JoP Journal of Pharmacopuncture

Journal of Pharmacopuncture 2023;26(2):124-138
pISSN: 2093-6966 • eISSN: 2234-6856
https://doi.org/10.3831/KPI.2023.26.2.124

Review Article

Efficacy of Herbal Medicines on Lung Function in Asthma: a systematic review and meta-analysis of randomized controlled trials

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Received September 14, 2022
Reviewed September 20, 2022
Accepted February 17, 2023

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Objectives: The present study was designed to conduct a comprehensive systematic review and meta-analysis to assess the efficacy of herbal medicines as add-on therapy on lung function in asthmatic patients.

Methods: A comprehensive search of online databases was performed up to December 2021 to identify randomized controlled trials that used orally herbal preparations for asthma as add-on therapy. Studies were assessed for methodological quality using the Cochrane Collaboration's Risk of Bias tool. The main outcome was percent predicted value of forced expiratory volume (% predicted FEV1). Pooled weighted mean difference (WMD) estimate with corresponding 95% confidence interval (CI) was calculated using inverse-variance weights method while random effects meta-analysis was used, taking into account clinical and conceptual heterogeneity.

Results: As a result, 1,525 studies were identified. 169 studies were reviewed in-depth and 23 studies met our systematic review inclusion criteria. Finally, nine randomized controlled trials were included in the meta-analysis. Findings indicated that use of herbal medicines in patients with asthma significantly improved % predicted FEV1 (WMD: 3.73, 95% CI: 1.76-5.70), with no evidence for significant heterogeneity (p = 0.56 [Q statistic], I^2 = 0.0%). In subgroup analysis by age, improvement in % predicted FEV1 was higher and significant in adults (WMD: 5.16; 95% CI: 2.68-7.63) compared to children (WMD = 1.27; 95% CI: −1.98-4.51). Sensitivity analysis showed the significant effect of herbal medicine consumption on improving FEV1 was consistently (range of summary WMDs: 3.27-4.59), indicating that the meta-analysis model was robust. There was no evidence of publication bias both visually and statistically.

Conclusion: Findings support, the complementary use of herbal medicines resulted in significant improvement in the lung function compared to standard treatment in asthmatic patients with no considerable adverse events. This improvement is more likely to be observed amongst adults.

Keywords: persian medicine, asthma, herbal drug, forced expiratory volume, meta-analysis

INTRODUCTION

Asthma is a chronic disease that can be controlled by a variety of medications, which can reduce airway inflammation and smooth muscle spasm, in the absence of a definitive cure [1]. There is a long history of using herbal remedies for asthma, with some common asthma medications, such as anticholinergics, β2 agonists, and methylxanthines, having natural sources [2, 3]. In recent decades, the use of herbal medicines in asthma management has increased, particularly for traditional medicine such as Chinese, Korean, and Iranian medicine, where many different formulations have been used to treat asthma [4-6]. However, despite the multiplicity of drug formulations in traditional medical texts, few studies have analyzed their effectiveness and possible side effects [7-10]. Given the popularity of herbal medicines in recent years, it seems necessary, therefore, to evaluate the performance of these traditional remedies as well as their side effects [10-14]. The physiologic effects of medicinal plants vary depending on the plant or the various compounds within each formulation. The mechanisms of their effectiveness are complex, but experimental evidence does suggest that traditional formulations can reduce bronchospasm, airway inflammation, mucus buildup, and hyperresponsiveness in asthma patients [15-17].

There are several studies regarding the effects of herbal medicines on asthma. Most studies have examined the effect of one type of botanical plant in the treatment of asthma [2, 3, 6, 8-11, 15-26]. Few studies have investigated the effect of herbal remedies on asthma in general [27-32], although several studies have confirmed the effectiveness of herbal drugs in the treatment of asthma [33-37]. However, conflicting findings have also been observed from studies countries such as the USA, Brazil, the UK, New Zealand, and many Asian countries, although the variations in patient age, sample size, type of treatment, and other factors, could account for the inconsistencies in the findings.

Considering the conflicting results on the effect of herbal medicine on the predicted value of forced expiratory volume in asthmatic patients, there is value in conducting a comprehensive systematic review since it is vital to determine whether oral herbal preparations as add-on therapies for asthma can be effective in respiratory function tests. In addition, increasing the percent-predicted forced expiratory volume in one second (FEV1) output is vitally important. Therefore, we aimed to quantify the efficacy of herbal medicines on the predicted value of FEV by conducting a meta-analysis of relevant randomized controlled trials (RCTs). We conducted subgroup analyses based on patients' ages and considered the methodological limitations of the included studies and determined the potential sources of heterogeneity across the studies both statistically and clinically.

MATERIALS AND METHODS

This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42021268901, https://www.crd.york.ac.uk/PROSPERO/). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to review trials and to conduct and report the current systematic review and meta-analysis [38].

1. Search strategy

A comprehensive search of online electronic databases (Medline, Cochrane Library, EMBASE, Web of Science, and Scopus) was performed up until December 2021. The search was limited to blinded RCTs published in English. MeSH keywords were as follows: "herb" OR "herbal" OR "botanical" OR "medicinal plants" OR "Phototherapy" OR "Phytomedicine" OR "traditional medicine" AND "asthma" OR "dyspnea." Reference lists of retrieved studies and previously published reviews as well as gray literature were also reviewed in order to identify other relevant RCTs. Duplicate studies and publications were removed. The numbers and names of the authors (reviewers) who conducted the search, extracted the data, and assessed study quality were mentioned in the "search strategy," "data extraction," and "risk of bias assessment" sections, respectively. In order to resolve any disagreements, the authors first discussed among themselves, and any unresolved issues were arbitrated by a methodologist (third person). A comprehensive search of electronic databases as well as a reference list of retrieved studies was checked for additional pertinent studies.

2. Selection criteria

The RCTs included in this systematic review had to use orally administered herbal preparations for asthma. Patients of any sex or age, which were randomly assigned to either an intervention group (herbal medicines as add-on therapy to standard treatments) or a control group (standard treatment only or pla-

cebo with standard treatment) were considered in the review. Original, peer-reviewed RCTs, were included while single-arm before-after clinical trials were excluded. Interventions included oral herbal therapy plus standard treatment for at least one week. Herbs are defined as either the entire plant or roots, bark, stems, flowers, or fruits, which have been used as crude plants or extracts. The main outcomes of the present systematic review were respiratory function test parameters including FEV1 or peak expiratory flow rate (PEFR).

The reporting of PEFR data in some studies was neither accurate nor sufficient. Most studies reported either absolute or percent-predicted values of FEV1 or both. However, our meta-analysis only included studies that reported percent-predicted values of FEV1. Studies that did not provide data on the mean and standard deviation of predicted FEV1 in each intervention and control group were excluded. The diagnosis of asthma in the included studies was based on the Global Asthma Initiative (GINA) or equivalent criteria, such as an expert consensus-based assessment of symptoms and a respiratory function test, as determined by the results of the included studies [39, 40]. Cough-variant asthma, drug-induced asthma, and acute exacerbations of asthma were excluded. Persistent and moderate-to-severe asthma were also excluded from the meta-analysis in order to homogenize the study population in included studies. All designs and study types that were not RCTs were excluded from this review. Fig. 1 displays a flow diagram showing how the studies were selected.

3. Data extraction and risk of bias assessment

The main characteristics of the included studies in this systematic review were author's name, year, country, gender, age, study population, duration of follow-up, herbal name and form, respiratory function tests, mean and standard deviations, sample size for intervention and control groups, and study quality. Two reviewers (SS, MM) independently extracted data from all studies, and any discrepancies between investigators were resolved by discussion or after arbitration by a third reviewer

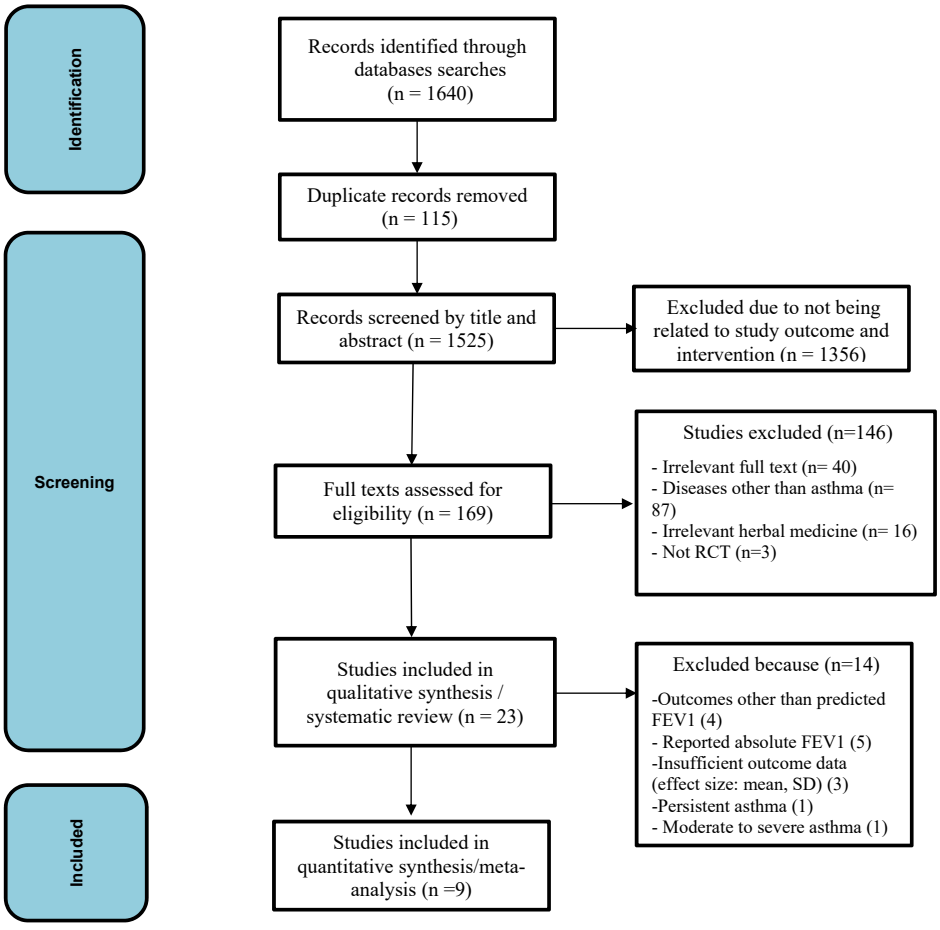

Figure 1. PRISMA flow diagram for selection of studies.

 https://doi.org/10.3831/KPI.2023.26.2.124

(MS). The methodological quality (risk of bias) of the included RCTs was assessed using the Cochrane Collaboration's Risk of Bias tool [41]. The seven risk areas that were rigorously assessed were sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other biases. Studies included in the systematic review were considered for "low risk," "unclear risk," or "high risk" of bias by two methodologist reviewers (MS, MD), with any discrepancies resolved by consensus.

4. Statistical analysis

Most RCTs report FEV1 (absolute volume or percent-predicted value) as the primary clinical outcome and consider it as a continuous variable. Studies that provided sufficient data on sample size, mean, and standard deviation/error of percent-predicted values for FEV1 in each intervention group and control group were included in the meta-analysis. Mean differences and 95% confidence intervals (CIs) were calculated using data from each study. Pooled weighted mean difference (WMD) was estimated, with the corresponding 95% CIs calculated using inverse variance weighting [42]. A random-effects meta-analysis was used to account for conceptual and clinical heterogeneity between studies, with a Forest plot displaying the WMD and corresponding 95% CIs for visual inspection across studies. Heterogeneity between studies was assessed using the I^2 statistic [43] (I^2 = 0% means no observed heterogeneity and $I^2 \geq 50\%$ indicates substantial heterogeneity), while Cochran's Q statistic was used to analyze the statistical significance of the heterogeneity [44]. Sensitivity analysis was performed by successively removing a specific study or group of studies to find which study (if any) had the greatest impact on the pooled estimates and to assess the robustness of the pooled results.

A subgroup meta-analysis on the effect of herbal remedies on the percent-predicted FEV1 by age group in asthmatic patients (adults and children) was also performed. Visual inspection of funnel plots was performed to assess publication bias [45], i.e. WMD was plotted against the inverse of the square of the standard error (a measure of study precision). The funnel plots were inspected visually to assess publication bias. Egger's regression asymmetry test and Begg's adjusted rank correlation test were also performed [46, 47]. All statistical analyses were performed using Stata version 14.0 software (Stata Corp., College Station, TX, USA). Statistical tests were two-tailed, and significance levels were considered as less than 0.10 for analyses.

RESULTS

A comprehensive literature search identified 1,525 relevant studies. After removing duplicates and screening of titles and abstracts, 169 studies were selected for an in-depth full-text review (Fig. 1). Twenty-three RCTs have pre-determined eligibility criteria for inclusion in the systematic review with 2,584 participants. Finally, nine studies [7, 34-37, 48-51] were included in the meta-analysis that reported percent-predicted values of FEV1 as the main outcome with complete statistical data (Fig. 1).

Table 1 presents the main characteristics of the 23 RCTs [7, 34-37, 48-68]. All included studies used botanicals from Persian, Chinese, Ayurveda, European and South American Materia Medica that meet the inclusion criteria; used extracts or compounds derived from herbs, combine herbal medicine with the pharmacotherapy (add-on therapy) and treatment duration was more than one week.

Symptom improvement was assessed in all studies. In 15 studies, one specific medicinal plant was used for the intervention. The single plants or their extracts which were used as interventions were *Nigella sativa* [35, 57, 65], *Crocus sativus* [48], *Zingiber officinalis* [56], Berry fruit polyphenolic extract [66], Magnoliae Flos [62], *Aegle marmelos* [67], *Passiflora edulis* [60], Saiboku [36], *Sophora flavescens* [58], Soy Isoflavone [63], *Drimia maritima* [37], *Curcuma longa* [68], and *Viola odorata* [69]. Combinations of several plants (between 3 and 15 components) were used in nine studies [7, 34, 52-55, 61, 62, 64], although the combined formulas were not mentioned in three studies [49, 50, 59]. Interventional medications used specific brands in 15 studies [7, 36, 49-55, 59, 61, 62, 64, 66, 67] with Glycyrrhiza (Licorice root), Rehmannia and Ginco Biloba, Curcuma longa, *Zingiber officinale*, and ginseng the most repeatedly used ingredients in these formulations. Nineteen studies used capsules, with the remaining studies using tablets [60, 63], powder [58], sachets [49, 50], syrups [37], or drops [56, 69]. All administration types were typical of herbal prescriptions and in appropriate dosages according to recommendations. Details of the type of drugs used as standard treatment, which were beta2 agonists and inhaled corticosteroids [58], theophylline [55, 57], oral corticosteroids [53], inhaled corticosteroids and oral theophylline [57] and Montelukast [50, 67], were only reported in five studies. Finally, the placebos, which were charcoal powder

Table 1. Main characteristics of randomized controlled trials included in the systematic review

Study, year (country)	Sex	Age	Study population	Herbal medicine name	Outcome	Intervention group			Control group		
						n1	mean1	sd1	n2	mean2	sd2
Urata et al. [36], 2002 (Japan)	M/F	42 ± 7	Patients with mild or moderate asthma, 4 weeks follow-up	TJ-96 capsule, freeze dried powder of Saiboku	FEV-1	16	86.9	7.1	17	82.1	5.6
Wen et al. [53], 2005	M/F	18-65	Patients with moderate-severe allergic asthma, 4 weeks follow-up	ASHMI capsule of Ganoderma lucidum, Sophora flavescens, and Glycyrrhiza uralensis	FEV-1	46	84.36	12.9	46	88.46	12.6
Chang et al. [54], 2006 (China)	M/F	5-20	Patients with mild or moderate asthma, 24 weeks follow-up	STA-1 capsule of decoction of Rehmanniae Preparata, Cortex Moutan Radicis, Fructus Corni, Poria, Rhizoma Alismatis and Dioscoreae, Ophiopogonis, Glycyrrhizae, Panacis Quinquefolii and Tuber Pinellia	FEV-1	44	80.70	NR	16	76.5	NR
Chang et al. [54], 2006 (China)	M/F	5-20	Patients with mild or moderate asthma, 24 weeks follow-up	STA-2 capsule of boiled of Rehmanniae Preparata, Cortex Moutan Radicis, Fructus Corni, Poria, Rhizoma Alismatis and Dioscoreae, Ophiopogonis, Glycyrrhizae, Panacis Quinquefolii and Tuber Pinellia	FEV-1	44	88.9	NR	16	76.5	NR
Wong et al. [51], 2009 (China)	M/F	Low than 18	Patients with mild or moderate asthma, 24 weeks follow-up	CUF2 capsule of Astragalus mongholius Bunge, Cordyceps sinensis Sacc., stemonae, Bulbus fritillariae cirrhosae, and scutellariae	FEV-1	43	96	15	42	96	19
Houssen et al. [34], 2010 (Egypt)	M/F	18-60	Patients with mild or moderate asthma, 4 weeks follow-up	Capsule of Glyserizia Glabra, Curcumim, Boswelic acid	FEV-1	39	72.75	10.41	24	68.4	13.62
Salem et al. [35], 2017 (Saudi Arabia)	M/F	18-65	Controlled asthmatic patients, 12 weeks follow-up	NS-1 capsule of Black Seed	FEV-1	26	87.7	15.8	24	80.8	20.6
Salem et al. [35], 2017 (Saudi Arabia)	M/F	18-65	Patients with mild or moderate asthma, 12 weeks follow-up	NS-2 capsule of Black Seed	FEV-1	26	85.5	22.9	24	80.8	20.6

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Table 1. Continued

Study, year (country)	Sex	Age	Study population	Herbal medicine name	Outcome	Intervention group			Control group		
						n1	mean1	sd1	n2	mean2	sd2
Wang et al. [49], 2017 (China)	M/F	18-60	Patients with mild or moderate asthma, 12 weeks follow-up	PCKL Sachet of not reported	FEV-1	36	73.2	14.3	36	67.7	14.5
Hosseini et al. [48], 2018 (Iran)	M/F	18-65	Patients with mild or moderate asthma, 8 weeks follow-up	Capsule of saffron	FEV-1	40	80.15	12.59	40	73.21	12.15
Nejatbakhsh et al. [37], 2017 (Iran)	M/F	18-65	Patients with mild or moderate asthma, 8 weeks follow-up	Syrup of Squill Oxymel	FEV-1	38	71.44	21.86	38	61.67	14.2
Nejatbakhsh et al. [37], 2017 (Iran)	M/F	18-65	Patients with mild or moderate asthma, 8 weeks follow-up	Syrup of Oxymel	FEV-1	38	61.11	15.7	38	61.67	14.2
Chan et al. [7], 2006 (Taiwan)	M/F	8-15	Children with mild or moderate asthma, 12 weeks follow-up	DCT capsule of G. biloba, E. sinica,T. farfara, M. alba, P. ternata, P. frutescens, P. armeniaca, S. baricalensis, and G. uralensis	FEV-1	28	93.85	102.71	24	87.97	98.53
Chan et al. [50], 2016 (Taiwan)	M/F	6-18	Children with mild or moderate asthma, 24 weeks follow-up	YPFS sachet of not reported	FEV-1	28	92.3	2.6	29	95.3	2.7
Murali et al. [55], 2006 (India)	M/F	15-50	Patients with moderate stable asthma, 12 weeks follow-up	DCBT4567-Astha-15 capsule of Woodfordia, Solanum xanthocarpum, Adathoda vasika, Acacia arabica, Ellateria cardamomum, Piper nigrum, Achyranthus aspera, Zingiber officinalis, Hollarhena antidysenterica, Curcuma longa, Syzygium aromaticum, Calotropis procera, Enicostemma littorale, Piper longum	FEV-1	19	1.69	0.52	22	1.5	0.51
Rouhi et al. [56], 2006 (Pakistan)	M/F	NR	Patients with low to severe asthma, 8 weeks follow-up	Oral drop of Ginger	FEV1	46	47.31	NR	46	45.31	NR
Boskabady et al. [57], 2007 (Iran)	M/F	48.2 ± 11.9	Patients with persistent mild or moderate asthma, 12 weeks follow-up	Capsule of Black Seed	FEV1	15	29.47	27.14	14	30.3	24.31

Table 1. Continued

Study, year (country)	Sex	Age	Study population	Herbal medicine name	Outcome	Intervention group			Control group		
						n1	mean1	sd1	n2	mean2	sd2
Thomas et al. [59], 2007 (Scotland)	M/F	18-75	Patients with persistent asthma, 12 weeks follow-up	AKL1 capsules of not reporter	NR	16	NR	NR	16	NR	NR
Watson et al. [60], 2008 (USA)	M/F	18-60	Patients with asthma, 4 weeks follow-up	Tablet of purple passion fruit	NR	22	NR	NR	21	NR	NR
Smith et al. [63], 2015 (USA)	M/F	> 12	Patients with poor control asthma, 24 weeks follow-up	Tablet of Soy Isoflavone	FEV1	193	2.39	3.68	193	2.44	3.19
Kong et al. [64], 2017 (China)	M/F	NR	Patients asthma, 48 weeks follow-up	BSYQ capsule of RadixAstragali, HerbaEpimedii, RehmanniaeRadi	NR	109	NR	NR	107	NR	NR
Kong et al. [64], 2017 (China)	M/F	NR	Patients asthma, 48 weeks follow-up	BSFC capsule of Herba Epimedii, Rehmanniae Radi, Cuscutaesemen, soraleae, oraleacoryl., ioscorea opposita Citri Reticulatae Aconitilateralis	NR	112	NR	NR	107	NR	NR
Koshak et al. [65], 2017 (UK)	M/F	18-65	Patients with mild or moderate asthma, 4 weeks follow-up	NSO capsules of Black seed	NR	40	NR	NR	40	NR	NR
Power et al. [66], 2017 (New Zealand)	M/F	18-75	Patients with mild asthma, 4 weeks follow-up	BFPE Berryfruit	FEV1	14	3.54	0.98	14	3.56	1
Yugandhar et al. [67], 2018 (India)	M/F	21-60	Patients with mild or moderate asthma, 6 weeks follow-up	Li131019F serrata, Marmelos fruit	FEV1	16	1.71	0.32	13	1.54	0.22
Manarin et al. [68], 2019 (Brazil)	M/F	7-18	Patients with persistent moderate to severe asthma, 8 weeks follow-up	Capsule of Curcuma longa	FEV1	40	NR	NR	27	NR	NR
Hsu et al. [52], 2005 (Taiwan)	M/F	5-18	Patients with persistent mild or moderate asthma, 16 weeks follow-up	MMDT40 mg/day Tuber Ophiopogonis Japonici, Panacis Quinquefoli. Tuber Pinellia, Rhizoma Pinellia Ternatae, Glycyrrhizae Uralensis, Herba Tridacis procumbentis	FEV-1	40	73.8	12.4	20	70.2	13.7

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Table 1. Continued

Study, year (country)	Sex	Age	Study population	Herbal medicine name	Outcome	Intervention group			Control group		
						n1	mean1	sd1	n2	mean2	sd2
Hsu et al. [52], 2005 (Taiwan)	M/F	5-18	Patients with persistent mild or moderate asthma, 16 weeks follow-up	MMDT80 mg/day Tuber Ophiopogonis Japonici, Panacis Quinquefoli. Tuber Pinellia, Rhizoma Pinellia Ternatae, Glycyrrhizae Uralensis, Herba Tridacis procumbentis	FEV-1	40	87.7	12.6	20	70.2	13.7

M, male; F, female; NR, not reported; FEV1, forced expiratory volume 1th second; n, number of cases; sd, standard deviation.

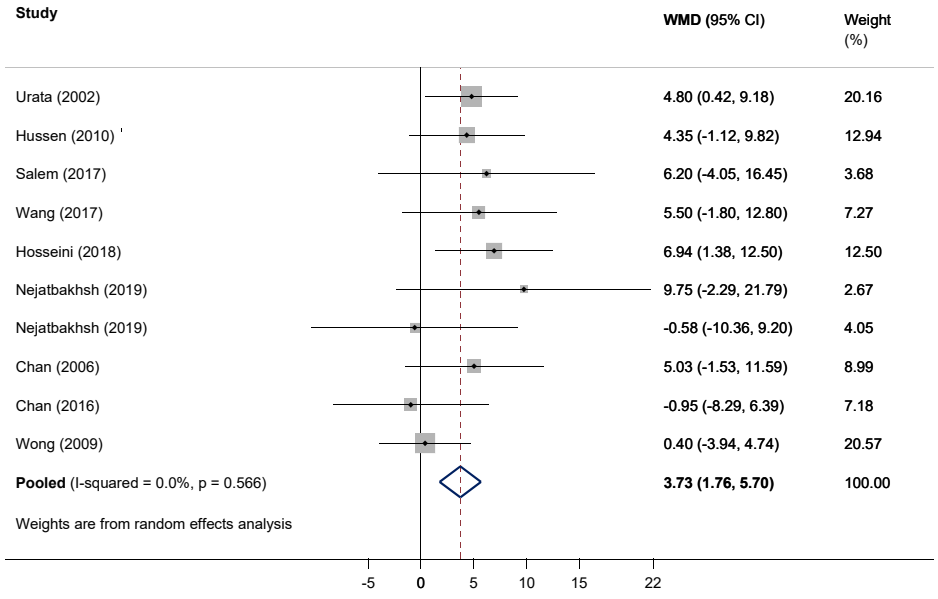

Figure 2. Forest plot of the efficacy of herbal medicine as add-on therapy on lung function (percent predicted FEV1) in patients with asthma using random effects meta-analysis. Diamond represents the summary weighted mean difference (pooled WMD) estimate and its width shows corresponding 95% CI with random effects estimate. The size of the square and its central point reflects the study specific statistical weight (inverse of variance) and point estimate of the WMD and horizontal line reflects corresponding 95% CI of the study. I^2 test and Cochran's Q statistic were used to assessing the statistical heterogeneity ($p < 0.10$) across studies.

[35], boiled honey [37], lactose [34, 55], maltodextrin [50], virgin olive oil [65], and semi-roasted glucose solution [57], were only mentioned in seven studies.

The results of a random-effects meta-analysis of RCTs using Forest plots showed that herbal prescriptions significantly improved respiratory function test results in asthmatics (Fig. 2). The WMD of the percent-predicted FEV1 in asthma patients taking herbal medicines was 3.73 (95% CI: 1.76-5.70) compared with standard asthma medicines. There was no evidence for significant heterogeneity across studies ($p = 0.56$ [Q statistic], $I^2 = 0.0\%$). Subgroup meta-analysis by age demonstrated that there was substantial variation in the percent-predicted FEV1 levels between patients treated with herbal medicines and the control group in adults (WMD = 5.16, 95% CI: 2.68-7.63) compared with children (WMD = 1.27; 95% CI, –1.98-4.51). In other words, improvement in percent-predicted FEV1 was significantly higher in adult asthmatic patients compared with children. No statistical heterogeneity was found within any of the subgroups (Fig. 3). Sensitivity analysis by successively removing a particular study at a time to assess the influence of every single study on the pooled WMD showed that herbal medicines consistently and significantly improved percent-predicted FEV1 (range of summary WMDs: 3.27-4.59), indicating the robustness of our meta-analysis findings. A visual inspection and assessment of the funnel plot using statistical tests indicated that publication bias was unlikely in studying the effects of herbal medicines on respiratory function tests in asthmatics (Fig. 4). Also, statistical tests showed no evidence of publication bias both visually and statistically ($p = 0.53$, for Begg's adjusted rank correlation test: 0.53 and $p = 0.58$, for Egger's regression

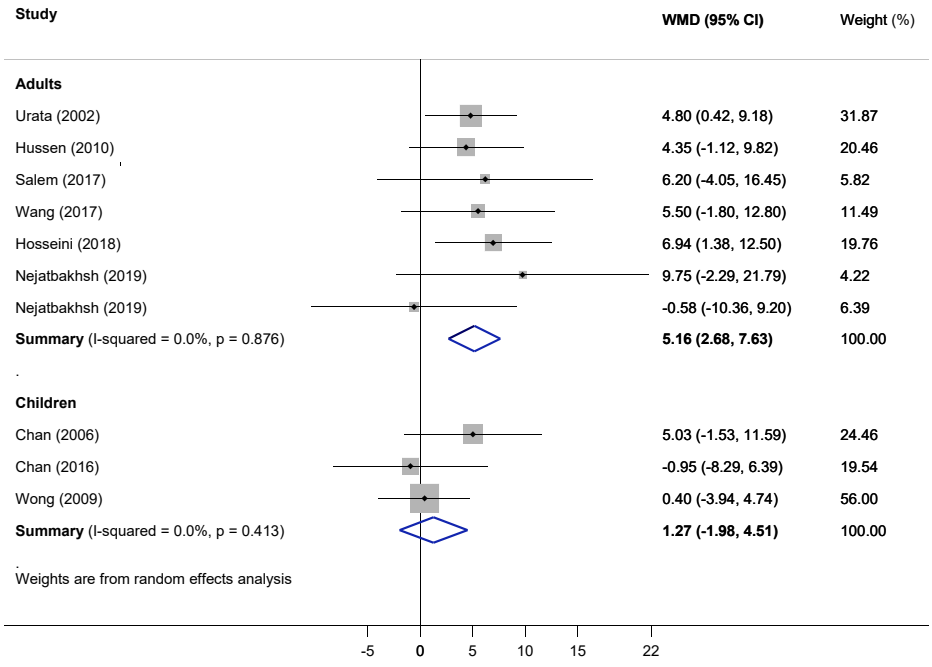

Figure 3. Subgroup meta-analysis of the effect of herbal medicine on lung function (percent predicted FEV1) in patients with asthma based on patients' age (adults vs. children).

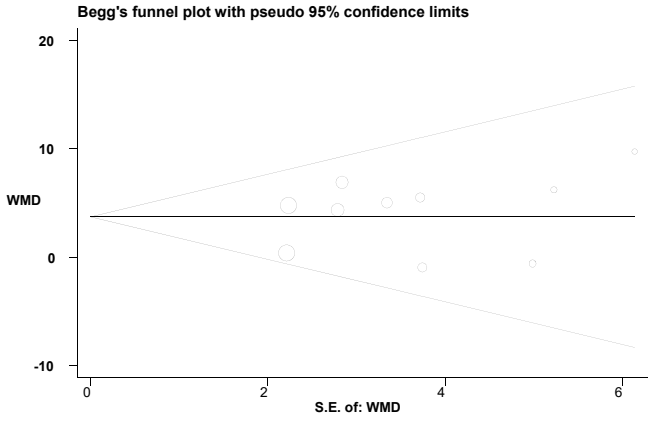

Figure 4. Begg's funnel plot for assessing the presence of publication bias. Weighted mean difference was plotted against the precision of the study (p = 0.53, for Begg's adjusted rank correlation test and p = 0.58, for Egger's regression asymmetry test).

asymmetry test).

Cochrane's Risk of Bias (ROB) tool for randomized controlled studies was used to assess the risk of bias for all 23 studies included in the systematic review (Table 2). The results showed that 20% and almost half (48%) of the studies were placed at high and low risk of bias respectively. Sequence generation and allocation concealment were major problems in three studies, while only two studies had a bias regarding the selective outcome reporting area. The blinding of participants, personnel, and outcome assessors was accurately conducted in approximately half of the studies. The majority of the studies (about 90%) included in the meta-analysis were either in the unclear or low-risk bias categories.

DISCUSSION

Herbal compounds have a long history of treating asthma. The present systematic review and meta-analysis indicated that using herbal medicines as add-on therapy to standard treatment showed improvements in the respiratory function test, particularly the percent-predicted FEV1 in asthma patients. It also shows that the use of botanicals as a complementary treatment is more effective in adults than in children. In most studies, the target group consisted of patients with mild to moderate asthma. However, severe asthma patients were investigated in three studies [53, 58, 63], and patients with stable asthma were included in five studies [52, 57, 59, 62, 68]. Since the current meta-analysis included studies that involved mild to moderate asthmatic patients, differences in the target population did not confound the main findings, and the patients were homogeneous in this respect.

In seven studies, the target group of the intervention was asthma patients under 18 years old [7, 50-52, 54, 63, 69]; three of these studies were ultimately included in the meta-analysis [7, 50, 51]. In the subgroup meta-analysis of children and adults, treatment with herbal medicines did not significantly

 https://doi.org/10.3831/KPI.2023.26.2.124

Table 2. Risk of bias/methodological quality assessment of randomized controlled trials using Cochran risk of bias tool (ROB)

Study	Sequence generation	Allocation concealment	Blinding of participants & personnel	Blinding of outcome assessor	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall bias
Urata et al. [36], 2002	?	?	?	?	?	+	?	?
Wen et al. [53], 2005	?	?	?	?	+	+	+	?
Chang et al. [54], 2006	?	?	?	?	+	+	+	?
Wong et al. [51], 2009	?	?	?	?	+	+	+	?
Houssen et al. [34], 2010	-	-	-	-	-	-	-	-
Salem et al. [35], 2017	+	+	?	?	+	+	+	?
Wang et al. [49], 2017	+	+	+	+	+	+	+	+
Hosseini et al. [48], 2018	+	+	+	+	+	+	+	+
Nejatbakhsh et al. [37], 2017	+	+	+	+	+	+	+	+
Chan et al. [7], 2006	+	+	+	+	+	+	+	+
Chan et al. [50], 2016	+	+	+	+	+	+	+	+
Murali et al. [55], 2006	?	?	?	?	+	+	+	+
Rouhi et al. [56], 2006	-	-	-	-	-	-	-	-
Boskabady et al. [57], 2007	?	?	?	?	?	+	-	-
Thomas et al. [59], 2007	?	?	?	?	?	+	?	?
Watson et al. [60], 2008	?	?	?	?	+	+	+	?
Smith et al. [63], 2015	+	+	-	-	+	+	-	-
Kong et al. [64], 2017	+	+	+	+	+	+	+	+
Koshak et al. [65], 2017	-	-	-	-	+	+	+	-
Power et al. [66], 2017	+	+	+	+	+	+	+	+
Yugandhar et al. [67], 2018	+	+	+	+	+	+	+	+
Manarin et al. [68], 2019	+	+	+	+	+	+	+	+
Hsu et al. [52], 2005	+	+	+	+	+	+	+	+

+ Low risk of bias, ? unclear risk of bias, − high risk of bias.

improve lung capacity in children. This may be because of the limited number of studies related to children. In general, interventional studies in children have more ethical considerations than adults. Traditional medicine textbooks also mention various restrictions on the use of medicinal plants with children. More studies are needed, therefore, to clarify the effect of herbal medicines on pediatric asthma. Certainly, constructive answers can be obtained if the intervention is performed with the same plant in both the children and adult groups.

Asthma can be treated by reducing inflammation of the ducts, enhancing mucus absorption, and improving smooth muscle relaxation. The medicinal plants used in the included clinical trials had similar effects. The mechanisms of action expressed for the effect of herbal interventions included inhibition of airway inflammation [57], inhibition of eosinophilic p38-dependent leukotriene synthesis [63], reducing asthma symptoms through a direct effect on the gastrointestinal tract [56], and reducing advanced pro-inflammatory glycosylation of IgE in the gut [66]. The effects of the plants selected for intervention in the included studies were investigated by dividing them into two categories: single-plant interventions and formula or multidrug interventions. In the single-plant studies, commonalities were observed in the molecular types that make up plants, including polyphenols, despite differences in plant names and classes. Polyphenols are micronutrients found in fruits, vegetables, tea, and spices. There are more than 8,000 polyphenols, including flavonoids such as quercetin, polyphenol amides such as capsaicin, phenolic acids such as gallic acid, and others such as salicylic acid.

Polyphenols are potent antioxidants that can mitigate or

reverse cellular damage, thereby reducing the risk of many chronic diseases. They can also help maintain heart health, blood pressure, blood sugar levels, and chronic inflammation. The antioxidant and anti-inflammatory effects of polyphenols can inhibit tumor growth and kill active cancer cells, activate the immune system, and enhance the gut microbiota. Different classes of polyphenols, including anthocyanin, have strong protective effects on pulmonary function parameters. Polyphenols inhibit the induced expression of nitric oxide synthase and prevent oxidative and nitric oxidative damage to the lung [70-72].

From among the polyphenols in the present study, quercetin, terpene, and kaempferol of flavonoids and turmerones, saponin, gallic acid, and frolic acid of phenolic acids, more than their other groups, were observed in the compounds used for drug intervention [70, 72-80]. Although the main isoforms of polyphenolic molecules are different in each plant, all these forms have relatively similar functions in the human body, all causing reduced inflammation and mucus and relaxation of smooth muscle [35, 48, 53, 56, 57, 62, 81]. It also seems the variety in plant selection is caused by availability, cost, or other reasons.

Razi suggests that it is preferable to use one type of herbal drug in therapy [82]. Formulated and multi-herbal therapies are used in cases of advanced disease. In the present study, 15 single herbs and eight formulation studies were reviewed. Most single-plant studies either did not provide complete results, or the results and data were not suitable for meta-analysis; so most of the studies with formulations were included in the meta-analysis. Further meta-analyses comparing single-plant and formulation studies will be useful. Common adverse events reported in the included studies were mild and low-risk and reported in the studies on interventions using formulations that were negligible.

1. Strengths and limitations of the study

All designs were RCTs and the blinding process was conducted as accurately as possible in most included studies. The studies included in the meta-analysis were homogenous in terms of disease severity, with most patients having mild to moderate asthma. Hence, one of the reasons for the lack of heterogeneity between studies in the current meta-analysis was the presence of these two important and influential factors (i.e., homogeneous design and population). Also, despite the variety of herbal drugs that are used as interventions, they all share active molecules of polyphenols with anti-inflammatory and antioxidant effects. Nevertheless, the findings of this meta-analysis should be interpreted with caution in the context of limitations of the available data.

Since FEV1 was the main data for the meta-analysis, the difference in the type of reporting was one of the limitations of the present study. Five studies did not report pulmonary function tests as outcomes [56, 58, 59, 68, 83]. FEV1 has been presented in various methods and formats in other studies. For example, in four studies, respiration volume was recorded without mentioning the percent-predicted, [55, 57, 62, 66], and only changes in respiration volume were reported in some studies [49, 53, 65, 67]. Also, the results in four studies were presented in graphs and could not be extracted for meta-analysis [51, 60, 61, 64].

CONCLUSION

The findings of the present systematic review and meta-analysis indicated that the complementary use of herbal medicines resulted in significant improvements in lung function (percent-predicted FEV1) compared with standard treatment in asthmatic patients with no significant adverse events. Improvements in percent-predicted FEV1 were more likely to be observed among adults, which was significantly higher in adults than in children. Our meta-analysis sought to fill in the research gap and provide new up-to-date evidence. However, further RCTs with larger sample sizes and scales and high validity will be needed to establish and confirm our findings.

ACKNOWLEDGEMENTS

The research was supported by the Vice-Chancellor for Research at the Mashhad University of Medical Sciences (MUMS) as part of a traditional Persian medical doctoral dissertation. Funding sources had no role in study design, data collection, analysis, interpretation, and manuscript preparation.

AUTHORS' CONTRIBUTIONS

SS and RS conceived the idea. SS and AD designed the study. SS, AA, MM, and FJ collected data, reviewed literature and extracted data. MS and MD rechecked the quality assessment of studies and participated in analysis of data and interpreted the results. SS, RS, and MS conceived the study aims and design, provide the data the analysis. MS, MD, AD and MK performed

data re-analysis. They played an important role in interpreting the data, drafting, Manu scripting and revising it. All authors contributed to the discussion and endorsement of the final version. The responsible author had full access to all study data and was ultimately responsible for the decision to submit.

INSTITUTIONAL STATEMENT

This study does not require ethical approval. It is registered on the Prospero (Code: CRD42021268901).

CONFLICTS OF INTEREST

The authors declared there were no conflicts of interest related to the study.

FUNDING

Vice-Chancellor for Research, Mashhad University of Medical Sciences (MUMS).

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