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# The Simultaneous Effect of Ginger Supplementation and Exercise on Inflammatory Factors: Systematic Review and Meta-analysis

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**Abstract**

**Introduction:** Chronic inflammation is associated with the onset and progression of wide range diseases. Supplementation with ginger due to its bioactive compounds and exercise as a non-pharmacological intervention has both shown anti-inflammatory effects. However, the available evidence on their synergistic effects is sparse. Therefore, the aim of the present study was to systematically review and Meta-analyze randomized clinical trials on the simultaneous effect of ginger supplementation and exercise on inflammatory markers.

**Methods**: A comprehensive search of articles published in Persian and English in Pub Med, Science Direct, Scopus, SID, and Magiran databases was conducted until 2025, and eligible articles were extracted and entered into the meta-analysis. Random effects models were used to meta-analyze the average effect size in the study of interleukin-6 and C-reactive protein, and Also Fixed effects models were used for tumor necrosis factor alpha using CMA2 software.

**Results**: A total of 16 studies that examined the effects of ginger supplementation and exercise on inflammatory factors were meta-analyzed. The results of the meta-analysis showed that the effects of ginger supplementation and exercise on inflammatory factors did not significantly affect C-reactive protein (ES=-0.41, 95% CI=-0.23 to -1.06, p=0.20), but significantly reduced interleukin-6 (ES=-0.619, 95% CI=-0.054 to -1.184, p=0.03) and tumor necrosis factor alpha (ES=-0.741, 95% CI=-0.459 to -1.023, p=0.001).

**Conclusions:** The results of the meta-analysis indicate that the combination of ginger supplementation and exercise has significant anti-inflammatory effects through the reduction of interleukin-6 and tumor necrosis factor alpha, although no significant effect was shown on C-reactive protein.

**Key Words:** Ginger supplementation, exercise, C-reactive protein, interleukin-6, tumor necrosis factor alpha.

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## 1. Introduction

Inflammation is a vital and complex physiological response to harmful stimuli, such as infection, tissue injury, or chemical stressors—that is essential for maintaining homeostasis and facilitating the body's repair processes (1). However, when this inflammatory response shifts from an acute, controlled state to a chronic condition, it plays a key pathophysiological role in the onset and progression of a wide range of non-communicable diseases, such as cardiovascular diseases, metabolic syndrome, type 2 diabetes, non-alcoholic fatty liver disease (NAFLD), and certain cancers (2). This chronic inflammatory state is characterized by persistently elevated serum levels of pro-inflammatory biomarkers, particularly C-reactive protein, tumor necrosis factor-alpha, and interleukin-6 (3). C-reactive protein—an acute-phase protein synthesized primarily in the liver in response to interleukin-6 signaling—serves as a sensitive and reliable marker of systemic inflammation (4). Tumor necrosis factor-alpha is also a pivotal pro-inflammatory cytokine secreted by immune cells, such as macrophages, that initiates and amplifies the inflammatory cascade (5). Given the fundamental role of chronic inflammation in the pathogenesis of various diseases, identifying and developing effective, safe, and accessible strategies to modulate inflammatory responses has become a key priority in the field of health. In this context, regular physical activity is recognized as one of the most powerful non-pharmacological interventions for reducing chronic inflammation and preventing associated diseases (6). Numerous epidemiological and clinical studies have shown that physically active individuals have lower baseline levels of inflammatory factors compared to sedentary individuals (7,8). Several mechanisms have been proposed for the anti-inflammatory effects of regular exercise, including: a reduction in visceral fat mass—itself a major source of pro-inflammatory cytokines, increased secretion of anti-inflammatory myokines (such as interleukin-6 from contracting muscle, which paradoxically exerts systemic anti-inflammatory effects); increased production of anti-inflammatory cytokines like interleukin-10; and the inhibition of pro-inflammatory signaling pathways such as nuclear factor-kappa B (NF-κB) (9,10). However, the inflammatory response to exercise is a double-edged sword. While regular physical activity exerts anti-inflammatory effects, acute, intense, or unaccustomed exercise acts as a physiological stimulus that leads to microscopic damage in skeletal muscles. This damage triggers an inflammatory response to facilitate tissue repair and regeneration, accompanied by a significant, transient increase in levels of C-reactive protein, tumor necrosis factor-alpha, and interleukin-6 (11).

Although this acute inflammatory response is essential for long-term training adaptations, excessive inflammation can lead to severe delayed-onset muscle soreness, functional impairment, and delayed recovery (12). This dual nature of the inflammatory response to exercise has heightened interest in identifying supportive strategies, particularly nutritional interventions to optimally modulate these responses.

In recent years, the use of medicinal plants and their bioactive compounds has gained increasing popularity due to their anti-inflammatory properties and fewer side effects compared to non-steroidal anti-inflammatory drugs (13). Ginger (Zingiber officinale Roscoe) is the rhizome of a flowering plant that has been used for centuries in traditional Asian medicine as a spice and herbal remedy to treat a wide range of ailments, including inflammatory disorders such as arthritis and muscle pain; its medicinal properties are primarily attributed to its phenolic and pungent compounds, particularly gingerols and shogaols (14–16). These bioactive compounds possess potent antioxidant, anti-cancer, and—notably—anti-inflammatory properties (17,18). The molecular mechanisms underlying the anti-inflammatory effects of ginger have been well studied and involve the inhibition of key enzymes in the inflammatory cascade, such as cyclooxygenase (COX) and 5-lipoxygenase (5-LOX), leading to reduced production of prostaglandins and leukotrienes (19). Furthermore, evidence indicates that ginger compounds can inhibit the NF-κB signaling pathway, thereby preventing the expression of genes encoding pro-inflammatory cytokines such as tumor necrosis factor-alpha and interleukin-6; these biochemical properties make ginger an attractive supplement for modulating systemic inflammation across various pathological and physiological conditions, including exercise-induced inflammation (20,21). Given the strong theoretical basis for the independent anti-inflammatory effects of regular physical activity and ginger supplementation, it is logical to hypothesize that combining these two interventions could yield synergistic or additive effects in controlling inflammation. Physical activity acts as a physiological stimulus for long-term anti-inflammatory adaptations, whereas ginger can facilitate and enhance this process by modulating the acute inflammatory response and reducing underlying inflammation.

However, the available evidence in this area, while growing, is highly fragmented, and the results are inconsistent. For instance, Zahsaz et al. (2014), in a study involving male endurance runners, found that six weeks of ginger supplementation combined with a training program led to a significant reduction in plasma levels of interleukin-6 and tumor necrosis factor-alpha compared to the placebo group (2). Similarly, Abbaspour et al. (2020) demonstrated that eight weeks of endurance training combined with the daily consumption of one gram of ginger had a significant interactive effect on reducing C-reactive protein and tumor necrosis factor-alpha levels in young women (8). Studies conducted on clinical populations—such as obese women with diabetes (12) —have also supported the beneficial effects of this combined intervention on reducing inflammatory markers. In contrast to these positive findings, the results of some other studies have been inconsistent. For example, Vahdatpour et al. (2016), in a study involving overweight girls, found that two weeks of ginger supplementation—despite inducing a downward trend—did not have a statistically significant effect on post-exercise C-reactive protein levels following exhaustive eccentric exercise (6). Similarly, although the study by Banitalebi et al. (2017) reported a significant reduction in tumor necrosis factor-alpha and interleukin-6 in the combined group, this reduction did not demonstrate a marked superiority compared to the exercise-only or supplement-only groups(12).

This wide variation in study designs and heterogeneous results underscores the importance of conducting systematic reviews and meta-analyses. Although meta-analyses have examined the isolated effects of ginger supplementation on inflammatory markers (13,22), to date, no systematic review or meta-analysis has specifically quantitatively evaluated the combined and interactive effects of exercise and ginger supplementation on key inflammatory markers (tumor necrosis factor-alpha, C-reactive protein, and interleukin-6) in humans. Bridging this knowledge gap is essential for providing evidence-based recommendations to athletes, coaches, and clinical populations seeking effective strategies for managing inflammation. Therefore, the primary objective of this study is to examine the effects of a combined intervention of exercise and ginger supplementation on levels of tumor necrosis factor-alpha, C-reactive protein, and interleukin-6 through a systematic review and comprehensive meta-analysis of randomized controlled trials.

## 2. Methods

The present study is a systematic review and meta-analysis conducted in accordance with the Cochrane and PRISMA guidelines.

### *2.1. Data Sources and Search Methodology*

To retrieve articles, an advanced search was conducted in the Scientific Information Database, Civilica, Magiran, ScienceDirect, Scopus, and PubMed databases—without time restrictions up to August 31, 2025—for English and Persian language studies involving human subjects, using the following keywords.
Ginger supplementation", "Exercise", "Interleukin-6", "C-reactive protein", "Tumor Necrosis Factor alpha" and "Inflammation".

### *2.2. Inclusion and exclusion criteria*

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For the present meta-analysis, articles meeting the following criteria were included: 1. randomized controlled trials in English and Persian; 2. studies conducted on human subjects; 3. studies examining the effects of exercise and ginger supplementation compared to a control group; 4. studies measuring interleukin-6, C-reactive protein, and tumor necrosis factor-alpha; 5. Availability of mean and standard deviation data for the aforementioned variables in both pre-test and post-test phases. 6. Publication of full-text articles in reputable journals and high article quality (PEDRO score > 4). Exclusion criteria for the present study included the following: 1. Studies conducted without a control group. 2. Studies conducted on animal subjects. 3. Conference papers and theses. 4. Review studies and meta-analyses. 5. Use of nutritional supplements other than ginger.

### *2.3. Assessment of Article Quality*

In the present study, the quality of the studies was assessed using the 9-item PEDro checklist. The assessment criteria include the following: 1. Eligibility. 2. Random allocation. 3. Allocation concealed. 4. Groups similar at baseline. 5. Assessors blinded. 6. Outcome measures assessed in 85% of participant. 7. Intention to treat analysis. 8. Statistical comparison between groups. 9. Measurement at steps and intervals. All questions in the aforementioned checklist were dichotomous (Yes: 1, No: 0). Scores ranged from a minimum of zero to a maximum of nine, with higher numerical values indicating higher research quality.

### *2.4. Data extraction*

Data from the identified articles were recorded on specialized data extraction forms. This information encompassed various elements, such as article details, the first author, year of publication, research design, participant characteristics, exercise characteristics, green tea supplement dosage, duration of supplementation, and the various variables examined in the studies (Table 1). In cases where insufficient data was available for a meta-analysis, the required data were obtained by contacting the corresponding author via email. In instances where the corresponding author failed to respond or provide the data, information was extracted from the articles' graphs using "Get Data" software, or the standard deviation (SD) was estimated from the standard error of the mean (SEM).

Table 1. Participants' characteristics and exercise protocols

| Number | Study, Year | Study design - Country | Gender, Characteristics of the subjects | Characteristics of the subjects | Variables | Age (year) | Duration of use (Day) | Daily dose | Type of Exercise Training |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Daryanush et al 2012 | RCT-Iran | Female | Non-athlete | IL-6 | 22.02±2.48 | acute | 2 g | Aerobic |
| 2 | Zehsaz et al 2014 | RCT-Iran | Male | Athlete | IL-6 TNF-α | 23.21±2.77 | 42 | 0.5 g | Aerobic |
| 3 | Rajabi Shahrabadi et al 2021 | RCT-Iran | Female | Athlete | CRP | 19-26 | 7 | 1 g | Aerobic |
| 4 | Kazemi et al 2020 | RCT-Iran | Male | Athlete | IL-6 | 22.8±0.62 | 7 | 1 g | Aerobic |
| 5 | Barzanjeh et al 2016 | RCT-Iran | Male | Athlete | TNF-α | 22±1.32 | 7 | 3 g | Resistance |
| 6 | Soleimani et al 2024 | RCT-Iran | Female | Obese | CRP | 24.89±3.7 | 28 | 2 g | Aerobic Eccentric-concentric |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 7 | Dabidi Roshan et al 2015 | RCT-Iran | Male | Athlete | CRP | 19±1.63 | 7 | 3 g | Resistance |
| 8 | Vahdat Poor et al 2016 | RCT-Iran | Female | Overweight | CRP | 28-32 | 14 | 2 g | Aerobic Eccentric |
| 9 | Atashak et al 2011 | RCT-Iran | Male | Obese | CRP | 18-30 | 70 | 1 g | Resistance |
| 10 | Abbaspour et al 2020 | RCT-Iran | Female | Non-Athlete | TNF-α CRP | 20-30 | 56 | 1 g | Aerobic |
| 11 | Hoseinzadeh et al 2015 | RCT-Iran | Female | Healthy | IL-6 | 21-24 | Acute | 2 g | Aerobic Eccentric |
| 12 | Barari et al 2016 | RCT-Iran | Female | Sedentary | TNF-α | 32±2 | 42 | 10 mg/kg | Aerobic |
| 13 | Atashak et al 2010 | RCT-Iran | Male | Obese | CRP | 18-32 | 70 | 1 g | Resistance |
| 14 | Salimi Safar et al 2024 | RCT-Iran | Female | Athlete | IL-6 | 19.75±2.03 | 65 | 2 g | High intensity interval |
| 15 | Rahimlou et al 2015 | RCT-Iran | Female | Fatty liver | TNF-α CRP | 45±2.14 | 84 | 2 g | Aerobic |
| 16 | Banitalebi et al 2017 | RCT-Iran | Female | Obese | TNF-α IL-6 | 45-60 | 70 | 1 g | Aerobic |

TNF-α: tumor necrosis factor alpha, IL-6: Interleukin-6, CRP: C-reactive protein

An initial search of scientific databases yielded 841 articles. Subsequently, 409 articles were excluded after a review of their titles and abstracts. Following a full-text review, another 93 articles were excluded due to factors such as the absence of the variables under study, inadequate analysis, the use of human subjects, the use of other supplements, and so forth; ultimately, 16 articles meeting the inclusion criteria were selected for the present study.

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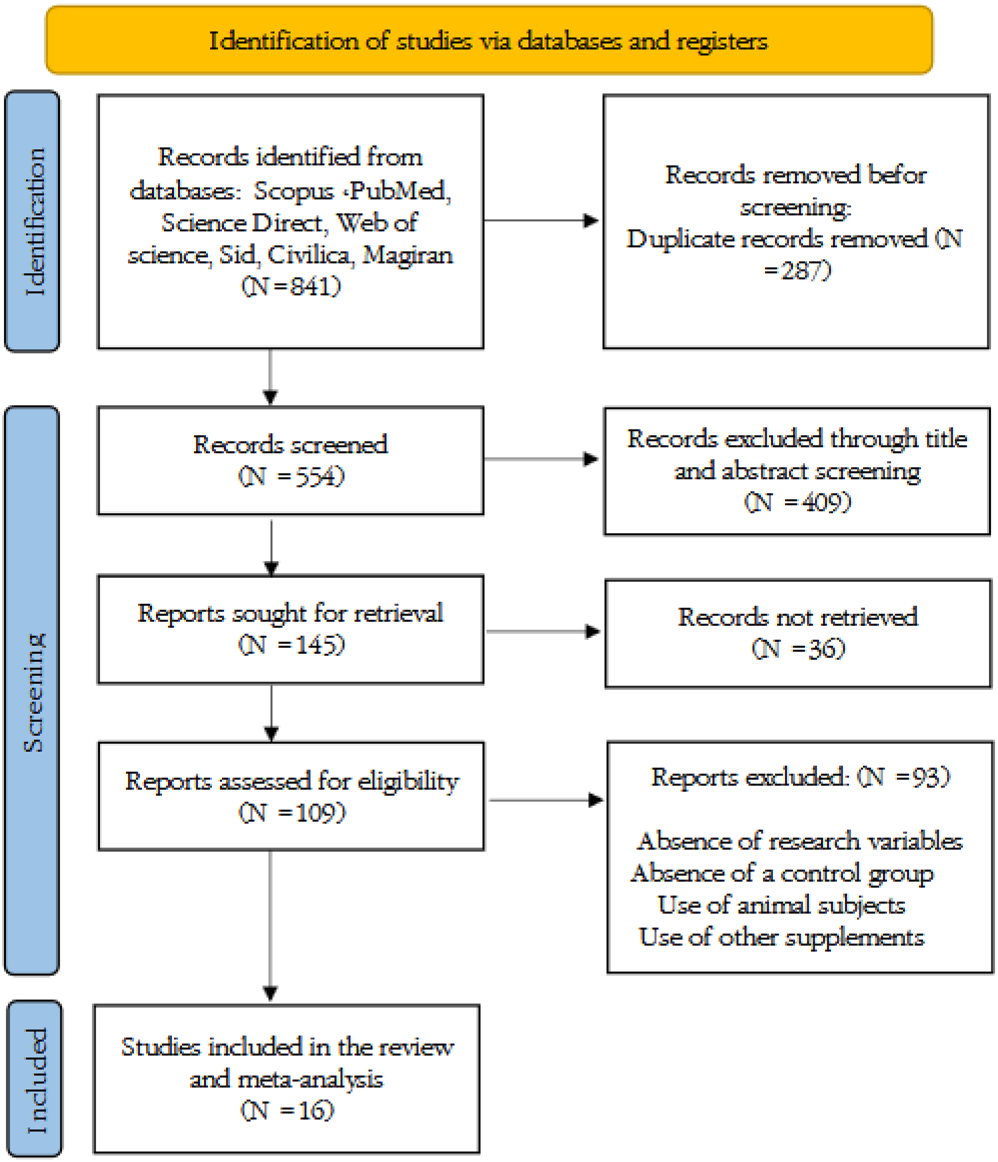



**Figure 1.** Flow chart of study selection according to PRISMA guidelines.

### *2.5. Statistical analysis*

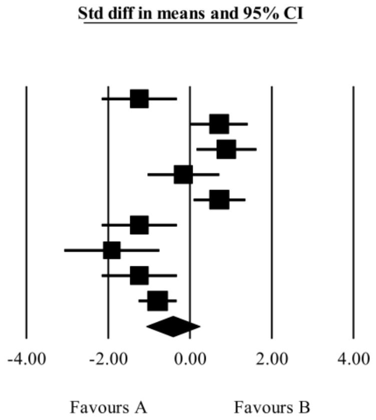
This systematic review and meta-analysis was conducted to examine the simultaneous effects of ginger supplementation and exercise on the inflammatory markers C-reactive protein, interleukin-6, and tumor necrosis factor-alpha in human studies. Statistical analysis of the data was performed using Comprehensive Meta-Analysis software (Version 2); mean, standard deviation, and sample size were used for the analysis. Additionally, the I-squared ($I^2$) index was used to assess study heterogeneity; based on the guidelines associated with Cochran's test, $I^2$ values are interpreted as follows: low heterogeneity (<25%), moderate heterogeneity (≤50%), and high heterogeneity (>75%). In the present meta-analysis, heterogeneity was defined by the criteria $I^2 > 50\%$ and $p < 0.05$; a random-effects model was employed in the presence of heterogeneity, whereas a fixed-effects model was used in its absence, with mean differences and 95% confidence intervals being considered. Furthermore, to quantitatively assess publication bias, funnel plots of effect size versus standard error were generated, and funnel plot asymmetry was evaluated using Egger's test. The trim-and-fill method was also utilized to account for publication bias.

## 3. Results

### 3.1. C-reactive protein:

To investigate the simultaneous effect of ginger supplementation and exercise on the inflammatory marker C-reactive protein (CRP), 9 studies were entered into CMA software and analyzed. The calculated $I^2$ value exceeded 50% ($I^2$ = 57.84%); therefore, a random-effects model was used for data analysis (P = 0.001). The results indicate no significant change in C-reactive protein (ES = -0.41; 95% CI: -1.06 to 0.23; p = 0.20) (Figure 1). No asymmetry was observed in the assessment of publication bias (Egger's regression p-value = 0.45) (Figure 2). Furthermore, an analysis of individual studies revealed a significant increase in 3 studies, a significant decrease in 5 studies, and no significant change in 1 study (p > 0.05).

| Study name | Std diff in means | Standard error | Variance | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|---|---|
| Rajabi Shahrabadi et al 2021 | -1.237 | 0.470 | 0.221 | -2.158 | -0.317 | -2.634 | 0.008 |
| Soleimani et al 2024C | 0.715 | 0.354 | 0.126 | 0.021 | 1.410 | 2.019 | 0.044 |
| Soleimani et al 2024E | 0.892 | 0.374 | 0.140 | 0.159 | 1.625 | 2.386 | 0.017 |
| Dabidi Roshan et al 2015 | -0.161 | 0.448 | 0.201 | -1.038 | 0.717 | -0.358 | 0.720 |
| Vahdatpoor et al 2016 | 0.719 | 0.324 | 0.105 | 0.084 | 1.354 | 2.220 | 0.026 |
| Atashak et al 2011 | -1.237 | 0.470 | 0.221 | -2.158 | -0.317 | -2.634 | 0.008 |
| Abbaspour et al 2020 | -1.912 | 0.595 | 0.353 | -3.077 | -0.747 | -3.216 | 0.001 |
| Atashak et al 2010 | -1.237 | 0.470 | 0.221 | -2.158 | -0.317 | -2.634 | 0.008 |
| Rahimlou et al 2015 | -0.791 | 0.239 | 0.057 | -1.259 | -0.322 | -3.310 | 0.001 |
| | -0.419 | 0.331 | 0.110 | -1.069 | 0.230 | -1.265 | 0.206 |




Meta Analysis

Figure 1. Forest plot. The simultaneous effect of ginger supplementation and exercise on the inflammatory factor C-reactive protein.

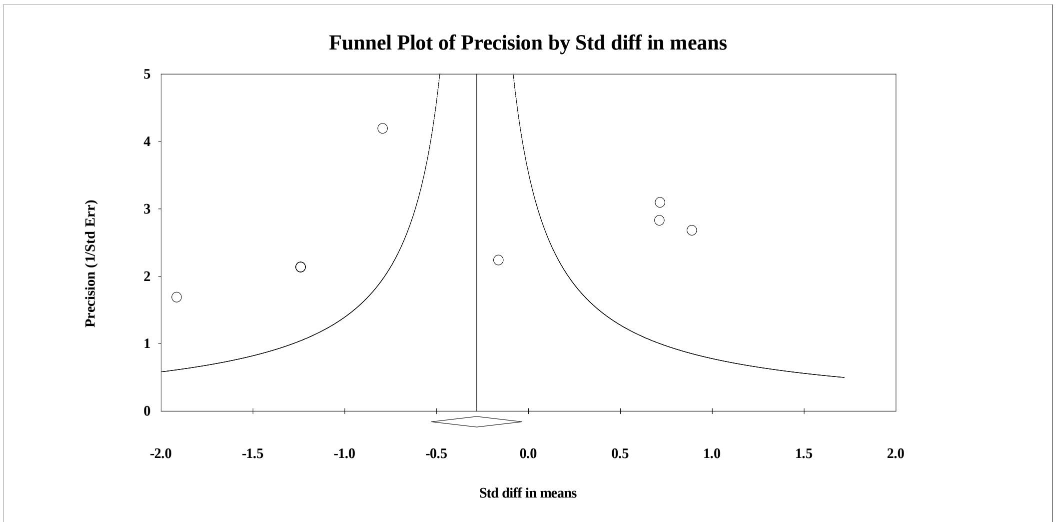



Figure 2 - Funnel plot. The simultaneous effect of ginger supplementation and exercise on the inflammatory factor C-reactive protein

## 3.2. Interleukin-6:

To examine the simultaneous effect of ginger supplementation and exercise on the inflammatory marker Interleukin-6, 6 studies were entered into CMA software and analyzed. The calculated $I^2$ value exceeded 50% ($I^2$ = 77.62); therefore, a random-effects model was used for data analysis (P = 0.001). The results indicate a significant reduction in Interleukin-6 (ES = -0.619; 95% CI: -1.184 to -0.054; p = 0.03) (Figure 3). An assessment for publication bias revealed asymmetry (Egger's regression p-value = 0.01) (Figure 4). Following the application of the trim-and-fill method, 1 study was added to the right side of the funnel plot (Figure 4), and the adjusted effect size shifted from -0.619 (Figure 3) to -0.442 (95% CI: -1.101 to -0.126). Furthermore, an examination of the individual studies revealed that the results of 3 studies showed a significant decrease, while 3 others showed no significant change (p > 0.05).

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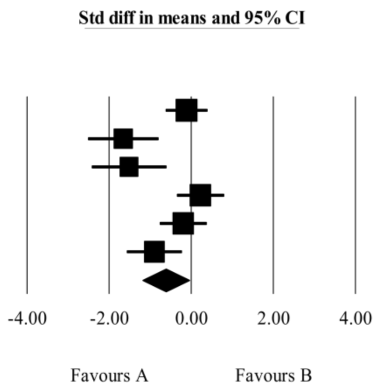
| Study name | Std diff in means | Standard error | Variance | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|---|---|
| Daryaniish et al 2012 | -0.112 | 0.259 | 0.067 | -0.620 | 0.395 | -0.434 | 0.664 |
| Zehsaz et al 2014 | -1.654 | 0.438 | 0.192 | -2.512 | -0.796 | -3.778 | 0.000 |
| Kazemi et al 2020 | -1.512 | 0.463 | 0.214 | -2.419 | -0.605 | -3.266 | 0.001 |
| Hoseinzadeh et al 2015 | 0.226 | 0.292 | 0.085 | -0.347 | 0.799 | 0.773 | 0.439 |
| Salimi Saffar et al 2024 | -0.192 | 0.291 | 0.085 | -0.763 | 0.379 | -0.659 | 0.510 |
| Banitalebi et al 2017 | -0.897 | 0.342 | 0.117 | -1.566 | -0.227 | -2.623 | 0.009 |
| | -0.619 | 0.288 | 0.083 | -1.184 | -0.054 | -2.147 | 0.032 |




Meta Analysis

Figure 3. Forest plot. Combined effect of ginger supplementation and exercise on the inflammatory marker Interleukin-6.

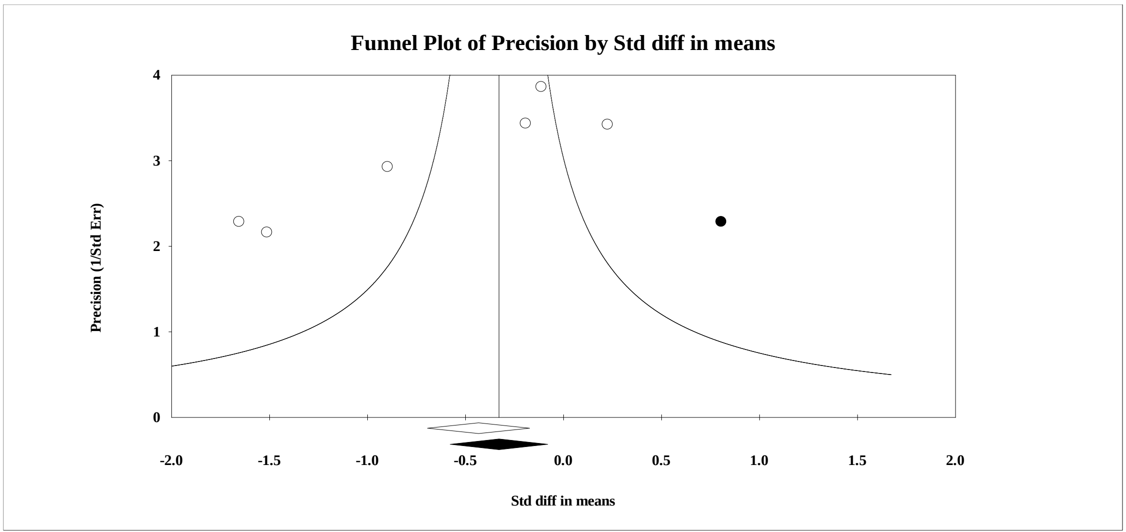
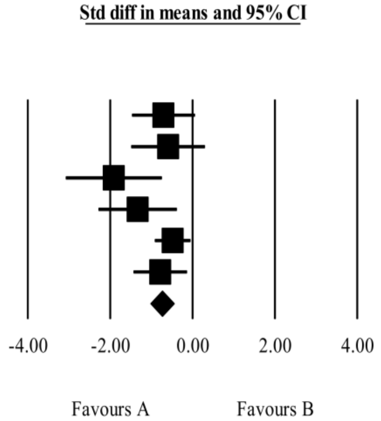



Figure 4. Funnel plot. Simultaneous effect of ginger supplementation and exercise on the inflammatory factor interleukin-6.

### 3.3. Tumor necrosis factor-alpha:

Examining the simultaneous effects of ginger supplementation and exercise on tumor necrosis factor-alpha (TNF-α), 6 studies were entered into CMA software and analyzed. The calculated $I^2$ value was below 50% ($I^2 = 27.04$); therefore, a fixed-effect model was used for data analysis (p = 0.001). The results indicate a significant reduction in TNF-α (ES = -0.741; 95% CI: -1.023 to -0.459; p = 0.001) (Figure 5). An assessment for publication bias revealed asymmetry (Egger's regression P-value = 0.04; Figure 6). Following the application of the trim-and-fill method, the software added 2 studies to the right side of the funnel plot (Figure 6), and the adjusted effect size shifted from -0.740 (Figure 5) to -0.599 (95% CI: -0.335 to -0.862). Furthermore, an individual analysis of the studies indicated a significant reduction in 4 studies, while 2 studies showed no significant change (p > 0.05).

| Study name | Std diff in means | Standard error | Variance | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|---|---|
| Zehsaz et al 2014 | -0.708 | 0.390 | 0.152 | -1.471 | 0.056 | -1.816 | 0.069 |
| Barzanje et al 2016 | -0.593 | 0.457 | 0.209 | -1.488 | 0.303 | -1.297 | 0.195 |
| Abbaspour et al 2020 | -1.912 | 0.595 | 0.353 | -3.077 | -0.747 | -3.216 | 0.001 |
| Barari et al 2016 | -1.332 | 0.486 | 0.236 | -2.284 | -0.380 | -2.743 | 0.006 |
| Rahimlou et al 2015 | -0.484 | 0.220 | 0.049 | -0.916 | -0.052 | -2.195 | 0.028 |
| Banitalebi et al 2017 | -0.785 | 0.330 | 0.109 | -1.432 | -0.138 | -2.377 | 0.017 |
| | -0.741 | 0.144 | 0.021 | -1.023 | -0.459 | -5.144 | 0.000 |




Meta Analysis

**Figure 5.** Forest plot. Combined effect of ginger supplementation and exercise on tumor necrosis factor-alpha.

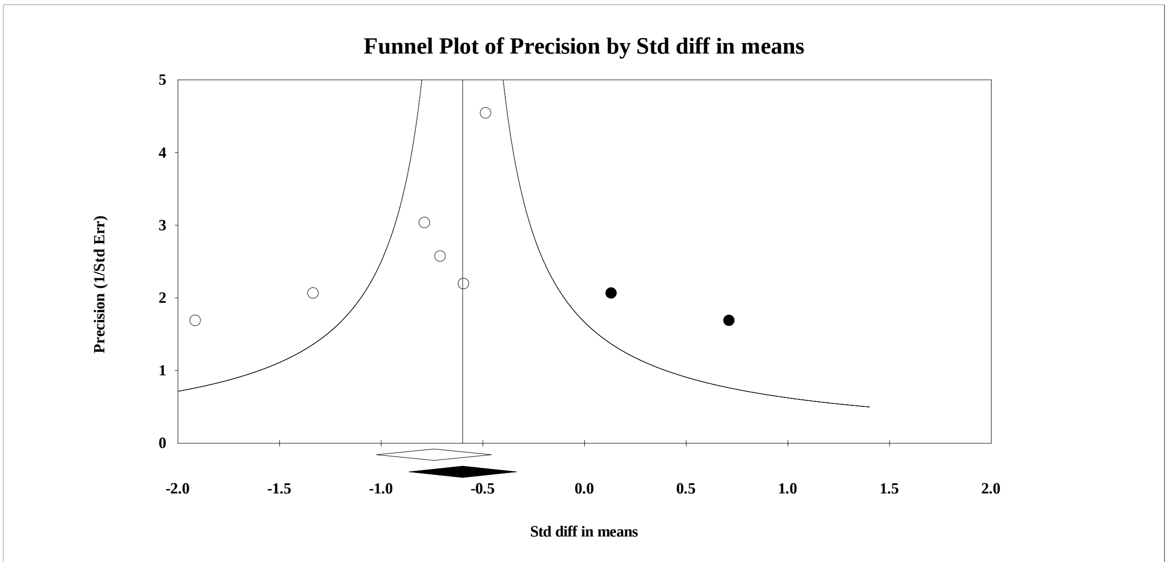



**Figure 6.** Funnel plot. Combined effect of ginger supplementation and exercise on tumor necrosis factor-alpha.

## 4. Discussion

This systematic review and meta-analysis, representing the first comprehensive synthesis of existing evidence, quantitatively evaluated the effect of a combined intervention of exercise and ginger supplementation on key markers of inflammation in humans. The key findings of this study paint a multifaceted and thought-provoking picture of this interaction: the combined intervention led to a significant reduction in the levels of key pro-inflammatory cytokines—specifically tumor necrosis factor-alpha and interleukin-6. In contrast, the intervention did not have a significant effect on C-reactive protein levels in the overall analysis. While filling a significant gap in the research literature, these results offer new insights into the specific molecular mechanisms by which this compound modulates systemic inflammatory responses and highlight the complexity of the interplay between physical activity and nutritional interventions. The findings indicate that the combined intervention of exercise and ginger supplementation specifically targets the cytokines that initiate the inflammatory cascade, whereas its effect on downstream acute-phase proteins—such as C-reactive protein—is more complex and dependent on multiple factors.

A significant reduction with a substantial effect size (ES = -0.741) in tumor necrosis factor-alpha levels—

a key initiator of the inflammatory cascade—stands out as the strongest and most distinct finding of this meta-analysis. This result aligns perfectly with a growing body of evidence demonstrating the potent anti-inflammatory properties of ginger (22).

The primary bioactive compounds in ginger exert inhibitory effects on pro-inflammatory signaling pathways. These compounds can act as key regulators of tumor necrosis factor-alpha (TNF-α) gene expression, thereby inhibiting the production and secretion of this cytokine (1,27).

Furthermore, regular, long-term physical exercise independently exerts anti-inflammatory effects and enhances the secretion of anti-inflammatory myokines from contracting muscles (25).

The results of the present meta-analysis indicate that combining these two interventions produces a synergistic effect in suppressing tumor necrosis factor-alpha (ES = -0.741). This finding aligns with the results of several clinical trials included in the analysis, such as the study by Zehsaz et al. (2014), which reported a significant reduction in tumor necrosis factor-alpha among endurance runners following six weeks of training combined with ginger supplementation (2), the study by Banitalebi et al. (2017), which observed a similar reduction in obese women with type 2 diabetes (12); and the study by Abbaspour et al. (2020), which confirmed a significant interactive effect in reducing tumor necrosis factor-alpha in young women after eight weeks of endurance training and ginger consumption (8). This reduction in tumor necrosis factor-alpha is of significant clinical importance, as elevated levels of this cytokine are associated with the pathogenesis of numerous conditions, including insulin resistance, atherosclerosis, non-alcoholic fatty liver disease, and cardiovascular diseases (6,26). By synthesizing this evidence, the present study provides a robust statistical overview demonstrating that this combined strategy can effectively contribute to reducing the chronic low-grade inflammation that underlies many metabolic diseases.

A significant reduction in interleukin-6 levels (ES = -0.619) is another key finding of this study, adding to our understanding of the modulatory effects of this intervention.

Interleukin-6 is a cytokine with a dual role: it acts as a pro-inflammatory molecule in response to tissue injury and infection, yet it is secreted as a myokine in response to muscle contraction, exerting metabolic and even systemic anti-inflammatory effects (24,28). In conditions of low-grade chronic inflammation, such as those observed in obesity and diabetes; basal levels of interleukin-6 primarily play a pro-inflammatory role (12). Ginger has been shown to reduce interleukin-6 production through mechanisms similar to the inhibition of tumor necrosis factor-alpha—specifically, by suppressing the NF-κB pathway (29). Our results align with the findings of Kazemi et al. (2020), who reported a reduction in interleukin-6 following exhaustive exercise in male athletes who had consumed ginger for one week (23), as well as with the study by Hosseinzadeh et al. (2015), who observed similar reductions in healthy women following eccentric exercise (9). These findings indicate that ginger supplementation, particularly when combined with exercise, can modulate the pro-inflammatory aspects of the interleukin-6 response. This may be beneficial both for reducing chronic systemic inflammation and for modulating the inflammatory response during strenuous exercise associated with excessive increases in interleukin-6 (1,9). However, a meta-analysis focusing solely on the effect of ginger did not show a significant impact on interleukin-6 (13); this suggests that ginger's anti-inflammatory effect on this specific cytokine becomes more pronounced and tangible in the presence of a physiological stimulus, such as physical exercise.

Perhaps the most complex, challenging, and—from an interpretive standpoint—interesting finding of this meta-analysis is the absence of a significant change in C-reactive protein levels (ES = -0.41, p = 0.20). At first glance, this result appears highly counterintuitive, given that C-reactive protein is a classic acute-phase protein whose hepatic production is directly and potently stimulated by pro-inflammatory cytokines, particularly interleukin-6 (12,30). Given the significant and substantial reduction in interleukin-6 and tumor necrosis factor-alpha observed in our meta-analysis, it was reasonable to expect that C-reactive protein levels—as a downstream marker—would decrease in a similar manner. However, several key overlapping factors can fully explain this finding, demonstrating that the result, rather than indicating an "absence of effect; reflects the biological complexities and methodological limitations inherent in early studies. The first and most significant biological factor is the differing response kinetics of these markers.

The C-reactive protein response to inflammatory stimuli occurs with a significant delay compared to cytokines. While interleukin-6 and tumor necrosis factor-alpha can reach peak plasma concentrations within a few hours of a stimulus, there may not be sufficient time for the decline in upstream cytokines to be reflected at the level of hepatic C-reactive protein synthesis and secretion (3). The second key factor is likely the very high statistical heterogeneity among the studies that measured C-reactive protein. As indicated by the high $I^2$ statistic for C-reactive protein, the intervention effect varied considerably across studies, ranging from a significant increase to a significant decrease. The studies included in this meta-analysis were diverse in the study populations. In the study by Atashak et al. (2011), a significant reduction in C-reactive protein was observed in obese men following 10 weeks of resistance training and ginger consumption (25 ), whereas in the study by Vahdatpour et al. (2016) involving overweight girls, this effect was not significant after two weeks (6). Furthermore, the type of physical activity, as well as the dosage and duration of ginger supplementation during the intervention, varied—ranging from 0.5 g (2) to 3 g per day (5). It appears that longer-term interventions hold greater potential for influencing C-reactive protein (25,26). The third factor is likely related to the complexity of the biological regulation of C-reactive protein. Although interleukin-6 is the primary driver of C-reactive protein production, it is not the sole stimulus, and other cytokines also play a role in its regulation. Consequently, in certain situations, the observed reduction in interleukin-6 may be insufficient to cross the threshold required to produce a significant and measurable change in C-reactive protein levels. Therefore, the lack of statistical significance for C-reactive protein in this meta-analysis does not necessarily imply the absence of a biological effect; rather, it reflects limitations stemming from the response kinetics of this marker, the high heterogeneity among the primary studies, and the inherent complexities of its regulation.

## 5. Conclusion

Overall, the findings of this systematic review and meta-analysis provide, for the first time, integrated quantitative evidence demonstrating that the combination of exercise and ginger supplementation is an effective method for reducing key pro-inflammatory cytokines—such as interleukin-6 and tumor necrosis factor-alpha—in humans. Although the overall effect of this intervention on C-reactive protein was not statistically significant—due to the complexities of response kinetics and the high heterogeneity of the included studies—the robust reduction in upstream cytokines highlights the significant potential of this combined strategy to modulate inflammatory pathways. These results support the use of ginger as a natural, safe, and accessible supplement alongside physical activity to manage low-grade chronic inflammation and promote health.

## 6. Highlights

The findings of the present systematic review and meta-analysis demonstrated that ginger supplementation is an effective method for reducing the inflammatory markers interleukin-6 and tumor necrosis factor-alpha during physical activity.

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### Conflicts of Interest

This article has no conflict of interest

### Authors' Contributions

The authors contributed equally to the conceptualization and writing of the article. All authors approved the content of the article and reached a consensus on all aspects of the work.

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