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REVIEW

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Effect of ginger (*Zingiber officinale*) supplementation on oxidative stress parameters: A systematic review and meta-analysis

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Abstract

A wide variety of antioxidant properties are attributed to ginger (*Zingiber officinale*) and several randomized controlled trials (RCTs) have investigated the effect of ginger intake on major oxidative stress (OS) parameters. We conducted a systematic review and meta-analysis to evaluate the effects of using ginger to improve OS levels. Medline, Scopus, ISI Web of Science, EMBASE, and the Cochrane Central Register of Controlled Trials were systematically searched up until March 2020 to gather RCTs that evaluated the impact of ginger intake on the levels and activity of OS parameters in adult subjects. Means and standard deviations for relevant OS variables were extracted and evaluated to assess the quality of the trials based on the Cochrane risk-of-bias tool for randomized trials. The gathered data were pooled and expressed as standardized mean difference (SMD) with 95% Confidence Intervals (95% CI). Twelve trials were included in this review. Ginger intake was shown to significantly increase glutathione peroxidase (GPx) activity (SMD: 1.64; 95% CI: 0.43, 2.85; I^2 = 86.8%) and total antioxidant capacity (TAC) (SMD: 0.40; 95% CI: 0.06, 0.73; I^2 = 42.8%) and significantly decrease malondialdehyde (MDA) levels (SMD: −0.69; 95% CI: −1.26, −0.12; I^2 = 85.8%) compared to control groups. Ginger supplementation also non-significantly associated with an increase in CAT activity (SMD: 1.09; 95% CI: −0.07, 2.25; I^2 = 87.6%). This systematic review and meta-analysis presents convincing evidence supporting the efficacy of ginger supplementation on improving OS levels.

Practical implications: In health sciences, OS, due to its pivotal role in the pathophysiology of several chronic diseases, is a subject with a long history. Recent research strives for a safe, ideal, and effective antioxidant. Ginger is herbal medicine, which has been widely used in traditional and complementary medicine. Proving the antioxidant effect and potential benefit of ginger has positive clinical implications for the application of this practical herb.

KEYWORDS

ginger, glutathione peroxidase, malondialdehyde, oxidative stress, total antioxidant capacity

Abbreviations: BMI, body mass index; CAT, catalase; CI, confidence intervals; F2α IsoP, PGF2α-isoprostanes; GPx, glutathione peroxidase; GSH, glutathione; MDA, malondialdehyde; NAFLD, non-alcoholic fatty liver disease; NO, nitric oxide; OS, oxidative stress; RA, rheumatoid arteritis; RCTs, randomized controlled trials; ROS, reactive oxygen species; *SD*, standard deviation; SE, standard error; SMD, standardized mean difference; SOD, superoxide dismutase; TAC, total antioxidant capacity; TBARS, thiobarbituric acid-reactive substances.

1 | INTRODUCTION

Ginger (*Zingiber officinale*) is a popular spice in the *Zingiberaceae* family that is consumed in traditional diets all over the world (Lin et al., 2016). Due to the multitude of health benefits attributed to ginger consumption, it is notably used in the treatment of diabetes(Arzati et al., 2017), osteoarthritis, rheumatoid arthritis (RA) (Funk et al., 2016), fatty liver (Zhu et al., 2018), migraine (Diaz et al., 2018), nausea during pregnancy and chemotherapy as it exerts antioxidant activity (Sharifzadeh et al., 2018).

Markers of OS, such as free radicals and reactive oxygen species (ROS), play a crucial role in the etiology of metabolic syndrome, cardiovascular disease, type 2 diabetes, and psychological disorders (Rahimlou et al., 2019; Wang et al., 2017). ROS inhibit antioxidant enzyme functions and cause cellular destruction (Maleki et al., 2019; Sánchez, 2017). Antioxidants are known to be a body defense mechanism to help with the purging of OS (Ray et al., 2012). OS conditions are diagnosed by measuring levels of MDA, SOD, GSH, GPx, CAT, and TAC (Ray et al., 2012).

Recent studies have indicated that ginger can be beneficial in improving OS parameters by suppressing the translocation of NF-κB (Saedisomeolia et al., 2019; Toma et al., 2018). However, inconsistent and conflicting results have also been reported. A systematic review and meta-analysis could shed light on this issue. The aim of this study is thus to evaluate the beneficial effects of ginger on OS parameters MDA, TAC, CAT, GSH, SOD, NO, GR, and GPx in published RCTs.

Highlights

- This systematic review and meta-analysis demonstrated that ginger supplementation to improve oxidative stress levels.
- This research was according to a comprehensive search strategy, and, therefore, the outcomes are expected to support strong evidence for clinical decision making.

2 | METHODS

This study was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009).

2.1 | Search strategy

We searched the following electronic databases: Medline, Cochrane CENTRAL, Scopus, Web of Sciences, and EMBASE up until March 2020. The following key search terms were used: ("Ginger" OR "*Zingiber officinale*") and ("Oxidative Stress OR Total Antioxidant Capacity OR antioxidant OR Oxidant OR reactive oxygen species OR Catalase OR Malondialdehyde OR Nitric oxide"). There was no language restriction. All key search terms and each database syntax is listed in Appendix S1.

2.2 | Study selection

Two independent reviewers (SF and MM) screened the databases listed. In the primary assessment, eligible studies were identified by title and abstract. After evaluating titles and abstracts, the full texts of the respective articles were reviewed. All RCTs which evaluated the impacts of ginger supplementation on OS parameters (TAC, MDA, GPx, GSH, SOD, CAT) were included. We defined the following as exclusion criteria: (a) animal or in vitro studies; (b) review, case reports, case control, and other observational studies; (c) articles that prescribe ginger in combination with other interventions; (d) articles with less than 1-week follow-up duration. Any discrepancies in the selection process of the studies were resolved by a third researcher (JH).

2.3 | Data extraction and quality assessment

The two researchers (SHH and ES) separately extracted data from each included paper using a predefined data extraction protocol. Discrepancies were resolved by discussion. The following information was extracted as the primary characteristics of the included articles: first author name, year of publication, study population characteristics [number, gender, age and body mass index (BMI)], ginger supplementation doses and duration, and main outcome of the relevant variables. To prevent carry-over bias (Elbourne et al., 2002) in trials with a cross-over design, only data from the first period were included in the cross-over studies. When interventions were performed over multiple periods, only the longest intervention period was considered. The Cochrane risk-of-bias tool was used to evaluate the methodological quality of the included articles (Shuster, 2011). The following aspects were evaluated: (a) selection bias (random sequence generation and allocation concealment), (b) performance bias (patients and participant blinding), (c) detection bias (assessor blinding), (d) attrition bias (incomplete outcome data) and (e) reporting bias (selective outcome reporting). The grade of bias was assigned using terms "low," "unclear," and "high." Discrepancies were resolved by discussion between the two researchers. If no agreement could be reached, the third researcher (JH) was consulted for a final decision.

2.4 | Statistical analysis

Statistical analyses were performed using the STATA software (version 11.0; Stata Corporation). The pooled standard mean difference (SMD) and its 95% confidence interval (CI) were estimated to evaluate the impact of ginger on the OS parameters. The mean and standard deviation (*SD*) of the OS parameter levels before and after the intervention in both the treatment and placebo groups were used to estimate the pooled effects. According to the method of Hozo

et al. (2005) all reported median values with their respective CI or their ranges were converted to mean ± *SD*. When standard errors (SE) were reported instead of *SD*, we calculated the *SD* for further analysis: $SD = SE \times \sqrt{n}$; *n* = number of participants. Due to the high heterogeneity of the included studies, a random effects model was applied in the meta-analysis. Heterogeneity among the included articles was evaluated by assessing the P value and I^2 statistic (I^2 0%–30%, <30% to 60% and >60% shows low, moderate and high heterogeneity, respectively) (Higgins & Wells, 2011). To determinate the potential cause of between-study heterogeneity, we performed a pre-planned subgroup analysis according to intervention duration, ginger dose, age group, and health status of the subjects.

3 | RESULTS

3.1 | Study selection

The electronic database search strategy yielded a total of 453 studies (19 records from Cochrane, 23 records from PubMed, 55 from Web of Science, 252 from EMBASE, and 104 from Scopus). After removing duplicates, 322 studies were screened at the title and abstract level and 304 articles were excluded. The remaining 18 were assessed at the full-text level, after which 12 were included in this study (Attari et al., 2015; Azimi et al., 2014; Danwilai et al., 2017; Gholinezhad et al., 2020; Imani et al., 2015; Javid et al., 2019; Kulkarni & Deshpande, 2016; Naderi et al., 2016; Nikkhah-Bodaghi et al., 2019; Rafie et al., 2020; Seddik, 2015; Shidfar et al., 2015) (Figure 1).

3.2 | Characteristics of included studies

The main characteristics of the included studies are displayed in Table 1. Data were pooled from the 12 eligible studies comprising 26 treatment arms reporting on a total of 649 randomly assigned participants. The number of subjects in these studies ranged from thirty (Seddik, 2015) to one hundred (Naderi et al., 2016). The studies were published between 2014 and 2020 and performed in Iran (9 studies) (Attari et al., 2015; Azimi et al., 2014; Gholinezhad et al., 2020; Imani et al., 2015; Javid et al., 2019; Naderi et al., 2016; Nikkhah-Bodaghi et al., 2019; Rafie et al., 2020; Shidfar et al., 2015), Thailand (Danwilai et al., 2017), Saudi Arabia (Seddik, 2015) and India (Kulkarni & Deshpande, 2016). The mean age of the subjects ranged from 31 to 58 years. Two studies were performed exclusively on women (Attari et al., 2015; Danwilai et al., 2017). All remaining studies were performed on both sexes. The supplemented ginger dose during the studies ranged from 1,000 to 3,000 mg/day. The duration of

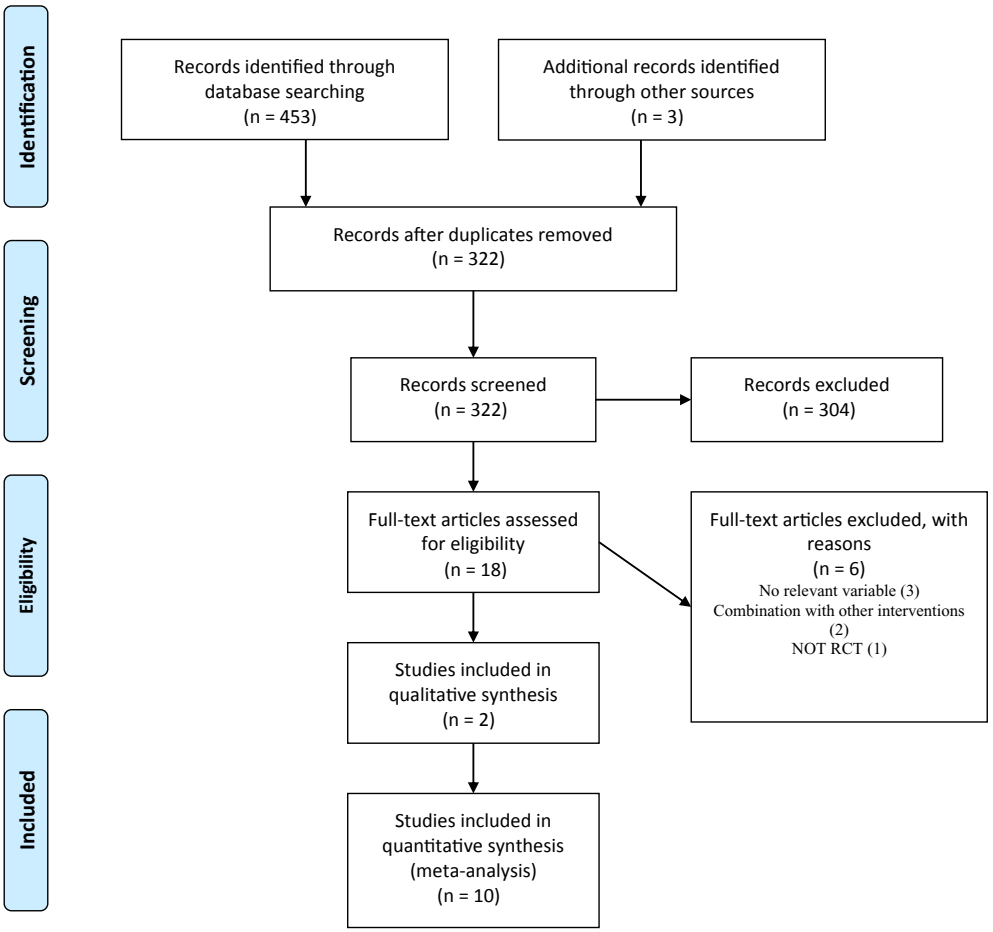


FIGURE 1 PRISMA Flow diagram of study selection

TABLE 1 The summaries of RCTs to investigate the effects of ginger supplementation on oxidative stress parameters

First author, year	Country	Population	Type of ginger	Dose of Ginger (mg)	Sample size (including in analyses)	duration (weeks)	Gender (percentage of women)	Age (mean ± *SD*)		BMI (mean ± *SD*) kg/m^2		Main results[a]
								Intervention Group	Control Group	Intervention Group	Control Group	
Danwilai et al. (2017)	Thailand	Cancer patients	Extract powder	1,430	43	9	100	52.9 ± 8.0	52.0 ± 10.1	—	—	↑ CuZn-SOD, ↑ CAT, ↑ GPx, ↑ GSH/GSSG, ↓ MDA, ↓ NO_2^-/NO_3^-
Attari et al. (2015)	Iran	Obese patients	Dried rhizomes powder tablets	2,000	70	12	100	35.25 ± 7.30	34.54 ± 7.91	34.34 ± 3.61	35.46 ± 3.41	↑ MDA, ↔ TAC
Azimi et al. (2014)	Iran	T2DM patients	Rhizome of the Zingiber officinale	3,000	80	8	61.3%	55.21 ± 1.1	53.64 ± 1.3	29.05 ± 0.2	28.40 ± 0.2	↔ F2-isoprostan
Gholinezhad et al. (2020)	Iran	T2DM and CP patients	Dried extract tablets	2,000	42	8	54.8%	52.81 ± 6.44	51.62 ± 5.95	26.06 ± 7.20	27.18 ± 2.15	↔ TAC, ↓ MDA
Nikkhah-Bodaghi et al. (2019)	Iran	UC patients	Dried ginger powder capsules	2,000	46	12	37%	41.41 ± 11.4	39.21 ± 11.81	26.35 ± 3.93	24.73 ± 3.67	↔ TAC, ↓ MDA
Imani et al. (2015)	Iran	Peritoneal dialysis patients	Dried ginger powder capsules	1,000	36	10	41.5%	56.00 ± 2.5	58.00 ± 3.0	27.00 ± 1.0	27.00 ± 1.0	↔MDA
Javid et al. (2019)	Iran	T2DM patients	Dried extract tablets	2,000	42	8	54.8%	52.81 ± 6.44	51.62 ± 5.95	26.06 ± 3.33	27.18 ± 2.15	↔ CAT, ↑ GPx, ↑ SOD
Kulkarni and Deshpande (2016)	India	Tuberculosis patients	Dried Extract powder	3,000	69	4	—	31.62 ± 6.0	31.62 ± 6.0	—	—	↓ MDA
Naderi et al. (2016)	Iran	Knee osteoarthritis patients	Dried Extract powder	1,000	100	12	90%	57.98 ± 6.2	59.1 ± 6.1	26.1 ± 2.9	25.5 ± 2.0	↓ NO
Rafie et al. (2020)	Iran	NAFLD patients	Dried ginger powder capsules	1,500	46	12	56.5%	50.04 ± 10.26	47.95 ± 9.24	31.70 ± 3.75	30.94 ± 1.98	↔ TAC
Shidfar et al. (2015)	Iran	T2DM patients	Dried ginger powder capsules	3,000	45	12	—	45.2 ± 7.64	47.1 ± 8.31	29.5 ± 2.8	29.2 ± 3.1	↑ TAC, ↓ MDA
Seddik (2015)	Saudi Arabia	ESRD patients	Dried ginger powder capsules	1,500	30	8	40%	51 ± 1.36	49 ± 2.97	—	—	↓ MDA, ↑ RBC GPx, ↑ RBC CAT, ↔ RBC GR

Abbreviations: CAT, catalase; CP, chronic periodontitis; ESRD, end-stage renal disease; GPx, glutathione peroxidase; GSH/GSSG, total glutathione; MDA, malondialdehyde; NAFLD, non-alcoholic fatty liver disease; NO, nitric oxide; NR, not reported; RBC CAT, red blood cell catalase activity; RBC GPX, red blood cell glutathione peroxidase activity; RBC GR, red blood cell glutathione activity; SOD, superoxide dismutase; T2DM, type 2 diabetes mellitus; TAC, total antioxidant capacity; UC, ulcerative colitis.

[a]↓ 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.

ginger consumption varied from four to 12 weeks. Of the 12 studies, four included participants with type 2 diabetes (Azimi et al., 2014; Gholinezhad et al., 2020; Javid et al., 2019; Shidfar et al., 2015), two included participants with final stage renal disease and peritoneal dialysis (Imani et al., 2015; Seddik, 2015), one included participants with cancer (Danwilai et al., 2017), one included obese participants (Attari et al., 2015), one included participants with ulcerative colitis (Nikkhah-Bodaghi et al., 2019), one included subjects with non-alcoholic fatty liver disease (Rafie et al., 2020), one included knee osteoarthritis patients (Naderi et al., 2016), and one included adults with tuberculosis (Kulkarni & Deshpande, 2016).

3.3 | Risk of bias assessment

The quality of the studies was assessed, as shown in Appendix A. The included studies held a low ($N = 5$) or unclear ($N = 6$) risk of bias based on the methods used to generate the random allocation. Five studies held a high risk of bias and two studies were deemed to be of unclear risk of bias due to allocation concealment. The majority of the studies ($N = 8$) were considered to hold a low risk of bias regarding the blinding of participants and personnel. None of the studies applied an intention-to-treat analysis.

3.4 | Qualitative synthesis

3.4.1 | F2-isoprostane and NO

F2-isoprostanes are prostaglandin-like ingredients produced from free fatty acids and have functions in immune activation, vasoconstriction, and other specific disease mechanisms (Montuschi et al., 2004). Some researchers consider F2-isoprostane concentration as a gold standard parameter of OS in vivo, because of its stability, specificity, high sensitivity, and detectability in a wide range of body fluids (Milne et al., 2007, 2015; Morrow & Roberts, 2002). There was only one study that investigated the effect of ginger supplementation on F2-isoprostane concentration; therefore, we could not perform a meta-analysis in regard to this. Azimi et al. (2014) showed that ginger supplementation did not change the F2-isoprostane concentration in type 2 diabetes patients compared to the control group. One study evaluated the effect of ginger on NO levels, showing that doses of 1,000 mg/day for 12 weeks decreased NO levels significantly compared to the control group (Naderi et al., 2016).

3.5 | Meta-analysis

3.5.1 | Effect of ginger on OS parameters

The meta-analysis of data from eight results indicated a significant reduction in plasma MDA concentration following ginger supplementation (SMD: −0.69; 95% CI: −1.26, −0.12; $I^2 = 85.8\%$) (Figure 2a). A subgroup analysis based on disease type show that ginger supplementation significantly reduces MDA levels in non-metabolic patients (SMD: −0.70; 95% CI: −1.27, −0.12; $I^2 = 70.3\%$) compared to metabolic patients (SMD: −0.72; 95% CI: −1.79, 0.35; $I^2 = 91.9\%$) (Figure 2b). Metabolic patients are classified as those with metabolic diseases, such as overweight and obesity, type 2 diabetes, and non-alcoholic fatty liver disease, whereas non-metabolic diseases comprise diseases such as cancer, ulcerative colitis, peritoneal dialysis, tuberculosis infection, and knee osteoarthritis patients (Matsuzawa, 2005).

In addition, the stratification of MDA results according to the dose of ginger indicated that ginger supplementation <10 weeks significantly reduces MDA levels (SMD: −0.89; 95% CI: −1.66, −0.12; $I^2 = 82.9\%$), whereas ginger supplementation ≥ 10 weeks reduces MDA levels non-significantly (SMD: −0.50; 95% CI: −1.38, 0.38; $I^2 = 85.8\%$) (Figure 2c). A subgroup analysis based on the dose of ginger and the age of participants did not change the meta-analysis results regarding MDA levels (Figure 2d,e, respectively). Figure 3 displays the meta-analysis results of three studies that investigated the effect of ginger on CAT activity. Ginger supplementation non-significantly increases CAT activity (SMD: 1.09; 95% CI: −0.07, 2.25; $I^2 = 87.6\%$). The results of our meta-analysis further show that ginger supplementation significantly increases GPx activity (three studies) (SMD: 1.64; 95% CI: 0.43, 2.85; $I^2 = 86.8\%$) (Figure 4). Danwilai et al. (2017) and Seddik (2015) reported that ginger intake significantly increases CAT and GPx activity and Javid et al. (2019) reported that ginger intake has no effect on CAT and GPx activity. Our meta-analysis also showed that ginger supplementation significantly increases TAC levels (five studies) (SMD: 0.40; 95% CI: 0.06, 0.73; $I^2 = 42.8\%$) (Figure 5). Four studies (Attia et al., 2013; Gholinezhad et al., 2020; Nikkhah-Bodaghi et al., 2019; Rafie et al., 2020) have shown that ginger intake non-significantly increases TAC. One study showed that ginger intake increases TAC significantly (Shidfar et al., 2015).

4 | DISCUSSION

The results of this systematic review showed that ginger consumption could significantly reduce plasma MDA concentration, significantly increase TAC levels, and significantly increase GPx activity. In addition, our results indicated that ginger supplementation increases CAT activity non-significantly. Due to the strong heterogeneity among the included studies and the limited number of primary studies for some of the relevant variables, these results are viewed with caution. This is not the first systematic review and meta-analysis investigating the impact of supplemental ginger on OS parameters in human adults, as two other systematic reviews also investigated its effect on inflammatory and oxidative stress factors (Askari et al., 2020; Jalali et al., 2020). In line with our results, Jalali et al. showed that ginger intake significantly increases TAC and decreases MDA; however, they did not evaluate the effect of ginger on GPx levels. In contrast to our results, Askari et al., reported that ginger

intake has no effect on MDA levels. Differences in included studies may have led to this discrepancy. However, Askari et al. also reported that ginger intake causes a significant increase in TAC. Alike Jalali et al., they did not evaluate GPx and other OS parameters. The antioxidant properties of ginger have been verified in several RCTs (Danwilai et al., 2017; Mashhadi et al., 2013; Shidfar et al., 2015) and

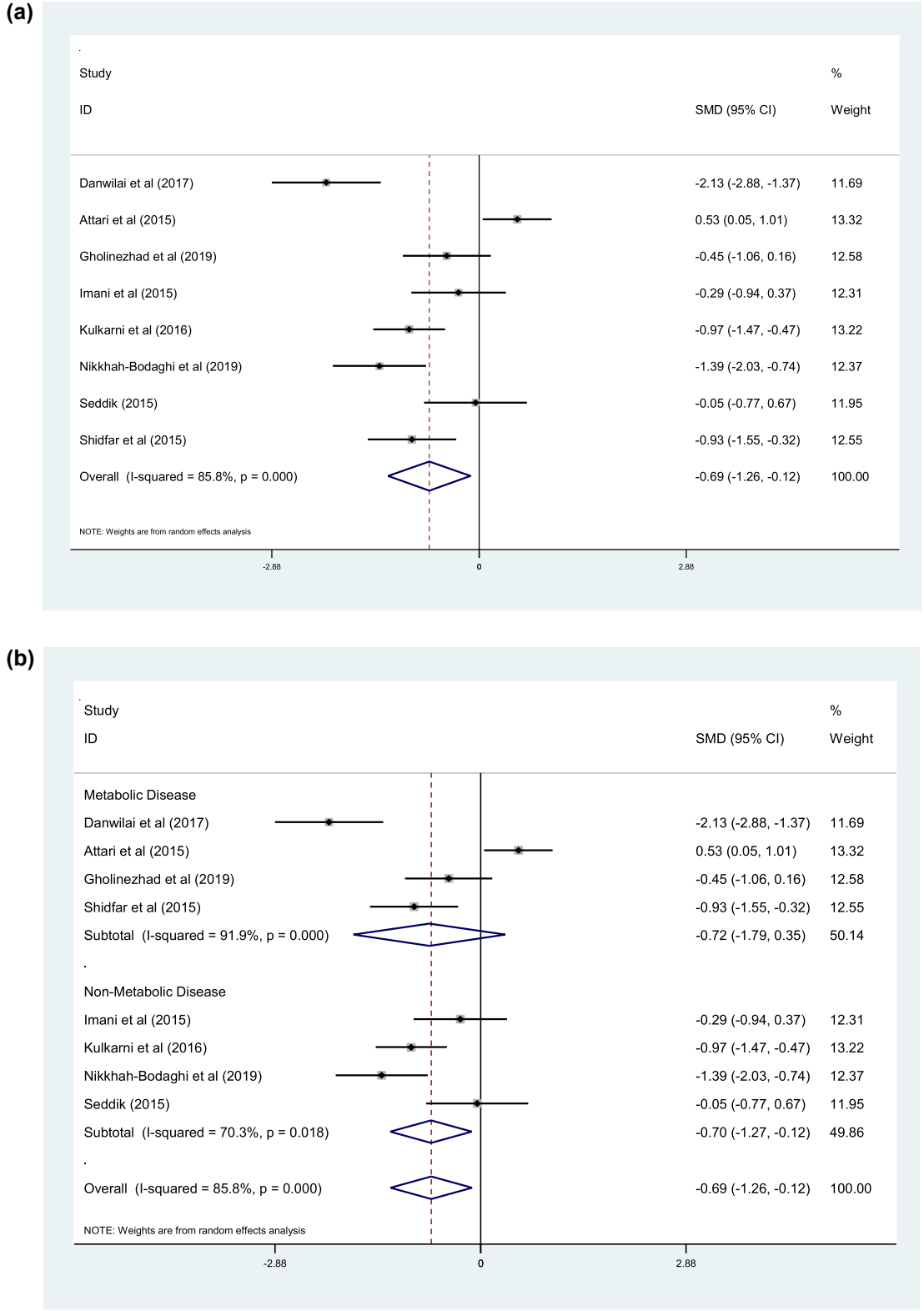
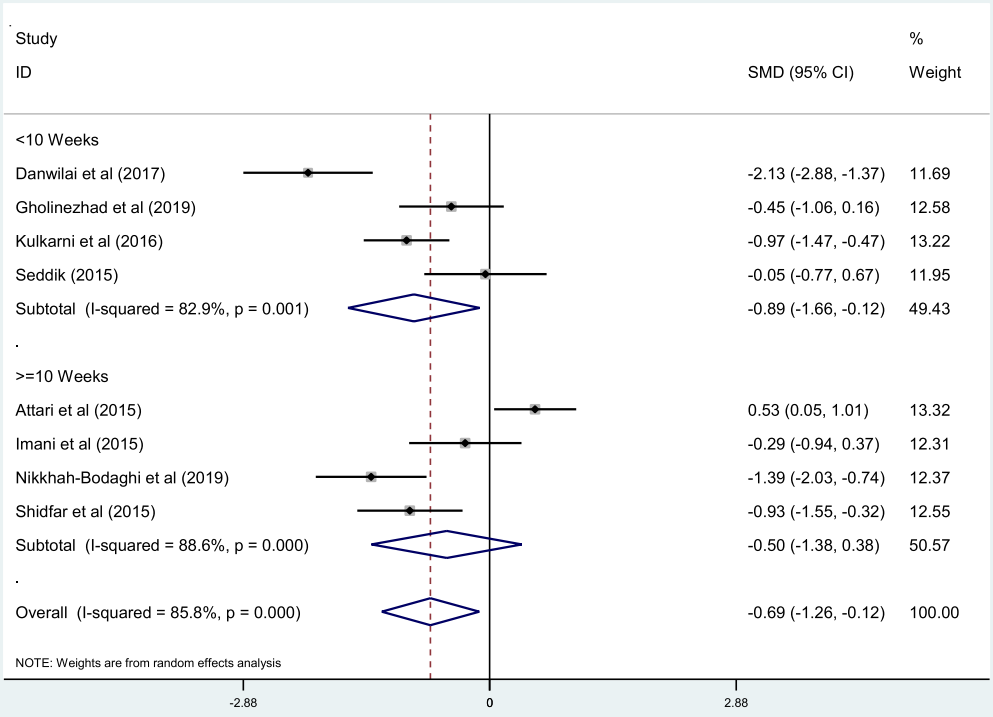


FIGURE 2 Forest plot detailing the mean difference and 95% confidence intervals for the impact of ginger supplementation on MDA. (a) Overall. (b) Stratified by the disease type. (c) Stratified by the ginger supplementation duration. (d) Stratified by the ginger supplementation dose. (e) Stratified by the age

experimental studies (Ahmed et al., 2000; Khaki et al., 2014). The properties have been attributed to substances, such as ascorbic acid, beta-carotene, alkaloids, terpenoids, and polyphenols including flavones, flavonoids, rutin, and glycosides (Aruoma et al., 1997).

Our meta-analysis results indicated that ginger supplementation significantly reduces MDA levels, which is relevant as MDA is a marker of lipid peroxidation (Gaweł et al., 2004). The positive effect of ginger on MDA has been proven in previous RCTs (Atashak

(c)



(d)

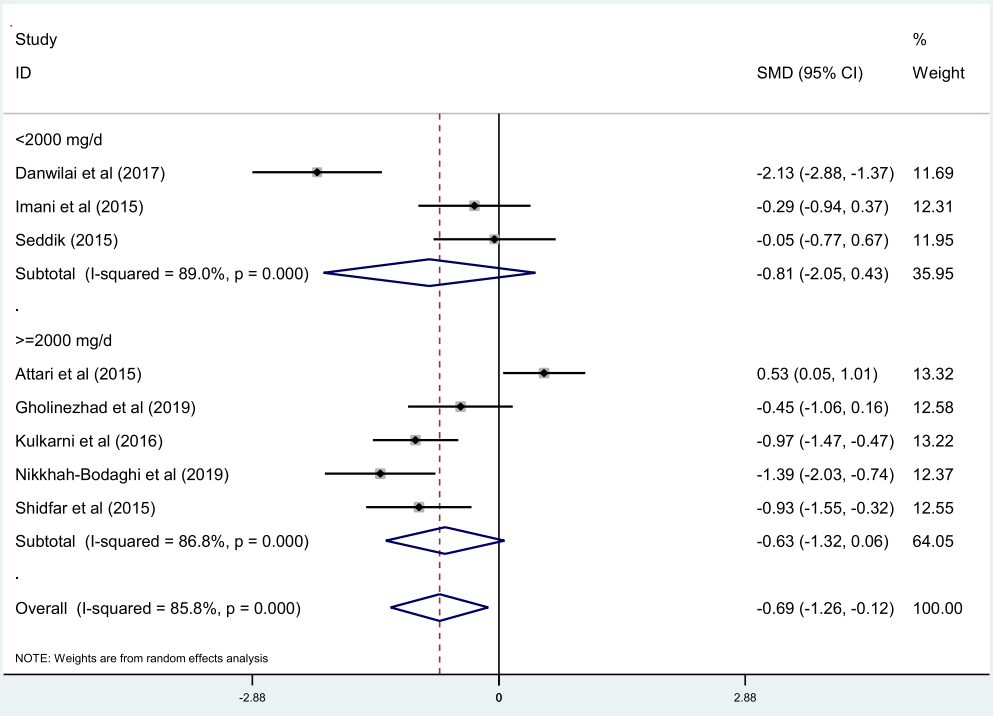
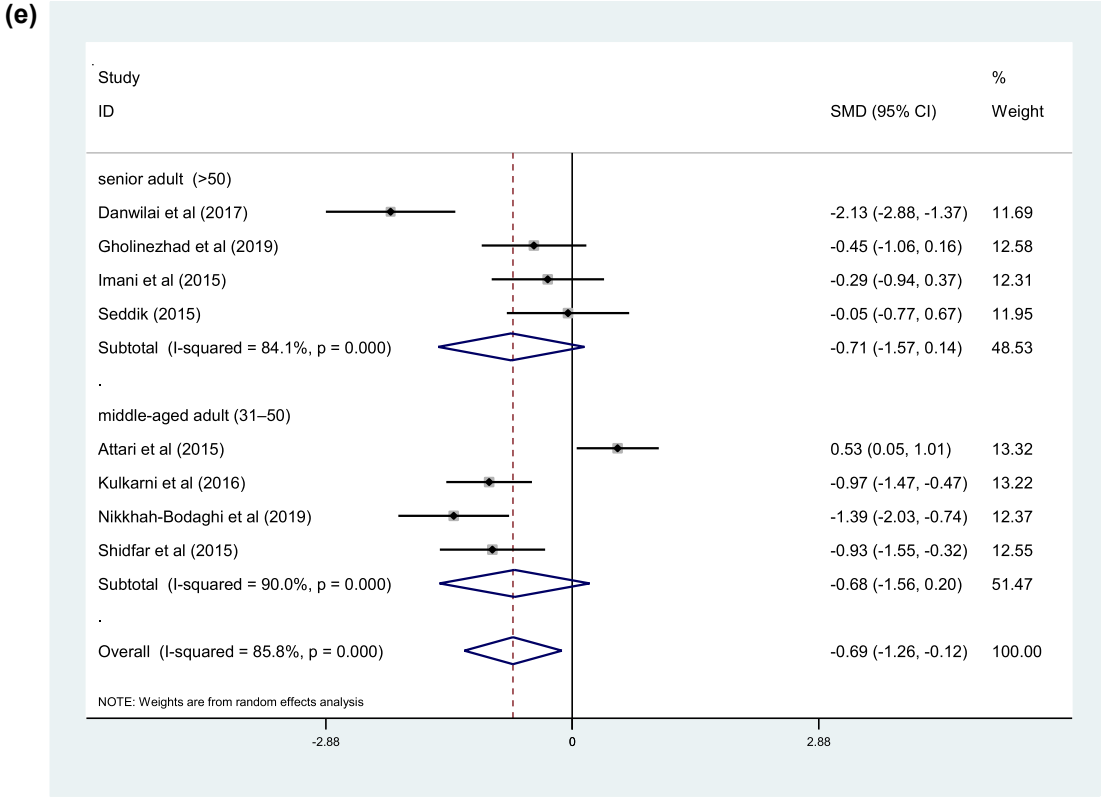


FIGURE 2 (Continued)



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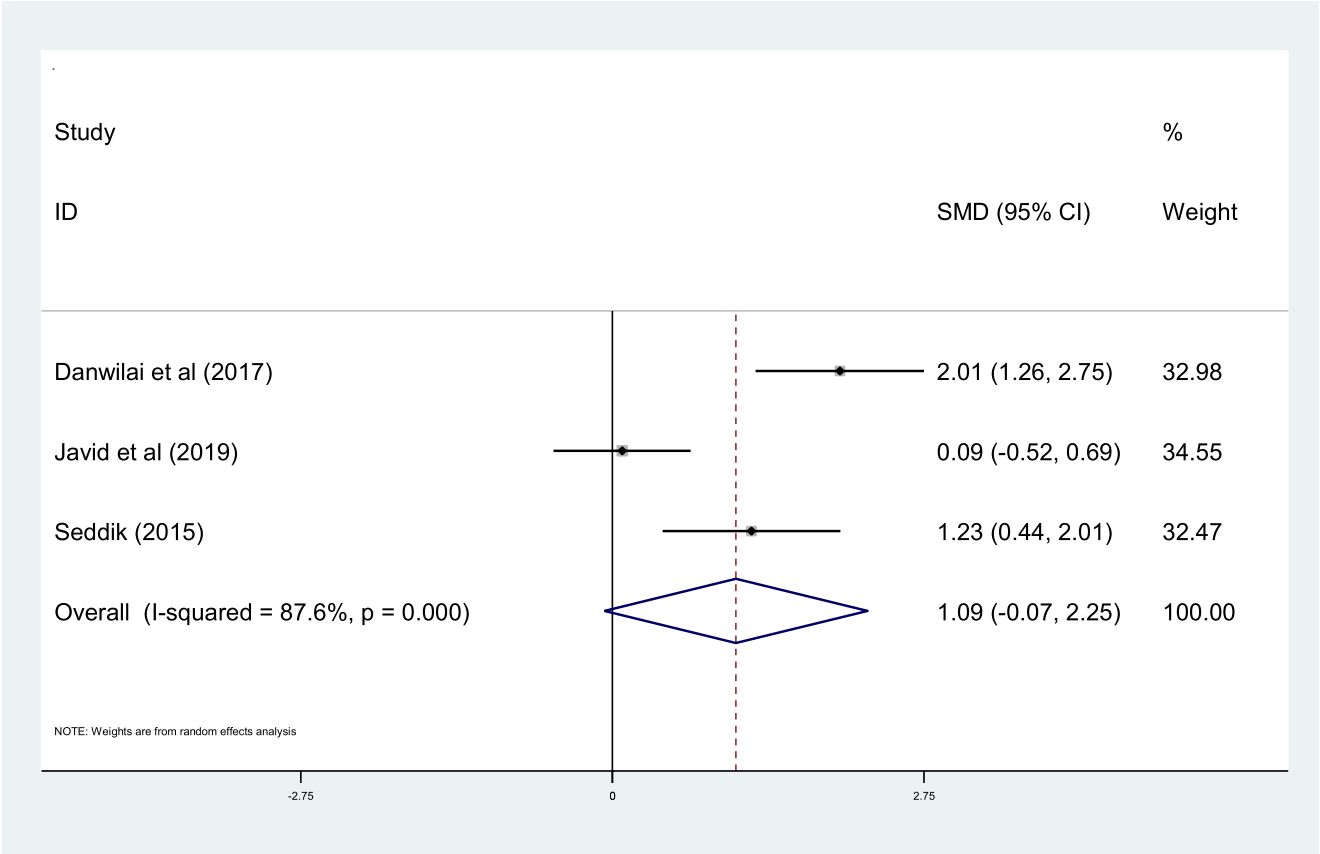

FIGURE 3 Forest plot detailing the mean difference and 95% confidence intervals for the impact of ginger supplementation on CAT activity

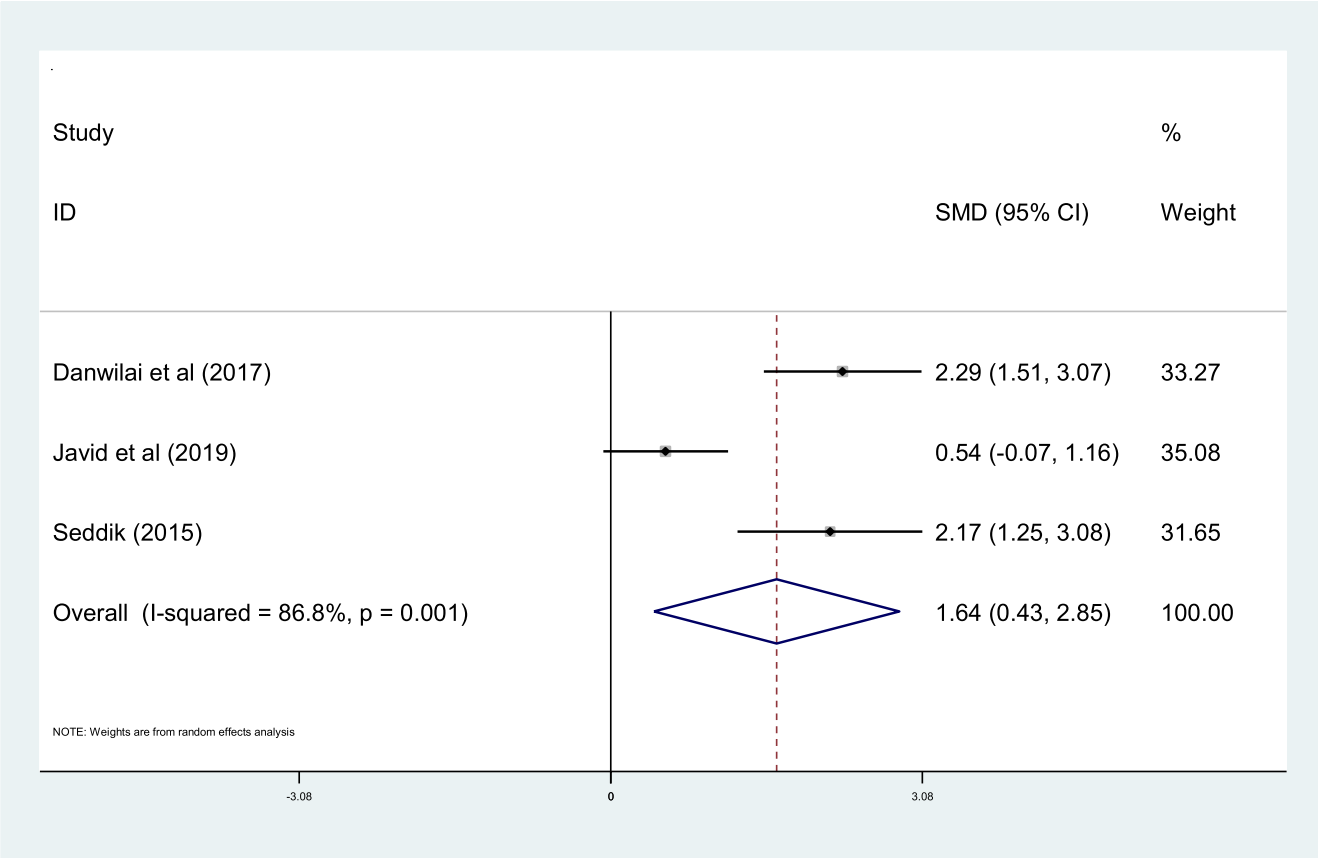

FIGURE 4 Forest plot detailing the mean difference and 95% confidence intervals for the impact of ginger supplementation on GPx activity

et al., 2012; Khandouzi et al., 2015) and in vivo studies (Afshari et al., 2007). Several possible mechanisms could be attributed to the effect of ginger on lipid peroxidation. The administration of ginger has been shown to significantly reduce thiobarbituric acid-reactive substances (TBARS) levels, which can be considered to be an indicator of oxidative stress damage and lipid peroxidation (Stoilova et al., 2007). This decrease in TBARS levels may elevate the function and impact of GPx activity and therefore cause inactivation of lipid peroxidation reactions (Aydın et al., 2001). In vitro studies have also indicated that ginger inhibits lipid peroxidation with its phenolic acid profiles, such as 6-gingerol and 6-shogaol (Vipin et al., 2017). In addition, it has been shown that ginger supplementation decreases lipid peroxidation through its antioxidant activity, OH scavenging ability, and Fe2+ chelating properties (Oboh et al., 2012). A subgroup analysis further indicated that ginger intake significantly reduces MDA in non-metabolic disease and non-significantly reduces MDA in metabolic diseases. The results may be attributed to different baseline levels of MDA. A subgroup analysis based on the duration of supplementation also showed that ginger intake for fewer than 10 weeks reduced MDA significantly. A high level of heterogeneity and limited number of included studies may have influenced these results. In order to determine the long-term effect of ginger on MDA, further studies evaluating the effect of ginger in longer durations are warranted.

The results of the presented meta-analysis show that ginger supplementation increases CAT activity non-significantly. CAT is an essential enzyme for neutralizing noxious hydrogen peroxide radicals (Tehrani & Moosavi-Movahedi, 2018). The limited number of included studies and great heterogeneity among them has potentially impeded the discovery of the significant effects of ginger in this regard. Our results also demonstrated that ginger supplementation could significantly increase GPx activity, which is in line with previous studies (Jeena et al., 2013). Jeena et al. also showed that supplementation can increase glutathione levels. Ginger supplementation has also been shown to directly decrease ROS levels which leads to an increase in GPx activity (Akbari et al., 2020; Attia et al., 2013). Moreover, it is believed that ginger exerts potent anti-oxidant functions by scavenging ROS and restoring the balance between anti-oxidant/oxidant homeostasis (Reddy et al., 2014; Shanmugam et al., 2011). Recent research has shown that 6-shogaol is one of the main active ingredients of ginger (Kim et al., 2020). Based on previous findings, 6-shogaol rich ginger extract may lead to an improved antioxidant defense system via the induction of HO-1 and the nuclear factor E2-related factor2 (Nrf2)/antioxidant response element (ARE) pathway. It has been shown that Nrf2/ARE elements are also regulated by PI3k/Akt and the p38 MAPK pathway in vivo and in vitro (Bak et al., 2012). It has been determined that 6-shogaol achieves its effects through the phosphorylation of mitogen-activated protein

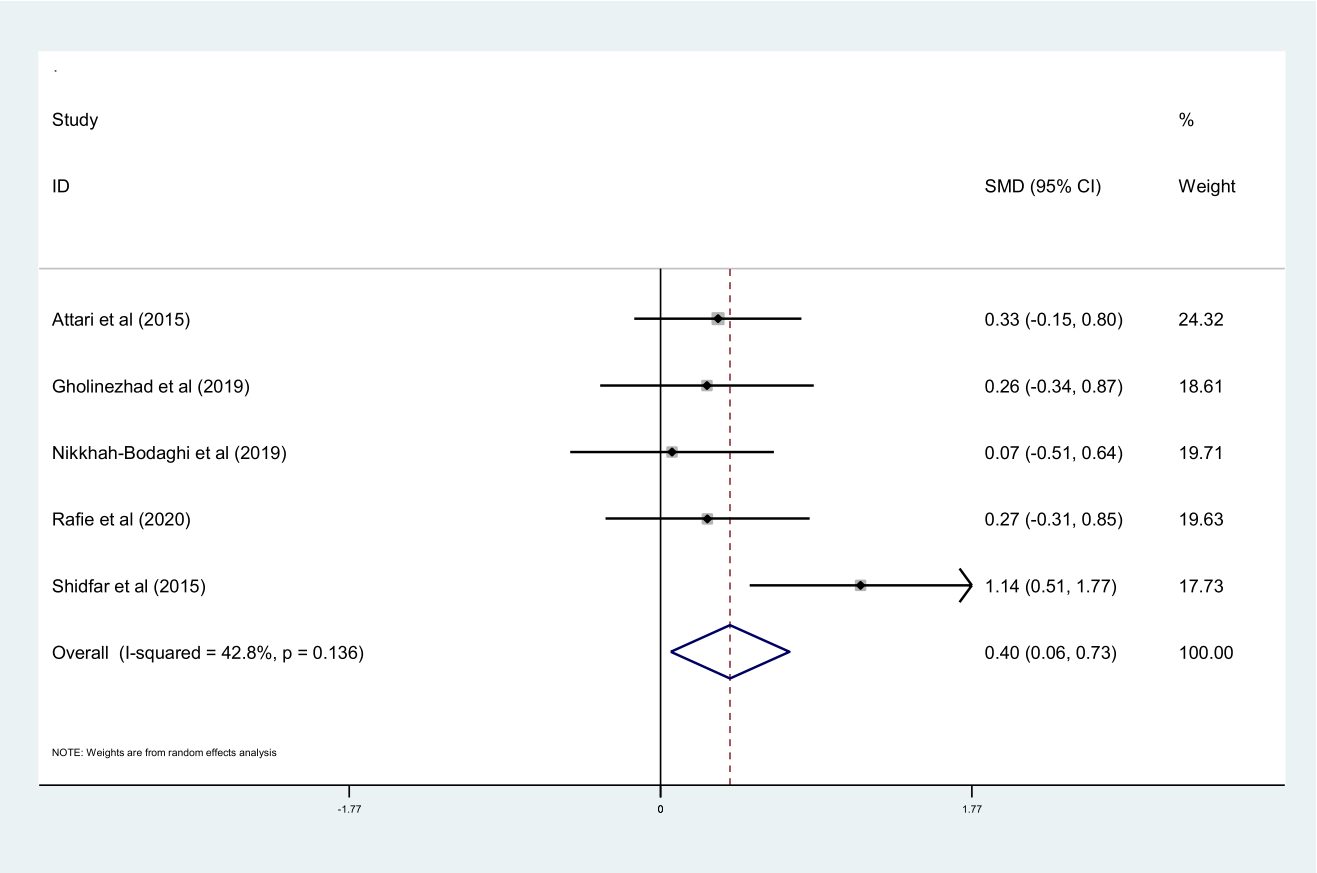

FIGURE 5 Forest plot detailing the mean difference and 95% confidence intervals for the impact of ginger supplementation on TAC

kinases (MAPKs), such as p38, extracellular signal-regulated kinase (ERK), and c-Jun N-terminal kinase (JNK) (Wu et al., 2010). Furthermore, the administration of 6-shogaol in mice has also been shown to reduce the function of diethylnitrosamine and gene expression of hepatic antioxidant enzymes, including GPx, SOD and CAT (Fahmi et al., 2019). In our results, the meta-analysis also indicated that ginger supplementation significantly increases TAC levels. TAC is an antioxidant defense system indicator (Lorente et al., 2018) and it is thus reasonable that when the determinants of TAC, namely GPx, CAT, and MDA, have improved due to the ginger supplementation, TAC levels would also increase (Mozaffari et al., 2020).

Although we conducted a comprehensive search and covered most of the major databases in the field, the risk of publication bias is still possible. Hence this review may have some limitations. Most of our included studies were performed in Iran. This may affect the generalizability of our results. Additionally, pooling the results of studies performed on different participants with various disease backgrounds increased the heterogeneity of the results. However, we attempted to reduce this heterogeneity by applying a random-effect model and subgroup analysis. As ginger is an herbal product, it would be preferable to have standardization criteria on dried drugs, oils, and extracts to obtain a measure for the amount of active constituents present in them. The included primary studies did not report on this issue.

5 | CONCLUSION

In conclusion, this systematic review and meta-analysis present convincing results supporting the efficacy of ginger supplementation on improving oxidative stress levels.

CONFLICTS OF INTEREST

Authors have no conflict of interest to declare.

AUTHOR CONTRIBUTION

Mojgan Morvaridzadeh: Conceptualization; Data curation; Formal analysis; Investigation; Resources; Writing-original draft. Ehsan Sadeghi: Formal analysis; Supervision; Writing-original draft. Shahram Agah: Data curation; Investigation; Resources; Software; Writing-original draft. Siavash Fazelian: Methodology; Writing-original draft; Writing-review & editing. Mehran Rahimlou: Investigation; Resources; Software. Ferdinand Georg Kern: Investigation; Writing-review & editing. Shilan Heshmati: Investigation; Writing-original draft. Amirhosein Omidi: Investigation; Methodology; Validation; Writing-review & editing. Emma Persad: Supervision; Validation; Writing-review & editing. Javad Heshmati: Conceptualization; Data curation; Investigation; Methodology; Validation; Writing-original draft.

ETHICAL APPROVAL

Ethical approval was not applicable for this systematic review and meta-analysis.

DATA AVAILABILITY STATEMENT

All the materials used in this systematic review and meta-analysis have been fully referenced.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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APPENDIX A

TABLE A1 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
Azimi et al. (2014)	?	+	+	−	+	−	−
Danwilai et al. (2017)	?	+	−	−	+	?	−
Ebrahimzadeh-Attari et al. (2015)	?	−	−	−	+	−	−
Gholinezhad et al. (2020)	−	−	−	−	+	−	−
Imani et al. (2015)	?	+	+	−	+	−	−
Javid et al. (2019)	−	?	−	−	+	−	−
Kulkarni and Deshpande (2016)	?	+	+	−	+	−	−
Naderi et al. (2016)	−	?	−	−	+	−	−
Nikkhah-Bodaghi et al. (2019)	−	−	−	−	+	−	−
Rafie et al. (2020)	−	−	−	−	+	−	−
Seddik (2015)	?	+	−	−	+	−	−
Shidfar et al. (2015)	?	+	−	−	+	−	−

Note: +, high risk; −, low risk; ?, unclear.