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Review

Efficacy and safety of cinnamon in type 2 diabetes mellitus and pre-diabetes patients: A meta-analysis and meta-regression

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ABSTRACT

Introduction: Cinnamon has been used as a dietary component and in the management of diabetes mellitus. This study systematically reviewed and synthesized evidence on the efficacy of cinnamon for the treatment of type 2 diabetes mellitus (T2DM) and pre-diabetes patients.

Methods: Databases of Web of Sciences, the Cochrane library, PubMed, CINAHL and SCOPUS were searched. Stata version 13 (College Station, Texas 77845 USA) and RevMan var. 5.3 software were used for meta-analysis. Heterogeneity was assessed using Chi-square and I^2 tests.

Results: Sixteen randomized controlled studies were included in the meta-analysis. Cinnamon significantly reduced fasting blood glucose (FBG) and homeostatic model assessment for insulin resistance (HOMA-IR) level compared to placebo with weighted mean difference (WMD) of −0.545 (95% CI: −0.910, −0.18) mmol/L, $I^2 = 83.6\%$ and −0.714(−1.388, −0.04), $I^2 = 84.4\%$ respectively. There was no significant change in weighted mean difference of gly-

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; DM, diabetes mellitus; FBG, fasting blood glucose; Hb1Ac, glycosylated hemoglobin 1Ac; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RBG, random blood glucose; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglycerides; WMD, weighted mean difference

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cosylated hemoglobin A1C (HbA1c) % and lipid profiles (mmol/L). Meta-regression did not show any factor significantly affecting the treatment response.
Conclusion: Cinnamon reduced FBG and HOMA-IR, level in T2DM and pre-diabetes patients compared to placebo. High heterogeneity observed among included studies warrants further clinical trials after standardization of cinnamon formulation.
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1. Introduction

Diabetes is a chronic metabolic disorder characterized by elevated blood glucose level resulting from a defect in insulin secretion, insulin action, or both [1]. Long-term complications of diabetes mellitus (DM) include retinopathy, nephropathy, neuropathy, periodontal disease, sexual dysfunction, and increased risk of cardiovascular diseases ([2,3]. Over 90% of all DM cases are type 2 DM (T2DM) (IDF, 2017; [4]. The increase in T2DM is predominantly related to increasing urbanization, population ageing, obesity, ethnicity, family history of diabetes [4], history of gestation diabetes [5], increasing physical inactivity [6], and unhealthy diet [7].

Management of T2DM involves the use of modern anti-diabetic drugs. However, the anti-diabetic drugs are expensive [8], have significant adverse effects [9] and fail to effectively control the glycemia [10]. Herbal medicines become the alternative way for DM management as they have few adverse effects and readily accessible to the majority of the populations. Cinnamon is among the many herbal medicines used for the treatment of DM. It has two main varieties, *Cinnamomum cassia* (also known as *Cinnamomum aromaticum*) and *Cinnamomum zeylanicum* [11]. *In vitro* and *in vivo* studies have shown that cinnamon is an insulin sensitizer [12]. Clinical trials evaluated the efficacy of cinnamon in glycemic control among people with T2DM.

Previous four meta-analytic studies produced inconsistent results [13,14,15,16]. Since the last meta-analysis, several clinical trials were conducted and published. The findings of these studies have been included in the current meta-analysis and meta-regression to update the relevance of the previous systematic review and meta-analysis and also identify possible explanation for heterogeneity. Hence, this study systematically reviewed and synthesized evidence on the efficacy of cinnamon for the treatment of patients with T2DM and pre-diabetes patients.

2. Methods

2.1. Study design

This is a meta-analysis based on electronic databases. The meta-analysis is prepared and structured in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines [17]. The protocol of this study was registered (PROSPERO 2018 = CRD42018106474) [18].

2.2. Search strategy

PubMed databases were initially searched to outline the study and construct keywords. After construction of search words, further searches were made in databases of Web of Sciences, SCOPUS, CINAHL, and the Cochrane library. The keywords used include [*cinnamon* OR *Cinnamomum*] AND [diabetes OR glycem* OR hyperglyce* OR hypoglyce*] AND Clinical trial OR controlled trial OR randomized trial. Then text words contained in the title and abstract were analyzed. A second search using all identified keywords and index terms was undertaken across all included databases. Thirdly, the reference list of all identified studies was searched for additional studies. Unpublished studies were searched in Google and Google Scholar. Ongoing clinical trials were also searched through clinicaltrials.gov.

Two independent reviewers (KE & SS) conducted the title and abstract screening in duplicate to identify eligible articles using predefined criteria with support of SD. Full texts of the eligible articles were obtained and assessed against the inclusion and exclusion criteria. Any disagreements between the reviewers during full-text assessment were resolved by discussion and consensus, when no resolution reached, a third reviewer (SD) was involved in a decision.

2.3. Inclusion and exclusion criteria

The predefined inclusion criteria for this meta-analysis were as follows: 1, Randomized Controlled Trials (RCTs) in T2DM patients or pre-diabetes patients 2, Participants of the studies should be aged greater than 18 years and older of either sex 3, Studies with follow up duration of at least four weeks for both primary and secondary outcomes were considered. Since clinical studies have indicated that this is the minimum period required for treatments to produce meaningful changes in glucose control as assessed by HbA1c concentrations [19]. This systematic review excluded non-randomized clinical trials, cross-sectional studies, case series and case reports studies, studies conducted on patients younger than 18 years, and T2DM patients.

2.4. Data extraction

Joanna Briggs Institutes Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) tools were used to extract the data [20]. Data extracted include last name of the first author, year of study, the dosage of the cinnamon and the control (placebo), type of population, duration of the follow-up, and the primary and secondary outcomes of interest. The primary outcomes were FBG, HbA_{1c}, insulin level, LDL, HDL, TC, BMI, HOMA-IR, Alanine aminotransferase (ALT), and Aspartate aminotransferase (AST). In general, specific details about the interventions and populations were extracted.

2.5. Study quality assessment

Two independent reviewers (KE and SS) assessed the eligibility of articles for methodological validity before inclusion in the review using standardized Cochrane risk of bias tool for a randomized clinical trial [21]. Disagreements between the two reviewers were resolved through discussion with a principal investigator (SD). The bias was graded as high, low, or unclear. Publication bias was tested using Egger's test [22].

2.6. Statistical analysis

RevMan5.3 software (Cochrane Informatics and Knowledge Management Department, London, UK) and Stata version 13.0 (StataCorp, LP, college station, TX) were used for the analysis of the data. All of the variables in this study were continuous, and the inverse of the variance-weighted method was used for pooling the weighted mean differences and its 95% confidence intervals (CI). Clinical and methodological heterogeneity were assessed using Chi-square test and I^2 tests [21]. Because of significant heterogeneity amongst the studies, the random-effects model (REM) was used to estimate the pooled mean difference and 95% CIs using the DerSimonian and Laird method [23]. The presence of publication bias was tested using Egger's test [22]. This meta-analysis was conducted as per the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines [17]. Subgroup analysis and meta-regression were performed to identify the sources of heterogeneity.

3. Results

3.1. Characteristics of included studies

A total of 572 articles were identified through the electronic database search. After removing duplications and screening the articles based on titles and abstracts, 347 articles remained. Further screening for inclusion and exclusion criteria left 35 for full-text examination. Nineteen were further excluded with reasons. Reasons for exclusion: four of the articles were not conducted on DM patients [24,25,26,27], six articles did not address the study question [28–33], three were review papers [34,35,36], four were meta-analysis [13,14,15,16], one did not report standard deviation [37], one was conducted in type 1 DM [38]. This exclusion left sixteen articles for inclusion in the meta-analysis, [39,40,41,42,43 44,45,46,47,48,49,50,51,52, 53,54]. These sixteen studies enrolled a total of 1098 participants. A PRISMA flowchart is presented to show the screened, excluded and included articles (Fig. 1) and characteristics of included studies were summarized in Table 1.

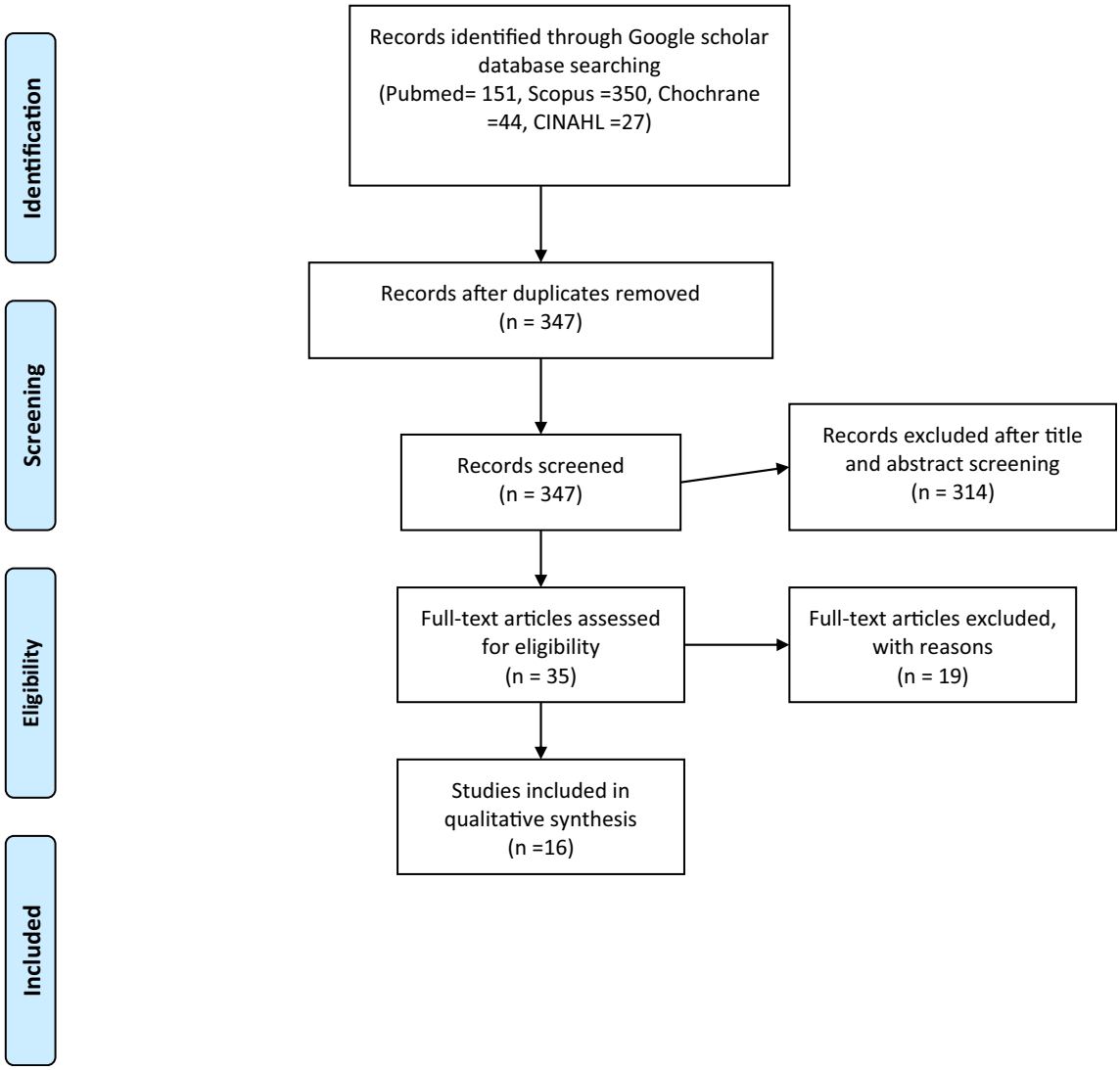

Fig. 1 – Flow diagram of study selection, screening, inclusion and exclusion.

Table 1 – Characteristics of included studies.

Study	Type of DM	Total participants		Dosage	Follow up duration	Cinnamon botanical source &formulation	Placebo formulation
		Enrolled	Completed				
[39]	Type II	58	58	2 g/d	12 week	C. cassia,	Starch
[40]	Pre-diabetes	173	137	1 g/d	3 month	Commercial spray-dried extract of cinnamon	Wheat flour
[47]	Type II	60	43	1 g/d	3 month	C. cassia, capsules	Wheat flour
[41]	Type II	109	89	1 g/d	3 month	C. cassia, capsules	Usual care
[42]	Type II	35	35	1 g/d	60 days	C. *cassia*, capsules	Not specified
[52]	Type II	14	14	1.5 g	30 days	Not given, capsules	Maize flour
[51]	Type II	60	60	6 g/d	60 days	C. *cassia*	Wheat flour
[43]	Pre-diabetic	62	52	1.2 g	4 month	C. cassia, capsules	
[53]	Type II	69	66	14.4 g/d	3 month	C. *aromaticum*	Not specified
[48]	Type II	79	65	3 g/d	4 month	C. *cassia*,	cellulose
[44]	Type II	105	102	1 g/d	3 month	Not specified	Starch
[54]	Type II	44	39	3 g/d	8 week	C. *zeylanicum*	Cellulose
[49]	Type II	44	37	3 g/d	8 week	C.*zeylanicum*	Wheat flour
[50]	Type II	25	25	1.5 g/d	6 week	C. *cassia*	Wheat flour
[45]	Pre-diabetes	21	17	12 g/d	12 week	C. *cassia, capsules*	Cellulose
[46]	Type II	140	138	1 g/d	3 month	C. *verum*, capsules	Starch

3.2. Heterogeneity and publication bias in the included studies

All of the sixteen included studies in the systematic review were randomized controlled trials. However, there were significant variations among the included studies, both clinically and statistically. Clinical variations include; the strength of the dosage used, duration of the treatment, and type of patients included. The strength of the cinnamon used for the treatment ranges from 1 g to 14.4 g. The follow-up period ranges from one month to four months. Three studies were conducted in adults with T2DM patients either on oral anti-hyperglycemic agents or recently diagnosed T2DM. Some of the studies have background oral hypoglycemic as standard treatment while others do not have or have not provided evidence on the background therapy. The heterogeneity in the included studies was witnessed by high I^2 ranging from 49.3% to 86%, all p-value greater than 0.05. Egger's publication bias test were significant for TG (p-value = 0.032) while all other parameters which satisfied conditions for Eggers test did not show significant value.

3.3. Risk of bias in the included study

The risk of bias was particularly high in the domain of detection, selection and performance bias due to failure of the included studies to adequately blind participants, personnel and outcome assessment as well as to sufficiently conceal allocation sequence. Low risk of bias were given when specific methods for random sequence generation were described using one of computer-generated random sequence, permuted block method, sealed envelope, random numeric table, numerical code, and RAS software. The risk of bias graph and risk of bias summary were given in Fig. 2 and Fig. 3.

3.4. Effect of interventions

Fifteen studies evaluated cinnamon effect on FBG. Cinnamon significantly reduced FBG (mmol/L) and compared to placebo respectively with weighted mean difference (WMD) of −0.545 (95% CI: −0.910, −0.18), high heterogeneity was observed, I^2 = 83.6%, Fig. 4. Four studies reported HOMA-IR and meta-analysis revealed significant reduction in WMD (−0.714 (95% CI: 1.388, −0.040), I^2 = 84.4.1%), Fig. 5. Eight studies evaluated effect on insulin (μU/mL) and found non-significant insulin reduction (−0.964[95% CI: −1.97, −0.042], I^2 = 55.4%), Fig. 6. Other evaluating the effectives of cinnamon on biochemical parameters such as HbA1c (%), LDL (mmol/L), HDL (mmol/L), TC (mmol/L), TG (mmol/L), and BMI (kg/m^2) respectively included twelve, twelve, eleven, eleven, twelve, and seven studies. All these parameters did not show significant differences in WMD reduction between cinnamon and placebo treated groups. The reduction in WMD for these parameters were: HBA_{1c}% (−0.104 [95% CI: −0.138, 0.110], I^2 = 69.6%), LDL (mmol/L) (−0.115 [95%CI: −0.270, 0.039], I^2 = 86.01%), HDL (mmol/L) (-0.004 [95%CI: −0.059 to 0.050], I^2 = 81.0%), TC (mmol/L) (−0.198[95% CI: −0.405,0.010], I^2 = 86.4%, TG (mmol/L) (−0.100 [95% CI: −0.221,0.022], I^2 = 69.0%, and BMI (kg/m^2) (−0.37[95% CI: −1.12, 0.39], I^2 = 57.0%). The forest plots for these parameters were respectively presented as Figs. 7–12 for HBA1c, LDL, HDL, TC, TG, and BMI.

3.5. Heterogeneity and publication bias

Considerable heterogeneity was observed in the included studies, I^2 ranging from 55.4% to 86.0%. Meta-regression performed to account for heterogeneity using type of DM, type of cinnamon, the dosage of cinnamon, and baseline values did not show significant values, Table 2.

3.6. Safety outcomes

Almost all of the studies included reported that cinnamons were tolerated in individuals taking the medications. Two studies evaluated specific parameters for safety [53,45], reported ALT and AST values. Both parameters did not show significant variation in cinnamon compared to placebo. Liver function test performed using AST (μkat/L) and ALT (μkat/L)

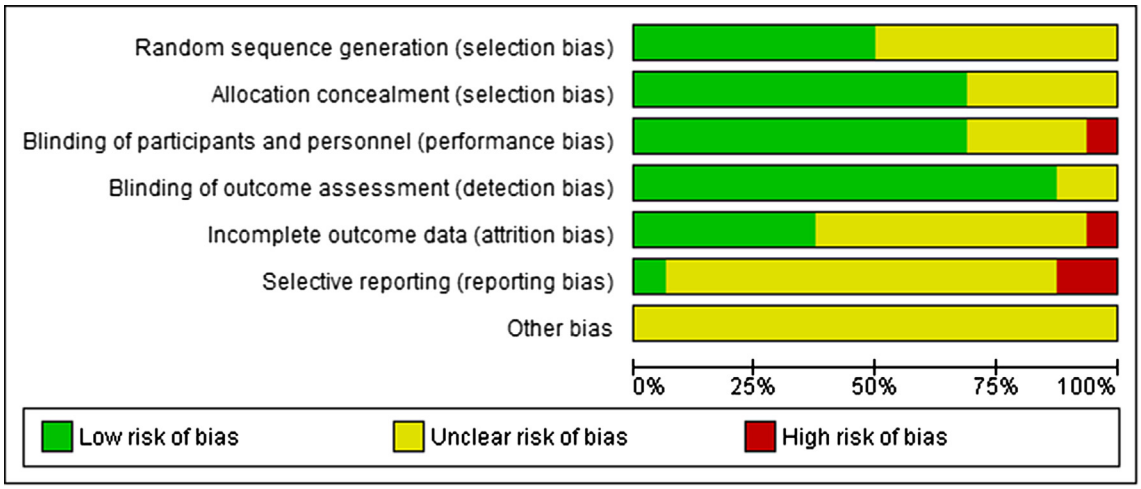

Fig. 2 – Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

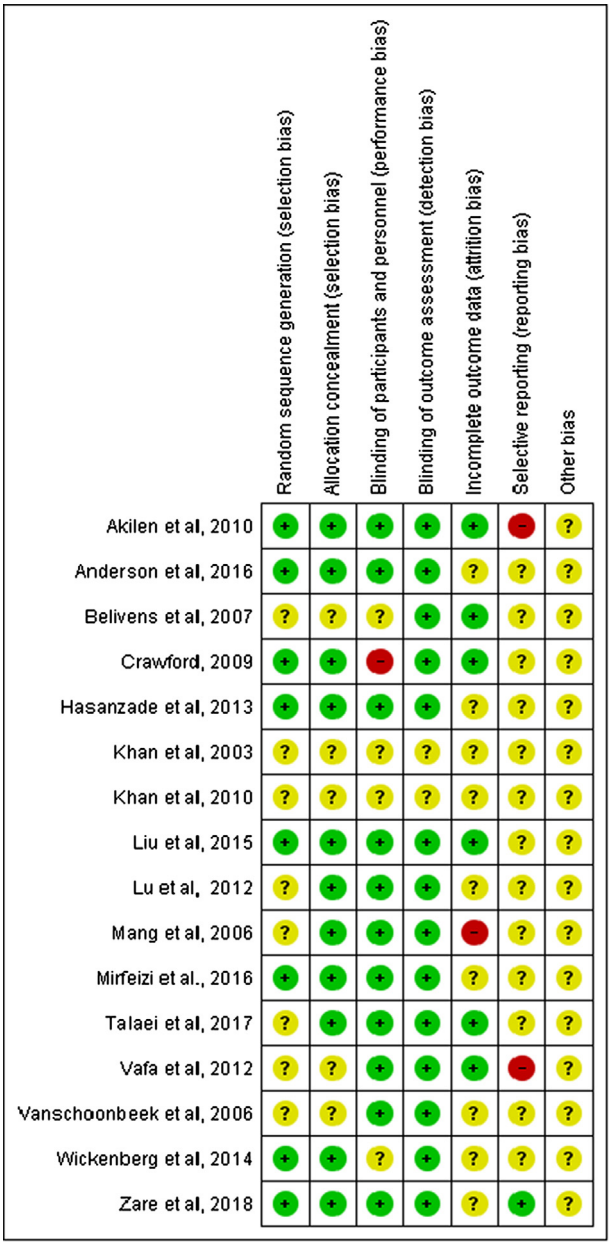

Fig. 3 – Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

on two studies revealed WMD respectively as 0.27(95% CI: −3.20, 3.74), I^2 = 58% and 3.5(95% CI: −3.43, 10.44), I^2 = 63%.

4. Discussion

4.1. *Current findings*

This study revealed that cinnamon significantly reduced FBG and HOMA-IR level in patients with T2DM or pre-diabetes compared to placebo. However, there is no significant difference in HBA1c level, in various lipid profiles and BMI between cinnamon and placebo-treated groups. Cinnamon is generally reported as well tolerated in all of the included studies.

Herbal medications are used along with modern medicine to attain glycemic control as adjuvant therapy. The ability of cinnamon to control FBG but not HbA1c could be due to short duration of therapy where the follow-up period ranges only from one month to four months [55,56]. HbA1c also correlates well with the prevention of the risk of long-term diabetes complications [57,58]. The significant reduction in FBG and HOMA-IR could indicate that the possible mechanism of action could be due to insulin sensitization effect [12]. Cinnamon could, therefore, be anticipated to do better when combined with anti-diabetic agents with secretagogue activity [59] or insulin itself compared to drugs with insulin sensitizers [60]. Cinnamon has shown an increasing effect on Phosphorylation activity of insulin receptors, decreasing effect on tyrosine phosphatase activity, showing insulin-like properties [61] possibly due to its insulin sensitizer effect. Studies have also shown that cinnamon inhibits glycogen synthase activity [62].

4.2. *Findings of the current study in light of previous meta-analysis*

A total of ten reviews on the efficacy of cinnamon for treatment of DM were obtained, among which four were meta-analysis [13,14,15,16]. The conclusion in the meta-analyses varied possibly due to the difference in dosage strength, frequency of administration, cinnamon formulation, source and type, clinical variability, or background therapy. One study ended up with in-depth narrative review due to heterogeneity amongst the included studies [63].

The first meta-analysis concluded that cinnamon does not appear to improve HbA1C, FBG, or lipid parameters in DM [16] while the second meta-analysis showed a significant decrease in HbA1c and FBG level. The meta-analysis by [15] was inconclusive with non-significant difference in HbA1c, serum insulin, or postprandial glucose where the authors concluded that there is insufficient evidence to support the use of cinnamon for DM. The last meta-analysis by [13] established that cinnamon significantly reduced FBG compared to placebo while [15] failed to provide conclusive evidence. No significant differences were observed on the level of HbA1c in both meta-analyses [15,13]. Costello and colleagues concluded that cinnamon supplements added to standard hypoglycemic medications and other lifestyle therapies had modest effects on FBG and HbA1c [63]. In general, all of the meta-analyses revealed high heterogeneity and inconsistency which could be attributed to variation in both clinical and methodological parameters.

4.3. *Limitation of the study*

High heterogeneity was observed which is not resolved by meta-regression. Majority of included studies did not report safety data which make this study fall short of conclusive tangible safety data. High heterogeneity, small sample size and unavailability of specific safety require cautious interpretation of the findings. Despite this limitation, the current study provides useful evidence for clinical decision making and planning future studies.

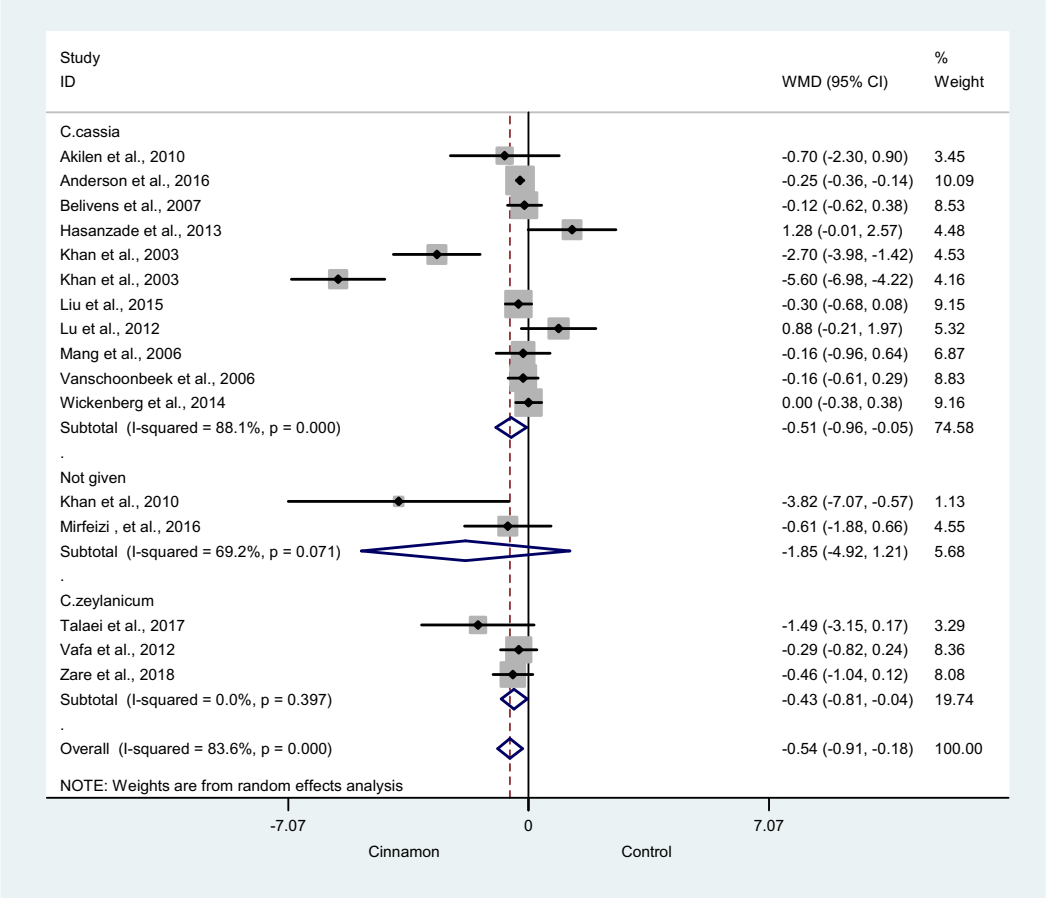

Fig. 4 – Forest plot showing reduction in FBG (mmol/L) in cinnamon treated group versus placebo treated group.

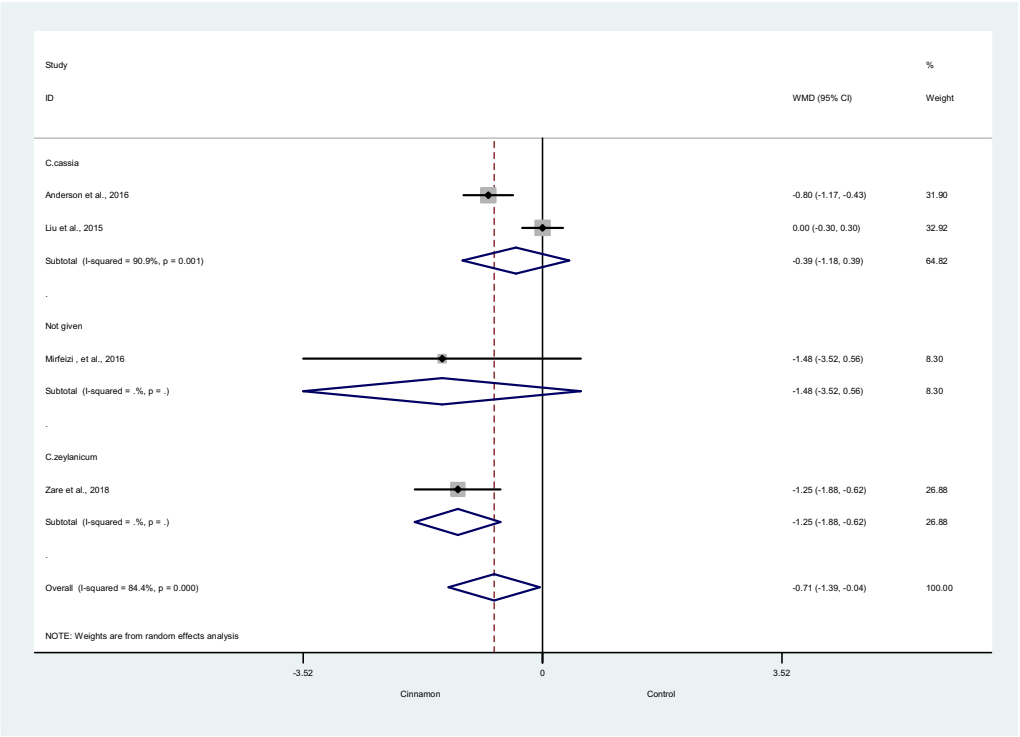

Fig. 5 – Forest plot showing homeostatic model assessment for insulin resistance (HOMA-IR) in cinnamon treated versus placebo treated group.

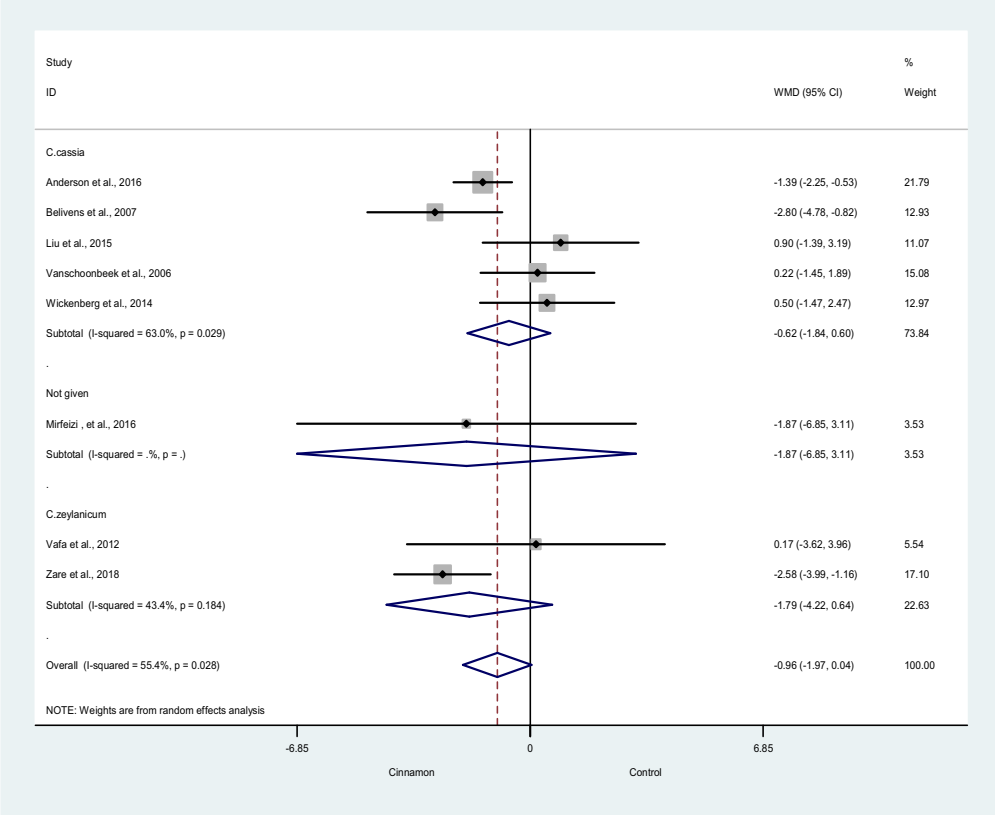

Fig. 6 – Forest plot showing Insulin (μU/mL) level in cinnamon treated group versus placebo treated group.

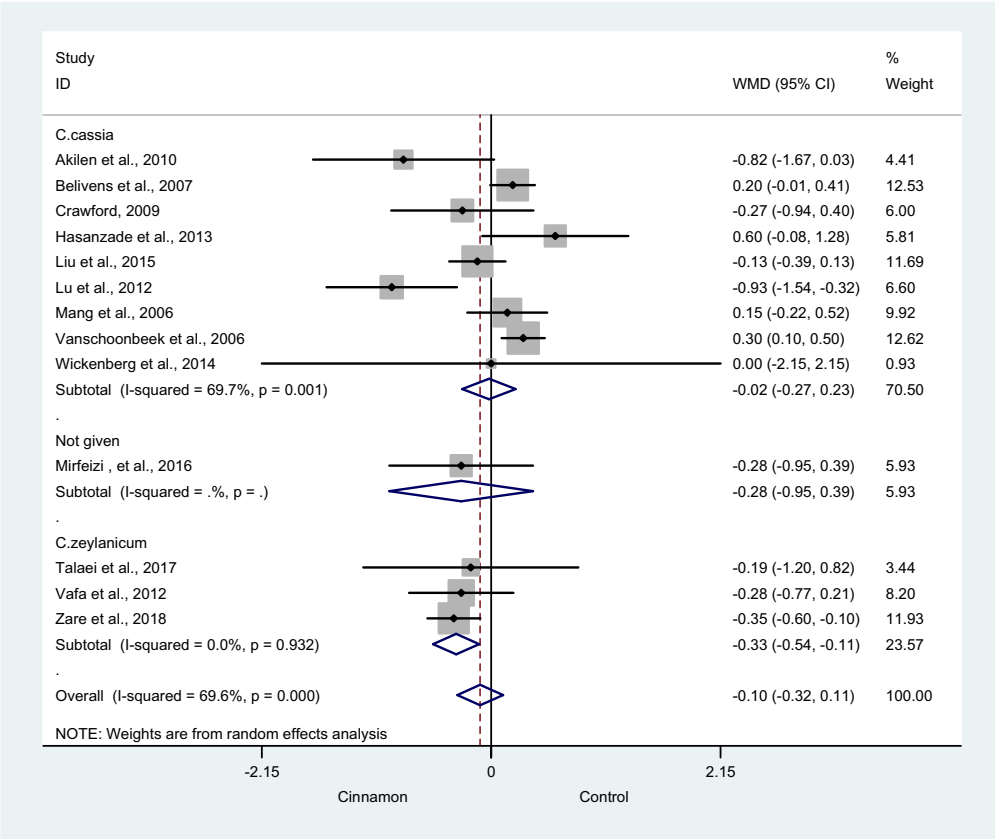

Fig. 7 – Forest plot showing HbA1c level in cinnamon treated versus placebo treated group.

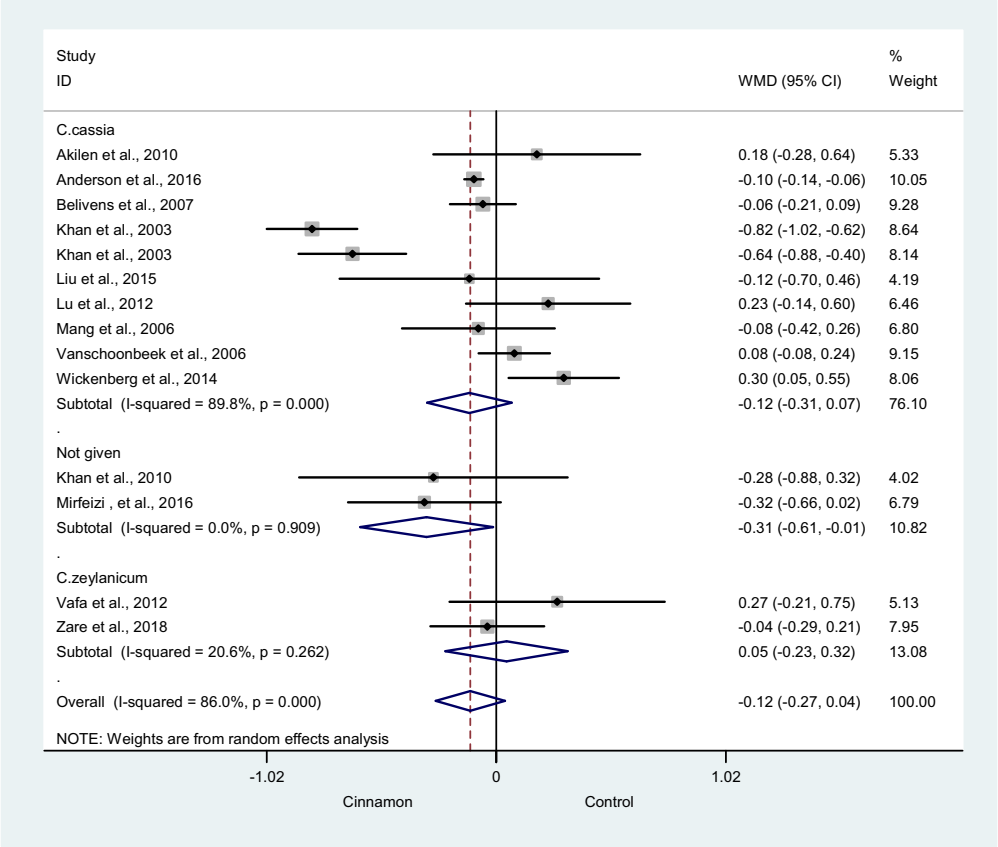

Fig. 8 – Forest plot showing LDL (mmol/L) level in cinnamon treated versus placebo treated group.

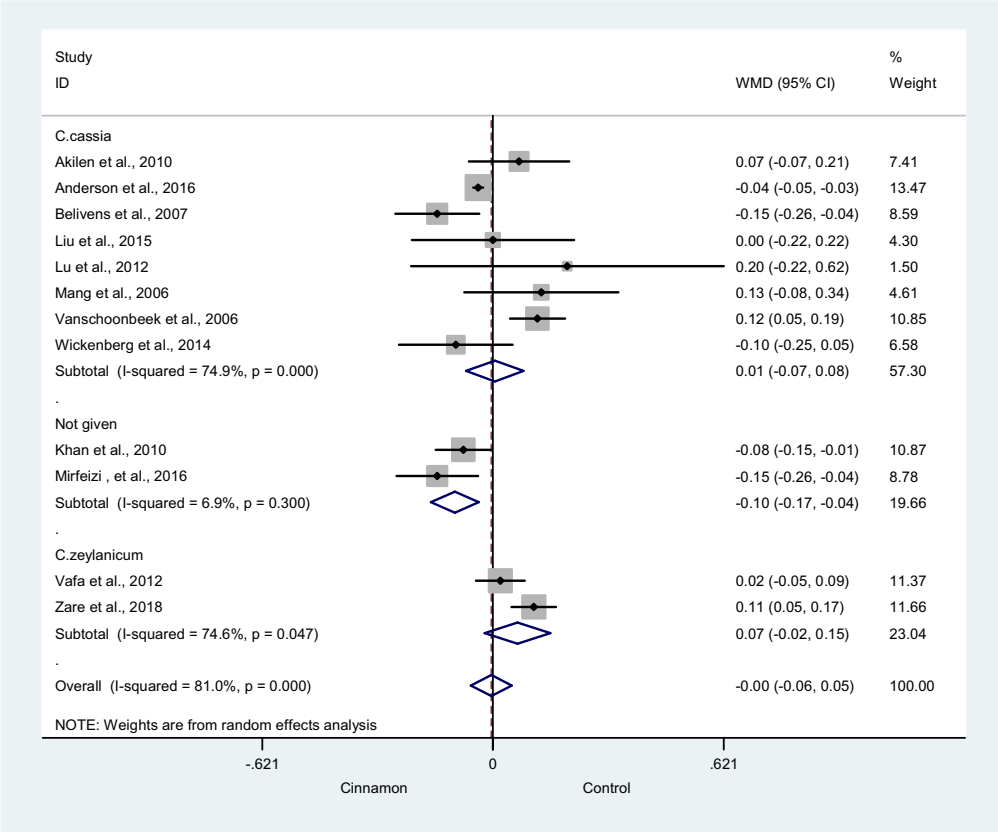

Fig. 9 – Forest plot showing HDL (mmol/L) in cinnamon treated group versus placebo treated group.

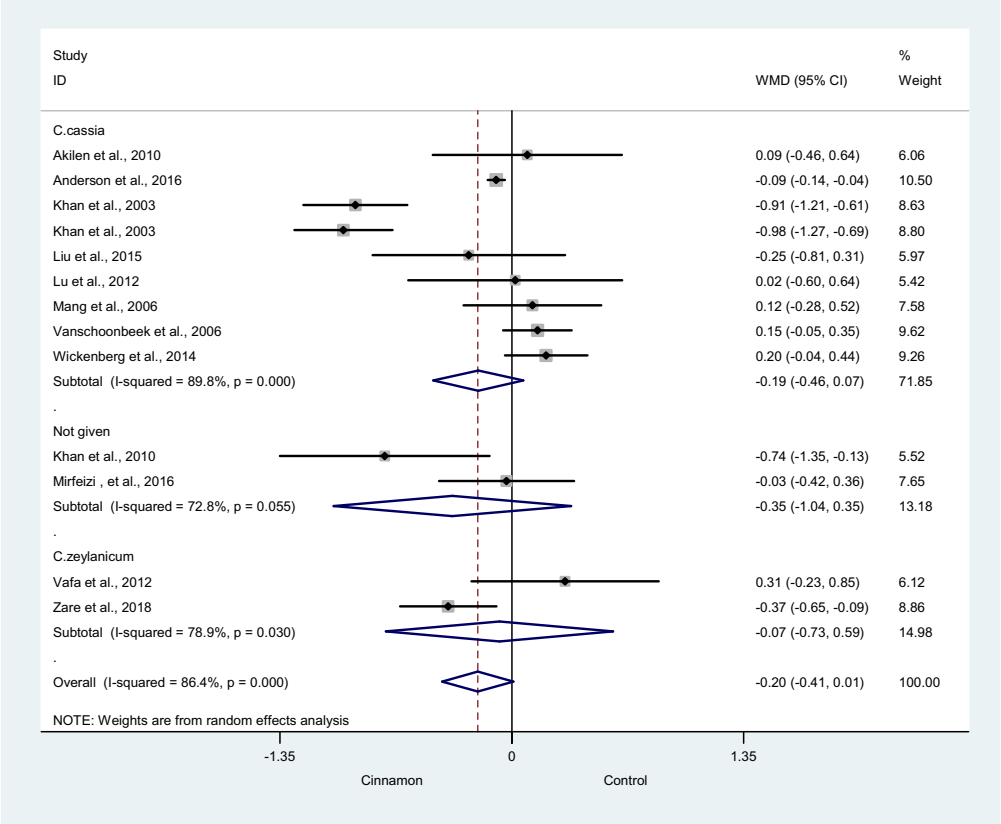

Fig. 10 – Forest plot showing TC level (mmol/L) in cinnamon treated group versus placebo treated group.

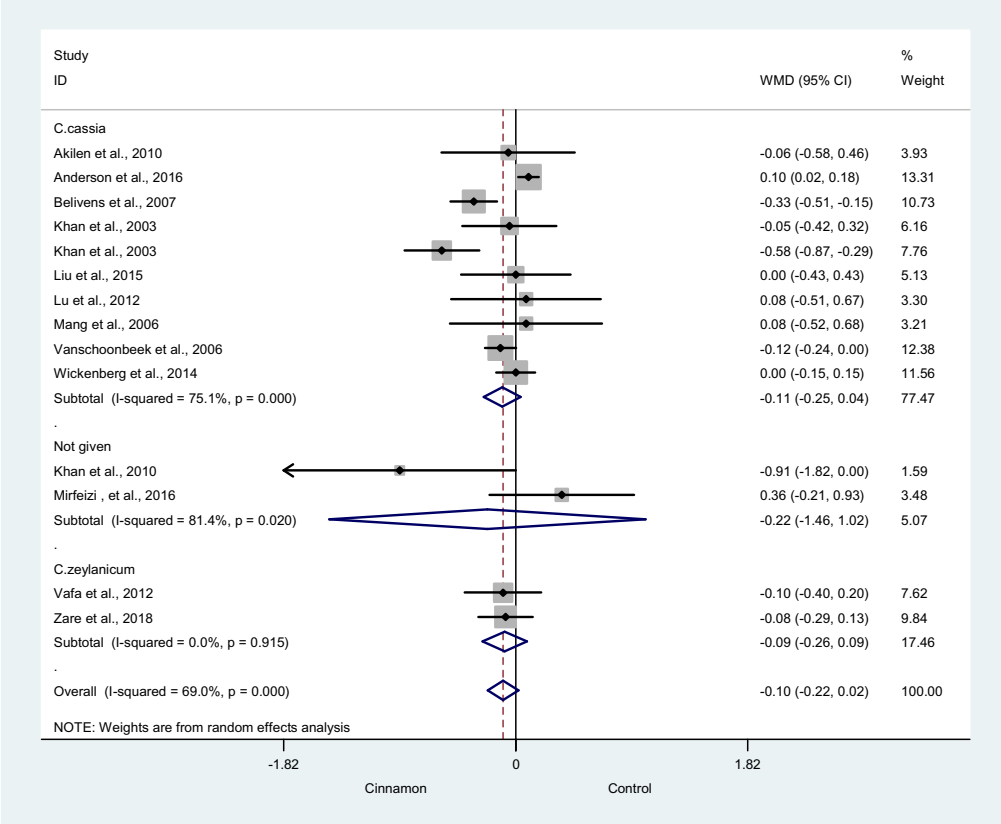

Fig. 11 – Forest plot showing TG (mmol/L) level in cinnamon treated group versus placebo treated group.

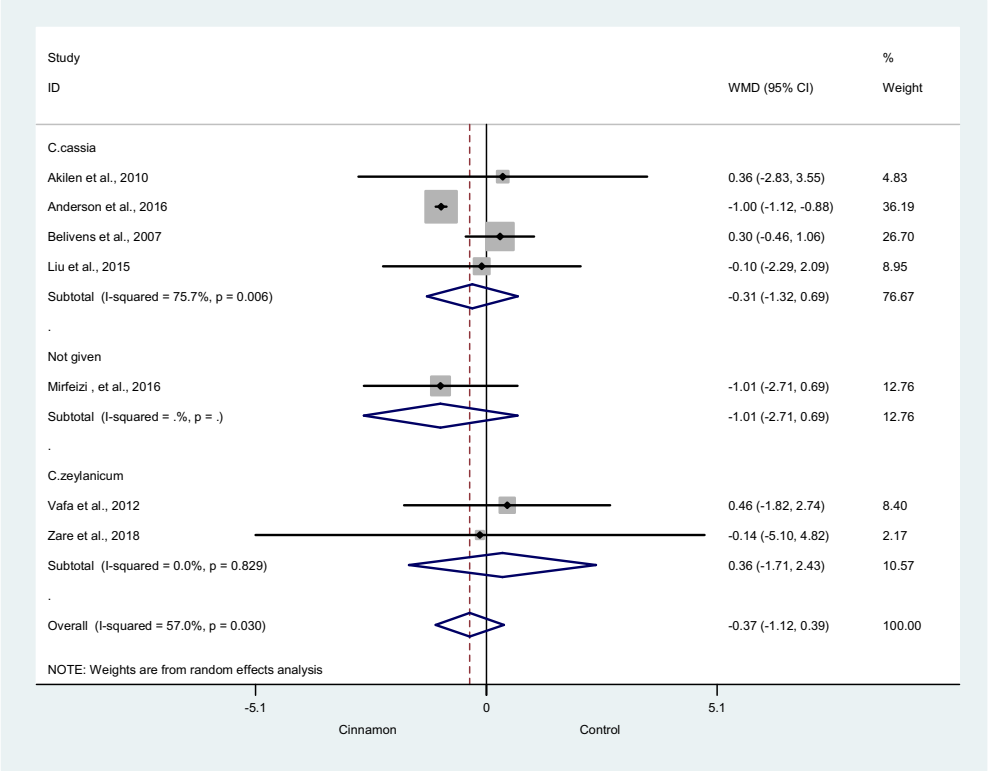

Fig. 12 – Forest plot showing BMI (kg/m^2) in cinnamon treated group versus placebo treated group.

Table 2 – Meta-regression on factors affecting treatment response.

Parameters	Independent variable	Coefficient	95% CI		P-value	
					unadjusted	adjusted
FBG	Type of DM	0.6837343	−3.130722	4.498191	0.651	0.977
	Cinnamon type	−0.3673474	−1.474011	0.7393162	0.552	0.939
	Dose strength	−0.1566368	−0.5677789	0.2545053	0.418	0.832
	Follow-up days	−0.0164402	−0.0331336	0.0660139	0.489	0.903
HBA1c	Type of DM	0.1153504	−0.8404791	1.07118	0.828	1.000
	Cinnamon type	−0.1519301	−0.5070144	0.2031542	0.333	0.724
	Dose strength	−0.0926305	−0.2728043	0.0875433	0.241	0.610
	Follow-up days	−0.0050237	−0.0175607	0.0075133	0.386	0.803
TC	Type of DM	0.0931593	−1.18078	1.367099	0.794	0.998
	Cinnamon type	−0.0310705	−0.3674204	0.3052795	0.852	0.999
	Dose strength	−0.0003277	−0.1371922	0.1365368	0.954	1.000
	Follow-up days	0.0041113	−0.0121693	0.020392	0.534	0.930
LDL	Type of DM	0.1633249	−0.8060875	1.132737	0.590	0.957
	Cinnamon type	−0.0255926	−0.273205	0.2220198	0.801	0.995
	Dose strength	0.0060709	−0.0956677	0.1078094	0.942	1.000
	Follow-up days	0.0025773	−0.0091249	0.0142795	0.568	0.945
HDL	Type of DM	−0.1083974	−0.4794793	0.2626845	0.548	0.933
	Cinnamon type	−0.0441675	−0.1170607	0.0287256	0.234	0.547
	Dose strength	0.0001992	−0.0398358	0.0402342	0.989	1.000
	Follow-up days	0.0001691	−0.0038792	0.0042173	0.924	1.000
TG	Type of DM	0.1905146	−0.5258414	0.9068705	0.558	0.940
	Cinnamon type	0.0181225	−0.2076415	0.2438865	0.866	1.000
	Dose strength	−0.0166791	−0.0855962	0.0522381	0.602	0.955
	Follow-up days	0.0013554	−0.0076775	0.0103883	0.721	0.991
Insulin	Type of DM	5.941361	−0.2838175	12.16654	0.026	0.063
	Cinnamon type	0.6095515	−1.795996	3.015099	0.504	0.802
	Dose strength	−0.2005707	−0.7162316	0.3150902	0.231	0.587
	Follow-up days	−0.0651718	−0.1446713	0.0143277	0.077	0.150

5. Conclusion

Cinnamon significantly reduced elevated FBG and HOMA-IR compared to placebo. However, there is no significant reduction in HbA1c and lipid profiles levels between cinnamon treated and placebo-treated T2DM patients or pre-diabetes patients. Meta-regression did not provide evidence for high level of heterogeneity. Further research is warranted for standardization of cinnamon formulation, clinical validation of the standardized formulation and further clinical trials.

Authors' contributions

SD, SS, and KE conceptualized the idea and design of the study. KE and SS screened the studies and extracted the data. SD drafted the manuscript. SD and ELP conducted data analysis. CUT and PEO mentored. NT, RA, ELP, CUP, and PEO revised the manuscript for important intellectual contents. All authors read and approved the final manuscript.

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Declaration of Competing Interest

The authors have no competing interests.

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