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

Naheed Aryaeian
Iran University of Medical Sciences
Fahimeh Agh
Saveh University of Medical Sciences
Seyed Mojtaba Ghoreishy
Iran University of Medical Sciences
Amirhossein Ramezani Ahmadi
Isfahan University of Medical Sciences
Narges Sadeghi
Ahvaz Jundishapur University of Medical Sciences
Narges Dehghan
Ahvaz Jundishapur University of Medical Sciences
Mehrnaz Morvaridi (mehrnaz.morvaridi@gmail.com)
Iran University of Medical Sciences

Research Article

Keywords: Zataria multiflora, Respiratory symptoms, Pulmonary function, oxidative stress

Posted Date: October 23rd, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3362817/v1

Additional Declarations: No competing interests reported.

Abstract

Background

Zataria multiflora Boiss. is a medicinal plant with multiple pharmacological effects. This systematic review aims to review the available randomized controlled trials (RCTs) to assess the effects of zataria multiflora on respiratory symptoms, pulmonary function, and oxidative stress parameters.

Materials & Methods

We conducted a systematic review by searching the PubMed, Scopus, EMBASE, Cochrane Central for Randomized Clinical Trials. All statistical analyses were performed using STATA.

Results

Z. multiflora had a significant effect on cough, day wheezing, night wheezing and chest wheezing. Also, significantly improved FEV, FVC, MMEF, and PEF. In addition, significantly reduced MDA levels and increased CAT levels.

Conclusion

The meta-analysis showed that the consumption of ZT significantly reduced respiratory symptoms compared to the control group. Also, Zataria multiflora might be beneficial in improving pulmonary function. Except MDA, the result of this study indicated that Zataria multiflora did not have any significant effect on oxidative stress parameters.

Introduction

Zataria multiflora Boiss. or Shirazi thyme is a medicinal plant that grows in Iran, Afghanistan and Pakistan. It is thyme like herb that belongs to Lamiaceae family (1). The essential oil of the Z. multiflora contains significant amounts of phenols and flavonoids that among them, carvacrol and thymol are the main compounds. The other major components if this plant are P-cymene, linalool, caryophyllene, -terpinene and borneol (2). As well as, among the phytochemicals reported from Z. multiflora are Flavonoids like apigenin, luteolin and 6-hydroxy luteolin (3).

The plant and its ingredients have multiple pharmacological effects such as antioxidant, anti-inflammatory, immunomodulatory (1, 4–6). Moreover, Z. multiflora is used as antiseptic, antispasmodic and treatment of cold and cough in traditional medicine (2). The results from previous studies suggested the protective effects of Z. multiflora on animal models of asthma and chronic obstructive pulmonary disease (COPD) because of their antioxidant, anti-inflammatory, immunomodulatory effects (7, 8). In addition, Z. multiflora also has other therapeutical uses include e treatment of some GI disorders, such as bloating, dyspepsia and irritable bowel syndrome, fever, premature labor pain, rupture, bone and joint pain, headache, migraine, gastrodynia, diarrhea, vomiting and the common cold (9).

The respiratory system primary function is gas exchange, and its anatomy and physiology are suitable to fulfil this function (10). The respiratory function of the lung is critical and important for survival because oxygen is a vital molecule for the production of energy that is essential for the life of organisms (11). Respiratory disorders are a common cause of illness and death all over the world. Asthma, bronchitis, common colds and cough are among the most common disorders of the respiratory system (12). Immune and inflammatory responses are associated with respiratory disorders such as asthma and COPD. Furthermore, oxidants also are related to respiratory disorders and they are significantly increased in them (13).

Medicinal plants are used for the medical treatment of several disorders (14). Traditionally various herbal products used for the treatment of respiratory disorders including asthma and bronchitis (15). Z. multiflora is one of the medicinal herbs that used as a treatment for disorders of respiratory tract and common cold due to antiseptic and anti-tussive effect (16). Moreover, Z. multiflora can moderate oxidative stress, inflammation and immunological parameters (5, 8, 17–19). Previous studies reported that Z. multiflora has a decreasing effect on tracheal responsiveness, long inflammation, pathological change and cytokine levels in animal models of asthma and COPD (20–22). The therapeutic effects of this plants may be due to its main compounds including thymol and carvacrol (23). Significant antioxidant activity of the Z. multiflora is shown in the previous studies (17, 24, 25). To the best of our knowledge, the results of previous clinical trials conducted to assess the effect of zataria multiflora are inconsistent and controversial and there is no meta-analysis available that evaluates these results to achieve a consistent and reliable conclusion. So, this systematic review and meta-analysis aims to review the available randomized controlled trials (RCTs) to assess the effects of zataria multiflora on respiratory symptoms, pulmonary function, and oxidative stress parameters.

Materials and Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The protocol was registered in PROSPERO (number: CRD42022374477).

Search strategy and study selection

We conducted a systematic review by searching the PubMed, Scopus, EMBASE, Cochrane Central for Randomized Clinical Trials and Web of Science databases up to October 2022. The following keywords were used for identifying studies on zataria multiflora, pulmonary functions, respiratory symptoms, and oxidative stress: ("zataria multiflora" OR "Z. multiflora" OR "Z. multiflora Boiss" OR "zataria multiflora Boiss" OR "zataria bracteata Boiss" OR "avishan-e-shirazi" OR "shirazi thyme") AND (wheeze OR wheezing OR "chest wheeze" OR cough OR coughing OR respiratory OR "respiratory symptoms" OR breath OR pulmonary OR "pulmonary symptoms" OR lung OR "lung symptoms" OR "respiratory assessment" OR "pulmonary function" OR "pulmonary function test" OR "lung function" OR "lung function test" OR "spirometry" OR "total lung capacity" OR "vital capacity" OR "forced expiratory volume" OR "forced vital capacity" OR "maximal voluntary ventilation" OR "diffusing capacity for carbon monoxide" OR "transfer factor of the lung for carbon monoxide" OR "forced oscillation technique" OR "maximal inspiratory pressure" OR "maximal expiratory pressure" OR "maximum mid-expiratory flow" OR "maximal expiratory flow" OR "peak expiratory flow" OR "TLC" OR "VC" OR "FVC" OR "FEV" OR "DLCO" OR "TLCO" OR "MIP" OR "MEP" OR "MVV" OR "MMEF" OR "MEF" OR "PEF" OR "oxidative stress" OR malondialdehyde OR MDA OR thiol OR "superoxide dismutase" OR SOD OR catalase OR CAT OR nitrite OR oxidant OR antioxidant). We had no language, time, and location restrictions for identified studies. The reference lists of relevant reviews were manually screened by two independent reviewers (FA, MM) to find other eligible articles.

Eligibility criteria

Eligibility criteria are based on the PICOS approach: Population (P): Adults, Intervention (I): zataria multiflora, Comparison (C): placebo or no intervention, Outcome (O): pulmonary functions, respiratory symptoms, and oxidative stress (S): randomized controlled trial (RCT). Published studies were excluded with the following criteria: (1) animal or in vitro studies, (2) duplicate or overlapping data, (3) cross sectional, case reports, and case series studies (4) articles without available full text

Data extraction

Data extraction form was designed and completed for collecting the information of studies by two independent reviewers (FA, MM). Extracted data included: the first author's name, year of publication, country, study design, total sample size, intervention dose, characteristics of participants, duration of supplementation, study quality, and outcomes.

Risk of bias assessment

We evaluated the quality of each eligible study based on Cochrane Risk Assessment Tool selection bias with the following 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. Each item was categorized as low, high, or an unclear risk of bias.

Statistical analysis

We extracted all data in Mean + SD format and converted other formats to SD if necessary. For evaluating the effects of zataria multiflora on respiratory symptoms, pulmonary functions, and oxidative stress parameters, weighted mean difference (MD) and 95% confidence interval (CI) were applied. All statistical analyses were performed using STATA (version 15). Heterogeneity was assessed using the I^2 statistic, if I^2 was less than 50%, we used a fixed effects model, and a random effects model was applied for I^2 more than 50%. P value < 0.05 was considered as statistically significant for our systematic review.

Results

Study selection

The search strategy and screening for identifying eligible studies was shown in Fig. 1. Initially, 673 publications were identified through searching over databases. In the first screening phase, 245 articles were excluded after titles and abstracts screening due to being duplicates. Then, irrelevant articles to this meta-analysis (n = 410) were excluded. Following this, full texts of 18 potentially relevant articles were reviewed. Finally, 9 articles that met the eligibility criteria were included (26–34).

Characteristics of the studies

Table 1 outlined the general characteristics of included studies. All studies were conducted in Iran. Seven studies used the Zataria multiflora (Z. multiflora) extract (26–32), one study used Z. multiflora syrup (33), and one study used Z. multiflora supplement (34). We analysis the effect of Z. multiflora on many outcomes, respiratory symptoms like cough, day wheezing, night wheezing and chest wheezing, pulmonary functions such as forced expiratory volume (FEV), forced vital capacity (FVC), maximal mid-expiratory flow (MMEF) and peak expiratory flow (PEF), and oxidative stress parameters including malondialdehyde (MDA), nitrite, thiol, superoxide dismutase (SOD), and catalase (CAT).

Table 1
Main characteristics of the included studies.

Author, year (ref)	Health condition	Duration (week)	Participants, (n)	Intervention type	Z. multiflora Dose, Unit	Age range, years Mean ± SD		BMI, kg/m2 Mean ± SD		Main outco
						Intervention	Control	Intervention	Control	
Ghorani et al. 2022 (45)	chronic obstructive pulmonary diseases	8	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	Coug FEV, F PEF
Khazdair et al. 2020 (46)	sulfur mustard exposed veterans	8	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	Coug Night whee Chest whee FEV
Alavinezhad et al. 2022 (44)	asthmatic patients	8	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 whee FVC, MME PEF
Alavinezhad et al. 2017 (29)	asthmatic patients	8	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 whee FEV, nitrite
Alavinezhad et al. 2020 (30)	asthmatic patients	8	36( ) Int:24 Cnt:12	Z. multiflora extract	5 and 10 mg/kg/day	45.30 ± 11.27	48.0 ± 9.6	NM	NM	Coug Night whee Chest whee FEV SOD, MDA, Thiol, CAT, nitrite
Ghorani et al. 2020 (31)	Chronic obstructive pulmonary disease	8	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 whee FEV, MME SOD, MDA, Thiol, CAT, nitrite
Khazdair et al. 2018 (47)	veterans	8	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, MDA, Thiol
Khazdair et al. 2019 (48)	sulfur mustard exposed patients	8	34( ) Int:22 Cnt:12	Z. multiflora syrup	5 and 10 mg/kg/day	55.45 ± 3.68	54.10 ± 4.01	NM	NM	MME
Ghanbari-Niaki et al. 2018 (49)	Postmenopausal	8	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 (49)	Postmenopausal	8	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

Effects of Zataria multiflora on respiratory symptoms

Three studies, including 74 intervention and 27 control participants, evaluated the effect of Z. multiflora on the cough (26, 27, 30), two studies, including 44 intervention and 22 control participants evaluated the effect of Z. multiflora on the day wheezing (28, 29), two studies, including 46 intervention and 24 control participants evaluated the effect of Z. multiflora on the nigh wheezing (27, 30), and three studies, including 75 intervention and 37 control participants evaluated the effect of Z. multiflora on the chest wheezing (27, 30, 31). According to the meta-analysis (Table 2), Z. multiflora had a significant effect 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 = 0.000), night wheezing (WMD: -0.74; 95% CI: -1.09, -0.37; P = 0.0001) and chest wheezing (WMD: -1.15; 95% CI: -1.65, -0.64; P = 0.000) compared to the control group (Fig. 2). As there was a high level of heterogeneity between studies for cough and chest wheezing (I2 = 74.67; P = 0.019 and I2 = 86.86; P = 0.0005 respectively), a random-effects model was used to analyze this outcome. We performed sensitivity analysis in each meta-analysis for respiratory symptoms variables and found no single study could significantly affect the pooled results, indicating a high stability of our analysis.

Table 2
Overall estimates of meta-analysis for the effect of Zataria multiflora on respiratory symptoms, pulmonary functions, and oxidative stress parameters

Outcome variables	Reference	WMD (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	(30, 45, 46)	-0.99 (-1.66, -0.33)	0.003	74.67	0.01	Random-effect model	0.96	1.00
Day wheezing	(29, 44)	-1.18 (-1.44, -0.92)	0.000	0.00	0.79	Fixed-effect model	NA	NA
Night wheezing	(30, 46)	-0.74 (-1.09, -0.37)	0.0001	0.00	0.92	Fixed-effect model	NA	NA
Chest wheezing	(30, 31, 46)	-1.15 (-1.65, -0.64)	0.000	86.86	0.0005	Random-effect model	0.74	1.00
Pulmonary functions								
FEV	(29–31, 45, 46)	11.38 (7.40, 15.35)	0.000	10.27	0.35	Fixed-effect model	0.60	0.81
FVC	(44, 45, 47)	16.01 (12.26, 19.75)	0.000	0.00	0.46	Fixed-effect model	0.21	1.00
MMEF	(31, 44, 48)	9.41 (3.47, 15.36)	0.0019	0.00	0.40	Fixed-effect model	0.73	1.00
PEF	(44, 45, 47)	8.78 (4.13, 13.43)	0.0002	25.78	0.26	Fixed-effect model	0.50	1.00
Oxidative stress parameters								
MDA	(30, 31, 47, 49)	-1.28 (-1.97, -0.59)	0.0002	94.73	0.000	Random-effect model	0.000	0.08
SOD	(30, 31)	0.12 (-0.43, 0.67)	0.66	61.73	0.11	Random-effect model	NA	NA
Thiol	(30, 31, 47)	SMD: 0.942 (-0.16, 2.04)	0.093	85.76	0.0009	Random-effect model	0.0002	0.29
CAT	(30, 31)	0.97 (0.46, 1.46)	0.0001	33.76	0.22	Fixed-effect model	NA	NA
Nitrite	(29–31)	-1.9 (-12.21, 8.39)	0.71	96.13	0.000	Random-effect model	0.74	1.00

NA, not applicable

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

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 shown in Table 2. The pooled results showed 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). Sensitivity analysis was performed for all variables, after this analysis for MMEF we found removing Alavinezhad's study (28), changes the significance of this relationship MMEF (WMD: 7.09; 95% CI: -0.02, 14.22; P = 0.05); about other variables sensitivity analysis did not show further results. Meta-regression found a direct association between age with change FEV following consumption of Z. multiflora (Table 3). As shown in Fig. 6, meta-regression bubble plot showing the effect of Z. multiflora decreases with increasing age.

Table 3
Meta-regression for the effect of **Age**

Variable	N	Coefficient	SE	P-value
Cough	3	-0.05	0.099	0.61
Chest wheezing	3	0.032	0.072	0.65
FEV	5	-0.87	0.42	**0.04**
FVC	3	-0.28	0.47	0.55
MMEF	3	-0.87	0.72	0.23
PEF	3	-0.85	0.68	0.21
MDA	5	0.16	0.09	0.08
Thiol	3	-0.023	0.19	0.90
Nitrite	3	-1.20	0.87	0.17

FEV: forced expiratory volume, FVC: forced vital capacity, MMEF: maximum mid-expiratory flow, PEF: peak expiratory flow, MDA: malondialdehyde

Effects of Zataria multiflora on oxidative stress parameters

The overall effect of Z. multiflora on oxidative stress parameters are presented in Table 2. One clinical trial had a two-arm with a different dose of Z. multiflora (34). We considered each arm as a separate study. The results of the random-effects analysis on five included trials (30–32, 34) showed that Z. multiflora significantly reduced MDA levels (WMD: -1.28; 95% CI: -1.97, -0.59; P = 0.0002). The meta-analysis of included trials showed that Z. multiflora did not have any significant effect on SOD (WMD: 0.12; 95% CI: -0.43, 0.67; P = 0.66), Thiol (SMD: 0.942; 95% CI: -0.16, 2.04; P = 0.093) and nitrite levels (WMD: -1.9; 95% CI: -12.21, 8.39; P = 0.71) (Fig. 4). Due to obvious heterogeneity (Table 2), a random-effects model was used to examine these outcomes. Our sensitivity analysis results regarding Thiol indicate that the study reported by Ghorani et al. (31) significantly affected the pooled effect, so we removed this study and the results obtained reveal a significant effect of Z. multiflora on Thiol (SMD: 1.43; 95% CI: 0.40, 2.45; P = 0.006). Two included trials assessed the effect of Z. multiflora on CAT levels by using the fixed-effects model. The pooled effect size indicated that Z. multiflora significantly increased CAT levels (WMD: 0.97; 95% CI: 0.46, 1.46; P = 0.0001).

Publication bias

We tested for the presence of publication bias using several methods, and a summary of publication bias analyses is provided in Table 2. The funnel plot is based on the fact that precision in estimating the underlying treatment effect will increase as the sample size of component studies increases. Funnel plot (Fig. 5) suggested a certain degree of asymmetry of the data distribution, and presence of publication bias and an overestimation of the overall effect size of Z. multiflora in MDA and thiol levels. Also, such visual impression was confirmed by the Egger's test (Egger's, P = 0.000, P = 0.0002; for MDA and Thiol, respectively) but was not confirmed by the Begg's rank correlation analysis (Begg's, P = 0.08, P = 0.29; for MDA and Thiol, respectively). Using the trim and fill analyses the intervention effect is adjusted for possible missing studies (filled orange dots) amongst published data (filled dark dots) (Fig. 5). The 'trim and fill' method applied to the funnel plot imputed 2 missing studies for MDA and 2 missing studies for thiol, and the resulting adjusted estimate of the overall effect size was WMD: -0.40; 95% CI: -1.17, 0.36 for MDA, and SMD: 0.00; 95% CI: -1.25, 1.25 for thiol.

Discussion

In the current systematic review and meta-analysis, we summarized available data from 9 RCTs which evaluated 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 (P = 0.003), day wheezing (P = 0.000), night wheezing (P = 0.0001) and chest wheezing (P = 0.000) compared to the control group. Also, Z. multiflora significantly improved FEV (P = 0.000), FVC (P = 0.000), MMEF (P = 0.0019), and PEF (P = 0.0002). About the effect of Z. multiflora on oxidative stress parameters, our finding showed that Z. multiflora significantly reduced MDA levels (P = 0.0002). But this effect was not significant on SOD (P = 0.66), Thiol (P = 0.093) and nitrite levels (P = 0.71). In contrast with another oxidative stress parameters, Z. multiflora significantly increased CAT levels (P = 0.0001). Finally, meta-regression analysis showed a negative marginally significant association between age and FEV (P = 0.04). But this result was not significant for other variables. 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.

Different mechanisms of the relaxant effects of Z. multiflora extracts on tracheal smooth muscle including: antagonistic effect on histamine H1 receptors (20), and muscarinic (35) and also stimulatory effect on β-adrenoceptors (36) were examined. The preventing effect of Z. multiflora extract on voltage dependent calcium channels in ileum smooth muscle was also revealed (37). Furthermore, the effect of Z. multiflora on symptoms and FEV1 can lead to improveming the quality of life. Z. multiflora have antioxidant function through direct and indirect pathways (38, 39). In addition, administration of Z. multiflora decreased different markers of inflammatory activity in healthy subjects (40). Z. multiflora reduced gene expression of inflammatory cytokines including TGF-β, IL-4, and IL-17 while raised gene expression of IFN-γ and FOXP3 as anti-inflammatory cytokines (41, 42). The suppressive effect of Z. multiflora extract on angiogenesis and migration on human umbilical vein endothelial cells (HUVECs) was also identified (42). Also, cancer cell metastasis was inhibited through a decline in matrix metalloproteinases-2 (MMP) and VEGFA expression in the HeLa cells (43).

In line with our finding, forty-seven veterans allocated to three groups included: placebo group (P) and two groups treated with 5 and 10 mg/kg/day of Z. multiflora (Zat 5 and Zat 10) (32). FVC and PEF values were significant increase in Zat 5 and 10 mg/kg treated groups in step I and II compared to step 0. Also, the level of malondialdehyde (MDA) significantly decreased in two treatment groups compared to Step 0. We indicated that Z. multiflora did not have any significant effect on SOD, Thiol and nitrite levels. But in mentioned study the levels of thiol, superoxide dismutase (SOD) and catalase (CAT) in Zat 5 and 10 mg/kg treated groups in step I and II were significantly increased. This difference in the results can be attributed to the small sample size and the difference in laboratory kits and methods. As in our study, Ghorani et al. (31), showed that after 2 months breathlessness and chest wheeze in treated (Z. multiflora) groups were improved. In addition, MDA levels were significantly decreased while catalase activities were increased. But the results of the effect of Z. multiflora on SOD, nitrate and thiol were different from our findings. Another studies indicated that Z. multiflora significantly improved pulmonary function including MMEF (33), FEV (27). Due to the controversy in the results, this meta-analysis study was conducted in order to summarize the obtained results.

Our study had several strengths. First, this is the first study summarizing the effect of Z. multiflora on respiratory symptoms, pulmonary functions, and oxidative stress parameters. Second, we performed sensitivity analysis and we found after this analysis for MMEF, removing Alavinezhad's study (44), changes the significance of this relationship MMEF (WMD: 7.09; 95% CI: -0.02, 14.22; P = 0.05). Also, Our sensitivity analysis results regarding Thiol indicate that the study reported by Ghorani et al.(31) significantly affected the pooled effect (SMD: 1.43; 95% CI: 0.40, 2.45; P = 0.006). However, some limitations need to be considered when interpreting our results. Most included had few participants and the total number of included studies was low. Also, the amount of heterogeneity was remarkable in studies on oxidative stress parameters, cough and chest wheezing.

Conclusion

The present meta-analysis showed that the consumption of Zataria multiflora signifcantly reduced cough, day wheezing, night wheezing and chest wheezing compared to the control group. Also, Zataria multiflora might be beneficial in improving FEV, FVC, MMEF, and PEF. Except MDA, the result of this study indicated that Zataria multiflora did not have any significant effect on oxidative stress parameters.

Declarations

Ethics approval and consent to participate

Not applicable in the declarations section.

Consent for publication

Not applicable in the declarations section.

Availability of data and materials

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

Competing interests

The authors declare no conflicts of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' contributions

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

Acknowledgements

The authors thank and appreciate all the professors of Nutrition Department of Iran University of Medical Sciences.

References

1. Hosseinzadeh H, Ramezani M, Salmani G-a. Antinociceptive, anti-inflammatory and acute toxicity effects of Zataria multiflora Boiss extracts in mice and rats. Journal of ethnopharmacology. 2000;73(3):379-85.
2. Sajed H, Sahebkar A, Iranshahi M. Zataria multiflora Boiss.(Shirazi thyme)—an ancient condiment with modern pharmaceutical uses. Journal of ethnopharmacology. 2013;145(3):686-98.
3. Ali MS, Saleem M, Ali Z, Ahmad VU. Chemistry of zataria multiflora (lamiaceae). Phytochemistry. 2000;55(8):933-6.

4. Boskabady MH, Mehrjardi SS, Rezaee A, Rafatpanah H, Jalali S. The impact of Zataria multiflora Boiss extract on in vitro and in vivo Th1/Th2 cytokine (IFN-γ/IL4) balance. Journal of ethnopharmacology. 2013;150(3):1024-31.
5. Nakhai LA, Mohammadirad A, Yasa N, Minaie B, Nikfar S, Ghazanfari G, et al. Benefits of Zataria multiflora Boiss in experimental model of mouse inflammatory bowel disease. Evidence-Based Complementary and Alternative Medicine. 2007;4(1):43-50.
6. Malekinejad H, Khoramjouy M, Hobbenaghi R, Amniattalab A. Atorvastatin attenuates the paraquat-induced pulmonary inflammation via PPARγ receptors: a new indication for atorvastatin. Pesticide biochemistry and physiology. 2014;114:79-89.
7. Boskabady MH, Jalali S. Effect of carvacrol on tracheal responsiveness, inflammatory mediators, total and differential WBC count in blood of sensitized guinea pigs. Experimental Biology and Medicine. 2013;238(2):200-8.
8. Khazdair MR, Ghorani V, Alavinezhad A, Boskabady MH. Pharmacological effects of Zataria multiflora Boiss L. and its constituents focus on their anti-inflammatory, antioxidant, and immunomodulatory effects. Fundamental & clinical pharmacology. 2018;32(1):26-50.
9. Naghibi F, Mosaddegh M, Motamed SM, Ghorbani A. Labiatae family in folk medicine in Iran: from ethnobotany to pharmacology. Iranian Journal of Pharmaceutical Research. 2022;4(2):63-79.
10. Raymond JL, Morrow K. Krause and mahan's food and the nutrition care process e-book: Elsevier Health Sciences; 2020.
11. Semenza GL. Oxygen sensing, homeostasis, and disease. New England Journal of Medicine. 2011;365(6):537-47.
12. Reddy K, Reddy C, Trimurthulu G. Ethnobotanical survey on respiratory disorders in Eastern Ghats of Andhra Pradesh, India. Ethnobotanical leaflets. 2006;2006(1):16.
13. Sethi GS, Dharwal V, Naura AS. Immunological basis of Oxidative stress-induced lung inflammation in asthma and COPD. Oxidative stress in lung diseases: Springer; 2019. p. 195-223.
14. Kayani S, Ahmad M, Zafar M, Sultana S, Khan MPZ, Ashraf MA, et al. Ethnobotanical uses of medicinal plants for respiratory disorders among the inhabitants of Gallies–Abbottabad, Northern Pakistan. Journal of ethnopharmacology. 2014;156:47-60.
15. Singh V, Kumar K, Purohit D, Verma R, Pandey P, Bhatia S, et al. Exploration of therapeutic applicability and different signaling mechanism of various phytopharmacological agents for treatment of breast cancer. Biomedicine & pharmacotherapy. 2021;139:111584.
16. Aynehchi Y. Pharmacognosy and medicinal plants of Iran. Tehran university. 1986.
17. Babaie M, Yasa N, Mohammadirad A, Khorasani R, Abdollahi M. On the anti oxidative stress potential of Zataria multiflora Boiss (Avishan shirazi) in rats. Int J Pharmacol. 2007;3(6):510-4.
18. Jaffary F, Ghannadi A, Siahpoush A. Antiinflammatory activity of Zataria multiflora Boiss. 2000.
19. Sheikhzadeh N, Soltani M, Ebrahimzadeh-Mousavi H, Shahbazian N, Norouzi M. Effects of Zataria multiflora and Eucalyptus globolus essential oils on haematological parameters and respiratory burst activity in Cyprinus carpio. 2011.
20. Boskabady MH, Jafari Z, Pouraboli I, Babazade B, Rahbardar MG. Anti-cholinergic effect of Zataria multiflora Boiss on guinea pig tracheal chains. Natural Product Research. 2012;26(16):1523-8.
21. Boskabady MH, Jalali S, Farkhondeh T, Byrami G. The extract of Zataria multiflora affect tracheal responsiveness, serum levels of NO, nitrite, PLA2, TP and histamine in sensitized Guinea pigs. Journal of ethnopharmacology. 2014;156:301-8.
22. Gholami Mahtaj L, Boskabady M, Mohamadian Roshan N. The effect of Zataria multiflora and its constituent, carvacrol, on tracheal responsiveness and lung pathology in guinea pig model of COPD. Phytotherapy Research. 2015;29(5):730-6.
23. Patil SM, Ramu R, Shirahatti PS, Shivamallu C, Amachawadi RG. A systematic review on ethnopharmacology, phytochemistry and pharmacological aspects of Thymus vulgaris Linn. Heliyon. 2021;7(5):e07054.
24. Sharififar F, Moshafi M, Mansouri S, Khodashenas M, Khoshnoodi M. In vitro evaluation of antibacterial and antioxidant activities of the essential oil and methanol extract of endemic Zataria multiflora Boiss. Food control. 2007;18(7):800-5.
25. Hosseinimehr SJ, Ahmadashrafi S, Naghshvar F, Ahmadi A, Ehasnalavi S, Tanha M. Chemoprotective effects of Zataria multiflora against genotoxicity induced by cyclophosphamide in mice bone marrow cells. Integrative Cancer Therapies. 2010;9(2):219-23.
26. Ghorani V, Khazdair MR, Mirsadraee M, Rajabi O, Boskabady MH. The effect of two-month treatment with Zataria multiflora on inflammatory cytokines, pulmonary function testes and respiratory symptoms in patients with chronic obstructive pulmonary disease (COPD). Journal of ethnopharmacology. 2022;293:115265.
27. Khazdair MR, Rezaeetalab F, Rafatpanah H, Boskabady MH. The effect of Zataria multiflora on inflammatory cytokine and respiratory symptoms in veterans exposed to sulfur mustard. Environmental Science and Pollution Research. 2020;27(18):22451-60.
28. Alavinezhad A, Ghorani V, Rajabi O, Boskabady MH. Zataria multiflora extract influenced asthmatic patients by improving respiratory symptoms, pulmonary function tests and lung inflammation. Journal of ethnopharmacology. 2022;285:114888.
29. Alavinezhad A, Hedayati M, Boskabady MH. The effect of Zataria multiflora and carvacrol on wheezing, FEV1 and plasma levels of nitrite in asthmatic patients. Avicenna journal of phytomedicine. 2017;7(6):531.
30. Alavinezhad A, Ghorani V, Rajabi O, Boskabady MH. Zataria multiflora affects clinical symptoms, oxidative stress and cytokines in asthmatic patient: A randomized, double blind, placebo-controlled, phase II clinical trial. Cytokine. 2020;133:155169.
31. Ghorani V, Rajabi O, Mirsadraee M, Rezaeitalab F, Saadat S, Boskabady MH. A randomized, doubled-blind clinical trial on the effect of Zataria multiflora on clinical symptoms, oxidative stress, and C-reactive protein in COPD patients. The Journal of Clinical Pharmacology. 2020;60(7):867-78.
32. Khazdair MR, Rajabi O, Balali-Mood M, Beheshti F, Boskabady MH. The effect of Zataria multiflora on pulmonary function tests, hematological and oxidant/antioxidant parameters in sulfur mustard exposed veterans, a randomized doubled-blind clinical trial. Environmental toxicology and

pharmacology. 2018;58:180-8.
33. Khazdair MR, Ghorani V, Alavinezhad A, Boskabady MH. Effect of Zataria multiflora on serum cytokine levels and pulmonary function tests in sulfur mustard-induced lung disorders: A randomized double-blind clinical trial. Journal of ethnopharmacology. 2020;248:112325.
34. Ghanbari-Niaki A, Saeidi A, Ahmadian M, Gharahcholo L, Naghavi N, Fazelzadeh M, et al. The combination of exercise training and Zataria multiflora supplementation increase serum irisin levels in postmenopausal women. Integrative medicine research. 2018;7(1):44-52.
35. Boskabady MH, Tabanfar H. Effect of Zataria multiflora Bois L. on histamine (H 1) receptor of guinea pig tracheal chains. 2011.
36. Boskabady M, Kaveh M, Eftekhar N, Nemati A. The effect of Zataria multiflora boiss on β 2-adrenoceptors of guinea pig tracheal cahins. Evid Based Complement Alternat Med. 2009;2011:1-9.
37. GHARIB NMK, MAZLOUMI H, Goshayesh M, Vakilzadeh G, HEYDARI A. Antispasmodic effect of Zataria multiflora Boiss. Leaf extract on the rat uterus. 2006.
38. Stey C, Steurer J, Bachmann S, Medici T, Tramer M. The effect of oral N-acetylcysteine in chronic bronchitis: a quantitative systematic review. European Respiratory Journal. 2000;16(2):253-62.
39. Eklund A, Eriksson O, Hakansson L, Larsson K, Ohlsson K, Venge P, et al. Oral N-acetylcysteine reduces selected humoral markers of inflammatory cell activity in BAL fluid from healthy smokers: correlation to effects on cellular variables. European Respiratory Journal. 1988;1(9):832-8.
40. Ghorani V, Alavinezhad A, Rajabi O, Mohammadpour AH, Boskabady MH. Safety and tolerability of carvacrol in healthy subjects: a phase I clinical study. Drug and Chemical Toxicology. 2021;44(2):177-89.
41. Kianmehr M, Rezaei A, Boskabady MH. Effect of carvacrol on various cytokines genes expression in splenocytes of asthmatic mice. Iranian journal of basic medical sciences. 2016;19(4):402.
42. Kianmehr M, Rezaei A, Hosseini M, Khazdair MR, Rezaee R, Askari VR, et al. Immunomodulatory effect of characterized extract of Zataria multiflora on Th1, Th2 and Th17 in normal and Th2 polarization state. Food and Chemical Toxicology. 2017;99:119-27.
43. Baharara J, Ramezani T, Hosseini N, Mousavi M. Silver nanoparticles synthesized coating with Zataria Multiflora leaves extract induced apoptosis in hela cells through p53 activation. Iranian journal of pharmaceutical research: IJPR. 2018;17(2):627.
44. Alavinezhad A, Ghorani V, Rajabi O, Boskabady MH. Zataria multiflora extract influenced asthmatic patients by improving respiratory symptoms, pulmonary function tests and lung inflammation. J Ethnopharmacol. 2022;285:114888.
45. Ghorani V, Khazdair MR, Mirsadraee M, Rajabi O, Boskabady MH. The effect of two-month treatment with Zataria multiflora on inflammatory cytokines, pulmonary function testes and respiratory symptoms in patients with chronic obstructive pulmonary disease (COPD). J Ethnopharmacol. 2022;293:115265.
46. Khazdair MR, Rezaeetalab F, Rafatpanah H, Boskabady MH. The effect of Zataria multiflora on inflammatory cytokine and respiratory symptoms in veterans exposed to sulfur mustard. Environmental science and pollution research international. 2020;27(18):22451-60.
47. Khazdair MR, Rajabi O, Balali-Mood M, Beheshti F, Boskabady MH. The effect of Zataria multiflora on pulmonary function tests, hematological and oxidant/antioxidant parameters in sulfur mustard exposed veterans, a randomized doubled-blind clinical trial. Environ Toxicol Pharmacol. 2018;58:180-8.
48. Khazdair MR, Ghorani V, Alavinezhad A, Boskabady MH. Effect of Zataria multiflora on serum cytokine levels and pulmonary function tests in sulfur mustard-induced lung disorders: A randomized double-blind clinical trial. J Ethnopharmacol. 2019;248:112325.
49. Ghanbari-Niaki A, Saeidi A, Ahmadian M, Gharahcholo L, Naghavi N, Fazelzadeh M, et al. The combination of exercise training and Zataria multiflora supplementation increase serum irisin levels in postmenopausal women. Integr Med Res. 2018;7(1):44-52.

Figures

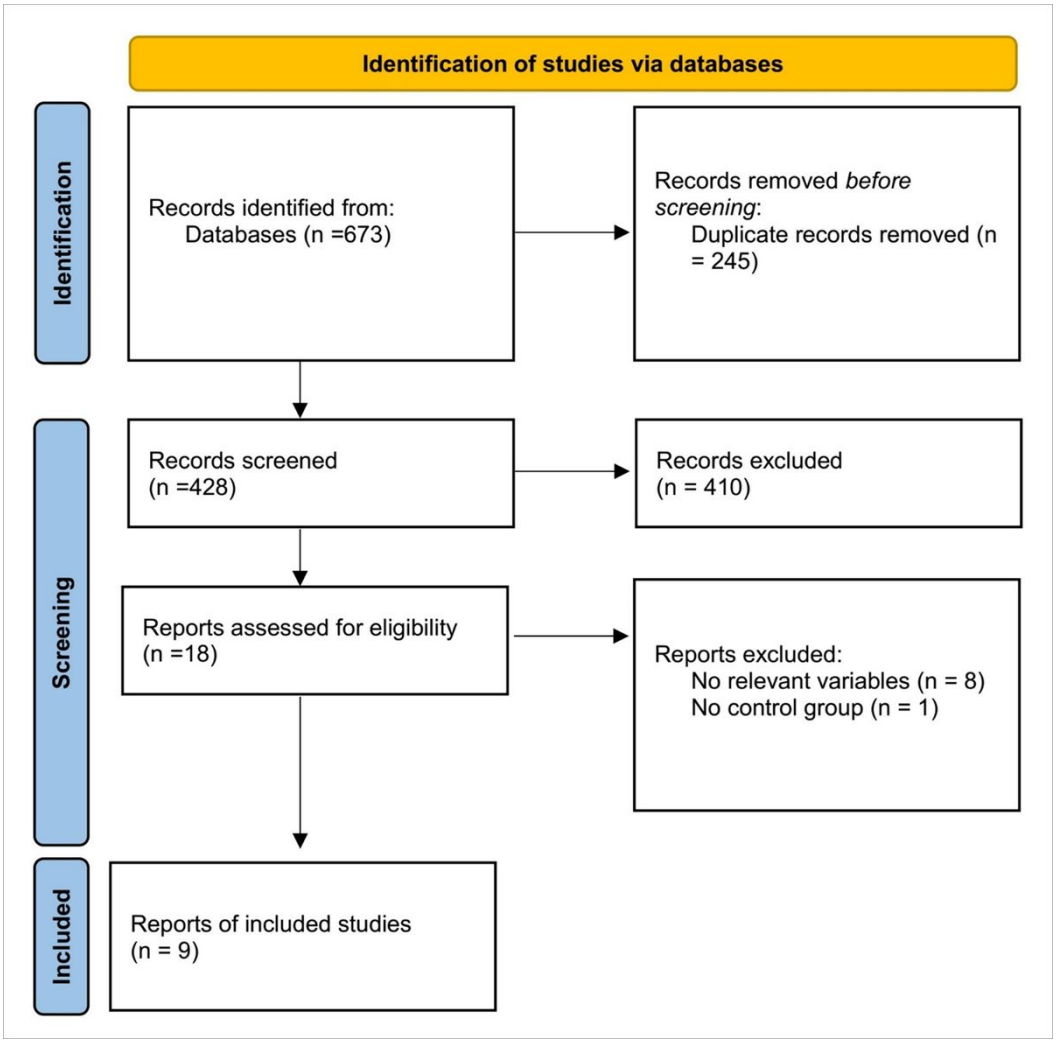


Figure 1

PRISMA Flow diagram of the study selection process

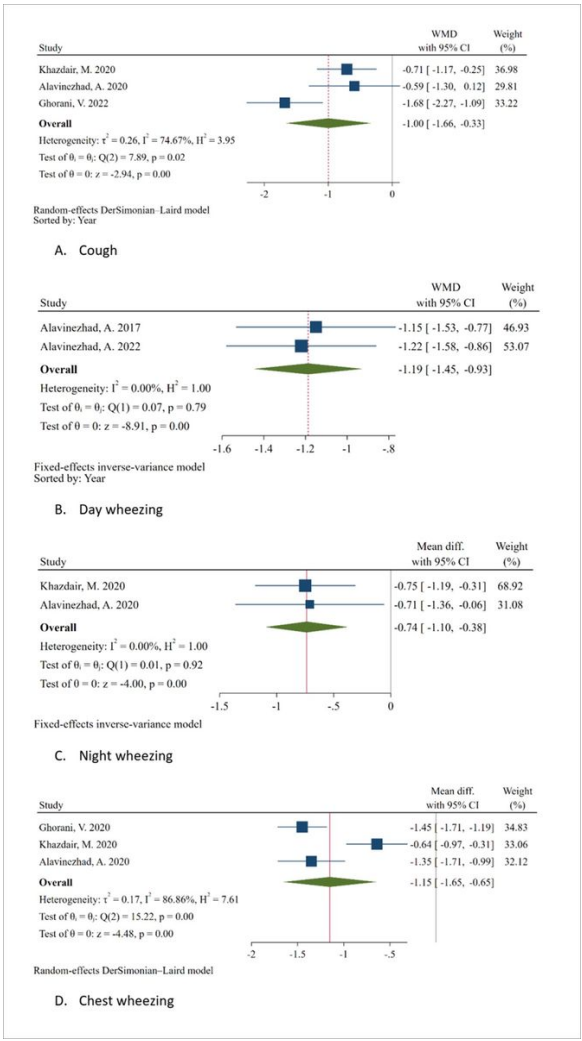


Figure 2

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

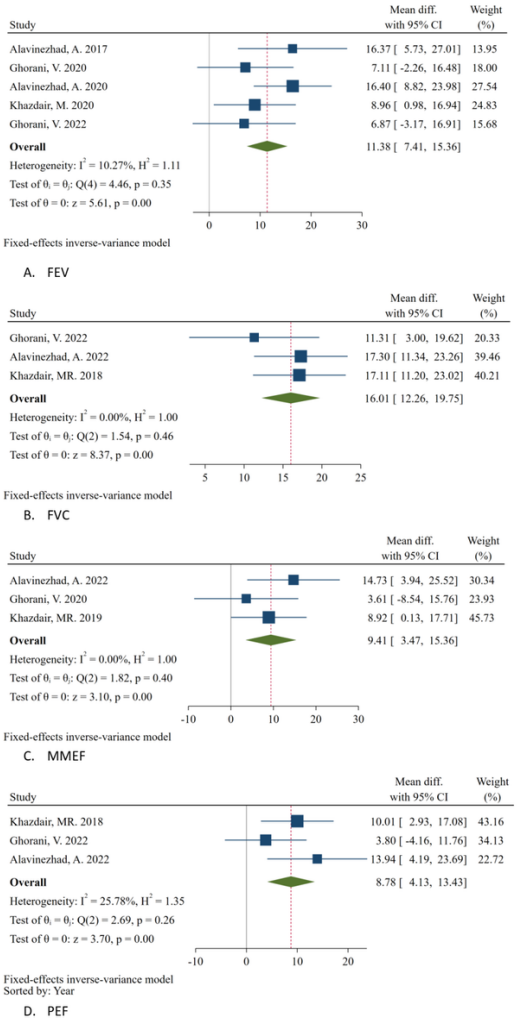


Figure 3

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

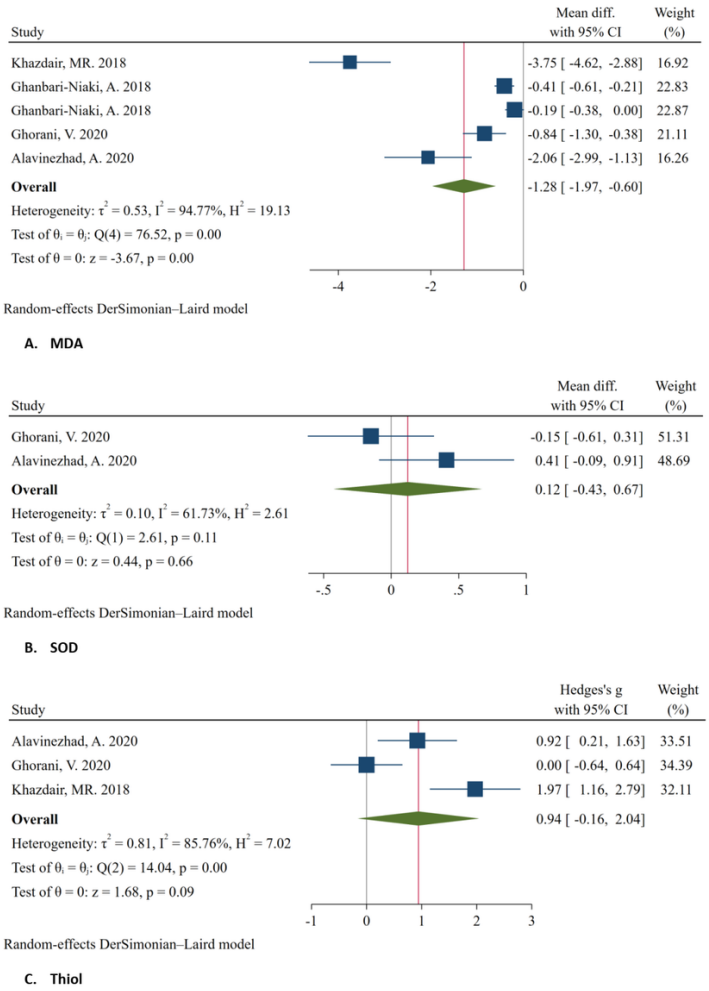
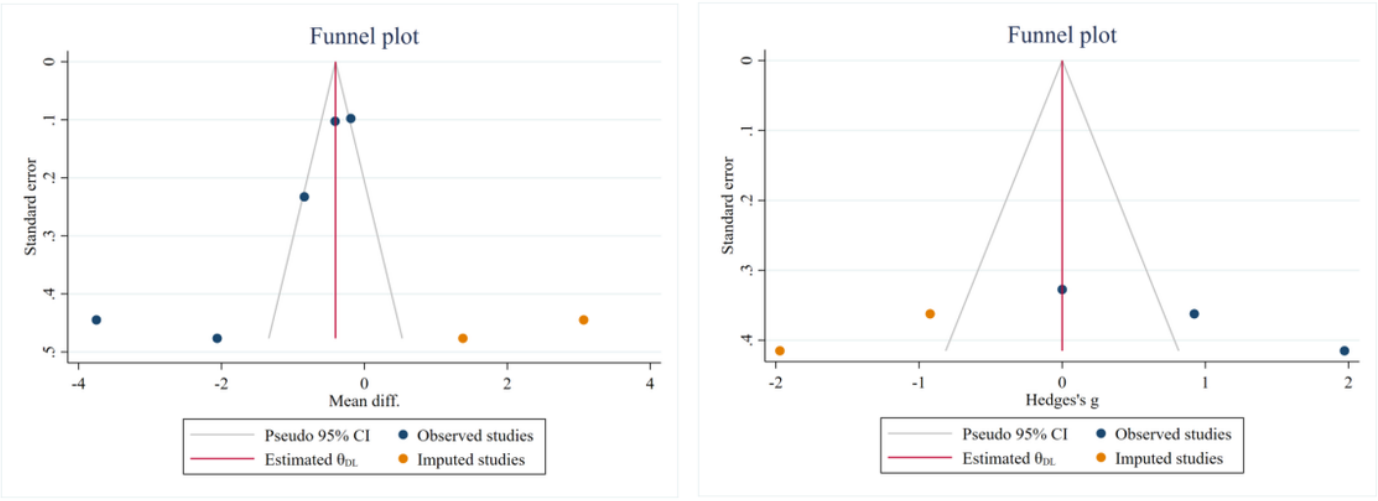


Figure 4

Forest plot detailing weighted 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

MDA: malondialdehyde, SOD: superoxide dismutase, CAT: catalase



A. MDA

B. Thiol

Figure 5

Funnel plot representing publication bias in the studies reporting the effect of Zataria multiflora on (A) MDA (malondialdehyde) (B) Thiol

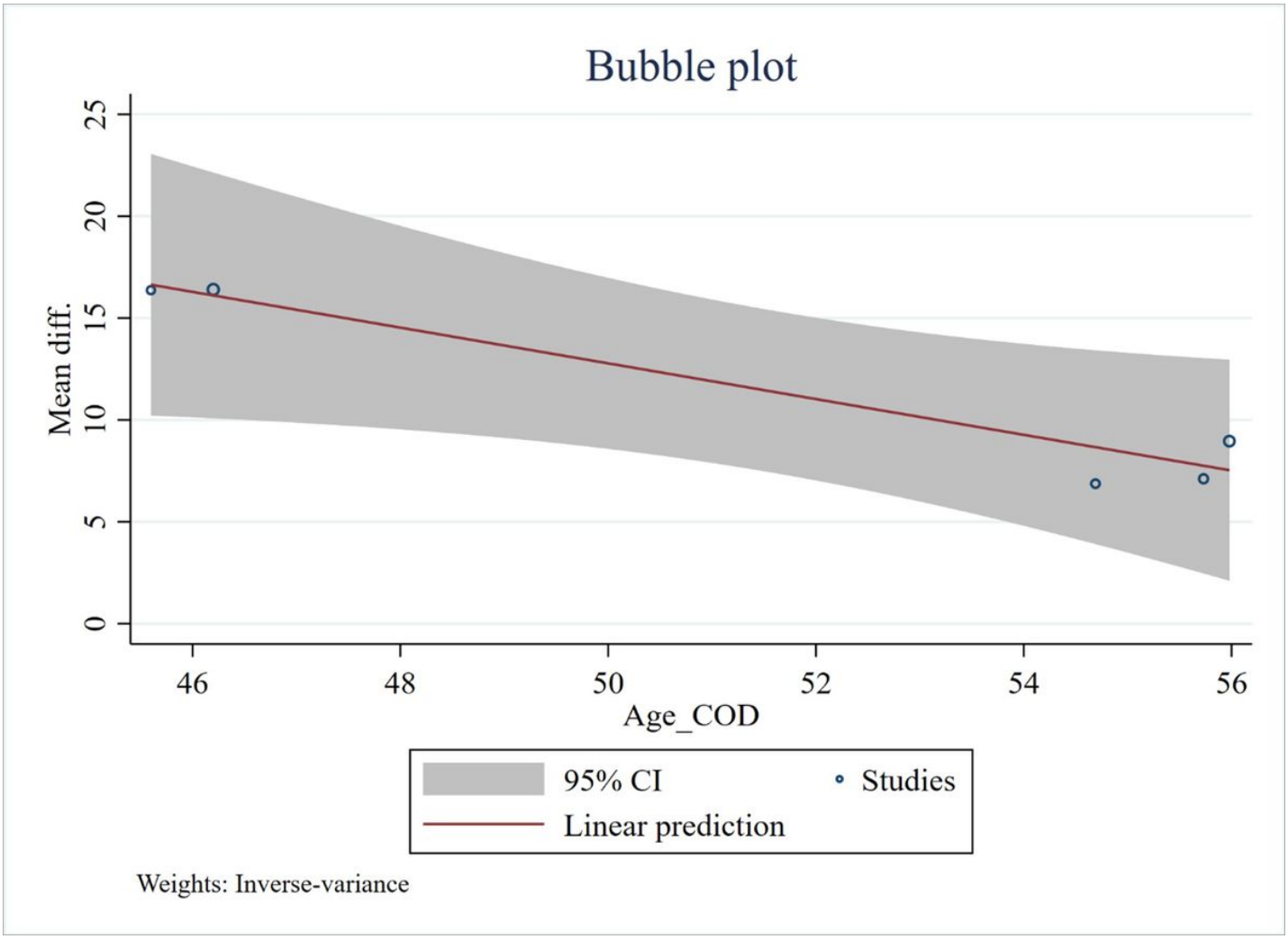


Figure 6

Meta-regression bubble plot of the correlation between the age and FEV