interaction With Diabetes Medication and Other Drugs

Although participants in diabetic studies have used different medications, no intragroup differences are identified, despite the most impressive cinnamon results achieved by participants taking only sulphonylureas [4]. Sulphonylureas increase insulin secretion and have been shown to reduce HbA_{1c} more other diabetic medications [65]. Although HbA_{1c} was not measured by Khan *et al.* [4], baseline FBG was the highest of all studies reviewed and the ethnicity of participants indicates greater risk of insulin resistance [66]. This may indicate that sulphonylurea effectiveness could have been reduced in the presence of insulin resistance (illustrated by elevated FBG levels), enabling cinnamon to lower blood glucose using the pathways normally activated by insulin [5]. Higher insulin resistance is associated with increased BMI and central adiposity [57,67], but measures were not taken in the aforementioned study to support this theory.

Biguanides such as metformin decrease gluconeogenesis [68] and alpha-glucosidase inhibitors modify starch digestion, both decreasing blood glucose levels. Insulin resistance may reduce in conjunction with lower glucose levels [57], enabling some insulin activity and reducing the opportunity for cinnamon to share cellular pathways [7,52]. Thiazolidinediones sensitize hepatic and muscle cells to accept insulin more readily, also limiting cinnamon potential if glucose uptake pathways are shared [69]. It may be hypothesized that these drug actions in combination with cinnamon have contributed to the contrasting results between studies, although considering the combination of drug therapies used in trials reporting significant and insignificant results, and lack of intragroup classifications, this seems less likely. Further research is required to quantify the effect of drug therapy upon insulin resistance, impaired glucose tolerance and impaired fasting glucose levels, the parameters which are likely to affect cinnamon activity. Hypertensive and lipid-lowering medications constitute a further heterogeneous factor which may have affected study outcomes, although differing results were reported in studies where participants took these drugs, and no subgroups were noted.

Dietary Analysis in Cinnamon Studies

Dietary intake has a significant likelihood of influencing study outcome [70], and must be controlled to reduce the impact of independent variables. It appears that in studies involving participants with type 2 diabetes, the tighter the dietary control the less significant the results were; however, non-diabetic trials report significant results ($p < 0.01$) with an analysed food diary [30], or with food intake replicated prior to OGTT [26]. Most trials administered cinnamon with meals, which potentially maximized the effects of delayed gastric emptying and reduced glucose absorption, limiting postprandial hyperglycaemia and protein glycation [22]. However, this is not illustrated when comparing results between trials.

Duration of Studies

It appears that there may be a stronger correlation between baseline FBG and cinnamon efficacy rather than duration, considering the insignificant results reported by Blevins *et al.* [33] over a 3-month period. As considerable blood glucose reductions have been illustrated following cinnamon intake with glucose load [19,26], this suggests an immediate therapeutic effect, and with no FBG measures taken or reported in less than the 20 days of Khan *et al.* [4] in diabetic studies reporting significant results, it remains unknown whether cinnamatic effects are because of the most recent dose, one single dose, or a shorter duration than that tested. The postintervention wash-out of Khan

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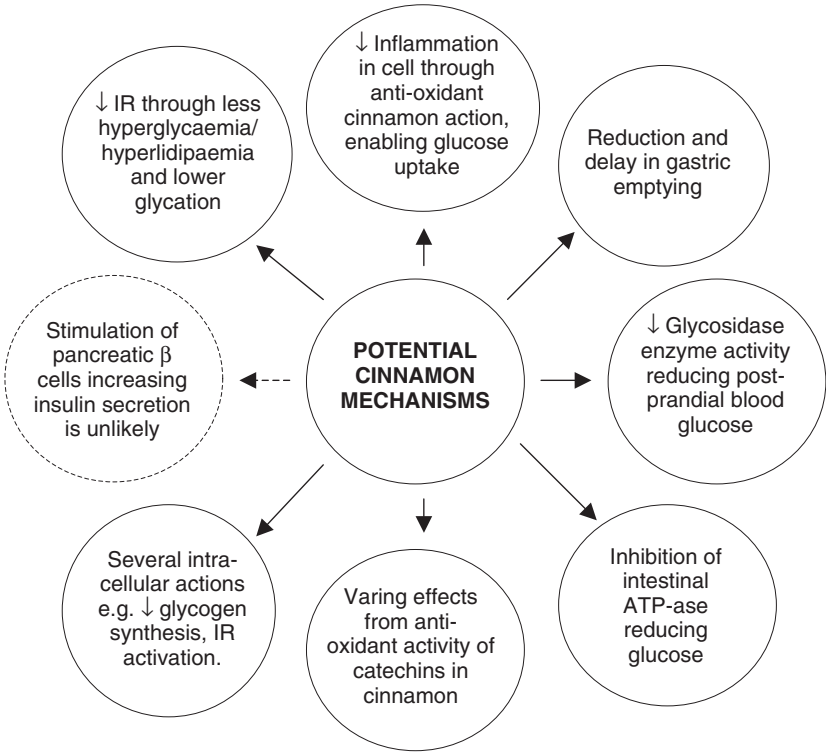

Fig. 1 Potential antihyperglycaemic actions of cinnamon.

et al. [4] illustrated that a cinnamatic effect continues postsupplementation, although effectiveness reduces; gradual blood glucose increase without cinnamon and no changes in the placebo group supports the theory that cinnamon possesses antihyperglycaemic properties.

Conclusion

Although insulin sensitivity improved following OGTTs [19,26], plasma insulin in diabetic human studies has remained unchanged [32,33]. Therefore, it is deducted that where blood glucose was reduced by cinnamon, this was not through increased insulin secretion but through gastrointestinal mechanisms reducing gastric emptying and glucose absorption, and through improved cellular uptake and glucose utilization, and that factors such as timing cinnamon supplementation with meals may have a significant effect upon cinnamon's glucose lowering ability. It appears that at a certain dose, possibly relative to baseline FBG, cinnamon is able to lower blood glucose, but whether there is a lasting therapeutic effect upon insulin resistance and sensitivity, with promise to improve the pathophysiology of type 2 diabetes, remains to be discovered. If there is an association between cinnamon efficacy and baseline FBG levels, or if cellular cinnamon-activated glucose uptake is limited in the presence of insulin, it may be hypothesized that antihyperglycaemic benefits are through delayed gastric emptying [20] and reduced glucose absorption [24] in subjects with lower blood glucose levels or less insulin resistance. It is suggested that HbA_{1c} and insulin parameters are measured in future studies to ascertain changes in glycosylated haemoglobin, insulin sensitivity and insulin secretion following blood glucose reduction, to determine the potential longer term effects of cinnamon use.

Early studies report promising results in subjects with type 2 diabetes, but it may be erroneous to apply the results achieved by Khan *et al.* [4] to the general diabetic population when factors such as elevated baseline FBG, BMI and adiposity levels could have a considerable effect upon cinnamon efficacy. As significant results have been limited to specific and relatively small patient populations, more research with larger subject numbers is required to detect statistically significant FBG reductions following cinnamon supplementation. In a meta-analysis of diabetic trials to date, Baker *et al.* [37] suggest a sample size in excess of 1000 participants. As this analysis included the significant results from Khan *et al.* [4], if the correlation between baseline FBG and cinnamon efficacy is correct, it is likely that an even larger sample size will be required to produce statistically significant results within a Westernized diabetic population with lower blood glucose levels [71].

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However, such research may provide clinically effective results, and enable relative and absolute risk reductions to be expressed, potentially confirming the external validity of cinnamon use in the community.

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