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Original Article

Utilization of apitherapy in allergic asthma: A systematic review of clinical and preclinical studies

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Abstract

Objectives: This systematic review aimed to summarize the benefit of apitherapy in human and animal models of asthma. **Materials and Methods:** The procedures in this review were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 protocol, where MEDLINE, ProQuest, and EBSCOhost databases were used to obtain eligible studies dating to 2023. Furthermore, the risk of bias was assessed using Risk of Bias Tool 2.0 (RoB-2) for randomized-control trials and Systematic Review Centre for Laboratory Animal Experimentation's RoB for animal studies. **Results:** A total of 12 studies were included in the review based on the predetermined eligibility criteria, consisting of 4 human and 8 animal model reports. Among the four human studies, two had a low risk, while the other two had some concerns of bias. In the case of eight animal model of asthma, a total of three domains had a high risk of bias. Moreover, the anti-inflammatory properties of apitherapy were demonstrated by its capacity to inhibit NF-κB, nuclear factor of activated T cells, and IgE antibodies, leading to decreased production of tumor necrosis factor-α, interleukin-2 (IL-2), IL-6, and IL-8, and an increase in IL-10 levels. These beneficial effects were reported to be associated with improvements in clinical manifestations and lung function parameters in human subjects. The use of apitherapy was also related to the restoration of airway structure, and reduction of inflammatory cell infiltration, epithelial thickness, and mucus secretion in lung tissue of animal model of asthma. **Conclusion:** Based on the results, apitherapy was effective in improving asthma symptoms and reducing inflammation in human and animal models of asthma.

Keywords: *Apitherapy, Asthma, Bee product, Honey, Propolis*

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Introduction

Asthma is a chronic airway disease characterized by inflammation and narrowing of the small air passages in the lungs [1]. This condition affects an estimated 262 million individuals worldwide, causing approximately 455,000 deaths [2]. Furthermore, it has been a persistent health concern for centuries, leading to a significant burden in terms of morbidity and mortality. This shows that asthma still requires significant attention, thereby necessitating appropriate treatment [2].

The management of asthma is a multifaceted process requiring continuous therapy, and the existing medications have been reported to have certain side effects. These include tremors, increased nervousness, and insomnia in children, as well as urinary retention and nasopharyngitis [3]. Sulaiman *et al*. suggested that the existing medications can become ineffective due to incorrect inhaler usage and lack of adherence [4]. Therefore, adjunctive therapies with anti-inflammatory effects must be considered for the treatment of the condition.

Complementary and alternative medicine (CAM) has gained increasing popularity as an alternative therapy, with apitherapy being one notable method. Apitherapy comprises the use of bee products, such as honey, propolis, pollen, royal jelly, and bee venom, for the prevention and treatment

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of various diseases [5]. These materials have been reported to possess anti-inflammatory, antioxidant, anti-proliferative, antibacterial, and immunomodulatory effects [6,7]. Propolis is bee product containing various anti-inflammatory elements, including indomethacin, nordihydroguaiaretic acid, quercetin, naringenin, caffeic acid phenethyl ester (CAPE), and a new lipoxygenase inhibitor named N, N′-dicyclohexyl-O-(3,4 dihydroxycinnamoyl) isourea (DCHCU) [8]. Several studies have shown that interleukin-2 receptor (IL-2R) and T lymphocyte activity were reduced due to CAPE's inhibition of the synthesis of NF-κB and nuclear factor of activated T cells [9]. A previous study also reported that CAPE restricted the inflow of eosinophils and inhibited eotaxin [10,11]. Another major component of propolis, namely naringenin, showed effective anti-inflammatory properties by reducing eosinophilic inflammation and CD^{4+} activity [12].

According to Mirsadraee *et al.*, 75 mg of propolis taken three times per day for a month successfully suppressed the main clinical symptoms of asthma, such as coughing and dyspnea [13]. This supplementation also increased the sensitivity of the airways, reduced nighttime symptoms, and improved asthma control as measured by the Asthma Control Test (ACT) score. A more recent study by Kaveh *et al*. showed that 10 mL of compound honey syrup in 100 mL of warm water, taken three times per day after a meal for 12 weeks, significantly ameliorated shortness of breath, wheezing, activity limitation, and use of SABA in asthmatic patients [14]. Khayyal *et al*. reported the absence of changes in the incidence and intensity of nocturnal attacks, pulmonary ventilatory functions, and serum levels of the inflammatory mediators in patients given an aqueous extract of propolis as a suspension in water, once a day for 2 months [15]. Therefore, this systematic review aimed to summarize the benefit of apitherapy in human and animal models of asthma.

Materials and methods

This systematic review was designed and conducted under the Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 statement [16]. This review was registered in PROSPERO on July 25th, 2023, with the registration number of CRD42023439498.

Eligibility criteria

Types of studies

This systematic review included all published and unpublished randomized-control trials (RCTs) investigating the effects of bee product supplementation on patients with asthma, along with preclinical studies using animal model of asthma. Furthermore, reviews, observational studies (cross-sectional, case–control, and cohort studies), commentaries/editorials, case reports, case series, conference abstracts, and book sections were excluded. Articles with unavailability of full-text and irrelevant subject matter were also disregarded.

Participants

Human

All patients with a diagnosis of asthma were included in this study. Asthma was diagnosed based on either The National Institutes of Health and Global Initiative for Asthma Management [17] or by history taking, physical examination, and spirometry test by an expert pulmonologist. Furthermore, all asthmatic patients in the included studies experienced respiratory symptoms of cough, wheezing, and/or dyspnea, had a positive history of airway hyperreactivity and recurrent episodes, and reported spirometry results of obstructive patterns with a significant improvement in post-bronchodilator. During the selection process, there was no limitation for gender and race.

Animal

All animal models of asthma were included in this study, and some of the samples were prepared in the laboratory for the acclimation period. The majority of studies [18-21] used female BALB/c mice, aged between 6 and 12 weeks, and weighed 15–20 g. Meanwhile, three distinct studies used female C57BL/6 [22,23] and CD-1 mice [24] without specifying particular age or weight criteria. A particular study used New Zealand white rabbits (*Oryctolagus cuniculus*) as experimental subjects, consisting of both males and females [25]. Induction of asthma was carried out using white-egg matter (ovalbumin [OVA] or conalbumin), either by intraperitoneal injection, inhalation, or combination.

Variable and outcome of interest

The main outcomes in humans were the improvement of asthma symptoms (frequency and severity of nocturnal attack), pulmonary functions (forced vital capacity [FVC], forced expiratory volume at 1 s [FEV1], peak expiratory flow rate [PEFR], fraction of expiratory nitric oxide [FENO], forced expiratory flow in 25-75% of vital capacity [FEF_{25-75}]), inflammatory parameters (tumor necrosis factor-α [TNF-α], Intercellular Adhesion Molecule-1, IL-6, IL-8, IL-10, prostaglandin E_2, prostaglandin $F_2α$, leukotriene D_4, eosinophil count), and ACT score (cough, dyspnea, wheeze, nocturnal symptoms, airway hyperresponsiveness, and acute attack reduced).

In animals, data were collected on cell count (differential cell count, number of cells in peritoneal cavity and lymphoid organs, and bronchoalveolar lavage fluid), histopathology results (cell infiltration, epithelial desquamation, mucus secretion, and submucosal thickness), inflammatory parameters and transcription factor (Interferon-γ, IL-4, IL-5, IL-13, Nuclear Factor Kappa-B [NF-κB]), airway resistance, and antibody titers (IgE, IgG_1, IgG_{2a}).

Search strategy and study selection

Eligible studies were searched using MEDLINE, EBSCO-Host, and ProQuest electronic databases by 2023. Furthermore, the papers were identified by five independent authors using the following keywords:

(("Honey" OR "Propolis" OR "Apitherapy" OR "Bee Products") AND ("Asthma" OR "Bronchial Hypersensitivity" OR "Bronchial Hyperreactivity" OR "Respiratory Hypersensitivity" OR "Airway Hypersensitivity" OR "Airway Hyperreactivity")).

All studies obtained were exported into the Mendeley reference manager software and screened for duplicates. Titles and abstracts were independently reviewed by authors and

excluded when the title and/or abstract were not suitable for the aim of the review. The selected papers were thoroughly assessed in full text using the eligibility criteria described above. In addition, any form of disagreement was resolved among the review team. EBSCO-Host and ProQuest databases were screened for gray literature to identify potential unpublished studies with suitable PICO criteria.

Data collection process

The included studies were analyzed and the data extracted were the name of the primary author, year of publication, country of origin, study design, number of population, age, and sex of the participants, administration protocol for each group, asthma diagnosis criteria in human or induction method in animal model of asthma, adjusted confounding factors in human and animal models of asthma, and all the respective outcomes.

Summary measures and synthesis of results

The results were outlined and presented quantitatively as mean ± standard deviation for normally distributed data or median (interquartile range) for nonnormally distributed data. Each outcome of interest was summarized qualitatively by comparing the intervention and control groups.

Assessment risk of bias/quality assessment

Each human study was assessed using the Cochrane Risk of Bias Tool 2.0 (RoB 2) for RCTs and Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) for animal *(in vivo)* reports. Cochrane RoB 2 tool consisted of seven main domains, including (a) random sequence generation, (b) allocation concealment, (c) blinding of participants and personnel, (d) blinding of outcome assessment, (e) incomplete outcome data, (f) selective reporting, and (g) other source of bias. From each domain, the risk of bias was considered as low, high, and some concerns. Each trial's overall quality was divided into three groups based on the degree of bias present: (1) low risk of bias (low risk of bias across all domains), (2) high risk (high risk of bias across multiple domains or some worries), and (3) some concerns (some concerns across at least one domain). SYRCLE's risk of bias tool for animal studies consisted of ten domains, including (1) random sequence generation, (2) baseline characteristics, (3) allocation concealment, (4) random housing, (5) blinding performance bias, (6) random outcome assessment, (7) blinding detection bias, (8) incomplete outcome data, (9) selective outcome reporting, and (10) other sources of bias. The tools evaluated each study to further categorize them into high, unclear, or low risk. A total of two reviewers separately evaluated each article, and any disagreements were addressed among the whole review team until an agreement was obtained.

Ethical clearance

This study did not require ethical clearance as it was a systematic review and no interventions were conducted on humans/animals.

Results

A flow chart of the study selection process and its results is summarized in Figure 1. The search strategy yielded 201 potentially relevant papers. After the removal of duplicates, a total of 124 of them were eligible for title and abstract screening. According to the selection criteria, 16 studies were identified for further full-text assessment, of which 4 were excluded due to the combined interventions of other active substances or herbal remedies (n = 1), mini review (n = 1), and inappropriateness of the outcome of interests (n = 2). Subsequently, 12 studies were included in a systematic review and were all published between 2003 and 2023. Unpublished studies that met the inclusion criteria were not found, hence, it did not affect the conclusions of the review.

Quality assessment

The comprehensive analysis comprised a total of 12 studies, which used stringent evaluation tools to assess the risk of bias. A total of four human studies underwent assessment using the Cochrane RoB-2 and the remaining eight animal reports were assessed using SYRCLE's risk of bias tool, as shown in Figures 2 and 3, respectively.

In humans, two reports had low [13,14] and the other two [15,26] had some risk of bias concerns. The domain of concern was in the awareness of assigned intervention and the randomization process. Meanwhile, three out of ten SYRCLE's risk of bias domains showed high-risk results, namely allocation concealment, blinding of outcome assessor, and selective outcome of data. These concerns could lead to the paucity of outcomes and non-generalization into broader demographics, as they were likely not to accurately reflect the characteristics of the overall population.

Study characteristics

The age of human samples in the studies ranged from 6 to 73 years old, and two different intervention methods were given, either aqueous extract [14,15,26] or tablet propolis [13]. Meanwhile in animals, each study differed from one another in terms of subject grouping and asthma induction protocols. The animals were classified into three distinct categories, namely positive control/non-treated, negative control/naive, and intervention groups. The positive control groups were only given OVA [18-23,25] or conalbumin [24], through injection or aerosol, while the negative control groups were only administered saline. Different methods of honey administration were carried out for the intervention groups with each particular dose [Table 1].

The outcome in human and animal studies showed improvement in both laboratory and histopathological results. Human reports also showed an improvement in clinical symptoms and pulmonary function tests [Table 2].

Discussion

The pathogenesis of asthma exacerbations comprised two phases, including the early and late stages. The early phase was initiated by IgE antibodies, which bind to high-affinity mast cells and basophils. Furthermore, when an allergen was inhaled, the mast cells released cytokines (histamine, prostaglandins, and leukotrienes) and degranulated, leading to smooth muscle contraction and restricted airway. In the late phase, eosinophils, basophils, neutrophils, and T-cells were all localized to the lung, causing bronchoconstriction and airway

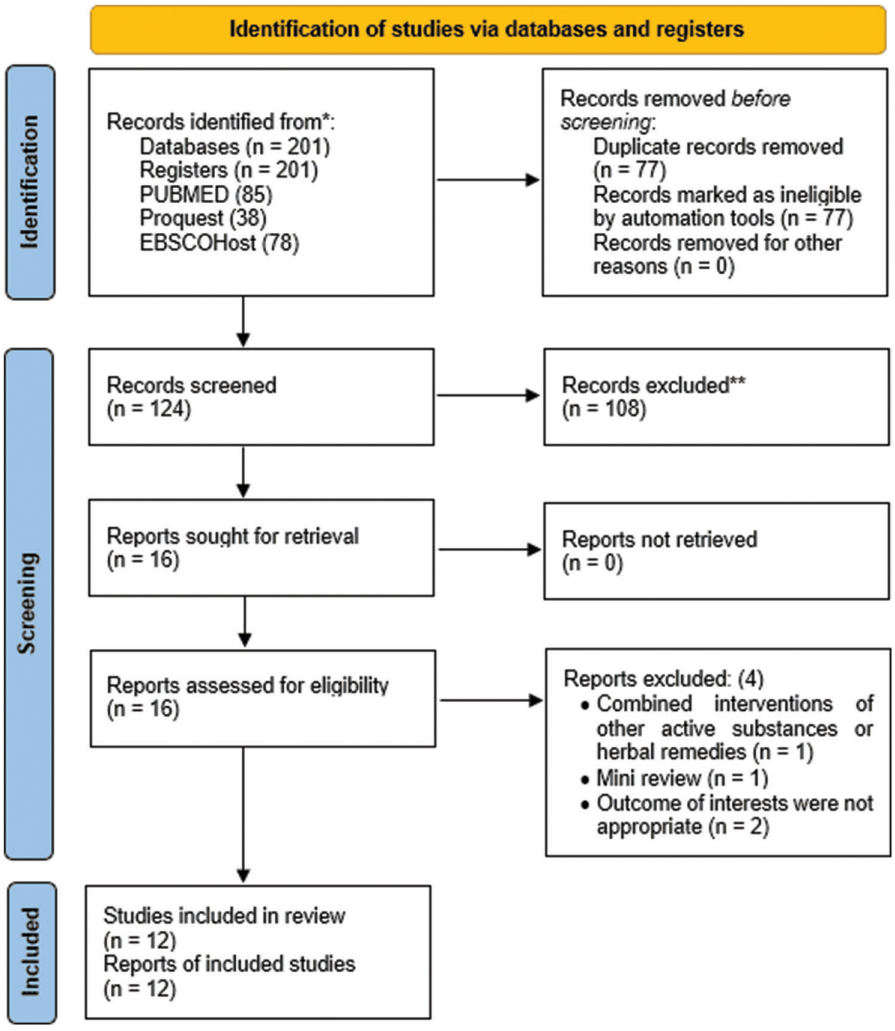

Figure 1: Preferred reporting items for systematic reviews and meta-analysis 2020 flow diagram of included studies

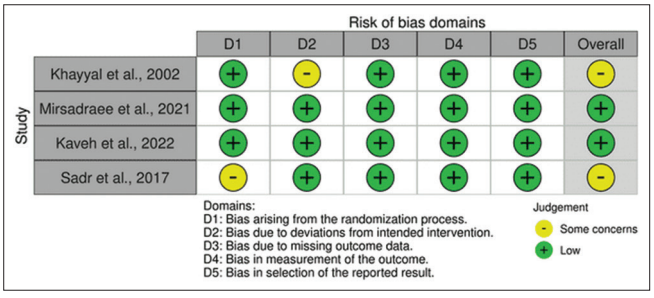

Figure 2: Results of study quality assessment in human study

inflammation [27]. The Th_2 lymphocytes had been reported to have an important role in maintaining inflammation by producing a series of IL-4, IL-5, and IL-13 and GM-CSF that helped cells to communicate with one another. IL-3 and IL-5 helped eosinophils and basophils to survive, while IL-13 alone was engaged in the remodeling, fibrosis, and hyperplasia of smooth muscle cells [28]. Compared to humans, animal models of allergic asthma induced by OVA and conalbumin had experienced an increase in Th_2 cells' response, leading to an escalated number of leukocytes in the lungs [29].

According to previous studies, conventional medications for asthma, such as glucocorticoids had some reported side effects [30]. Apitherapy, as a part of CAM, had gained popularity in the management of asthma due to its ability to inhibit the release of histamine, leukotrienes, prostaglandin D2, IL-4, IL-13, and GM-CSF from mast cells, which played an important role in the pathogenesis of the condition [31,32]. Forbye, apitherapy along with its phenolic constituents and derivatives had been shown to exhibit several biological effects, including anti-inflammatory, immunomodulatory, and antioxidant activities [19]. Since the main pathological feature of the condition was driven by complex interactions between immunological and inflammatory mediators, it had been identified as a promising immunotherapeutic agent.

Apitherapy use in human studies

The results of this review showed that propolis extract and honey syrup significantly reduced the frequency and severity of nocturnal attacks [14,15,26], as well as inflammatory parameters [13,15,26]. The treatments also improved pulmonary and spirometry function tests [13-15,26]. Furthermore, apitherapy ameliorated asthmatic symptoms,

Table 1: Human study characteristics

Author, year, country, type of study	Population				Administration protocol	Asthma diagnosis criteria	Adjusted cofounding factors	Outcome of interest (in propolis group compared to the placebo group)
	Number		Age					
	Intervention	Control	Intervention	Control				
Khayyal *et al*., 2003 [15] Egypt, RCT	22	24	19–52-year-old		Intervention group: 13% solution of AEP Control group: Placebo Duration of treatment: 2 months	The National Institutes of Health and Global Initiative for Asthma Management in 1998	Patients aged 19–52 year old with mild to moderate asthma for the last 2–5 years. There is no further information regarding the adjusted confounding factors	Reduction in the frequency and severity of nocturnal attacks Improvement in pulmonary functions (FVC, FEV_1, PEFR, $FEF_{25–75}$) Reduction in the concentration of TNF-a, ICAM-1, IL-6, and IL-8 by 52%, 65%, 44%, and 30% A 3-fold increase in cytokine IL-10 Declension in the levels of leukotriene D4, prostaglandins E2, and F2a
Mirsadraee *et al*., 2021 [13] Iran, RCT	26	26	44.6±18.5 years old		Intervention group: 75 mg of propolis in the form of a tablet with a dosage of 3 tablets per day Control group: Placebo were coded by a nondependent colleague and prescribed by a blinded pharmacist Duration of treatment: 30 days	Respiratory symptoms and spirometry	Patients were all newly diagnosed or previously untreated asthmatic subjects in the moderate stage who were over 15 year old. Furthermore, there was no further information regarding adjusted confounding factors	Enhancement in ACT score Improvement in almost all spirometry values Improvement of inflammatory parameters (FENO) Reduction in eosinophil level
Kaveh *et al*., 2022 [14] Iran, RCT	40	40	18–60-year-old		Intervention group: 10 mL of compound honey syrup in 100 mL warm water (3x per day after meal) Control group: 10 mL of placebo in 100 mL of warm water (3x per day after meal) Duration of treatment: 12 weeks	Diagnosed by experts through history taking, clinical examination, and spirometry	Patients aged 18–60 year old with a diagnosis of asthma, and there was no information regarding adjusted confounding factors	Improvement in night and morning symptoms, as well as wheezing after 4 weeks Lowering of ACT score after 4 weeks Improvement of activity limitation and shortness of breath after 12 weeks
Sadr *et al*., 2017 [26] Iran, RCT	40	40	6–16 years old		Classical treatment of asthma: Fluticasone spray 50 µg every 12 h Intervention group: 5 mL of compound honey syrup in 100 ml warm water 3 times a day and classical treatment of asthma Control group: Classical treatment of asthma Duration of treatment: 8 weeks	Diagnosed by a pediatric pulmonologist through clinical symptoms and pulmonary function tests	No information regarding adjusted confounding factors	Symptoms and total ACQ scores were reduced in both intervention and control groups After the intervention, the mean SD of variables (scores of night symptoms, morning symptoms, activity limitation, shortness of breath, wheeze, short-acting bronchodilator, $FEV_{1\%}$, total ACQ) in experimental groups were lower than in the control group, and all were significant except for $FEV_{1\%}$

AEP: Aqueous extract of propolis, SD: Standard deviation, FVC: Forced vital capacity, FEV1: Forced expiratory volume at 1 s, PEFR: Peak expiratory flow rate, FENO: Fraction of expiratory nitric oxide, FEF25–75: Forced expiratory flow in 25%–75%, TNF-α: Tumor necrosis factor-α, ICAM-1: Intercellular Adhesion Molecule-1, IL-6: Interleukin-6, RCT: Randomized-control trial, ACT: Asthma control test, ACQ: Asthma control questionnaire

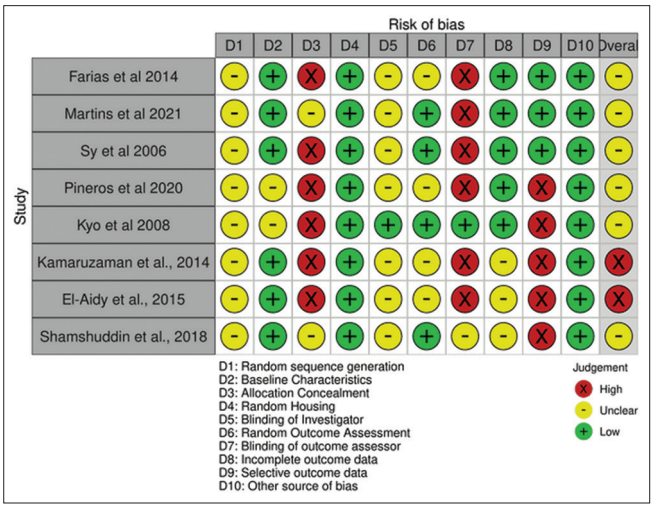

Figure 3: Results of study quality assessment in animal study

proven by an increased in ACT [13,14] and decreased in ACQ [26] scores. The circadian rhythms, which had an impact on inflammatory cells, mediators, hormone levels, and cholinergic tone, were directly related to the processes of nocturnal asthma. The sinusoidal pattern of circadian fluctuation showed that all spirometry parameters expressed lower values at night and higher values during the day [33]. According to a study by Kraft *et al*., the nocturnal asthmatic group's alveolar tissue had significantly higher eosinophils and macrophages at 4:00 A.M. compared to 4:00 P.M [34]. Kelly *et al*. reported that CD^{4+} lymphocyte, neutrophil, and IL-5 levels were significantly increased, while FEV1 decreased during the night [35]. After apitherapy, these inflammatory cells (eosinophil and lymphocyte) [13] and biomarkers (IL-6, IL-8, and leukotriene) [15] significantly reduced, leading to better night symptoms and fewer required doses of asthma medications.

Honey supplementation also improved lung capacity after several treatment cycles. Sadr *et al*. reported a significant decrease in four components of ACQ scores, including shortness of breath (1.02 ± 1.36–0.11 ± 0.31, $P < 0.000$), wheezes (1.33 ± 1.24–0.05 ± 0.23, $P < 0.000$), short-acting bronchodilator (2.11 ± 1.28–0.02 ± 0.16, $P < 0.000$), and increased FEV_1% (99.77 ± 15.10–114.30 ± 25.47, $P = 0.004$). Other lung parameters, such as FVC [13,15], PEFR [13,15], FEF_{25-75} [13,15], FENO [13], and ACT score [13,14] also showed improvement after apitherapy in both small and large airways. These outcomes were explained by a positive bronchodilator activity induced by honey, as reported in an RCT evaluating the effect of compound honey syrup in chronic obstructive pulmonary disease (COPD) patients [36]. Similar results were reported by Taşdoğan *et al*., who found that supplementation of 1000 mg/day pure royal jelly (a material released by honey bees to nourish their queen larvae) for 21 days, led to a significantly higher mean of FEV1 in an active smoker ($P < 0.001$) [37]. Given that COPD and smoking habits had a common chronicity duration with asthma, improvement in lung parameters due to apitherapy suggested a substantial benefit towards most chronic lung conditions.

Acute cough, as one of the asthma symptoms, was lower in almost all patients receiving apitherapy as an adjunctive treatment, compared to the standard regimens group. These results showed a short-term protective effect of honey in controlling asthma symptoms. A study by Oduwole *et al*., demonstrated that the administration of honey for 3 days was likely more beneficial in reducing cough symptoms in children, compared to placebo or salbutamol [38].

Despite the efficacy of propolis treatment, it had been reported to have few side effects. Mirsadraee *et al*. [13] stated that two participants in the propolis group experienced allergic skin rashes. Although this adverse event was present, the medication was not discontinued, only requiring symptomatic therapies, and could later diminish over time due to the desensitization process.

The patient age characteristics in human studies varied from 5 to 60 years old. The prevalence of current and ever asthma was higher among younger children aged 5–9 years old [39]. Sadr *et al*. [26] carried out an assessment using younger participants aged 6–16 years old. Trivedi *et al*. [40] reported that adult-onset of asthma was associated with more respiratory symptoms and appeared to be less stable with more frequent relapse and less remission compared to childhood-onset [40].

Among the human subjects, there were more male patients compared to female. A study by Chowdhury *et al*. [41] also reported a higher prevalence of asthma in males under 13 years old, but the percentages were higher in adult women compared to adult men. This shift in asthma prevalence suggested a role for sex hormones and socioeconomic factors in the occurrence of the occurrence [41].

Based on demographics, three studies were conducted in Iran, and one study was carried out in Egypt. In 2019, the African continent had the highest overall prevalence of the condition among individuals aged 5–69 [39]. However, in this review, studies with the largest number of participants were obtained from Asia (Iran), such as Sadr *et al*. [26] and Kaveh *et al*. [14], with 80 asthma patients in each report. This could be attributed to an increasing prevalence of asthma in developing countries due to factors, such as poor housing conditions, overcrowding, damp environments, and exposure to second-hand smoke [39].

Apitherapy use in animal studies

The results showed that bee product successfully inhibited airway inflammation in an OVA-induced mice model of allergic asthma. The induced condition was characterized by significant features, such as excessive mucus production, increased levels of inflammatory cell infiltration into the lungs, airway blockage, and thickening of the bronchial walls, which were classic indicators of allergic asthma. The presence of phenolic compounds, such as ellagic acid, quercetin, chrysin, and caffeic acid in honey contributed to its antioxidative and radical scavenging properties [20].

Animal species included in this review comprised C57BL/6, BALB/c, and Albino CD1 mice, as well as *Oryctolagus cuniculus* New Zealand white rabbits, with their ages ranging from 2 weeks to 3 months old [18-25]. The majority of these studies used female BALB/c mice [18-21], due to their

Table 2: Animal study characteristics

Author, year, country, type of study	Population		Administration protocol	Asthma induction in animal models	Animal characteristics	Outcome of interest
	Intervention Group (*n*)	Control Group (*n*)				
de Farias *et al*., 2014 [18] Brazil, Experimental *in vivo*	5 each group, aged 2–3 months		DEXA group (positive control): 100 ul dexamethasone injection (1 mg/kg/animal) OVA group (negative control): oral saline solutions PHE group (hydroalcoholic extract of propolis) further divided into P50 and P200: Oral PHE 100 uL (at doses 50 or 200 mg/kg/animal) Duration of treatment: 14 days	Day 0, 7: OVA subcutaneous 4 ug in 1.6 mg aluminum hydroxide Day 14: Anesthetized with 0.4 mL xylazine hydrochloride solution (20 mg/kg) + challenged with OVA solution intranasal 50 uL (10 ug OVA in 50 uL PBS) Day 21: OVA solution intranasal 50 uL	Adult female BALB/c mice Housing and foods: Kept in an animal facility under a controlled environment; foods and water were given ad libitum	Compared to the OVA control group: DEXA and PHE groups had lower total cell numbers PHE P50 and PHE200 had higher percentages of mononuclear cells than polymorphonuclear cells Non-OVA group showed clean parenchyma without infiltration in the histology study DEXA, PHE P50, and PHE P200 had lower levels of IFN-gamma DEXA group significantly had a decreased number of cells in the peritoneal cavity and lymphoid organ, but no change in the PHE group
Martins *et al*., 2021 [22] Brazil, Experimental *in vivo* and in vitro	ArtC 4–5/group MDSC 3–4/group ArtC-induced M-MDSC 4–5/group	Vehicle 4–5/group MDSC 3–4/group ArtC-induced M-MDSC 4–5/group	Control group: PBS/saline intranasal 24 h after 3rd allergen challenge (7 doses/7 days) Intervention group (ArtC): ArtC 80 ug intranasal 24 h after 3rd allergen challenge (7 doses/7 days) Duration of treatment: 7 days	Day 0, 7, 14: 10 ug albumin in 2 mg aluminum hydroxide intraperitoneal Day 21, 22, 23: OVA 30 ug intranasal challenged with ketamine 100 mg/kg and xylazine 10 mg/kg	Female C57BL/6 mice aged 6–8 weeks Housing and foods: Kept in sterile environmental conditions in a ventilated rack and received sterile food and water	Compared to the positive or negative control group In BALF analysis, the ArtC group had a significant decrease of eosinophil, IL-5 level, % inflammation score, and mucus score, but a higher level of MN cells, and PMN cells compared to the vehicle group In histopathological analysis, the ArtC group showed a reduction in the perivascular and peribronchial cellular infiltrates and mucus secretion ArtC-induced Treg cell differentiation *in vitro* but not *in vivo* ArtC augmented M-MDSC frequency in vitro and *in vivo* ArtC-induced M-MDSC reduced allergic airway inflammation in mice
Sy *et al*., 2006 [19] Taiwan, Experimental *in vivo*	6 each group Divided into 4 groups (positive control, low-dose propolis, high-dose propolis, and negative control)		Positive control group (immunized) Low dose group: 65 mg propolis extract/kg body weight High dose group: 325 mg propolis extract/kg body weight Negative control group: Unimmunized group	10 and 12 weeks: Intraperitoneal OVA 20 and 50 ug/mL in PBS + aluminum hydroxide Negative control: Intraperitoneal injection of PBS 14 and 20 weeks: Exposed to 6–8 mL of 2% OVA aerosols in 20 min period in a chamber	BALB/c female mice weighed 15–20 g, aged 6–8 weeks Housing: Kept on standard laboratory chow ad libitum with room temperature 19–24°C and humidity 50%–70%	Compared to the positive or negative control group The low-dose propolis group showed a significant decrease in IgE and IgG1 titer (in weeks 18 and 21) High dose propolis group had a significant increase in IgG2a titer (in week 21) and decreased level of interleukin-5 level in BALF analysis Propolis group had fewer inflammatory cells in the peribronchial and peribronchiolar regions Compared to the positive control group Mice fed with a low dose of propolis had lower airway resistance

Contd...

Table 2: Contd...

Author, year, country, type of study	Population		Administration protocol	Asthma induction in animal models	Animal characteristics	Outcome of interest
	Intervention Group (*n*)	Control Group (*n*)				
			Duration of treatment: 10 weeks			Propolis group had significantly higher IFN-γ levels and lower IL-10 levels in ConA-stimulated splenocytes, and significantly lower IL-6, IL-10, and IFN-γ in OVA-stimulated cultured splenocytes
Kamaruzaman *et al*., 2014 [25] Experimental *in vivo*	4 groups in total with 5 rabbits in each group	4 groups in total with 5 rabbits in each group	Control group: Intraperitoneal OVA, aerosolized OVA, intraperitoneal phosphate buffer saline Intervention group: Injected OVA, treated with 25% (v/v) aerosol-honey, 50% (v/v) aerosol-honey, and aerosolized honey Note: Intraperitoneal OVA: 0.1 mg OVA+10 mg of aluminum hydroxide in 2 mL of PBS Aerosolized OVA: 10 mg/mL Aerosol honey: 20 min with 5 mL of aerosolized Tualang honey Aerosol OVA: 10 mg/mL	Control group Group 1: Naive Group 2: Injected OVA intraperitoneal day 1 and 14 Group 3: Injected OVA. intraperitoneal twice at the same time and aerosolized OVA at days 28, 29, and 30 (3 days) Group 4 (negative control): Injected phosphate buffer saline intraperitoneal twice at the same time and aerosolized PBS at days 28, 29, and 30 (3 days) Intervention group injected with OVA (day 1 and 14) Group 5: Treated with 25% (v/v) aerosol honey at days 23–27 Group 6: Treated with 50% (v/v) aerosol honey on days 23–27 aerosolized with honey continued with OVA Group 7 and 8: Aerosolized with honey within the same concentration and time then aerosolized with OVA for 3 consecutive days	Rabbits breed: New Zealand white, *Oryctolagus cuniculus* Sex: Male=37, Female=3 Weight: 2.40±0.56 g Housing and food: All animals were housed in an air-conditioned room, kept on a 12 h light/dark cycle, and had access to clean food and water	Honey group compared to the OVA group Had reduction of goblet cells/100 epithelial cells, inflammatory cell in right lung segment in BALF analysis Had restoration of airway structure OVA group compared to the control group Had reduction of goblet cell numbers/100 epithelial cells

Contd...

Table 2: Contd...

Author, year, country, type of study	Population		Administration protocol	Asthma induction in animal models	Animal characteristics	Outcome of interest
	Intervention Group (*n*)	Control Group (*n*)				
El-Aidy *et al*., 2015 [24] Experimental *in vivo*	5 group (6 mice each group) Group 2: Conalbumin Group 3: Conalbumin and dexa (positive control) Group 4, 5, 6: Conalbumin and propolis, honey, royal jelly	1 group (6 mice) Group 1: Not sensitized (negative control)	Intervention groups: Sensitized and challenged with conalbumin Note: Conalbumin: 100 ug/50 ul PBS (applied to the back of the tongue)	Group 1: Not sensitized Group 2, 3, 4, 5, 6: Sensitized and challenged with conalbumin	Mice breed: CD1 male mice, 6 weeks old, weighing 18–20 g Housing: Room maintained a 12 h light-dark schedule at a temperature of 25±2°C and a relative humidity of 58.41%–72.18%	Compared to asthma group Honey group did not have a reduction in inflammatory cells of lung tissue and inflammatory cells in peripheral blood remained similar to asthma group Aqueous propolis group and ethanolic propolis group had a reduction in inflammatory cells of lung tissue Aqueous propolis group and ethanolic propolis group had improvement in inflammatory cells
Shamshuddin and Mohd Zohdi 2018 [20] Experimental *in vivo*	6 each group, aged 8–12 weeks The intervention group was divided into 6 subgroups		Control group: No sensitized Intervention group Group 1: 10% Honey Group 2: 40% Honey Group 3: 80% Honey Group 4: 3 mg/kg body weight diluted in PBS Group 5: PBS Group 6: No treatment Treatment given orally (10 ul/g body weight) on days 23–27 (5 days)	Intervention group Sensitized: OVA IP + OVA inhalation OVA IP: Chicken OVA 50 ug and aluminum hydroxide 1 mg in 100 ml PBS OVA inhalation: OVA intranasal 100 ug in PBS 50 ul (on day 14, 25, 26, 27)	BALB/c mice, 8–12 week old Acclimatation for 1 week, normal mice diet, filtered tap water ad lib	Compared to asthma group Eighty percent of honey group expressed less mucus, reduced inflammatory cell infiltration in the lung segment, and reduced the thickness of epithelium Forty percent of honey group showed a reduction in epithelium thickness
Piñeros *et al*., 2020 [23] Brazil, Experimental *in vivo*	6–8 weeks old		The intervention was done with OVA Propolis EPP-AF® dry extract was obtained by hydro-alcoholic extraction using maceration followed by a turbo extraction process After the last OVA sensitization and for 17 or 22 days, mice received y	Mice were subcutaneously sensitized with 100 g of OVA and 1.6 mg of aluminum hydroxide adjuvant, and then received an intraperitoneal injection of 50 g of OVA in 100 l of saline fourteen days following the initial sensitization. Mice were given 100 g of OVA by intranasal route twice	C57BL/6 female mice were obtained from the breeding facility of Ribeirao Preto Medical School and were in ventilated cages under barrier conditions with free access to sterile food and water	Compared to allergic group (OVA), propolis therapy (OVA + Propolis) Had a lower total number of cells in the BALF and the frequency and quantity of eosinophils in the BALF Had lower IL-5 levels in the BALF and lower IL-13 gene expression in the lung specimen Had lower IL-13 production on lymph node cell culture re-stimulated with OVA Had a significant decrease in mucus production as well as in the cellular infiltration

Contd...

Table 2: Contd...

Author, year, country, type of study	Population		Administration protocol	Asthma induction in animal models	Animal characteristics	Outcome of interest
	Intervention Group (*n*)	Control Group (*n*)				
			150 mg/kg of propolis through gavage each da	for 7 days following the second sensitization		No difference in the quantity and frequency of neutrophils, macrophages, and lymphocytes
Jung *et al*., 2008 [21] Japan, Experimental *in vivo*	6–8 weeks old		The intervention was done with OVA and CAPE The nontreated group was done with OVA The Naïve group was only given saline From days 16 to 20 on successive days, mice were intraperitoneally injected with 10 mg/kg/day in 200 l of CAPE each day	On days 1 and 15, mice received intraperitoneal injections of 20 g of OVA emulsified in 1.0 mg of aluminum hydroxide adjuvant. From days 22 to 24, the samples underwent daily challenges via the trachea with OVA (50 mg/mL of saline). Aerosolized saline was used on the control animals. The mice were placed in a chamber (15 cm×25 cm×15 cm) linked to the ultrasonic nebulizer for 20 min to accomplish aerosolization	Female BALB/c mice were obtained from the Charles River Laboratories (Yokohama, Japan), and were kept in the animal facility for at least 1 week before use	Compared to allergic group (OVA), the CAPE-treated group (OVA + CAPE) Had a lower number of eosinophils in the BAL fluid (only 5.3-fold) Marked reductions in the infiltration of inflammatory cells within the peribronchiolar and perivascular regions Marked improvement of luminal narrowing by reduced mucus secretion in the airway Marked reductions in the concentration of IL-4, IL-5, and TNF-α each by 65%, 88%, and 75%, respectively Marked 52% reduction of OVA-specific IgE Increased levels of NF-κB p65 in nuclear protein extracts from lung tissues at 2 h after inhalation of OVA were decreased by the administration of CAPE The decreased levels of NF-κB p65 in cytosolic protein extracts from lung tissues at 2 h after inhalation of OVA were increased by the administration of CAPE

OVA: Ovalbumin, IL-6: Interleukin-6, TNF-α: Tumor necrosis factor-α, IFN: Interferon, CAPE: Caffeic acid phenethyl ester, NF-κB: Nuclear Factor Kappa-B, IgE: Immunoglobulin E, ArtC: Artepillin C, MDSC: Myeloid-Derived Suppressor Cells, PHE: Propolis hydroalcoholic extract, DEXA: Dexamethasone, PBS: Phosphate-buffered saline, BALF: Bronchoalveolar Lavage Fluid, MN: Mononuclear, PMN: Polymorphonuclear

nature as an IgE responder to several allergens, leading to the development of good Th_2 immunological responses. Besides, the female sex could be more susceptible to allergic airway inflammation due to their abundant progesterone hormones, which exacerbated the inflammation process [42].

Asthma induced by OVA led to chronic inflammation in the airways and was typically linked with the infiltration of various types of immune cells, such as lymphocytes, eosinophils, macrophages, and neutrophils into an area around the bronchial tubes [25]. In some studies, treatment with bee product decreased the number of inflammatory cells, specifically eosinophils in the airway regions [19-23,25]. Kamaruzaman *et al*. [25] showed that the use of a nebulizer for honey administration provided optimal effects in rabbits as it ensured maximum deposition on the airway surface. Another study stated that delivering aerosols through nasal inhalation in smaller animals led to the deposition of more than 80% of the aerosol particles in the nasal region, thereby tapering its effectivity [43]. However, Martins *et al*. [22], who used mice with intranasal administration, reported positive results marked by decreased eosinophil count, IL-5 levels, inflammation score, perivascular and peribronchial cellular infiltrates, and mucus secretion. This method also led to a reduction in allergic airway inflammation in mice, showing that honey's effectiveness was more driven by its dosage and proper delivery method compared to the administration route.

In vitro studies showed that various types of honey, such as Gelam, Manuka, and buckwheat each had anti-inflammatory effects. The Manuka type was associated with an elevation of the pro-inflammatory cytokine (TNF-α) levels, along with an increase in the anti-inflammatory cytokines (IL-10, IL-1ra) and several growth factors (PDG and TGF-β) [44]. According to Kassim *et al.* [45], the ability of bee product to reduce inflammation could link to the presence of phenolic compounds. Furthermore, CAPE, one of the major anti-inflammatory components, was recognized as an inhibitor of NF-KB, which effectively lowered the concentrations of pro-inflammatory cytokines (TNF α and IL-1 β) in rats [21].

Excessive mucus production was a key histopathological characteristic in allergic asthma and was evident in mice induced with OVA [20,25]. In asthmatic conditions, goblet cells underwent hyperplasia, leading to an increased number of goblet cells and the enlargement of submucosal glands. This often caused excessive mucus production, which significantly contributed to airflow limitation. Based on previous studies, treatment with bee product, particularly honey, regardless of dosage and its underlying mechanism, effectively curbed goblet cell hyperplasia and excess mucus production in animal-induced models. These results showed that honey could potentially have a mucus-suppressing effect, thereby reducing airway obstruction.

Strength and limitation of the study

Our study has several strengths, as it represents the first systematic review to evaluate bee product without any addition of other herbal substances, as an adjunctive treatment of asthma, beside standard regimens using corticosteroid and beta-adrenergic therapies. This review comprised both human RCT studies and *in vivo* animal studies, thereby facilitating the comprehensive evaluation of clinical manifestations in humans and structural changes in animal model of asthma. However, there were some limitations, including the use of a varying type and dosage of apitherapy. Asthma diagnosis criteria in humans and the dosage of OVA or conalbumin used to induce the condition in animal models were also not uniform. Despite the inclusion of several studies in this systematic review, the heterogeneous data obtained impeded the quantitative meta-analysis.

Future directions

RCTs using human subjects with a larger number of populations are advised for future investigation. Standardization of the compounds used in honey product and asthma induction must be achieved, and addressing the variation in intervention administration and their outcomes is essential. Moreover, uniformity of the study outcome must be fulfilled to conduct a meta-analysis.

Conclusion

Apitherapy has evidence of being effective in improving asthma symptoms and biological markers, both in asthmatic patients and experimental animal models. These results offered a new promising adjunctive therapy in asthma control with lower cost and better outcomes.

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Data availability statement

All data generated or analyzed during this study are included in this published article.

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Conflicts of interest

There are no conflicts of interest.

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