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Review article

Effect of ginger (Zingiber officinale) on inflammatory markers: A systematic review and *meta*-analysis of randomized controlled trials

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ABSTRACT

The aim of this systematic review and *meta*-analysis was to investigate the efficacy of ginger supplementation on circulating levels of C-reactive protein (CRP), high sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-alpha (TNF-α), soluble intercellular adhesion molecule (sICAM), and interleukin-6 (IL-6) concentrations in randomized controlled trials (RCTs).

The search included PubMed-Medline, EMBASE, Scopus, Web of Science and Cochrane Library databases to identify randomized clinical trials on the effect of ginger supplementation on circulation levels of CRP, hs-CRP, IL-6, sICAM, and TNF-α published up until February 1st, 2020. We did not restrict articles based on language of publication. Standard mean differences and 95% confidence intervals were calculated for net changes in inflammatory mediators using a random-effects model.

Sixteen RCTs comprising 1010 participants were found to be eligible for this *meta*-analysis. There was a significant reduction of circulating CRP (SMD: −5.11, 95% CI: −7.91, −2.30, I^2 = 98.1%), hs-CRP (SMD: −0.88, 95% CI: −1.63, −0.12, I^2 = 90.8%) and TNF-α levels (SMD: −0.85, 95% CI: −1.48, −0.21, I^2 = 89.4%) following ginger supplementation. However, *meta*-analysis results did not show any significant impact of ginger supplementation on IL-6 (SMD: −0.45, 95% CI: −1.29, 0.38, I^2 = 89.2%), and sICAM levels (SMD: −0.05, 95% CI: −0.36, 0.26, I^2 = 00.0%).

This systematic review and *meta*-analysis of RCTs demonstrates a significant impact of ginger in lowering circulating CRP, hs-CRP and TNF-α levels. Large-scale RCTs are still needed to draw concrete conclusions about the effect of ginger on other inflammatory mediators.

1. Introduction

Ginger rhizome (Zingiber officinale) is a popular spice with negligible side effects all over the world [1]. Health benefits of ginger in chronic disease recently became one of the top topics in complementary medicine [2]. Phenolic compounds in ginger include gingerol, paradol, and shogaol; these compounds reduce the risk of atherosclerosis, inflammation, angiogenesis and oxidative stress [3]. More than 40

Abbreviations: CRP, C-reactive protein; hs-CRP, high sensitivity C-reactive protein; TNF-α, tumor necrosis factor-alpha; sICAM, soluble intercellular adhesion molecule; IL-6, interleukin-6; SMD, standardized mean difference; CI, confidence intervals; CVD, Cardiovascular disease; NF-κB, nuclear factor- kappa-B; PPAR-γ, peroxisome proliferator-activated receptor-gamma; VCAM-1, Vascular cell adhesion molecule-1; PD, peritoneal dialysis; PGE2, prostaglandin E2; COX-2, cyclooxygenase-2; MCP-1, chemoattractant protein-1; MIPs, migration inhibition proteins; MAPK, mitogen-activated protein kinase; INF-γ, Interferon gamma; EGF, Epidermal growth factor; RCTs, randomized controlled trials; ROS, Reactive oxygen sepsis

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antioxidants have been extracted from ginger rhizome [4].

Cardiovascular disease (CVD) is one of the most prevalent diseases affecting all countries [5]. Increased systemic inflammatory indicators such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α) and C-reactive protein (CRP) are associated with an increased risk of CVD [6]. These elevated markers result from increased expression of immune system factors, including nuclear factor- kappa-B (NF-κB) and peroxisome proliferator-activated receptor-gamma (PPAR-γ) [7]. Additionally, proinflammatory cytokines may increase the serum level of the adhesion molecules, a type of membrane protein that can result in peritoneal membrane fibrosis and angiogenesis [8,9]. Vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) can also be used as predictor for CVD [10]. Furthermore, high sensitivity C-reactive protein (hs-CRP) is considered to be involved in the pathogenesis of insulin resistance, diabetes mellitus and metabolic syndrome. Hence, suppression of the inflammatory response is an important point in the management of chronic diseases [11,12].

Recent literature has found that ginger can reduce fasting blood sugar and ameliorate blood lipids by increasing the function of antioxidant enzymes [13]. Several clinical trials have been conducted to demonstrate the effect of ginger treatment on oxidative stress and inflammation by the suppression of NF-κB translocation [14–16]. While few review articles have been published in this regard, we found no sufficient evidence and *meta*-analysis in all of inflammatory cytokines such as ICAM-1, IL-6 and TNF-α [15,17]. The aim of this systematic review and *meta*-analysis of published randomized controlled trials (RCTs) is to evaluate the effect of ginger supplementation on the reduction of inflammatory markers.

2. Methods

2.1. Search strategy

This systematic review and *meta*-analysis was performed based on a pre-specified protocol consistent with the Cochrane Collaboration [18]. We searched the databases PubMed/MEDLINE, EMBASE, Scopus, ISI Web of Science, and Cochrane up through January 31st, 2020, to find associated randomized, placebo-controlled trials assessing the effect of ginger on inflammatory markers. Search strategies including the key terms and the queries for each database is attached in **Appendix A**. We have no language limitation in this review.

2.2. Selection criteria

We selected randomized controlled trials with either parallel or cross-over design which evaluated the effect of ginger on inflammatory markers in adults over than 18 years old. Studies were included if they had sufficient data on inflammatory markers at baseline and at the end of the intervention in both ginger and control groups to compare the difference in means with 95% confidence intervals (95% CI). Exclusion criteria were non-original publications, observational design (case studies, case series, cross-sectional, case-control, cohort), non-randomization, absence of a control group, animal studies, and studies presented only as abstracts, review articles, and letters to the editor. Table 1 indicates the Cochrane PICO search criteria for our *meta*-analysis.

Table 1
Description of PICO.

Condition	Description
Participant	Non healthy adults
Intervention	Oral Ginger supplementation
Comparison	Treatment group versus placebo group
Outcome	CRP, hs-CRP, IL-6, IL-18, IL-1β, ICAM-1, VCAM1, TNF-α
Study designs	Randomized clinical trial studies parallel or cross-over design

2.3. Data extract & analysis

All primary studies were reviewed by one author (J.H.). The data was then reviewed by a second author (S.F), and any discrepancies were discussed by a third author (M.R). Data extracted included: author, year of publication, country, subjects (number, age, sex), ginger dosage, and period of supplementation information from included trials. The standardized mean difference (SMD) was calculated for continuous and binary data. Standard errors for each inflammatory marker in the ginger and placebo groups, before and after intervention, were converted to standard deviations. The random effect model based on Inverse-Variance method was used in STATA (version 13) to pool the data. We assessed and quantified heterogeneity using heterogeneity chi-squared test with a P-value less than 0.1 and I^2 statistic over 50% considered as significant heterogeneity among studies. We considered statistically significant if $P < 0.05$. The Cochrane risk of bias assessment tool [19] was used to evaluate the quality of included studies.

3. Results

3.1. Study selection

An initial electronic database search yielded a total of 407 records. After duplicates were removed, a total of 247 studies were excluded. After title and abstract evaluation, 25 studies were examined in their full text. Nine additional studies were removed after full text evaluation. Finally, 16 RCTs [16,20–34] met the inclusion criteria to include in this systematic review and *meta*-analysis (Fig. 1).

3.2. Study characteristics

The articles included in this study were published from 2013 to 2020. Main characteristics of the included primary articles are presented in Table 2. All included articles were of parallel design. Although ginger is usually consumed worldwide, surprisingly 15 of the studies were performed in Iran [16,20–26,28–34] and one was performed in India [27]. A total of 1010 participants were included in the intervention and control arms of included studies, ranging from 36 in the smallest trial [33] to 100 participants in the largest trial [29]. The mean age of subjects in trials ranged from 31.62 [27] to 59 years [16]. Ginger was administered as a range of doses from 1000 to 3000 mg per day in these studies. Duration of intervention ranged from 4 to 12 weeks. Among the 15 trials included in the *meta*-analysis: seven studies included subjrcts with type 2 diabetes [20,22,23,26,28,32,34]; two trials included patients undergoing peritoneal dialysis (PD) [25,33]; two trials included subjects with non-alcoholic fatty liver disease [30,31]; two studies included patients with osteoarthritis [16,29]; one article included overweight women with breast cancer [21]; one trial included participants with low back pain [24]; and one study included subjects with tuberculosis [27]. Ginger supplementation appeared well-tolerated and safe in all included trials in this *meta*-analysis.

3.3. Effect of ginger administration on inflammatory factors

The pooled estimate (SMD) of the impact of ginger supplementation on CRP levels showed a significant decrease in CRP (SMD: −5.11, 95% CI: −7.91, −2.30, I^2 = 98.1%) across four studies (Fig. 2-**A**). The Hashemi et al. [24] study was identified as considerably contributing to the heterogeneity in this pooled effect. After performing sensitivity analysis and after dropping out of Hashemi et al. article, the effect of ginger supplementation on CRP still remained significant (SMD: −0.75, 95% CI: −1.34, −0.15, I^2 = 67.5%) (Fig. 2-**B**). Meta-analysis of seven trials indicated that ginger supplementation also significantly reduced hs-CRP (SMD: −0.88, 95% CI: −1.63, −0.12, I^2 = 90.8%) (Fig. 3-**A**). Subgroup analysis based on background illness of participants showed that ginger supplementation significantly reduced levels of hs-CRP in

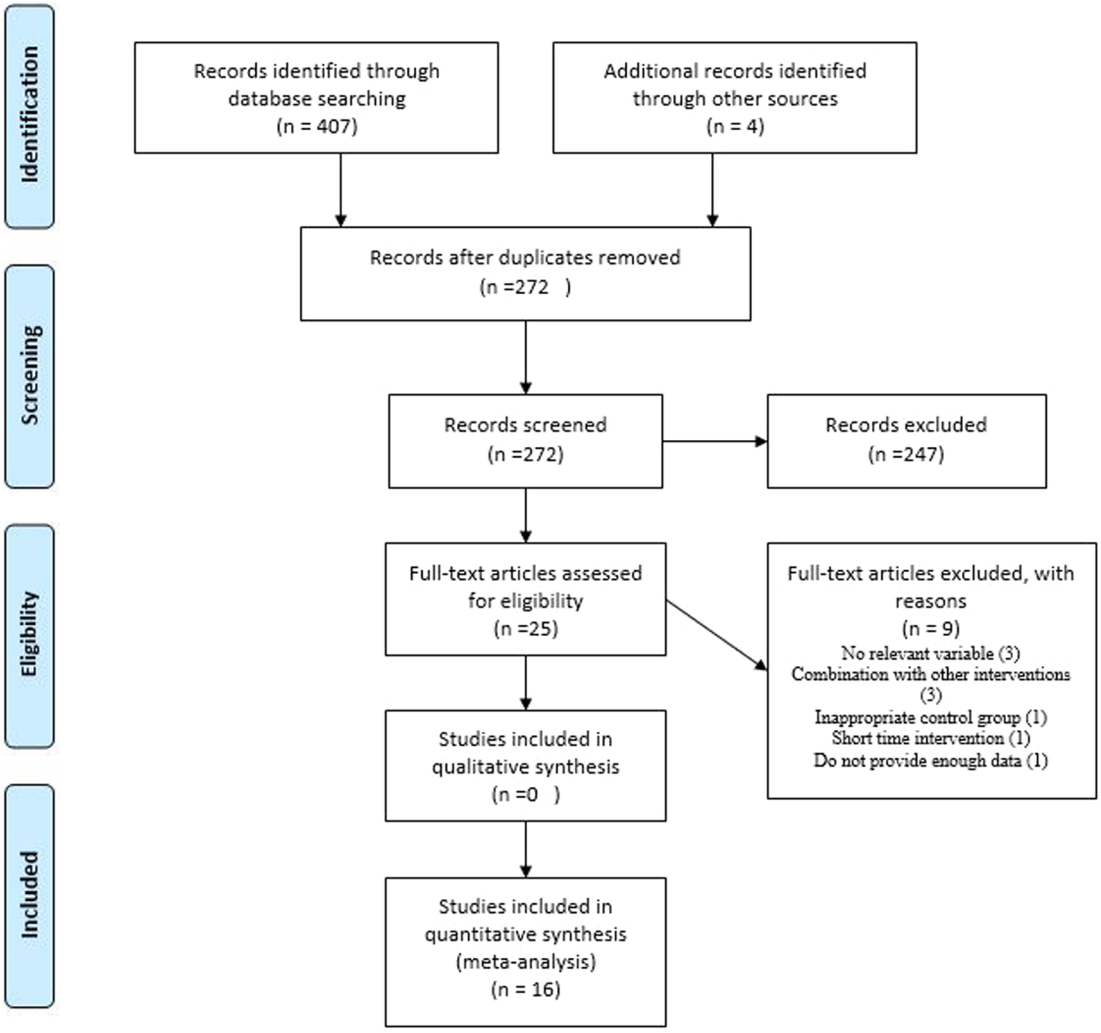

Fig. 1. PRISMA Flow Diagram of study selection.

diabetic patients compared to non-diabetic patients (SMD: −0.37, 95% CI: −0.73, −0.02, I^2 = 43.8%) (Fig. 3-**B**). Patients who took ginger supplements for fewer than 10 weeks had significantly decreased levels of hs-CRP compared to patients who took ginger supplements for greater than 10 weeks (SMD: −0.46, 95% CI: −0.91, −0.01, I^2 = 55.9%) (Fig. 3-**C**). Patients who took a ginger supplement dose of ≥ 2000 mg/day had significantly decreased levels of hs-CRP compared to patients who took a lower daily dose (SMD: −1.26, 95% CI: −2.32, −0.19, I^2 = 93.6%) (Fig. 3-**D**). Meta-analysis of five clinical trials did not show any significant impact of ginger supplementation on IL-6 concentration (SMD: −0.45, 95% CI: −1.29, 0.38, I^2 = 89.2%) (Fig. 4), or sICAM levels (SMD: −0.05, 95% CI: −0.36, 0.26, I^2 = 00.0%) (Fig. 5). The impact of ginger supplementation on TNF-α levels was assessed in seven trials. Pooled analysis indicated a significant reduction in TNF-α levels after ginger supplementation (SMD: −0.85, 95% CI: −1.48, −0.21, I^2 = 89.4%) (Fig. 6-**A**). Subgroup analysis based on disease type (diabetic vs. non-diabetic) (Fig. 6-**B**) and duration of supplementation (Fig. 6-**C**) did not show any change in this significant effect. Only in cases of more than or equal to 2000 mg/d was a non-significant decrease of TNF-α observed (SMD: −0.69, 95% CI: −1.56, 0.17, I^2 = 88.5%) (Fig. 6-**D**)

3.4. Risk of bias assessment

The summary of the risk of bias evaluation is presented in **Appendix B**. The random allocation was unclear in nine included studies. Three of the included studies were judged to be at high-risk for bias for random allocation. Methods of blinding of participants and personnel was unclear in three studies and six trials assessed high-risk of blinding of participants and personnel. Ten trials were at high-risk for attrition bias. Blinding of outcome evaluation (detection bias) was satisfactory in all included studies. There was no selective reporting (reporting bias) in any of the included articles.

4. Discussion

This *meta*-analysis demonstrated the anti-inflammatory benefits of ginger supplementation reflected in the reduction of serum inflammatory markers. Ginger consumption was associated with decreased CRP, hs-CRP and TNF-α. Ginger supplementation was not associated with a change in IL-6 and sICAM levels. To the best of our knowledge this is the first *meta*-analysis that exclusively evaluates the effect of ginger supplementation on inflammatory markers. Mazidi et al

Table 2
The Summaries of 16 Randomized Clinical Trials to Investigate the Effects of Ginger Supplementation on Inflammatory markers.

First author, Year	Country	Population	Dose of Ginger (mg)	Sample size (including in analyses)	duration (weeks)	Gender (percentage of women)	Age (mean ± SD)		BMI (mean ± SD) kg/m2		Main results*
							Intervention Group	Control Group	Intervention Group	Control Group	
Arablou et al., 2014 [20]	Iran	T2DM patients	1600	63	12	76.2%	52.6 ± 8.4	52.0 ± 9.0	26.9 ± 3.6	26.8 ± 3.4	↓ CRP, ↔ TNF-α
Ayaz et al., 2012 [21]	Iran	Overweight Women with Breast Cancer	3000	80	6	100%	46.4 ± 5.5	50.4 ± 3.4	32.18 ± 2.9	32.77 ± 2.9	↓ CRP, ↓ IL-6
Azimi et al., 2014 [22]	Iran	T2DM patients	3000	80	8	61.3%	55.21 ± 1.1	53.64 ± 1.3	29.05 ± 0.2	28.40 ± 0.2	↓ hs-CRP
Azimi et al., 2016 [23]	Iran	T2DM patients	3000	80	8	61.3%	55.21 ± 1.1	53.64 ± 1.3	29.05 ± 0.2	28.40 ± 0.2	↓ sICAM
Hashemi et al., 2019 [24]	Iran	adults with low back pain	–	80	6	–	–	–	–	–	↓ CRP, ↓ IL-6
Imani et al., 2015 [25]	Iran	peritoneal dialysis patients	1000	36	10	41.5%	56.00 ± 2.5	58.00 ± 3.0	27.00 ± 1.0	27.00 ± 1.0	↔hs-CRP, ↔sICAM-1, ↔sVCAM-1, ↔sE-selectin
Javid et al., 2019 [26]	Iran	T2DM patients	2000	42	8	54.8%	52.81 ± 6.44	51.62 ± 5.95	26.06 ± 3.33	27.18 ± 2.15	↓IL-6, ↓hs-CRP, ↓TNF-α
Kulkarni et al., 2016 [27]	India	Tuberculosis patients	3000	69	4	–	31.62 ± 6.0	31.62 ± 6.0	–	–	↓TNF-α
Mahluji et al., 2013 [28]	Iran	T2DM patients	2000	64	8	37.5%	49.27 ± 5.18	53.14 ± 7.9	29.2 ± 4.07	29.8 ± 5.05	↓IL-6, ↓hs-CRP, ↓TNF-α
Mozaffari-Khosravi et al., 2016 [16]	Iran	Patients with Osteoarthritis	2000	100	8	90%	57.98 ± 6.2	59.1 ± 6.1	26.1 ± 2.9	25.5 ± 2.0	↓TNF-α, ↓IL-1β
Naderi et al., 2016 [29]	Iran	Knee osteoarthritis patients	1000	100	12	90%	57.98 ± 6.2	59.1 ± 6.1	26.1 ± 2.9	25.5 ± 2.0	↓ CRP
Rafie et al., 2020 [30]	Iran	NAFLD patients	1500	46	12	56.5%	50.04 ± 10.26	47.95 ± 9.24	31.70 ± 3.75	30.94 ± 1.98	↓ hs-CRP, ↔ TNF-α
Rahimlou et al., 2016 [31]	Iran	NAFLD patients	2000	44	12	54.5%	45.45 ± 2.31	45.00 ± 2.14	30.55 ± 0.95	31.53 ± 0.47	↓ hs-CRP, ↓ TNF-α
Shidfar et al., 2015 [32]	Iran	T2DM patients	3000	45	12	–	45.2 ± 7.64	47.1 ± 8.31	29.5 ± 2.8	29.2 ± 3.1	↓ hs-CRP
Tabibi et al., 2016 [33]	Iran	peritoneal dialysis patients	1000	36	10	41.5%	56.00 ± 2.5	58.00 ± 3.0	27.00 ± 1.0	27.00 ± 1.0	↔ IL-6
Zarezadeh et al., 2018 [34]	Iran	T2DM patients	2000	45	10	–	51.74 ± 8.58	49.59 ± 8.58	29.94 ± 3.52	29.23 ± 4.58	↔sICAM-1

¥ T2DM: Type 2 diabetes mellitus, T1DM: Type 1 diabetes mellitus, RA: rheumatoid arthritis, CRP: C-Reactive Protein, TNF-α: Tumor necrosis factor alpha, IL-6: Interleukin 6, hs-CRP: High-sensitivity C-reactive Protein, sICAM: soluble Intercellular adhesion molecule, sVICAM: soluble vascular cell adhesion molecule, IL-1β: interleukin-1β, NAFLD: Nonalcoholic fatty liver disease.

* ↓ This symbol is a sign of decreasing variables in the intervention group, ↑ This symbol is a sign of increasing variables in the intervention group, ↔ This sign indicates that there is no difference between the two groups. NR: not reported.

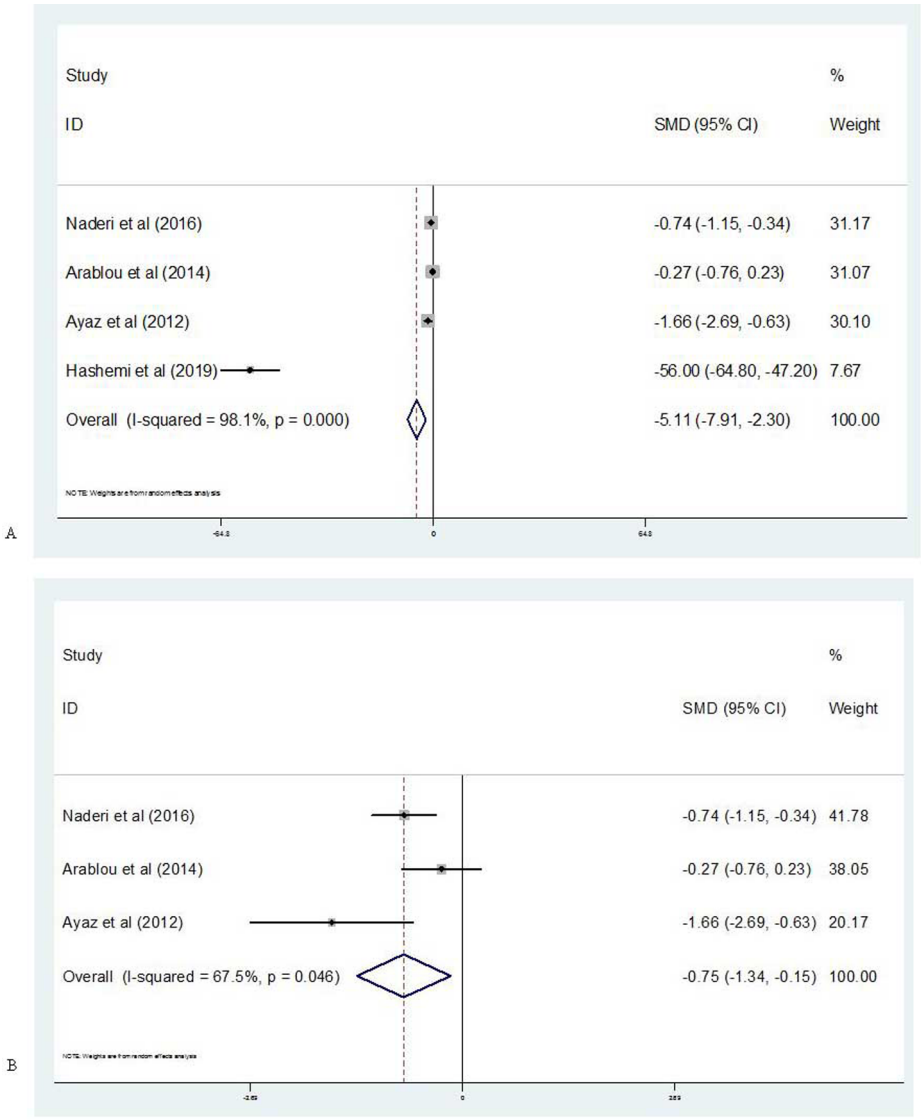

Fig. 2. A: Overall Forest plot of the effect of ginger supplementation on CRP. **B**: Forest plot of the effect of ginger supplementation on CRP when Hashemi et al dropout.

conducted a systematic review of the impact of ginger and other supplements on CRP in 2016, and previous narrative reviews have discussed the anti-inflammatory effects of ginger [35–37]. Recently Jalali et al. also demonstrated the anti-inflammatory and anti-oxidant impact of ginger [38]. In line with our results, Jalali et al. demonstrated that ginger intake decreased CRP and TNF-α, but unlike our systematic review, they did not evaluate the imact of ginger on hs-CRP and sICAM levels. There are several primary studies that evaluated the impact of ginger on hs-CRP instead of CRP which we have separated in this systematic review to grant us a more clear conclusion in these regards.

This systematic review and *meta*-analysis was conducted according to the rigorous standards of the 'Methodological Expectations for Cochrane Intervention Reviews' (MECIR) and reported based on the PRISMA statement, and we believe this has minimized the potential for bias [18].

Our results indicate that ginger supplementation reduces CRP levels. This is in agreement with the systematic review by Mazidi et al. [35], which reported that ginger supplementation could reduce CRP levels. The Mazidi et al study, however, included primary studies with ginger in combination with other treatments. Our study strengthens the findings in the Mazidi et al review by demonstrating an independent decrease in CRP with ginger supplementation.

Subgroup analysis in our results indicated that ginger supplementation reduces hs-CRP to a high degree in diabetic patients compared to non-diabetic patients. Previous systematic reviews and *meta*-analysis also reported that ginger supplementation improves glycemic control in diabetic patients [39]. Inflammation plays a key role in the pathophysiology of diabetes, so the anti-inflammatory benefits of ginger along with its improved glycemic control can be useful in the treatment of diabetes. Our results also indicated that a shorter duration of ginger supplementation (fewer than 10 weeks) and a higher dose (greater than 2000 mg per day) resulted in a significant reduction in hs-CRP levels. The variable baseline levels of hs-CRP from different studies included in this systematic review may have impacted these results, especially since the disease profile in each study population differed. The literature does support the hypothesis that ginger exerts its effects in a dose-dependent manner [40,41]. In addition, it is plausible that short-term intake of ginger (fewer than 10 weeks) is more efficient to reduce hs-CRP levels because of body adaptation to its anti-inflammatory effects.

The pharmacological impacts of ginger are mainly associated with shogaols, gingerols, paradols, and zingerone [42]. 6-gingerol is one of

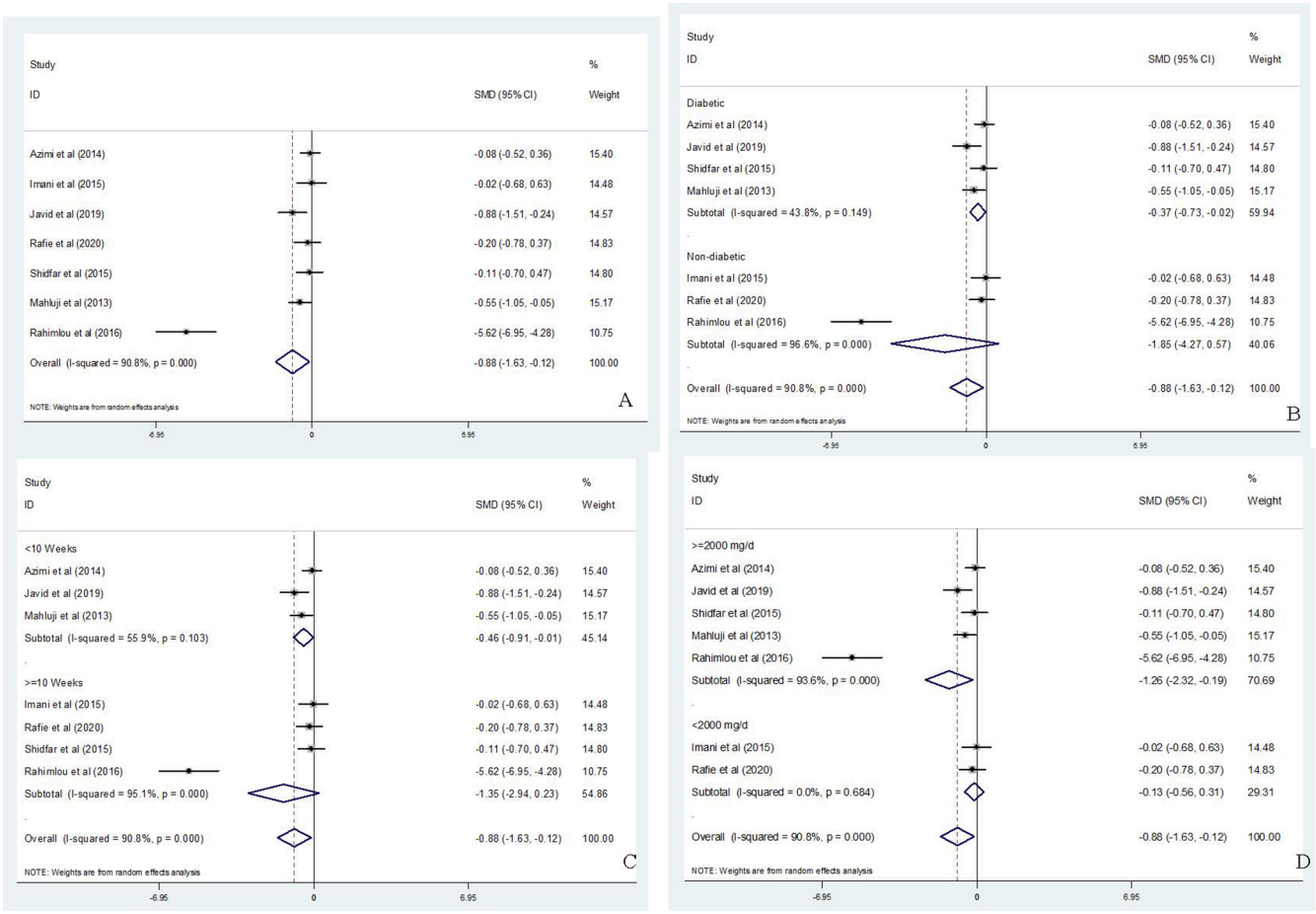

Fig. 3. A: Overall Forest plot of the effect of ginger supplementation on hs-CRP. **B**: Forest plot of the effect of ginger supplementation on hs-CRP stratified based on disease type. **C**: Forest plot of the effect of ginger supplementation on hs-CRP stratified based on duration. **D**: Forest plot of the effect of ginger supplementation on hs-CRP stratified based on dose of Ginger.

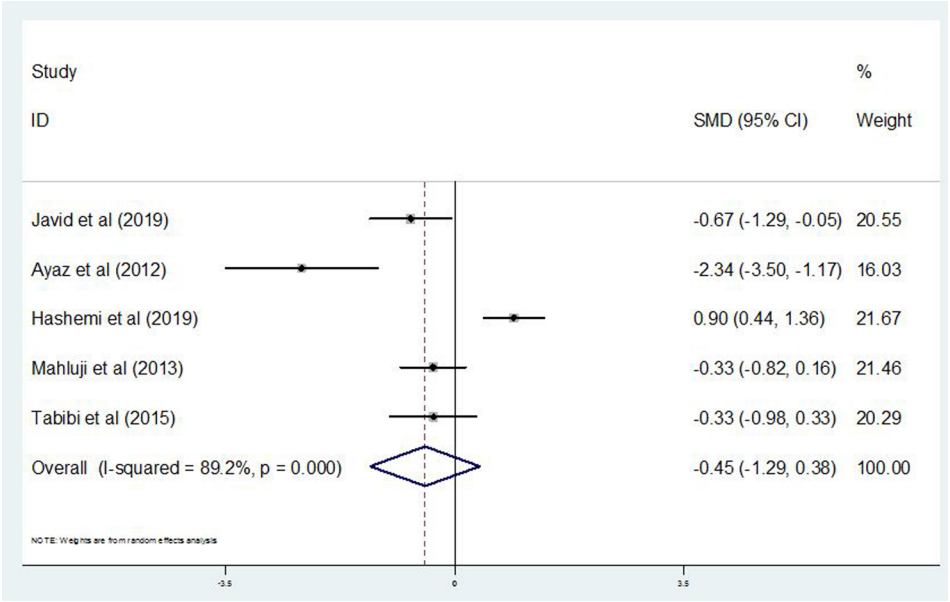

Fig. 4. Forest plot of the effect of ginger supplementation on IL-6.

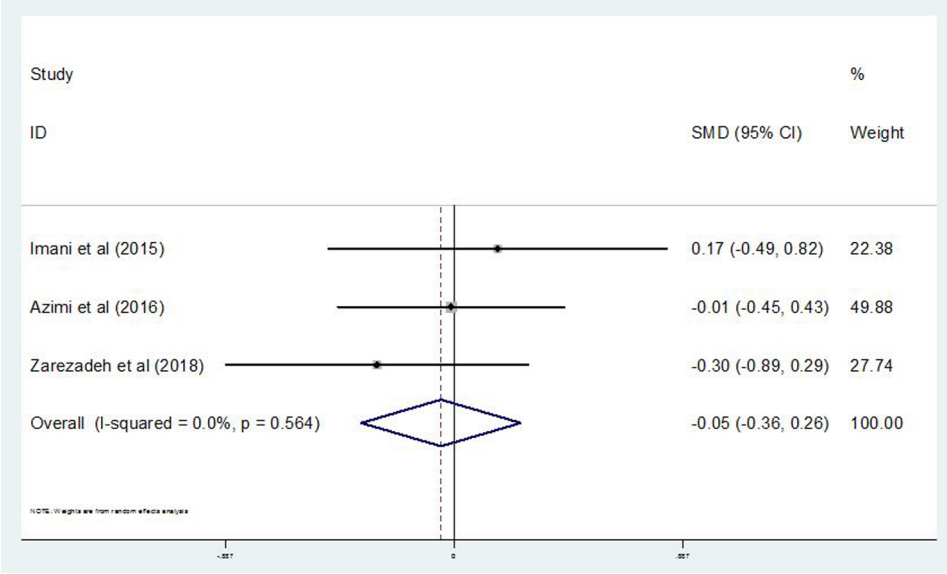

Fig. 5. Forest plot of the effect of ginger supplementation on sICAM.

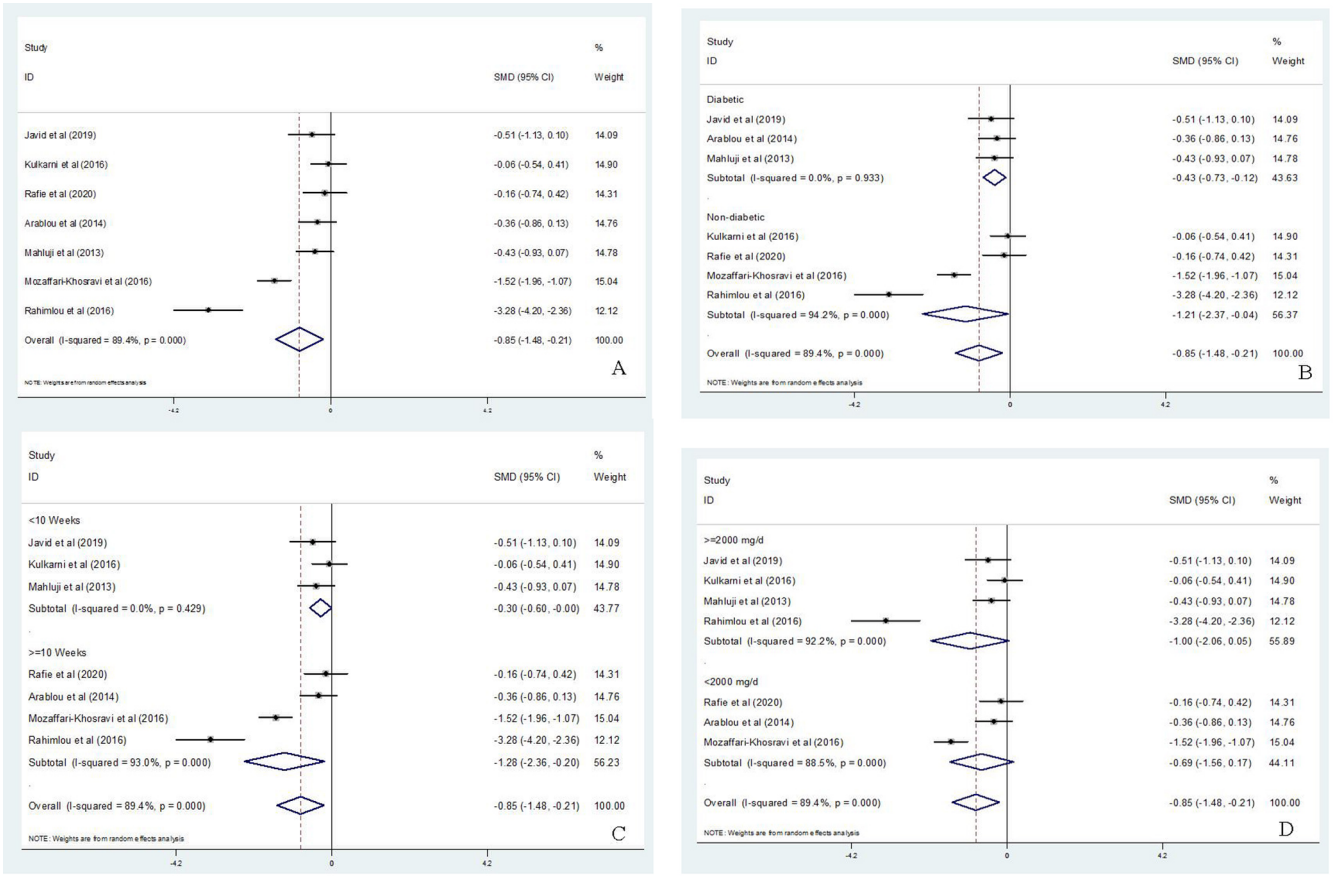

Fig. 6. A: Overall Forest plot of the effect of ginger supplementation on TNF-α. **B**: Forest plot of the effect of ginger supplementation on TNF-α stratified based on disease type. **C**: Forest plot of the effect of ginger supplementation on TNF-α stratified based on duration. **D**: Forest plot of the effect of ginger supplementation on TNF-α stratified based on dose of Ginger.

the major ingredients in ginger that has been shown to improve a number of chronic complications in experimental and humans models [43,44]. 6-shogaol, a stable and more effective pharmacological component than 6-gingerol, is produced after dehydration of 6-gingerol [45]. 6-paradol is produced from 6-shogaol by microbial activity that responsible for anti-inflammatory and anti-oxidative effects of ginger [46]. 6-paradol and 6-gingerol have been shown to reduce several inflammatory mediators such as prostaglandin E2 (PGE2) [47,48]. PGE2 is related with higher levels of CRP and hs-CRP [49]. Regarding the mechanism of the impact of ginger and its ingredients on PGE2, a suppression of cyclooxygenase-2 (COX-2) mRNA expression and direct suppression of this enzyme function is also suggested [50]. An additional proposed mechanism could be the impact of ginger extract on other inflammatory mediators such as monocyte chemoattractant protein-1 (MCP-1) and migration inhibition proteins (MIPs). It has been shown that ginger can reduce MCP-1 levels and inhibit pathways related to this protein [51], as well as MIPs [52]. MCPs and MIPs are also related to inflammation and CRP levels [53].

Our *meta*-analysis results indicate that ginger intake significantly reduces TNF-α levels. There are no systematic reviews which assessed the impact of ginger on TNF-α levels. But the impact of ginger in reducing TNF-α levels has been demonstrated in randomized clinical trials [31] and experimental studies [54]. Subgroup analysis in this review indicates that disease type and duration do not change the significant reduction imapct of ginger on TNF-α levels, but subgroup analysis according to doses show that ginger supplementation in ≥2000 mg/day significantly decreases TNF-α levels compared to > 2000 mg/d doses. Both 6-shogaol and 6-gingerol have been shown to significantly inhibit TNF-α [54]. *In vitro* studies demonstrate that 6-shogaol act as a PPARγ agonist and attenuate inflammation and TNF-α levels by activating of PPARγ [55]. 6-gingerol is not a PPARγ agonist, but does behave as a powerful suppressor of TNF-α induced c-Jun-NH2-terminal kinase signaling activation [56]. In addition, ginger ingredients have been shown to reduce TNF-α levels also by impacting up-stream gene expression in its pathway. The nuclear factor kB (NF-kB) is a transcription factor involved in the modulation of several biological responses, including inflammation and TNF-α levels [57,58]. *In vitro* findings show that S-[6]-gingerol reduces inflammatory response by suppressing the reactive-oxygen-species- (ROS-) activated NFκB/COX2 pathway [59]. In addition, it has been shown that 6-shogaol exerts its anti-inflammatory impacts by suppressing the synthesis of PGE2 and proinflammatory cytokines, including TNF-α, by down regulating COX-2, p38 mitogen-activated protein kinase (MAPK), and NF-κB gene expression [44].

Our *meta*-analysis results demonstrate that ginger supplementation does not have any significant effect on IL-6 and sICAM levels. However, the heterogeneity and limited number of included studies which investigated the impact of ginger on IL-6 and sICAM, may contribute to our inability to find a significant effect in these regards. The most important limitation resulting in the heterogeneity of the results stems from the many different disease types included in these trials. However, we tried to minimize the impact of heterogeneity by conducting a random-effects model as well as performing subgroup analysis based on disease type (diabetic vs. non-diabetic). Regardless, conclusions about the impact of ginger on inflammatory mediators in specific diseases need to be investigated separately. A limited number of included studies included variables such as IL-6 and sICAM, and there were no sufficient data in primary studies about the impact of ginger on other inflammatory mediators such as IL-18, IL1-β, INF-γ, sVCAM, Homocysteine and EGF. These limitations contributed to our inability to find resolute conclusions in these regards. In addition, another limitation that may have impacted the results of this systematic review was the different type and stage of diseases in primary studies which likely impacted inflammatory marker levels. More confirmatory evidence from large-scale studies is needed to compensate for the small sample size of studies available in the current literature.

5. Conclusion

Our *meta*-analysis indicated a significant lowering-effect of ginger supplementation on circulating CRP, hs-CRP, and TNF-α concentration. However, these outcomes should be declared with caution due to the limited number of studies and the evidence of heterogeneity. Further large-scaled trials are encouraged to translate this biochemical impact into clinical advantages for patient care.

6. Author's contributions

J.H., S.F., and M.M. contributed to acquisition of the data; M.KH. and M.R. participated in its design, coordination and statistical analysis; SH.H. and J.H. performed the extra analyses; M.M., E.P and J.H drafted the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cyto.2020.155224.

Appendix B:. Assessment of the risk of bias in the included studies

Author, year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Arablou et al, 2014[20]	?	–	+	–	+	–	–
Ayaz et al, 2012[21]	?	+	+	+	–	–	–
Azimi et al, 2014[22]	–	?	+	–	+	–	–
Azimi et al, 2016[23]	?	?	+	–	+	–	–
Hashemi et al, 2019[24]	?	–	+	–	+	–	–
Imani et al, 2015[25]	?	+	?	–	–	–	–
Javid et al, 2019[26]	–	–	–	–	?	–	–
Kulkarni et al, 2016[27]	?	?	+	+	?	–	–
Mahluji et al, 2013[28]	?	?	?	–	+	–	–
Mozaffari-Khosravi et al, 2016[16]	–	–	–	–	+	–	–
Naderi et al, 2016[29]	–	–	–	–	+	–	–
Rafie et al, 2020[30]	–	?	–	–	+	–	–
Rahimlou et al, 2016[31]	–	–	–	–	+	–	–
Shidfar et al, 2015[32]	?	?	–	–	+	–	–
Tabibi et al, 2016[33]	?	+	?	–	–	–	–
Zarezadeh et al, 2018[34]	–	?	–	?	?		

+: High risk, -: Low risk, ?:Unclear.

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