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Effects of Cinnamon Supplementation on Systolic and Diastolic Blood Pressure: a Systematic Review and Meta-analysis of Randomized Controlled Clinical Trials

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ABSTRACT

Background: Hypertension is a chronic condition that might lead to renal and cardiovascular diseases. Previous clinical trials examining the effect of cinnamon supplementation on blood pressure have led to conflicting results. The present study aimed to summarize the effect of cinnamon supplementation on blood pressure using a meta-analysis of published randomized controlled clinical trials.

Methods: To identify the eligible articles, MEDLINE, SCOPUS, ISI Web of Science, and Google Scholar were searched from inception until September 2019 for relevant articles. The risk of bias assessment was performed using the Cochrane collaboration's tool. A Random-effects model was applied to calculate the summary effects.

Results: Totally, 11 trials with 686 participants were included in this systematic review and meta-analysis. The dose of cinnamon supplement consumption varied from 500 to 10000 mg/d. The meta-analysis revealed that cinnamon supplementation significantly decreases systolic blood pressure (SBP) [WMD (weighted mean difference) = -5.72 mmHg, 95% confidence interval (CI): -8.63 to -2.80; P<0.001, I2= 81.1)] and diastolic blood pressure (DBP) (WMD= -4.06 mmHg, 95% CI: -6.68 to -1.44; P= 0.002, I2 = 88.6). Subgroup analysis suggested no significant reduction in DBP in subjects with diabetes (WMD= -2.015 mmHg, 95% CI: -4.55 to 0.52; P= 0.12, I2 = 72.3) and prediabetes or metabolic syndrome (WMD= -4.8 mmHg, 95% CI: -10.06 to 0.44; P= 0.073, I^2= 92.5).

Conclusions: Cinnamon supplementation could be beneficial in lowering SBP and DBP in adults. Further studies with different doses are recommended to confirm the present findings.

Keywords: Blood pressure; Cinnamon; Randomized controlled clinical trials; Systematic review; Meta-analysis

Introduction

Hypertension is an important public health problem, leading to complications such as cardiovascular diseases, renal damage, and stroke; as it is considered as a substantial cause of death, worldwide *[1]*. It is proposed that approximately 35-45% of the world population and also 21.4% of Iranians suffer from hypertension *[2, 3]*. Common treatments consist of health behavior modification and then antihypertensive drugs; therefore, lifestyle

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and nutrition are considered as important steps for its prevention and control *[4, 5]*. Recently, there has been a focus on the role of functional foods such as garlic, dietary fiber, licorice and also cinnamon in the treatment of hypertension *[6-9]*.

Cinnamon is one of herbal medicines that is used for the treatment of intestinal colic, common cold, and respiratory and gastrointestinal disorders *[10]*. Nowadays, studies have found that it has antioxidant, anti-inflammatory, antidiabetic, and antihyperlipidemic effects, and also might improve cardiovascular diseases *[11-13]*. Cinnamon consists of a variety of bioactive ingredients, including cinnamaldehyde, cinnamic acid, cinnamate *[14]*, and numerous antioxidants, polyphenols, and flavonoids *[15]*. Animal studies have postulated that cinnamaldehyde might be able to regulate blood pressure by peripheral vasodilatation and also to dilate vascular smooth muscle via an endothelium-independent manner *[16]*. The vasodilatory effect of cinnamaldehyde maybe because of inhibiting both Ca^{2+} influx and release *[17]*. A study revealed that cinnamic aldehyde and cinnamic acid of cinnamon have cardioprotective effects against myocardial ischemia injury *[13]*. Cinnamon polyphenols could impact insulin activity and diabetes symptoms *[18]*. Cinnamaldehyde may also prevent the development of hypertension in type 1 and 2 diabetes through normalization of vascular contractility, as well as its insulinotropic effect in hypoinsulinemia *[19]*.

Some clinical trials have suggested that cinnamon consumption reduces the elevated systolic blood pressure (SBP) *[20-25]*. However, other studies could not confirm this finding *[26-30]*. Besides, findings regarding the effect of cinnamon supplementation on diastolic blood pressure (DBP) are inconclusive, as several trials observed significant improvements *[20-23, 27]* and the others reported no effect on DBP *[24-26, 28-30]*. Due to the contradictions observed in the literature, the present systematic review and meta-analysis of randomized controlled trials (RCTs), was conducted to clarify the effect of cinnamon on SBP and DBP in adults. Moreover, this study aimed to assess the possible difference in the effect of cinnamon on blood pressure based on gender, supplementation dose, duration, and participants' health status.

Materials and Methods

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement was followed *[31]* for reporting this systematic review and meta-analysis. The protocol was registered in the international prospective register of systematic reviews (PROSPERO) in July 2019 (registration code: CRD42019137565).

Search strategy

A comprehensive literature search was done from inception up to September 15th, 2019, in electronic databases including PubMed/Medline, ISI Web of Science, Scopus, and Google Scholar. The search was carried out without any language or time restriction. To find the relevant papers and the following Medical Subject Headings (MeSH) and non-MeSH keywords were used: 1) "cinnamomum aromaticum", cinnamon*, "cinnamomum cassia", "cinnamomum zeylanicum", rinnamomum*, cinnamaldehyde, "cinnamic aldehyde"; 2) "blood pressure", BP, "diastolic pressure", "systolic pressure", "pulse pressure", hypertension, "arterial tensions", "systolic blood pressure", "diastolic blood pressure", SBP, DBP, "systolic arterial pressure"; and 3) rats, mice, mouse, "in vitro", "in vivo", "animal experimentation", "animal Model", "laboratory animals". The searched studies were included the keywords group 1 and 2 in their titles/abstracts without keywords group 3. We also used keywords related to anthropometric indices, inflammatory and antioxidant factors, blood lipids, glucose, and CVD since BP might be regarded as a secondary outcome in some related studies. In addition, reference lists of related articles were checked manually to find the possibly missing papers.

Eligibility criteria

The following inclusion criteria were applied to select the related articles: (1) the design of the study should be randomized controlled trial (RCT); (2) performed in adults (aged 18 years or older); (3) reporting blood pressure as a primary or secondary outcome variable; (4) evaluating the effect of oral cinnamon supplementation (extract or powder) vs. either placebo, or no intervention. Trials were excluded if they (1) used a mixture of cinnamon supplementation and other herbs for intervention, and the difference between the intervention and control group was not only in cinnamon supplementation; (2) examined only the short-term or immediate post-consumption effect of cinnamon supplementation (less than 7 days of intervention); (3) reported duplicate data; (4) were letters, editorial articles, case reports or review article.

Data extraction

Three researchers (MAY, HH, ZY) conducted the initial screening of articles (title and abstract) and examined the full-text of relevant studies. Two investigators (ZY, MA) independently extracted data (the last name of the first author, year of publication, country, study design, gender, sample size, age, subjects' health status, type and dosage of supplementary cinnamon, duration (weeks), and mean [standard deviation (SD)] for SBP and DBP changes in the intervention and the placebo groups) from eligible studies. Means ± SDs for baseline and after intervention period were used to calculate mean change ± SD in SBP and DBP for each group. For studies that did not report the change values, P values or estimated correlation coefficient (r = 0.63 for SBP and r = 0.75 for DBP) for baseline and endpoint values which were extracted from the other clinical trials were used to impute the SE for mean changes. All processes were checked by the other authors.

Risk of bias assessment

The quality of included publications were evaluated using Cochrane Collaboration's Risk of Bias tool (16) based on the following criteria: (1) random sequence generation (selection bias), (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding outcome data, (5) incomplete outcome data, and (6) selective reporting. These studies were classified as "high risk" of bias, "low risk" of bias and" unclear risk" based on each domain. Two authors (ZY and MA) independently assessed the methodological quality of the eligible studies against the six criteria. Any discrepancy was resolved by discussing a third author (AN).

Statistical analysis

The difference in mean change values and its standard error between the intervention (cinnamon supplementation) and control groups was calculated for each trial and used as effect size for meta-analyses. A DerSimonian and Laird random-effects model was applied to calculate the weighted mean difference (WMD) and the corresponding 95% confidence interval (CI) *[32]*.

Cochran's Q test and the I^2 statistic (I^2) were used to evaluate the inter-study heterogeneity *[33]*. Different subgroup analyses were performed to detect the possible sources of between-study heterogeneity by considering the following variables: gender (both, female, and male), health status (T2DM, prediabetes/ metabolic syndrome, and others), duration of intervention (<12 weeks and ≥12 weeks), dosage of cinnamon supplementation (<2000, 2000-3000, and ≥3000 mg/day), the time of cinnamon consumption (with meals, immediately after meals, and others), and the results found for glycemic indicators (significant decrease, no change). To determine the influence of each eligible study on the overall effect size, a sensitivity analysis was conducted by excluding studies one by one from meta-analyses *[34]*. Publication bias was investigated for each outcome through visual inspection of funnel plots and conducting statistical asymmetry tests

(Begg's and Egger's tests) *[35]*. STATA software (version 11.2; Stata Corp, College Station, TX) was used for all statistical analyses. P values lower than 0.05 were considered as statistically significant.

Results

Study selection

The initial database search resulted in 4337 potentially relevant studies of which 3497 records remained after removing duplicate references. Based on the screening of the titles/abstracts, 99 studies were identified to be carefully checked by reading their full-texts; of these, 88 articles were excluded for the following reasons: (1) did not assess the effect of cinnamon supplementation on BP (n = 82), (2) had no control group (n = 1), (3) data were already reported in another included publication (n = 2), (4) examined the immediate post-consumption effect of cinnamon (n = 1), and (5) study participants were younger than 18 years (n = 2). The references for excluded studies and the reason for their exclusion are available in **Table 1**. Finally, 11 eligible RCTs were included in the current systematic review and meta-analysis *[20-30]*. The study selection flow diagram is illustrated in **Figure 1**.

Table 1. Excluded studies with reasons (n = 88)

Reason for exclusion	References
Not systolic and diastolic blood pressure as outcome (n= 82)	*[36-117]*
Evaluation of immediate post-consumption effect (n=1)	*[118]*
Duplicate data of other studies (n=2)	*[119, 120]*
Had no control group (n= 1)	*[121]*
Studies conducted in children (n= 2)	*[122, 123]*

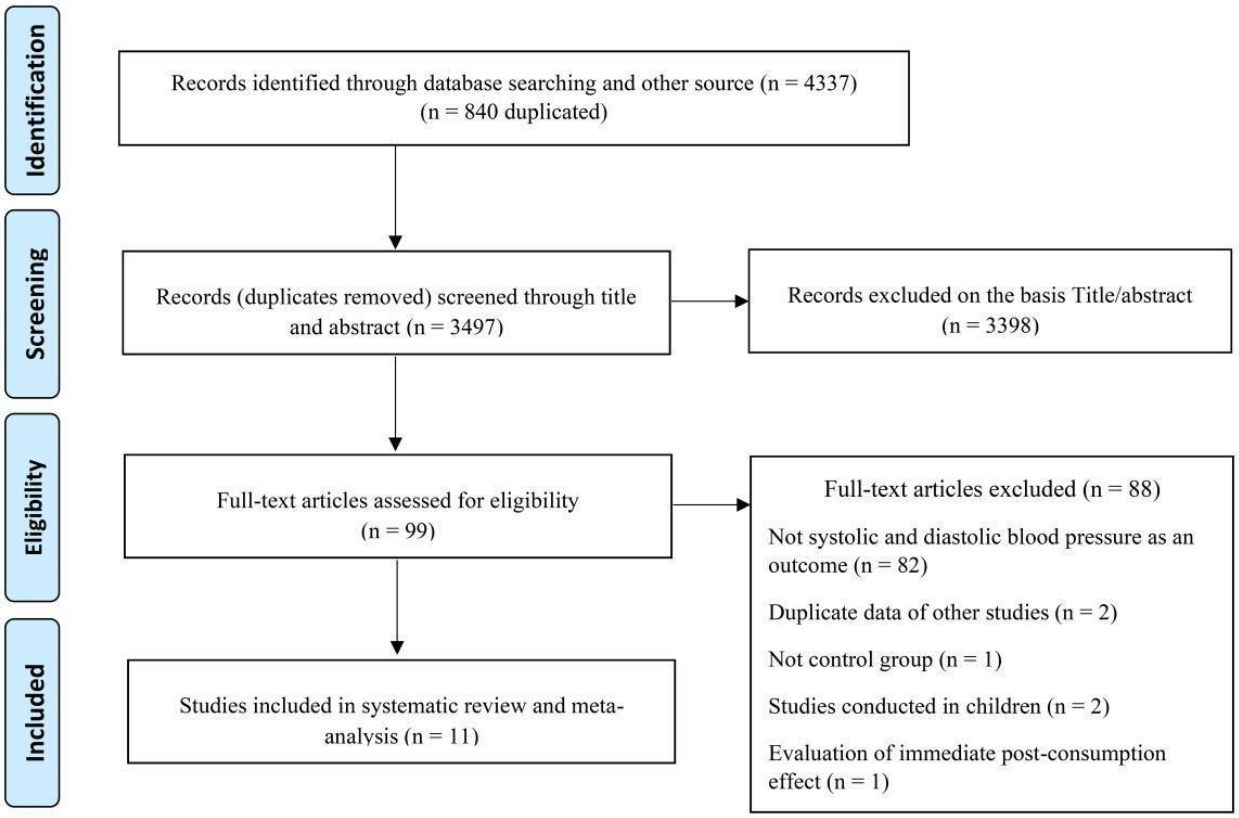

Figure 1. Study selection flow diagram

Characteristics of included articles

The characteristics of the eleven clinical trials which were eligible to be included in the current systematic review and meta-analysis are presented in **Table 2**. All studies had a parallel design, and their duration varied from 6 to 16 weeks. The studies were published between 2006 and 2018 in the United Kingdom *[20, 21]*, Iran *[27, 28, 30]*, India *[22, 24]*, USA *[25, 26]*, and other countries *[23, 29]*. Eight studies included both genders *[20, 22, 23, 25, 26, 28-30]*, two were conducted only in females *[21, 27]* and one only included male participants *[24]*, with the age ranging from 44 to 64.5 years. One study used cinnamon supplementation in the form of dried water extract *[26]*, and other studies administered cinnamon powder with a dose of 500 to 10000 mg/d *[20-25, 27-30]*. Moreover, of the 11 included studies, five presented dietary intakes of participants during the study *[20, 21, 25, 27, 30]*. Two studies mentioned that they instructed their participants to maintain their previous food habits *[24, 28]* and also in two studies, participants continued the diet that was recommended during the run-in period *[22, 23]*. The remaining studies did not report information about dietary intake *[26, 29]*. Four included trials reported a reduction in both SBP and DBP *[20-23]*, and some found a significant decline only in SBP *[24, 25]* or DBP *[27]*. However, four trials did not observe a significant difference between intervention and control groups *[26, 28-30]*. The effects of cinnamon supplementation were evaluated in different health status, as six studies focused on T2DM patients *[20, 23, 24, 28-30]*, and the other studies included subjects with metabolic syndrome (MetS) and prediabetes *[22, 25, 26]*, rheumatoid arthritis *[27]*, and overweight *[21]*.

Table 2. Characteristics of eligible studies evaluating the effect of cinnamon supplementation on SBP and DBP

Author (Ref)	Publication year	Participants	Gender	Sample size (control / intervention)	Age (years)	Study design	Duration (wk)	Intervention/control (name and daily dose)	Result	Diet	Notes about glycemic indicators (cinnamon vs. placebo group)	The time of consumption
Akilen et al. *[20]*	2010	T2DM	Both	30/28	54.9 ± 9.8	RCT double blind	12	2000 mg of cinnamon powder (Cinnamomum cassia)/starch	↓ DBP ↓ SBP	Follow their normal routine diet	Significant decrease	With meals
Azimi et al. *[30]*	2014	T2DM	Both	40/39	54.33 ± 0.5	RCT single blind	8	3000 mg of cinnamon powder (Cinnamomum verum) + three glasses of tea/three glasses of tea	↔ DBP ↔ SBP	Follow their normal routine diet	No change	Three times throughout the day
Aldayel et al. *[124]*	2016	Overweigh t	F	8/7	Control= 53 ± 2.7 Intervention= 56 ± 1.3	RCT single blind	8	5000 mg of cinnamon powder (Cinnamomum cassia)/corn flour	↓ DBP ↓ SBP	Follow their normal routine diet	No change	Immediately after meals
Gupta et al. *[22]*	2017	MetS	Both	58/58	44.8 ± 7.8	RCT double blind	16	3000 mg of cinnamon powder/ wheat flour	↓ DBP ↓ SBP	Macronutrie nts equal to placebo group	Significant decrease	Immediately after meals
Vafa et al. *[28]*	2012	T2DM	Both	19/18	Control= 55.67 ± 7.98 Intervention= 54.11 ± 10.37	RCT double blind	8	3000 mg of cinnamon powder (Cinnamomumzeylanic um)/wheat flour	↔ DBP ↔ SBP	Follow their normal routine diet	Significant decrease	With meals
Shishehb or et al. *[125]*	2018	RA	F	18/18	Control= 49.11 ± 7.45 Intervention= 44.66 ± 11.22	RCT double blind	8	2000 mg of cinnamon powder (Cinnamomum burmannii)/starch	↓ DBP ↔ SBP	Follow their normal routine diet	No change	Immediately after meals

Author (Ref)	Publication year	Participants	Gender	Sample size (control / intervention)	Age (years)	Study design	Duration (wk)	Intervention/control (name and daily dose)	Result	Diet	Notes about glycemic indicators (cinnamon vs. placebo group)	The time of consumption
Soni et al. *[24]*	2015	T2DM	M	15/15	52 (40-60)	RCT, parallel	6	2000 mg of cinnamon powder (Cinnamomum cassia)/ no receiving supplementation	↔ DBP ↓ SBP	Follow their normal routine diet	Significant decrease	Immediately after meals
Wainstein et al. *[29]*	2011	T2DM	Both	29/30	63.05 ± 10.85	RCT, parallel	12	1200 mg of cinnamon powder (Cinnamomum cassia)/ microcrystalline cellulose	↔ DBP ↔ SBP	NA	No change	With meals
Anderson et al. *[26]*	2015	Prediabetic	Both	63/72	61.3 ± 6.36	RCT double blind	8	500 dried water extract of cinnamon (Cinnamomum cassia)/ wheat flour	↔ DBP ↔ SBP	NA	Significant decrease	Twice a day
Sengsuk et al. *[23]*	2016	T2DM	Both	49/50	control= 56.9 ± 1.2 Intervention= 57.2 ± 1.1	RCT double blind	8	1500 mg of cinnamon powder/ placebo	↓ DBP ↓ SBP	Macronutrients equal to placebo group	Significant decrease	Immediately after meals
Zeigenfuss et al. *[126]*	2006	Prediabetes & MetS	Both	12/10	46.0 ± 9.7	RCT double blind	12	500 mg of water soluble extract (equivalent to 10000 mg of whole cinnamon powder)/ microcrystalline cellulose	↔ DBP ↓ SBP	Follow their normal routine diet	Significant decrease	With meals

SBP, systolic blood pressure; DBP, diastolic blood pressure; Ref, reference; F, females; M, males; T2DM, type 2 diabetes mellitus; MetS, metabolic syndrome; RA, rheumatoid arthritis; RCT, randomized clinical trial; NA, not available; ↓, reduction; ↔, no change

Risk of Bias Assessment

Results of the quality assessment based on the Cochrane Collaboration's tool are summarized in **Table 3**. In brief, five trials had a low risk of bias for all items of methodological quality assessment *[20, 22, 23, 27, 29]*. The method used to generate the random sequence and allocation concealment were unclear in four studies *[21, 24, 25, 28]*. Also, two included studies were high risk regarding blinding of personnel and outcome assessment *[21, 30]*. All of the studies were "low risk" regarding the incomplete outcome data and selective reporting.

Table 3. Study quality and risk of bias assessment

Author, year (reference)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Akilen, 2010 *[20]*	L	L	L	L	L	L
Azimi, 2014 *[30]*	L	L	H	H	L	L
Aldayel, 2016 *[124]*	U	U	H	H	L	L
Gupta, 2017 *[22]*	L	L	L	L	L	L
Vafa, 2012 *[28]*	U	U	L	L	L	L
Shishehbor, 2018 *[125]*	L	L	L	L	L	L
Soni, 2015 *[24]*	U	U	U	U	L	L
Wainstein, 2011*[29]*	L	L	L	L	L	L
Anderson, 2015 *[26]*	L	L	L	U	L	L
Sengsuk, 2016 *[23]*	L	L	L	L	L	L
Zeigenfuss, 2006 *[126]*	U	U	L	U	L	L

Ref, reference; L, low risk; H, high risk; U, unclear

Meta-analysis results

Effect of cinnamon supplementation on systolic blood presssure

The pooled analysis of eleven trials with 686 participants, demonstrated an overall significant reduction in SBP by -5.72 mmHg (95% CI: -8.64, -2.80; P < 0.001), and the between-study heterogeneity was significant (Cochran's Q statistic = 23.38, P < 0.001, I^2 = 81.1%) (**Figure 2**). The subgroup analysis according to the administered dose, revealed a significant decrease 2000-3000 mg/d (WMD = -6.04 mmHg; 95% CI: -9.81, -2.27 mmHg; P= 0.002); however, the supplementation was not significant at the dose of ≥3000 mg/d (WMD = -5.52; 95% CI: -11.44, 0.39 mmHg; P = 0.067). The subgroup analysis based on participants' health status showed that SBP was significantly declined by cinnamon supplementation in subgroups (T2DM, prediabetes/Mets and others). Moreover, significant decrease in SBP following cinnamon consumption was observed in both subgroups of duration, and the effect was considerable in studies with more than 12 weeks of follow-up (WMD = -6.62 mmHg; 95% CI: -9.23, -4.02 mmHg; P <0.001; I^2 = 53%). Subgroup analysis revealed that cinnamon supplementation with or immediately after meals could decrease systolic blood pressure; however, the reducing effect was greater when the supplementation was done after meals (WMD = --9.5 mmHg; 95% CI: -8.63, -2.80 mmHg; P <0.001; I^2 = 36.8%). The results of subgroup analyses, as well as overall analyse are illustrated in **Table 4**.

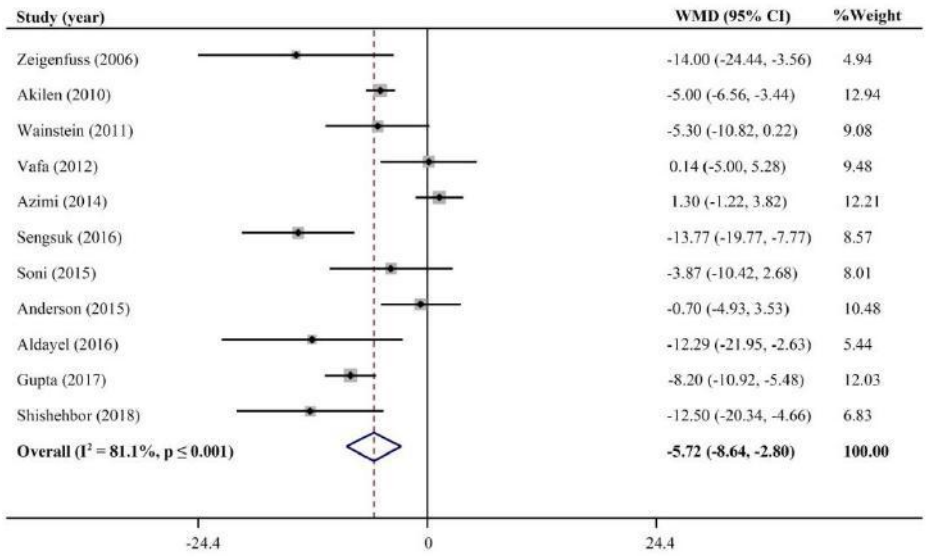

Figure 2. Forest plot summarizing the effects of cinnamon supplementation on systolic blood pressure

Effect of cinnamon supplementation on diastolic blood pressure

The meta-analysis of 11 trials suggested that cinnamon supplementation considerably decreased DBP (WMD = -4.06 mmHg, 95% CI: -6.68, -1.44, P = 0.002) and the heterogeneity among studies was significant (Cochran's Q statistic = 88.08, P < 0.001, I^2 = 88.6%) (**Figure 3**). The subgroup analysis based on the health status of participants revealed that cinnamon could not significantly lower DBP in patients with T2DM (WMD = -2.01, 95% CI: -4.55, 0.52, P = 0.12). It appears that the consumption of cinnamon supplement immediately after meals can lead to a greater reduction in DBP (WMD = -7.32; 95% CI: -11.50, -3.15 mmHg; P = 0.001). The results of subgroup analyses indicated that trials with a significant decrease in glycemic indicators (fasting blood glucose or hemoglobin A1c) were associated with further DBP reduction. The subgroup analyses based on gender, health status, duration, and dose as well as overall analysis are provided in **Table 4**.

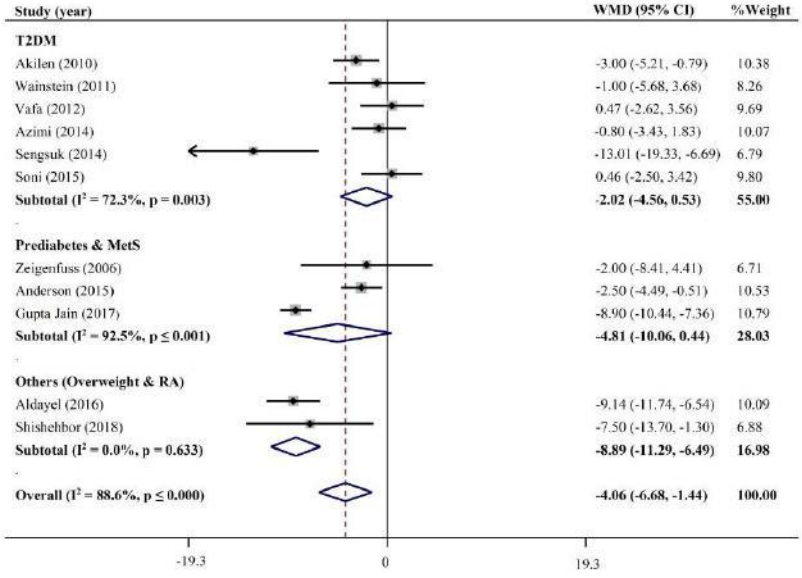

Figure 3. Forest plot summarizing the effects of cinnamon supplementation on diastolic blood pressure

Table 4. Results of overall and subgroup analysis of relevant randomized controlled trials in meta-analysis of the effect of cinnamon supplement on systolic and diastolic bllod pressure[1]

Study group	No. of trials	Systolic blood pressure						Diastolic blood pressure					
		Meta-analysis		Heterogeneity				Meta-analysis		Heterogeneity			
		WMD[2] (95%CI)	P effect	*Q* statistic	P within group	I^2 (%)	P between subgroups	WMD (95%CI)	P effect	*Q* statistic	P within group	I^2 (%)	P between subgroups
Overall	11	-5.72 (-8.63, -2.80)	<0.001	53.04	<0.001	81.1	-	-4.06 (-6.68, -1.44)	0.002	88.08	<0.001	88.6	-
Gender													
Both	8	-4.87 (-8.15, -1.60)	0.004	46.29	<0.001	84.9		-3.641 (-6.66, -.61)	0.0018	64.29	<0.001	89.1	
Females	2	-12.41 (-18.5, -6.33)	<0.001	0.00	0.97	0.00	0.034	-8.89 (-11.29, -6.49)	<0.001	0.23	0.63	0	<0.001
Males	1	-3.87 (-10.42. 2.68)	0.24	0.00	-	-		0.4 (-2.5, 3.42)	0.72	0.00	-	-	
Health status													
T2DM	6	-4.06 (-7.84, -.27)	0.035	31.07	<0.001	83.9		-2.015 (-4.55, 0.52)	0.12	18.08	0.003	72.3	
Prediabetes & MetS	3	-6.57 (-13.05, -0.098)	0.047	10.69	0.005	81.3	0.004	-4.8 (-10.06, 0.44)	0.073	26.68	<0.001	92.5	<0.001
Others (Overweight & RA)	2	-12.41 (-18.5, -6.33)	<0.001	0.00	0.97	0		-8.89 (-11.29, -6.49)	<0.001	0.23	0.63	0	
Duration													
<12 wk	7	-5.19 (-9.90, -0.47)	0.03	33.97	<0.001	82.3	<0.001	-4.03 (-7.31, -0.75)	0.016	46.02	<0.001	87.0	<0.001
≥12 wk	4	-6.62 (-9.23, -4.02)	<0.001	6.39	0.094	53		-4.11 (-8.48, 0.24)	0.064	26.2	<0.001	88.6	
Dose													
<2000 mg/d	3	-6.63 (-13.79, 1.07)	0.094	12/19	0.002	83.6		-4.88 (-10.44, 0.66)	0.085	10.58	0.005	81.1	
2000-3000 mg/d	3	-6.04 (-9.81, -2.27)	0.002	3.56	0.16	43.8	0.22	-2.58 (-6.09, 0.92)	0.14	6.41	0.04	68.8	<0.001
≥ 3000 mg/d	5	-5.52 (-11.44, 0.39)	0.067	34.34	<0.001	88.4		-4.27 (-8.67, 0.13)	0.057	52.40	<0.001	92.4	
The time of consumption													
With meals	5	-4.67 (-8.20, -1.13)	0.01	6.62	0.085	54.7		-1.65 (-3.43, 0.11)	0.067	3.32	0.34	9.7	
Immediately after meals	4	-9.5 (-8.63, -2.80)	<0.001	6.33	0.17	36.8	<0.001	-7.32 (-11.50, -3.15)	0.001	35.36	<0.001	88.7	<0.001
Others	2	0.77 (-1.39, 2.41)	0.48	0.63	0.42	0.00		-1.87 (-3.48, -0.27)	0.022	1.02	0.31	1.7	
The results of glycemic indicators													
Significant decreased	7	-5.72 (-8.81, -2.64)	<0.001	23.82	0.001	74.8	0.001	-3.81 (-7.21, -0.42)	0.027	65.30	<0.001	90.8	0.92
No change	4	-6.35 (-13.56, 0.85)	0.084	18.92	<0.001	84.1		-4.54 (-9.54, 0.44)	0.074	22.78	<0.001	86.8	

[1] All analyses were performed using random effects model

WMD, weighted mean difference. T2DM, type 2 diabetes mellitus; MetS, metabolic syndrome; wk, week; RA, rheumatoid arthritis

Sensitivity analysis and publication bias

The results of the sensitivity analysis indicated that excluding each study from the whole sample or subgroups did not change the overall effect of the cinnamon supplementation on SBP and DBP. Egger's and Begg's tests showed no presence of publication bias for meta-analyses assessing the effect of cinnamon supplementation on SBP (Begg's test, P = 0.21; Egger's test, P = 0.37) and DBP (Begg's test, P = 1; Egger's test, P = 0.49).

Discussion

The results of the present study showed that cinnamon consumption can be beneficial in reducing SBP and DBP (-5.72, -4.06 mmHg, respectively). This supplement significantly reduced SBP in patients with T2DM, whereas failed to find any significant effect on DBP in these subjects. These findings might be of clinical importance. A meta-analysis of controlled trials reported that each 5 mmHg SBP or 2 mmHg reduction in DBP could lead to lower risk of cardiovascular morbidity and mortality *[127]*. On the other hand, it is proposed that cinnamon and its components may be important in the prevention and alleviation of all factors associated with metabolic syndrome including insulin sensitivity, body weight, inflammation and blood pressure *[128]*.

Our result regarding the effect of cinnamon supplementation on DBP is consistent with a meta-analysis by Akilen et al. *[9]*, which evaluated the effects of short-term administration of cinnamon on blood pressure in T2DM and prediabetes and found a significant benefit in terms of DBP decline in these patients. However, the mentioned meta-analysis included three studies with 139 subjects.

Advanced glycation end products (AGEs) have a substantial role in the pathophysiology of coronary heart disease *[129]*. Increased AGEs result in endothelial dysfunction, oxidative stress and inflammation, which can cause hypertension and atherosclerosis. It is proposed that therapies that reduce insulin resistance and/or AGEs levels are effective in attenuating blood pressure, oxidative stress, and atherosclerotic vascular changes *[130]*. Recent studies demonstrated that cinnamon compounds, such as catechin, epicatechin, procyanidin B2, proanthocyanidin oligomers, and phenol polymers could scavenge reactive carbonyl species and thus effectively prevent the formation of AGEs *[131, 132]*. The other main ingredient of cinnamon is cinnamaldehyde, which is a potent agonist of epithelial transient receptor potential ankyrin 1 (TRPA1) *[133]*, and stimulates the release of calcitonin gene-related peptide and causes vasodilation in peripheral arteries *[134]*. The results of published studies have shown that cinnamaldehyde relaxes blood vessels by the inhibition of endogenous vasoconstrictors such as angiotensin II, and also dilates the smooth muscle by interfering with both Ca^{2+} influx and release *[17, 19, 135]*. The other possible antihypertensive mechanism of cinnamon might be its ability to increase the endothelial nitric oxide and activate the ATP-sensitive potassium (KATP) channels in vascular smooth muscle *[13, 17, 19, 135]*. Moreover, improvement of insulin resistance is one of the presumptive mechanisms for the effect of cinnamon on blood pressure *[136-138]*. Nevertheless, it is expressed that more research is necessary to be done to exactly understand the underlying mechanism of how cinnamon supplementation could help to prevent and treat hypertension *[139]*.

The findings of the current meta-analysis suggested that daily consumption of cinnamon with a dose of 2000-3000 mg is the most beneficial dose for lowering SBP. A recent systematic review of RCTs that investigated the association between cinnamon supplementation and obesity, reported a non-significant dose-response trend of cinnamon supplementation with body mass index, and fat mass *[140]*. Furthermore, several human and animal studies have mentioned that there is no evidence of a

dose-response relationship between cinnamon supplementation and several markers including blood pressure and response to all dosages of cinnamon was similar *[135, 138, 141]*. It seems that the detailed mechanism of cinnamon on BP is not well understood and needs to be further investigated. Moreover, it was shown that the consumption of cinnamon supplements immediately after meals can significantly reduce DBP. Cinnamon can delay gastric emptying and thereby acts as a factor in blood glucose homeostasis *[142, 143]*. Since a close association exists between glycemic indicators and blood pressure levels *[9, 20, 25]*, cinnamon consumption might reduce BP more effectively if ingested after meals. The subgroup analyses also demonstrated that there is a relationship between glycemic indicators and SBP or DBP values, which is consistent with the proposed mechanism in this context and the results of meta- analyses done by Akilen et al. *[9]* in patients with prediabetes and type 2 diabetes.

The present study was undertaken based on a comprehensive and systematic search to identify all relevant literature and no evidence for publication bias was detected. Furthermore, to minimize bias, the study was restricted to RCTs. In addition, this review included all related published research and even those assessed BP as a secondary outcome in adults. Another strength of the current study is that the overall results were not sensitive to any single study. Even though, the present review has some limitations which need to be addressed. It should be considered that heterogeneity remained even after subgroup analyses. The heterogeneity might be explained by other variables not reported in the included studies. For instance, some studies did not report the species and composition of cinnamon used for supplementation and the dietary intake evaluation of participants. Moreover, the low number of studies included in some subgroup analyses restricted the interpretation of findings.

Conclusion

In summary, the present systematic review and meta-analysis suggest that cinnamon supplementation reduces SBP and DBP in adults, but has not significant effect on DBP in subjects with T2DM. Furthermore, cinnamon has a DBP lowering effect when ingested immediately after meals. Albeit, the mechanism of its effect is not fully clear and requires subsequent investigation. Further studies with different doses are recommended to confirm the present findings and to give a definitive answer to the question about the best effective dose of cinnamon that might decline blood pressure.

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Authors' contribution

ZY designed the search strategy, conducted data extraction, analyzed the data, interpreted the results and wrote the first draft of the manuscript; MA conducted data extraction and quality of the eligible studies; HH conducted the study selection; MAY conducted the study selection; AN conceived the study, interpreted the results and critically revised the manuscript. All authors read and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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