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The effect of *Zataria multiflora* on respiratory symptoms, pulmonary functions, and oxidative stress parameters: a systematic review and meta-analysis

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Abstract

Background *Zataria multiflora (Z. multiflora)*, also known as Shirazi thyme, is recognized for its medicinal properties, including antioxidant, anti-inflammatory, and immunomodulatory effects. Its longstanding use in traditional medicine for respiratory ailments underscores its significance. Given the widespread prevalence of respiratory disorders and inconclusive outcomes from previous trials, this research aims to conduct a systematic review and meta-analysis to evaluate *Z. multiflora*'s impact on respiratory symptoms, pulmonary function, and oxidative stress markers using available randomized controlled trials (RCTs).

Methods In this systematic review and meta-analysis, a comprehensive search of published literature was conducted up to January 2024, encompassing databases such as PubMed, Scopus, Web of Science, and the Cochrane Central for Randomized Clinical Trials. The assessment of the quality of each eligible study was conducted using the Cochrane risk-of-bias tool. The random-effects model was used in the meta-analysis to determine the weighted mean difference (WMD) with 95% confidence intervals (CIs). All statistical analyses were conducted using STATA (version 15).

Results A total of 9 studies involving 394 participants were included. The administration of *Z. multiflora* showed significant effects on cough (WMD: -0.99; 95% CI: -1.66, -0.33; $P=0.003$), day wheezing (WMD: -1.18; 95% CI: -1.44, -0.92; $P<0.001$), night wheezing (WMD: -0.74; 95% CI: -1.09, -0.37; $P<0.001$), chest wheezing (WMD: -1.15; 95% CI: -1.65, -0.64; $P<0.001$), forced expiratory volume (WMD: 11.38; 95% CI: 7.40, 15.35; $P<0.001$), forced vital capacity (WMD: 16.01; 95% CI: 12.26, 19.75; $P<0.001$), and peak expiratory flow (WMD: 8.78; 95% CI: 4.13, 13.43; $P<0.001$) compared to the control group. Additionally, *Z. multiflora* significantly reduced malondialdehyde levels (SMD: -1.54; 95% CI: -2.17, -0.90; $P<0.001$) and increased catalase levels (SMD: 0.97; 95% CI: 0.46, 1.46; $P<0.001$).

Conclusion *Z. multiflora* shows potential as a complementary treatment for respiratory diseases by improving symptoms, pulmonary functions, and reducing oxidative stress. However, due to the limited number of trials, findings should be interpreted cautiously, and further research is needed.

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Keywords *Zataria multiflora*, Thymus plant, Respiratory signs and symptoms, Respiratory function tests, Oxidative stress

Introduction

Zataria multiflora (Z. multiflora), also known as Shirazi thyme, is a medicinal plant native to Iran, Afghanistan, and Pakistan, belonging to the Lamiaceae family [1]. Its essential oil is rich in phenols and flavonoids, with carvacrol and thymol as the main components, along with other compounds such as P-cymene, linalool, and borneol [2]. The plant exhibits antioxidant, anti-inflammatory, and immunomodulatory properties and has traditional uses as an antiseptic, antispasmodic, and treatment for colds and coughs [1–5]. Studies have demonstrated its protective effects in animal models of asthma and COPD and its therapeutic potential for conditions like gastrointestinal disorders, fever, labor pain, headaches, and the common cold [6–8].

The primary function of the respiratory system is gas exchange. Its anatomy and physiology are well-suited to fulfill this crucial role [9]. The respiratory function of the lungs is vital for survival because oxygen is essential for energy production, a fundamental requirement for the life of organisms [10]. Respiratory disorders are a common cause of illness and death worldwide, with conditions like asthma, bronchitis, common colds, and coughs being among the most prevalent respiratory issues [11]. Immune and inflammatory responses are associated with respiratory disorders such as asthma and COPD. Additionally, oxidants play a significant role in the pathophysiology of these disorders, with their levels significantly increased in respiratory diseases [12].

Traditionally, herbal products, including *Z. multiflora*, have been used for treating respiratory disorders like asthma and bronchitis, due to their antiseptic and antitussive effects [13, 14]. *Z. multiflora* has been shown to moderate oxidative stress, inflammation, and immune parameters, with studies reporting its ability to reduce tracheal responsiveness, inflammation, and cytokine levels in animal models of asthma and COPD [4, 7, 15–20]. These therapeutic effects are primarily attributed to its main compounds, thymol and carvacrol, which also exhibit significant antioxidant activity [15, 21–23]. Clinical evidence highlights some inconsistencies: Alavinezhad et al. observed improved maximum mid-expiratory flow (MMEF) in asthmatic patients treated with *Z. multiflora* [24], but no effect was found in COPD patients [25]. Considering oxidative factors, Ghorani et al. reported a significant reduction in nitrite levels in COPD patients [25], while no notable changes were observed in asthmatic patients [26].

Respiratory diseases, such as asthma and COPD, are characterized by shared underlying mechanisms, including inflammation, oxidative stress, and impaired pulmonary function. *Z. multiflora* has demonstrated pharmacological properties targeting these mechanisms [27]. To the best of our knowledge, the results of previous clinical trials conducted to assess the effect of *Z. multiflora* are inconsistent and controversial. Additionally, there is no available meta-analysis that evaluates these results to achieve a consistent and reliable conclusion. Therefore, this systematic review and meta-analysis aim to assess the effects of *Z. multiflora* on respiratory symptoms, pulmonary function, and oxidative stress parameters by reviewing the available randomized controlled trials (RCTs).

Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol for this review was registered in PROSPERO with the following number: CRD42022374477. We analyzed the effects of *Z. multiflora* on various outcomes, including respiratory symptoms such as cough, daytime wheezing, nighttime wheezing, and chest wheezing. Additionally, we examined pulmonary functions, including forced expiratory volume (FEV), forced vital capacity (FVC), maximal mid-expiratory flow (MMEF), and peak expiratory flow (PEF). Furthermore, oxidative stress parameters, including malondialdehyde (MDA), nitrite, thiol, superoxide dismutase (SOD), and catalase (CAT), were also assessed.

Search strategy

We conducted a systematic review by searching the PubMed, Scopus, Cochrane Central for Randomized Clinical Trials, and Web of Science databases up to January 2024. The detailed search strategy is provided in Supplementary Material 1. We imposed no language or location restrictions on the identified studies.

Study selection

Two reviewers (FA and MM) independently performed an initial screening of all identified publications by reviewing their titles and abstracts. The decision for final inclusion was made after a detailed reading of the full texts. The eligibility of identified studies was primarily assessed using the PICOS approach: Population (P) being adults, Intervention (I) being limited to the use of *Z. multiflora*, Comparison (C) being placebo or no intervention, Outcome (O) including pulmonary functions, respiratory symptoms, and oxidative stress, and Study design

(S) being randomized controlled trials (RCTs). Published studies were excluded based on several criteria: (1) animal or in vitro studies, (2) duplication or overlap of data, (3) review articles, cross-sectional studies, case reports, and case series studies, (4) articles lacking full text availability, (5) conference abstracts, (6) research articles lacking data, and (7) RCTs utilizing combinations of *Z. multiflora* with other plants as interventions. Reasons for excluding trials were documented in the PRISMA flow diagram (Fig. 1). The reference lists of pertinent reviews were manually examined by two independent reviewers (FA, MM) to identify additional eligible articles. Any discrepancies were resolved through discussion among all team members to reach a consensus.

Data extraction

A data extraction form was designed and completed by two independent reviewers (FA, MM) to collect information from studies. Extracted data included the first author's name, year of publication, country, study design, total sample size, intervention dose, characteristics of

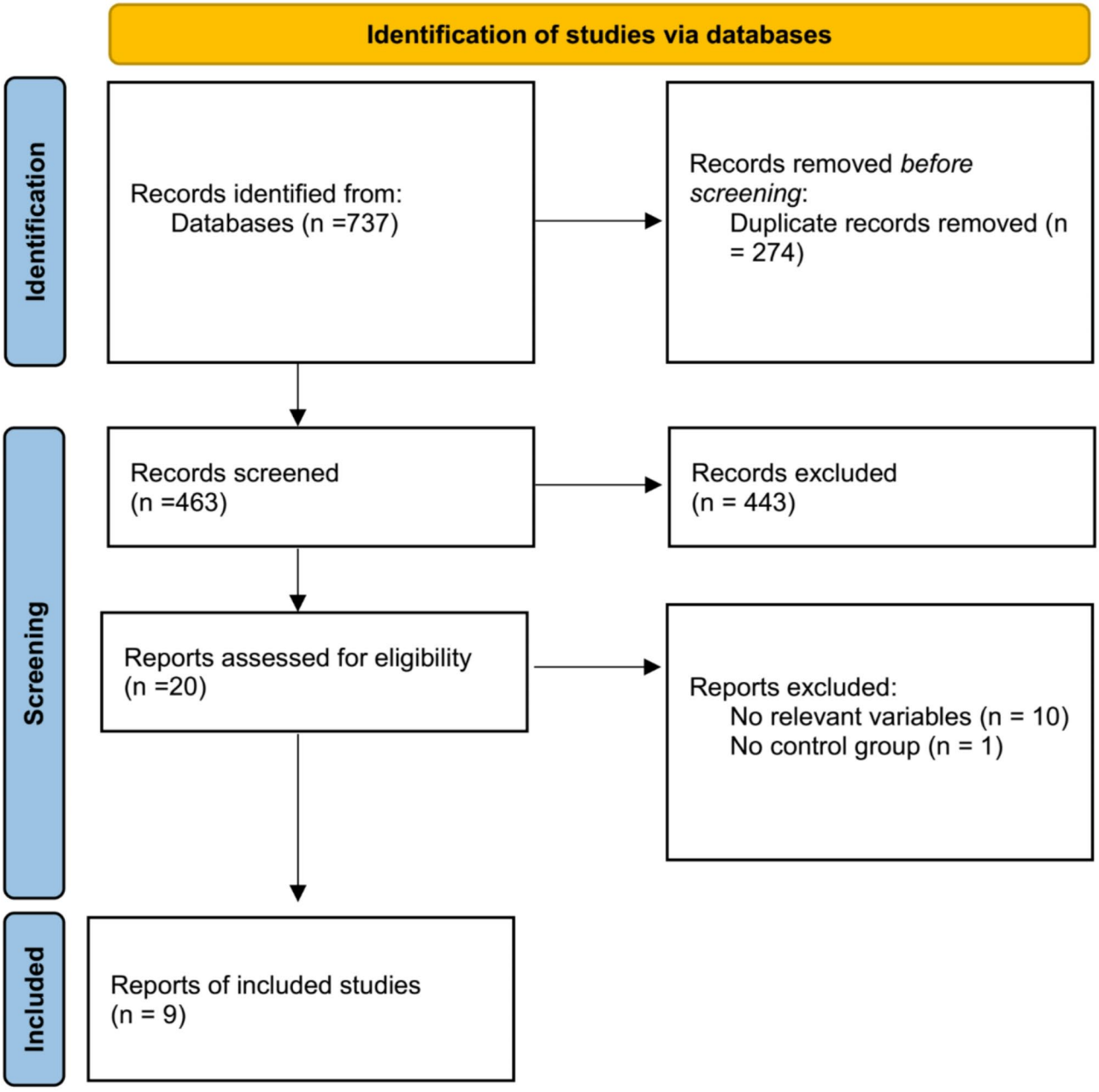


Fig. 1 PRISMA Flow diagram of the study selection process

participants, duration of supplementation, study quality, and outcomes.

Risk of bias assessment

We assessed the quality of each eligible study using the Cochrane Risk of Bias Tool for Randomized Trials (RoB 2), considering seven domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and assessors (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. Based on this assessment, the included studies were categorized as good, fair, or poor quality, following the protocol outlined in the Cochrane Handbook for Systematic Reviews of Interventions. The GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach was applied to assess the certainty of evidence across included studies. This method evaluates risk of bias, inconsistency, indirectness, imprecision, and other potential concerns (e.g., publication bias or strong associations) to determine the strength of the evidence supporting each outcome.

Statistical analysis

We gathered all information in mean and standard deviation (SD) structure and transformed alternative formats, such as standard error (SE), confidence interval (CI), interquartile range (IQR), and minimum-maximum values, into SDs following guidelines and equations outlined in the Cochrane Handbook for Systematic Reviews of Interventions whenever required [28]. For evaluating the effects of *Z. multiflora* on respiratory symptoms and pulmonary functions, weighted mean difference (WMD) and 95% confidence interval (CI) were used, while oxidative stress biomarkers were reported as standardized mean difference (SMD). The data were pooled using a random-effects model, employing the inverse-variance approach. Heterogeneity was assessed using Higgins' I^2 statistic. If I^2 was less than 50%, a fixed-effects model was employed; for I^2 values exceeding 50%, a random-effects model was applied. A p-value < 0.05 was considered statistically significant in our meta-analysis.

To investigate potential publication bias, Egger's and Begg's tests were performed as statistical assessments. Additionally, sensitivity analysis was conducted using the leave-one-out method, where each included study was sequentially removed to assess its impact on the overall effect size. All statistical analyses were performed using STATA (version 15).

Subgroup analysis was conducted to explore the potential sources of heterogeneity; however, due to the limited number of studies, it was only feasible for FEV and MDA. The analysis was performed for MDA based on (1) sample size categorized as < 30 and ≥ 30, and (2) health status (respiratory diseases versus others). For FEV, subgroup analysis was only feasible based on sample size (< 40 and ≥ 40), as all included studies involved participants with respiratory diseases. The effect sizes were calculated using Hedges' g for MDA due to variations in measurement scales across studies, while the mean difference (MD) was used for FEV since all studies reported it in the same unit. A random-effects model was applied due to anticipated heterogeneity, and 95% confidence intervals (CIs) were reported. To test for subgroup differences, the Q-test for subgroup differences (Q_b) was performed, with statistical significance set at $p < 0.05$.

Results

Studies selection

The search strategy and screening process for identifying eligible studies are illustrated in Fig. 1. Initially, 737 publications were identified through searches across various databases. Upon removing duplicate articles ($n = 274$), the initial screening was conducted using the titles and abstracts. In this screening phase, 443 articles were excluded. Following this, the full texts of 20 relevant articles were thoroughly reviewed. Ultimately, 9 articles that satisfied the eligibility criteria were included [24–26, 29–34].

Studies characteristics

Table 1 outlines the general characteristics of the included studies. This systematic review and meta-analysis comprised nine trials, involving a total of 394 participants. The publications spanned the years 2017 to 2022 and were exclusively conducted in Iran. The durations of the interventions ranged from 8 weeks to 2 months, with participant numbers varying from 34 to 48. The mean age of participants fell within the range of 45 to 58 years. The daily dosage of *Z. multiflora* administered ranged from 3 to 10 mg/kg/day. Seven studies utilized *Z. multiflora* extract [24–26, 29–32], one study employed *Z. multiflora* syrup [33], and another study utilized *Z. multiflora* supplement [34].

Effects of Zataria multiflora on respiratory symptoms

Three studies investigated the influence of *Z. multiflora* on cough [26, 29, 30], while two studies explored its impact on daytime wheezing [24, 31]. Additionally, two studies examined the effect of *Z. multiflora* on nighttime wheezing [26, 30], and finally, three studies investigated its effect on chest wheezing [25, 26, 30]. According to the meta-analysis (Table 2), *Z. multiflora* exhibited a significant effect on cough (WMD: -0.99; 95% CI: -1.66, -0.33; $P = 0.003$), daytime wheezing (WMD: -1.18; 95% CI: -1.44, -0.92; $P = 0.000$), nighttime wheezing (WMD: -0.74; 95% CI: -1.09, -0.37; $P = 0.0001$), and chest wheezing

Table 1 Main characteristics of the included studies

Author, year (ref)	Health condition	Duration	Participants (*n*)	Intervention type	Dose, Unit	Age (years)*		BMI (kg/m^2) *		Outcomes
						Intervention	Control	Intervention	Control	
Ghorani et al. 2022 [29]	Chronic obstructive pulmonary diseases	2 months	41(♀♂) Int:28 Cnt:13	*Z. multiflora* extract	3 and 6 mg/kg/day	54.69 ± 5.06	54.69 ± 4.13	24.83 ± 1.58	28.05 ± 1.7	Cough, FEV, FVC, PEF
Khazdair et al. 2020 [30]	Sulfur mustard exposed veterans	8 weeks	34(♂) Int:22 Cnt:12	*Z. multiflora* extract	5 and 10 mg/kg/day	56.84 ± 4.13	54.40 ± 5.51	25.99 ± 1.35	25.87 ± 1.19	Cough, night wheezing, chest wheezing, FEV
Alavinezhad et al. 2022 [24]	Asthmatic patients	2 months	36(♀♂) Int:24 Cnt:12	*Z. multiflora* extract	5 and 10 mg/kg/day	45.33 ± 4.22	47.75 ± 2.78	NM	NM	Day wheezing, FVC, MMEF, PEF
Alavinezhad et al. 2017 [31]	Asthmatic patients	2 months	40(♀♂) Int:20 Cnt:10	*Z. multiflora* extract	5 and 10 mg/kg/day	45.35 ± 6.44	46.1 ± 9.6	NM	NM	Day wheezing, FEV, nitrite
Alavinezhad et al. 2020 [26]	Asthmatic patients	2 months	36(♀♂) Int:24 Cnt:12	*Z. multiflora* extract	5 and 10 mg/kg/day	45.30 ± 11.27	48.0 ± 9.6	NM	NM	Cough, night wheezing, chest wheezing, FEV SOD, MDA, thiol, CAT, nitrite
Ghorani et al. 2020 [25]	Chronic obstructive pulmonary disease	2 months	42(♀♂) Int:29 Cnt:13	*Z. multiflora* extract	3 and 6 mg/kg/day	56.73 ± 12.79	53.5 ± 14.91	24.95 ± 5.18	28.1 ± 6.42	Chest wheezing, FEV, MMEF, SOD, MDA, thiol, CAT, nitrite
Khazdair et al. 2018 [32]	Veterans	2 months	35(♂) Int:22 Cnt:13	*Z. multiflora* extract	5 and 10 mg/kg/day	54.75 ± 2.81	53.30 ± 5.01	26.34 ± 0.94	26.87 ± 0.99	FVC, PEF, MDA, thiol
Khazdair et al. 2020 [33]	Sulfur mustard exposed patients	8 weeks	34(♂) Int:22 Cnt:12	*Z. multiflora* syrup	5 and 10 mg/kg/day	55.45 ± 3.68	54.10 ± 4.01	NM	NM	MMEF
Ghanbari-Niaki et al. 2018 [34]	Postmenopausal	8 weeks	48(♀) Int:12 Cnt:12	*Z. multiflora* supplement	500 mg/day	54.4 ± 3.9	56.5 ± 4.2	25.6 ± 2.2	27.9 ± 2.2	MDA
Ghanbari-Niaki et al. 2018 [34]	Postmenopausal	8 weeks	48(♀) Int:12 Cnt:12	Circuit resistance training program and *Z. multiflora* supplementation	500 mg/day	53.8 ± 6	58.03 ± 4.7	27.6 ± 2.7	26.6 ± 3.1	MDA

*Data reported as mean ± standard deviation

Abbreviations: Intervention (Int), Control (Cnt), *Zatartia multiflora (Z. multiflora)*, Body mass index (BMI), Not mentioned (NM), Forced expiratory volume (FEV), Forced vital capacity (FVC), Maximal mid-expiratory flow (MMEF), Peak expiratory flow (PEF), Malondialdehyde (MDA), Superoxide dismutase (SOD), Catalase (CAT)

Table 2 Overall estimates of the meta-analysis for the effect of *Zataria multiflora* on outcomes

Outcome variables	Reference	WMD or SMD (95% CI)	*P* value	Assessment of heterogeneity		Pooling Method	Publication bias	
				I^{2**} (%)	Q-statistic *P* value		Egger test *P* value	Begg's test *P* value
Respiratory symptoms								
Cough*	[26, 29, 30]	-0.99 (-1.66, -0.33)	0.003	74.67	0.01	Random-effect model	0.96	1.00
Day wheezing*	[24, 31]	-1.18 (-1.44, -0.92)	0.000	0.00	0.79	Fixed-effect model	NA	NA
Night wheezing*	[26, 30]	-0.74 (-1.09, -0.37)	0.0001	0.00	0.92	Fixed-effect model	NA	NA
Chest wheezing*	[25, 26, 30]	-1.15 (-1.65, -0.64)	0.000	86.86	0.0005	Random-effect model	0.74	1.00
Pulmonary functions								
FEV (L)*	[25, 26, 29–31]	11.38 (7.40, 15.35)	0.000	10.27	0.35	Fixed-effect model	0.60	0.81
FVC (L)*	[24, 29, 32]	16.01 (12.26, 19.75)	0.000	0.00	0.46	Fixed-effect model	0.21	1.00
MMEF (L/s)*	[24, 25, 33]	9.41 (3.47, 15.36)	0.0019	0.00	0.40	Fixed-effect model	0.73	1.00
PEF (L/min)*	[24, 29, 32]	8.78 (4.13, 13.43)	0.0002	25.78	0.26	Fixed-effect model	0.50	1.00
Oxidative stress parameters								
MDA (mg/dL)¥	[25, 26, 32, 34]	-1.54 (-2.17, -0.90)	0.000	67.07	0.01	Random-effect model	0.07	0.22
SOD (U/mg protein)¥	[25, 26]	0.16 (-0.58, 0.91)	0.66	60.68	0.11	Random-effect model	NA	NA
Thiol (µmol/L)¥	[25, 26, 32]	0.94 (-0.16, 2.04)	0.093	85.76	0.0009	Random-effect model	0.0002	0.29
CAT (U/mg protein)¥	[25, 26]	0.97 (0.46, 1.46)	0.0001	33.76	0.22	Fixed-effect model	NA	NA
Nitrite (µmol/L)¥	[25, 26, 31]	-0.50 (-2.53, 1.53)	0.62	95.28	0.000	Random-effect model	0.01	0.29

*Data reported as mean ± standard deviation

*Data reported as WMD

¥Data reported as SMD

**I^2 index ≥ 50% indicates moderate-to-high heterogeneity

Abbreviations: Weighted mean difference (WMD), Standardized mean difference (SMD), Not applicable (NA), Forced expiratory volume (FEV), Forced vital capacity (FVC), Maximal mid-expiratory flow (MMEF), Peak expiratory flow (PEF), Malondialdehyde (MDA), Superoxide dismutase (SOD), Catalase (CAT)

(WMD: -1.15; 95% CI: -1.65, -0.64; $P = 0.000$) compared to the control group (Fig. 2). Due to a high level of heterogeneity between studies for cough and chest wheezing ($I^2 = 74.67$; $P = 0.019$ and $I^2 = 86.86$; $P = 0.0005$, respectively), a random-effects model was employed to analyze these outcomes.

Effects of Zataria multiflora on pulmonary functions

All pulmonary function outcomes were examined using a fixed-effects model due to low heterogeneity. Heterogeneity values for each variable are displayed in Table 2. The pooled results indicated that *Z. multiflora* significantly improved FEV (WMD: 11.38; 95% CI: 7.40, 15.35; $P = 0.000$), FVC (WMD: 16.01; 95% CI: 12.26, 19.75; $P = 0.000$), MMEF (WMD: 9.41; 95% CI: 3.47, 15.36; $P = 0.0019$), and PEF (WMD: 8.78; 95% CI: 4.13, 13.43; $P = 0.0002$) (Fig. 3).

Effects of Zataria multiflora on oxidative stress parameters

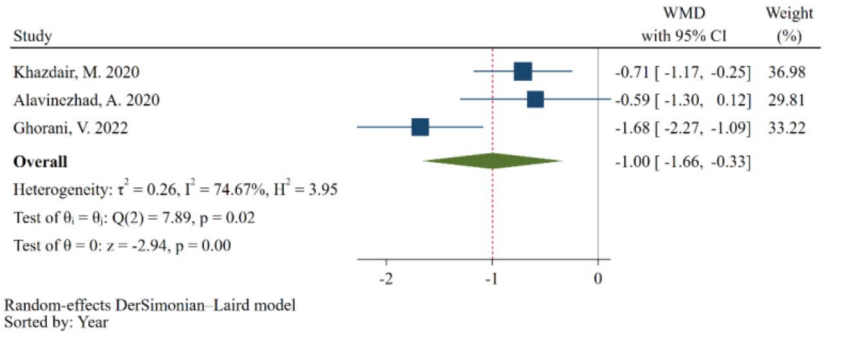
The overall effects of *Z. multiflora* on oxidative stress parameters are presented in Table 2. One clinical trial had a two-arm design with different doses of *Z. multiflora* [34]. In our analysis, we treated each arm as a separate study. The results of the random-effects analysis on five included trials [25, 26, 32, 34] revealed that *Z. multiflora* significantly reduced MDA levels (SMD: -1.54; 95% CI: -2.17, -0.90; $P = 0.000$). The meta-analysis of the included trials showed that *Z. multiflora* did not have any significant effect on SOD (SMD: 0.16; 95% CI: -0.58, 0.91; $P = 0.66$), thiol (SMD: 0.942; 95% CI: -0.16, 2.04; $P = 0.093$), and nitrite levels (SMD: -0.50; 95% CI: -2.53, 1.53; $P = 0.62$) (Fig. 4). Due to evident heterogeneity (Table 2), a random-effects model was employed to examine these outcomes. Two included trials assessed the effect of *Z. multiflora* on CAT levels using a fixed-effects model. The pooled effect size indicated that *Z. multiflora* significantly increased CAT levels (SMD: 0.97; 95% CI: 0.46, 1.46; $P = 0.0001$).

Publication bias

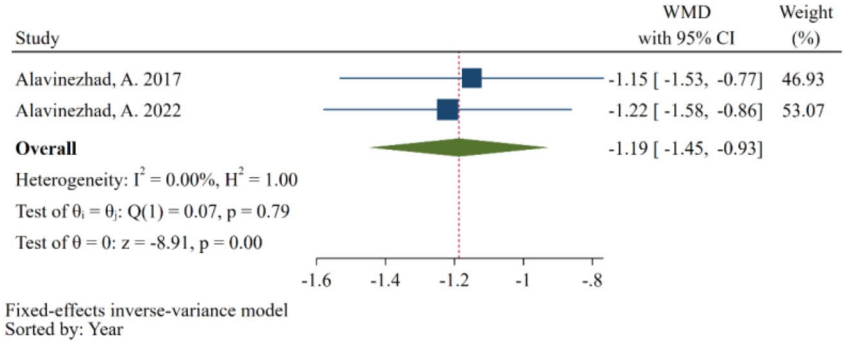
Publication bias was evaluated using Egger's test and Begg's test (Table 2). The results indicated no significant evidence of publication bias for most outcome variables, as reflected by non-significant *p*-values in both tests. However, for Thiol (Egger's test: $p = 0.0002$) and Nitrite (Egger's test: $p = 0.01$), some potential asymmetry was detected, suggesting the possibility of bias.

Sensitivity analyses

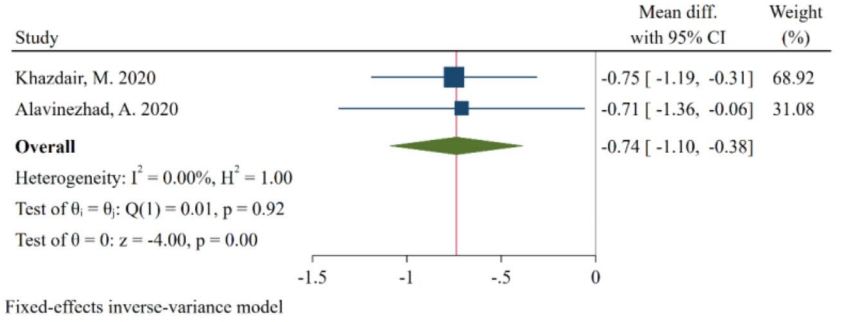
We conducted sensitivity analyses for all variables in the present study. When analyzing respiratory symptom variables, no single study significantly influenced the pooled



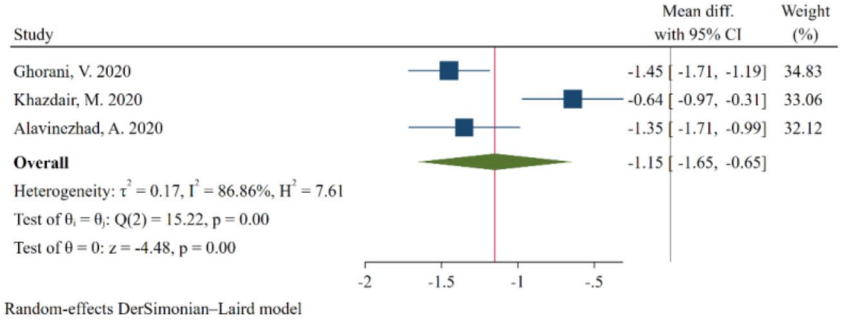
A. Cough



B. Day wheezing

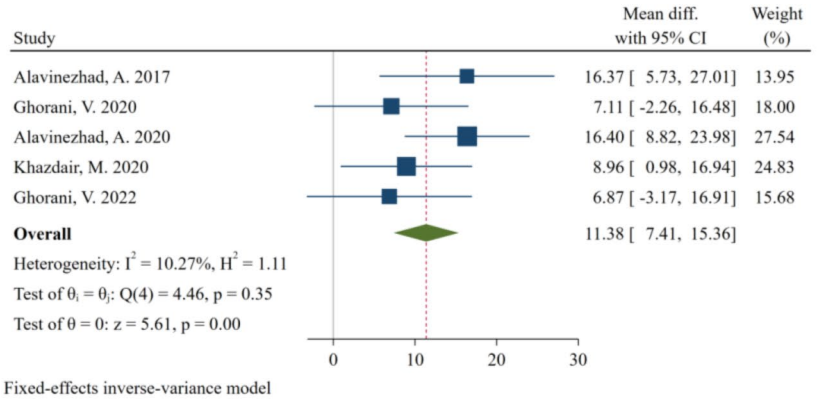


C. Night wheezing

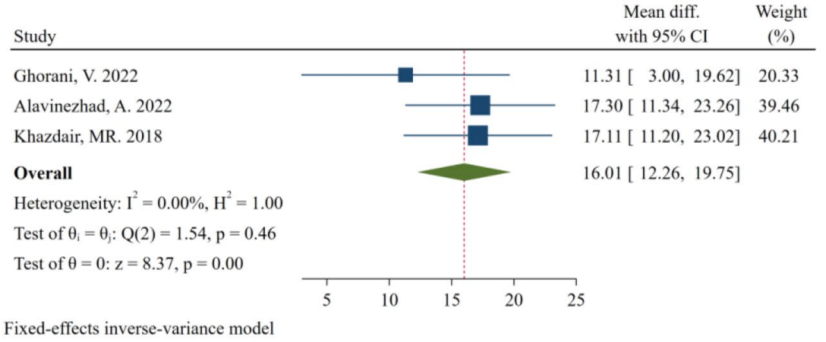


D. Chest wheezing

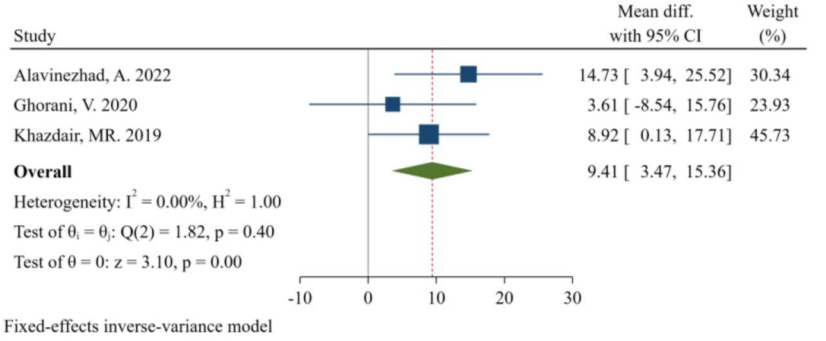
Fig. 2 Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of *Zataria multiflora* on respiratory symptoms, (**A**) Cough, (**B**) Day wheezing, (**C**) Night wheezing, (**D**) Chest wheezing



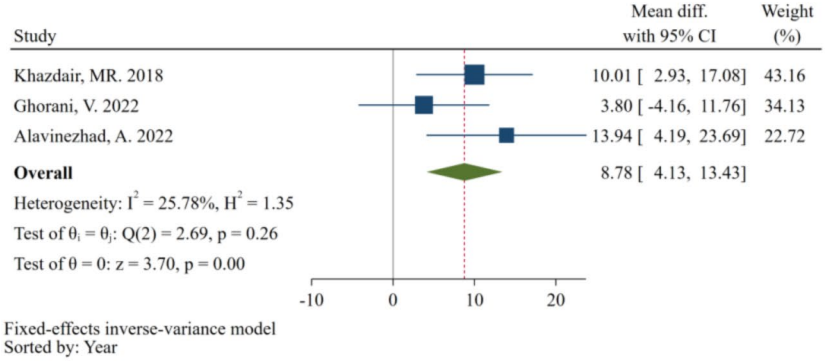
A. FEV



B. FVC

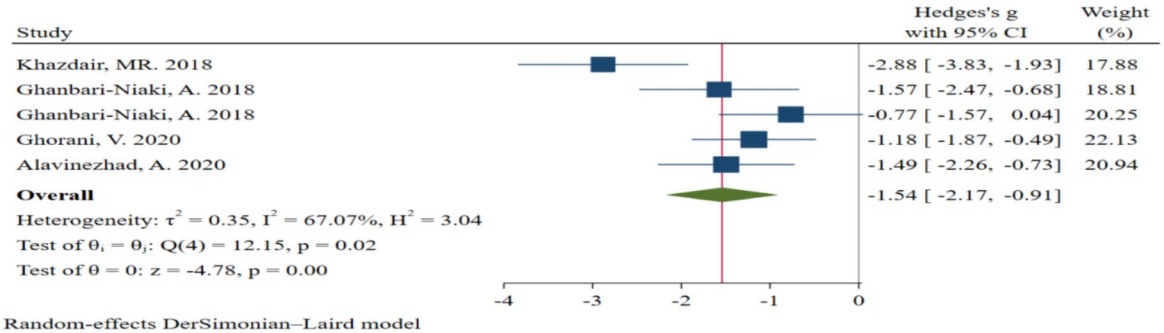


C. MMEF

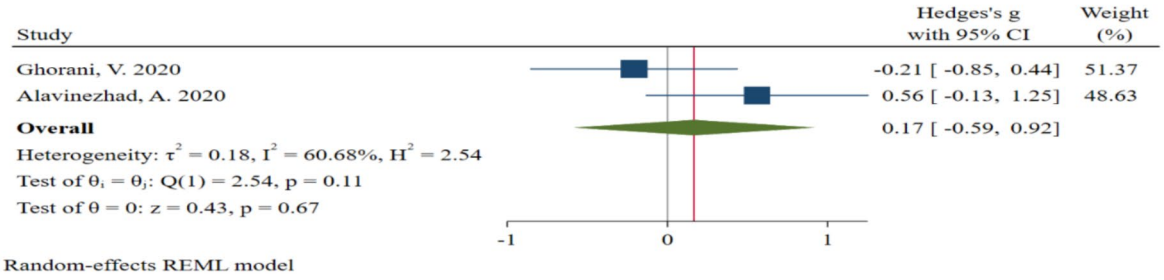


D. PEF

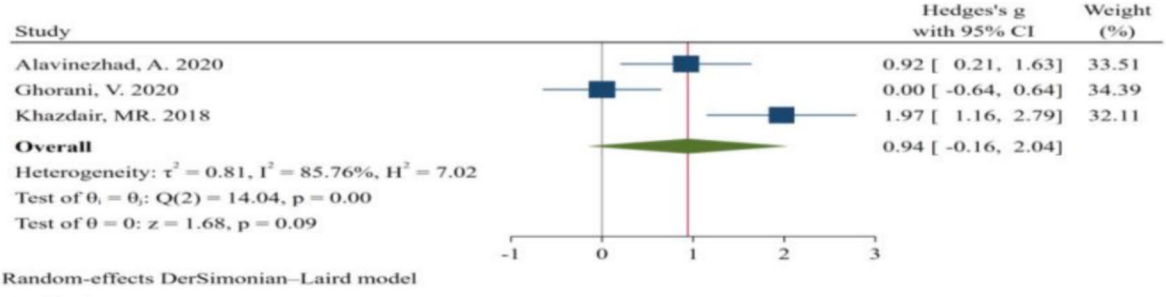
Fig. 3 Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of *Zataria multiflora* on pulmonary functions, (**A**) FEV, (**B**) FVC, (**C**) MMEF, (**D**) PEF. Abbreviations: Forced expiratory volume (FEV), Forced vital capacity (FVC), Maximal mid-expiratory flow (MMEF), Peak expiratory flow (PEF)



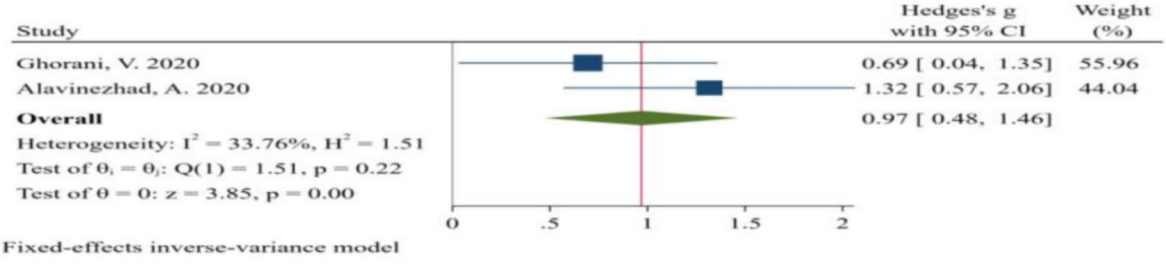
A. MDA



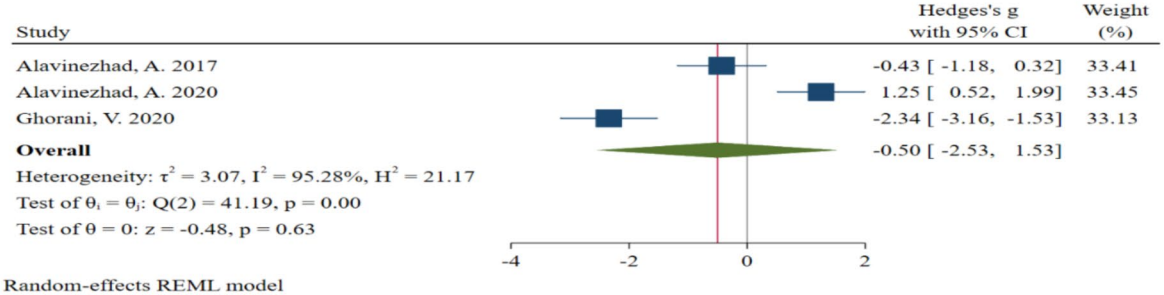
B. SOD



C. Thiol



D. CAT



E. Nitrite

Fig. 4 Forest plot detailing standardized mean difference and 95% confidence intervals (CIs) for the effect of *Zataria multiflora* on oxidative stress parameters (**A**) MDA, (**B**) SOD, (**C**) Thiol, (**D**) CAT (**E**) Nitrite. Abbreviations: Malondialdehyde (MDA), Superoxide dismutase (SOD), Catalase (CAT)

Table 3 Subgroup analysis

MDA				
Subgroup	**Number of studies**	**Hedges' g (95% CI)**	***p*-value**	**Q-test for subgroup differences (Q b, *p*-value)**
Sample size				Q b = 1.11, *p* = 0.293
< 30	2 [34]	-1.146 (-1.936, -0.356)	0.004	
≥ 30	3 [25, 26, 32]	-1.804 (-2.742, -0.866)	0.000	
Health status				Q_b = 0.36, *p* = 0.551
Respiratory diseases	3 [25, 26, 32]	-1.323 (-1.834, -0.812)	0.000	
Other conditions	2 [34]	-1.720 (-2.918, -0.521)	0.005	
FEV				
Subgroup	**Number of studies**	**Mean Difference (95% CI)**	**p-value**	**Q-test for subgroup differences (Q b, *p*-value)**
Sample size				
< 40	3 [26, 30, 31]	13.607 (8.725 to 18.489)	0.000	Q_b = 2.37, *p* = 0.124
≥ 40	2 [25, 29]	6.998 (0.148 to 13.849)	0.124	

The Q-test for subgroup differences (Q_b) was used to assess heterogeneity between subgroups

A random-effects model was applied for meta-analysis, and a significance level of $p < 0.05$ was considered statistically significant

Abbreviations: Forced expiratory volume (FEV), Malondialdehyde (MDA), Confidence interval (CI)

results, indicating high stability in our analysis. However, in terms of pulmonary functions, specifically for MMEF, the exclusion of Alavinezhad's study [24] altered the significance of the relationship: MMEF (WMD: 7.09; 95% CI: -0.02, 14.22; $P = 0.05$). Additionally, our sensitivity analysis concerning oxidative stress parameters, specifically thiol, revealed that the study reported by Ghorani et al. [25] significantly influenced the pooled effect. Consequently, upon excluding this study, the results obtained showed a significant effect of *Z. multiflora* on thiol (SMD: 1.43; 95% CI: 0.40, 2.45; $P = 0.006$).

Subgroup analysis

Subgroup analysis for MDA revealed significant results in both sample size categories and health status groups (Table 3). Studies with a smaller sample size (< 30) reported a pooled effect size of Hedges' g = -1.146 (95% CI: -1.936 to -0.356, $p = 0.004$), while those with ≥ 30 participants showed a larger effect (Hedges' g = -1.804, 95% CI: -2.742 to -0.866, $p = 0.000$). When stratified by health status, studies involving respiratory diseases had a pooled effect of Hedges' g = -1.323 (95% CI: -1.834 to -0.812, $p = 0.000$), whereas those in the "other" category showed a stronger effect (Hedges' g = -1.720, 95% CI: -2.918 to -0.521, $p = 0.005$). These results suggest that larger sample sizes and different health conditions may influence the estimated intervention effect on MDA levels.

For FEV, studies with a smaller sample size (< 40) had a pooled mean difference of 13.607 (95% CI: 8.725 to 18.489, $p = 0.000$), while those with ≥ 40 participants showed a lower mean difference (6.998, 95% CI: 0.148 to 13.849, $p = 0.124$). The Q-test for subgroup differences (Q_b = 2.37, $p = 0.124$) indicated that the observed effect size differences between sample size groups were not statistically significant (Table 3). This suggests that while there was a numerical difference, sample size may not be a major factor influencing FEV outcomes.

GRADE assessment

The certainty of evidence for respiratory symptoms, pulmonary function, and oxidative stress biomarkers varied across different outcomes. The assessment of respiratory symptoms, including cough and wheezing, indicated very low certainty due to a high risk of bias, small sample sizes, and heterogeneity across studies. Pulmonary function tests, including FEV, FVC, MMEF, and PEF, demonstrated low to moderate certainty, with FEV showing the highest level of certainty due to its larger sample size and lower heterogeneity. Among oxidative stress biomarkers, MDA exhibited moderate certainty because of its strong association with disease severity and acceptable heterogeneity levels. In contrast, SOD, Thiol, and Nitrite were classified as very low certainty due to serious risk of bias, small sample sizes, and potential publication bias, as suggested by significant Egger's test results. CAT was rated as low certainty despite its strong association, as concerns regarding imprecision remained. The detailed GRADE assessment results are available in Supplementary Material 2.

Discussion

In the current systematic review and meta-analysis, we summarized available data from nine RCTs that enrolled 394 participants. The dosage of *Z. multiflora* ranged from 3 to 10 mg/kg/day, and the intervention duration varied from 8 weeks to 2 months in different studies, all of which were conducted in Iran. To the best of our knowledge, this is the first meta-analysis that examined the effect of *Z. multiflora* on respiratory symptoms, pulmonary functions, and oxidative stress parameters. The main result of this study was that *Z. multiflora* had a significant effect

on cough, day wheezing, night wheezing, and chest wheezing compared to the control group. Additionally, *Z. multiflora* significantly improved FEV, FVC, and PEF. Concerning the intervention's effect on oxidative stress parameters, our findings showed that *Z. multiflora* significantly reduced MDA levels. Furthermore, *Z. multiflora* increased catalase and thiol levels.

Various mechanisms of the relaxant effects of *Z. multiflora* extract on tracheal smooth muscle, including an antagonistic effect on histamine H1 receptors [18], a muscarinic effect [35], and a stimulatory effect on β-adrenoceptors [36], were examined. The preventive effect of *Z. multiflora* extract on voltage-dependent calcium channels in ileum smooth muscle was also revealed [37]. Furthermore, the impact of *Z. multiflora* on symptoms and FEV1 can lead to an improvement in the quality of life. *Z. multiflora* has demonstrated positive effects on respiratory symptoms, including cough, day wheezing, night wheezing, and chest wheezing in clinical trials [27]. In patients with COPD, treatment with *Z. multiflora* extract resulted in a significant improvement in respiratory symptoms such as cough and chest tightness [38]. Additionally, *Z. multiflora* extract demonstrated bronchodilatory effects in asthmatic patients, resulting in a reduction of respiratory symptoms, including cough and wheezing [29]. Furthermore, *Z. multiflora* mouthwash was found to be effective in reducing the microbial load of the oral cavity, which can help reduce respiratory symptoms associated with ventilator-associated pneumonia [39]. Consistent with the results of our study, Ghorani et al. demonstrated that after 2 months, breathlessness and chest wheeze in the treated (*Z. multiflora*) groups showed improvement [25]. In addition, in COPD patients, treatment with *Z. multiflora* extract resulted in significant improvements in FVC and FEV1, reflecting positive effects on pulmonary function [29, 38]. In asthmatic patients, *Z. multiflora* extract demonstrated a bronchodilatory effect comparable to theophylline but with a longer duration of action [39]. Additionally, *Z. multiflora* extract improved pulmonary function tests, including FEV1, in veterans exposed to sulfur mustard [25]. Another study indicated that *Z. multiflora* significantly improved pulmonary function, including MMEF and FEV [33].

Z. multiflora has antioxidant functions through both direct and indirect pathways [40, 41]. It down-regulates the activity of oxidative stress markers such as reduced nicotinamide adenine dinucleotide oxidase (NOX) and nuclear factor kappa B (NF-kB), while up-regulating the expression and activity of transcription factors involved in oxidative stress, such as nuclear respiratory factor 2 (NRF2) [42]. In addition, the administration of *Z. multiflora* decreased various markers of inflammatory activity in healthy subjects [43]. *Z. multiflora* reduced the gene expression of inflammatory cytokines, including transforming growth factor-β (TGF-β), interleukin 4 (IL-4), and interleukin 4 (IL-17), while increasing the gene expression of anti-inflammatory cytokines such as interferon gamma (IFN-γ) and forkhead box P3 (FOXP3) [44, 45]. The suppressive effect of *Z. multiflora* extract on angiogenesis and migration in human umbilical vein endothelial cells (HUVECs) was also identified [45]. Furthermore, cancer cell metastasis was inhibited through a decrease in matrix metalloproteinases-2 (MMP) and vascular endothelial growth factor A (VEGFA) expression in the HeLa cells [46].

In a clinical trial, forty-seven veterans were allocated to three groups, including the placebo group (P) and two groups treated with 5 and 10 mg/kg/day of *Z. multiflora* [32]. FVC and PEF values significantly increased in the *Z. multiflora* 5 and 10 mg/kg treated groups in steps I and II compared to step 0. Additionally, the level of MDA significantly decreased in the two treatment groups compared to step 0. We observed that *Z. multiflora* did not have any significant effect on SOD and nitrite levels. However, in the mentioned study, the levels of thiol, SOD, and CAT in the *Z. multiflora* 5 and 10 mg/kg treated groups in steps I and II were significantly increased. This difference in results could be attributed to the small sample size and variations in laboratory kits and methods. Ghorani et al. showed that after 2 months, breathlessness and chest wheezing in the treated (*Z. multiflora*) groups improved. Additionally, MDA levels were significantly decreased, while catalase activities increased. However, the results regarding the effect of *Z. multiflora* on SOD and nitrate were different from our findings [25]. One study found that *Z. multiflora* extract reduced MDA levels and increased thiol, SOD, and CAT levels in the brain [47]. Another study showed that *Z. multiflora* supplementation improved MDA and homocysteine (Hcys) levels but had no significant effect on thiobarbituric acid reactive substances (TBARS) [38]. Additionally, *Z. multiflora* and carvacrol were found to restore SOD, CAT, and thiol levels in lipopolysaccharide-induced cardiovascular injury [48]. Due to the controversy in the results, this meta-analysis study was conducted to summarize the obtained results. The subgroup analysis indicated that larger sample sizes and differences in health status may influence the effect of *Z. multiflora* on MDA levels, while for FEV, sample size differences were not statistically significant. The GRADE assessment revealed low to very low certainty for most outcomes due to small sample sizes, heterogeneity, and potential bias, except for MDA, which had moderate certainty.

Our study had several strengths. First, this is the first study summarizing the effects of *Z. multiflora* on respiratory symptoms, pulmonary functions, and oxidative stress parameters. Second, we conducted a sensitivity

analysis, and we found that after this analysis for MMEF, removing Alavinezhad's study [24] changes the significance of the relationship with MMEF. Also, our sensitivity analysis results regarding thiol indicated that the study reported by Ghorani et al. [25] significantly affected the pooled effect. However, some limitations need to be considered when interpreting our results. Because all the studies were conducted in Iran, we were not able to investigate the effects of racial, ethnic, and cultural differences in the present study. Additionally, environmental factors, such as air quality, climate, and exposure to pollutants, which can vary significantly across different locations, were not accounted for in this study. These factors may influence respiratory health and could impact the generalizability of the findings. Also, the limited number of studies and variability in health conditions may have impacted the findings. The low certainty of evidence highlights the need for larger, high-quality trials. Additionally, the amount of heterogeneity was remarkable in studies on oxidative stress parameters, cough, and chest wheezing. Further, respiratory diseases encompass a broad spectrum of conditions. While this study focused on asthma and COPD due to shared mechanisms such as inflammation and oxidative stress, it does not generalize the effects of *Z. multiflora* to all respiratory diseases. Future research should evaluate its effects in specific respiratory conditions individually to provide more targeted conclusions.

Conclusion

This study offers a comprehensive analysis of the impact of *Zataria multiflora* on respiratory symptoms, pulmonary function, and oxidative stress markers. It represents the first systematic evaluation of *Z. multiflora*'s effects in this field. The findings indicate significant improvements in respiratory symptoms and pulmonary function, as well as reduced oxidative stress, suggesting the potential therapeutic value of *Z. multiflora* in respiratory disorders. Additionally, the study suggests that *Z. multiflora* holds promise as a natural remedy for respiratory ailments, providing potential benefits such as symptom relief and improved quality of life.

However, due to the small number of included trials (mostly 2–3) for each outcome variable, these results should be interpreted with caution. Further research should address limitations, including the lack of geographical diversity, study heterogeneity, and the small sample size of included trials. Expanding the scope of research to include larger and more diverse populations will enhance the robustness of findings and improve their applicability in clinical practice. Moreover, additional studies are needed to comprehensively evaluate the safety profile of *Z. multiflora* to address any potential concerns and ensure its safe application in clinical settings.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

NA supervised the work, FA extracted data, AN drafted and revised the work, SMG drafted the work, ARA analyzed and interpreted the data, NS drafted the work, ND drafted the work, MM supervised the work.

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Data availability

The datasets used and analyzed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study received approval from the Medical Ethics Committee of Iran University of Medical Sciences (IR.IUMS.REC.1403.551), confirming adherence to the ethical guidelines outlined in the Declaration of Helsinki.

Consent for publication

Not applicable in the declarations section.

Competing interests

The authors declare no competing interests.

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