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REVIEW

WILEY

The effect of cinnamon supplementation on glycemic control in patients with type 2 diabetes mellitus: An updated systematic review and dose-response meta-analysis of randomized controlled trials

Amir Hossein Moridpour[1] | Zeynab Kavyani[1,2] | Somaye Khosravi[3] | Elahe Farmani[4] | Maziar Daneshvar[4] | Vali Musazadeh[1,2] | Amir Hossein Faghfouri[5]

[1]Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran

[2]School of Nutrition and Food Sciences, Tabriz University of Medical Sciences, Tabriz, Iran

[3]Department of Medicine, Tehran University of Medical Sciences, Tehran, Iran

[4]Tehran University of Medical Sciences, Tehran, Iran

[5]Maternal and Childhood Obesity Research Center, Urmia University of Medical Sciences, Urmia, Iran

Correspondence
Amir Hossein Faghfouri and Vali Musazadeh, School of Nutrition and Food Sciences, Tabriz University of Medical Sciences, Tabriz, Iran.
Email: amir.nut89@gmail.com; mosazadeh.vali05@gmail.com

Abstract

Although many randomized controlled trials (RCTs) have revealed the benefits of cinnamon on type 2 diabetes mellitus (T2DM), the effects of cinnamon supplementation on glycemic control in patients with T2DM are inconclusive. Therefore, the aim of this meta-analysis of RCTs was to assess the effects of cinnamon supplementation in managing glycemic control in patients with T2DM. Scientific international databases including Scopus, Web of Sciences, PubMed, Embase, and the Cochrane Library were searched till December 2022. For net changes in glycemic control, standard mean differences (SMDs) were calculated using random-effects models. Findings from 24 RCTs revealed that cinnamon supplementation had a statistically significant reduction in fasting blood sugar (SMD: −1.32; 95% CI: −1.77, −0.87, $p < 0.001$), Homeostatic Model Assessment for Insulin Resistance (SMD: -1.32; 95% CI: −1.77, −0.87, $p < 0.001$), and hemoglobin A1C (SMD: −0.67; 95% CI: −1.18, −0.15, $p = 0.011$) compared with the control group in patients with T2DM. Additionally, cinnamon did not change the serum levels of insulin (SMD: −0.17; 95% CI: −0.34, 0.01, $p = 0.058$) significantly. Our analysis indicated that glycemic control indicators are significantly decreased by cinnamon supplementation. Together, these findings support the notion that cinnamon supplementation might have clinical potential as an adjunct therapy for managing T2DM.

KEYWORDS
cinnamon, glycemic control, meta-analysis, systematic review, type 2 diabetes

1 | INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a metabolic disease that affects many people around the world (Galicia-Garcia et al., 2020). It was estimated that 415 million people would suffer from diabetes until 2015 and also predicted that the number of diabetes patients will reach 642 million worldwide by 2040 (Atlas, 2015). It puts a lot of pressure on the socioeconomic status of people and has a huge financial impact on the health systems of the world (Seuring et al., 2015). Diabetes management can avoid or lessen the likelihood of these consequences. According to reports, a 1% decrease in hemoglobin A1C (HbA1c) is related with a 21% decreased risk of diabetic complications (Tang et al., 2016). It is worthwhile to investigate methods for

Amir Hossein Moridpour and Zeynab Kavyani have contributed equally to this work and share first authorship.

lowering blood glucose levels. The major treatments for T2DM involve weight loss, improvements in other anthropometric measurements (such as waist circumference), and changes in metabolism along with dietary changes and medication (Association, 2018; Franz et al., 2015).

As herbal medicines are known for their health-promoting and disease-preventing properties, recent years have seen an increased interest in them (Khorshidi et al., 2016; Mousavi et al., 2019). However, there is frequently insufficient data to support their benefits or safety. The effects of several medicinal plants on T2DM and obesity have already been studied (Asadi-Samani et al., 2017; Bahmani et al., 2016; Namazi et al., 2012; Namazi et al., 2018). One of these herbs is cinnamon, which is mostly prepared from cinnamon leaves and bark of the plant. It is an evergreen tree of the Lauraceae family (Błaszczyk et al., 2021). The three most well-known varieties are *Cinnamomum zeylanicum*, *Cinnamomum camphora*, and *Cinnamomum cassia* (L.) J. Presl (Błaszczyk et al., 2021). Cinnamaldehyde, cinnamate, and cinnamic acid are the three primary compounds in cinnamon and are important for a variety of biological processes (Namazi et al., 2019).

There is evidence of positive health effects of cinnamon such as possessing anti-diabetic, lipid-lowering, anti-tumor, anti-inflammatory, and antioxidant properties (Błaszczyk et al., 2021; Namazi et al., 2019). Cinnamon may affect the glycemic control by acting as insulin-like molecules, strengthening beta-cell function, antioxidant activity, lowering insulin resistance and gluconeogenesis, improving insulin sensitivity, and increasing insulin secretion (Akilen et al., 2010; Sengsuk et al., 2016; Vanschoonbeek et al., 2006; Zare et al., 2019). However, there are contradictory findings from randomized controlled trials (RCTs) (Mirfeizi et al., 2016a; Vanschoonbeek et al., 2006). Due to a significant degree of heterogeneity, recent meta-analyses on the effects of cinnamon in T2DM patients were unable to reach a definitive result (Deyno et al., 2019; Namazi et al., 2019). Therefore, the present meta-analysis study aimed to examine the effects of cinnamon supplementation on glycemic control, including serum levels of fasting blood sugar (FBS), Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), insulin, and HbA1c in patients with T2DM.

2 | METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed to conduct and report the current meta-analysis (Moher et al., 2015). Additionally, we registered our study protocol with PROSPERO, the prospective international register of systematic reviews (ID: CRD42023394231).

2.1 | Search strategy

Scientific international databases including Scopus, Web of Sciences, PubMed, Embase, and the Cochrane Library were searched by two independent reviewers (VM, AHF). Relevant studies published till December 2022 were searched from these databases without language restrictions. The pattern of the search strategy is provided in Table S1. Both text words and headings for medical subjects were used in the keyword search. In order to find additional potentially pertinent works, the reference lists of the chosen publications and earlier systematic reviews were separately examined.

2.2 | Inclusion and exclusion criteria

Two researchers (ZK and AHM) individually reviewed the article titles and abstracts to find relevant studies. To make the final study selection for this meta-analysis, the same authors independently reviewed the full texts of all included abstracts. Retrieved studies were included in our meta-analysis if they met the following evidence-based PICOS criteria: (1) Patients: adult individuals >18 years old with T2DM; (2) Intervention: cinnamon supplementation; (3) Control: placebo intervention; (4) Outcomes: sufficient data for extraction regarding serum FBS, serum insulin, HbA1c, or HOMA-IR; and (5) Study design: RCTs. Excluded studies had the following criteria: (1) utilized a treatment in which cinnamon was used in combination with other dietary supplements or medications; (2) the intervention lasted less than 2 weeks; (3) the mean age of the participants was less than 18 years old (adolescents or children); (4) experimental studies, observational studies; and (5) animal or in vitro/in vivo studies. Any disagreement about the choice of studies was settled by consensus (AHF).

2.2.1 | Study selection and data extraction

Data were extracted using a data collection sheet by two researchers (ZK and AHM), each working individually and in pairs. In addition to participant information (gender, health status, baseline body mass index [BMI], and mean age), study details (first author's last name, study location, study design, total sample size, and year of publication), intervention information (study duration, type of intervention, dose of cinnamon), and the main findings are also included in these data. Discussions were arranged to settle disagreements on data extraction (AHF).

2.3 | Assessment of study quality and assessment of the meta-evidence

Using the Cochrane risk-of-bias tool, two investigators (ZK and AHM) individually evaluated the risk of bias of the included studies. The seven questions on this scale are as follows: (a) allocation concealment, (b) random sequence generation, (c) other sources of bias and (d) selective reporting, (e) incomplete outcome data, (f) blinding (outcome assessment), and (g) blinding of personnel and participants. The risk of bias for each item was classified as low, high, or unclear. A third author (AHF) reevaluated any discrepancies in the quality rating.

The RCTs' credibility was evaluated using the GRADE (Grading of Recommendations, Assessment, and Evaluation) approach, which consisted of five factors: risk of bias; consistency of results; directness; precision; and potential for publication bias. Evidence is categorized into four categories: high, moderate, low, or very low.

2.4 | Statistical analysis

STATA version 16 was used to conduct statistical analysis (Stata Corp, College Station, TX). When data were presented as standard errors (SEs), 95% confidence intervals (CIs), and interquartile ranges (IQRs), they were converted to the means and standard deviations (SDs). Between-study heterogeneity was quantified using Cochran's *Q* test and evaluated using an *I*-square (I^2) statistic. Significant between-study heterogeneity was considered to be present when the I^2 value was more than 50.5% or the *p*-value was less than 0.1. Analyzing subgroups was conducted to determine the parameters that induced heterogeneity, based on average age, baseline BMI, the dosage of cinnamon, sample size, duration, type of cinnamon, and study quality. Additionally, a random-effects model was used to estimate the standardized mean differences (SMDs) with 95% CIs (Van Tulder, Furlan, Bombardier, Bouter, & Group, 2003). A sensitivity analysis was performed to assess the effect of a single study on the overall SMDs. Begg's adjusted rank correlation and Egger's regression asymmetry test were both employed to explore the impacts of small studies (Begg & Mazumdar, 1994; Egger et al., 1997). Funnel plots were used to assess publication bias. We used the "trim and fill" method to attribute studies that may have been overlooked when publication bias was recognized because of this. We examined the evidence of any linear, and nonlinear relationship between the observed SMDs and sample size, duration, and dose of cinnamon.

3 | RESULTS

3.1 | Literature search

The study inclusion process is illustrated in Figure 1. In total, 797 records were identified in a combined search of electronic databases; of the 449 papers after removing duplicated papers, 420 were excluded because they were animal studies ($n = 64$), not relevant to the topic ($n = 356$). Finally, 24 studies were included in the current meta-analysis.

3.2 | Study characteristics

Table 1 gives a summary of the characteristics of the included studies. The total number of subjects included was 1815 (case = 922; control = 893), and the publication dates ranged from 2003 to 2021. A total of 20 to 200 participants made up the sample, and the study

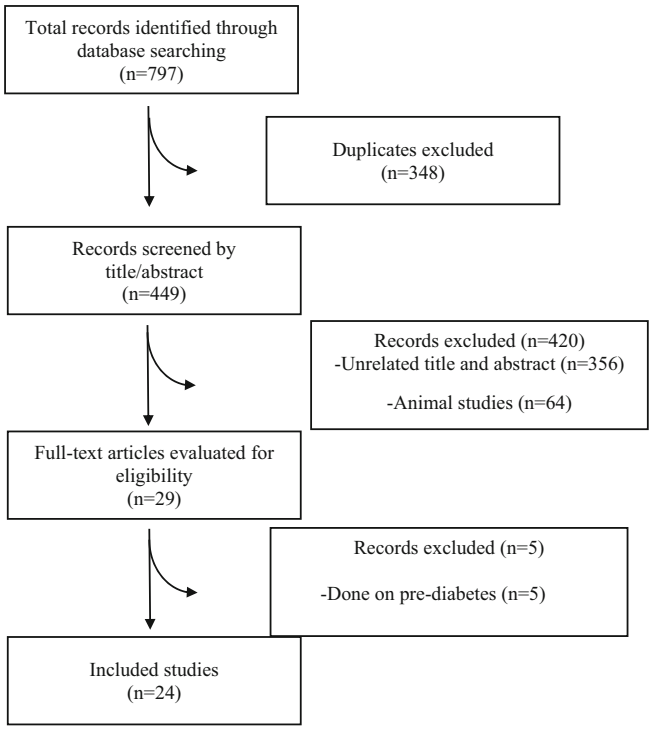

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses flowchart diagram.

lasted 6 to 16 weeks. Most studies used *Cinnamomum cassia* or *Cinnamomum verum*, and daily doses of cinnamon ranged from 120 to 6000 mg/day, with a mean of 2100 mg/day in this collection. The included RCTs were all done on T2DM patients.

The following nations participated in the studies: Iran (Azimi et al., 2014; Davari et al., 2020; Hasanzade et al., 2013; Hosseini et al., 2014; Khadem et al., 2011; Mirfeizi et al., 2016b; Mirmiran et al., 2019; Talaei et al., 2017; Vafa et al., 2012; Zahedifar et al., 2018; Zahmatkesh et al., 2012; Zare et al., 2019), Thailand (Sengsuk et al., 2016; Tangvarasittichai et al., 2015), India (Hendre et al., 2019; Soni & Bhatnagar, 2009), China (Lu et al., 2012), Brazil (Lira Neto et al., 2022), the United Kingdom (Akilen et al., 2010), Israel (Wainstein et al., 2011), the United States (Crawford, 2009), the Netherlands (Vanschoonbeek et al., 2006), Pakistan (Khan et al., 2003), and Germany (Mang et al., 2006).

3.3 | Risk of bias assessment and quality of evidence

Of the 24 RCTs included in the present review, almost all of the included RCTs were of high quality. The assessment of the risk of bias in the included studies using Cochrane criteria is shown in Table 2. HbA1c and HOMA-IR had low-quality evidence, while insulin and FBS had moderate-quality, and very low-quality evidence based on the GRADE approach, respectively (Table 3).

TABLE 1 Characteristics of included studies in meta-analysis.

Author, year	Design	Participants, *n*	Health condition	Age, year	Intervention		Duration (week)
					Treatment group	Control group	
Khan et al. (2003)	RA/parallel	M/F: 20 Int: 10, Con: 10 M/F: 20 Int: 10, Con: 10 M/F: 20 Int: 10, Con: 10	T2DM	52	1000 mg/d Cinnamon (capsule) (*Cinnamomum cassia*) 3000 mg/d Cinnamon (capsule) (*Cinnamomum cassia*) 6000 mg/d Cinnamon (capsule) (*Cinnamomum cassia*)	Placebo: Wheat Flour	8
Mang et al. (2006)	RA/DB/parallel	M/F: 65 Int: 33, Con: 32	T2DM	Int: 62.8, Con: 63.7	3000 mg/d Cinnamon (capsule) (*Cinnamomum cassia*)	Placebo: Microcrystalline Cellulose	16
Vanschoonbeek et al. (2006)	RA/DB/parallel	F: 25 Int: 12, Con: 13	T2DM	Int: 62, Con: 64	1500 mg/d Cinnamon (capsule) (*Cinnamomum cassia*)	Placebo: Wheat Flour	6
Crawford (2009)	RA/SB/parallel	M/F: 109 Int: 55, Con: 54	T2DM	Int: 60.5, Con: 59.9	1000 mg/d Cinnamon (capsule) (*Cinnamomum cassia*)	Placebo: Usual Care	12
Soni and Bhatnagar (2009)	RA/parallel	M: 30 Int: 15, Con: 15	T2DM	40–60	2000 mg/d Cinnamon (capsule) (*Cinnamomum cassia*)	Placebo No Supplement	6
Akilen et al. (2010)	RA/DB/parallel	M/F: 58 Int: 30, Con: 28	T2DM	Int: 54.9, Con: 54.43	2000 mg/d Cinnamon (capsule) (*Cinnamomum cassia*)	Placebo: Starch	12
Khadem et al. (2011)	RA/DB/parallel	M/F: 60 Int: 30, Con: 30	T2DM	Int: 59.1, Con: 54.6	4500 mg/d Cinnamon (capsule) (*Cinnamomum cassia*)	Placebo: Placebo	8
Wainstein et al. (2011)	RA/parallel	M/F: 59 Int: 29, Con: 30	T2DM	Int: 61.7, Con: 64.4	1200 mg/d Cinnamon (capsule) (*Cinnamomum cassia*)	Placebo: Microcrystalline Cellulose	12
Lu et al. (2012)	RA/DB/parallel	M/F: 43 Int: 23, Con: 20 M/F: 43 Int: 23, Con: 20	T2DM	Int: 62.4, Con: 60 Int: 58.9, Con: 60	120 mg/d Cinnamon (Tablet) (*Cinnamomum aromaticum*) 360 mg/d Cinnamon (Tablet) (*Cinnamomum aromaticum*)	Placebo: Placebo	12
Vafa et al. (2012)	RA/DB/parallel	M/F: 37 Int: 19, Con: 18	T2DM	Int: 54.11, Con: 55.67	3000 mg/d Cinnamon (capsule) (*Cinnamomum zeylanicum*)	Placebo: Wheat Flour	8
Zahmatkesh et al. (2012)	RA/DB/parallel	M/F: 61 Int: 31, Con: 30	T2DM	Int: 56.8, Con: 53.1	2000 mg/d Cinnamon (capsule) (*Cinnamomum zeylanicum*)	Placebo: Placebo	
Hasanzade et al. (2013)	RA/DB/parallel	M/F: 71 Int: 35, Con: 36	T2DM	Int: 53.7, Con: 54.7	1000 mg/d Cinnamon (capsule) (*Cinnamomum cassia*)	Placebo: Placebo	8
Hosseini et al. (2014)	RA/DB/parallel	M/F: 47 Int: 24, Con: 23	T2DM	52	3000 mg/d Cinnamon (capsule)	Placebo: Wheat Flour	8
Azimi et al. (2014)	RA/SB/parallel	M/F: 79 Int: 40, Con: 39	T2DM	Int: 54.15, Con: 53.64	3000 mg/d Cinnamon (*Cinnamomum verum*)	Placebo: Tea	8
Mirfeizi et al. (2016a)	RA/DB/parallel	M/F: 72 Int: 27, Con: 45	T2DM	Int: 52, Con: 54	1000 mg/d Cinnamon (capsule)	Placebo: Starch	12
Sengsuk et al. (2016)	RA/DB/parallel	M/F: 99 Int: 49, Con: 50	T2DM	Int: 57.2, Con: 56.9	1500 mg/d Cinnamon (capsule) (*Cinnamomum cassia*)	Placebo: Placebo	8
Tangvarasittichai et al. (2015)	RA/DB/parallel	M/F: 106 Int: 49, Con: 57	T2DM	Int: 57.5, Con: 56.9	1500 mg/d Cinnamon (capsule) (*Cinnamomum cassia*)	Placebo: Placebo	8

TABLE 1 (Continued)

Author, year	Design	Participants, *n*	Health condition	Age, year	Intervention		Duration (week)
					Treatment group	Control group	
Talaei et al. (2017)	RA/DB/parallel	M/F: 39 Int: 20, Con: 19	T2DM	Int: 58.9, Con: 56.26	3000 mg/d Cinnamon (capsule) (*Cinnamomum zeylanicum* Blume)	Placebo: Microcrystalline Cellulose	8
Zahedifar et al. (2018)	RA/DB/parallel	M/F: 136 Int: 68, Con: 68	T2DM	54.04	1500 mg/d Cinnamon (capsule)	Placebo: Wheat Bran	12
Zare et al. (2019)	RA/DB/parallel	M/F: 138 Int: 69, Con: 69	T2DM	Int: 52.1, Con: 53.2	1000 mg/d Cinnamon (capsule) (*Cinnamomum verum*)	Placebo: Starch	12
Hendre et al. (2019)	RA/parallel	M/F: 200 Int: 100, Con: 100	T2DM	35–65	500 mg/d Cinnamon (capsule) + Metformin	Placebo: Metformin	12
Mirmiran et al. (2019)	RA/DB/parallel	M/F: 39 Int: 20, Con: 19	T2DM	Int: 58.9, Con: 56.26	3000 mg/d Cinnamon (capsule)	Placebo: Microcrystalline Cellulose	8
Davari et al. (2020)	RA/DB/parallel	M/F: 39 Int: 20, Con: 19	T2DM	Int: 58.9, Con: 56.26	3000 mg/d Cinnamon (capsule)	Placebo: Microcrystalline Cellulose	8
Lira Neto et al. (2022)	RA/DB/parallel	M/F: 140 Int: 71, Con: 69	T2DM	Int: 61.7, Con: 60.8	3000 mg/d Cinnamon (capsule) (*Cinnamomum verum*)	Placebo: Microcrystalline Cellulose	12

3.4 | Cinnamon on fasting blood sugar

Of the included trials, 23 RCTs with 26 arms (Akilen et al., 2010; Azimi et al., 2014; Davari et al., 2020; Hasanzade et al., 2013; Hendre et al., 2019; Hosseini et al., 2014; Khadem et al., 2011; Khan et al., 2003; Lira Neto et al., 2022; Lu et al., 2012; Mang et al., 2006; Mirfeizi et al., 2016a; Mirmiran et al., 2019; Sengsuk et al., 2016; Soni & Bhatnagar, 2009; Talaei et al., 2017; Tangvarasittichai et al., 2015; Vafa et al., 2012; Vanschoonbeek et al., 2006; Wainstein et al., 2011; Zahedifar et al., 2018; Zahmatkesh et al., 2012; Zare et al., 2019) reported the effect of cinnamon on FBS levels with 1673 participants ($n = 824$ interventions). Cinnamon results in a significant FBS change (SMD: -1.32; 95% CI: −1.77, −0.87, $p < 0.001$; $I^2 = 94.0\%$, $p < 0.001$) (Figure 2a). *Cinnamomum cassia* supplement ≥3000 mg/day among subjects with age < 50 years, and duration of ≤10 weeks contributed to a substantial reduction in FBS levels (Table.4). A small-study effect was shown by Egger's and Begg's analyses ($p < 0.05$). Moreover, an uneven distribution of trials was detected after visual inspection of the funnel plot (Figure 2b). Therefore, trim and fill methods were performed with 30 effect size (four imputed trials) and the findings were still significant (SMD: −1.82; 95% CI: −2.39, −1.25, $p < 0.05$).

3.5 | Cinnamon on hemoglobin A1c

HbA1c level was significantly decreased by cinnamon therapy (SMD: −0.67; 95% CI: −1.18, −0.15, $p = 0.011$; $I^2 = 94.7\%$, $p < 0.001$, RCTs = 18 with 19 arms [1309 participants]) (Figure 3a) (Akilen et al., 2010; Azimi et al., 2014; Crawford, 2009; Davari et al., 2020; Hasanzade et al., 2013; Lira Neto et al., 2022; Lu et al., 2012; Mang et al., 2006; Mirfeizi et al., 2016b; Mirmiran et al., 2019; Sengsuk et al., 2016; Talaei et al., 2017; Tangvarasittichai et al., 2015; Vafa et al., 2012; Vanschoonbeek et al., 2006; Wainstein et al., 2011; Zahedifar et al., 2018; Zahmatkesh et al., 2012; Zare et al., 2019). Subgroup analysis showed that *Cinnamomum cassia* in dosage of <3000 mg/day, mean age of <50 years, and duration more than 10 weeks are associated with a notable cinnamon impact on HbA1c levels (Table 4). Begg's and Egger's tests revealed no significant small-study effect ($p > 0.05$). In addition, publication bias was observed by visual inspection of the funnel plot (Figure 3b). Thus, trim and fill methods were carried out with three imputed trials (22 studies) (SMD: −0.95; 95% CI: −1.49, −0.41, $p < 0.05$).

3.6 | Cinnamon on Homeostatic Model Assessment for Insulin Resistance

Eight RCTs (Davari et al., 2020; Hendre et al., 2019; Lira Neto et al., 2022; Mirfeizi et al., 2016a; Mirmiran et al., 2019; Talaei et al., 2017; Tangvarasittichai et al., 2015; Zare et al., 2019)

TABLE 2 Results of risk of bias assessment for randomized clinical trials included in the current meta-analysis on the effects of cinnamon supplementation on glycemic control.

Study	Random sequence generation	Allocation concealment	Reporting bias	Other sources of bias	Performance bias	Detection bias	Attrition bias
Khan et al. (2003)	L	U	H	H	U	U	H
Mang et al. (2006)	L	H	L	H	L	L	L
Vanschoonbeek et al. (2006)	U	U	L	H	L	L	U
Crawford (2009)	L	L	H	H	H	L	L
Soni and Bhatnagar (2009)	U	U	H	H	U	U	U
Akilen et al. (2010)	L	L	L	H	L	L	L
Khadem et al. (2011)	L	L	H	H	L	L	L
Wainstein et al. (2011)	L	U	L	H	U	U	H
Lu et al. (2012)	L	H	L	H	L	L	L
Vafa et al. (2012)	L	U	L	L	L	L	U
Zahmatkesh et al. (2012)	L	U	L	H	L	L	L
Hasanzade et al. (2013)	L	L	L	H	L	L	H
Hosseini et al. (2014)	L	U	H	H	L	L	L
Azimi et al. (2014)	L	L	L	L	L	H	L
Mirfeizi et al. (2016b)	L	L	L	L	L	L	L
Sengsuk et al. (2016)	L	L	L	H	L	L	L
Tangvarasittichai et al. (2015)	L	L	L	H	L	L	L
Talaei et al. (2017)	L	L	L	H	L	L	L
Zahedifar et al. (2018)	L	L	L	H	L	L	H
Zare et al. (2019)	L	L	L	L	L	L	L
Hendre et al. (2019)	L	H	L	H	U	U	H
Mirmiran et al. (2019)	L	L	L	H	L	L	L
Davari et al. (2020)	L	L	L	H	L	L	L
Lira Neto et al. (2022)	L	L	L	H	L	L	L

Note: Each study was assessed for risk of bias using the Cochrane Risk of Bias Assessment tool. Domains of assessment included were random sequence generation, allocation concealment, reporting bias, performance bias, detection bias, attrition bias, and other sources of bias. Each domain was scored as "high risk" if it contained methodological flaws that may have affected the results, "low risk" if the flaw was deemed inconsequential, and "unclear risk" if information was insufficient to determine. If a study got "low risk" for all domains, it is considered as a high-quality study with totally low risk of bias.

investigated the impact of cinnamon on HOMA-IR with 773 participants ($n = 376$ interventions). Overall, the forest plot's findings showed that cinnamon significantly affected HOMA-IR levels (SMD: −0.44; 95% CI: −0.77, −0.10; $p = 0.011$; $I^2 = 79.1\%$; $p < 0.001$) (Figure 4). A more noticeable decrease in HOMA-IR was seen with cinnamon supplements of less than 3000 mg/day, interventions lasting longer than 10 weeks, and samples larger than 50 participants (Table 4). According to the results of Begg's tests ($p = 0.621$), there was no significant publication bias.

3.7 | Cinnamon on insulin

The efficacy of cinnamon on insulin was reported by 12 RCTs on 973 participants. No substantial improvement was observed in patients who received supplementation (SMD: −0.17; 95% CI: −0.34, 0.01, $p = 0.058$; $I^2 = 40.8\%$, $p = 0.069$) (Figure 5a) (Azimi et al., 2014; Davari et al., 2020; Hendre et al., 2019; Lira Neto et al., 2022; Mirfeizi et al., 2016b; Mirmiran et al., 2019; Talaei et al., 2017; Tangvarasittichai et al., 2015; Vafa et al., 2012;

TABLE 3 Summary of findings and quality of evidence assessment using the GRADE approach.

	Summary of findings		Quality of evidence assessment (GRADE)					
Glycemic measures	No of patients (trials)	SMD* (95% CI)	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias[e]	Quality of evidence[f]
FBS	1673 (23)	−1.32 (−1.77, −0.87)	Serious	Serious	Not Serious	Serious	Not Serious	Very Low
HbA1c (%)	1309 (18)	−0.67 (−1.18, −0.15)	Serious	Serious	Not Serious	Not Serious	Not Serious	Low
HOMA-IR	773 (8)	−0.44 (−0.77, −0.10)	Not Serious	Serious	Not Serious	Serious	Not Serious	Low
Insulin	973 (12)	−0.17 (−0.34, 0.01)	Not Serious	Not Serious	Not Serious	Serious	Not Serious	Moderate

Abbreviations: FBS, Fasting blood sugar; HbA1C, Hemoglobin A1c; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance.
[a]Risk of bias based on the Cochrane risk of bias tool. This tool assesses selection bias, performance bias, detection bias, attrition bias, and reporting bias. Five of eight included studies had incomplete outcome data (attrition bias). Half of included studies had performance bias.
[b]Downgraded if there was a substantial unexplained heterogeneity (I^2 > 50%, p < 0.10) that was unexplained by meta-regression or subgroup analyses.
[c]Downgraded if there were factors present relating to the participants, interventions, or outcomes that limited the generalizability of the results.
[d]Downgraded if the 95% confidence interval (95% CI) crossed the minimally important difference (MID) for benefit or harm. MIDs used for each outcome were: 0.3% for HbA1c, 9 mg/dL for FBS, 1.2 μIU/dL for insulin, 1.77 for HOMA-IR, 3.09 for HOMA-β, and 0.32 for QUICKI.
[e]Downgraded if there was an evidence of publication bias using funnel plot that affected overall results detecting by trim and fill analysis.
[f]Since all included studies were randomized controlled trials, the certainty of the evidence was graded as high for all outcomes by default and then downgraded based on prespecified criteria. Quality was graded as high, moderate, low, very low.
*Presented as standard mean difference (SMD) of all outcomes.

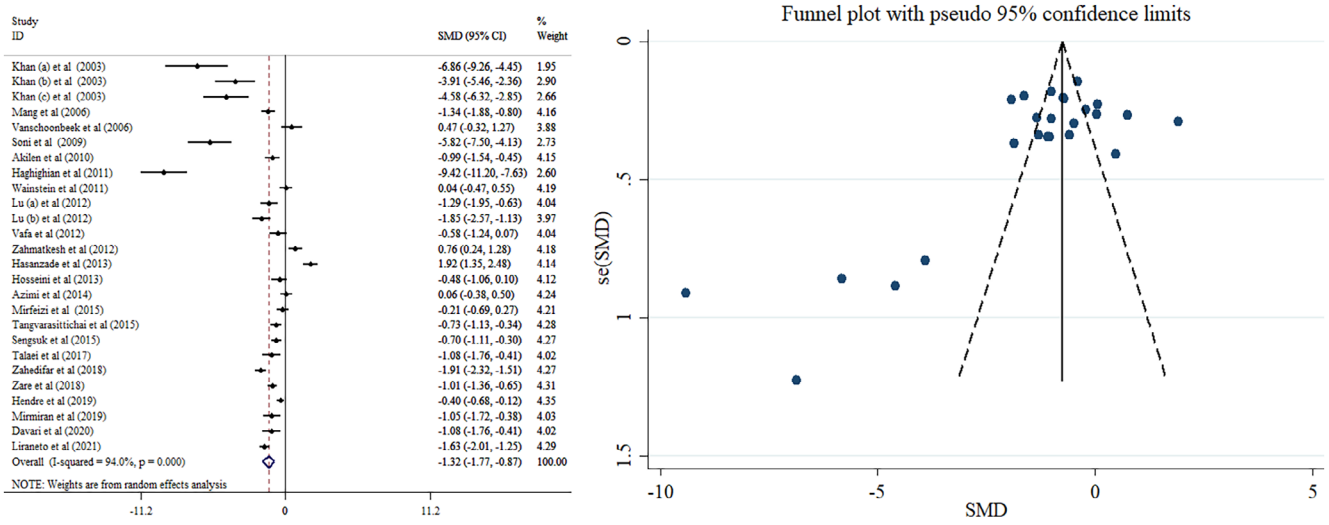

FIGURE 2 Forest plot (a) detailing mean difference and 95% confidence intervals and funnel plot (b) displaying publication bias in the studies reporting the effects of cinnamon supplementation on fasting blood sugar levels.

Vanschoonbeek et al., 2006; Wainstein et al., 2011; Zare et al., 2019). With a sample size of more than 50 patients, cinnamon cassia in a dosage of about 3000 mg/day contributed to a greater reduction in insulin levels (Table.4). No significant small-study effect was found by Egger's and Begg's tests (p > 0.05). Due to the funnel plot assessment's visual inspection results, which showed an uneven distribution of studies (Figure 5b), therefore, we used 15 effect sizes (three imputed studies) in the trim and fill test, and led to the results were significant (SMD: −0.234; 95% CI: −0.396, −0.071; p < 0.05).

3.8 | Meta-regression and sensitivity analyses

A meta-regression analysis was done to look into any possible relationships between cinnamon supplementation's dose (mg/day), sample size, and duration (weeks), and changes in FPG, HbA1c, HOMA-IR, and insulin. There was no evidence of a linear relationship between dosage, sample size, duration, and absolute change in glycemic control, according to meta-regression analysis. After performing sensitivity analyses for FBS, HOMA-IR, and HbA1c, there was no discernible difference when one specific study was excluded. Moreover, the

TABLE 4 Subgroup analyses for the effects of cinnamon supplementation on glycemic control.

	NO	SMD (95% CI)[a]	*p*-within[b]	I^2 (%)[c]	*p*-heterogeneity[d]
Cinnamon supplementation on FBS					
Overall	26	−1.32 (−1.77, −0.87)	<0.001	94.0	<0.001
Age(year)					
<55	13	−1.46 (−2.16, −0.77)	<0.001	94.9	<0.001
≥55	13	−1.21 (−1.82, −0.61)	<0.001	93.2	<0.001
Intervention duration (week)					
≤10	16	−1.70 (−2.48, −0.93)	<0.001	95.3	<0.001
>10	10	−1.05 (−1.47, −0.62)	<0.001	88.9	<0.001
Dosage of cinnamon (mg/day)					
<3000	15	−0.90 (−1.45, −0.34)	<0.001	94.3	<0.001
≥3000	11	−1.95 (−2.73, −1.17)	<0.001	93.4	<0.001
Type of cinnamon					
Cinnamomum cassia	14	−2.17 (−3.06, −1.28)	<0.001	95.7	<0.001
Cinnamomum verum	6	−0.58 (−1.30, 0.13)	0.111	92.7	<0.001
Not given	6	−0.85 (−1.43, −0.27)	0.004	88.8	<0.001
Sample size					
≤50	11	−2.15 (−2.99, −1.31)	<0.001	90.0	<0.001
>50	15	−0.84 (−1.39, −0.30)	<0.001	95.3	<0.001
BMI					
≤25	2	−0.72 (−1.00, −0.44)	<0.001	0.0	0.917
25–30	11	−1.01 (−1.77, −0.24)	0.010	95.1	<0.001
>30	2	−0.29 (−1.72, 1.14)	0.691	88.7	0.003
NR	11	−2.12 (−2.91, −1.33)	<0.001	94.6	<0.001
Study quality					
Low	14	−2.20 (−3.09, −1.30)	<0.001	96.2	<0.001
High	12	−0.68 (−1.05, −0.32)	<0.001	85.5	<0.001
Cinnamon supplementation on HbA1c					
Overall	19	−0.67 (−1.18, −0.15)	0.011	94.7	<0.001
Age(year)					
<55	7	−1.07 (−2.09, −0.05)	0.039	96.6	<0.001
≥55	12	−0.43 (−0.99, 0.13)	0.136	92.4	<0.001
Intervention duration (week)					
≤10	9	−0.04 (−0.67, 0.59)	0.901	90.9	<0.001
>10	10	−1.24 (−1.98, −0.49)	<0.001	95.7	<0.001
Dosage of cinnamon (mg/day)					
<3000	12	−0.91 (−1.68, −0.13)	0.022	96.3	<0.001
≥3000	7	−0.29 (−0.76, 0.18)	0.226	81.8	<0.001
Type of cinnamon					
Cinnamomum cassia	9	−0.74 (−1.38, −0.10)	0.023	92.1	<0.001
Cinnamomum verum	6	−0.32 (−1.09, 0.44)	0.405	93.5	<0.001
Not given	4	−1.03 (−3.14, 1.07)	0.337	98.1	<0.001
Sample size					
≤50	7	−0.68 (−1.53, 0.18)	0.120	90.5	<0.001
>50	12	−0.66 (−1.32, −0.01)	0.048	96.0	<0.001
BMI					
≤25	1	−0.97 (−1.39, −0.56)	<0.001	-	-

TABLE 4 (Continued)

	NO	SMD (95% CI)[a]	*p*-within[b]	I^2 (%)[c]	*p*-heterogeneity[d]
25–30	9	−0.06 (−0.49, 0.36)	0.769	81.9	<0.001
>30	4	−0.81 (−1.28, −0.34)	<0.001	72.7	0.012
NR	5	−1.69 (−3.63, 0.25)	0.088	98.2	<0.001
Study quality					
Low	9	−0.91 (−2.06, 0.24)	0.120	97.3	<0.001
High	10	−0.49 (−0.84, −0.15)	0.005	79.9	<0.001
Cinnamon supplementation on HOMA-IR					
Overall	8	−0.44 (−0.77, −0.10)	0.011	79.1	<0.001
Age (year)					
<55	3	−0.66 (−1.45, 0.14)	0.559	92.7	<0.001
≥55	5	−0.35 (−0.56, −0.15)	0.008	0.0	0.614
Intervention duration (week)					
≤10	4	−0.28 (−0.55, −0.02)	0.038	0.0	0.596
>10	4	−0.61 (−1.16, −0.06)	0.028	89.3	<0.001
Dosage of cinnamon (mg/day)					
<3000	4	−0.61 (−1.18, −0.05)	0.034	89.2	<0.001
≥3000	4	−0.30 (−0.55, −0.06)	0.015	0.0	0.546
Type of cinnamon					
Cinnamomum cassia	1	−0.48 (−0.86, −0.09)	0.016	-	-
Cinnamomum verum	3	−0.70 (−1.50, 0.09)	0.084	90.4	<0.001
Not given	4	−0.25 (−0.46, −0.04)	0.021	0.0	0.824
Sample size					
≤50	3	−0.11 (−0.47, 0.25)	0.559	0.0	0.985
>50	5	−0.58 (−1.02, −0.15)	0.008	85.8	<0.001
Cinnamon supplementation on insulin					
Overall	12	−0.17 (−0.34, 0.01)	0.058	40.8	0.069
Age (year)					
<55	5	−0.26 (−0.54, 0.02)	0.064	56.3	0.058
≥55	7	−0.08 (−0.29, 0.12)	0.431	15.2	0.314
Intervention duration (week)					
≤10	7	−0.10 (−0.32, 0.11)	0.356	6.2	0.380
>10	5	−0.25 (−0.53, 0.03)	0.077	63.9	0.026
Dosage of cinnamon (mg/day)					
<3000	6	−0.35 (−0.57, −0.12)	0.003	42.1	0.124
≥3000	6	0.05 (−0.15, 0.25)	0.634	0.0	0.986
Type of cinnamon					
Cinnamomum cassia	3	−0.34 (−0.63, −0.05)	0.020	0.0	0.389
Cinnamomum verum	5	−0.15 (−0.52, 0.22)	0.420	70.1	0.010
Not given	4	−0.10 (−0.32, 0.11)	0.331	0.0	0.648
Sample size					
≤50	5	0.11 (−0.19, 0.40)	0.473	0.0	0.997
>50	7	−0.27 (−0.48, −0.05)	0.015	55.0	0.038
BMI					
≤25	1	−0.51 (−0.90, −0.12)	0.010	-	-
25–30	8	−0.14 (−0.40, 0.12)	0.283	48.9	0.057
>30	1	0.01 (−0.77, 0.80)	0.974	-	-

(Continues)

TABLE 4 (Continued)

	NO	SMD (95% CI)[a]	*p*-within[b]	I^2 (%)[c]	*p*-heterogeneity[d]
NR	2	−0.09 (−0.32, 0.13)	0.428	10.4	0.291
Study quality					
Low	4	−0.15 (−0.36, 0.05)	0.144	0.0	0.947
High	8	−0.16 (−0.43, 0.11)	0.251	60.9	0.012

Abbreviation: SMD: standard mean difference, CI: confidence interval, T2DM: type 2 diabetes mellitus, NAFLD: non-alcoholic fatty liver disease.
[a]Obtained from the random-effects model.
[b]Refers to the mean (95% CI).
[c]Inconsistency, percentage of variation across studies due to heterogeneity.
[d]Obtained from the *Q*-test.

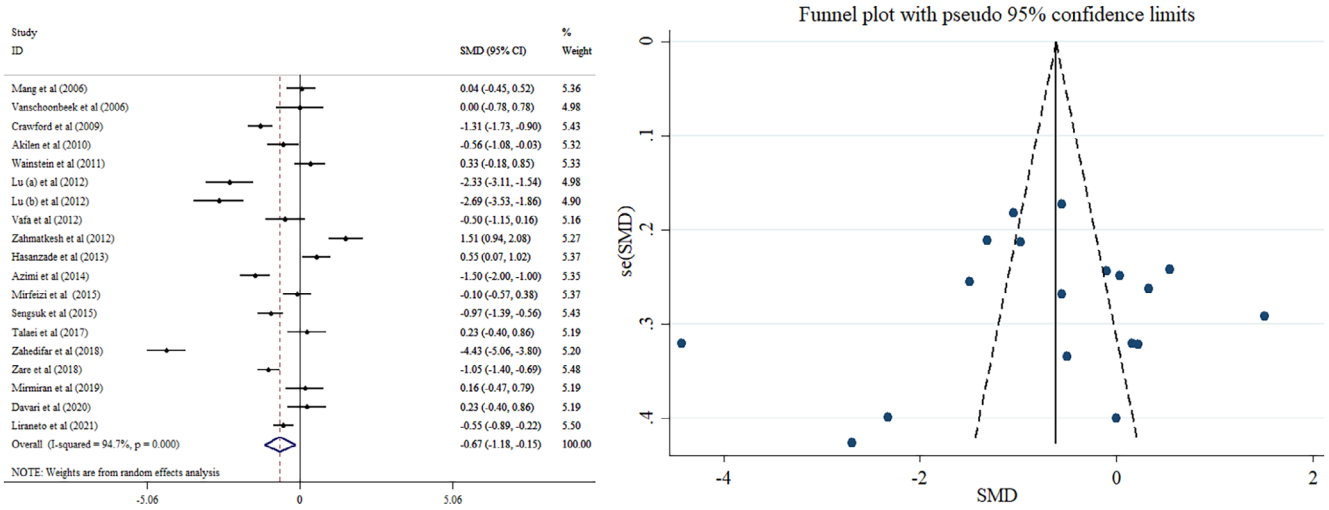

FIGURE 3 Forest plot (a) detailing mean difference and 95% confidence intervals and funnel plot (b) displaying publication bias in the studies reporting the effects of cinnamon supplementation on hemoglobin A1c levels.

overall effects of cinnamon on insulin were altered to statistically significant by excluding the Davari et al. (2020), Lira Neto et al. (2022), Mirmiran et al. (2019), and Talaei et al. (2017) studies using sensitivity analysis.

3.9 | Nonlinear dose-responses between dosage and duration of cinnamon supplementation and glycemic parameters

Cinnamon supplementation altered HOMA-IR and insulin in a nonlinear fashion, according to dose-response analysis (*p*-non-linearity = 0.027 and *p*-non-linearity = 0.019, respectively). However, the duration of the intervention determined how the cinnamon supplementation affected HOMA-IR (*p*-non-linearity = 0.039) (Figure S1–S8).

4 | DISCUSSION

According to our pooled analysis, cinnamon can be considered as an anti-hyperglycemic agent in patients with T2DM by reducing FBS, HbA1c, and HOMA-IR. This property was more robust in doses ≥3000 mg/day for ≤10 weeks to reduce FBS and in doses <3000 mg/day for >10 week of supplementation to reduce HbA1c and HOMA-IR. In addition, *Cinnamomum cassia* had a more ameliorating effect on glycemic indices. Contrary to the nonsignificant results in the low sample size subgroup, cinnamon supplementation in the higher sample size resulted in a significant improvement in HOMA-IR and HbA1c. In terms of the baseline characteristics of the study participants (BMI and mean age), there were no specific trends for the anti-hyperglycemic effects of cinnamon. Therefore, it can be concluded that patients with all age and BMI groups can be benefited from cinnamon supplementation. However, due to the existence of only one study in some subgroups, accurate interpretation of the anti-hyperglycemic effects of cinnamon in different population subgroups should be done with precaution.

The strongest improving effect of cinnamon on HbA1c in >10 weeks of supplementation was not surprising. HbA1c is a long-term glycemic index that measures the mean of glucose concentration over 12 weeks (Sherwani et al., 2016). The nonsignificant effect of cinnamon on HbA1c at higher doses (≥3000 mg/day) could be related to the shorter duration of supplementation (≤10 weeks) in

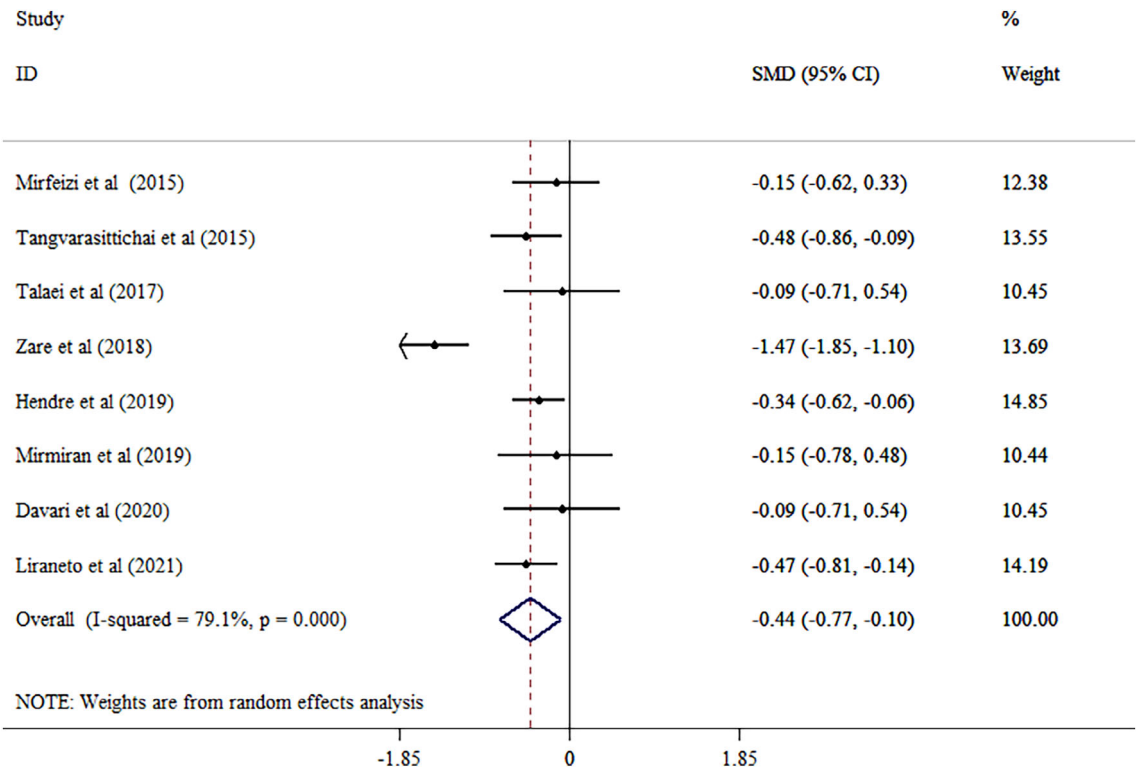

FIGURE 4 Forest plot detailing mean difference and 95% confidence intervals, the effects of cinnamon supplementation on Homeostatic Model Assessment for Insulin Resistance levels.

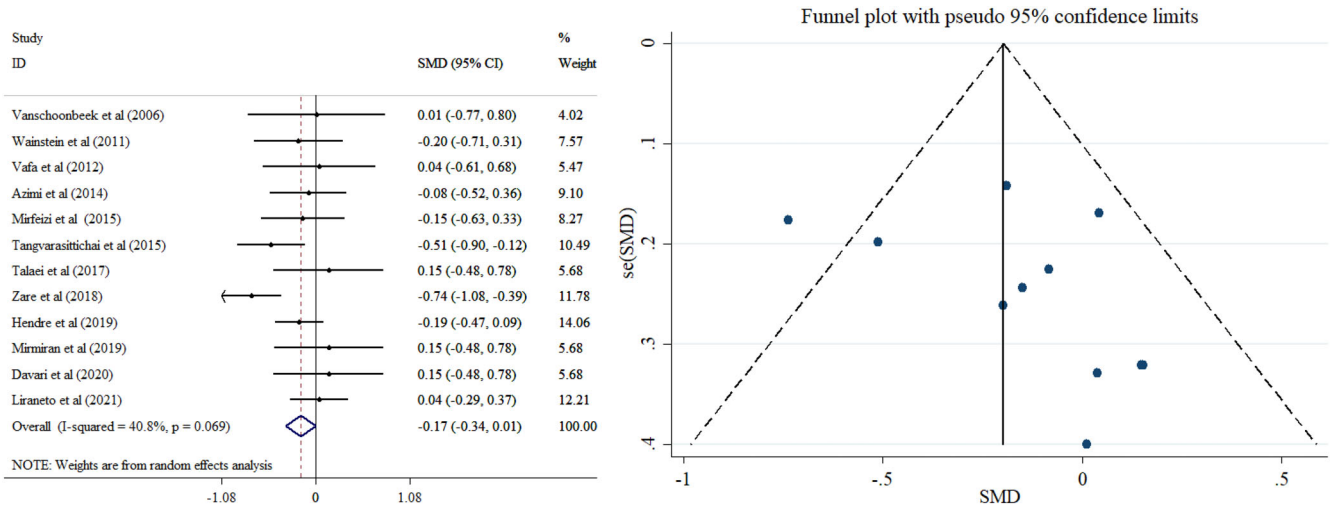

FIGURE 5 Forest plot (a) detailing mean difference and 95% confidence intervals and funnel plot (b) displaying publication bias in the studies reporting the effects of cinnamon supplementation on insulin levels.

five of seven comparisons in this subgroup (Azimi et al., 2014; Davari et al., 2020; Mirmiran et al., 2019; Talaei et al., 2017; Vafa et al., 2012). In terms of HOMA-IR measurement, all studies with longer durations (>10 week) (Hendre et al., 2019; Lira Neto et al., 2022; Mirfeizi et al., 2016b; Zare et al., 2019) and lower doses (<3000 mg/day) (Hendre et al., 2019; Mirfeizi et al., 2016a; Tangvarasittichai et al., 2015; Zare et al., 2019) had higher sample sizes (>50) compared with studies in short-term and higher-dose subgroups (≤50). As a basic principle in studies, the greater sample size can lead to a higher probability of statistically significant differences between groups (Andrade, 2020). Time- and dose-response analyses revealed that only HOMA-IR response to cinnamon supplementation was in dose- and time-dependent manners. However, both subgroups in duration and administered dose of cinnamon led to a significant improvement in HOMA-IR. Despite more decreasing effect of cinnamon on FBS in shorter duration and higher doses, the subgroup analysis showed

that both lower doses and longer durations of cinnamon supplementation led to a significant improvement in FBS levels. Moreover, both dose- and time-response analyses revealed that the effect of cinnamon on FBS level was not in any specific manner.

The type of cinnamon is another factor that modifies the improving effect of cinnamon on FBS, HOMA-IR, and HbA1c. *Cinnamomum cassia* known as *Cinnamomum aromaticum* or Chinese cinnamon is the most common type of cinnamon. The main constituent of its oil is cinnamaldehyde (almost 95%). *Cinnamomum zeylanicum*, also known as *Cinnamomum verum*, Ceylon cinnamon, Sri Lanka cinnamon, and true cinnamon, is another commonly used type of cinnamon, with approximately 60% cinnamaldehyde in its oil. The main distinguishing method of *Cinnamomum cassia* and *Cinnamomum verum* is based on the presence of increased content of benzaldehyde, methoxycinnamaldehyde, and coumarin in *Cinnamomum cassia* oil. This higher content of coumarin in *Cinnamomum cassia* with strong anticoagulant, hepato-toxic, and carcinogenic properties makes recommending high consumption of *Cinnamomum cassia* with precaution (Ranasinghe et al., 2013). However, the higher content of cinnamaldehyde in *Cinnamomum cassia* with anti-hyperglycemic properties (Plaisier et al., 2011) could justify its more improving effects on glycemic indices and insulin resistance compared to *Cinnamomum verum*.

Our findings did not support the beneficial effect of cinnamon on insulin level. However, cinnamon could significantly decrease insulin level in some subgroups, including doses <3000 mg/day, *Cinnamomum cassia* type, sample size >50, and BMI ≤25. Assessment of included studies revealed that all studies in the *Cinnamomum cassia* subgroup prescribed it at doses <3000 mg/day (Tangvarasittichai et al., 2015; Wainstein et al., 2011; Zare et al., 2019). Moreover, five of six studies in <3000 mg/day subgroup had higher sample size (>50) (Hendre et al., 2019; Mirfeizi et al., 2016b; Tangvarasittichai et al., 2015; Wainstein et al., 2011; Zare et al., 2019). Therefore, the type of cinnamon and sample size were the most important variables affecting the insulin-lowering properties of cinnamon in included studies.

Various reviews (Medagama, 2015; Silva et al., 2022) and original research papers (Cao et al., 2007; Sheng et al., 2008) have described the possible anti-diabetic mechanism of action of cinnamon. In summary, cinnamon can regulate glycemic responses by three endogenous pathways, including (i) increase in glucose transporter 4 (GLUT4) production and translocation and subsequent glucose uptake in muscle and adipose tissue, (ii) decrease in glycogen synthase kinase 3 (GSK3) activity and subsequent promotion of glycogen synthase activity, and (iii) decrease in phosphoenolpyruvate carboxykinase (PEPCK) and the glucose-6-phosphatase activity and subsequent gluconeogenesis in the liver (Silva et al., 2022). It seems that bioactive compounds of cinnamon exert these actions by activating insulin signaling pathways (Maleki et al., 2021). The AMP-activated protein kinase (AMPK) plays a mediating role between cinnamon and insulin signaling pathways. Kopp et al. reported that trans-cinnamic acid acts as a ligand for the G-protein-coupled receptors, thereby stimulating AMPK (Kopp et al., 2014). In addition, cinnamon increases the expression of peroxisome proliferator-activated receptor (PPAR) (alpha) and (gamma) (Sheng et al., 2008). It has been shown that PPAR-γ is effective in insulin signaling pathways at various steps (Leonardini et al., 2009). Moreover, PPAR-α activation could ameliorate hepatic insulin resistance (Chan et al., 2013). Furthermore, the anti-inflammatory and anti-oxidant effects of cinnamon can cause an improvement in insulin resistance (Dugoua et al., 2007). With regard to toxicological profile, cinnamon is generally considered safe by the United States Food and Drug Administration and no serious side effects have been reported in trials. However, only one study reported mild, short-lived gastric upset, and headache after administration (Akilen et al., 2010).

There were some limitations that must be mentioned. First, due to the limited number of studies on each gender, subgroup analysis based on gender was not performed. Second, some studies did not provide the prescribed form of cinnamon. Therefore, subgroup analysis based on cinnamon form was limited to only *Cinnamomum cassia* and *Cinnamomum verum*. Third, serious risk of bias due to poor study design was detected in some included studies. Therefore, additional studies with proper study design are needed to obtain high-quality evidence.

5 | CONCLUSION

Cinnamon supplementation has improving effects on FBS and insulin sensitivity in T2DM patients in a wide range of doses and durations. The beneficial effect of cinnamon on HbA1c has been shown in >10 weeks of supplementation. *Cinnamomum cassia* has a more improving effect on glycemic indices. Patients of all ages and BMI groups can be benefited from cinnamon supplementation to improve glycemic indices.

AUTHOR CONTRIBUTIONS

Amir Hossein Moridpour: Conceptualization; formal analysis; funding acquisition; methodology; resources; software; supervision; validation; visualization; writing – original draft. **Zeynab Kavyani:** Conceptualization; data curation; formal analysis; funding acquisition; methodology; software; supervision; visualization; writing – original draft; writing – review and editing. **Somaye Khosravi:** Data curation; methodology; supervision; writing – original draft. **Elahe Farmani:** Data curation; formal analysis; methodology; resources; software; supervision; writing – original draft. **Maziar Daneshvar:** Conceptualization; data curation; methodology; supervision; visualization; writing – original draft. **Vali Musazadeh:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing – original draft; writing – review and editing. **Amir Hossein Faghfouri:** Formal analysis; methodology; resources; software; supervision; validation; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

There is no conflict of interest in this study.

DATA AVAILABILITY STATEMENT

Data sharing not applicable.

ORCID

Vali Musazadeh https://orcid.org/0000-0002-4978-9474

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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