



The impact of cinnamon on anthropometric indices and glycemic status in patients with type 2 diabetes: A systematic review and meta-analysis of clinical trials



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ABSTRACT

Background and aims: There is some evidence regarding the positive effects of cinnamon on metabolic status in patients with type 2 diabetes (T2DM). However, they are conflicting. In the present study, we aimed to systematically review the effects of cinnamon on glycemic status and anthropometric indices in patients with T2DM.

Methods: Five electronic databases including PubMed/Medline, SCOPUS, Web of Sciences, EMBASE, and the Cochrane library were searched until 31 February 2018 with no language limitation. Randomized clinical trials that examined the effects of cinnamon on at least fasting blood sugar (FBS) were included. Other glycemic parameters and anthropometric indices were also extracted. A random effects model with DerSimonian and Laird method was used for pooling the effect sizes.

Results: Finally, 18 studies were included in the meta-analysis. Supplementation with cinnamon reduced FBS by -19.26 mg/dL (95% CI: -28.08 , -10.45 ; I^2 : 96.5%; $p = 0.0001$) compared to placebo. However, the effects of cinnamon on HbA1C (-0.24% ; 95% CI: -0.48 , -0.01 ; I^2 : 76.8%, $p = 0.0001$), body weight (-0.46 , 95% CI: -1.87 , 2.30 ; I^2 : 0%; $p = 0.79$), body mass index (WMD: -0.05 kg/m²; 95% CI: -0.52 , 0.42 ; I^2 : 0%; $p = 0.91$), and waist circumference (WMD: -0.53 cm; 95% CI: -3.96 , 2.81 ; I^2 : 0%; $p = 0.66$) were not significant. Additionally, cinnamon did not change the serum levels of insulin and insulin resistance significantly.

Conclusion: Supplementation with cinnamon can reduce serum levels of glucose with no changes in other glycemic parameters and anthropometric indices. However, due to high heterogeneity findings should be interpreted with great caution.

1. Introduction

Type 2 diabetes (T2DM) is a metabolic disorder, which is known as a global health problem. It is predicted that the number of adult patients with T2DM will reach 300 million by 2030.¹ Diabetes not only increases the risk of macrovascular and microvascular diseases, but also poses a considerable economic burden and influences the quality of life.²

Diabetes management can prevent or reduce the risk of such complications. It is reported that a 1% reduction in HbA1C is associated with a 21% less risk for diabetes complications.³ Strategies to improve

glycemic status are worth investigating. Losing weight, improving other anthropometric indices (e.g. waist circumference), and body composition along with lifestyle modifications and drug therapy are main treatment for T2DM.^{4,5}

Despite treatment strategies and the existence of different biochemical anti-diabetic medications, the findings of interventions are not satisfactory. Tendency of people to various types of complementary and alternative therapies are considerably increasing.⁶ However, in many cases there is not sufficient evidence regarding their efficacy or safety. Anti-diabetic and anti-obesity effects of many medicinal herbs have been examined, so far.^{7–10} Cinnamomum (cinnamon) that is a

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Table 1
PICO criteria for the present systematic review.

PICO	Descriptors
Participants:P	Adult subjects with type 2 diabetes
Intervention: I	Cinnamon OR Cinnamons OR Cinnamomum verum OR Cinnamomum zeylanicum OR Cinnamomum OR Ceylon cinnamon
Comparison: C	Placebo group
Outcome: O	Weight OR “BMI” OR Body mass index OR Quetelet OR Glucose OR Sugar OR FBS OR Insulin OR HOMA-IR OR “insulin resistance” OR QUICKI OR “insulin sensitivity” OR HbA1c OR Diabetes OR Diabetic OR DM

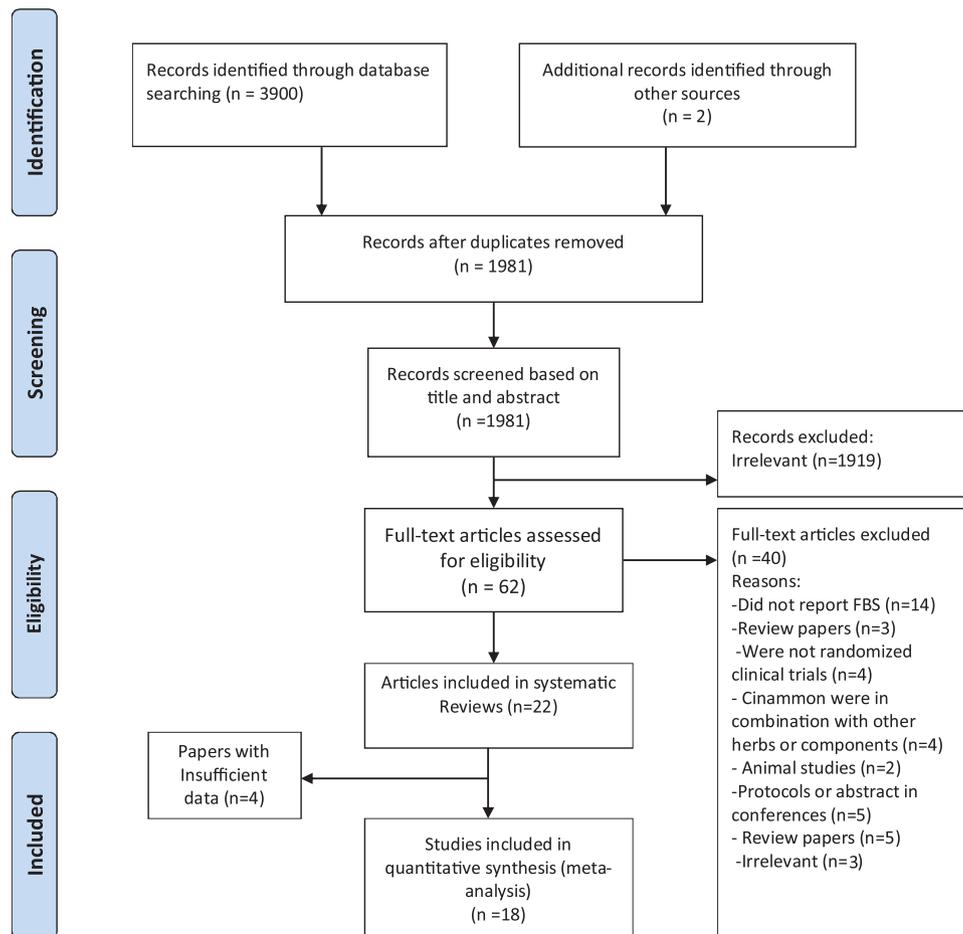


Fig. 1. Procedures of study selection.

genus from the *Lauraceae* family is an example of such herbs.^{11,12}

Cinnamon means sweet wood and is obtained from the inner bark of cinnamon trees as a spice or traditional remedy for several diseases including common cold, gastrointestinal disorder and diabetes.¹³ It possesses several species including *C.cassia*, *C.burmannii*, *C.verum*, *C.loureiroi*, *C.citriodorum*, and *C.tamale*. Various beneficial effects for cinnamon such as anti-microbial, anti-inflammatory, antioxidant, antifungal, and anti-diabetic properties have been reported.¹⁴ The main components of Cinnamon are cinnamaldehyde, cinnamic acid, and cinnamate, which play key roles in different biological activities. Cinnamon also contains several polyphenols such as rutin (72%), catechin (1.9%), quercetin (0.17%), kaempferol (0.016%), and isorhamnetin (0.103%), which can mimic insulin activity and improve glycemic status.¹⁵ Several clinical trials^{16–22} have reported positive effects of cinnamon not only on glycemic status, but also on other metabolic parameters. Acting as insulin-like molecules, antioxidant activities, improving beta-cell function, reducing gluconeogenesis and insulin resistance, enhancing insulin secretion, and insulin sensitivity are plausible mechanisms of action of cinnamon on glycemic status and anthropometric indices.^{19,23–25} However, findings of clinical trials are conflicting.

Recent meta-analyses failed to lead to a certain conclusion on the effects of cinnamon in patients with T2DM, because of the high heterogeneity. In the study by Allen and colleagues, it was concluded that cinnamon reduced fasting blood sugar (FBS) with no significant changes in glycated hemoglobin A1c (HbA1c). However, they did not examine other glycemic parameters (insulin, insulin resistance, insulin sensitivity) and anthropometric indices.¹⁹ Additionally, subgroup analysis was not conducted and methodological quality of the included studies was not taken into account, which might make bias in findings. Based on the meta-analysis done by Leach et al, the effect of cinnamon on diabetes was inconclusive because of high risk of bias in the included studies, and more studies are needed to make decision about its efficacy. Besides, the researchers did not examine anti-obesity effects of cinnamon.²⁶ In the present meta-analysis, to identify possible anti-diabetic mechanisms for cinnamon, we examined serum levels of insulin, insulin resistance and insulin sensitivity as well as obesity indices. The purpose of the current meta-analysis was to systematically review the effects of cinnamon on glycemic status and anthropometric indices in patients with T2DM.

Table 2
Characteristics of the included papers in the systematic review.

Author/Year	Location	Study design	Gender (Male/ Female)	Mean age	Sample size	Dosage (g/ day)	Duration (day)	Form	Adjustment	Side effects	Type of Cinnamon	Quality score
Zare et al (2018)	Iran	R/P triple	Both	52.6	138	1	90	powder	No	No	Not clear	3
Zahedifar et al (2018)	Iran	R/P double	Both	54.6	55	2	56	powder	No	No	Not clear	2
Talaie et al (2017)	Iran	R/P double	Both	57	39	3	56	powder	No	No	C. cassia	4
Sengsuk et al (2016)	Thailand	R/P double	Both	57	99	1.5	60	powder	No	No	Not clear	5
Tangvarasittichai et al (2015)	Thailand	R/P double	Both	57	106	1.5	60	powder	No	No	c.cassia	5
Azimi et al (2014)	Iran	R/P Single	Both	53.8	79	3	56	powder	Yes/ covariates were not mentioned	No	Not clear	3
Mirfeizi et al (2014)	Iran	R/P triple	Both	> 18	72	1	90	powder	Yes/ Baseline value	Yes/ Skin Allergy (n = 1)	Not clear	4
Hasanzadeh et al (2013)	Iran	R/P double	Both	54.3	70	1	60	powder	No	No	c.cassia	3
Vaia et al (2012)	Iran	R/P double	Both	55	37	3	56	powder	No	No	Not clear	2
Lu et al (2012)	China	R/P double	Both	61	43	0.12	91	extract	No	No	Not clear	2
Zahmatkesh et al (2012)	Iran	R/P double	Both	55	55	2	56	powder	No	No	Not clear	3
Haghighian et al (2011)	Iran	R/P double	Both	56.8	60	1.5	60	powder	No	No	Not clear	2
Aklien et al (2010)	England	R/P Single	Both	55	58	2	84	powder	Yes, covariates were not clear	No	C. cassia	5
Otto et al (2010)	USA	R/P double	Both	46	22	0.5	84	Aqueous extract	Not clear	Not clear	Not clear	2
Blevins et al (2007)	USA	R/P double	Both	60.8	57	1	90	powder	No	Not clear	c.cassia	2
Mang et al (2006)	Germany	R/P double	Both	63	65	3	120	powder	No	No	Not clear	2
Vanschoonbeek et al (2006)	Netherlands	?R/P double	Female	62.5	25	1.5	42		No	No	C. cassia	3
Khan et al (2003)	Pakistan	R/P/ double	Both	> 40 years	20	1	40	powder	No	No	C. cassia	1
					3							
					6							

R/P: Randomized placebo.

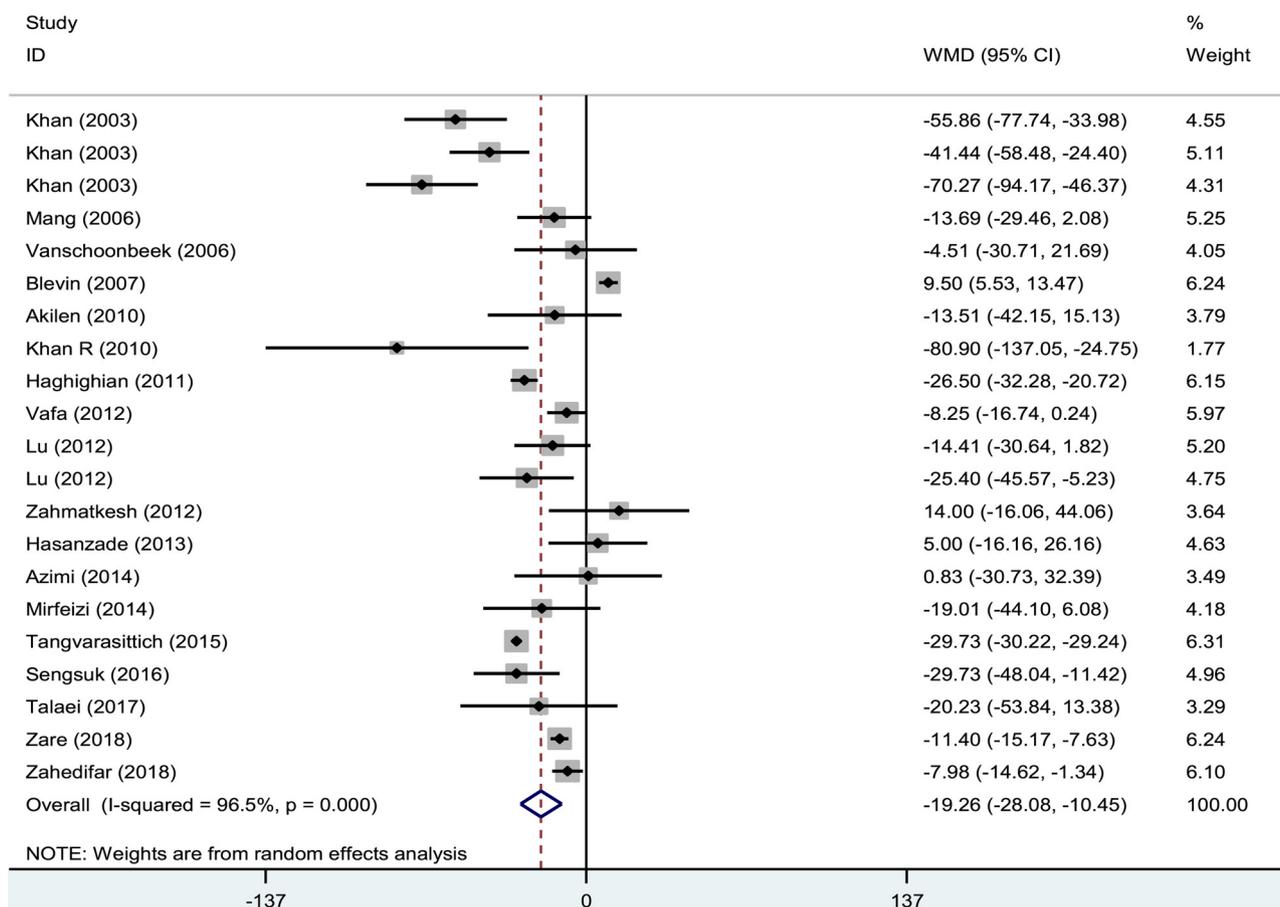


Fig. 2. Forest plot for the effects of supplementation with cinnamon on fasting blood sugar.

2. Methods

2.1. Search strategy

The current systematic review and meta-analysis was designed and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.²⁷

At the first step, PICOS criteria were defined as represented in Table 1. In the next step, five main electronic databases including PubMed/Medline, SCOPUS, Web of Sciences, EMBASE, and the Cochrane library were searched by two independent reviewers (N.N, J.H). Search was restricted to papers published between January 2000 and 31 February 2018 with no language limitation. Details of search strategies containing both medical subject headings (MeSH) and non-medical subject heading key terms for each database are provided in Appendix S1.

To avoid missing any relevant paper, apart from the electronic search, the reference lists of the relevant original articles, narrative reviews, systematic reviews and meta-analyses were hand searched. Additionally, to be notified when new relevant paper is published, alert service of PubMed was set up.

2.2. Inclusion and exclusion criteria

The primary outcome for the present study was the effects of supplementation with cinnamon on FBS concentrations. Therefore, when any paper did not report this parameter, even if it reported other glycemic status and anthropometric indices, it was not included. Other inclusion criteria were as follows: (i) randomized clinical trials (parallel or cross-over design), (ii) existence of a placebo group, (iii) included

adult subjects, (iv) examined the effects of cinnamon on at least FBS at baseline and at the end of the trial in both intervention and placebo groups, (v) examined T2DM, and (vi) examined any form of cinnamon (whole herb not effective components). Additionally, papers reported sufficient information including mean or mean differences with standard deviation (SD), standard error (SE) or 95% confidence intervals (95% CI) were included. Papers were excluded if they had any study design other than clinical trials such as animal or in vitro/In vivo studies, (ii) before-after studies, (iii) examined other types of diabetes, diseases or healthy subjects, (iv) examined effective components of cinnamon or food/beverages with added cinnamon, (v) in combination with other herbal or non-herbal ingredients, (vi) include children/adolescent (younger than 18 years old), and (vii) athletes.

Grey literature including theses, abstract in conferences, interviews, books, etc were not included as well. Corresponding authors of the relevant papers with insufficient data were asked by emails to send necessary data. When they did not answer after sending three emails in reasonable time intervals, they were excluded.

Inclusion/ exclusion screening forms based on the aforesaid criteria were used to identify eligible papers by two independent reviewers (N.N, J.H). Any disagreement was resolved by third reviewer (M.H, A).

2.3. Data extraction

After identification of eligible papers, the two reviewers (P.Kh, K.Kh) independently extracted the following characteristics based on the pre-defined form: first author's name, publication year, country, study design, randomization, blinding, sample size (after drop out), gender, mean age, dosage, form of supplement (extract, powder, etc) and placebo, duration of the intervention, participant's status,

Table 3
Subgroup analysis for the effects of cinnamon on fasting blood sugar in patients with type 2 diabetes.

Variables	No. study	Pooled effect size (95% CI)	I ² (%)	P _{heterogeneity}
Fasting blood sugar				
Blindness				
Double	13	-13.83 (-25.29, -2.37)	97.1	0.0001
Single	3	-16.75 (-55.64, 22.13)	75	0.01
Adjustment				
Yes	5	-14.42 (-29.33, 0.49)	45.1	0.12
No	13	-19.89 (-29.83, -9.95)	97.2	0.0001
Diet				
Yes	4	-19.86 (-35.47, -4.26)	67.9	0.02
No	14	-19.21 (-28.13, -10.29)	91.6	0.0001
Location				
Asia	14	-22.32 (-29.75, -14.89)	92.1	0.0001
Non-Asia	3	-11.66 (-23.8, 0.56)	0	0.83
Age (year)				
≤ 56	7	-20.57 (-32.73, -8.42)	86	0.0001
> 56	9	-16.15 (-29.97, -2.33)	97.8	0.0001
Dosage (g/day)				
≤ 1.8	5	-13.56 (-27.92, 0.79)	94.2	0.0001
> 1.8	14	-21.55 (-29.37, 13.73)	86.5	0.0001
Form				
Powder	15	-18.98 (-29.06, -8.90)	97.2	0.0001
Extract	2	-16.76 (-26.6, -6.89)	0	0.62
BMI at baseline (kg/m ²)				
≤ 29	7	-9.95 (-24.19, 4.28)	95.7	0.0001
> 29	6	-15.81 (-28.53, -3.09)	84.8	0.0001
Study quality				
< 3	8	-23.48 (-36.75, 10.20)	94.9	0.0001
≥ 3	10	-15.21 (-26.17, -4.26)	92.5	0.0001

adjustment, mean or mean difference and standard deviation (SD) or standard error (SE) for the outcomes of interest (FBS, HbA1c, insulin, insulin resistance, insulin sensitivity, weight, body mass index (BMI), waist circumference) at baseline and after the intervention in both cinnamon and placebo group.

When different dosages of cinnamon, BMI range, or age range examined in the study, all of the classifications were extracted and considered as a separate group. When both crude and adjusted findings were reported, we extracted adjusted one with the most controlled variables. If more than one paper was published from a same population, the newest one with more complete data (larger sample size, longer duration of the study) was extracted. Besides, when in a clinical trial a measurement was performed more than twice, only baseline and endpoint values were extracted. In studies with multiple arms, in which different interventions (cinnamon in combination with different ingredients) were administered, only groups with cinnamon and placebo were considered, not other intervention groups. Any discrepancies in the extracted characteristics were resolved by the third investigator (H.A.).

2.4. Quality assessment

The methodological quality assessment of the eligible papers was examined using the Jadad checklist²⁸ using two reviewers independently (N.N, K.KH). The Jadad scale contains items relevant to random assignment (2 items), blindness (2 items), and the flow of participants (1 item). The maximum score is five. Papers with at least 3 scores considered as high quality papers. Any discrepancies were also resolved by the third reviewer (B.L.).

2.5. Quantitative synthesis and statistical analysis

The effect of supplementation with cinnamon was examined on the

following outcomes: (i) FBS (mg/dL); (ii) HbA1c (%); (iii) insulin levels (pmol/L); (iv) HOMA-IR; and (v) QUIKI; (vi) weight (kg); (vii) BMI (kg/m²); (viii) waist circumference (cm). Wherever needed, conversion of units for the variables was conducted. The units of blood glucose were converted to mg/dL. Multiplication by 18 was used to convert the unit of glucose from mmol/L to mg/dL.

Effect estimates were reported as weighted mean differences (WMDs) and 95% CI. They were pooled using a random effects model with DerSimonian and Laird method.²⁹ When the mean changes were not reported, it was calculated using the following formula for cinnamon and placebo group: (value at end of study in the group- value at baseline in the group). To calculate the SD, the following formula was used: SD = square root [(SD pre-treatment)² + (SD post-treatment)² - (2R × SD pre-treatment × SD post-treatment)], considering R = 0.5. When an SE was reported instead of SD, with the following formula, SD was calculated: SD = SEM × square root (n), that 'n' is the number of sample size in each group. When medians and ranges or 95% CIs were reported, they were estimated using converting formulas. To obtain the values that were shown only in the graphic format, Plot digitizers software was used.

Heterogeneity was assessed by Cochran's Q test and the I² test. I² > 50% was assumed as high heterogeneity. To find the parameters induced heterogeneity, subgroup analysis was conducted, if possible. The possibility of subgroup analysis means the existence of at least two trails in each category of age, gender, adjustment, dosage, duration of the intervention, location, quality, and species of cinnamon. To assess the effect of each study on the pooled effect estimate, sensitivity analysis was conducted.

Potential publication bias was identified using the funnel plot, Begg's rank correlation (existence of more than 10 studies) and Egger's regression tests (existence of fewer than 10 studies). When there was a publication bias, "trim and fill" methods were used to correct the pooled estimates. All statistical analysis was performed using STATA version 11.0 (Stata Corp, College Station, TX). P values less than 0.05 were considered statistically significant.

3. Study characteristics

The process of publication selection was depicted in Fig. 1. Our search yielded 3902 publications, of which 1921 were duplicates. After the first screening based on titles and abstracts, 1919 studies were excluded. Sixty-two papers seemed to meet the inclusion criteria of the present meta-analysis. After the evaluation of the full-texts, we excluded 40 studies due to the following reasons: did not report FBS (n = 14), were review papers (n = 3), were not randomized clinical trials (n = 4), cinnamon was in combination with other herbs or components (n = 4), were animal studies (n = 2), were protocols or abstract in conferences (n = 5), review papers (n = 5), and irrelevant (n = 3). It is notable that four clinical trials did not have sufficient data and their authors did not answer to our emails. Therefore, they were excluded from the meta-analysis. Finally, 18 clinical trials were included in the meta-analysis.

3.1. Study characteristics and quality assessment

The characteristics of the included clinical trials (n = 18)^{14,16–20,22–25,30–37} are represented in Table 2. The clinical trials included 1100 participants and were published between 2003 and 2018. They were conducted in Asian (n = 13),^{14,17,18,20,22,23,25,30–32,34–36} European countries (n = 3)^{16,19,24} and US (n = 2).^{33,37} The range of age was between 46 and 63 years old. All studies except Vanschoonbeek et al.²⁴ examined both genders. Baseline body mass index (BMI) ranged 24.7–33.2 kg/m².

Cinnamon was recommended in the form of powder (n = 15)^{14,16,18–20,22–25,30–32,34–37} and extract (n = 2).^{17,33} The form of cinnamon supplement in the study by Vanschoonbeek et al was not clear.²⁴

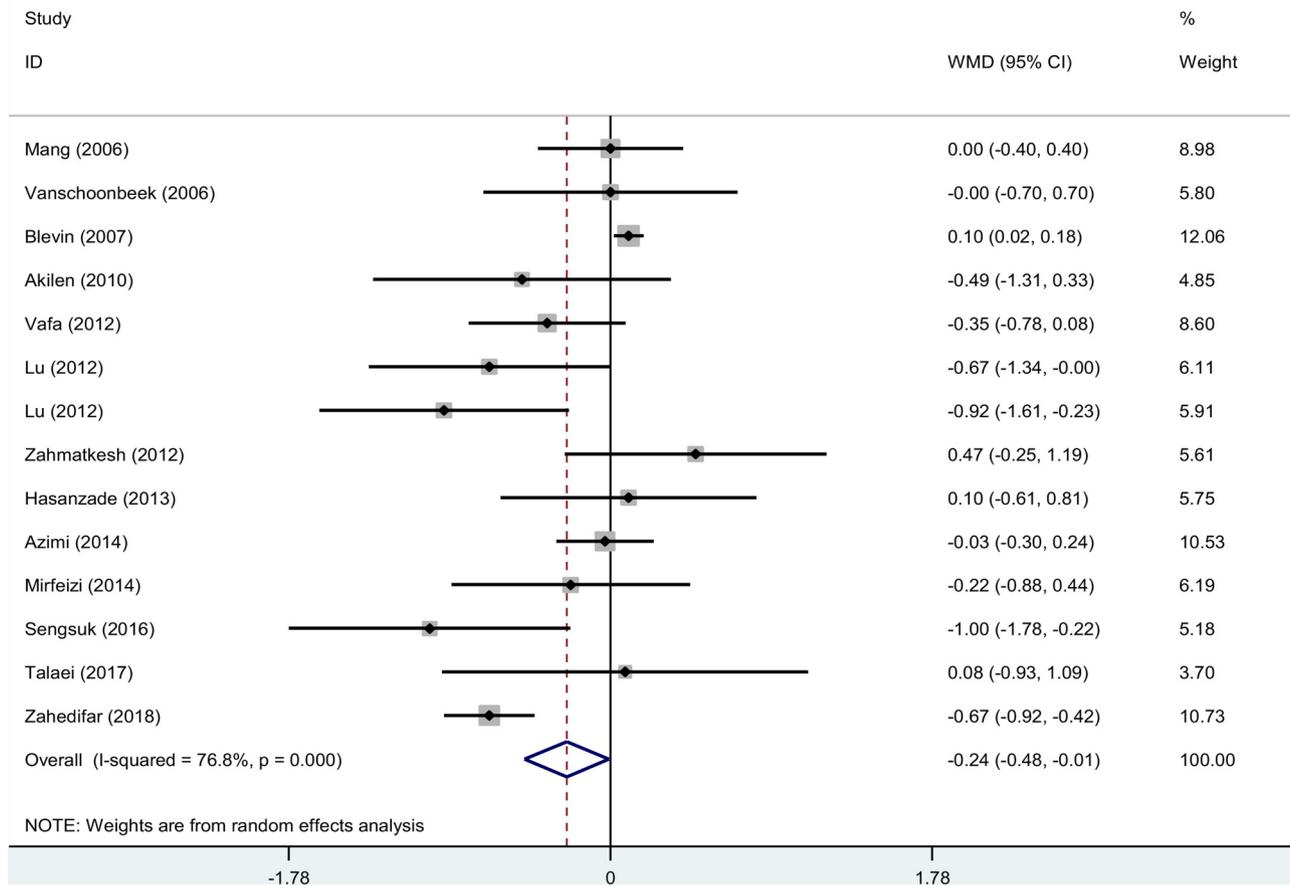


Fig. 3. Forest plot for the effects of supplementation with cinnamon on HbA1c.

Table 4
Subgroup analysis for the effects of Cinnamon on HbA1c in patients with type 2 diabetes.

Variables	No. study	Pooled effect size (95% CI)	I ² (%)	P heterogeneity
HbA1c				
Blindness				
Double	11	-0.30 (-0.58, -0.01)	80.3	0.0001
Single	2	-0.01 (-0.26, 0.24)	0	0.0001
Adjustment				
Yes	4	-0.15 (-0.36, 0.06)	0	0.0001
No	9	-0.25 (-0.57, 0.08)	82.6	0.51
Diet				
Yes	3	-0.33 (-1.20, 0.55)	73.9	0.02
No	10	-0.23 (-0.48, 0.02)	78.6	0.0001
Dosage (g/day)				
≤ 1.8	3	-0.30 (-0.83, 0.24)	72.2	0.004
> 1.8	10	-0.24 (-0.50, 0.02)	61.5	0.005
Duration (days)				
≤ 67	8	-0.38 (-0.72, -0.04)	84.6	0.0001
> 67	5	-0.05 (-0.26, 0.15)	0	0.41
Study quality				
< 3	6	-0.33 (-0.69, 0.03)	87	0.0001
≥ 3	7	-0.12 (-0.42, 0.18)	34.7	0.16

The species of cinnamon were not clear in 10 clinical trials. However, 6 studies examined the effects of *C. cassia*.^{18,19,24,32,35,37} Dosage for cinnamon powder varied from 1 to 6 g/day, and for extract from 0.12¹⁷ and 0.5 g/day.³³ The duration of intervention was between 40¹⁸ to 120 days.¹⁶ In four clinical trials, patients with T2DM adhered to a low-calorie diet, dietary advice, or physical activity recommendations,

while in the remaining trials, no life style intervention was reported. In the included studies, FBS (n = 18), HbA1c (n = 13), body weight (n = 4), BMI (n = 5), waist circumference (n = 2), insulin (n = 7), Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) (n = 4), quantitative insulin-sensitivity check index (QUICKI) (n = 1) were reported. According to Jadad scale, 10 studies had high quality (score ≥ 3)^{14,19,22–25,30,32,34,35} and the remaining (n = 8)^{16–18,20,31,33,36,37} posed low quality (score < 3).

All clinical trials except two that examined the effects of cinnamon on insulin and HOMA-IR, showed no significant changes after supplementation compared with placebo group. Additionally, only Tangvarasittichai et al, assessed the impact of supplementation on QUICKI and found a significant increase in insulin sensitivity following cinnamon supplementation.³²

3.2. Adverse effects

None of the included clinical trials except the one done by Mirfeizi et al, reported any side effects. In the study by Mirfeizi et al, skin allergy was reported after supplementation with 1 g/day cinnamon powder for 90 days. Only in one subject, this side effect was observed, which led to drop out.³⁴

3.3. Findings from meta-analysis

3.3.1. The effects of cinnamon on FBS

Pooling effect estimates of 18 clinical trials (21 effect sizes) revealed that supplementation with cinnamon reduced FBS by -19.26 mg/dL (95% CI: -28.08, -10.45) compared with the placebo (Fig. 2). However, the heterogeneity among the studies was dramatically high (I²:

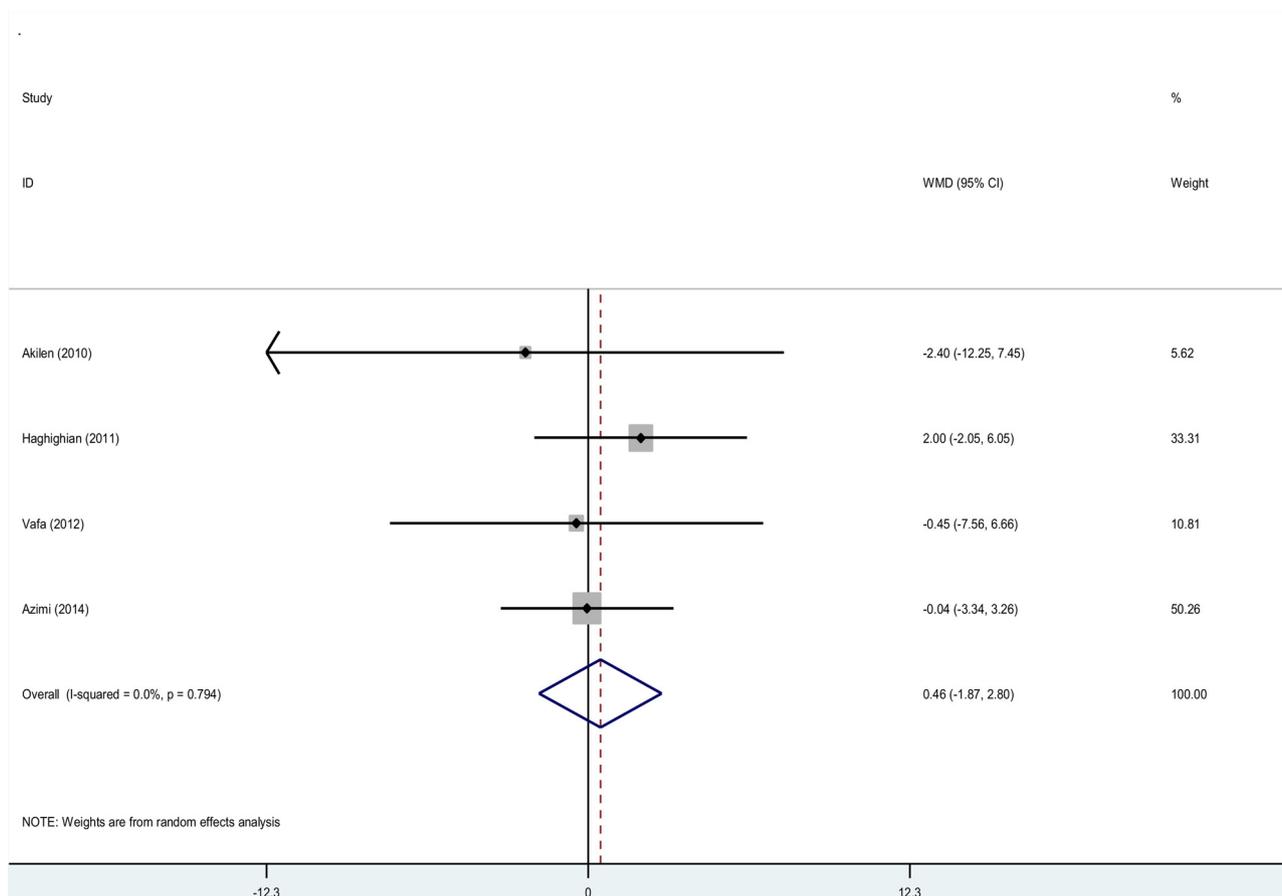


Fig. 4. Forest plot for the effects of supplementation with cinnamon on body weight.

96.5%; $p = 0.0001$). To identify the sources of the between-study heterogeneity, subgroup analyses were conducted (Table 3). After stratification by blindness, adjustment, adherence to diet, and study quality, we did not observe a considerable reduction in the heterogeneity.

3.3.2. The effects of cinnamon on HbA1c

The pooled WMD of 14 effect sizes showed a non-significant reduction in HbA1c in the cinnamon group compared with the placebo group (-0.24% ; 95%CI: $-0.48, -0.01$; $I^2: 76.8\%$, $p = 0.0001$) (Fig. 3). As represented in Table 4, stratification by blindness, adjustment, diet, dosage, duration of the intervention, and study quality did not attenuate the between-study heterogeneity.

3.3.3. The effects of cinnamon on body weight

A forest plot of four datasets indicated that supplementation with cinnamon did not reduce body weight significantly compared to placebo (-0.46 , 95%CI: $-1.87, 2.30$; $I^2: 0\%$; $p = 0.79$) (Fig. 4). As showed in Table 3, there were no significant differences between the powder and extract forms of cinnamon on losing weight. We found no differences on the effects of cinnamon supplement on body weight between low and high quality.

3.3.4. The effects of cinnamon on BMI

Pooling five effect sizes revealed no significant reduction in BMI following supplementation with cinnamon compared to placebo group (WMD: -0.05 kg/m^2 ; 95% CI: $-0.52, 0.42$; $I^2: 0\%$; $p = 0.91$) (Fig. 5).

3.3.5. The effects of cinnamon on Waist circumference

Among the included studies, only two clinical papers examined WC. The overall effect size showed no significant reduction in WC after the supplementation with cinnamon compared to placebo (WMD: -0.53 cm ;

95% CI: $-3.96, 2.81$; $I^2: 0\%$; $p = 0.66$) (Fig. 6).

3.4. Publication bias & sensitivity analysis

Funnel plot showed no publication bias for FBS and HbA1c that was confirmed with Begg's test. Based on Begg's test, there was no publication bias for FBS concentrations ($p = 0.28$) and HbA1c ($p = 0.78$). Besides, no publication bias was existed for body weight ($p = 0.51$) and BMI ($p = 0.52$) (Egger's regression test). Based on sensitivity analysis, excluding no clinical trial changed the pooled effect sizes.

4. Discussion

Supplementation with cinnamon can reduce serum levels of glucose with no changes in other glycemic parameters and anthropometric indices. However, because of high heterogeneity, findings should be interpreted with great caution. Based on our findings, taking cinnamon did not have any serious side effects. Findings of the present study can be helpful for clinicians and other health care providers.

There are two prior meta-analyses on the effects of cinnamon on glycemic parameters. Our findings were similar to the meta-analysis done by Allen et al.¹⁹ In their study, 10 randomized clinical trials were included until 2012. They found that supplementation with cinnamon reduced FBS (-24.6 mg/dL) with no changes in HbA1c, whereas the between-study heterogeneity was high.¹⁹ However, they did not examine insulin status. Findings obtained from our meta-analysis showed that cinnamon can reduce FBS by 19 mg/dL . Differences in the amount of reduction may be related to the number of included studies and the role of study weight on the pooled effect size. In another meta-analysis by Akilen et al, (including 6 clinical trials), similar to our findings it was revealed that cinnamon reduced FBS by 15 mg/dL . However, in

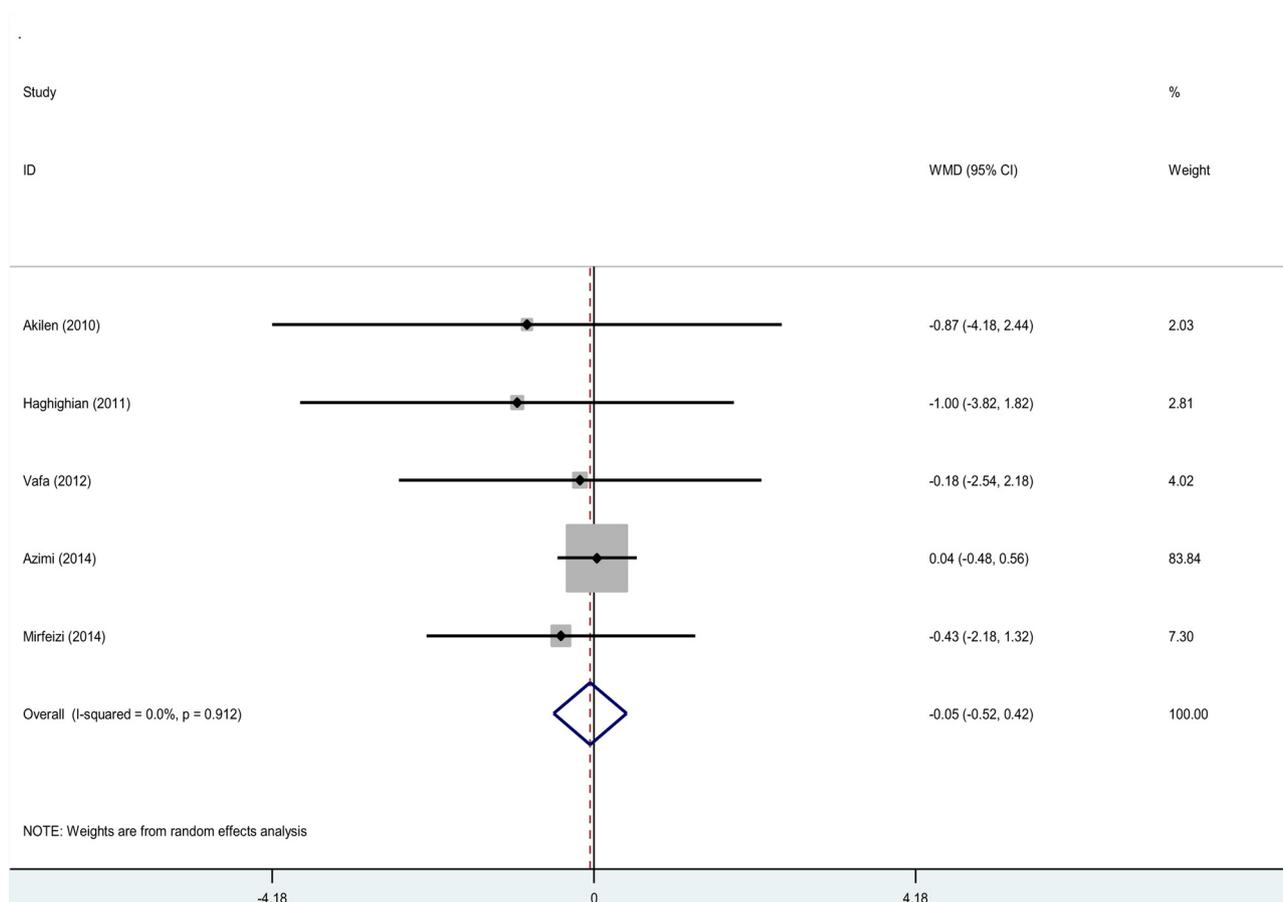


Fig. 5. Forest plot for the effects of supplementation with cinnamon on body mass index.

constant with our results they reported a positive effect of cinnamon on HbA1c.¹⁹ Different findings might be due to differences in inclusion criteria between the two studies. Akilen et al, included all clinical trials without considering randomization. Non-randomized study design can cause bias in findings. Therefore, extracting findings based on only randomized clinical trials can attenuate the risk of bias as was considered in our meta-analysis. Even without considering this point, -0.09% reduction in HbA1c following supplementation with cinnamon was not clinically considerable.

In a meta-analysis on *in-vivo/in vitro* studies, it was demonstrated that Cinnamomum zeylanicum reduced post-prandial intestinal glucose absorption, stimulated glucose uptake, glucose metabolism and glycogen synthesis, inhibited gluconeogenesis and stimulated insulin release and insulin receptor activity. The pooled findings of animal studies indicated that this type of cinnamon species reduced body weight, FBS, HbA1c, and enhanced circulating insulin levels.³⁸ In this meta-analysis, human studies were not included so that we could not compare findings; however our attention can be drawn to the effects of different herb species on metabolic status. In our meta-analysis, the cinnamon species used in the half of clinical trials were not clear and in the remaining the effects of *C. cassia* were examined. Therefore, we could not compare the effects of difference species of cinnamon.

In the present study to attenuate heterogeneity, subgroup analyses were conducted. However, the heterogeneity was not reduced considerably even after stratification by study quality. Therefore, although we found a significant reduction in FBS levels, findings should be interpreted with caution. Based on these findings, clinicians cannot recommend cinnamon as a complementary therapy in patients with T2DM.

In the present meta-analysis, no studies but one reported side effects. Only skin allergy was observed in one study subject.³⁴ In line with

our findings, Leach et al, reported that adverse effects to oral cinnamon were mild and infrequent in patients with type 1 and type 2 diabetes.²⁶ Moreover, in a systematic review regarding the adverse event of cinnamon, it was reported that gastrointestinal disorders and allergic reactions were the most frequent side effects of cinnamon regardless of their disease background. They suggested that in spite of its safety as a spice, high dosages of cinnamon that are used for medical therapy can be accompanied by considerable adverse effects that should be clinically monitored.³⁹

Mechanisms by which cinnamon showed anti-diabetic activities have not been thoroughly identified.⁴⁰ However, several pathways are suggested as follows:

4.1. Effects on insulin receptor

Cinnamtannin B1, a proanthocyanidin component extracted from Ceylon cinnamon, can stimulate the phosphorylation of insulin receptor β -subunit on adipocytes and other insulin receptors; thereby it can enhance insulin sensitivity.⁴⁰

4.2. Effects on glucose transporter-4 (GLUT-4)

Nikzamid et al found a significant increase in the expression of GLUT-4 receptor and its mRNA, in cinnamaldehyde treated C2C12 skeletal muscle cells.⁴¹ Furthermore, cinnamon extract can induce GLUT-4 translocation through the AMPK signaling pathway. Based on evidence, cinnamon can enhance both GLUT-4 receptors and IR substrates and facilitate glucose entry into cells.^{42,43}

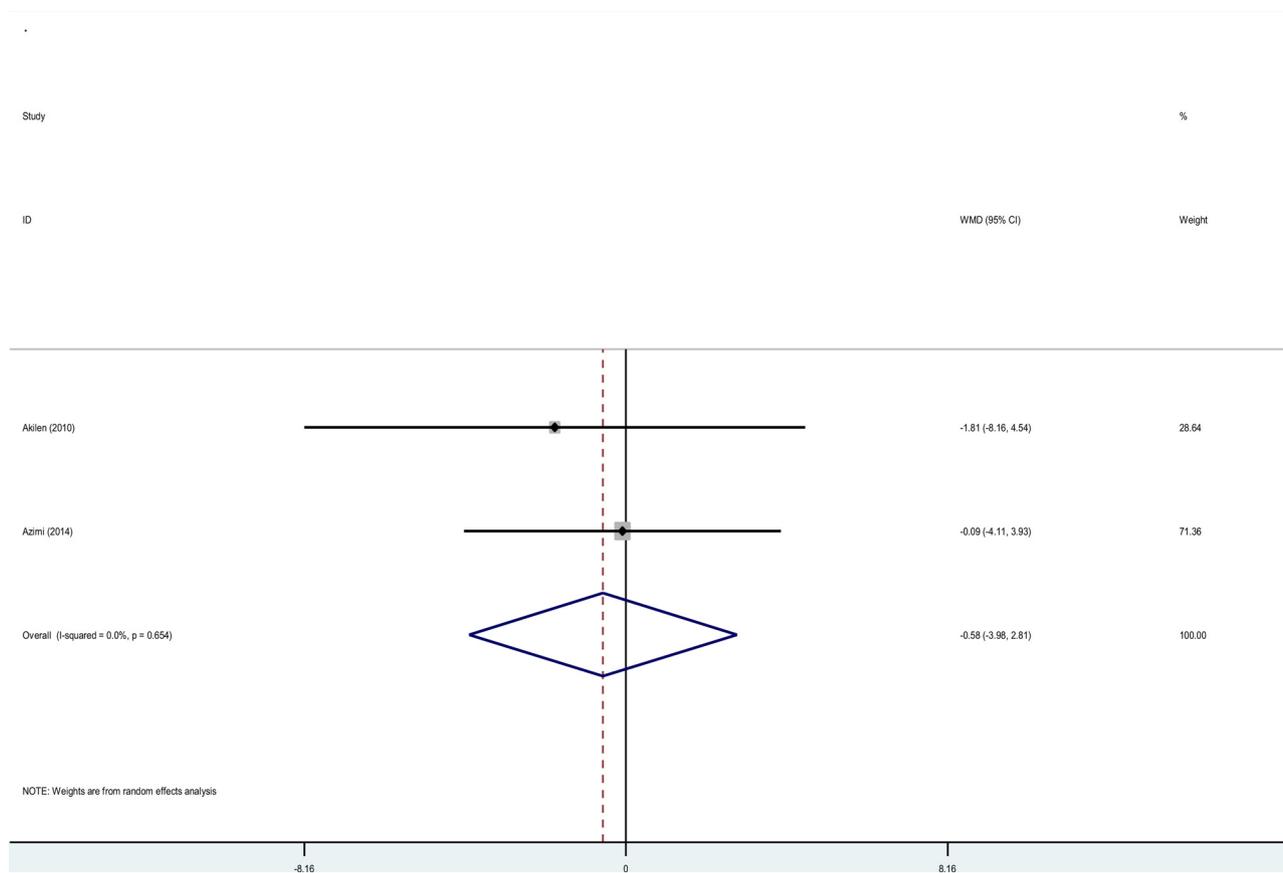


Fig. 6. Forest plot for the effects of supplementation with cinnamon on waist circumference.

4.3. Effects on gluconeogenesis

Pyruvate kinase (PK) and Phosphoenol Pyruvate Carboxikinase (PEPCK) enzymes are involved in the regulating of hepatic glucose metabolism. In diabetic rats, the PK activity is decreased and PEPCK activity is increased. The reduced PK activity of Streptozotocin treated rats can come back to near normal value after treatment with cinnamon.⁴⁴

4.4. Effects on Peroxisome proliferator activator receptor (PPAR)

Cinnamon can enhance the expression of Peroxisome proliferator-activated-alpha (PPAR- α) and PPAR- γ . Thus, it can increase insulin sensitivity.⁴⁵

Based on evidence, cinnamon can also increase glucose uptake and glycogen synthesis.^{23,25} It is likely to initiate insulin cascade system and act as insulin sensitizer.²⁵ In an experimental study, it was shown than cinnamon can enhance the activity of insulin 3 times in glucose metabolism.⁴⁶ Through activation of insulin receptor kinase and the inhibition insulin receptor dephosphorylation, cinnamon can have positive effects on glycemic status.^{23,24} Furthermore, it was indicated that cinnamon increased UCP3 gene expression that plays a pivotal role in fatty acid metabolism. UCP3 gene expression involves in carbohydrate and lipid oxidation and affects BMI. It also participates in energy metabolism and delays gastric emptying.¹⁹ Therefore, it can indirectly participate in losing weight. However, in the present study we found no significant effect of cinnamon on anthropometric indices including weight, BMI, and WC. Most included studies recommended cinnamon powder with maximum 6 g/day. Probably more dosages, other forms (extract, oil) or species are needed to reach weight loss. As we examined the effects of cinnamon on anthropometric indices, insulin secretion and insulin resistance, no significant findings were obtained. Other

mechanisms are likely to involve in a reduction in glucose level.

The present meta-analysis have several limitations as follows: i) although we did subgroup analyses, the heterogeneity remained substantially high for most variables, ii) we could not do meta-analysis on different indices of insulin resistance and insulin sensitivity due to limited studies, iii) as the species for cinnamon were not clear in half of the studies, subgroup analysis for different species was not possible, and iv) most studies did not control covariates and the pooled effect size can be affected by this issue. Doing subgroup analysis, examining the quality of studies, and reporting the results based on this factor, considering different glycemic parameters and anthropometric indices to clarify possible anti-diabetic mechanisms of cinnamon, covering the limitations of the previous meta-analyses, and updating the results due to a substantial increase in the number of clinical trials compared with the previous meta-analyses were among the strength points for the current systematic review and meta-analysis.

5. Conclusion

Supplementation with cinnamon can reduce serum levels of glucose with no changes in other glycemic parameters and anthropometric indices. Mechanisms other than losing weight, increasing serum levels of insulin, and reduction in insulin resistance following cinnamon intake might be involved in its anti-diabetic effects. However due to high heterogeneity, findings should be interpreted with great caution. More high quality randomized clinical trials that consider and control covariates are necessary to draw a certain decision on the efficacy of cinnamon as a complementary therapy for type 2 diabetes.

Conflict of interest

Authors declared no conflict of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ctim.2019.01.002>.

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