Caspian Journal of Environmental Sciences
Online ISSN: 1735-3866
Print ISSN: 1735-3033

Ethnobotanical study on medicinal plants used for Asthma: Systematic review on current knowledge

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ABSTRACT

This systematic review explores the ethnobotanical knowledge surrounding medicinal plants utilized in the treatment of asthma. The study highlights the significance of various phytochemicals, including polyphenols, alkaloids, and terpenoids, in managing asthma symptoms. Research indicates that polyphenols, such as curcumin, exhibit anti-inflammatory properties by modulating cytokine levels and reducing eosinophil recruitment, alleviating airway hyperresponsiveness and inflammation. Alkaloids, particularly total alkaloids from *Alstonia scholaris*, have shown promise in diminishing pulmonary inflammation and restoring the balance of Th1, Th2, and Th17 cytokines, which are crucial in asthma pathophysiology. Furthermore, terpenoids like astragaloside IV and paeoniflorin have demonstrated efficacy in reducing airway hyperresponsiveness and eosinophilia while promoting a shift towards a Th1 phenotype, thus enhancing the immune response against asthma. The findings underscore the potential of these natural compounds as therapeutic agents in asthma management, emphasizing the need for further research to validate their efficacy and mechanisms of action. This review serves as a comprehensive resource for understanding the current knowledge of medicinal plants in asthma treatment, paving the way for future studies to integrate traditional knowledge with modern pharmacological approaches.

Keywords: Asthma, Herbal medicine, Ingredients, Bioactive pharmaceutical.
Article type: Review Article.

INTRODUCTION

Asthma is primarily characterized by airway obstruction resulting from a decrease in airway diameter. This narrowing is driven by chronic inflammation of the airway walls, marked by the infiltration and activation of various immune cells, including dendritic cells (DCs), eosinophils, neutrophils, lymphocytes, innate lymphoid

cells (ILCs), and mast cells (Yang *et al.* 2024). The intricate interactions among these immune cell types and adjacent structural cells, such as epithelial cells, contribute to the manifestation of asthma-related features, including bronchial hyperresponsiveness (BHR), which is typically reversible with bronchodilator therapy. However, in more severe cases of asthma, airway obstruction may not fully resolve with treatment. In these patients, persistent mucus plugs in the smaller airways may account for the fixed nature of the obstruction. Furthermore, in individuals with severe asthma, additional mechanisms such as airway remodeling—which encompasses airway smooth muscle hyperplasia, goblet cell metaplasia, and increased subepithelial collagen deposition—may significantly influence the disease's pathogenesis (Baş *et al.* 2019; Dilip & Menon 2021; Obeagu *et al.* 2023; Lommatzsch *et al.* 2024). Asthma is one of the most common chronic non-contagious diseases that affects over 260 million people and is responsible for over 450000 deaths each year worldwide, most of which are preventable. Over the past three decades, the prevalence of asthma has escalated, influenced by evolving environmental conditions, particularly in low- and middle-income nations that are least equipped to mitigate its effects. The increase in asthma prevalence has been linked to environmental influences such as urban expansion, industrial growth, and adopting Western lifestyles. Numerous medicinal plants traditionally employed in asthma treatment belong to various families, including Euphorbiaceae, Mimosaceae, Asteraceae, and Amaryllidaceae (Nnaemeka *et al.* 2021; Lommatzsch *et al.* 2024). This review study presents active pharmaceutical ingredients derived from plants and their *in vivo* and *in vitro* studies.

Asthma prevalence

Based on a meta-analysis study, from 1990 to 2019, the global incidence of asthma among young adults rose from approximately 6,487,957 to about 7,604,488 cases. Concurrently, the age-standardized incidence rate (ASIR) for this demographic experienced a decline, decreasing from 580.09 per 100,000 individuals to 504.28 per 100,000. The estimated annual percentage change (EAPC) for the incidence of asthma in young adults was a reduction of 0.47% (Supplemental Table S1). During the same period, the age-standardized death rate (ASDR) fell from 11.91 per 100,000 to 5.8 per 100,000, with an average annual decrease in deaths of 2.65%. In terms of prevalence, the number of asthma cases among young adults in 1990 increased from 62,962,010 to 72,443,314; however, the EAPC for prevalence declined by approximately 1.04% per year. The age-standardized prevalence rate (ASPR) also decreased from 4,496.93 to 3,415.53 per 100,000. Additionally, disability-adjusted life years (DALYs) associated with asthma in 1990 decreased from 4,552,087 to 4,474,740.06 (Le *et al.* 2024; C. Yang *et al.* 2024).
An additional analysis of the Global Burden of Disease (GBD) and the temporal trends across 21 GBD regions indicated that the highest incidence of asthma among young adults is observed in South Asia, High-income North America, North Africa, and the Middle East. Furthermore, the highest age-standardized incidence rate (ASIR) for young adult asthma is found in High-income North America, Tropical Latin America, and the Caribbean. At the same time, the most significant decline in the estimated annual percentage change (EAPC) occurs in High-income Asia Pacific and Eastern Europe. The analysis by gender indicates that the highest proportion of female patients is found in the 15–19 age group globally, while the peak percentage of females occurs in the 30–34 age bracket within High SDI regions. It is essential to recognize that this pattern may vary across different nations. For instance, a detailed investigation conducted in seven major Chinese cities demonstrated a markedly higher incidence of asthma among males aged 15 years and older in six of those cities. We hypothesize that the increased prevalence of asthma in females post-puberty may be linked to the pathogenic effects of sex hormones (Le *et al.* 2024; Lommatzsch *et al.* 2024; Yang *et al.* 2024). The trends and patterns of reported and projected asthma incidence from 1990 to 2030. Complementing the results of the Joinpoint regression analysis, an increase in asthma incidence rates was noted in two East and Southeast Asian nations, specifically China and Thailand, as well as in France and the United States. Conversely, asthma incidence rates declined in four other East and Southeast Asian countries and three additional high-income Western nations. The average annual percentage change (AAPC) for China and Thailand was recorded at 1.82% and 0.70%, respectively, demonstrating a "V"-shaped trajectory. Initially, both countries experienced a decrease (with an APC of -2.53% for China from 1990 to 2010 and -0.69% for Thailand from 1990 to 2017), followed by a significant increase (with an APC of 6.36% post-2010 in China and 3.64% post-2017 in Thailand). In contrast, the AAPC for the remaining four East and Southeast Asian countries—Japan, Korea, Singapore, and the Philippines—ranged from -2.00% to -0.51%. Since 1995, three of these nations have consistently exhibited a downward trend, while Japan reached its lowest incidence rate around 2011 before beginning to rise again (Yang *et al.* 2024; Zheng *et al.* 2024). Analytical study

indicates that the United States will exhibit the highest age-standardized incidence rate in 2030, estimated at 902.71 per 100,000. Conversely, Korea is anticipated to have the lowest incidence rate at 176.46 per 100,000. In East Asia, Japan is expected to maintain the highest incidence rate, while China's rate is predicted to surpass Korea's by 2030. In Southeast Asia, Singapore is forecasted to record the lowest incidence rate, reflecting a decrease of 50.16% compared to 2020. Furthermore, all high-income Western nations are expected to experience a decline in incidence rates post-2020, with Australia projected to see the most significant reduction at -54.98% (Zheng *et al.* 2024).

Asthma pathophysiology

Asthma is a chronic inflammatory condition affecting the airways, resulting in symptoms such as coughing, wheezing, dyspnea, and chest constriction. The manifestation of asthma symptoms is primarily influenced by airway inflammation, which instigates mechanisms including the production of mucus, remodeling of the airway structure, and bronchial hyperresponsiveness (BHR), defined as the propensity of smooth muscle cells to respond to non-specific stimuli, including cold air. Asthma frequently manifests during early life (childhood-onset asthma), although some individuals may develop the condition later in life (late-onset asthma). The two forms of asthma present distinct differences (Maddox & Schwartz 2002). Late-onset asthma is generally more severe and exhibits a lower correlation with allergic responses compared to childhood-onset asthma. In pediatric populations, factors such as atopy, diminished lung function, and respiratory infections, particularly those involving rhinovirus, are significant risk factors for the chronicity of asthma. The relationship between the underlying inflammation in asthmatic children and the pathogenicity of respiratory viruses, or whether early viral infections predispose individuals to asthma, remains an area of ongoing inquiry. Given the pivotal role of inflammation in the pathogenesis of asthma, it is unsurprising that the primary objective of asthma management has been to establish control over symptoms and underlying inflammatory processes to mitigate the risk of future exacerbations (Mims 2015). The application of plant-based remedies for asthma management has been documented in traditional medicine for more than 5,000 years, notably through the Chinese practice of utilizing an infusion of *Ephedra sinica*, recognized for its ability to stimulate the immune system and mitigate asthma attacks. In more contemporary research, Costa and colleagues identified key natural resources employed by families in the northeast region of Brazil for asthma treatment. Their investigation highlighted a range of natural products, including beet, honey, onion, lemon, garlic, yarrow, and mint, underscoring the diverse array of remedies utilized for treating asthma in children. Furthermore, various other naturally derived substances, such as essential oils from both plant and animal sources, have been extensively referenced in the context of asthma treatment, with these oils being extracted through various methods. Allergic asthma frequently occurs during childhood and is characterized by T helper 2 (Th2) cell responses, also prevalent in various allergic disorders such as atopic dermatitis and allergic rhinitis. This variant of asthma is triggered by early-life exposure to environmental allergens, including house dust mites (HDM), pollen, cockroach remnants, or animal dander (Murphy & O'Byrne 2010). However, it can also manifest later in life upon exposure to new allergens, such as those encountered in occupational settings. Upon the identification of allergens, allergen-specific Th2 cells release type 2 cytokines (interleukin [IL]-4, IL-5, IL-9, and IL-13), resulting in a significant influx of eosinophils in the airway tissue, excessive mucus production, and the generation of immunoglobulin E (IgE) by allergen-specific B cells, detectable in serum or through positive skin-prick testing (Yönden *et al.* 2022). Despite a comprehensive understanding of the mechanisms, environmental risk, and protective factors influencing allergic sensitization during childhood, extensively modeled in murine studies, the reasons behind the disease's localization to the airways and its persistence in adulthood remain ambiguous. However, the onset of the disease aligns with a critical developmental phase of the immune system and lung structure in early childhood (Barrios *et al.* 2006). The lifelong equilibrium and vulnerability to immune-mediated disorders such as asthma are influenced during the neonatal phase. Thus, modifications in the pulmonary environment during this "window of opportunity" could precipitate alterations in immune cell and organ functionality, effects that may endure long after the initial allergenic exposure has ceased. Conversely, non-allergic asthma typically presents later in life, is more prevalent among females and individuals with obesity, and can often prove challenging to manage. Late-onset asthma phenotypes have been categorized into Th2 and non-Th2 late-onset asthma. The non-Th2 variant is frequently linked to obesity, advanced age, and tobacco use. The Th2-associated variant is often accompanied by recurrent and chronic rhinosinusitis with nasal polyps (CRSwNP) and sensitivity to aspirin, and it may be associated with

elevated eosinophil levels in the airways (Maddox & Schwartz 2002; Mims 2015). As with numerous chronic inflammatory conditions, medical professionals have come to recognize that the categorization of asthma into merely two clinical forms has been an oversimplification. In recent years, the classification of asthma phenotypes has advanced towards asthma endotypes, including the type 2-high or -ultra-high (predominantly eosinophilic) and type 2-low (non-eosinophilic, occasionally neutrophilic, and metabolic). Endotypes are delineated by their underlying pathophysiological mechanisms, which may result in distinct differences in responsiveness to standard treatments such as inhaled corticosteroids or specific biologic agents. Consequently, the type 2-high endotype is driven by Th2-associated cytokines such as IL-4, IL-5, and IL-13, with ultra-type 2-high asthma representing a more severe manifestation of the illness. The type 2-low endotype presents greater complexity, and no biomarkers have yet been identified. Therefore, type 2-low asthma generally encompasses all asthmatic patients without type 2-high inflammation (Barrios *et al.* 2006; Ji *et al.* 2014; Fig. 1).

Asthma and environmental factors

In recent years, the effects of climate change on the environment, biosphere, and biodiversity have become increasingly apparent. Respiratory health is particularly vulnerable to the consequences of climate change. Climate changes have been shown to affect pollen allergies, altering both the duration and intensity of pollen seasons. Additionally, flooding contributes to increased mold growth. Thunderstorms occurring during pollen seasons can exacerbate severe asthma symptoms in individuals with allergic rhinitis; a similar trend is noted with mold exposure (Strachan 2000). The frequency and severity of wildfires are also rising due to climate change, with wildfire-specific fine particulate matter (PM2.5) found to be approximately ten times more detrimental to children's respiratory health than $PM_{2.5}$ from other sources, especially in children aged 0 to 5 years. The underlying immunological mechanisms involve interleukin-1 beta (IL-1β) and C-reactive protein. The interaction between the exposome and the immune system is crucial for resilience and immune homeostasis. Key factors such as diet, microbiome, and the integrity of the epithelial barrier play significant roles in regulating the communication that enables the immune system to adapt to various challenges, thereby establishing and maintaining an appropriate immune response. A notable shift in prevention strategies is occurring, moving from avoidance to fostering immunological tolerance and resilience, as demonstrated by the Finnish Allergy Program. A longitudinal study involving 1,050 children from a population-based birth cohort in Portugal revealed that residing near greener environments at birth protected against the development of allergic diseases and asthma by age seven. In contrast, living in areas with a high diversity of fauna species was associated with an increased risk of allergies, asthma, and wheezing (Samet 1995; Toskala & Kennedy 2015; Biagioni *et al.* 2023; Onur *et al.* 2024;).

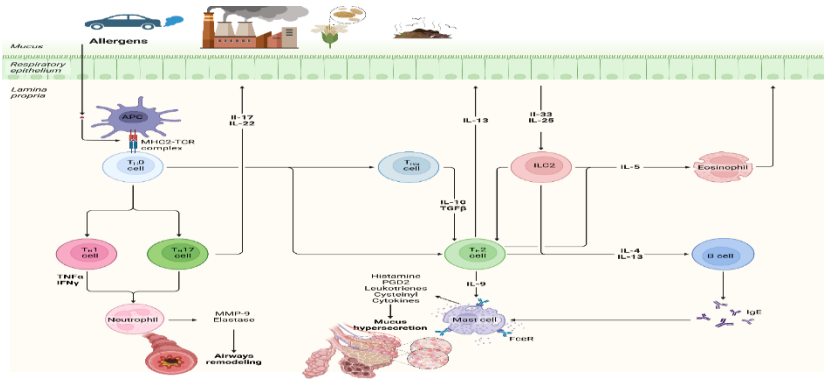

Fig. 1. The schematic of allergens and effects on cytokines and chemokines and remodeling the tissue and hypersecretion of the mucus.

Natural herbal-based therapeutic agents on asthma

The pharmacologically active components in Traditional Medicine (TM) serve as the foundation for preventing and treating various ailments. These active compounds demonstrate anti-inflammatory and antioxidant properties and other biological effects by modulating multiple molecular targets and associated signaling pathways (Safdarpour *et al.* 2022; Widoyo *et al.* 2022). Fig. 2 provides a summary of plant components and their effect on asthma pathophysiology.

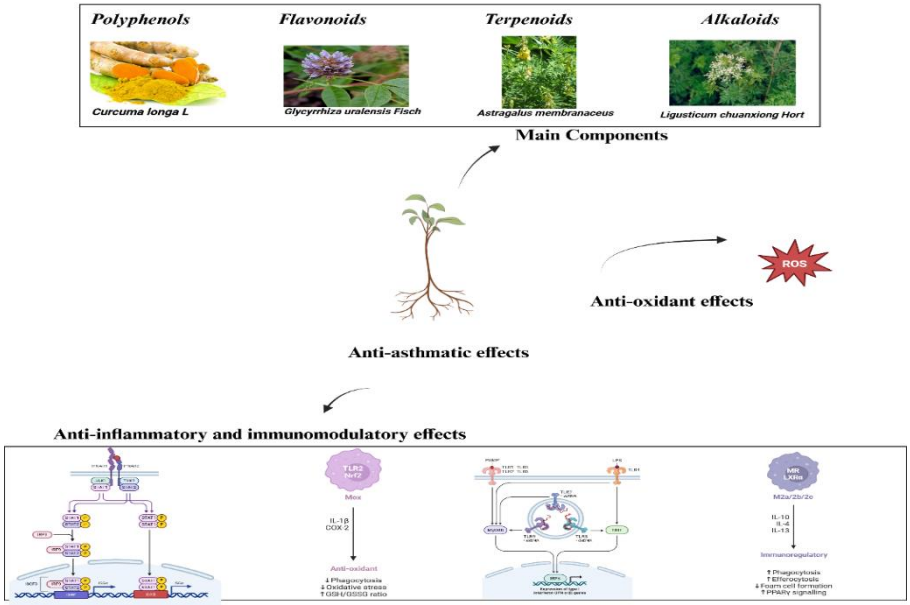

Fig. 2. The polyphenols, flavonoids, terpenoids, and alkaloids isolated from herbals to ameliorate the asthma.

Polyphenols

Curcumin, a principal component derived from *Curcuma longa* L., is frequently utilized as a flavoring agent. Research indicates that curcumin is employed in treating various diseases, particularly those associated with chronic or abnormal inflammation, such as asthma. Evidence suggests that curcumin can diminish airway hyperresponsiveness (AHR) and the infiltration of inflammatory cells in the airways of asthmatic mice by inhibiting NF-κB signaling pathways. Furthermore, curcumin has been shown to activate the Nrf2/HO-1 pathway in asthmatic models, leading to a reduction in pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, and eosinophils present in bronchoalveolar lavage fluid (BALF). Additionally, curcumin appears to alleviate airway inflammation and mucus hypersecretion in mice sensitized to ovalbumin (OVA) while also suppressing the upregulation of MCP-1 and MUC5AC induced by OVA and IL-4, likely through a PPARγ-dependent mechanism involving NF-κB signaling (Karaman *et al.* 2012; Zhu *et al.* 2019). The suppression of Th17 cell activity and the enhancement of Treg cell function, leading to a reduction in IL-17A levels and an elevation in IL-10, may contribute to the anti-asthmatic properties of curcumin. Furthermore, curcumin may also exert its effects by inhibiting the production of IL-2, IL-5, granulocyte-macrophage colony-stimulating factor (GM-CSF), and IL-4, as well as by reducing lymphocyte proliferation, eosinophil recruitment, and Th2 cell differentiation, potentially through the downregulation of nitric oxide (NO) and inducible nitric oxide synthase (iNOS; Karaman *et al.* 2012; Zhu *et al.* 2019). In a study by Karaman *et al.* in 2012, forty-two BALB/c mice were allocated into six distinct groups: I, II, III, IV, V, and a control group. All groups, with the exception of the control, underwent sensitization and subsequent challenges with ovalbumin. During the challenge phase, Group I was treated with nebulized saline. Mice in Groups II, III, IV, and V received intraperitoneal injections of curcumin at doses of 10 mg kg^{-1}, 20 mg kg^{-1}, dexamethasone at 1 mg kg^{-1}, and dimethyl sulfoxide at 1 mg kg^{-1}, respectively, once daily for the last five days of the challenge period. The animals were euthanized 24 hours following the final drug administration, and airway samples were subjected to histological evaluation via light microscopy. Histological assessments revealed that the parameters in Group III exhibited improvements comparable to those in Group IV when compared to Group I. In Group II, a significant reduction in epithelial thickness was noted compared to Group I. Furthermore, all measured variables, with the exception of epithelial thickness, showed considerable enhancement in Group III compared to Group II. The findings indicate that curcumin administration mitigates the pathological alterations associated with chronic asthma. This suggests that curcumin may represent a potential future therapeutic option for asthma management (Karaman *et al.* 2012). On the other hand, Yang's study on mouse model C57BL/6 immunized with ovalbumin (OVA) underwent three challenges with an aerosolized form of OVA administered every other day over eight days. On day 24, either dexamethasone or curcumin was given intraperitoneally to the OVA-immunized C57BL/6 mice once daily for nine consecutive days. The study aimed to evaluate the impact of

curcumin on asthma, specifically focusing on inflammatory cell infiltration and cytokine levels within lung tissue. The findings indicated that OVA exposure increased inflammatory mediators within bronchoalveolar lavage fluid (BALF) and heightened lung inflammation scores in the mice. Notably, curcumin demonstrated a dose-dependent ability to mitigate the changes induced by OVA in asthmatic mice. Furthermore, curcumin was found to activate the Wnt/β-catenin signaling pathway in both DCs and the lungs of asthmatic mice. In conclusion, curcumin appears to modulate the morphology and functionality of DCs, alleviating asthma symptoms and inflammatory responses by activating the Wnt/β-catenin signaling pathway. These findings offer new insights into the potential therapeutic application of curcumin in asthma (Yang *et al.* 2017). *In vivo* and *in vitro* studies by Zhu *et al.* exhibited that curcumin significantly mitigated OVA-induced airway inflammation and mucus hypersecretion in murine models. Specifically, it was observed that curcumin effectively reduced the upregulation of MCP-1 and MUC5AC induced by OVA and IL-4 while also inhibiting the suppression of PPARγ and the activation and translocation of NF-κB p65, both *in vivo* and *in vitro*. Furthermore, the application of shRNA-PPARγ notably diminished the beneficial effects of curcumin. These findings suggest that curcumin alleviates OVA-induced airway inflammation and mucus hypersecretion in mice, likely via a PPARγ-dependent mechanism involving the NF-κB signaling pathway (Zhu *et al.* 2019). Resveratrol, a natural phenolic compound derived from *Polygonum cuspidatum*, has been shown to benefit respiratory conditions. A total of 111 species from 71 genera and 34 families have been detected to contain Resveratrol, for instance, *Alnus* species, *Aster tataricus* L. f., *Syneilesis aconitifolia* (Bge.) Maxim, *Vaccinium dendrocharis* Hand.-Mazz., *Vaccinium chaetothrix* Sleumer, *V. moupinense* Franch., *V. sikkimense* C. B. Clarke, *Euphorbia humifusa* Willd. ex Schlecht., *Poa annua* L., *Festuca ovina* L., and *Stipa tianschanica* (Roshev.; Bralley 2007; Ma & Li 2020). The compound phenol resveratrol (3,4´,5-trihydroxytrans-stilbene, 5-[(1E)-2-(4-hydroxyphenyl) ethenyl]-1,3-benzenediol) is a phytoalexin that is synthesized in plants as a defense mechanism against pathogens and environmental stressors. This molecule exists in two isomeric forms, E and Z, and glycosylated derivatives. Additionally, resveratrol is recognized for its potent antioxidant properties (Chung *et al.* 2012). Administration of oral resveratrol has been associated with a reduction in airway hyperresponsiveness (AHR), eosinophilia, and mucus hypersecretion, likely due to its inhibitory effects on Th2-related cytokines, specifically interleukin-4 (IL-4) and interleukin-5 (IL-5). In a model of asthma induced by house dust mites (HDM), resveratrol significantly decreased levels of tumor necrosis factor-alpha (TNF-α), fibrosis, and airway inflammation. The proposed mechanism involves the downregulation of Syk protein expression and the inhibition of mast cell degranulation. Resveratrol has been effective in mitigating airway inflammation and remodeling caused by ovalbumin (OVA) exposure, as well as in decreasing markers of epithelial-mesenchymal transition (EMT), including Snail, Slug, vimentin, and alpha-smooth muscle actin (α-SMA). These beneficial effects are thought to be mediated through the inhibition of the TGF-β1/Smad signaling pathway and the EMT process (Bralley 2007; Zang *et al.* 2015; Kim 2017; Pathak et al. 2023; Bejenaru *et al.* 2024). A concurrent investigation revealed that resveratrol inhibited the advancement of asthma by enhancing the phosphatase, tensin homolog (PTEN) and SIRT1 signaling pathways. Additionally, the overexpression of PTEN led to a reduction in the size of smooth muscle, the inner airway wall, and mucous glands, thereby ameliorating asthma symptoms, an effect that was counteracted by the SIRT1 inhibitor and shRNA. Transforming growth factor-β1 (TGF-β1) interacts with TGF receptors to activate the mothers against the decapentaplegic homolog (Smad) pathway, which facilitates the production and accumulation of extracellular matrix (ECM), ultimately resulting in fibrosis (Ma & Li 2020). It is well-established that the onset of epithelial-mesenchymal transition (EMT) in lung tissues correlates with an increase in α-smooth muscle actin (α-SMA) expression and a decrease in E-cadherin expression. Furthermore, resveratrol has been shown to significantly improve airway structural alterations and inflammation in a murine model of bronchial asthma by reducing TGF-β1 expression, thereby inhibiting the TGF-β1/Smad2/3 signaling pathway and the EMT process. In response to IL-1 or TNF-α stimulation, high mobility group box 1 (HMGB1) is released by macrophages, mononuclear cells, and other immune cells, activating TLR2 and TLR4, which subsequently triggers an inflammatory response through the NF-κB pathway (Zang *et al.* 2015; Kim 2017; Bejenaru *et al.* 2024). Recent findings indicate that resveratrol treatment reduced inflammatory cell infiltration into the airway epithelium and decreased airway collagen deposition. Additionally, resveratrol lowered serum levels of inflammatory cytokines, such as IL-1, IL-10, and TNF-α, by inhibiting the HMGB1/TLR4/NF-κB pathway in an OVA-induced asthma rat model (Wood *et al.* 2010). Additionally, a separate investigation revealed that the administration of resveratrol enhanced allergic airway inflammation and mitigated the exacerbation of obesity-related asthma. This effect was attributed to the

restoration of insulin-induced phosphorylation of Akt, insulin receptor substrate 1 (IRS-1), and insulin receptor β (IRβ), alongside a reduction in the signaling pathways of JNK and NF-κB within the lung tissues of obese mice (Samaha *et al.* 2024). Tea polyphenols, especially when delivered via nanoparticle encapsulation, have effectively decreased the production of reactive oxygen species (ROS) and influenced inflammatory pathways associated with asthma. This method has improved lung tissue retention and a favorable safety profile, positioning it as a potentially effective therapeutic approach. Furthermore, *in vitro* investigations have underscored the capacity of tea polyphenols to impede the proliferation and migration of airway smooth muscle cells, which play a critical role in the constriction of airways in asthma (Mokra *et al.* 2022; Chen *et al.* 2023). The impact of another flavonoid, apigenin, warrants attention. Apigenin, a type of flavone, is prevalent in various fruits and vegetables, with particularly high concentrations found in onions, parsley, citrus fruits, tea, and wheat germ. *In vitro* studies have demonstrated that apigenin exerts anti-inflammatory effects by inhibiting the transcription factor NFkB, thereby reducing the production of cytokines such as IL-6, IL-8, and certain prostaglandins (Li *et al.* 2010). Research conducted by Pang *et al.* and Choi *et al.* in animal models has indicated that apigenin mitigates allergic inflammation within the bronchial tree. Their findings suggest that apigenin decreases the population of Th2 cells and the synthesis of IL-4 by obstructing the transcription factor GATA 3. Furthermore, analyses of bronchial washings revealed a notable reduction in lymphocyte counts, particularly eosinophils, attributed to the inhibition of adhesion molecules ICAM-1 and VCAM-1 by apigenin. Earlier investigations utilizing both in vitro and animal models, have also indicated that apigenin hinders the maturation of dendritic cells, thereby influencing the early stages of inflammatory development (Choi *et al.* 2010; Pang *et al.* 2010). In studies assessing bronchial reactivity in test subjects, a marked decrease in the propensity for bronchial obstruction was observed following apigenin administration. This flavonoid may play a role in remodeling the bronchial tree in asthma, as it has been shown to inhibit the activity of metalloproteinases 2 and 9 (MMP-2, MMP-9). Additionally, studies highlight the effects of apigenin on tumor cells, indicating that this compound can inhibit the proliferation of leukemic cells as well as breast and colorectal cancer cells (Zhou *et al.* 2016). Research on the influence of flavonoids in bronchial asthma also encompasses quercetin, the most widely distributed plant flavone globally. This compound is typically found in conjunction with sugars such as rhamnose and rutinose, with the highest concentrations located in onions, particularly red onions.

Flavonoids

Flavonoids are naturally occurring compounds in various plants, nuts, and fruits. They are characterized by their unique chemical structure, which includes two benzene rings (designated as A and B) connected by a heterocyclic pyrene ring (C). This class of compounds encompasses a significant array of polyphenolic secondary metabolites, with over 8,000 distinct compounds identified to date. Based on their chemical configuration, flavonoids can be categorized into several subclasses: flavans, flavanones, isoflavones, flavones, isoflavones, anthocyanidins, and flavonolignans. Flavans and isoflavones are defined by a heterocyclic hydrocarbon framework known as chromane, which features a phenyl group (B ring) substituting at either carbon 2 or 3 of the C ring. Flavanones and isoflavones are characterized by the presence of an oxo group at position 4, while a double bond distinguishes flavones and isoflavones between carbons 2 and 3. Additionally, anthocyanidins are identified by a double bond between carbons 1 and 2 (Treutter 2006; Janićijević *et al.* 2007; Samanta *et al.* 2011). The structural diversity of flavonoids is linked to their extensive range of physiological and biological effects, including notable antioxidant, anti-inflammatory, antiallergic, antiviral, hepatoprotective, antithrombotic, and anticarcinogenic properties. In the context of asthma treatment, 14 studies have identified flavonoids as a promising group of compounds. The subsequent sections will detail the primary flavonoids recognized for their antiasthmatic properties in the literature and their applications in traditional medicine. These studies suggest that the antiasthmatic effects of plant extracts containing flavonoids are partly attributable to the presence of these compounds within the phytocomplex (Amaral-Machado *et al.* 2020; Borghi *et al.* 2022).

Flavonol Compounds: Quercetin, Galangin, and Kaempferol. Quercetin (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one) is a flavonol compound prevalent in various foods. It is recognized as the primary bioactive component in these plants, which contributes to their extensive application in traditional medicine for managing inflammatory, allergic, and viral conditions (Amaral-Machado *et al.* 2020). Research investigating the antiasthmatic properties of quercetin has been conducted using both *in vitro* cell cultures and *in vivo* rat models, demonstrating its significant ability to mitigate inflammatory responses. The anti-inflammatory effects of

quercetin are primarily linked to its inhibition of lipoxygenase and phosphodiesterase 4 (PDE4), as well as its capacity to decrease the release of histamine and leukotrienes, leading to a reduction in the production of proinflammatory cytokines and interleukin-4 (IL-4). Furthermore, quercetin has been shown to inhibit the activation of human mast cells by blocking calcium ion influx and reducing prostaglandin release, thereby providing therapeutic benefits for asthma symptoms and lowering reliance on short-acting β-agonists (Tijjani *et al.* 2020; Borghi *et al.* 2022). Kaempferol, a flavonol characterized by its chemical structure as 3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one, is prevalent in various plant sources, including citrus fruits, broccoli, and apples. This compound has garnered attention for its pharmacological properties, particularly in the context of anti-inflammatory effects (Tijjani *et al.* 2020). Research conducted by Chung *et al.* utilized a mouse model of asthma induced by ovalbumin (OVA) to investigate the effects of kaempferol. The findings indicated that kaempferol significantly mitigates the inflammatory response, as evidenced by a reduction in the infiltration of inflammatory cells and a decrease in the production of inflammatory cytokines and IgE antibodies. Furthermore, kaempferol was shown to diminish intracellular reactive oxygen species (ROS) production during the airway inflammatory response (Chung *et al.* 2015; Park *et al.* 2015).

Flavone Compounds: Chrysin, Baicalin, Luteolin, and Oroxylin A. Chrysin, chemically characterized as 5,7-dihydroxy-2-phenyl-1-4H-chromen-4-one, is a flavone that occurs in the flowers of *Passiflora caerulea* and *P. incarnata*, as well as in *Matricaria chamomilla*, commonly referred to as chamomile. Additionally, chrysin is found in propolis and various other plant sources (Yao *et al.* 2016; Roy *et al.* 2020). Luteolin, a compound extracted from *Chrysanthemum indicum* L., is commonly used to treat inflammatory diseases, particularly asthma. Its anti-asthmatic properties are attributed to several mechanisms: it promotes the production of IFN-γ while decreasing the levels of OVA-specific IgE antibodies; it inhibits the levels of pro-inflammatory cytokines; it prevents the degradation of IκBα induced by PMA and the subsequent nuclear translocation of NF-κB p65; and it stimulates the induction of FOXP3 and regulatory T cells (Kang *et al.* 2023; Qiao *et al.* 2023). Additionally, icariin is a significant bioactive compound derived from *Epimedium brevicornu* Maxim. Research indicates that icariin can restore the equilibrium between the Th1 and Th2 cytokines, specifically T-bet and GATA3, while also inhibiting NF-κB p65 in models of asthma. In experiments involving OVA-stimulated asthmatic mice, treatment with icariin resulted in a substantial reduction of IL-17 levels and a notable increase in FOXP3 expression within splenic $CD4^+$ T cells, thereby facilitating the regulation of the Th17/Treg balance. Furthermore, icariin exhibits anti-inflammatory properties by diminishing PGD2 and CRTH2 levels in eosinophils in both OVA- and RSV-induced asthma models (Agrawal et al. 2024). Licochalcone A (LA), a significant bioactive compound derived from *Glycyrrhiza uralensis* Fisch, exhibits a range of biological activities both *in vitro* and *in vivo*. *In vitro* studies have demonstrated that LA diminishes VEGF-induced proliferation of airway smooth muscle cells (ASMC) by inhibiting the activity of VEGFR2, ERK1/2, and caveolin-1. *In vivo*, LA has been shown to effectively reduce Th2 cytokine levels, lower eosinophil counts, and mitigate mucus hypersecretion in asthmatic airways through the inhibition of the ERK and p38 signaling pathways. Additionally, further investigations indicate that LA decreases the expression of ICAM-1 in BEAS-2B cells, hinders monocyte adhesion, and alleviates oxidative stress and inflammation, thereby addressing various pathological alterations associated with asthma by suppressing Th2-type cytokines (Li *et al.* 2022; Shaikh *et al.* 2024). Naringin, a prominent compound derived from *Exocarpium Citri grandis* , is related to flavonoids and is recognized for its notable antitussive properties. Recent studies have revealed its potential anti-inflammatory effects in the context of chronic inflammatory diseases (Guihua *et al.* 2016; Jasemi *et al.* 2022). In a guinea pig model of ovalbumin-induced cough-variant asthma (CVA), naringin (18.4 mg kg^{-1}, orally) was administered, and its effects on cough induced by inhaled capsaicin following exposure to an aerosolized antigen in sensitized guinea pigs. The influence of naringin on AHR in response to inhaled methacholine was measured 24 hours post-cough. Airway inflammation was analyzed through bronchoalveolar lavage fluid (BALF) cytology and lung histopathological examination. The consecutive administration of naringin significantly mitigated the ovalbumin-induced exacerbation of cough and AHR, while also reducing the levels of leukocytes, interleukin-4 (IL-4), IL-5, and IL-13 in BALF compared to the control group. So, naringin treatment notably improved the pathological alterations observed in lung tissues. These findings indicate that naringin may serve as a promising therapeutic agent for the management of CVA. In the rat model, naringenin significantly enhanced the management of ovalbumin-induced allergic asthma due to its distinct antioxidant and anti-inflammatory properties. The therapeutic efficacy of naringenin at 40 mg kg^{-1} was notably more significant than that observed at 20 mg kg^{-1} (Jiao *et al.* 2015). Chronic asthma in mice was induced by Seyedrezazadeh *et al.* and

the mice were given hesperetin combined with naringenin (HN), orange and grapefruit juice (OGJ), orange juice (OJ), or grapefruit juice (GJ). In contrast, the asthmatic control (AC) and non-asthmatic control (NC) groups were allowed to drink water freely. Histopathological analysis revealed an absence of goblet cell metaplasia in the HN, OJ, and GJ groups, along with a reduction in intra-alveolar macrophages when compared to the AC group. The combination of hesperetin and naringenin significantly reduced subepithelial fibrosis, smooth muscle hypertrophy in the airways, and lung atelectasis relative to the AC group. Additionally, a decrease in subepithelial fibrosis in the airways was observed in the OJ and GJ groups compared to the AC group, although this effect was not seen in the OGJ group. Analysis of bronchoalveolar lavage fluid indicated a decrease in macrophage counts in the OJ and OGJ groups, while eosinophil counts were elevated in the OJ group compared to the NC group. These findings suggest that hesperetin combined with naringenin is more effective in mitigating airway structural remodeling than either orange juice or grapefruit juice in a murine model of HDM-induced asthma (Seyedrezazadeh *et al.* 2015).

Terpenoids

Paeoniflorin, a bioactive compound derived from *Paeonia lactiflora*, can suppress inflammatory responses. This compound may exert anti-asthmatic effects by modulating fatty acid metabolism and adhesion pathways (Sun *et al.* 2015). Lung function assessments in a study by Shou *et al.* indicate that, in contrast to mice exposed to ovalbumin (OVA), administering paeoniflorin at a dosage of 50 mg kg^{-1} significantly diminishes bronchial reactivity to methacholine. This finding suggests that paeoniflorin may confer protective effects on lung function in a murine model of allergic asthma (Shou *et al.* 2019). Previous research by Zhang *et al.* indicated that paeoniflorin significantly reduced the ovalbumin (OVA)-induced elevations in both raw and eosinophil counts. Additionally, levels of interleukin (IL)-4 and IgE in bronchoalveolar lavage fluid were restored, while there was an increase in IFN-γ levels in the same fluid. Histological analyses revealed that paeoniflorin markedly mitigated OVA-induced eosinophilia in lung tissue when compared to the model group. Furthermore, paeoniflorin has the capacity to modulate the Th_1/Th_2 balance. These results imply that paeoniflorin may serve as an effective intervention for the advancement of asthma and could be considered a therapeutic option for individuals suffering from allergic asthma (Simón-Rodríguez *et al.* 2022; Sinha *et al.* 2022; Safari Kakroudi *et al.* 2019; Zhang *et al.* 2015). Emerging evidence bolsters the hypothesis that astragaloside IV is the principal bioactive compound derived from *Astragalus membranaceus* (Fisch.) Bunge, possesses significant anti-inflammatory and antioxidative properties. Astragaloside IV has effectively diminished airway hyperresponsiveness, collagen accumulation, mucus secretion, and inflammatory cell presence in various asthma models while simultaneously elevating interferon-gamma (IFN-γ) levels (D'Avino *et al.* 2023). Research conducted by Qiu *et al.* (2014) demonstrated that astragaloside IV mitigates ovalbumin-induced airway inflammation by restoring the balance between key regulatory proteins GATA3 and T-bet, shifting $CD4^+$ T cells towards a Th1 phenotype. Furthermore, astragaloside IV has been found to alleviate eosinophilic asthma by reducing the expression of CCR3, ICAM-1, α-SMA, VEGF, TGF-β1, TNF-α, GM-CSF, as well as eosinophil activation and migration, while promoting the proliferation of regulatory T cells (Tregs) and other cytokines. Additional studies suggest that the anti-asthmatic effects of astragaloside IV may be linked to various signaling pathways, including mTORC1, JAK2/STAT6, NF-κB, MAPK, or HO-1/Nrf2(Qiu *et al.* 2014). The mechanism by which AS-IV mitigates airway inflammation and modulates immune responses involves several key processes. AS-IV effectively diminishes airway inflammation through the suppression of cytokines such as IL-4, IL-5, IL-6, and IL-13, as well as a reduction in the populations of eosinophils and neutrophils. Furthermore, the immunoregulatory effects of AS-IV are achieved by rectifying the imbalance between Th1 and Th2 cells, as well as the ratio of Th17 cells to regulatory T cells (Tregs). Additionally, researchers have demonstrated that AS-IV suppresses the growth of airway smooth muscle cells through the downregulation of TGF-β1, VEGF, and α-SMA expression in mice with asthma induced by ovalbumin (Broide 2008; Qiu *et al.* 2014; D'Avino *et al.* 2023).

Alkaloids

An experimental study examined the impact of total alkaloids (TA) extracted from *Alstonia Solaris* (L.) R. Br, in a murine model of asthma induced by Ovalbumin (OVA). The administration of TA reduced pulmonary inflammatory symptoms, decreased Mucin5AC levels in BALF, and alleviated airway hyperresponsiveness (AHR). Furthermore, TA was found to inhibit eotaxin production and the recruitment of eosinophils. Notably, TA

significantly lowered the levels of Th2 and Th17 cytokines while enhancing Th1 cytokine levels, thereby aiding in restoring the balance among Th1, Th2, and Th17 cytokines. TA may diminish the population of ILC2s by suppressing the levels of IL-33, IL-25, and thymic stromal lymphopoietin (TSLP) in BALF and inhibiting IL-33/ST2 signaling lung. Ultimately, TA decreased tIgE, OVA-IgE, and MCP-1 levels, inhibiting mast cell activation and the release of leukotrienes. These results suggest that TA could serve as a promising immunoregulatory agent for treating and preventing asthma (Safdarpour *et al.* 2022; Tong *et al.* 2024). Ligustrazine is a significant active compound derived from *Ligusticum chuanxiong* Hort., known for its ability to invigorate vital energy and enhance blood circulation. Research indicates that ligustrazine can mitigate allergic airway inflammation, inhibit the production of IL-4, and modulate immune responses related to Th1/Th2 cytokines in individuals with asthma and in asthmatic rat models. A separate investigation revealed that ligustrazine acts as an inhibitor of AHR, diminishes the presence of inflammatory cells, lowers the levels of Th1-type cytokines and chemokines, and downregulates the protein levels of STAT3 and p38 MAPK. These findings suggest that the anti-asthmatic properties of ligustrazine are associated with the modulation of the STAT3 and p38 MAPK signaling pathways (Hua *et al.* 2022; Wang *et al.* 2023). Previous research has demonstrated that ligustrazine can influence the expression of transcription factors associated with Th1 (T-bet) and Th2 (Gata-3) cells in the context of asthma (Mohammadi *et al.* 2023, 2024). Additionally, investigations reveal that ligustrazine mitigates allergic airway inflammation in a murine model of asthma by decreasing the recruitment of eosinophils and neutrophils. This effect appears to be partially mediated through the modulation of Th1/Th2 and Treg/Th17 pathways, achieved by re-establishing the balance of cytokine profiles and the ratios of transcription factors, specifically T-bet/Gata-3 and Foxp3/RORγt. In addition, ligustrazine significantly reduces IL-4, IL-5, IL-17A, CCL3, CCL19, and CCL21 levels in BALF of asthma mice. Furthermore, ligustrazine induces down-regulation of CCL19 receptor CCR7, STAT3, and p38 MAPK protein expression. So, ligustrazine can inhibit AHR in response to methacholine (Mch) , thereby diminishing inflammation and decreasing the influx of inflammatory cells into the lungs of asthmatic mice (Ji *et al.* 2014; Wei *et al.* 2016). Matrine, a principal active compound derived from *Sophora flavescens*, has been studied for its impact on the aryl hydrocarbon receptor (AHR) and inflammatory processes in murine models. Research indicates that matrine effectively reduces pulmonary eosinophilia and inflammation by suppressing Th2-type cytokines and eotaxin in an asthma model (Fu *et al.* 2014). Wen-Chung Huang and colleagues demonstrated that matrine significantly reduced airway hyperresponsiveness (AHR) and inhibited goblet cell hyperplasia, eosinophil infiltration, and the inflammatory response within the lung tissue of asthmatic mice. Additionally, matrine lowered the concentrations of Th2 cytokines and chemokines in bronchoalveolar lavage fluid and diminished the production of OVA–IgE in serum. Moreover, treatment with matrine in activated BEAS-2B cells led to a decrease in the production of proinflammatory cytokines and eotaxins while also inhibiting ICAM-1 expression, thereby reducing eosinophil adhesion to inflammatory BEAS-2B cells *in vitro*. These results indicate that matrine may ameliorate allergic asthma in mice, suggesting its potential as a therapeutic agent for human applications (Huang *et al.* 2014). Previous research by Qiang Fu *et al.* indicated that matrine effectively reduced the increases in airway resistance and eosinophil counts induced by OVA while levels of IL-4 and IL-13 were restored. Histological analyses revealed that matrine significantly mitigated OVA-induced eosinophilia within lung tissue. Additionally, Western blotting results showed a marked decrease in the protein level of STAT6 due to matrine treatment (Fu *et al.* 2014).

Recent studies on herbal medicine against asthma

The 2024 review by Rajizadeh *et al.* identifies 58 plants and 32 herbal compounds with confirmed antiasthmatic effects. Additionally, 32 plants demonstrate anti-inflammatory, antioxidative, or bronchodilator properties, highlighting their potential for developing new antiasthmatic drugs and improving asthma symptoms (Rajizadeh *et al.* 2024). Verma *et al.* emphasize the role of herbal medicine in asthma management, noting several herbal drugs with potential antiasthmatic activity, including ginger, *Echinacea*, and garlic. They also identified mangiferonic acid, withaferin A, and stigmasterol as promising anti-asthmatic herbal drugs, exhibiting good bioactivity towards nuclear receptors and favorable pharmacokinetic properties (Verma *et al.* 2023; Verma *et al.* 2024). In an experimental study, *Tinospora cordifolia* leaf extract showed significant anti-asthmatic effects in a rat model of asthma induced by citric acid and acetylcholine, suggesting it as an alternative to conventional inhalers and oral medications (Gupta *et al.* 2024). Poyil *et al.* highlighted an ethanolic herbal composite from *Bacopa monnieri* and *Euphorbia hirta*, which demonstrated significant anti-asthmatic activity by increasing

preconvulsive time, reducing inflammatory cell counts, and enhancing antioxidant activity, indicating its potential as an alternative treatment (Poyil *et al.* 2022). Ethanolic extract of *Scrophularia striata* suppressed Th2 cytokines and inflammatory cells in asthmatic mice (Azadmehr *et al.* 2013). At the same time, *Lavandula dentata* reduced serum levels of IgE, triglycerides, total cholesterol, and glucose in guinea pigs with OVA-induced asthma, indicating its potential to ameliorate asthma and oxidative stress (Almohawes & Alruhaimi 2019). The protective effect of *Pistacia weinmannifolia* root against inflammation and mucus hypersecretion in BALB/c mice was also studied (Lee *et al.* 2019). *Ocimum basilicum* leaves exhibited anti-inflammatory and immunomodulatory activity in OVA-challenged rats, decreasing IL-4 and IgE levels while increasing the IFN-γ/IL-4 ratio. The anti-inflammatory effects of *Polyscias fruticosa* leaves were tested, showing a reduction in white blood cell counts and C-reactive protein to normal levels in OVA-induced asthma (Azadmehr *et al.* 2013). Recent studies on OVA-sensitized mice treated with *Herissantia tiubae* increased plasma IL-13 levels (Mozzini Monteiro *et al.* 2016). Mahmoudabady *et al.* reported that the extract of *Crocus sativus* flowers effectively reduced lung inflammatory cells in OVA-sensitized rats (Mahmoudabady *et al.* 2013). Similarly, the aqueous extract of *Urtica dioica* leaves significantly decreased serum eosinophilia, leukocytes, and lymphocytes in the bronchoalveolar lavage fluid (BALF) of asthmatic rats (Zemmouri *et al.* 2017). Administration of *Asparagus cochinchinensis* root extract lessened bronchial thickness and inflammatory cell infiltration while reducing macrophages, eosinophils, IgE, and Th2 cytokines in OVA-induced animals (Choi *et al.* 2018). The aqueous extract of *Allium cepa* normalized levels of nitrogen dioxide, nitrate, MDA, IL-4, IgE, and various antioxidant markers (SOD, catalase, thiol, IFN-γ) in OVA-sensitized animals (Marefati *et al.* 2018). *Zingiber officinale* rhizomes reduced total WBC, eosinophils, and neutrophils in BALF and significantly inhibited the Th2-mediated immune response by decreasing IL-4 and IL-5 mRNA expression levels (Khan *et al.* 2015).

CONCLUSION

The analysis indicates that many phytochemicals, especially polyphenols, and flavonoids, demonstrate notable anti-inflammatory and immunomodulatory properties. For instance, curcumin has been identified as an inhibitor of critical cytokines associated with asthma, including IL-4 and IL-5, which diminishes eosinophil recruitment and airway hyperreactivity. Alkaloids, particularly those extracted from *Alstonia solaris*, have shown the capacity to restore equilibrium among Th1, Th2, and Th17 cytokines, a factor essential for alleviating asthma symptoms. This finding suggests that alkaloids may function as effective immunoregulatory agents. Flavonoids such as hesperetin and naringenin have been observed to significantly alleviate airway structural remodeling and inflammation in animal models of asthma. The synergistic effects of these compounds indicate their potential to reduce asthma symptoms effectively. The review underscores the importance of conducting more comprehensive studies to confirm the therapeutic efficacy of these medicinal plants and their bioactive constituents. A deeper understanding of their mechanisms of action is crucial for merging traditional practices with contemporary pharmacological strategies in asthma management. In summary, the findings indicate that medicinal plants possess substantial potential as alternative or adjunctive therapies for asthma, highlighting the need for further investigation in clinical environments to improve asthma management approaches.

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