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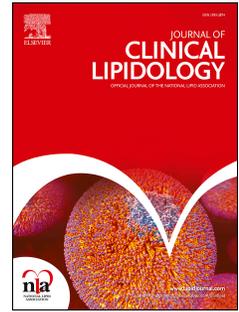
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The Effects of Cinnamon Supplementation on blood Lipid Concentrations: A Systematic Review and Meta-Analysis

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ABSTRACT:

Background: Cinnamon is a rich botanical source of polyphenols, whose positive effects on blood lipid concentrations have been hypothesized, but have not been conclusively studied.

Objective: To systematically review and evaluate the effect of administration of cinnamon on blood lipid concentrations.

Methods: We assessed 13 RCTs with 750 participants investigating the effect of cinnamon supplementation on blood lipid concentrations. A meta-analysis was performed using random-effect models, with weighted mean differences (with 95% CI) for endpoints calculated using a random-effects model.

Results: No statistically significant effect of cinnamon was observed on blood LDL-C (WMD: -0.16 mmol/L [-6.19 mg/dL], 95% CI: -0.35, 0.03 [-13.53, 1.16], $p = 0.10$) and HDL-C (WMD: 0.05 mmol/L [1.92 mg/dL], 95% CI: -0.03, 0.12 [-0.03, 4.64], $p = 0.21$) concentrations. However, a statistically significant reduction in blood triglycerides (WMD: -0.27 mmol/L [-23.91 mg/dL], 95% CI: -0.39, -0.14 [-34.54, -12.40], $p < 0.01$) and total cholesterol concentrations (WMD: -0.36 mmol/L [-13.92 mg/dL], 95% CI: -0.63, -0.09 [-24.36, -3.48], $p < 0.01$) was observed. HDL-C was significantly elevated following the omission of one study (WMD: 0.04 mmol/L [1.54 mg/dL], 95% CI: 0.03, 0.06 [1.16, 2.32], $p < 0.01$) during our sensitivity analysis. A meta-regression analysis was conducted and no significant association was found between changes in lipid parameters and cinnamon dose. In contrast, changes in blood levels of total cholesterol (slope: 0.09; 95% CI: 0.02, 0.16; $p < 0.01$), LDL-C (slope: 0.05; 95% CI: 0.001, 0.10; $p = 0.05$) and triglycerides (slope: 0.06; 95% CI: 0.04, 0.09; $p < 0.01$) were significantly and positively associated with the duration of supplementation. No statistically significant association was found between blood HDL-C changes and duration of supplementation.

Conclusion: Cinnamon supplementation significantly reduced blood triglycerides and total cholesterol concentrations without any significant effect on LDL-C and HDL-C.

Keywords: Cinnamon, cholesterol, triglycerides, lipid profiles, nutraceuticals.

INTRODUCTION

It is well known in current medical practice that blood lipids are associated with coronary heart disease, and that their blood levels are good indicators of cardiovascular risk and good predictors of coronary disease outcome [1]. Considering the association between blood lipid concentrations and cardiovascular disease, organic compounds like herbal polyphenols and other natural substances found in different plants may be potential adjuvants in the treatment of various cardiovascular pathologies, and are being intensely studied [2]. In this regard, spices such as cinnamon are important because they are inexpensive, safe, and available globally [3]. Research into herbs and spices is made especially important due to the fact that recently, the United States Food and Drug Administration (FDA) withdrew its approval for the combined use of a statin with extended-release niacin and extended-release fenofibric acid preparations for the treatment of various dyslipidemias [4]. The current limitation on effective combination therapy with statins enhances the importance of research into spices and other bioactives.

Cinnamon is extracted from the inner bark of trees from the genus *Cinnamomum* and belongs to the *Lauraceae* family widely spread in Asia, Australia and South America [5]. It is largely consumed as a spice being considered harmless to ingest [6]. Due to its pharmacological benefits, such as antibacterial and antioxidant properties, cinnamon is a significant element of the Chinese medicine [7]. The genus *Cinnamomum* contains two main species, *Cinnamomum zeylanicum* and *Cinnamomum cassia*, which has proven favorable antitumoral and antioxidant effects [8]. The main difference between these two varieties is their coumarin (1,2-benzopyrone) content [9]. Otherwise, both plant species possesses many active substances in different proportions, mainly eugenol (leaf), cinnamaldehyde (bark), and camphor (root) [10]. The

antioxidant phenolic constituents of cinnamon extracts have been suggested to diminish oxidative stress, bear anti-inflammatory properties, and improve cognitive function in animals [11]. As an important natural source of polyphenols, cinnamon has also been found to aid in the regulation of blood glucose in humans in the systematic review of randomized controlled trials [12], though the impact of cinnamon on blood lipids is still a controversial idea and the mechanism by which the cinnamon supplements potentially influence the level of blood lipids needs more clarification.

Accordingly, this meta-analysis reviewed a number of different randomized, placebo-controlled clinical trials, evaluating the effect of cinnamon on blood lipid concentration, specifically on different fractions of cholesterol and triglycerides, as they are important cardiovascular risk factors.

METHODS

Search Strategy

This study was designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement. A systematic literature search was performed in SCOPUS, Embase and Medline databases. The search terms (in titles and abstracts) were: (randomized controlled trials OR RCT OR randomized OR lipid OR total cholesterol OR LDL-cholesterol OR HDL-cholesterol OR triglycerides) and (cinnamon). The wild-card term “*” was used to increase the sensitivity of the search strategy. The search was not limited to articles published in any specific language. The literature was searched from inception to date 31 July 2015.

Study Selection

The following criteria was used to identify eligible studies: (i) Randomized placebo controlled trials with either a simple or cross-over design, (ii) investigation of the effects of any cinnamon species (*Genus cinnamomum*) or standardized cinnamon-enriched extracts on blood lipid concentrations, (iii) providing sufficient information on baseline and end-trial blood lipid concentrations in both cinnamon and control groups. Exclusion criteria were (i) animal and observational studies, (ii) uncontrolled studies, (iii) administration of non-standardized extracts or extracts containing negligible amounts of cinnamon resulting in a daily intake of < 5 mg, and (iv) lack of sufficient information on baseline or end-trial lipid concentrations. In case of the latter item, authors of the article(s) were contacted and requested to provide numerical data.

A systematic assessment of bias in the included studies was performed using the Cochrane criteria [13].

Quantitative Data Synthesis

Meta-analysis was conducted using Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) [14]. All values were collated as in mmol/L and mg/dL. Standard deviations (SDs) of the mean difference were calculated using the following formula: $SD = \text{square root} [(SD_{\text{pre-treatment}})^2 + (SD_{\text{post-treatment}})^2 - (2R \times SD_{\text{pre-treatment}} \times SD_{\text{post-treatment}})]$, assuming a correlation coefficient (R) = 0.5. If the outcome measures were reported in median and range (or 95% confidence interval [CI]), mean and standard SD values were estimated using the method described by *Wan et al.* Where standard error of the mean (SEM) was only reported, standard deviation (SD) was estimated using the following formula: $SD = SEM \times \text{sqrt}(n)$, where n is the number of subjects.

Net changes in measurements (change scores) for the trials were calculated using the following formula: (measure at the end of follow-up in the treatment group – measure at baseline in the treatment group) – (measure at the end of follow-up in the control group – measure at baseline in the control group). A random-effects model (using DerSimonian-Laird method) and the generic inverse variance method were used to compensate for the heterogeneity of studies in terms of study design, treatment duration, and the characteristics of populations being studied. Inter-study heterogeneity was assessed using Cochran Q test and I^2 index. In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using leave-one-out method, i.e. iteratively removing one study each time and repeating the analysis. Effect sizes were expressed as weighted mean difference (WMD) and 95% CI.

Meta-regression

A weighted random-effects meta-regression using unrestricted maximum likelihood model was performed to assess the association between the overall estimate of effect size with potential moderator variables including dose and duration of supplementation with cinnamon.

Publication bias

Potential publication bias was explored using visual inspection of Begg's funnel plot asymmetry, Egger's weighted regression, and "fail safe N" tests. Duval & Tweedie "trim and fill" method was used to adjust the analysis for the effects of publication bias.

RESULTS

Flow and characteristics of included studies

The initial screening for potential relevance removed the articles in whose titles and/or abstracts were obviously irrelevant (**Figure 1**). After assessment, 13 RCTs achieved the inclusion criteria and were preferred for the final meta-analysis.

Characteristics of included studies

In total, 750 participants were randomized, of whom 388 were allocated to cinnamon supplementation groups and 362 to control groups in the 13 selected studies [15-27]. The number of participants in these trials ranged from 17 to 137. Included studies were published between 2003 and 2015, and were conducted in China, Germany, Iran ($n = 3$), Netherlands, Pakistan, Sweden, Taiwan, Thailand, the United Kingdom, and the United States of America ($n = 2$). The following cinnamon supplementation was administered in the included trials: Between 1g and 6g of cinnamon powder per day in different trials (as noted in **Table 1**), 500mg of spray-dried water extract of cinnamon containing more than 4% type A procyanidins, and 1g Cinnulin PF® equivalent to 20g ground cinnamon per day. The duration of supplementation with cinnamon or its extracts ranged between 60 days and 4 months. All thirteen studies were designed as parallel-group trials. **Table 1** shows the demographic characteristics and baseline parameters of the included studies.

Effect of cinnamon supplementation on blood lipid concentrations

Overall, the impact of cinnamon supplementation on blood concentrations of total cholesterol, LDL-C, HDL-C and triglycerides was assessed in 16, 16, 13 and 16 treatment arms,

respectively. No significant effect of cinnamon was observed on blood LDL-C (WMD: -0.16 mmol/L [-6.19 mg/dL], 95% CI: -0.35, 0.03 [-13.53, 1.16], $p = 0.10$; **Figure 2**) and HDL-C (WMD: 0.05 mmol/L [1.92 mg/dL], 95% CI: -0.03, 0.12 [-0.03, 4.64], $p = 0.21$; **Figure 3**) concentrations. However, a significant reduction in blood triglycerides (WMD: -0.27 mmol/L [-23.91 mg/dL], 95% CI: -0.39, -0.14 [-34.54, -12.40], $p < 0.01$; **Figure 4**) and total cholesterol concentrations (WMD: -0.36 mmol/L [-13.92 mg/dL], 95% CI: -0.63, -0.09 [-24.36, -3.48], $p < 0.01$; **Figure 5**) was observed. All these effects were robust in sensitivity analysis (**Figures 2, 4, 5**), apart from a significant elevation of blood HDL-C concentration following omission of one study [22] from meta-analysis (WMD: 0.04 mmol/L [1.54 mg/dL], 95% CI: 0.03, 0.06 [1.16, 2.32], $p < 0.01$; **Figure 3**).

Meta-regression

Meta-regression analysis was conducted to evaluate the association between changes in blood lipid concentrations and potential confounders including dose and duration of supplementation with cinnamon. No significant association was found between changes in lipid parameters and cinnamon dose (**Figure 6**). In contrast, the difference in mean blood values of total cholesterol (slope: 0.09; 95% CI: 0.02, 0.16; $p < 0.01$), LDL-C (slope: 0.05; 95% CI: 0.001, 0.10; $p = 0.05$) and triglycerides (slope: 0.06; 95% CI: 0.04, 0.09; $p < 0.01$), between those receiving cinnamon and controls, were significantly and positively associated with the duration of supplementation (**Figure 7**). It means that longer duration of supplementation was correlated with an smaller effect size of cinnamon on its reduction of total cholesterol, LDL-C, and triglycerides. No significant association was found between blood HDL-C changes and duration

of supplementation (**Figure 7**).

Publication bias

Visual inspection of funnel plots suggested an asymmetry in the meta-analyses of cinnamon's effects on blood lipid concentrations. Using “trim and fill” method, 3, 5, 5 and 1 potentially missing studies were imputed for the meta-analyses of total cholesterol, LDL-C, HDL-C and triglycerides (**Figure 8**). Corrected effect sizes (following imputation of potentially missing studies) and the results of Egger’s linear regression, Begg’s rank correlation, and “fail safe N” tests are summarized in **Table 3**.

DISCUSSION

Dietary supplements, as a whole, can potentially provide us with a rich source of relatively inexpensive, safe, and healthy adjuvants to medicinal therapy for a wide range of diseases. If such products are tested and proven to be useful, it would bring a great benefit to the population by reducing the total number of medicines required by the patient, and by supplementing vitamins and other nutrients that these patients might be lacking. Furthermore, they could help reduce medication side-effects, including those that are psychogenic (i.e. *nocebo* effect) [28, 29], and limit their associated residual risks by reducing the need to increase medication dose if patient response is low or moderate [30]. In the case of statins, the dose is sometimes increased if the patient's total blood cholesterol remains unacceptably elevated, increasing the risk of statin intolerance [31, 32]. Cinnamon could curb this risk by potentially helping lower total blood cholesterol, reducing the need to increase Statin dose by as much. Other supplements have also shown similar promising results [33], such as spirulina for its effects on blood cholesterol [34]

and astaxanthin for its effects on blood glucose [35], which further accentuates the need to expand research in the field.

This meta-analysis aimed to determine whether cinnamon supplementation has the potential to be used as an adjuvant therapy for persons who are at a high risk for cardiovascular disease, by improving their blood lipid profile. This, and other studies like it, are very relevant and necessary, as on April 18th 2016, the United States Food and Drug Administration (FDA) withdrew its approval of the co-administration, with statins, of niacin extended-release tablets and fenofibric acid delayed-release capsules, in the treatment of multiple dyslipidemias, for their inability to show an improvement in morbidity and mortality over their individual monotherapies [4]. Such news warrants more research into herbs, spices, and other supplements as potential replacements for niacin and fenofibric acid specifically, and in the treatment of other diseases in general.

Our finding that cinnamon supplementation decreases blood triglycerides and total cholesterol contradicts the findings of another meta-analysis on this subject [36]. One possible explanation is that Baker *et al.* investigated only a handful of small studies, and might have lacked the power to detect statistically significant differences [36]. Another explanation might be that Baker *et al.* incorporated studies that specifically focused on patients with diabetes mellitus, a demographic that might be statistically different from the general population in this regard [36]. Previous meta-analysis, which only included diabetic patients (n=543), corroborates the findings of our study, finding statistically significant reductions in blood total cholesterol (-15.60 mg/dL; 95% CI, -29.76 to -1.44 mg/dL) and triglycerides (-29.59 mg/dL; 95% CI, -48.27 to -10.91 mg/dL), but also significant reduction of LDL-C (-9.42 mg/dL; 95% CI, -17.21 to -1.63

mg/dL) and an increase of HDL-C (1.66 mg/dL; 95% CI, 1.09 to 2.24 mg/dL) [37].

There are some proposed mechanisms of action of cinnamon, which could help explain our findings. In regards to the decrease in blood triglyceride concentration, studies have shown that polyphenols found in cinnamon increase glycogen synthesis and decrease glycogenolysis [12], decrease the absorption of glucose by the small intestine [38], and regulate peroxisome proliferator-activated receptor alpha (PPAR- α) and gamma-mediated metabolism [39], findings which are corroborated by other research [40]. In this way, the decrease in chylomicron absorption and possible increase in triglyceride uptake by adipocytes could explain our findings. The possible activation of PPAR- α receptors by cinnamon could help explain the reduction in blood cholesterol [41]. Another possible explanation might be that the vitamin content might be responsible for an increased lipid metabolism [5].

In regards to the safety of cinnamon supplementation, the European Food Safety Authority (EFSA) states that a prudent Tolerable Daily Intake (TDI) for coumarin is 0.1mg/kg body weight/day [42]. One study that tested 60 samples of ground cinnamon, obtained in the Czech Republic from normal supermarkets, found that the averages of their samples contained coumarin in a range from 2650 to 7017mg/kg [43]. As such, for an adult male that weighs 70 kg, an average of 1g – 2.6g of ground cinnamon per day, depending on the source and type of cinnamon, would be sufficient to reach the EFSA's TDI limit. A 2012 systematic review and meta-analysis described the safety of *C. zeylanicum* (i.e. 'true' cinnamon) on rats with streptozocin-induced diabetes by evaluating 4 animal studies [39]. They calculated the equivalent human LD50 (median lethal dose) of *C. zeylanicum* to be 11.4 ± 0.2 g/kg, which would be almost 800g for the average 70kg male. For comparison, the highest single dose given to any subject in

the studies we evaluated was the equivalent of 10g of cinnamon (with an average of approximately 2g per dose across all studies) although the species of *Cinnamomum* administered did differ across studies. The aforementioned meta-analysis also discussed a study where rats exposed to doses of cinnamon up to 20x higher than their target therapeutic dose displayed no change in behavior across the 3 weeks that they were studied, nor did they exhibit any statistically significant blood elevations in liver enzymes. However, significant elevations of blood urea and uric acid were found at therapeutic doses in two of the studies [39]. Of concern is a case report, which details a patient presenting with acute hepatitis after concomitantly taking rosuvastatin 40mg and cinnamon supplements for some undisclosed period of time. However the authors did not present which supplement and in what dose it was taken [44]. Unfortunately, no animal or human studies evaluating the long-term safety of cinnamon administration are available, and none of the studies we evaluated mentioned their subjects receiving statin therapy during the trial. More research is necessary before long-term cinnamon administration, especially alongside statins, can be considered safe.

One of the main limitations of our meta-analysis is the fact that most of the studies done on the lipid-lowering effects of cinnamon were performed on diabetic patients. As a result, 12 out of the 13 studies were strictly conducted on patients with diabetes mellitus or impaired glucose tolerance. The presence of diabetes may be a confounding factor, and make extrapolating the results of this study to the general population difficult without further research. More research needs to be done to elucidate whether cinnamon is effective in non-diabetic patients. Another limitation is the heterogeneity of the cinnamon species examined in the individual studies. Some studies used *Cinnamomum cassia* extracts, while others used *C. loureiroi*, *C. Aromaticum*,

combinations of these species, or did not specify the species. It is yet unclear whether or not these differences may impact the presence and/or concentrations of the substances in cinnamon responsible for the possible effects observed in this meta-analysis. More research needs to be done focusing on individual cinnamon species in order to determine whether this impacts our observations. Finally, among the 13 studies analyzed, only 2 explicitly excluded patients taking lipid-lowering medication [17, 27], and 3 more (which focused on diabetic patients) mentioned which medications the patients were taking, but did not specifically mention the presence or absence of lipid-lowering medications [20, 23, 25]. Among the rest, either some patients were on statins and/or other lipid-lowering medications, or medications were not mentioned altogether. While not certain, these differences might serve as a source of bias in our results.

In conclusion, cinnamon supplementation significantly reduced blood triglycerides and total cholesterol concentrations but had no effects on blood LDL-C and HDL-C concentrations. These results indicate that cinnamon supplementation may be of marginal benefit to diabetic patients and patients with impaired glucose tolerance, especially with atherogenic dyslipidemias. More research is necessary to elucidate whether these findings are also clinically significant.

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Declaration of interest:

The authors have no relevant interests to declare.

Authorship: All authors have materially participated in the research and/or article preparation.

Their roles in the realization of this paper are as follows:

Serban M. Maiercan – Drafting the article and revising it critically for important intellectual content.

Maria-Corina Serban – Conception study, acquisition of data, and analysis and interpretation of data.

Amirhossein Sahebar – Conception study, acquisition of data, and analysis and interpretation of data.

Sorin Ursoniu – Conception study, acquisition of data, and analysis and interpretation of data.

Alexandru Serban – Conception study, acquisition of data, and analysis and interpretation of data.

Peter Penson – Conception study, acquisition of data, and analysis and interpretation of data.

Maciej Banach – Drafting the article and revising it critically for important intellectual content, and final approval for submitted version of article.

All authors agree that their roles in the creation of this study, as enumerated above, are accurate.

All authors have approved of the contents of, and of the publication of this paper.

FIGURES LEGEND:

Figure 1. Flow chart of the number of studies identified and included into the meta-analysis.

Figure 2. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of cinnamon supplementation on blood LDL-cholesterol concentrations. Lower plot shows leave-one-out sensitivity analysis.

Figure 3. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of cinnamon supplementation on blood HDL-cholesterol concentrations. Lower plot shows leave-one-out sensitivity analysis.

Figure 4. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of cinnamon supplementation on blood triglycerides concentrations. Lower plot shows leave-one-out sensitivity analysis.

Figure 5. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of cinnamon supplementation on blood total cholesterol concentrations. Lower plot shows leave-one-out sensitivity analysis.

Figure 6. Random-effects meta-regression plots of the association between mean changes in blood concentrations of lipids and dose of cinnamon.

Figure 7. Random-effects meta-regression plots of the association between mean changes in blood concentrations of lipids and duration of supplementation with cinnamon.

Figure 8. Funnel plot displaying publication bias in the studies reporting the impact of cinnamon supplementation on blood concentrations of lipids.

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Table 1. Demographic characteristics of the included studies. All values for BMI, blood pressure, and plasma lipids are baselines.

	Cinna mon supple mentat ion	Akilen <i>et al.</i> (19)	Anderson <i>et al.</i> (20)	Askari <i>et al.</i> (21)	Blevins <i>et al.</i> (22)	Khan <i>et al.</i> (23)	Lu <i>et al.</i> (24)	Mang <i>et al.</i> (25)	Sengsuk <i>et al.</i> (26)	Vafa <i>et al.</i> (27)	Vanschoonbeek <i>et al.</i> (28)	Wickenberg <i>et al.</i> (29)	Zahmatkesh <i>et al.</i> (30)	Ziegenfuss <i>et al.</i> (31)
Year		2010	2015	2013	2007	2003	2012	2006	2015	2012	2006	2014	2014	2006
Location		UK	Taiwan	Iran	USA	Pakistan	China	Germany	Thailand	Iran	Netherlands	Sweden	Iran	USA
Study design		Randomized, placebo-controlled, double-blind clinical trial with two parallel groups	Randomized double-blind placebo controlled parallel group trial	Randomized double blinded, placebo controlled trial with two parallel groups	Randomized double-blind placebo-controlled parallel trial	Randomized, double-blind, placebo controlled, parallel clinical trial	Randomized, double-blind, placebo-controlled parallel trial	Randomized, double-blind placebo-controlled parallel trial	Randomized double-blind placebo-controlled parallel trial	Randomized double-blind placebo-controlled parallel trial	Randomized Double-blind placebo-controlled parallel trial	Randomized double-blind placebo-controlled parallel trial	Randomized Double-blind, randomized controlled trial	Randomized, double-blind, placebo controlled parallel trial
Duration of trial		12 weeks	2 months	12 weeks	3 months	60 days	3 months	4 months	60 days	8 weeks	6 weeks	12 weeks	8 weeks	12 weeks
Type and dose of cinnamon supplements		2 g cinnamon capsules	spray-dried water extract of cinnamon containing more than 4% type A procyanidins polyphenols, in 250 mg capsules, twice a day	1.5 g cinnamon capsules	1 g cinnamon capsules	1g cinnamon capsules ^A 3g cinnamon capsules ^B 6g cinnamon capsules ^C	60 mg cinnamon tablets given as: Low Dose = 2 Tab/d (120mg total) High Dose = 6 Tab/d (360 mg total)	3 x 112 mg aqueous cinnamon extract / day 112 mg aqueous extract corresponds to 1g of cinnamon	500 mg cinnamon capsules 1 capsule 3x / day (1500 mg total)	500 mg cinnamon capsules 2 capsules 3x / day (3000 mg total)	500 mg cinnamon capsules 1 capsule 3x / day (1500 mg total)	700 mg capsules containing 500mg C. cassia + 200 mg cellulose 1 capsule 2x / day (1000 mg total)	500 mg cinnamon capsules 2 capsules 2x / day (2000mg total)	250 mg capsules Cinnulin PF®, equivalent to 5g ground cinnamon. 2 capsules 2x / day (1000 mg total)
Participants	YES	30	64	23	30	10 ^A	23 _{LD}	33	49	19	12	9	31	12
						10 ^B	23 _{HD}							
						10 ^C								
	NO	28	73	22	28	10 ^D	20	32	50	18	13	8	30	10
						10 ^E								
Age (years)	YES	54.90 ±10.14	NS	NS	63.6	52.0±5.85	62.4 ± 7.9 _{LD}	62.8 ± 8.37	57.3 ± 1.1	54.11 ± 10.37	62.0 ± 2.0	73 ± 2	56.8 ± 6.0	46.3 ± 8.8
							58.9 ± 6.4 _{HD}							
	NO	54.43 ±12.53	NS	NS	58.0	52.0±6.87	60 ± 5.9	63.7 ± 7.17	56.9 ± 1.2	55.67 ± 7.98	64.0 ± 2.0	72 ± 2	53.1 ± 8.4	45.6 ± 11.1
Female (%)	YES	19 (63.4)	NS	NS	30 (51)	30 (50)	15 (65.2) _{LD}	12 (36.4)	33 (67.3)	13 (68.4)	12 (100.0)	5 (55.6)	(51)	4 (0.33)
							14 (60.9) _{HD}							
	NO	13 (46.4)	NS	NS			12 (60.0)	9 (28.1)	34 (68.0)	11 (61.1)	13 (100.0)	5 (62.5)	(45)	7 (0.7)
Male (%)	YES	11 (36.6)	NS	NS	28 (49)	30 (50)	8 (34.8) _{LD}	21 (63.6)	16 (32.7)	6 (31.6)	0 (0)	4 (44.4)	(49)	8 (0.66)
							9 (39.1) _{HD}							
	NO	15 (53.6)	NS	NS			8 (40.0)	23 (71.9)	16 (32.0)	7 (38.9)	0 (0)	3 (37.5)	(55)	3 (0.3)
BMI (kg/m²)	YES	33.36 ±4.20	24.8 ± 0.4*	29. 9 ± 3. 9	32.5± 1.7	NS ^A	NS ^{LD}	29.6 ± 4.64	24.7 (22.1-27.4)**	29.23 ± 3.98	30.7 ± 1.1	25.7 ± 1.3	NS	32.3 ± 5.7
						NS ^B								
						NS ^C	NS ^{HD}							
	NO	32.13 ± 8.31	25.8 ± 0.3*	30. 3 ± 4. 1	32.0±1.5	NS ^D	NS	30.1 ± 5.22	24.7 (22.5-	28.59 ± 3.54	30.1 ± 1.4	28.6 ± 1.9	NS	34.4 ± 12.6

						NS ^e			27.4)**					
						NS ^f								
Total cholesterol mmol/l (mg/dL)	YES	4.31 ± 1.07 (166.67 ± 41.38)	5.20 ± 0.14* (201.08 ± 5.41)	4.32 ± 1.53 (167.05 ± 59.17)	4.40 ± 0.21 (170.15 ± 8.12)	4.09 ± 0.30 ^A (158.16 ± 11.60)	4.96 ± 1.35 ^{BD} (191.80 ± 52.20)	5.29 ± 0.89 (204.56 ± 34.42)	4.26 (3.56-4.77)** (164.76-184.46)	4.38 ± 0.85 (169.37 ± 32.87)	5.05 ± 0.15 (195.28 ± 5.80)	4.9 ± 0.4* (189.48 ± 15.47)	5.85 ± 1.28 (226.22 ± 49.50)	4.78 ± 1.14 (184.84 ± 44.08)
						4.03 ± 0.34 ^B (155.84 ± 13.15)	5.18 ± 0.78 ^{BD} (200.31 ± 30.16)							
						4.86 ± 0.19 ^C (187.64 ± 7.35)								
	NO	4.10 ± 0.87 (158.55 ± 33.64)	5.12 ± 0.12* (197.99 ± 4.64)	4.84 ± 0.55 (187.16 ± 21.27)	4.56 ± 0.21 (176.34 ± 8.12)	4.78 ± 0.31 ^D (184.84 ± 11.99)	4.60 ± 1.04 (177.88 ± 40.22)	5.17 ± 0.75 (199.92 ± 29.00)	4.39 (3.79-5.02)** (169.76-194.12)	4.02 ± 0.91 (155.45 ± 35.19)	4.91 ± 0.30 (189.87 ± 11.6)	4.5 ± 0.2* (174.02 ± 7.73)	5.66 ± 0.78 (218.87 ± 30.16)	4.97 ± 1.27 (192.19 ± 49.11)
						4.94 ± 0.35 ^E (191.03 ± 13.53)								
						5.84 ± 0.42 ^F (225.83 ± 16.24)								
LDL-C mmol/l (mg/dL)	YES	2.47 ± 0.96 (95.51 ± 37.12)	3.48 ± 0.14* (134.57 ± 5.41)	1.93 ± 1.69 (74.63 ± 65.35)	2.62 ± 0.17 (101.32 ± 6.57)	2.35 ± 0.13 ^A (90.87 ± 5.03)	2.65 ± 0.76 ^{BD} (102.48 ± 29.39)	3.48 ± 0.71 (134.57 ± 27.46)	2.19 (1.63-2.61)** (84.69 (63.03-100.93))	2.44 ± 0.77 (94.35 ± 29.78)	3.06 ± 0.15 (118.33 ± 5.80)	3.2 ± 0.4* (123.74 ± 15.47)	3.44 ± 0.92 (113.02 ± 35.58)	2.77 ± 0.93 (107.12 ± 35.96)
						1.97 ± 0.18 ^B (76.18 ± 6.96)	3.14 ± 0.6 ^{BD} (121.43 ± 23.20)							
						2.72 ± 0.11 ^C (105.18 ± 4.15)								
	NO	2.27 ± 0.75 (87.78 ± 29.00)	3.45 ± 0.09* (133.41 ± 3.48)	2.47 ± 0.59 (95.51 ± 22.82)	2.72 ± 0.17 (105.18 ± 6.57)	2.40 ± 0.22 ^D (92.81 ± 8.51)	2.70 ± 0.86 (104.41 ± 33.26)	3.59 ± 0.69 (138.83 ± 26.68)	2.32 (1.86-2.83)** (89.71 (71.93-109.44))	2.39 ± 0.84 (92.42 ± 32.48)	3.04 ± 0.25 (117.56 ± 9.67)	2.7 ± 0.2* (104.41 ± 7.73)	3.43 ± 0.72 (132.64 ± 27.84)	2.72 ± 1.34 (105.18 ± 51.82)
						2.79 ± 0.27 ^E (107.89 ± 10.44)								
						3.36 ± 0.37 ^F (129.93 ± 14.31)								
HDL-C mmol/l (mg/dL)	YES	1.18 ± 0.29 (45.63 ± 11.21)	1.26 ± 0.04* (48.72 ± 1.55)	1.19 ± 0.21 (46.02 ± 8.12)	1.14 ± 0.04 (44.08 ± 1.55)	NS ^A	1.23 ± 0.36 ^{BD} (47.56 ± 13.92)	1.44 ± 0.49 (55.68 ± 18.95)	1.22 (1.01-1.44)** (47.18 (39.06-55.68))	1.12 ± 0.11 (43.31 ± 4.25)	1.42 ± 0.09 (54.91 ± 3.48)	1.4 ± 0.1* (54.14 ± 3.87)	0.98 ± 0.15 (37.90 ± 5.80)	1.29 ± 0.34 (49.88 ± 13.15)
						NS ^B	1.56 ± 0.49 ^{BD} (60.33 ± 18.95)							
						NS ^C								
	NO	1.16 ± 0.19 (44.86 ± 7.35)	1.28 ± 0.04* (49.50 ± 1.55)	1.09 ± 0.16 (42.15 ± 6.19)	NS***	NS ^D	1.43 ± 0.50 (55.30 ± 19.34)	1.34 ± 0.31 (51.82 ± 11.99)	1.42 (1.15-1.67)** (54.91 (44.47-64.58))	1.06 ± 0.14 (40.99 ± 5.41)	1.29 ± 0.11 (49.88 ± 4.25)	1.5 ± 0.1* (58.01 ± 3.87)	0.99 ± 0.12 (38.28 ± 4.64)	1.42 ± 0.36 (54.91 ± 13.92)
						NS ^E								
						NS ^F								
Triglycerides mmol/l (mg/dL)	YES	1.65 ± 0.93 (146.14 ± 82.37)	2.20 ± 0.21* (194.85 ± 18.60)	2.52 ± 1.0 (223.20 ± 88.57)	1.49 ± 0.18 (131.97 ± 15.94)	1.67 ± 0.21 ^A (147.91 ± 18.60)	2.93 ± 2.08 ^{BD} (259.51 ± 184.23)	1.96 ± 1.65 (173.60 ± 146.14)	1.32 (1.02-2.27)** (116.91 (90.34-201.05))	1.84 ± 0.59 (162.97 ± 52.26)	1.1 ± 0.1 (97.43 ± 8.86)	1.1 ± 0.1* (97.43 ± 8.86)	3.06 ± 0.56 (271.02 ± 49.60)	1.87 ± 1.60 (185.63 ± 141.71)
						2.16 ± 0.52 ^B (191.31 ± 46.06)	1.74 ± 1.05 ^{BD} (154.11 ± 93.00)							
						2.07 ± 0.32 ^C (183.34 ± 28.34)								

	NO	1.48 ± 1.04 (131.08 ± 92.11)	2.05 ± 0.17* (181.57 ± 15.06)	2.43 ± 0.94 (215.23 ± 83.26)	1.76 ± 0.26 (155.88 ± 23.03)	2.45 ± 0.32 ^D (217.00 ± 28.34)	1.68 ± 0.67 (148.80 ± 59.34)	1.66 ± 0.78 (147.03 ± 69.08)	1.40 (1.01-2.28)** (124.00 (89.46-201.94))	1.53 ± 0.46 (135.51 ± 40.74)	1.1 ± 0.1 (97.43 ± 8.86)	1.1 ± 0.1* (97.43 ± 8.86)	2.47 ± 0.34 (218.77 ± 30.11)	1.86 ± 1.21 (164.74 ± 107.17)
SBP (mmHg)	YES	133 ± 8.6	128.3 ± 1.9*	NS	NS	NS ^A	NS ^{LD}	NS	134.5 (126.8-144.0)**	123.42 ± 11.9	NS	140.5 ± 4.7*	NS	133 ± 14
						NS ^B	NS ^{HD}							
						NS ^C								
NO	134 ± 10.9	122.7 ± 1.5*	NS	NS	NS ^D	NS	NS	135.0 (127.0-142.0)**	125.56 ± 11.49	NS	122 ± 16.7*	NS	133 ± 22	
					NS ^E									
					NS ^F									
DBP (mmHg)	YES	85 ± 6.45	78.2 ± 1.1*	NS	NS	NS ^A	NS ^{LD}	NS	83.5 (79.0-91.3)**	80.0 ± 6.87	NS	82.0 ± 2.8*	NS	83 ± 6
						NS ^B	NS ^{HD}							
						NS ^C								
NO	87 ± 8.82	75.9 ± 0.9*	NS	NS	NS ^D	NS	NS	80.0 (73.5-90.0)**	80.56 ± 6.39	NS	80.0 ± 2.6*	NS	83 ± 14	
					NS ^E									
					NS ^F									

Values are generally expressed as mean ± SD, except:

* – Mean ± Standard Error of the Mean

** – Median (Interquartile Range)

ABBREVIATIONS:

A = Group receiving 1g cinnamon / day	B = Group receiving 3g cinnamon / day	C = Group receiving 6g cinnamon / day	D = Group receiving placebo corresponding to group A in number of tablets given
E = Group receiving placebo corresponding to group B in number of tablets given	F = Group receiving placebo corresponding to group C in number of tablets given	BMI = Body-mass index	DBP = Diastolic blood pressure
HD = High dose	HDL-C = High-density lipoprotein cholesterol	LD = Low dose	LDL-C = Low-density Lipoprotein Cholesterol
NS = Not specified	SBP = Systolic blood pressure	*** Paper and electronic sources for this study list value incorrectly.	

Table 2. Risk of bias assessment of the studies included in this meta-analysis

Study	SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS AND PERSONNEL	BLINDING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE OUTCOME REPORTING	OTHER POTENTIAL THREATS TO VALIDITY
Akilen et al. 2010	L	L	L	L	L	L	L
Anderson et al. 2015	U	L	L	U	L	L	L
Askari et al. 2014	L	L	L	L	L	L	L
Blevins et al. 2007	U	L	L	L	L	L	L
Khan et al. 2003	L	L	U	U	L	L	L
Lu et al. 2012	U	L	L	U	L	L	L
Mang et al. 2006	U	U	L	U	L	L	L
Sengsuk et al. 2015	L	L	L	L	L	L	L
Vafa et al. 2012	U	U	L	L	L	L	L
Vanschoonbeek et al. 2006	U	U	L	U	L	L	L
Wichenberg et al. 2014	L	L	L	U	L	L	L
Zahmatkash et al. 2014	U	U	L	U	L	L	U
Ziegenfuss et al. 2006	U	U	L	U	L	L	L

Table 3. Assessment of publication bias in the meta-analysis cinnamon's effects on plasma lipid concentrations of lipids

	Corrected effect size ^a		Begg's rank correlation test,			Egger's linear regression test			Fail safe N test
	WMD	95% CI	Kendall's Tau ^a	z-value	p-value	Intercept	95% CI	p-value	n ^b
Total cholesterol	-0.46	-0.77, -0.16	0.19	1.04	0.300	-2.31	-5.09, 0.47	0.096	243
LDL-C	-0.27	-0.47, -0.07	0.14	0.77	0.444	-1.32	-3.89, 1.25	0.289	61
HDL-C	0.08	0.02, 0.15	0.42	2.01	0.044	-0.10	-2.53, 2.34	0.933	85
Triglycerides	-0.26	-0.38, -0.14	0.04	0.23	0.822	-1.12	-2.34, 0.10	0.069	151

^aWith continuity correction; ^bNumber of theoretically missing studies to bring the p-value to > 0.05.

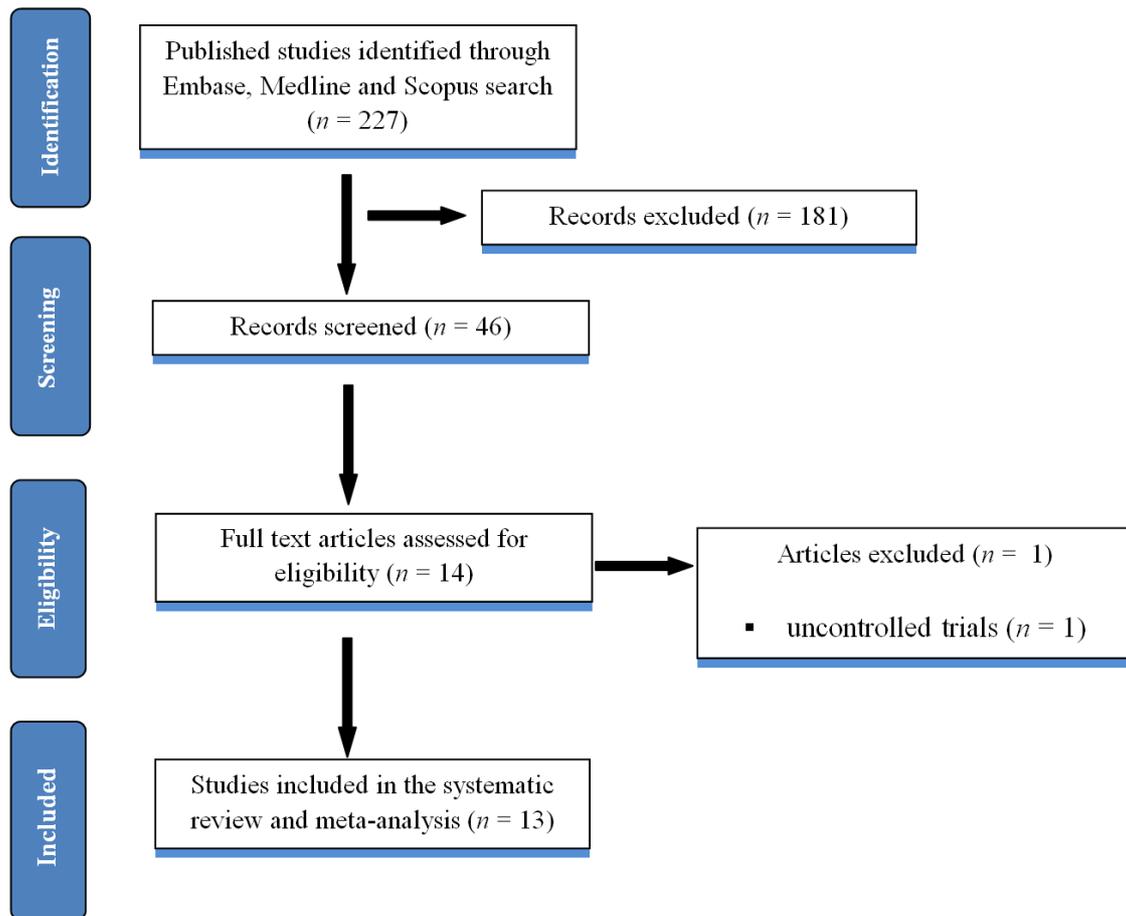
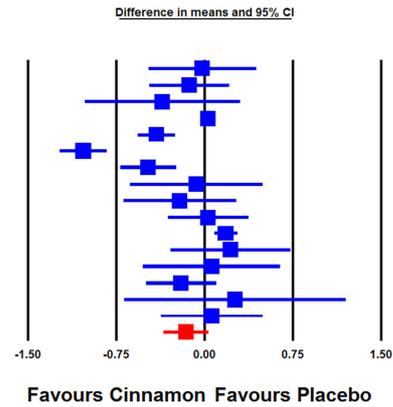
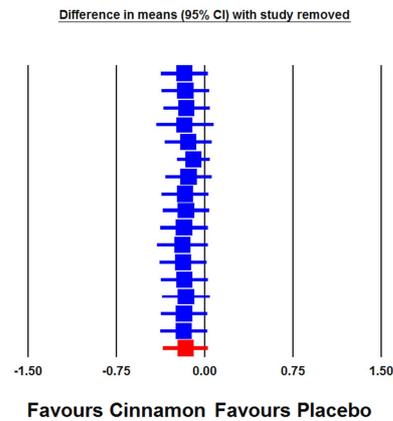


Fig 1. Flow chart of number of studies identified and included into the review

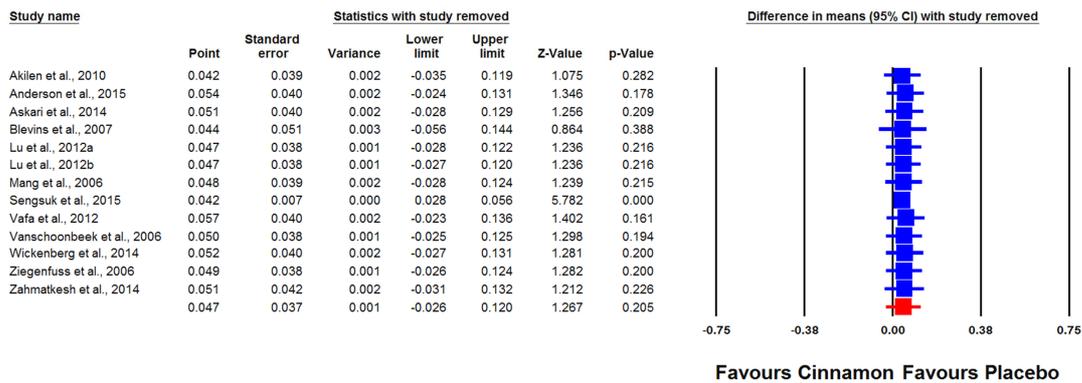
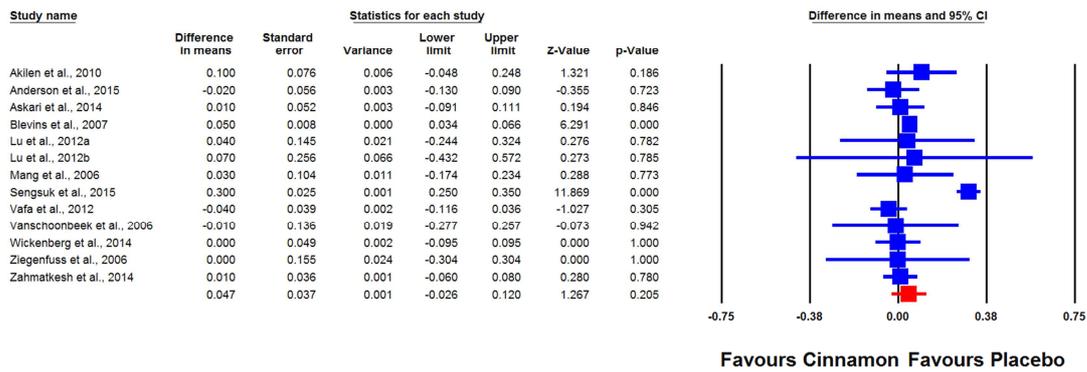
Study name	Difference in means	Standard error	Statistics for each study				
			Variance	Lower limit	Upper limit	Z-Value	p-Value
Akilen et al., 2010	-0.020	0.232	0.054	-0.475	0.435	-0.086	0.931
Anderson et al., 2015	-0.130	0.171	0.029	-0.466	0.206	-0.759	0.448
Askari et al., 2014	-0.360	0.335	0.112	-1.017	0.297	-1.074	0.283
Blevins et al., 2007	0.030	0.032	0.001	-0.032	0.092	0.947	0.344
Khan et al., 2003a	-0.410	0.080	0.006	-0.567	-0.253	-5.121	0.000
Khan et al., 2003b	-1.030	0.100	0.010	-1.226	-0.834	-10.285	0.000
Khan et al., 2003c	-0.480	0.120	0.014	-0.714	-0.246	-4.014	0.000
Lu et al., 2012a	-0.070	0.286	0.082	-0.630	0.490	-0.245	0.806
Lu et al., 2012b	-0.210	0.243	0.059	-0.686	0.266	-0.864	0.388
Mang et al., 2006	0.030	0.174	0.030	-0.310	0.370	0.173	0.863
Sengsuk et al., 2015	0.180	0.050	0.002	0.083	0.277	3.623	0.000
Vafa et al., 2012	0.220	0.258	0.066	-0.285	0.725	0.854	0.393
Vanschoonbeek et al., 2006	0.060	0.296	0.088	-0.520	0.640	0.203	0.839
Wickenberg et al., 2014	-0.200	0.151	0.023	-0.496	0.096	-1.324	0.186
Ziegenfuss et al., 2006	0.260	0.479	0.230	-0.679	1.199	0.542	0.588
Zahmatkesh et al., 2014	0.060	0.219	0.048	-0.368	0.489	0.274	0.784
	-0.159	0.097	0.009	-0.349	0.031	-1.645	0.100

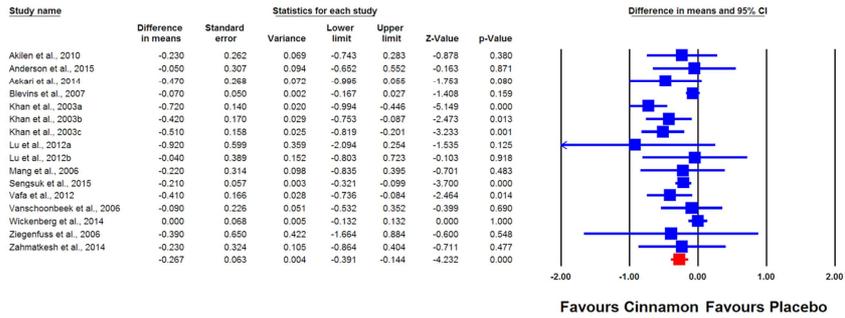


Study name	Point	Standard error	Statistics with study removed				
			Variance	Lower limit	Upper limit	Z-Value	p-Value
Akilen et al., 2010	-0.167	0.101	0.010	-0.365	0.030	-1.661	0.097
Anderson et al., 2015	-0.161	0.102	0.010	-0.361	0.039	-1.578	0.115
Askari et al., 2014	-0.150	0.099	0.010	-0.345	0.045	-1.512	0.131
Blevins et al., 2007	-0.167	0.123	0.015	-0.408	0.075	-1.354	0.176
Khan et al., 2003a	-0.137	0.102	0.010	-0.336	0.062	-1.351	0.177
Khan et al., 2003b	-0.092	0.071	0.005	-0.230	0.046	-1.304	0.192
Khan et al., 2003c	-0.133	0.100	0.010	-0.330	0.063	-1.331	0.183
Lu et al., 2012a	-0.164	0.100	0.010	-0.360	0.033	-1.635	0.102
Lu et al., 2012b	-0.156	0.101	0.010	-0.353	0.041	-1.552	0.121
Mang et al., 2006	-0.172	0.102	0.010	-0.372	0.027	-1.692	0.091
Sengsuk et al., 2015	-0.185	0.110	0.012	-0.401	0.031	-1.662	0.093
Vafa et al., 2012	-0.181	0.100	0.010	-0.377	0.016	-1.803	0.071
Vanschoonbeek et al., 2006	-0.170	0.100	0.010	-0.366	0.026	-1.701	0.089
Wickenberg et al., 2014	-0.156	0.102	0.010	-0.356	0.045	-1.520	0.128
Ziegenfuss et al., 2006	-0.171	0.099	0.010	-0.365	0.022	-1.736	0.082
Zahmatkesh et al., 2014	-0.173	0.101	0.010	-0.371	0.025	-1.712	0.087
	-0.159	0.097	0.009	-0.349	0.031	-1.645	0.100

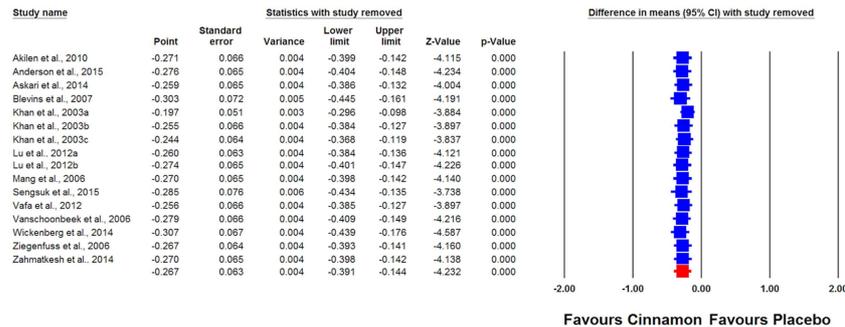


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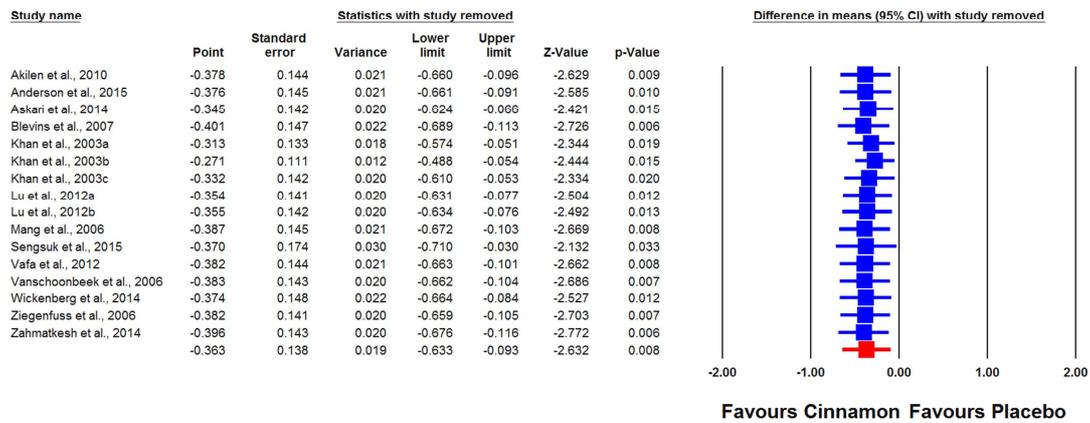
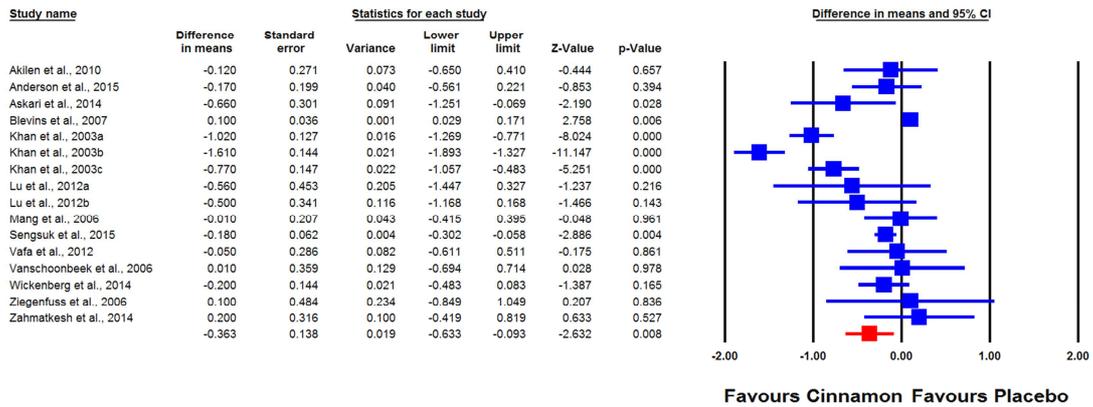




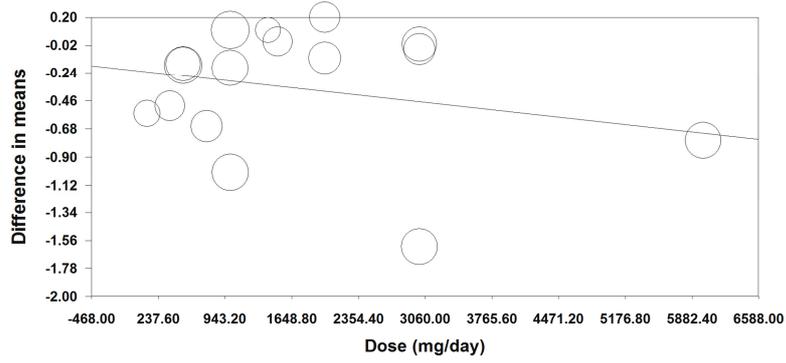
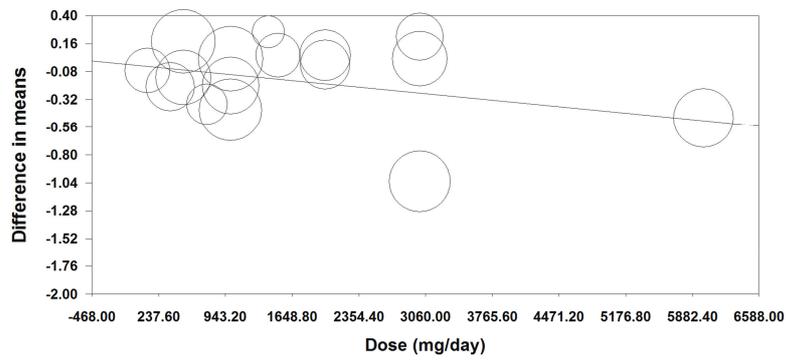
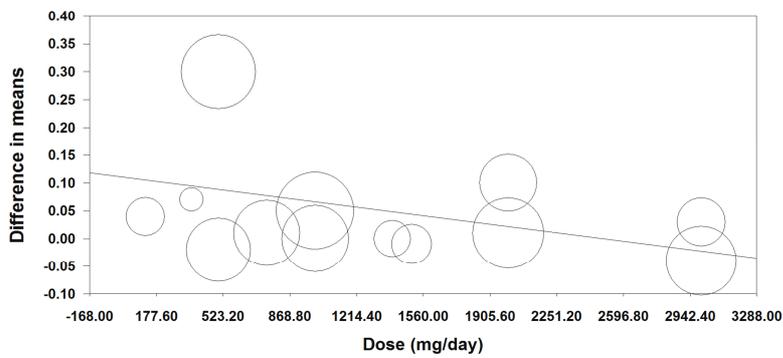
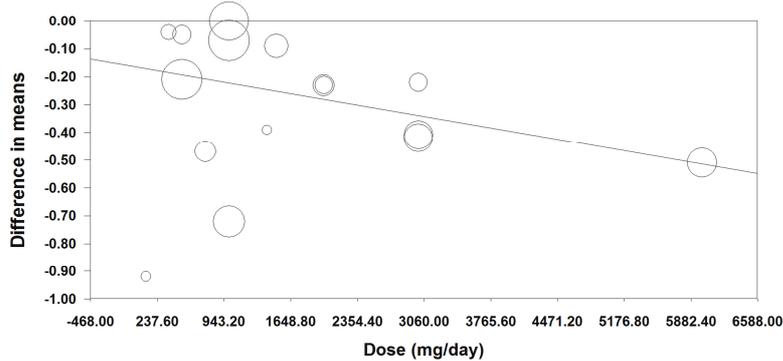
Favours Cinnamon Favours Placebo

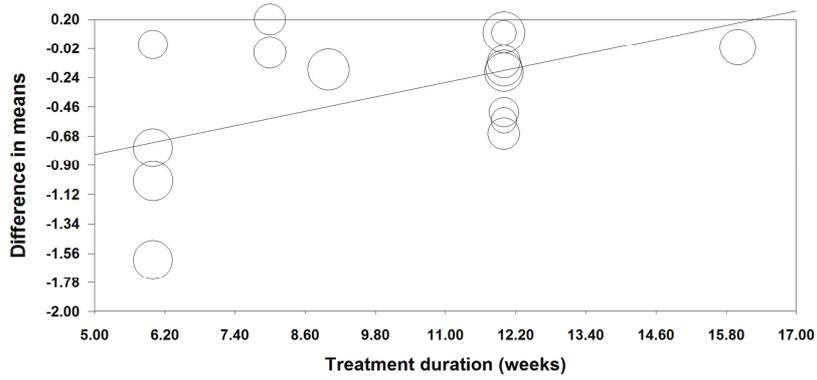
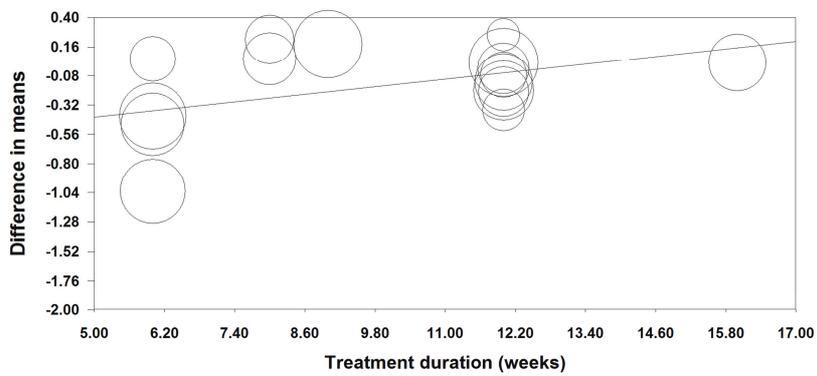
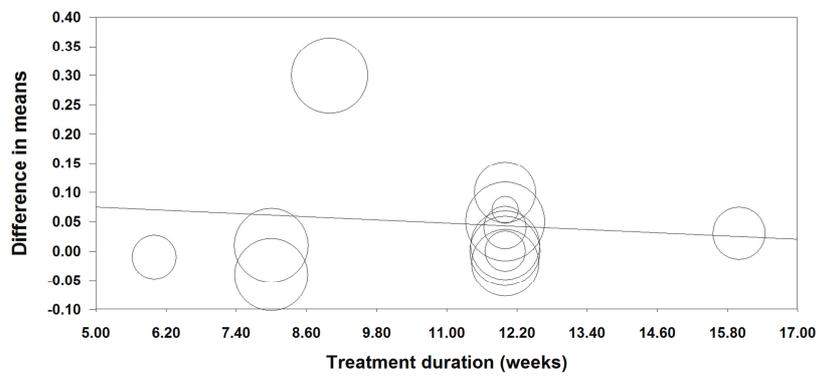
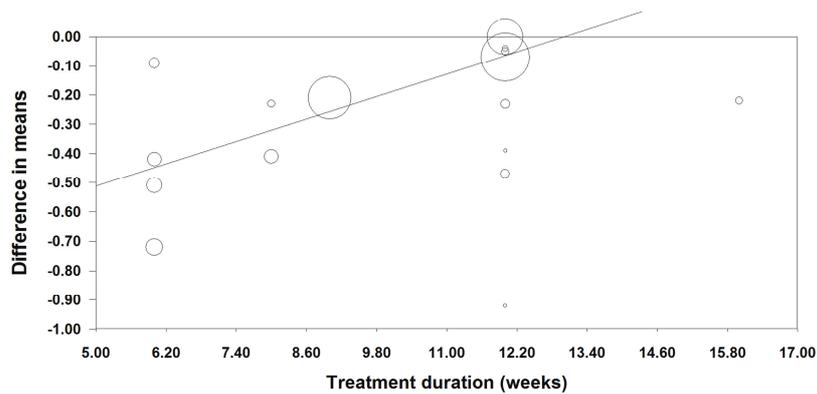


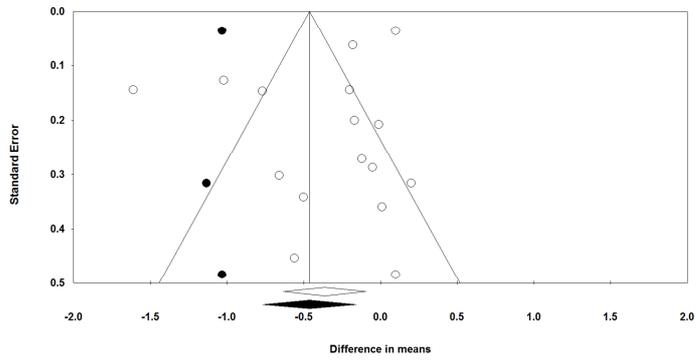
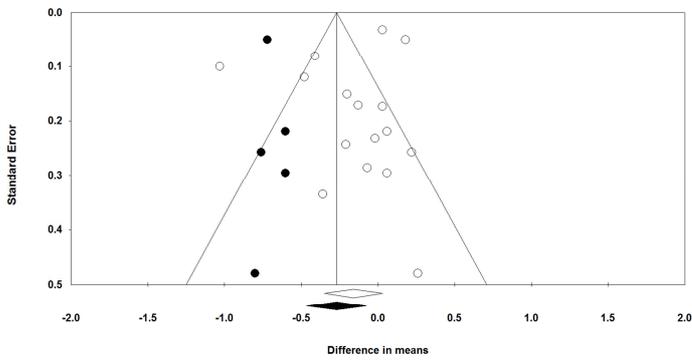
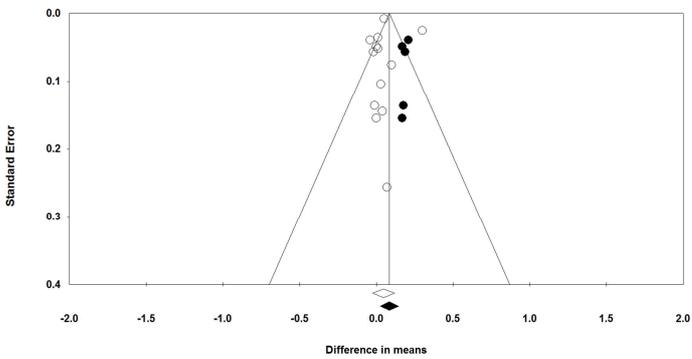
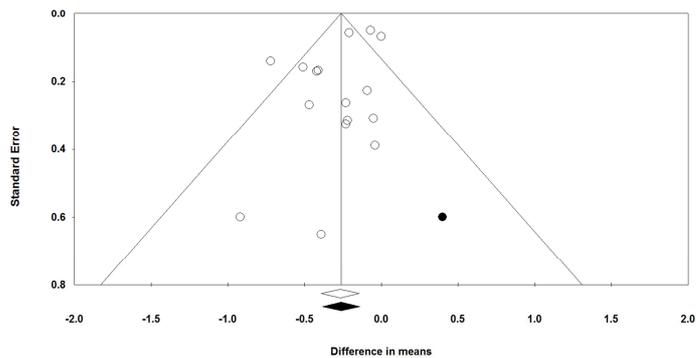
Favours Cinnamon Favours Placebo



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Total cholesterol**LDL-C****HDL-C****Triglycerides**

Total cholesterol**LDL-C****HDL-C****Triglycerides**

Total cholesterol**LDL-C****HDL-C****Triglycerides**

SCRIPT

The Effects of Cinnamon Supplementation on Plasma Lipid Concentrations: A Systematic Review and Meta-Analysis -- Highlights

- Cinnamon supplementation reduced total plasma cholesterol and triglycerides.
- Effect is correlated with duration of treatment, but not with dose administered.
- HDL was also significantly increased after removing one study from the analysis.

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