

## Original Article



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# The Effect of Garlic (*Allium sativum* L) Supplementation on Circulating Adiponectin: a Systematic Review and Meta-Analysis of Randomized Controlled Trials

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## ABSTRACT

Our aim was to conduct a systematic review and meta-analysis on randomized controlled trials (RCTs) evaluating the effect of garlic on serum adiponectin levels. We searched Scopus, Web of Science, PubMed, and Cochrane Library to databases up to January 2021. RCTs investigating the effects of garlic on serum adiponectin levels in adult participants were included. The change in serum adiponectin levels was estimated using weighted mean differences (WMD) and standard deviations (SD). The random effects model was used to provide a summary of mean estimates and their SDs. Out of 386 records, 6 trials with 8 arms treatment which enrolled 266 subjects were included. Garlic supplementation resulted in a non-significant increase in adiponectin concentrations when compared to placebo, according to the pooled data (WMD, 0.27 Hedges' g; 95% confidence interval [CI], -0.07, 0.62;  $p = 0.124$ ). Greater effects on adiponectin were observed in trials with supplementation dose less than 1.5 gram per day (WMD, 0.71 Hedges' g; 95% CI, -0.01, 1.43;  $p = 0.600$ ) and in trials with female subset (WMD, 0.62 Hedges' g; 95% CI, -0.96, 2.21;  $p = 0.441$ ). Garlic boosts adiponectin levels in general. However, due to different target population, various units for reporting adiponectin level and few eligible studies in final analysis, more research is needed to get a firm conclusion about the influence of garlic on adiponectin levels.

**Keywords:** Garlic; Adiponectin; Adipose tissue; Meta-analysis

## INTRODUCTION

Garlic (*Allium sativum* L), a member of the Alliaceae family, is one of the functional foods that is widely used as a herbal medicine to treat a variety of illnesses [1,2]. It contains a number of chemicals, including allicin, a sulfurcontaining substance with anticoagulant, antithrombotic, antioxidant, hypoglycemic, hypocholesterolemic, and hypotensive properties

### Conflict of Interest

The authors declare that they have no competing interests.

[3-6]. Furthermore, researchers have shown that garlic has antimicrobial, anti-carcinogenic, anti-mutagenic, anti-fungal, anti-asthmatic, immunomodulatory, and prebiotic effects [5,7]. Allicin and other sulfur-containing chemicals in garlic, including ajoene, S-allylcysteine (SAC), diallyl disulfide, S-methylcysteine, and sulfoxides, are responsible for the cardioprotective benefits [8,9]. On the other hand, garlic is a rich source of non-sulfur compounds such as polyphenols, as a powerful antioxidant, which may give beneficial effects for patients with metabolic and inflammatory disorders [10,11].

Adiponectin is an adipokine released by adipocytes that acts as a protective protein with anti-diabetic, anti-inflammatory, and anti-atherogenic properties. Many investigations have shown that the plasma concentration of adiponectin is much lower in obese adults, people with type 2 diabetes, people with metabolic syndrome (MetS), and those with cardiovascular illnesses [12,13]. Indeed, adiponectin improves glucose metabolism and insulin sensitivity while decreasing atherogenesis [14]. Adiponectin activates AMP-activated protein kinase, which leads to the transcription of peroxisome proliferator-activated receptor alpha, and thus plays a significant role in lipid metabolism [15]. The researchers have concentrated on increasing plasma adiponectin levels and, as a result, lowering the risk of chronic disease. Exercise, weight loss, and lifestyle changes, as well as the use of some herbal treatments and foods, are suggested to be further strategies to improve plasma adiponectin levels [16]. Several clinical trials have been conducted to examine the effect of garlic supplementation on circulating adiponectin levels in subjects with different conditions. Gómez-Arbeláez et al. [17] have demonstrated in a clinical trial that 12-week treatment with aged garlic extract (1.2 g/day) in people with MetS could enhance adiponectin levels. However, other research found that garlic had no significant influence on adiponectin levels [18-20]. The discrepancy among the studies for the effect of garlic supplementation on the adiponectin levels may be due to the differences of sample sizes, different types of garlic or garlic preparation method, and study subjects with different clinical conditions etc.

Therefore, to determine the effect of garlic supplementation on adiponectin levels in adults, we did a systematic review and meta-analysis.

## MATERIALS AND METHODS

### Search strategy

One of the authors (S. Sharifi) conducted the search using the preferred reporting item for systematic review criteria [21]. Four universal database including Scopus, PubMed, Cochrane Library, Web of Science, were searched up to January 2021, without any language or time restrictions. The search strategies included the following terms: (“Allicin” OR “allicine” OR “allitride” OR “garlicin” OR “garlic” OR “allium sativum” OR “organosulfur” OR “allixin” OR “alliin”) AND (“adipokines” OR “adiponectin” OR “adipocytokines”). To prevent missing other relevant research, we also examined the Iranian Registry of Clinical Trials ([www.irct.ir](http://www.irct.ir)), ClinicalTrials.gov, and the reference lists of included papers.

### Study selection

Before beginning the study selection procedure, the following inclusion criteria were determined: 1) garlic intervention in supplement form; 2) randomized controlled trials (RCT) with either parallel or crossover design; 3) The effect of garlic on plasma adiponectin levels was investigated; and 4) sufficient data on adiponectin levels in each group at baseline and at the end of the garlic intervention, or the net altered values. Exclusion criteria were:

1) uncontrolled trials; 2) observational studies with case-control, cross-sectional or cohort design, and 3) lack of sufficient information on baseline or follow-up adiponectin levels.

### Data extraction

Eligible studies were reviewed and the following data were abstracted: 1) first author's name; 2) year of publication; 3) country where the study was conducted; 4) study design; 5) target population; 6) age, sex, and body mass index of study participants; 7) number of participants in the garlic and control groups; 8) treatment duration; and 9) dose and type of garlic.

### Quality assessment

The Cochrane Collaboration's tool for assessing risk of bias was used to determine the risk of bias of the involved studies attaching either low, unclear or high risk of bias to the 6 domains (random sequence generation, allocation concealment, blindness of participants and personnel, blindness of outcome assessment, incomplete outcome data, and selective outcome report) to each study.

### Quantitative data synthesis

STATA 11 software was used for all examinations (Stata Corp, College Station, TX, USA). Effect size was conducted as: (measurement at the end of follow-up in the treatment group – measurement at baseline in the treatment group) – (measurement at the end of follow-up in the control group – measurement at baseline in the control group). Standard deviations (SDs) of the mean differences (MDs) were determined using the formula below:

$$SD^2 = [(SD \text{ baseline}^2 + SD \text{ final}^2) - (2 \times R \times SD \text{ baseline} \times SD \text{ final})]$$

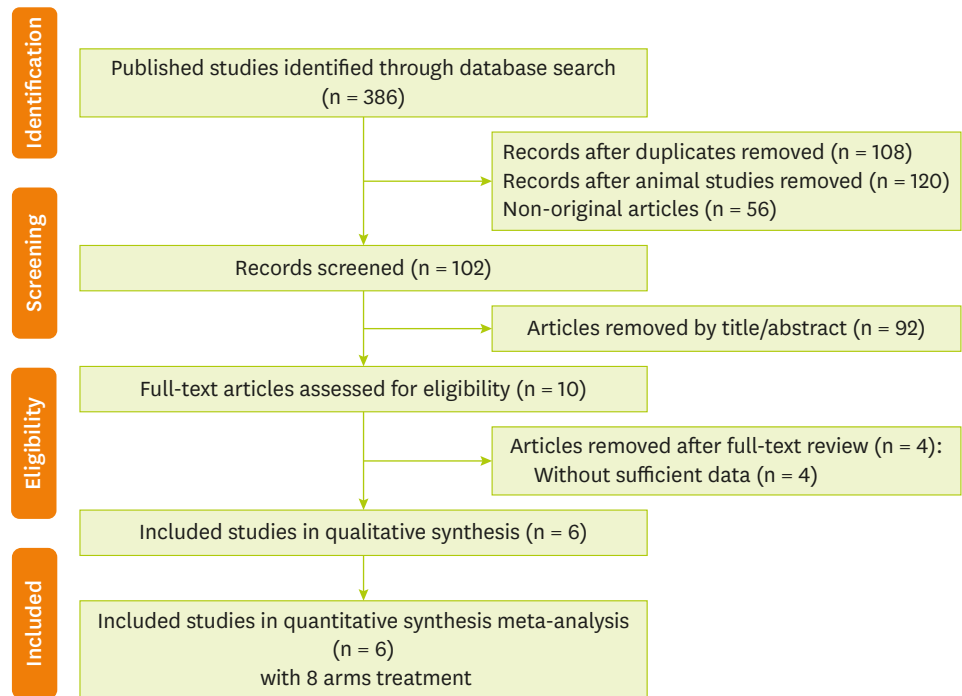
where correlation coefficient (R) was considered as 0.5 [22].

To confirm that our meta-analysis is not sensitive to the chosen correlation coefficient (R = 0.5), all plasma adiponectin studies were conducted using correlation coefficients ranging from 0.2 to 0.8. The MD and 95% confidence interval (CI) were calculated by combining the data. For each finding, STATA software-generated forest plots of the pooled MDs with 95% CIs were given. A random-effects model was used to pool the data, because of heterogeneity between the studies. Inter-study heterogeneity was assessed using  $I^2$  index. Subgroup analyses based on the following criteria were used to identify the sources of heterogeneity: duration of follow up (equal or above than 8 weeks and less than 8 weeks), intervention dosage (equal or above 1.5 g per day and less than 1.5 g per day), sex of participants (male/female/both of sex). Funnel plots, as well as Egger's regression and Begg's tests, were used to examine publication bias among the studies. The proportion of each study in the overall effect was assessed by sensitivity analysis. A p value < 0.05 was accepted as statistically significant, unless otherwise specified.

## RESULTS

### Flow and characteristics of included studies

From 386 possibly relevant citations identified in our systematic searches, 284 records were reviewed (after deleting duplicates (n = 108), animal studies (n = 120) and non-original article (n = 56) and 92 articles were removed after title and abstract were checked, then 10 The full-text papers were evaluated for eligibility. Next, 4 articles were excluded because those reports did not provide sufficient data for outcomes Finally, 6 trials with 8 arms treatment were included in this meta-analysis [18-20,23-25]. **Figure 1** depicts the flow chart for study selection.



**Figure 1.** Preferred reporting items for systematic reviews and meta-analyses flow diagram of study selection process.

Selected studies included 266 subjects in intervention (133 receiving garlic treatment) or control groups (133 participants receiving placebo treatment). These articles were published between 2009 and 2017, which among them, and 3 of them were conducted in Iran [18,20,24] and 3 other trials conducted in Columbia [23], USA [19] and South Korea [25] respectively. The design of 4 trials were parallel [18,19,24,25] and one study was cross over [23] and one study with 2 arms treatment was double-blind trial quasi-experimental design [20]. Two records examined the effect of garlic in both sex [19,23] other records conducted in male [18,24,25] and female [20]. These studies included people that were overweight or obese [19,20,25] and those with MetS and inactive participants [18,23,24]. The participants' mean age ranged from 18 to 49 years old. Garlic supplementation dosage ranged from 250 to 5,000 mg/day. The duration of intervention was between 5 and 16 weeks in different studies. **Table 1** summarizes the overall features of the included research.

**Table 1.** Characteristics of eligible studies

Study	RCT design (blinding)	Target population	Sex	Mean Age (yr)	Mean BMI (kg/m <sup>2</sup> )	Sample size (garlic/placebo)	Duration (wk)	Dose of garlic (g/day)	Type of garlic
Gómez-Arbeláez et al. [17]	Cross over	Metabolic syndrome	Both	41	33.07	86 (43/43)	12	1.2	Extract
Xu et al. [19]	Parallel (double)	Obesity	Both	46	36.1	48 (24/24)	6	3.6	Extract
Sharifi et al. [18]	Parallel (double)	Metabolic syndrome	Male	49	29.6	40 (20/20)	6	1.8	Tablet
Jahantigh et al. [24]	Parallel (double)	Inactive subjects	Male	20	ND	26 (13/13)	8	0.25	Tablet
Jahantigh et al. [24]	Parallel (double)	Inactive subjects	Male	20	ND	20 (10/10)	8	0.25	Tablet
Hamidnezhad et al. [20]	DBTQE	Overweight subjects	Female	21	27.2	16 (8/8)	5	1	Capsule
Hamidnezhad et al. [20]	DBTQE	Overweight subjects	Female	21	27.4	16 (8/8)	5	1	Capsule
Sung et al. [25]	Parallel (double)	Obesity	Male	18	ND	14 (7/7)	16	5	Pill

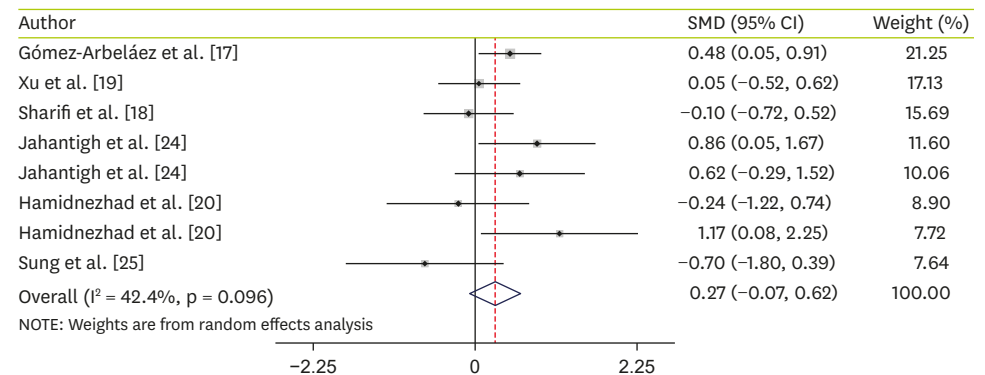
RCT, randomized controlled trial; BMI, body mass index; DBTQE, double-blind trial quasi-experimental design; ND, non-defended.

### The effect of garlic supplementation on plasma adiponectin levels

**Figure 2** depicts the individual trial results as well as the pooled estimate of the effect of garlic supplementation on adiponectin. Combining 8 effect sizes from 6 studies based on the random effects model, we observed that garlic supplementation shows a non-significant increase in adiponectin (WMD, 0.27 Hedges' g; 95% CI, -0.07, 0.62;  $p = 0.124$ ) compared to the control group. However, the heterogeneity among the studies was moderate ( $I^2 = 42.4\%$ ,  $p = 0.096$ ). Subgroup analyses were performed to determine the sources of the between-study heterogeneity (**Table 2**). Duration of intervention and sex did not explain this heterogeneity. The dosage of garlic supplements, on the other hand, could explain the heterogeneity ( $p = 0.486$ ). In this paper, we showed that the effect of garlic supplementation on circulating adiponectin was not statistically significant in the trials among female subset (WMD, 0.62 Hedges' g; 95% CI, -0.96, 2.21;  $p = 0.441$ ) and trials with supplementation dose less than 1.5 g per day (WMD, 0.71 Hedges' g; 95% CI, -0.01, 1.43;  $p = 0.600$ ). The removal of each trial had no significant effect on the pooled effect of garlic on adiponectin concentrations, according to sensitivity analysis. The funnel plot was visually symmetrical (**Figure 3**) and the result of Egger's test did not demonstrate any evidence of publication bias Begg's test ( $p = 0.621$ ) and Egger's test ( $p = 0.678$ ).

### Risk of bias assessment

All of the trials [17-20,24,25] provided sufficient information on the random sequence generation and allocation concealment methodologies. With the exception of two studies [24,25], all RCTs demonstrated a low risk of bias in terms of participant and personnel



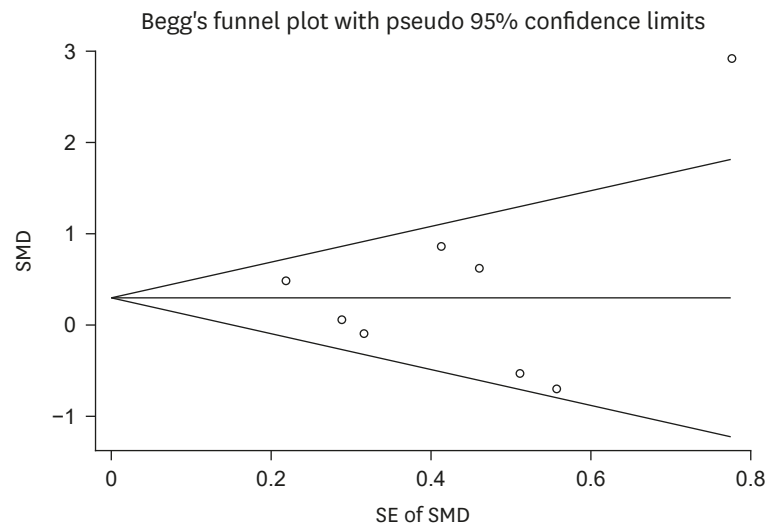
**Figure 2.** Forest plot of the effect of garlic supplementation on circulating adiponectin. SMD, standardized mean difference; CI, confidence interval.

**Table 2.** Result of subgroup analysis of included studies in meta-analysis

Sub-grouped by	No. of trials	Effect size*	95% CI	$I^2$ (%)	p for heterogeneity	p for between subgroup heterogeneity
<b>Adiponectin</b>						
<b>Duration (wk)</b>						
≥ 8	4	0.41	-0.10, 0.92	44.6	0.144	0.152
< 8	4	0.37	-0.56, 1.30	80.2	0.002	
<b>Dose (gr/day)</b>						
≥ 1.5	3	-0.10	-0.49, 0.29	0.0	0.486	0.010
< 1.5	5	0.71	-0.01, 1.43	72.4	0.006	
<b>Sex</b>						
Male	3	0.32	-0.56, 1.20	62.7	0.068	0.703
Female	3	0.62	-0.96, 2.21	86.8	0.001	
Both	2	0.31	-0.11, 0.72	29.8	0.233	

CI, confidence interval.

\*Calculated by random-effects model.



**Figure 3.** Funnel plot of studies evaluate on circulating adiponectin. SMD, standardized mean difference; SE, standard error.

blinding. Furthermore, with the exception of two trials, the number of drop-outs and reasons for withdrawal were well-documented [24,25]. No study reported any public, commercial or industry-funded support. **Table 3** outlines the author judgment's risk in each item of bias among included RCTs.

## DISCUSSION

To the best of the researchers' knowledge, this is the first quantitative review of RCTs investigating the efficacy of garlic supplementation on circulating adiponectin levels. Generally, pooled results revealed that garlic consumption could increase the circulating levels of adiponectin, whereas the change was not statistically significant. In addition, the results of the subgroup analysis showed that adiponectin change in female participants was greater than in male/both subjects after garlic therapy. Interestingly, we observed that garlic supplementation with a daily dose of < 1.5 g had a more beneficial effect on adiponectin levels. In other words, effect of garlic was attenuated in high dose ( $\geq 1.5$  g/day), which even led to a decrease in adiponectin concentration. In addition, results of subgroup analysis showed that dose of garlic supplementation was a source of heterogeneity in this study.

Adipocytokines or adipokines are general term for bioactive proteins synthesized and released from adipose tissue that are potentially involved in systemic metabolic regulation, inflammatory responses and physiologic processes [26]. Adiponectin is known as

**Table 3.** Cochrane risk of bias assessment

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Gómez-Arbeláez et al. [17]	L	L	L	L	L	L	L
Xu et al. [19]	L	U	L	U	L	L	U
Sharifi et al. [18]	U	L	L	U	L	L	U
Jahantigh et al. [24]	L	U	H	H	H	L	U
Hamidnezhad et al. [20]	U	L	U	L	L	L	U
Sung et al. [25]	L	L	H	U	H	L	U

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



anti-inflammatory and insulin-sensitive adipocytokine that circulates at high plasma concentrations ranging from 5 to 30 mg/mL [27]. Since adiponectin plays a protective role against obesity-linked metabolic dysfunction, its decreased level is associated with insulin resistance, glucose intolerance, dyslipidemia, hypertension, and cardiovascular disease [28-30]. Indeed, high levels of adiponectin have beneficial effects on metabolic alterations associated with obesity including glucose regulation and fatty acid oxidation [31]. In this way, it may help improve the complications of cardiovascular disease [28]. Garlic has been utilized as an anti-inflammatory biomarker and a preventative agent for cardiovascular disease. The main constituents of garlic are organosulfur compounds and flavonoids which have antioxidant and anti-inflammatory properties including allicin, methyl-allyl trisulfide and SAC, and diallyl disulfide, and sulfoxides [32,33]. Previous meta-analyses reported that garlic supplementation can reduce inflammation [34,35]. Garlic consumption reduces C-reactive protein (CRP) levels by controlling interleukin-10, which suppressed the production of pro-inflammatory cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) [36]. CRP known as an atherogenic risk factors for coronary artery disease is produced in response to pro-inflammatory cytokines, especially TNF- $\alpha$  [37]. Recent meta-analysis revealed that garlic supplements is linked to decreased systolic and diastolic blood pressure in hypertensive individuals. Garlic also has modulated cholesterol concentrations and enhanced the immune system [38]. Furthermore, garlic extract can protect against oxidative damage which is attributable to its antioxidant capacity [39]. The activity of nuclear factor-kappa B (NF- $\kappa$ B) can be activated by the expression of inflammatory genes and leading to inflammation and insulin resistance [40,41]. It seems that the SAC content of garlic may be responsible for inhibiting NF- $\kappa$ B activation [42] and may inhibit adipogenesis [43].

Accordingly, garlic administration may enhance cardiometabolic health by reducing inflammation and pro-inflammatory cytokine production and also possibly increasing adiponectin levels. Clinical study evidence suggests that garlic can increase adiponectin expression [23,24,39,44]. Gómez-Arbeláez et al. [23] observed a significant increase in adiponectin levels after 12 weeks of treatment with aged garlic extract in patient with MetS. Besides, Jahantigh et al. [24] stated that consumption of 0.25 g/day garlic among the inactive boys for 8 weeks increased adiponectin concentrations. This study also emphasized that garlic consumption combined with exercise had a greater effect. The exact mechanisms of the favorable effect of garlic on adiponectin were not elucidated yet. However, it may be attributed to elevated bioavailability of nitric oxide by garlic that positively affect adiponectin release [45]. Moreover, garlic purportedly contains a variety of water-soluble organosulfur compounds including SAC and S-allyl-mercaptocysteine which act as cellular donors of thiol containing reducing equivalents [45]. It could explain garlic's positive cardioprotective impact. An animal study done by Abou Zaid et al. [44] showed a significant rise in serum nitric oxide, adiponectin, and endothelin-1 concentrations after supplementation with garlic extract in hyperlipidemia rats. In addition, a study conducted on rats has shown that methanol extract of black garlic could improve insulin resistance by upregulated adiponectin and lead to increased lipolysis and oxidation of fatty acids [43]. In contrast, other studies showed no changes or reduction of adiponectin levels after intake of garlic supplements [19,20,25]. Variation in the adiponectin responses to garlic consumption may be related to garlic dose, type of garlic preparation, disease state of participants, or initial adiponectin concentrations of participants.

However, we found that garlic consumption could not significantly increase serum concentrations of adiponectin. The possible reasons for this result may be due to

heterogeneity across studies. We conducted various subgroup analyses to identify the heterogeneity source. Subgroup analysis demonstrated that garlic supplementation dosage ( $\geq 1.5$  g/day) represented a potential source of between-study heterogeneity. The other reason for the divergence in the results may include the following: 1) different type of the garlic preparation; 2) studies used aged garlic extract [19,23] but other trials utilized garlic in the forms of capsule/tablet/pill [18,20,24,25]. Due to the small number of eligible studies, we could not run subgroup analysis based on various types of garlic. 2) dose of garlic supplements used. The present meta-analysis represented that a lower dose of garlic ( $< 1.5$  g/day) has a potential benefit on adiponectin concentration. 3) follow-up duration among studies, subgrouping the studies by duration (equivalent or above 8 weeks/ below 8 weeks) had no significant effect on our results.

It should be mentioned that according to previous study, no toxicity of garlic supplementation was detected. The Food and Drug Administration has categorized garlic as generally recognized as safe [46]. However, moderate symptoms such as headache, dizziness, bloating, esophageal and abdominal pain, and profuse sweating can be expected as nonspecific side effects [47].

Several limitations exist in the present meta-analysis that need to be acknowledged. First, there were few eligible studies that were not sufficient to identify definitive conclusions. Second, as adiponectin was reported in different units between studies, we performed Hedges' g to calculate the effect size. Third, included trials were conducted in various disease states of populations (i.e. patients with MetS, obesity, and inactive subjects). It should be noted that these inconsistencies of participants' condition could affect in the initial adiponectin concentration. Despite these limitations, there were some strengths in the study. Our study was the first meta-analysis to assess the effect of garlic on adiponectin levels. Besides, all the articles had a high quality on the Cochran checklist.

## CONCLUSION

In conclusion, the findings of this meta-analysis indicate that garlic had no significant effect on circulating adiponectin levels. It must be mentioned that, although the effect of garlic on adiponectin levels was not significant, garlic is one of the herbal remedies that can be recommended as a practical strategy to reducing inflammation. However, further studies with larger sample sizes and prolonged durations are required to obtain the potential beneficial effect of garlic on adiponectin concentration.

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