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The effect of *Nigella sativa* L. supplementation on serum C-reactive protein: A systematic review and meta-analysis of randomized controlled trials

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**Running title: Nigella sativa L. on serum C-reactive protein concentrations**

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Abstract

Objective: Evidence on the efficacy of Nigella sativa supplementation is equivocal, thus the aim of this systematic review and meta-analysis of randomized clinical trials (RCTs) was to examine the effect of Nigella sativa (N. sativa) supplementation on plasma C-reactive protein (CRP) concentrations.

Methods: PubMed, Scopus, ISI Web of Science, Cochrane library, and Google Scholar databases were searched (up to April, 2019) to identify RCTs investigating the effects of N. sativa seed and seed oil supplementation on CRP. Weighted mean differences (WMD) was pooled using a random-effects model. Standard methods were also used for assessment of heterogeneity, sensitivity analysis, and publication bias.

Results: Eventually only five articles which reported data of interest entered for data analysis. The meta-analysis showed a significant reduction in serum CRP (WMD: -0.55 mg/L, 95% CI: -1.02, -0.08, P=0.02), with significant heterogeneity between selected studies (I²=77.3%). Between-study heterogeneity disappeared following subgroup analysis, stratified by baseline BMI (≥30 kg/m²: I²=2.8%). However, the effect of N. sativa seed and seed oil supplementation on CRP was only significant in studies that were conducted on participants with BMI≥30 kg/m² (WMD: -0.50 mg/L, 95% CI: -0.85, -0.15).

Conclusions: This meta-analysis suggests that N. sativa seed and seed oil supplementation can significantly reduce serum CRP level. However, RCTs with a larger sample size and longer follow-up periods should be conducted for future investigations to confirm the veracity of these results.

Key-words: N.sativa, C-reactive protein, Meta-analysis, Randomized controlled trial
Introduction

C-reactive protein (CRP) is an acute phase protein produced by liver, and its concentration is notably increased during infections and inflammation\(^1\). CRP is classified as first-line defence molecule against pathogenic organisms, particularly given its affinity for binding to phosphocholine of bacterial and fungal membranes\(^1,2\). It also functions to stimulate phagocytic cells that remove apoptotic and necrotic cells, further contributing to the healing of injured tissues\(^2,3\). Production of CRP from the liver is stimulated by cytokines associated with non-specific tissue injury, including; interleukin-1β, interleukin-6, and tumor necrosis factor alpha (TNF-α)\(^3,4\). It has been shown that CRP levels in apparently healthy humans may predict future risk for cardiovascular disease (CVD), independent of established risk factors. Moreover, serum CRP has been purported to predict incidence of myocardial infarction, coronary artery disease (CAD), stroke, peripheral arterial disease, and sudden death; concomitant to acting as a mediator of these conditions\(^5-7\). Whilst such non-communicable diseases are commonly treated by pharmacotherapies, the concept of complementary medicine is proliferating, with a reputed 80% of the global population utilising complementary therapies\(^8,9\).

Medicinal plants may serve as an adjuvant in the treatment and prevention of various non-communicable diseases as they contain a wide range of bioactive phytochemicals with diverse metabolic effects, and, moreover, have been asserted as safe adjuvant treatments to reduce the progression, morbidity as well as the cost of treatment\(^10-12\). One such example is *Nigella sativa L. (N. sativa)*, commonly known as black seed, which belongs to the botanical family of *Ranunculaceae*\(^13,14\). *N. sativa* has been traditionally in use in many Middle and Far East countries as a natural remedy for a wide range of illnesses, attributed to its wide range of pharmacological properties\(^14\). Among the active ingredients of *N. sativa*, thymoquinone (TQ)
is one of the most important ingredients, which purportedly contains anti-oxidant, anti-inflammatory and immunoprotective properties\textsuperscript{15-17}.

Although some evidence exists to support the use of \textit{N. Sativa seed and seed oil} to positively influence CRP\textsuperscript{12, 18-20}, the current evidence base is bereft of uniformity, and given the absence of a unifying and elucidatory analysis, we sought to systematically review and meta-analyse the effect of \textit{N. Sativa seed and seed oil} supplementation on serum CRP in humans.

**Methods**

The present systematic review was planned, conducted, and reported in adherence to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines\textsuperscript{21}.

**Search strategy**

Five databases, including PubMed (http://www.ncbi.nlm.nih.gov), Scopus (http://www.scopus.com), Cochrane Library (http://www.cochranelibrary.com), ISI Web of Science (http://www.webofscience.com) and Google Scholar (http://scholar.google.com) were explored with no language or time frame restriction up to April, 2019. The search strategy was drawn up using following keywords and medical subject heading (MeSH) terms: “\textit{Nigella sativa}” OR “black seed” OR “kalonji” OR “black cumin” OR “black caraway” combined with “C-Reactive Protein” OR “high-sensitivity CRP” OR “hs-CRP” OR “CRP”. In addition, we manually reviewed reference lists from the retrieved articles, systematic reviews, and meta-analyses to avoid missing any pertinent articles.

**Study selection**

EndNote software, version X6 (Thomson Reuters) was used for record management. After removing duplicates and publications without an English abstract, the remaining articles were independently screened by two authors (A.H and A.A) based on the title and abstract and
irrelevant records, animal studies and reviews were excluded. Then, the full text of remaining articles was investigated profoundly to choose only related studies. Finally, all randomized controlled trials (RCTs) (either parallel or cross-over designs) that examined the effects of N. sativa seed and seed oil supplementation on CRP in adults (age≥18-year old) were selected. Studies that prescribed N. sativa mixed with other substances, publications with duplicate data, and also trials without an appropriate control group were excluded. Disagreement between reviewers was resolved by discussion or, if it was necessary, by consulting with a third reviewer (E.Gh).

Data extraction

Two investigators (A.H and A.A) abstracted relevant data from the selected trials. This process was verified by another investigator (E.Gh). The following methodological and outcome variables from each included papers were extracted, using a data abstraction form: first author’s last name, publication time, country in which the study was performed, research design, participant characteristics (mean age, gender and body mass index [BMI]), sample size, intervention duration (week), type and dose of supplements/placebo used in intervention/control group, and the main results. When results were presented in multiple time points, only data relating to the longest duration of treatment were considered.

Quality assessment

The methodological quality of enrolled studies was assessed using the scoring system developed by Jadad et al.²², where total score ranges 0 to 5 points based on the 5 items: 1) randomization, 2) methods of randomization, 3) blinding, 4) suitable method of double blinding, and 5) withdrawn or drop-outs explanation. The scores of 3 or more represented high quality while 0-2 indicated a low-quality study. This section was also independently
accomplished by two researchers (A.H and A.A). Final scores were discussed by the investigators to make a consensus.

**Statistical analysis**

The pooled weighted mean difference (WMD) and its 95% confidence interval (CI) were estimated to assess the effects of *N. sativa* on levels of serum CRP. In studies in which the net changes were not directly reported, the WMD was calculated by 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). Also, the standard deviation (SD) of WMD was calculated as follows: $[SD= \text{square root } [(SD \text{ pre-treatment})^2 + (SD \text{ post-treatment})^2 - (2R \times SD \text{ pre-treatment} \times SD \text{ post-treatment})]],$ assuming a correlation coefficient of 0.5. To ensure that our meta-analysis was not sensitive to the selected correlation coefficient, all the analyses for each parameter was repeated using a correlation coefficient of 0.2 and 0.8. In the case that standard error (SE) of mean was only reported, SD was calculated using the following formula: $SD= SE \times \text{square root } (n),$ where n is the number of participants in each group. All meta-analyses were done using the random effects model which takes the between-study variability into account. The presence of between-study heterogeneity was assessed by the $I^2$ statistic. Low, moderate and high heterogeneity was ascribed to $I^2$ values less than 25%, between 25-50% and over 50%, respectively.$^{23}$ To find the potential sources of between-study heterogeneity, we carried out a pre-planned subgroup analysis based on based on baseline BMI ($\geq 30$ or $< 30$ kg/m$^2$), *N. sativa* dosage ($\geq 2$ or $< 2$ mg/day), and intervention form (powder or oil). Heterogeneity between subgroups was evaluated using a fixed-effect model. Sensitivity analysis was also executed in order to evaluate the influence of every single study on the overall effect size. Publication bias was evaluated using visual assessment of funnel plots and Egger's weighted regression tests.$^{24}$ All analyses were carried out using the STATA software (version 11.2, Stata Corp,
College Station, TX, USA) and two-sided p-values < 0.05 were considered statistically significant.

**Results**

**Flow of study selection**

Study selection and identification process are depicted in Figure 1. A total of 95 publications were identified using the search strategy previously described in the method part, from which 31 were excluded after duplicate deletion. By reviewing the title and abstracts of the remaining articles, 54 publications which were irrelevant to the study objectives were excluded. Subsequently, 10 full-text articles were carefully reviewed for eligibility and 3 clinical trials were excluded because of the following reasons: two studies had interventions using other components in addition to *N. sativa*, and one article included a duplicate population. Finally, 7 eligible trials 12, 18-20, 25-27 were considered eligible for the systematic review. However, two of the included articles 25, 26 did not report the data required for meta-analysis. We contacted the corresponding author of studies, twice, but did not receive any response. These 2 studies were therefore excluded, leaving 5 studies 12, 18-20, 27 for inclusion in the meta-analysis.

**Study and participant characteristics**

Details characteristics of the included trials are outlined in Table 1. In total, 439 participants were enrolled in selected articles, of which 222 individuals allocated to *N. sativa* supplementation group and 217 subjects to the control group. These studies were published between 2010 and 2019 and were carried out in the Iran18-20, 26, 27, Pakistan 12, and Indonesia 25. All studies except one 26 adopted a parallel study design. The mean age of the participants ranged from 37.02 to 47.48 years old and mean baseline BMI varied from 24.60 to 32.05 kg/m². Only, one out of included studies 25 was conducted exclusively in men, two in women
and the other trials\textsuperscript{12, 20, 26, 27} were performed in both genders. The follow-up period ranged from 6 to 12 weeks. Daily recommended dosage of \textit{N. sativa}-based natural products varied between 1 and 3 g/day in these studies, including both crushed seeds and seed oil. Included studies were carried out in various populations, including metabolic syndrome\textsuperscript{12, 26}, obese individuals\textsuperscript{19, 25}, rheumatoid arthritis\textsuperscript{18}, ulcerative colitis\textsuperscript{27}, and non-alcoholic fatty liver disease (NAFLD)\textsuperscript{20}.

\textbf{Quality assessment}

The Jaded checklist showed that all studies except one\textsuperscript{25} had high methodological quality. The details of quality assessment in individual studies are provided in Table 2.

\textbf{Findings from the systematic review}

Based on the present systematic review, 4 trials reported reduced CRP level with \textit{N. sativa} seed and seed oil supplementation\textsuperscript{12, 18-20}, while 2 studies did not find such an effect\textsuperscript{25, 26}. Moreover, a significant increase in the levels of serum CRP was observed following \textit{N. sativa} seed and seed oil supplementation in one of the trials\textsuperscript{27}.

\textbf{Findings from the meta-analysis}

The forest plot displaying the effect of \textit{N. sativa seed and seed oil supplementation} supplementation on circulating CRP is demonstrated in Figure 2. The pooled estimate from the random-effect model that performed on 5 studies including 175 cases and 173 controls, showed \textit{N. sativa seed and seed oil supplementation} significantly reduced CRP concentrations (WMD: -0.55 mg/L, 95\% CI: -1.02, -0.08, P=0.02). As there was a significant heterogeneity (P<0.001, $I^2=77.3\%$), we performed subgroup analysis and found that baseline BMI ($\geq$30 kg/m\textsuperscript{2}: P=0.31, $I^2=2.8\%$) could explain between-study heterogeneity. However, the effect of \textit{N. sativa seed and seed oil supplementation} on CRP was only significant in studies that were conducted on participants with BMI $\geq$30 kg/m\textsuperscript{2} (WMD: -0.50 mg/L, 95\% CI: -0.85,
-0.15, $I^2=2.8\%$). In another subgroup analysis by intervention forms, *N. sativa* powder subset showed non-significant differences in the mean change of CRP which is in contrast with the overall results. The subgroup analysis by dose of intervention did also not show any significant difference in the mean change of circulating CRP (*Table 3*).

Moreover, the sensitivity analysis demonstrated that with the removal of the study by Mahdavi et al. 19 and Amin et al. 12 the effect of *N. sativa* on CRP became non-significant (WMD: -0.53 mg/L, 95% CI: -1.17, 0.10, P=0.41 and WMD: -0.56 mg/L, 95% CI: -1.23, 0.10, P=0.39, respectively).

**Publication bias**

Assessment of publication bias by visual inspection of funnel plot indicated no evidence of publication bias in the meta-analysis of *N. sativa* supplementation on circulating CRP concentrations (*Figure 3*). Egger's linear regression test also showed the same result (P=0.77).

**Discussion**

The present meta-analysis included a total of 439 adults presenting with NAFLD, metabolic syndrome, obesity, ulcerative colitis and rheumatoid arthritis from 7 RCTs. Despite considerable heterogeneity among the studies, our findings indicate improvement in the levels of serum CRP following *N. sativa seed and seed oil* supplementation. To our knowledge, this is the first systematic review that has assessed the effects of *N. sativa* on serum CRP. Significant reductions in serum CRP levels by −0.55 mg/L were observed following *N. sativa seed and seed oil* supplementation with no detectable changes in the control group.

Reductions in the levels of serum CRP, as observed in the present study, are important in the clinical setting, because levels $\geq 3$ mg/dL are related to increases in the risk of coronary heart
disease by up to 58%\textsuperscript{28,29}. CRP, and particularly hs-CRP, is one of the most frequently used biomarkers for assessing the inflammatory status, with predictive values for various chronic diseases including CVD. Since metabolic syndrome is considered a chronic mild inflammatory state, levels of acute-phase reactants are usually elevated among patients with it\textsuperscript{30-32}. In this meta-analysis, patients with metabolic syndrome, or the hepatic component of it, i.e. NAFLD, and obesity were mainly included. Therefore, the chronic mild inflammatory state of the above-mentioned metabolic disorders could account for the association between the observed increases in CRP among those patients. On the contrary, when \textit{N. sativa} seed and seed oil was administered, the observed significant decreases in CRP levels could be due to the anti-inflammatory properties of \textit{N. sativa}.

When we categorized studies based on dose, the result was non-significant in both subsets, which may be attributable to the lower number of trials included in each subgroup. In addition, the findings showed that CRP reduction was more pronounced when \textit{N. sativa} was administrated as oil, suggesting that form of \textit{N. sativa} is one of the important factors which affect CRP responses. Previous meta-analysis which investigating effect of \textit{N. sativa} seed showed that \textit{N. sativa} seed oil were more effective in lowering low density lipoprotein (LDL) and cholesterol\textsuperscript{33} and glycaemic indexes\textsuperscript{34}. Such differences have previously been attributed to the chemical composition and preparation process of \textit{N. sativa} seed oil, as compared with seed powder that is prepared by crushing\textsuperscript{35,36}. Some potential anti-inflammatory mechanisms of \textit{N. sativa} seed in the most studies have been attributed to antioxidant activity\textsuperscript{37}. TQ and dithymoquinone are the major active antioxidant components of \textit{N. sativa}\textsuperscript{37}. Actually controlled thermal processing of the \textit{N. sativa} seeds, responsible for TQ accumulation at temperatures between 50 and 150°C; on the other hand TQ is fat soluble which can lead to higher biological activity of the TQ in the oil from\textsuperscript{38,39}.
In subgroup analyses, we also found that *N. sativa* supplementation could reduce CRP levels in participants with baseline BMI $\geq 30$ kg/m$^2$, a result which is not only interesting, but also important to emphasize. As we know, obese subjects have higher CRP levels than other people due to the accumulation of free fatty acid intermediates, which subsequently activate pro-inflammatory serine kinase cascades. Thus, it is logical that bigger changes in CRP concentration were manifest in subjects with baseline BMI $\geq 30$ kg/m$^2$.

The anti-inflammatory properties of *N. sativa* have already been reviewed, and several mechanisms of action have been described. TQ, the major constituent of *N. sativa* or black seed or black cumin, possesses anti-inflammatory properties that prevent the biosynthesis of important mediators in inflammatory processes, such as cyclooxygenase (COX), prostaglandin-2 and leukotrienes. TQ has been also shown to reduce LPS-induced pro-inflammatory cytokines, such as interleukins and TNF-$\alpha$.

Numerous studies have been reported that *N. sativa* could improve body antioxidant defence through enhancement of antioxidant enzymes activity and reduction of reactive oxygen species. Furthermore, it has been suggested that *N. sativa* supplementation, by scavenging various free radicals, including hydroxyl radicals, hypochlorous acid and singlet oxygen, suppresses inflammation and oxidative stress. Besides, considering the positive role of weight loss in improving the CRP level, the beneficial effects of *N. sativa* on the CRP can be attributed to its anti-obesity activity.

Generally, *N. sativa* is known as a safe herbal medicine and no serious adverse effect was reported among included studies. However, there is antecedent reports that suggest *N. sativa* consumption can result in some unwanted side effects, such as; dyspepsia, nausea, allergic reaction, dermatitis, diarrhoea, abdominal cramping and slight anorexia in high dosages. Furthermore, *N. sativa* is also known to adversely interact with both chemotherapy
medications and radiation therapy. Since it may act like an antioxidant in the body, this herbal supplement can decrease the efficacy of standard cancer treatments.

With respect to potential limitations in our study; first, a number of eligible studies in the present meta-analysis were relatively small which may have biased the results to some extent. Second, pathological status of participants was varied, including participants with NAFLD, metabolic syndrome, obesity, ulcerative colitis and rheumatoid arthritis. Third, a high degree of heterogeneity was detected in both outcomes, and although we have explored the source of heterogeneity, the interpretation of findings may be influenced by the level of heterogeneity observed. Fourth, most of the included studies have been conducted in Iran, which makes it difficult to generalize the results to the rest of the world. Fifth, given the limited studies on each gender, duration of intervention and CRP type, we could not examine the effects of the aforementioned parameters. And finally, trials used various durations and doses with two different forms, although subgroup analyses were assessed the effects of seed oil and powder.

**Conclusion**

This meta-analysis suggests that *N. sativa seed and seed oil* supplementation in doses of 1g to 3g daily can significantly reduce serum CRP level. This result may be attributable to the widely reputed anti-inflammatory properties of *N. sativa seed and seed oil*. However, RCTs with a larger sample size and a longer follow-up period should be considered in the near future in order to support the veracity these findings.

**Conflict of interest**

The authors declare no conflict of interest.

**Acknowledgments**
None.

**Author Contribution**

A.H and E.Gh carried out the concept, design, and drafting of this study. A.H, E.Gh and A.A searched databases, screened articles and extracted data. A.H and R.T performed the acquisition, analysis, and interpretation of data. C.C critically revised the manuscript. All authors approved the final version of the manuscript. A.H and E.Gh are the guarantor of this study.

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References


Legends of figures:

Figure 1. PRISMA flow diagram of study selection process

Figure 2. Forest plot of the effect of *Nigella sativa* supplementation on C-reactive protein

Figure 3. Funnel plots detailing publication bias in the studies selected for analysis
<table>
<thead>
<tr>
<th>First author (publication year)</th>
<th>Country</th>
<th>Sample size</th>
<th>Gender</th>
<th>Mean age (year)</th>
<th>Mean BMI (kg/m²)</th>
<th>RCT design (blinding)</th>
<th>Duration (week)</th>
<th>Target population</th>
<th>Intervention (name and daily dose)</th>
<th>Control</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Datau et al (2010)</td>
<td>Indonesia</td>
<td>40</td>
<td>Male</td>
<td>38</td>
<td>NR</td>
<td>Parallel (Yes)</td>
<td>12</td>
<td>Obese</td>
<td>1500 mg/day of <em>N. sativa</em> powder</td>
<td>Placebo</td>
<td>hs-CRP ↔</td>
</tr>
<tr>
<td>Amin et al (2015)</td>
<td>Pakistan</td>
<td>124</td>
<td>Both</td>
<td>43.33</td>
<td>27.45</td>
<td>Parallel (Yes)</td>
<td>8</td>
<td>Metabolic syndrome</td>
<td>1500 mg/day of <em>N. sativa</em> powder</td>
<td>Placebo</td>
<td>CRP ↓</td>
</tr>
<tr>
<td>Mahdavi et al (2016)</td>
<td>Iran</td>
<td>90</td>
<td>Female</td>
<td>40.25</td>
<td>32.05</td>
<td>Parallel (Yes)</td>
<td>8</td>
<td>Obese</td>
<td>3000 mg/day of <em>N. sativa</em> oil</td>
<td>Placebo</td>
<td>hs-CRP ↓</td>
</tr>
<tr>
<td>Kheirouri et al (2016)</td>
<td>Iran</td>
<td>43</td>
<td>Female</td>
<td>42.19</td>
<td>25.22</td>
<td>Parallel (Yes)</td>
<td>8</td>
<td>Rheumatoid arthritis</td>
<td>1000 mg/day of <em>N. sativa</em> oil</td>
<td>Placebo</td>
<td>hs-CRP ↓</td>
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<tr>
<td>Mohtashami et al (2016)</td>
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<td>51</td>
<td>Both</td>
<td>47</td>
<td>29.90</td>
<td>Cross-over (Yes)</td>
<td>8</td>
<td>Metabolic syndrome</td>
<td>Wheat bread + 3000 mg/day of <em>N. sativa</em> powder</td>
<td>Wheat bread</td>
<td>hs-CRP ↔</td>
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<tr>
<td>Darand et al (2019)</td>
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<td>Both</td>
<td>47.48</td>
<td>31.78</td>
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<td>8</td>
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<td>Placebo</td>
<td>hs-CRP ↓</td>
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<td>Nikkhah-Bodaghi et al (2019)</td>
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<td>48</td>
<td>Both</td>
<td>37.02</td>
<td>24.60</td>
<td>Parallel (Yes)</td>
<td>6</td>
<td>Ulcerative colitis</td>
<td>2000 mg/day of <em>N. sativa</em> powder</td>
<td>Placebo</td>
<td>hs-CRP ↑</td>
</tr>
</tbody>
</table>

RCT, randomized controlled trial; BMI, body mass index; NR, not reported; NAFLD, nonalcoholic fatty liver disease; CRP, C-reactive-protein; hs-CRP, high-sensitivity CRP
Table 2. Methodological quality scores for the included studies using the Jadad scale.

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomization</th>
<th>Methods of randomization</th>
<th>Blinding</th>
<th>Method of blinding</th>
<th>Description of withdrawal</th>
<th>Total Score</th>
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<td>-</td>
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<td>+</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>5</td>
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Table 3. Result of subgroup analysis of included studies in meta-analysis.

<table>
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<tr>
<th>Sub-grouped by</th>
<th>No. of trials</th>
<th>Effect size(^1)</th>
<th>95% CI</th>
<th>(I^2) (%)</th>
<th>P for heterogeneity</th>
<th>P for between subgroup heterogeneity</th>
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<td>Baseline BMI</td>
<td></td>
<td></td>
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<tr>
<td>≥30 kg/m(^2)</td>
<td>2</td>
<td>-0.50</td>
<td>-0.85, -0.15</td>
<td>2.8</td>
<td>0.31</td>
<td>0.88</td>
</tr>
<tr>
<td>&lt;30 kg/m(^2)</td>
<td>3</td>
<td>-0.64</td>
<td>-1.50, 0.23</td>
<td>87.9</td>
<td>&lt;0.001</td>
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</tr>
<tr>
<td>(N. sativa) dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>≥2 mg/day</td>
<td>3</td>
<td>-0.26</td>
<td>-0.74, 0.22</td>
<td>61.1</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>&lt;2 mg/day</td>
<td>2</td>
<td>-1.04</td>
<td>-2.16, 0.07</td>
<td>88.0</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Intervention type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Powder</td>
<td>3</td>
<td>-0.24</td>
<td>-0.65, 0.18</td>
<td>53.0</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Oil</td>
<td>2</td>
<td>-1.10</td>
<td>-2.11, -0.10</td>
<td>84.1</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)Calculated by Random-effects model

BMI, body mass index
Figure 1

Articles identified through databases searching (n=95)

Records after duplicates removed (n=64)

Records screened (n=64)

Articles removed by title/abstract (n=54)

Full-text articles assessed for eligibility (n=10)

Articles removed after full-text review (n=3):
Studies that administered arginine in combination with other components (n=2)
Duplicate data (n=1)

Included studies in qualitative synthesis (n=7)

Included studies in quantitative synthesis (meta-analysis) (n=5)

Relevant data were not represented (n=2)
<table>
<thead>
<tr>
<th>Study name</th>
<th>WMD (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darand et al (2019)</td>
<td>-0.25 (-0.84, 0.34)</td>
<td>18.73</td>
</tr>
<tr>
<td>Amin et al (2015)</td>
<td>-0.51 (-0.87, -0.16)</td>
<td>23.05</td>
</tr>
<tr>
<td>Nikkhah-Bodaghi et al (2019)</td>
<td>0.18 (-0.38, 0.74)</td>
<td>19.32</td>
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<tr>
<td>Kheirouri et al (2016)</td>
<td>-1.65 (-2.34, -0.97)</td>
<td>16.98</td>
</tr>
<tr>
<td>Mahdavi et al (2016)</td>
<td>-0.62 (-1.04, -0.21)</td>
<td>21.91</td>
</tr>
<tr>
<td><strong>Overall</strong> (I-squared = 77.3%, p = 0.001)</td>
<td>-0.55 (-1.02, -0.08)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

Figure 2
Figure 3