Effect of cinnamon (*Cinnamomum Zeylanicum*) supplementation on serum C-reactive protein concentrations: A meta-analysis and systematic review.

*Natalia Vallianou[1], Catherine Tsang[2], Mohsen Taghizadeh[3], Amirhossein Davoodvandi[4] , and Sadegh Jafarnejad[5]**

1- Departement of Internal Medicine, Evangelismos General Hospital, Athens, Greece, Email: nvallianou@mailfa.com

2- Faculty of Health and Social Care, Edge Hill University, Ormskirk, Lancashire, United Kingdom, Email: ctsang@mailfa.com.

3- Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, I.R. Iran. Email: mtaghizadeh@mailfa.com

4- Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, I.R. Iran. Email: adavoodvandi@mailfa.com

5- Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, I.R. Iran. Email: sjafarnejad@alumnus.tums.ac.ir

Running title: cinnamon on serum C-reactive protein concentrations

* Corresponding Author. Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, I.R. Iran. Tel: +98-31-55463378; Fax: +98-31-55463377. P.O.Box: 254756254

E-mail addresses: sjafarnejad@alumnus.tums.ac.ir

Abstract

Objective: The effect of cinnamon (*Cinnamomum Zeylanicum*) on serum C-reactive protein (CRP)**,** an acute phase protein commonly used as a marker of inflammation, is uncertain. Therefore, the objective of the present study was to conduct a systematic review and meta-analysis of published randomised controlled trials (RCTs) of cinnamon to determine the effect on levels of serum CRP, relative to controls.

Design: Studies were identified by a search of electronic databases including PubMed, Cochrane Library, Google Scholar and Scopus before August 2018. Combined and stratified analyses were used. Weighted mean differences (WMD) and its 95% confidence interval were estimated for net change in serum CRP by using random-effects model. The heterogeneity of meta-analysis was assessed by χ^2 and I^2 test.

Results: Six studies were identified, and data from 285 participants were included. Pooled analysis showed significant reductions in serum CRP (WMD: −0.81 mg/L, 95% CI: −1.36 to -0.26, p=0.004), with significant heterogeneity between selected studies. Improvements in sub-group analysis were observed when baseline CRP levels were greater than 3 mg/dL, and in trials of >12 weeks duration. Doses <1500 mg/day and ≥1500 mg/day were effective in lowering serum CRP (WMD: −0.56 mg/dL, 95% CI: −1.01 to -0.10, p=0.02 and WMD: −2.13 mg/dL, 95%

CI: −4.08 to -0.19, p=0.03), respectively, with significantly reduced heterogeneity in trials with lower doses of cinnamon <1500 mg/day (test for heterogeneity: P=0.22 and I2= 33%). No changes were found in controls.

Conclusion: Cinnamon supplementation improves levels of serum CRP, particularly in chronic conditions where basal CRP levels are raised.

Key-words: Anti-inflammatory; Cinnamon; CRP; meta-analysis; RCT.

Introduction.

Cinnamon (*Cinnamomum Zeylanicum*) belongs to the genus Cinnamomum of the Lauraceaeis family, derived from the Hebraic and Arabic term amomon, meaning fragrant spice plant. Comprising over 300 species, it is widely used for its culinary and medicinal properties with Ceylon and Cassia cinnamon being the most abundant in the U.S and EU markets[1-3]. Cinnamon has attracted much attention due to their putative health-related properties, which have been ascribed in part to their polyphenolic content; a diverse group of secondary plant metabolites classified as phenolic acids, flavonoids, stilbenes and lignans[4]. Evidence from experimental studies have shown anti-inflammatory and antioxidative properties, particularly in their ability to reduce reactive oxygen species (ROS), and improve insulin sensitivity and carbohydrate metabolism [5-8]. Clinical studies also indicate improvement in anthropometric parameters, inflammatory mediators, glycemic indices and lipid profiles in patients with type-2 diabetes mellitus (T2DM), nonalcoholic fatty liver disease and rheumatoid arthritis, and those with a BMI $\geq$ 27 kg/m^2, following cinnamon supplementation [9].

C-reactive protein (CRP) is an acute phase protein commonly used as a marker of inflammation, and is associated with early stages of several chronic conditions including coronary artery disease (CAD), T2DM, rheumatoid arthritis, pre-diabetes, obesity and nonalcoholic fatty liver disease [10-12]. This increases greatly in inflammation processes and shows specific responses in medical conditions such as polycythemia, anemia, and congestive heart failure with no significant changes. However, compared to conventional assessments of inflammation factors such as erythrocyte sedimentation rate (ESR) test, CRP assessment is an ideal indicator in inflammations [10-13]. Effects of cinnamon supplementation on serum CRP level have been investigated in clinical trial studies. However, evidence from RCTs are limited and remain inconclusive. Therefore, the aim of the present study was to conduct a systematic review and meta-analysis to assess the efficacy of cinnamon supplementation on serum CRP in several chronic inflammatory conditions.

Methods and Materials.

The present meta-analysis was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) requirements for interventional research [14].

Search Strategy

Four databases, including Pubmed™, Cochrane Library™, Google Scholar™ and Scopus™ were used to identify related publications.

Published RCTs were searched from inception to August 2018. Reference lists from retrieved studies were also manually searched for additional relevant publications. The following searches in titles, abstracts and keywords: “CRP or C reactive protein” in combination with “cinnamon” was performed. Studies were included if they followed a RCT study design with cinnamon supplementation as the intervention. Those published in English and/or Persian were included in the study.

Inclusion and exclusion criteria

The inclusion criteria for selected studies were based on the following; RCTs of oral cinnamon supplementation, those with a duration of more than one week and those reporting mean or median values of serum CRP levels at baseline and by the end of supplementation in control and intervention groups with SD, SEM or 95% CI. The exclusion criteria included duplicated studies, those with no control or placebo group, those with insufficient data at baseline and/or final levels of serum CRP in control and treatment groups, studies with case-control, cohort or cross-sectional design, in vitro and animal studies.

Data extraction

Data were extracted from published studies independently by three reviewers, and any disagreements were resolved by consensus among the researchers using the standardised extraction forms to guarantee accuracy and consistency. The following key data were extracted: year of publication, country where the intervention was conducted, sample size of both intervention and control groups, clinical condition of subjects, intervention/placebo details and composition including the dosage of cinnamon supplementation (gram or mg per day), treatment duration and significant outcomes. In addition, serum levels of CRP were reported as mg/dL. For papers containing data in mmol/l, a numerical conversion to mg/dL was carried out based on molecular weight. Corresponding authors of trials with no reported mean and SD values for any outcomes of interest were contacted to request their data. Only the studies providing these data were included in the present meta-analysis [15].

Quality assessment

We performed a systematic assessment of bias in the included study by using the Cochrane criteria[16]. The items used for each included study assessment were the following ones: adequacy of sequence generation, the allocation concealment, blinding of participants, personnel and outcome assessment, the addressing of drop-outs and incomplete outcome data, selective outcome reporting and other potential sources of bias. According to the recommendations of the Cochrane Handbook, the included studies were rated on each of the items as 'L' indicating a low risk of bias, 'h' indicating a high risk of bias or 'u' when the risk of bias was unclear[16].

Statistical analysis

The statistical analyses were performed using Review Manager Software (RevMan 5.3; Cochrane Collaboration, Oxford, England) and Comprehensive Meta-Analysis (version 3.2; Biostat). The pooled weighted mean difference (WMD) and its 95% confidence interval (CI) were estimated to assess the effects of cinnamon on levels of serum CRP. The mean and standard deviation (SD) of levels of serum CRP at baseline and after supplementation in both intervention and control groups were used. Based on the method of Hozo *et al*. all reported median values with their confidence intervals (CI) or their ranges were converted to mean and SD[17]. Existence of heterogeneity and the percentage of total variation between studies was assessed by the Cochran's Q-test at $P < 0.05$ level of significance and I2 test ($I2 < 50\%$). Based on the results (present significant heterogeneity with $p<0.05$ from $\chi 2$ test), a random effects model was used if $I2 > 50\%$ and $P<0.1$. A fixed effects model was used if $I2 < 50\%$ and $P>0.1$.To identify the influence of modulators, pre-defined subgroup analyses were conducted according to the Cochrane guidelines including treatment duration, dose of intervention, measuring serum CRP/hs-CRP and baseline CRP level. Sensitivity analysis was performed to estimate the effects of each trial on the pooled effect size, in which a single trial was omitted each time and the effect size was re-calculated to assess the influence on the overall effect size. In order to examine potential publication bias, the funnel plot test was performed. If publication bias exists, the funnel plot shows an asymmetric shape. Additionally, Begg's rank correlation test and Egger's weighted regression test were used to elucidate possible bias. A P-value <0.05 was considered statistically significant.

Results.

Search results and study selection

A flow chart depicting the process of selection and literature search is presented in Figure 1. The literature search of electronic databases identified 205 potential relevant articles. After removing duplicates (n=112), titles and abstracts were screened and sixty-four studies were excluded, as they were not relevant to our analysis or were not in English language. A further 23 studies were excluded after further evaluation due to molecular or animal experiments (n=11), observational studies (n=2), reviews or editorial papers (n=5), not enough data for characterisation of subjects or insufficient reporting of baseline and/or follow-up serum CRP levels in the cinnamon and/or control group (n=2), and studies with no control group (n=3). Finally, a total of 6 RCTs were included in this meta-analysis.

Description of the studies

All trials were published between 2014 to 2018 and were conducted in France, India, Iran and the USA [18-23]. A total of 285 adult participants were re-analysed in the study, of which 144 were allocated to receive cinnamon supplementation and 141 to a control group. Cinnamon dosage ranged from 1200 mg/day to 3000 mg/day, with a median dose of 1850 mg/day [18-23]. Cinnamon capsules, stick and extracts were the formulations used in these trials. Duration of supplementation ranged from 8 weeks to 24 weeks with a median duration of 14 weeks [18-23]. Selected studies enrolled patients with non-alcoholic fatty liver disease, T2DM, metabolic syndrome, obesity, pre-diabetes and rheumatoid arthritis [18-23].

Baseline level of serum CRP ranged from 1.69 mg/dL to 5.74 mg/dL with a median level of 3.76 mg/dL in the intervention and 3.75 mg/dL in the control groups, respectively. Five of the 6 studies were conducted in both males and females, with one study conducted only in female participants [18-23]. All included trials followed a parallel study design. Three trials evaluated cinnamon in combination with black tea, L-carnosine plus chromium guanylate and a multiple dietary supplement containing cinnamon powder [19, 22, 23] (Table 1). Cinnamon supplementation was apparently safe and well tolerated by participants in all of the included studies, and no adverse effects were reported.

Risk of bias assessment

An unclear risk of bias was observed in some of the items including allocation concealment and other potential sources of bias. However, most of the included studies were characterized by adequate information regarding sequence generation, allocation concealment and blinding of participants and personnel. The incomplete outcome data and selective outcome reporting showed a low risk of bias. Details of the quality of bias assessment are presented in Table 2.

Pooled estimate of the effect of cinnamon supplementation on serum CRP

Significant reductions in the levels of serum CRP were observed following cinnamon supplementation in 3 studies [20, 22, 23]. Weighted mean difference (WMD) of studies with random effects model analysis showed a significant improvement in serum CRP (WMD: −0.81 mg/L, 95% CI: −1.36 to -0.26, p=0.004) with a significant heterogeneity between the included trials (test for heterogeneity: $P < 0.0002$ and $I2= 79\%$)(Figure 2).

Subgroup analyses

Subgroup analysis was performed to determine the potential source of heterogeneity, based on study duration, cinnamon dose, serum CRP and/or high sensitivity CRP (hs-CRP) and baseline CRP following supplementation (Table 3). Results showed that cinnamon supplementation significantly reduced serum CRP levels in participants when the duration of the study was >12 weeks (WMD: −0.42 mg/L, 95% CI: −0.65 to -0.20, p=0.0002). The heterogeneity significantly decreased after subgroup analysis by duration of study (test for heterogeneity: P = 0.96 and I2= 0%). Subgroup analysis on studies with cinnamon doses of <1500 mg/day and ≥1500 mg/day also significantly influenced levels of serum CRP (WMD: −0.56 mg/dL, 95% CI: −1.01 to -0.10, p=0.02 and WMD: −2.13 mg/dL, 95% CI: −4.08 to -0.19, p=0.03), respectively. There was significantly reduced heterogeneity in studies with lower doses of cinnamon supplementation (test for heterogeneity: P=0.22 and I2= 33%). Results of subgroup analysis based on baseline serum CRP also showed that cinnamon supplementation decreased levels of CRP in those with baseline CRP levels of more than 3 mg/dL (WMD: −0.42 mg/L, 95% CI: −0.65 to -0.20, p=0.0002). Moreover, the heterogeneity decreased significantly after subgroup analysis by trials with baseline CRP levels of more than 3 mg/dL.

Sensitivity analysis

Sensitivity analysis was performed to determine the effect of each study on the estimated pooled effect size. Results of omitting each study on the effect size ranged from -0.55 mg/L (95% CI=-0.98, -0.11) to -1.07 mg/L (95% CI=-1.80,-0.35)(Figure 3).

Publication bias

The publication bias of this meta-analysis was assessed by examination of funnel plot. The symmetrical funnel plots suggested that the selection of publication was not a possible source of bias (Figure 4). The absence of publication bias was confirmed by Egger's linear regression (intercept: -3.9; standard error: 3.82; 95% CI: -5.91, 1.94; t= 1.4, df=4; two-tailed p=0.23). Moreover, Begg's rank correlation did not highlight any publication bias (Kendall's Tau with continuity correction:-0.4; z=1.12; two-tailed p=0.25).

Discussion

The present meta-analysis included a total of 285 adults presenting with non-alcoholic fatty liver disease, T2DM, metabolic syndrome, obesity, pre-diabetes and rheumatoid arthritis from 6 RCTs. Despite considerable heterogeneity among the studies, our findings indicate improvement in the levels of serum CRP following cinnamon supplementation. To our knowledge, this is the first systematic review that has assessed the effects of cinnamon supplementation on serum CRP.

Significant reductions in serum CRP levels by −0.81 mg/dL were observed following cinnamon supplementation with no detectable changes in the control group. These findings were consistent across four of the individual six RCTs assessed in this study[18, 20-22]. Reductions in the levels of serum CRP, as observed in the present study, are clinically important because levels <1 mg/dL are associated with a lower risk of cardiovascular events, with concentrations > 3 mg/dL exacerbating the risk of coronary heart disease up to 58%[24, 25].

There was significant heterogeneity between studies in this meta-analysis, and subgroup analysis indicated that cinnamon supplementation could lower the levels of serum CRP when the trial duration was >12 weeks. Evidence from other meta-analyses assessing the anti-inflammatory properties of complex medicinal herbs (cinnamon, ginger and other traditional herbs) have also demonstrated significant improvements in serum CRP levels with study durations exceeding 6 and 10 weeks[26, 27].

Subgroup analysis on studies with cinnamon doses of <1500 mg/day and ≥1500 mg/day found significant reductions in the levels of serum CRP. It therefore seems likely that lower doses are effective and may be better than using larger doses of cinnamon, which have been associated with certain adverse effects including diarrhea and headache [28]. However, there were no reported adverse effects observed in the included studies in the present meta-analysis. Similar studies have also failed to report any adverse effect or reaction following cinnamon supplementation. Talaei *et al*. reported beneficial effects of 1000 mg/day cinnamon (*Cinnamomum zeylanicum*) without side effects [29], and Tjandrawinata *et al*. reported a lower risk of hypoglycemic episodes with no effect on gastrointestinal symptoms [27]

Moreover, subgroup analysis based on baseline levels showed that cinnamon improved serum CRP levels in those with a higher baseline value (i.e. > 3 mg/dL), with heterogeneity decreasing significantly after subgroup analysis. This finding is in agreement with another studies in which vitamin E supplementation significantly reduced circulating levels of serum CRP only in those with a baseline value of > 3 mg/dL[30]. Therefore, the duration of the study and baseline serum CRP levels were considered to be important and potential sources of observed heterogeneity.

CRP, and indeed hs-CRP, is one of the most common and frequently used biomarkers for inflammation status with predictive values for several chronic diseases including CVD [31-39]. The anti-inflammatory properties of cinnamon has been reviewed extensively, and several mechanisms of action have been described [40-44]. In vitro and in vivo studies have reported inhibition of nuclear factor kappa B (NF-κB) by 2`-hydroxycinnamaldehyde isolated from C. cassia bark[41], and tumor necrosis factor-α (TNF-α) with extracts of cinnamon in a lipopolysaccharide (LPS) model [42]. Inhibition of TNF-α genes by cinnamon water extract via modulation of JNK, p38, ERK1/2 activation and Iκ-Bα degradation have also been demonstrated [43]. Hong *et al*. reported the inhibition of the expression of TNF-α by polyphenol-rich cinnamon water extract (CWE) fraction containing procyanidins, catechin, epicatechin and ellagic acid [44]. Cinnamon may also downregulate the expression of various NF-κB-regulated pro-inflammatory adipo-cytokines, (i.e. MCP-1, MCP-4, and eotaxin and interleukins)[45, 46], in addition to plasminogen activator inhibitor type-1 (PAI-1), through the inhibition of the transcription factor early growth response (Egr)-1 gene product, which has been closely linked with insulin resistance and obesity[47, 48].

Some limitations of this meta-analysis include not controlling for confounding factors (i.e. dietary intake, physical activity and medications for several chronic conditions), which may have influenced our results. Most of the RCTs included were of a relatively small sample size, and the characteristics of the study population was heterogeneous (i.e. patients with non-alcoholic fatty liver disease, T2DM, metabolic syndrome, obesity, pre-diabetes and rheumatoid arthritis). Despite these limitations, there were several strengths to this study. Firstly, it is to our knowledge, the first time a systematic review and meta-analysis has been performed in the evaluation of cinnamon supplementation on serum CRP levels. A random effects model was used for assessing heterogeneity between studies, and RCTs were assessed using subgroup analysis with performed sensitivity and meta-regression analyses.

Conclusion

In conclusion, the findings from this meta-analysis suggest some improvement in serum CRP levels following cinnamon supplementation, especially in patients with higher baseline CRP levels. However, due to the limited availability of RCTs further investigation is warranted.

Acknowledgements

We are grateful to our colleagues for their patience and their advice on searching the papers.

Funding

There is no funding sources in the writing of the manuscript, data collection, analysis, or interpretation; or the decision to submit it for publication. We have not been paid to write this article by a pharmaceutical company or other agency

Authors' contributions

N.V. and S.J. conceived and planned the experiments. S.J. and A.D. carried out the literature search in databases. S.J. and M.T. and A.D. contributed to quality assessment and statistical analysis. C.T. and N.V. contributed to the interpretation of the results. C.T. took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.

Conflict of interest

There is no conflict of interest regarding this manuscript.

References:

1. Ravindran P, Babu N, Shylaja M. Cinnamon and Cassia The Genus Cinnamomum: Medicinal and Aromatic Plants–Industrial Profiles. *Washington DC: CRC Press SGPT dan SGOT tikus putih J Gamma.* 2004;1(1): 45-53.
2. Ribeiro-Santos R, Andrade M, Madella D, et al. Revisiting an ancient spice with medicinal purposes: Cinnamon. *Trends in Food Science & Technology.* 2017;62: 154-169.
3. Woehrlin F, Fry H, Abraham K, Preiss-Weigert A. Quantification of flavoring constituents in cinnamon: high variation of coumarin in cassia bark from the German retail market and in authentic samples from Indonesia. *Journal of agricultural and food chemistry.* 2010;58(19): 10568-10575.
4. Vallverdu-Queralt A, Regueiro J, Martinez-Huelamo M, Rinaldi Alvarenga JF, Leal LN, Lamuela-Raventos RM. A comprehensive study on the phenolic profile of widely used culinary herbs and spices: rosemary, thyme, oregano, cinnamon, cumin and bay. *Food Chem.* 2014;154: 299-307.
5. Chen L, Sun P, Wang T, et al. Diverse mechanisms of antidiabetic effects of the different procyanidin oligomer types of two different cinnamon species on db/db mice. *Journal of agricultural and food chemistry.* 2012;60(36): 9144-9150.
6. Khan A, Safdar M, Khan MMA, Khattak KN, Anderson RA. Cinnamon improves glucose and lipids of people with type 2 diabetes. *Diabetes care.* 2003;26(12): 3215-3218.
7. Anderson RA. Chromium and polyphenols from cinnamon improve insulin sensitivity: Plenary Lecture. *Proceedings of the Nutrition Society.* 2008;67(1): 48-53.
8. Vallianou N, Evangelopoulos A, Kollas A, Kazazis C. *Hypoglycemic and hypolipidemic effects of cinnamon*2014.
9. Zare R, Nadjarzadeh A, Zarshenas MM, Shams M, Heydari M. Efficacy of cinnamon in patients with type II diabetes mellitus: A randomized controlled clinical trial. *Clinical Nutrition.* 2018.
10. Group MR, Kuller LH, Tracy RP, Shaten J, Meilahn EN. Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. *American journal of epidemiology.* 1996;144(6): 537-547.
11. Blake GJ, Ridker PM. C-reactive protein and other inflammatory risk markers in acute coronary syndromes. *Journal of the American College of Cardiology.* 2003;41(4): S37-S42.
12. Cesari M, Penninx W, Newman A. Inflammatory markers and onset of cardiovascular events. *ACC Current Journal Review.* 2004;13(2): 10.
13. Cesari M, Penninx BW, Newman AB, et al. Inflammatory markers and onset of cardiovascular events: results from the Health ABC study. *Circulation.* 2003;108(19): 2317-2322.
14. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of internal medicine.* 2009;151(4): 264-269, W264.
15. Jafarnejad S, Tsang C, Taghizadeh M, Asemi Z, Keshavarz SA. A meta-analysis of cumin (Cuminum cyminim L.) consumption on metabolic and anthropometric indices in overweight and type 2 diabetics. *Journal of Functional Foods.* 2018;44: 313-321.
16. Higgins J. Green S. Cochrane handbook for systematic reviews of interventions Version 5.1. 0. The Cochrane Collaboration. *Confidence intervals.* 2011.
17. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Medical Research Methodology.* 2005;5(1): 13.
18. Askari F, Rashidkhani B, Hekmatdoost A. Cinnamon may have therapeutic benefits on lipid profile, liver enzymes, insulin resistance, and high-sensitivity C-reactive protein in nonalcoholic fatty liver disease patients. *Nutrition research.* 2014;34(2): 143-148.

19. Azimi P, Ghiasvand R, Feizi A, Hariri M, Abbasi B. Effects of cinnamon, cardamom, saffron, and ginger consumption on markers of glycemic control, lipid profile, oxidative stress, and inflammation in type 2 diabetes patients. *The review of diabetic studies: RDS.* 2014;11(3): 258.

20. Jain SG, Puri S, Misra A, Gulati S, Mani K. Effect of oral cinnamon intervention on metabolic profile and body composition of Asian Indians with metabolic syndrome: a randomized double-blind control trial. *Lipids in health and disease.* 2017;16(1): 113.

21. Liu Y, Cotillard A, Vatier C, et al. A dietary supplement containing cinnamon, chromium and carnosine decreases fasting plasma glucose and increases lean mass in overweight or obese pre-diabetic subjects: a randomized, placebo-controlled trial. *PloS one.* 2015;10(9): e0138646.

22. Shishehbor F, Rezaeyan Safar M, Rajaei E, Haghighizadeh MH. Cinnamon Consumption Improves Clinical Symptoms and Inflammatory Markers in Women With Rheumatoid Arthritis. *Journal of the American College of Nutrition.* 2018: 1-6.

23. Soare A, Weiss EP, Holloszy JO, Fontana L. Multiple dietary supplements do not affect metabolic and cardiovascular health. *Aging (Albany NY).* 2014;6(2): 149.

24. Eisenhardt SU, Habersberger J, Murphy A, et al. Dissociation of pentameric to monomeric C-reactive protein on activated platelets localizes inflammation to atherosclerotic plaques. *Circ Res.* 2009;105(2): 128-137.

25. Saboori S, Falahi E, Eslampour E, Zeinali Khosroshahi M, Yousefi Rad E. Effects of alpha-lipoic acid supplementation on C-reactive protein level: A systematic review and meta-analysis of randomized controlled clinical trials. *Nutrition, metabolism, and cardiovascular diseases : NMCD.* 2018.

26. Chung VC, Chen M, Ying Q, et al. Add-on effect of chinese herbal medicine on mortality in myocardial infarction: systematic review and meta-analysis of randomized controlled trials. *Evidence-based complementary and alternative medicine : eCAM.* 2013;2013: 675906.

27. Mazidi M, Gao H-K, Rezaie P, Ferns GA. The effect of ginger supplementation on serum C-reactive protein, lipid profile and glycaemia: a systematic review and meta-analysis. *Food & Nutrition Research.* 2016;60: 10.3402/fnr.v3460.32613.

28. Wiweko B, Susanto CA. The Effect of Metformin and Cinnamon on Serum Anti-Mullerian Hormone in Women Having PCOS: A Double-Blind, Randomized, Controlled Trial. *Journal of Human Reproductive Sciences.* 2017;10(1): 31-36.

29. Talaei B, Amouzegar A, Sahranavard S, Hedayati M, Mirmiran P, Azizi F. Effects of Cinnamon Consumption on Glycemic Indicators, Advanced Glycation End Products, and Antioxidant Status in Type 2 Diabetic Patients. *Nutrients.* 2017;9(9): 991.

30. Saboori S, Shab-Bidar S, Speakman JR, Yousefi Rad E, Djafarian K. Effect of vitamin E supplementation on serum C-reactive protein level: a meta-analysis of randomized controlled trials. *European journal of clinical nutrition.* 2015;69(8): 867-873.

31. Black S, Kushner I, Samols D. C-reactive Protein. *The Journal of biological chemistry.* 2004;279(47): 48487-48490.

32. Eisenhardt SU, Habersberger J, Murphy A, et al. Dissociation of pentameric to monomeric C-reactive protein on activated platelets localizes inflammation to atherosclerotic plaques. *Circulation research.* 2009;105(2): 128-137.

33. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *New England Journal of Medicine.* 2000;342(12): 836-843.

34. Ridker PM, Rifai N, Clearfield M, et al. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *The New England journal of medicine.* 2001;344(26): 1959-1965.

35. Tracy RP, Lemaitre RN, Psaty BM, et al. Relationship of C-reactive protein to risk of cardiovascular disease in the elderly: results from the Cardiovascular Health Study and the Rural Health Promotion Project. *Arteriosclerosis, thrombosis, and vascular biology.* 1997;17(6): 1121-1127.
36. Koenig W, Sund M, Fröhlich M, et al. C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. *Circulation.* 1999;99(2): 237-242.
37. Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein (a), and standard cholesterol screening as predictors of peripheral arterial disease. *Jama.* 2001;285(19): 2481-2485.
38. Danesh J, Whincup P, Walker M, et al. Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. *Bmj.* 2000;321(7255): 199-204.
39. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. *Circulation.* 2003;107(3): 391-397.
40. Lee SH, Lee SY, Son DJ, et al. Inhibitory effect of 2′-hydroxycinnamaldehyde on nitric oxide production through inhibition of NF-κB activation in RAW 264.7 cells. *Biochemical pharmacology.* 2005;69(5): 791-799.
41. Muhammad JS, Zaidi SF, Shaharyar S, et al. Anti-inflammatory effect of cinnamaldehyde in Helicobacter pylori induced gastric inflammation. *Biological and Pharmaceutical Bulletin.* 2015;38(1): 109-115.
42. Yu T, Lee S, Yang WS, et al. The ability of an ethanol extract of Cinnamomum cassia to inhibit Src and spleen tyrosine kinase activity contributes to its anti-inflammatory action. *Journal of Ethnopharmacology.* 2012;139(2): 566-573.
43. Lee B-J, Kim Y-J, Cho D-H, Sohn N-W, Kang H. Immunomodulatory effect of water extract of cinnamon on anti-CD3-induced cytokine responses and p38, JNK, ERK1/2, and STAT4 activation. *Immunopharmacology and immunotoxicology.* 2011;33(4): 714-722.
44. Hong J-W, Yang G-E, Kim YB, Eom SH, Lew J-H, Kang H. Anti-inflammatory activity of cinnamon water extract in vivo and in vitro LPS-induced models. *BMC complementary and alternative medicine.* 2012;12(1): 237.
45. Shao-Ling W, Ying L, Ying W, et al. Curcumin, a potential inhibitor of up-regulation of TNF-alpha and IL-6 induced by palmitate in 3T3-L1 adipocytes through NF-kappaB and JNK pathway. *Biomedical and Environmental Sciences.* 2009;22(1): 32-39.
46. Woo H-M, Kang J-H, Kawada T, Yoo H, Sung M-K, Yu R. Active spice-derived components can inhibit inflammatory responses of adipose tissue in obesity by suppressing inflammatory actions of macrophages and release of monocyte chemoattractant protein-1 from adipocytes. *Life sciences.* 2007;80(10): 926-931.
47. Pendurthi UR, Rao LVM. Suppression of transcription factor Egr-1 by curcumin. *Thrombosis research.* 2000;97(4): 179-189.
48. Aggarwal BB. Targeting inflammation-induced obesity and metabolic diseases by curcumin and other nutraceuticals. *Annual review of nutrition.* 2010;30: 173-199.

Figure 1: *Meta-analysis Flow Diagram*

Figure 2: *Forest plots showing the pooled effect size of cinnamon supplementation on serum C-reactive protein (mg/L). Random effects model was used to pool the mean change of indicators. CI, confidence interval; I-squared inconsistency.*

Figure 3: *Sensitivity analysis for the effect of cinnamon supplementation on serum CRP levels.*

Figure 4: *Funnel plot of included studies measured serum CRP level. MD = Mean Difference, SE = standard error.*

Table 1: *General characteristics of the included studies in the meta-analysis*

Auther	Year	Country	Design	No. of Subjects in case group	No. of controls	Gender	Age(mean)-case group	Age(mean)-control	Inclusion criteria	Clinical Condition of Subjects	Follow-up Duration (weeks)	Dosage (mg/d)	Co-Supplements or other drugs	Significant Outcome	Baseline CRP level (mg/l)
Askari	**2014**	**Iran**	**R, DB, PC**	**23**	**22**	**F/M**	**44.8 ± 8.5**	**45.4 ± 8.2**	**Age between 20 and 65 ; ALT not greater than 60 U/L; no alcohol or drug abuse;no chemotherapy**	**Nonalcoholic fatty liver disease (NAFLD)**	**12**	**1500**	**No co-supplement**	**FBS, HOMA index, QUICKI index, total cholesterol, triglycerides, ALT, AST, GGT and hs-CRP changed significantly in the treatment group.**	**5mg/l**
Azimi	**2015**	**Iran**	**R, SB, PC**	**40**	**39**	**F/M**	**54.15± 1.0**	**53.64 ± 1.3**	**Subjects with T2D, aged ≥30 years, overweight, not on insulin therapy, not taking medications except for oral hypoglycemic agents.**	**Type 2 diabetes**	**8**	**3000**	**Three glasses of black tea**	**Significant reduction in total cholesterol, LDL, and elevation in HDL levels.**	**5.74mg/l**
Jain	**2017**	**India**	**R, DB, PC**	**58**	**58**	**F/M**	**44.3 ± 7.2**	**45.1 ± 8.4**	**Subjects suffering from other chronic diseases (except for metabolic syndrome) or those on medication of lipid lowering drugs were excluded.**	**Metabolic syndrome**	**16**	**3000**	**No co-supplement**	**Significantly decrease in weight, WC, WHR, percentage body fat, total cholesterol, serum triglycerides, LDL-C, SBP, DBP and significant increase in HDL-C.**	**2.8mg/l**
Liu	**2015**	**France**	**R, DB, PC**	**26**	**26**	**F/M**	**Not Mentioned**	**Not Mentioned**	**Subjects aged between 25 and 65 years, overweight and unwilling to change their usual dietary and activity were included for randomization.**	**Overweight or Obese Pre-Diabetic**	**16**	**456**	**200 mg/day L-carnosine 2.5 mg/day Chromium guanylate**	**Insulin secretion, evaluated by HOMA-B%, increased significantly in supplement group.**	**4mg/l**
Shishehbor	**2018**	**Iran**	**R, DB, PC**	**18**	**18**	**F**	**44.66 ± 11.22**	**49.11 ± 7.45**	**Having active Rheumatoid Arthritis, being under treatment with DMARDs, not receiving NSAIDs or cytokine inhibitors.**	**Rheumatoid Arthritis**	**8**	**2000**	**No co-supplement**	**There was a significant decrease of serum levels of CRP and TNF-a in the cinnamon group. Diastolic blood pressure was also significantly lower in the intervention group.**	**3.53mg/l**
Soare	**2014**	**USA**	**R, SB, PC**	**28**	**26**	**F/M**	**47±5**	**44±6**	**Participants were free of chronic disease. Exclusion criteria included chronic use of medications or dietary supplements, tobacco use, alcohol abuse, and habitual vigorous exercise.**	**Healthy adults**	**24**	**1700**	**100 mg of resveratrol, 800 mg of green, black, and white tea, 250 mg of pomegranate, 650 mg of quercetin, 500 mg of l carnitine, 600 mg of lipoic acid, 900 mg of curcumin, 1 g of sesamin and fish oil.**	**No significant outcomes.**	**1.69mg/l**

Table 2. *Quality of bias assessment of the included trials according to the Cochrane guidelines.*

Studies ,Year	Sequence Generation	Allocation Concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	selective outcome reporting	other potential sources of bias
Askari;2014	L	L	L	L	L	L	U
Azimi;2015	L	L	L	H	L	L	L
Jain;2017	L	U	L	H	L	L	H
Liu;2015	L	U	L	H	L	L	L
Shishehbor;2018	L	L	L	L	L	H	U
Soare;2014	L	U	H	L	L	L	L

L, low risk of bias; H, high risk of bias; U, unclear risk of bias.

Table 3: *Subgroup analysis of cinnamon supplementation on serum CRP level*

Subgroup		No	WMD (95% CI)	Test for overall effect	Test for heterogeneity	I2(%)
Duration of study, weeks						
	≤12 weeks	3	-1.37 [-2.86, 0.12]	p=0.07	p<0.0001	91
	>12 weeks	3	-0.42 [-0.65, -0.20]	P = 0.0002	P = 0.96	0
Cinnamon dose, mg/day						
	≥1500 mg/d	4	-0.56 [-1.01, -0.10]	P = 0.02	P = 0.007	76
	<1500 mg/d	2	-2.13 [-4.08, -0.19]	P = 0.03	P = 0.22	33
CRP/hsCRP						
	CRP	2	-0.96 [-2.14, 0.22]	P = 0.11	P = 0.003	89
	hsCRP	4	-0.83 [-1.78, 0.11]	P = 0.08	P = 0.002	79
Baseline CRP, mg/L						
	<3	2	-1.26 [-2.62, 0.10]	P = 0.07	P < 0.0001	87
	≥3	4	-0.42 [-0.65, -0.20]	P = 0.0002	P = 0.77	0

***:** *Abbreviations: CRP, C-reactive protein; hsCRP, high-sensitivity C-reactive protein; WMD, weighted mean difference; CI, confidence interval.*