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Title: Efficacy of Curcumin Supplementation in Asthma: A Systematic Review and Meta-Analysis

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Objective: Over 23 million people are affected by asthma in the United States and 262 million individuals globally. Asthma, if poorly controlled, is associated with significant morbidity as well as increased risk for mortality. Several complex inflammatory pathways and processes are involved leading to an increase in immune cell activation. Curcumin, the active constituent found in turmeric, has been studied in numerous in-vivo and in-vitro studies to generate anti-inflammatory effects in pulmonary diseases. More recently, an increase in clinical data has become available, and since the most recent review assessing the role of curcumin in pulmonary disorders, additional clinical trials have been published. We provide the first meta-analysis evaluating the efficacy of curcumin supplementation in asthma.

Methods: We searched PubMed and Google Scholar for eligible studies up to June 30, 2021, using medical subject headings and keywords for asthma. Any clinical trial design, conducted in humans, assessing the efficacy of curcumin on asthma related symptoms and lung functioning were included. Two authors, using predefined criteria, independently screened, extracted data, and assessed risk of bias from included studies using predefined criteria. Random effects meta-analysis was performed for each outcome, with effect size reported as mean difference (MD) or as a standardized mean difference.

Results: 1,216 studies were screened, 8 included for review (n = 509) and adequate data from 3 trials (n = 203) included for meta-analysis. Most participants were of female sex (52.2%) and the mean age (SD) of participants was 39.23 (14.7) years. The forced expiratory volume in one second (FEV1%) improved with curcumin supplementation (3 studies; pooled MD = 3.70 (1.00,

6.41), $p= 0.007$, $I^2=0\%$) compared to control. Efficacy of curcumin supplementation on asthma symptoms more generally were discordant and safety data was only reported in two trials.

Conclusions: Supplementation with curcumin may provide small improvements in FEV1%, however conclusions are limited by the small number of studies and sample sizes, poor methodological quality, inconsistent reporting of asthma related outcomes and high risk of bias of included studies. Additional, high-quality, human trials are needed to assess the efficacy of curcumin supplementation more robustly in asthma.

Introduction:

Asthma is a prevalent immune mediated disorder often associated with sensitivities to airborne environmental irritants. Globally, the World Health Organization (WHO) estimates 262 million people have asthma and an estimated 25 million individuals in the United States, according to The Center for Disease Control and Prevention (CDC).^{1,2} Asthma is more prevalent amongst females and direct and indirect costs result in an annual expenditure between \$56 to \$82 billion.²⁻⁴

Asthma's pathophysiology is complex, involving several mechanistic pathways ultimately leading to the interaction of Nuclear Factor kappa-light-chain-enhancer of activated B-cells (NFκB) cross-linking with IgE. This cross-linking activates mast cells, basophils and eosinophils causing a release of histamines and other inflammatory mediators such as c-reactive protein (CRP), tumor necrosis factor-α (TNF-α) and, interleukins.⁵⁻⁷ These inflammatory mediators result in the constriction of airways producing clinical symptoms of asthma such as wheezing, breathlessness and frequent nighttime awakenings due to coughing.⁵

The Global Initiative for Asthma (GINA) utilizes clinical symptoms in addition to spirometry testing to diagnose asthma and categorizes asthma by clinical phenotype with further subclassification based on severity (intermittent, mild, moderate, and severe).⁸ Suspicion for asthma can be confirmed by spirometry when the forced expiratory volume of air in one second (FEV1) is able to increase by at least 12% following the use of a short acting bronchodilating agent.⁸ The use of various bronchodilators, corticosteroids, anti-inflammatory, and/or biologic agents are routinely used as standard of care therapies for asthma, however, the use of complementary and integrative health (CIH) practices for asthma are also highly prevalent. An estimated 58.5% of adults in the U.S. use CIH practices for asthma, and although

data is sparse and varies by region, an estimated 27-76% of children with asthma also use some form of CIH.^{9,10} In U.S. based adults, herbal therapies comprised 21% of the natural products used for asthma, however, which herbal therapies are used specifically, is less certain.⁹

Curcuma longa (turmeric), a plant species native to tropical South Asia, has been traditionally used as a medicinal herb for centuries in Ayurvedic and Chinese medicine.^{5,11} Its rhizome is a common ingredient in many types of dishes such as curry, and Ng et al., suggested regular consumption of curry-based meals were independently associated with improvements in asthma after adjusting for gender, age, height, housing status, smoking, occupational exposure, asthma/COPD history, dietary, and other dietary supplemental intake.¹² The main constituent of *Curcuma longa*, curcumin, has also routinely demonstrated anti-inflammatory effects in a variety of health-related conditions.^{11,13,14} Recently, there has been an increasing amount of literature available on the potential therapeutic role of curcumin for the treatment of pulmonary disorders including asthma, however, reviews of the literature are largely limited to investigating its effects from in-vivo or in-vitro models.^{5,11}

Despite a recent 2017 comprehensive review assessing curcumin in pulmonary diseases, only two clinical trials assessing its role in asthma were included, provided conflicting results, and failed to include a 2010 randomized controlled trial.^{5,15} Given several clinical trials have been published since then, the purpose of this study is to systematically review the literature and provide the most up to date clinical evidence assessing the efficacy and safety of curcumin supplementation in asthmatics. To our knowledge, we are also the first authors to meta-analyze the effects of curcumin supplementation in asthma compared to controls.

Methods:

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹⁶ A protocol of this review was not prospectively registered.

Eligibility for inclusion:***Patients:***

Review authors included all randomized controlled trials (RCTs) and quasi-RCTs assessing the efficacy of curcumin supplementation for asthma. Studies were included if asthma participants were diagnosed by a physician or met asthma diagnostic criteria by spirometry at study entry. Primary study authors were contacted by email for any missing or unclear information, however, studies were not excluded from narrative review if no response was obtained, given the limited number of publications available. Conference abstracts of clinical data was also included if sufficient data could be obtained. No restrictions were placed on age, sex, or weight of participants; type of asthma; setting; or language of publication provided a publication written in any language other than English could be sufficiently translated via Google Translate.

Intervention:

No restrictions were placed on curcumin supplementation administered in any form (capsule, powder, etc.) route (oral, parenteral, etc.), dose, or length of time. Given curcumin is the main active constituent of turmeric, studies utilizing turmeric in any form, route, dose, or length of treatment time were also included.

Comparison:

Studies were eligible for inclusion if the intervention was compared to placebo, standard of care for asthma, or an active comparator.

Outcomes:

Studies were included if they measured at least one of the following outcome measures of interest: (1) asthma symptoms defined as the number of asthma exacerbations per week, nocturnal symptoms or awakenings due to asthma per week, frequency of rescue medication(s) used per week, number of daytime symptoms per week, and the total score on the Asthma Control Test (ACT) or Asthma Quality of Life Questionnaire (AQLQ); (2) lung functioning assessed by spirometry or peak flowmetry including the forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), ratio of FEV₁ to FVC (FEV₁/FVC), or the peak expiratory flow rate (PEFR); and (3) safety and tolerability of curcumin supplementation.

Exclusion criteria:

Studies were excluded if they: (1). were conducted in animals; (2). were in-vitro, prospective or retrospective cohorts, cross-sectional, case-series, or case-control study designs; (3). unable to be translated via Google Translate; (4). included participants with other respiratory conditions (COPD, restrictive lung disease, pneumonia etc.); (5). did not report on any outcomes of interest as previously listed.

Search strategy:

We searched PubMed and the first 1,000 results in Google Scholar from inception until June 2021 with the assistance of a university librarian trained in literature searches. Reference lists of included studies as well as previous reviews were hand searched. ClinicalTrials.gov and the International Clinical Trials Registry Platform Search Portal (ICTRP) were searched for ongoing or completed trials. The International Prospective Register of Systematic Reviews (PROSPERO) was searched for similar ongoing or recently completed systematic reviews addressing our study objectives. The search strategy can be accessed in the accompanying appendix at the end of the manuscript (appendix 1).

Data Collection:

Authors used Mendeley Desktop for literature search results and management of screening results. Studies meeting inclusion criteria were entered into Review Manager (RevMan) version 5.3 software to create risk of bias summaries, extract data from studies for meta-analysis, and present results in forest plots if appropriate.¹⁷ Both authors screened titles and abstracts independently, with disagreements settled via consensus between study authors. TG and AS conducted all data extraction and data was inputted into RevMan5.3. Any disagreement in extraction of data was settled via consensus. Data items collected can be seen in table 1.

Risk of Bias Assessment:

The Cochrane Collaboration's Risk of Bias tool was used to evaluate the risk of bias in seven selected domains included: 1) random sequence generation, 2) allocation concealment, 3) blinding of participants and personnel, 4) blinding of outcome assessment, 5) incomplete

outcome data, 6) selective reporting, and 7) other biases.¹⁸ Each domain of bias was rated as low risk, unclear risk, or high risk of bias, respectively.

Data Analysis:

Due to the heterogeneity across study methodologies in addition to adequate data only available for assessing FEV1%, a random-effects meta-analysis was used to derive pooled weighted mean differences (WMD) with 95% confidence intervals (95% CI) using an inverse variance model of post-intervention effects.¹⁹ Heterogeneity across studies was calculated using the I^2 statistic to assess heterogeneity between studies for study results. We considered an I^2 of 0-24% as low heterogeneity, 25-49% as mild heterogeneity, 50-74% as high heterogeneity, and $I^2 > 75%$ considered as extensive heterogeneity.²⁰ Given the lack of available studies for meta-analysis, heterogeneity was not further explored by sensitivity analyses or sub-group analyses. Furthermore, evidence for potential publication bias was not attempted given the paucity of data available.

Results:

1,216 studies were identified through database and registry search strategy; 8 were eligible for inclusion in the systematic review with 3 providing adequate data for meta-analysis (Figure 1). Two studies were identified in ClinicalTrials.gov of which, one was published and identified in our PubMed search, with another study currently in progress (NCT04353310). Two additional ongoing studies were found in the ICTRP (IRCT20191221045837N3) and IRCT20161226031584N2). No relevant reviews were identified in PROSPERO.

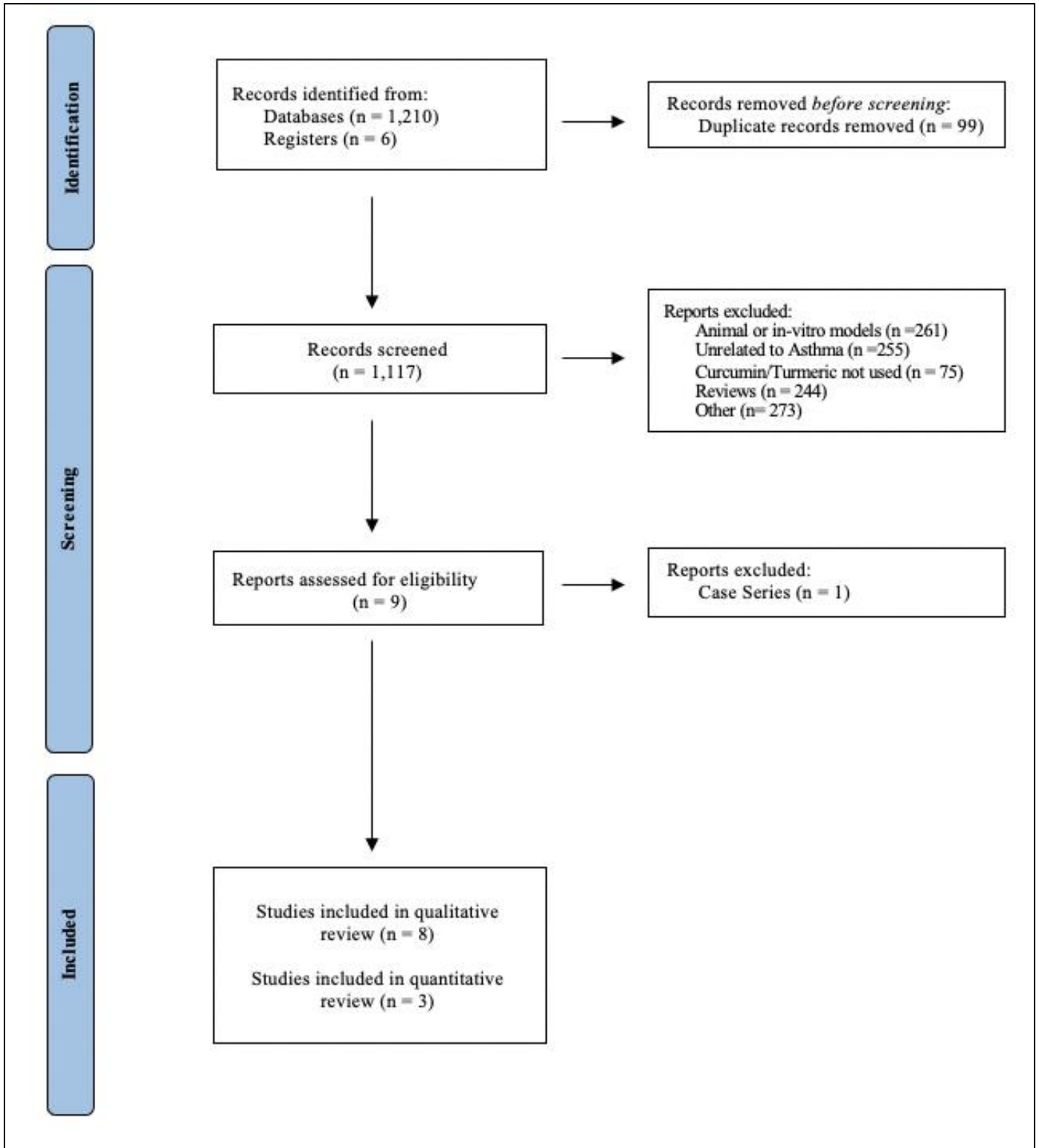


Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

Study characteristics:

Study characteristics can be seen in Table 1. Two studies were conducted in Bosnia and Herzegovina,^{23,27} with one study each conducted in Egypt¹⁵, India²⁶ Indonesia²⁴, Iraq²¹, Brazil²², and the United States of America.²⁵ Four studies compared curcumin to placebo^{15, 22, 25, 27}, five compared curcumin added to standard of care/active comparator vs standard of care/active comparator alone^{21, 23, 24, 26, 27}, two compared combination products containing curcumin to placebo or control^{15,21}, and one trial compared powdered whole turmeric to identical placebo.²² In one study, data was only available by conference abstract, however, despite attempts at contacting authors, further information was unable to be obtained.²³ The longest trial length was six-months²², with the shortest trial performed by Sutediyo et al, however, the exact length of the study was unclear.²⁴

Participant characteristics:

There was a total of n = 509 participants across 8 studies (n=203 included in meta-analysis) with a total of n = 240 in curcumin, n = 269 in control groups. Mean age (39.23 ± 14.7) of participants was reported in six studies, and 52.2% of study participants from six studies were female.

Risk of Bias in individual studies:

Summary of the risk of bias of included studies can be seen in Figure 2. One reference was judged as having unclear risk of bias as it was published as a conference abstract only, without an ability to contact abstract authors.²³ Due to significant drop out after randomization, one study was assessed as having high risk of bias for incomplete outcome data, and another

failed to report data on ACT scores, frequency of rescue inhaler use, or dose of inhaled corticosteroids.^{22,25}

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Abidi 2014	+	?	-	-	-	-	+
Houssen et al. 2010	?	?	?	?	+	+	+
Jusufovic 2017	?	?	?	?	?	?	?
Jusufovic 2019	+	?	?	-	+	+	+
Khadir 2019	+	?	-	-	+	+	+
Kim et al 2011	?	?	+	+	+	-	+
Manarin 2019	+	+	+	+	-	+	+
Sutedjo 2018	-	-	-	-	+	+	+

Figure 2: Risk of bias summary: review authors' judgements about each risk of bias item for each included study

Effect of curcumin on lung functioning:

Adequate data for meta-analysis was only available for FEV1%, which improved with the addition of curcumin relative to control (3 studies: MD = 3.7% (1.0, 6.4), P = 0.007, I² = 0%). Data was available from one abstract, however, reported mean FEV1% between groups were not incorporated into meta-analysis as it was unclear if standard deviations were reported despite efforts made in contacting corresponding authors.²³ Manarin et al., reported FEV1% graphically with medians and interquartile ranges, with no statistically significant difference between groups and was not incorporated into meta-analysis.²² Three studies (n=115) reported FEV1 in liters however, heterogeneity in reporting FEV1 measures limited pooling results into meta-analysis.^{21, 25, 26} Of these three studies, two found no statistically significant difference between groups.^{21,25}

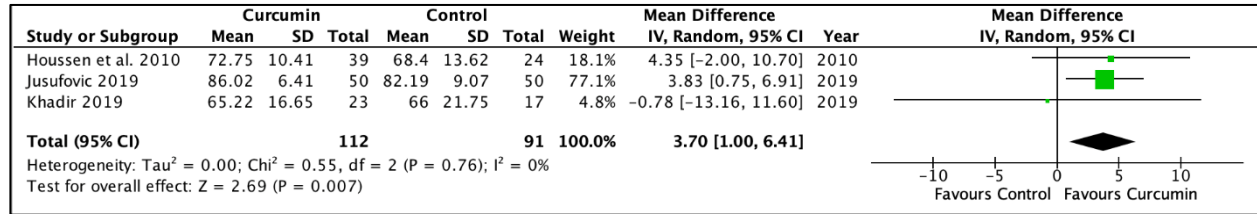


Figure 3: Forest plot for primary outcome comparing curcumin supplementation to controls. CI, confidence interval

Peak expiratory flow rate

Two studies (n = 93) evaluated effects of curcumin supplementation on peak expiratory flow rate; one as a RCT and the other as a quasi-experimental study in hospitalized asthmatic patients.^{15,24} Neither study found statistically significant differences between groups.

Effect of curcumin on asthma symptoms:

A lack of adequate data was reported to assess the effects of curcumin on asthma symptoms and results are described narratively. Improvements in asthma symptoms are conflicting; four studies (n = 347) were able to identify statistically significant improvements in asthma symptoms compared to controls,^{15, 22, 23, 27} with two studies (n = 75) finding no statistically significant improvements in asthma symptoms.^{25, 26} Asthma Control Test (ACT) scores were reported in two studies^{25, 27} (n=165) with conflicting results, and one abstract which found statistically significant improvements in the curcumin group compared to control.²³

Daytime symptoms

Two studies (n=123) reported the effects of curcumin supplementation for daytime symptoms with conflicting results.^{15, 26} One study found a median of four fewer daytime

symptoms per week compared to placebo group ($p < 0.001$)¹⁵, however, another found no differences between curcumin or control groups in any symptom including difficulty breathing, wheezing, cough, or chest tightness.²⁶

Nocturnal symptoms

Two studies ($n = 97$) reported statistically significant reductions in nocturnal symptoms relative to control groups.^{15,22} Houssen et al., found a median reduction of two nocturnal awakenings per week compared to placebo ($p < 0.001$),¹⁵ with another study finding no statistically significant differences between groups in reductions of nighttime symptoms.²⁶

Need for rescue inhaler

Two studies ($n = 97$) reported statistically significant reductions in the need for rescue inhalers with the addition of curcumin relative to control^{15,22}, with one able to demonstrate a median reduction of two fewer days per week of rescue inhaler use compared to placebo ($p < 0.001$).¹⁵ In the trial by Manarain et al, at baseline, over 20% of participants in the curcumin group required daily use of rescue inhaler with none requiring daily rescue medication after six-months.²² At baseline, greater than 25% of control participants required daily use of rescue inhaler, and greater than 20% still required daily use of rescue inhaler at six-months.²² Two studies ($n=75$) did not find any differences between groups in reliance on rescue inhalers, however, results were not readily available from one study despite attempts at contacting the authors.^{25,26}

Frequency of acute exacerbations

The number of exacerbations per week was only recorded by one study which found a median reduction of two exacerbations per week relative to control group ($p < 0.001$).¹⁵

Safety of Curcumin:

Only two trials ($n = 94$) reported safety data with neither study revealing increased risk of harm with curcumin.^{22,26}

Discussion:

Clinical data from eight studies ($n = 509$) were included in this review, providing some evidence of an effect on lung functioning as seen by a 4% increase in FEV1, as well as overall improvements in asthma symptoms. These improvements build upon prior evidence highlighting curcumin's ability to inhibit inflammatory cytokines and upregulate anti-inflammatory immune activation leading to a reduction of airway hyperresponsiveness and relaxation of smooth muscle cells within the bronchopulmonary system.^{5, 7, 28}

Heterogeneity in how asthma symptoms were reported by included studies prevented pooling of results to provide a quantitative estimate for how much of an effect curcumin supplementation can provide for specific asthma related symptoms (e.g., daytime symptoms, nocturnal symptoms, reliance on rescue inhaler). Despite most studies suggesting improvements in asthma related symptoms, the overall methodological quality of included studies was low, with only two double blinded RCTs available, and most studies at unclear or high risk of bias. As such, readers should interpret our findings with caution and three additional on-going clinical trials (NCT04353310, IRCT20191221045837N3 and IRCT20161226031584N2) are likely to impact our findings after data become available.

Strengths:

This is the first review the study authors are aware of that provides a meta-analysis of clinical data evaluating the effects of curcumin supplementation in asthma. We have included the largest number of studies conducted in humans with asthma compared to previously conducted reviews which were limited to only two studies.^{5,11} Additional strengths include a comprehensive search strategy not limited to the English language and adherence to the PRISMA checklist. Limiting assessments of lung function, asthma symptoms, and safety of curcumin supplementation to randomized trials provided for more robust conclusions about the efficacy of curcumin supplementation.

Limitations:

Our review is limited by the number of studies available, small sample sizes of included studies, duration of follow up/length of treatment, inconsistencies in reporting of outcome measures, and risk of bias of included studies. Two studies additionally utilized mixed products and dosing strategies varied widely between 15mg – 2,200mg across studies.^{15,21} Additionally, findings are further limited by a lack of sufficient data assessing the impact of curcumin supplementation across a spectrum of asthma severities.

Implications/Recommendations for research:

We recommend future investigations to report on all lung functioning measures available through spirometry and to report asthma symptoms in an identical and consistent manner utilizing standardized asthma symptom questionnaires such as the ACT or AQLQ with total and

sub-scores readily available. Future studies should address concerns around the paucity of data available in children and adolescents as well as safety of curcumin supplementation. Although curcumin in doses as high as 12,000mg appear to be safe with no severe adverse effects, future studies should assess this in individuals being treated for asthma more specifically.²⁹

Additionally, studies should utilize similar doses, dosing strategies, and formulations of curcumin, examine the impact of curcumin across asthma severities, and improve upon the methodological quality currently available.

Due to the hydrophobic and lipophilicity of curcumin, its bioavailability and absorption is notoriously low, known to degrade at physiological pH and rapidly metabolized, limiting its therapeutic effects.^{11,30} Chauhan et al., were able to demonstrate increased therapeutic efficacy, via intranasal administration in a murine model of asthma, finding a reduction in inflammatory signaling.³¹ However, additional research in humans is necessary to identify if intranasal applications provide any advantage over oral supplementation for individuals with asthma.

Implications for clinical practice:

Based on the results from our review, the use of curcumin to provide clinical benefit in asthma is likely minimal and recommending curcumin for asthma in clinical practice currently cannot be made and further high-quality research is necessary. Consistency in the reporting of lung functioning via spirometry as well as assessment of asthma symptoms are needed. It is still unclear at which dose/dosing strategy is most effective, how much benefit is provided to children or adolescents, if benefit is independent on asthma severity, and if benefits are sustained long term without significant adverse effects. If patients are utilizing curcumin supplementation with a perceived benefit, it is likely safe to continue supplementation as a dose escalation study of

curcumin was reported to be safe at an observed dosage of 12,000 mg in adults and adverse events were not associated with a dose dependent response.²⁹

Conclusions:

This is the first systematic review with meta-analysis that study authors are aware of evaluating the efficacy of curcumin supplementation in humans with asthma. Limited evidence suggests short-term improvement in lung functioning assessed by spirometry with curcumin supplementation compared to control. Overall, asthma symptoms also seemed to improve, however, improvements in lung functioning and asthma symptoms need to be interpreted with caution due to the lack of adequate high-quality studies at low risk of bias. Recommendations for use in clinical practice cannot be made at this time and additional research with consistencies in outcome reporting, dosing, safety, length of follow up, and effects of curcumin supplementation in children and adolescents are warranted.

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Table 1: Characteristics of studies assessing efficacy of curcumin supplementation for asthma in clinical trials

Author, Year	Location	Design	Sample size	Sample Characteristics	Duration	Intervention	Control	Outcome Measures	Results
Houssen et al 2010 ¹⁵	Egypt	RCT	n = 63	Non-smoking adults 18-60 years old, with at last 1-year of chronic bronchial asthma not adequately controlled with low to moderate inhaled corticosteroids	4-weeks	Combination product taken 3 times daily: 150mg boswellic acid, 50mg licorice extract, 15mg curcumin (n=39)	Identical placebo capsule (lactose) taken 3 times daily (n=24)	Daytime symptoms/wk; nocturnal symptoms/wk; need for rescue medication/wk; FVC%; FEV1%; PEFR; Frequency of acute exacerbations per wk, month, or year.	Improvements in number of exacerbations/wk, daytime and nighttime symptoms/wk, need for rescue medication/wk, FVC. All p<0.001 compared to placebo. No statistically significant difference between groups for FEV1%, or PEFR.
Kim et al. 2011 ²⁵	USA	Double Blind RCT	n = 15	Adults 18-60 years old with at least 1-year of stable persistent asthma, FEV1 ≥ 60%, use of low to moderate inhaled corticosteroids, and allergic to dust mites.	3 months	Curcumin 1,000mg twice daily (n=9)	Placebo (n=6)	Postbronchodilator FEV1; ACT scores; frequency of rescue inhaler use; dose of inhaled corticosteroids	No statistically significant difference in any outcome between groups
Abidi et al. 2014 ²⁶	India	Open label RCT	n = 60	Non-smoking adults 18-55 years old diagnosed with mild to moderate bronchial asthma and improvements in FEV1 ≥ 15% after salbutamol administration or FEV1 between 60-80%.	4-weeks	Curcumin 500mg twice daily added on to standard of care (n=37)	Standard of Care only (n=40)	Asthma symptoms (dyspnea, wheezing, cough, chest tightness, nocturnal symptoms, total symptom score); pre-bronchodilator FEV1; post-bronchodilator FEV1	No statistically significant difference between groups in improvement of clinical symptoms. Curcumin improved FEV1 measures compared to placebo, all p<0.001.
Jusufovic et al 2017 (abstract) ²³	Bosnia and Herzegovina	N/A	n = 100	Non-smokers with moderately controlled asthma on stable doses of inhaled glucocorticoids	2 months	Curcumin 500mg twice daily added to inhaled glucocorticoid therapy (n=50)	Inhaled glucocorticoid (n=50)	FEV1%, ACT, AQLQ	Curcumin improved FEV1% (p<0.001), ACT(p<0.001), and AQLQ (p=0.014) scores
Sutedijo et al 2018 ²⁴	Indonesia	Quasi-experimental study	n = 30	Non-smokers, at least 18 years old diagnosed with an acute asthma exacerbation requiring hospitalization	N/A	Curcumin 550mg four times daily added to standard of care (n=15)	Standard of care only (n=15)	PEFR; length of hospital stay	No statistically significant differences between groups in PEF improvement, or length of hospital stay.

FEV1: Forced Expiratory Volume in 1 second; FEV1%: Predicted Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; PEFR: Peak Expiratory Flow Rate; ACT: Asthma Control Test; AQLQ: Asthma Quality of Life Questionnaire; wk: week

Table 1 Continued

Author, Year	Location	Design	Sample size	Sample Characteristics	Duration	Intervention	Control	Outcome Measures	Results
Jusufovic et al 2019 ²⁷	Bosnia and Herzegovina	Single blind RCT	n = 150	Non-smoking adults at least 18 years old with moderate to severe asthma requiring moderate doses of inhaled glucocorticoids.	3 months	Curcumin 500mg twice daily added to inhaled glucocorticoid therapy (n=50)	Placebo added to inhaled glucocorticoid therapy (n=50) Inhaled glucocorticoid group alone (n=50)	FEV1%, ACT, AQLQ	FEV1%, ACT and AQLQ improved in all groups. Statistically significant improvements in FEV1%, ACT, and AQLQ with curcumin compared to both placebo and control group.
Khadir 2019 ²¹	Iraq	Open-Label RCT	n = 40	Chronic bronchial asthma	2 months	Curcumin 750mg + Piperine 5mg twice daily added to standard of care (n = 23)	Standard of care only (n = 17)	FEV1%; FEV1; FEV1/FVC	No statistically significant differences between groups for FEV1%, FEV1, or FEV1/FVC
Manarin 2019 ²²	Brazil	Double Blind RCT	n = 34	Children and adolescents between 7-18 years of age with persistent asthma	6 months	Powdered <i>Curcuma longa</i> 30mg/kg/day	Identical placebo (maltodextrin)	Frequency of respiratory symptoms; nighttime awakenings; use of rescue inhaler; interference with normal activity; FEV1	No difference between groups in frequency of symptoms, FEV1, or interference with normal activity. Curcumin improved frequency of nighttime awakenings (p<0.001), decreased frequency in use of rescue inhaler(p<0.0001), and overall disease control (p<0.01).

FEV1/FVC: FEV1 to FVC ratio

Appendix 1: Search strategy

PubMed:

1. Asthma [MeSH]
2. Asthma* [tw]
3. Respiratory hypersensitivity [MeSH]
4. Wheez* [tw]
5. airway responsiveness [tw]
6. airway hyperreactivity [tw]
7. airway hyper-reactivity [tw]
8. Airway hyper-responsiveness [tw]
9. Bronchospasm [tw]
10. bronchial responsiveness [tw]
11. bronchial disorder [tw]
12. bronchial hyperreactivity [tw]
13. bronchial hyper-reactivity [tw]
14. lung function [tw]
15. ventilatory function [tw]
16. Pulmonary function [tw]
17. Respiratory function tests [MeSH]
18. FEV [tw]
19. FEF [tw]
20. FVC [tw]
21. PEF [tw]
22. PTF [tw]
23. Interleukin-4 [tw]
24. Interleukin-5 [MeSH]
25. IL-5 [tw]
26. IL5 [tw]
27. Interleukin-13 [MeSH]
28. IL-13 [tw]
29. IL13 [tw]

30. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29
31. Curcuma [MeSH]
32. Curcumin [MeSH]
33. Turmeric [tw]
34. Tumeric [tw]
35. Tetrahydrocurcumin [tw]
36. Curcum* [tw]
37. #31 OR #32 OR #33 OR #34 OR #35 OR #36
38. #30 AND #37

Google Scholar:

All words: Curcuma and Asthma

At least one word: Turmeric OR Curcuma OR Curcumin OR Lung Function OR Respiratory Hypersensitivity

Appendix 2: PRISMA checklist:

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Figure 1, Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Figure 1, 8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	12
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	12
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Figure 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure 3 12-13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Figure 2 12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16-17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	19