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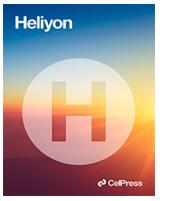

Review article

Revealing the mechanism and efficacy of natural products on treating the asthma: Current insights from traditional medicine to modern drug discovery

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ABSTRACT

Asthma remains a significant global health challenge, demanding innovative approaches to treatment. Traditional medicine has a rich history of using natural products to alleviate asthmatic symptoms. However, transitioning from these traditional remedies to modern drug discovery approaches has provided fresh insights into the mechanisms and effectiveness of these natural products. This study provides our comprehensive review, which examines the current state of knowledge in the treatment of asthma. It delves into the mechanisms through which natural products ameliorate asthma symptoms, and it discusses their potential in the development of novel therapeutic interventions. Our analysis reveals that natural products, traditionally employed for asthma relief, exhibit diverse mechanisms of action. These include anti-

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inflammatory, bronchodilatory, immunomodulatory effects, and reducing gene expression. In the context of modern drug discovery, these natural compounds serve as valuable candidates for the development of novel asthma therapies. The transition from traditional remedies to modern drug discovery represents a promising avenue for asthma treatment. Our review highlights the substantial efficacy of natural products in managing asthma symptoms, underpinned by well-defined mechanisms of action. By bridging the gap between traditional and contemporary approaches, we contribute to the growing body of knowledge in the field, emphasizing the potential of natural products in shaping the future of asthma therapy.

1. Introduction

Asthma stands as a prevalent global health challenge, impacting individuals and healthcare systems worldwide. Its pervasive influence spans diverse demographics, affecting people of varying ages and backgrounds. The ramifications extend beyond individual well-being, imposing substantial healthcare costs and impeding economic productivity. Recent decades have witnessed a significant surge in asthma prevalence, signaling its emergence as a critical global concern warranting closer attention. In 2019 alone, asthma afflicted approximately 262 million people worldwide, resulting in 455,000 deaths—a stark testament to its status as a major non-communicable disease [1].

Characterized by airway inflammation and constriction, asthma presents a complex and chronic respiratory ailment, manifesting through distressing symptoms such as breathlessness, wheezing, chest tightness, and coughing [2]. These symptoms vary in intensity and frequency, affecting individuals across all age groups. While a combination of genetic and environmental factors is implicated in its etiology [3], various triggers, including allergens, respiratory irritants, smoke, air pollution, cold air, and exercise, exacerbate asthma symptoms [3]. The pathophysiology involves inflammation and narrowing of respiratory airways, leading to compromised airflow and breathing difficulties [4]. Given the intricate interplay of genetic, environmental, and physiological factors, tailored treatment strategies that accommodate individual needs are essential.

Despite notable advancements in modern medicine, significant gaps and limitations persist in current asthma treatment modalities. Challenges in achieving long-term symptom control, potential side effects associated with medications, and the inability to address underlying causes beyond symptom management are evident. Moreover, disparities in healthcare access and medication availability, particularly in low-resource settings, further complicate asthma management. Therefore, continued research and innovation are imperative to address these limitations and enhance outcomes for individuals grappling with asthma.

At present, asthma remains incurable, with treatment primarily focusing on prevention and control. Strategies involve mitigating symptoms by avoiding triggers, alongside medication use and lifestyle adjustments [4]. Patient education plays a pivotal role, empowering individuals to identify and manage their specific triggers, while regular monitoring and action plans facilitate symptom tracking and treatment adjustments. Medication-based asthma management includes bronchodilators and anti-inflammatory medications, such as inhaled corticosteroids, aimed at reducing airway inflammation and enhancing lung function [5]. Despite the widespread use of modern medicines, evidence of traditional medicine's utility in asthma treatment persists globally [6].

Traditional medicine, comprises medical angles of traditional knowledge that evolved over generations prior to the era of scientific medicine, also known as modern medicine [7]. In accordance with World Health Organization (WHO), traditional medicine is defined as the sum total of the skills, practices, and knowledges based on the beliefs, experiences, and theories indigenous to diverse cultures, whether explainable or not, used in the health maintenance as well as in the diagnosis, prevention, treatment or improvement of mental and physical illness [8]. The practice of traditional medicine in human history can be traced back to as early as 5.000 years ago in the historical regions of Southern Mesopotamia [7]. The application of traditional medicine generally involves the use of plant-based and herbal ingredients that are served to the patients in the form of concoction or mixed powder. Many of the ingredients' efficacy in treating specific ailments were discovered based on empirical experiences or beliefs, and the knowledge has been transferred throughout generations [9]. Today, in many Asian and African countries, up to 80 % of the population relies on traditional medicine for their primary health care needs [7].

Traditional medicine has a long history of use in asthma management. It has been practiced in various cultures for centuries [6]. For instance, *ma huang* (*Ephedra sinica*) has been used to relieve symptoms related to asthma in the traditional Chinese medicine owing to its bronchodilatory properties [10]. In Ayurvedic medicine from India, herbs like turmeric (*Curcuma longa*) and *vasaka* (*Adhatoda vasica*) are employed to address respiratory issues, including asthma [11]. Similarly, the concoction of ginger (*Zingiber officinale*) along with other ingredients such as turmeric and honey, is used in *jamu*, a form of traditional herbal medicine in Indonesia, to treat asthma [12]. Despite the historical use of traditional medicine in asthma management, it is essential to approach these practices with caution and integrate them into a comprehensive asthma treatment plan. Modern medicine has made significant advancements in understanding asthma's underlying mechanisms based on scientific studies and developing evidence-based treatments.

The present study aims to review the mechanism and efficacy of traditional medicine in treating asthma. Indeed, numerous studies have been carried out to examine the potential effects of natural products in asthma treatment. This study sought to compile the existing studies and provide a comprehensive review regarding the use of natural products in treating asthma. By bridging the gap between the exploration of natural remedies and the research into their efficacy, this study contributes to our understanding of both conventional and natural approaches to asthma treatment. It offers valuable insights into the effects and biomechanisms of products that could be harnessed to manage asthma, from mitigating inflammation mechanisms to preventing tissue damage, ultimately aiming

to enhance the treatment landscape for this widespread condition.

Considering these considerations, bridging the gap between traditional medicine and modern drug discovery emerges as a critical imperative. Integrating insights from traditional medicinal practices with contemporary research can offer novel avenues for developing more effective asthma treatments. Such an approach holds promise in addressing the limitations of current therapies, potentially revolutionizing asthma management and improving outcomes for affected individuals worldwide.

2. Search strategy and study selection criteria

Scientific papers in regard to asthma and natural products were collected from Scopus databases (https://www.scopus.com), PubMed and PubMed Central databases (www.ncbi.gov/pubmed), and Web of Science databases (http://www.webofknowledge.com). "Asthma", "natural products", and "traditional medicine" were combined to search for relevant articles.

The inclusion criteria were as follows: (1) articles published between 2018 and 2023, (2) articles that described the efficacy of natural products of asthma, (3) articles written in English, (4) articles with in vitro, in vivo, or human studies were performed. The exclusion criteria were (1) case reports, (2) review articles, and (3) articles written not in English.

The natural products presented in this study were collected from reliable and reputable scientific publications. This review prioritized natural products with well-studied and documented effects on asthma supported by robust scientific evidence, potent further clinical relevance towards asthma medication, and well-understood mechanism of action. In the available literature, not all natural products are reported to be potential specifically for asthma treatment. Hence, rather than attempting to cover every possible natural product with empirical potential on asthma, this review focuses on providing a concise overview of the most prominent and well-studied natural products modulating asthma-related biomechanisms.

3. Potential finding of natural products in modern drug discovery and their role in asthma medication

The outcomes in the tables are grouped based on the research methods such as in vitro (Table 1), in vivo, and human studies.

3.1. In vitro studies claim the potential of natural products in asthma medication

This comprehensive in vitro study delves into the diverse array of compounds and extracts, each with its unique potential as an anti-asthma agent. Through a series of meticulously designed experiments, various substances were investigated for their ability to mitigate inflammation, oxidative stress, and allergic reactions—key factors in the development and exacerbation of asthma. The results presented in this paper not only highlight the efficacy of these compounds in suppressing key inflammatory pathways, but also underscore their antioxidant properties and capacity to regulate immune responses. These findings provide valuable insights into the development of novel treatments for asthma and potentially other inflammatory respiratory conditions.

The study involved an investigation into the properties of a compound or extract known as Chromenol, specifically Mojobanchromanol, which was sourced from *Sargassum horneri*. The experimental model utilized MLE-12 cells, and the treatment involved exposure to a dosage ranging from 3.9 to 250 μg/mL for a duration of 3 h. The treatment's effectiveness was assessed through several methods. Chromenol demonstrated significant potential in reducing oxidative stress by inhibiting MAPK signaling pathways, suppressing the secretion of pro-inflammatory cytokines, and modulating Toll-Like Receptors in alveolar epithelial cells. Additionally, it showcased its antioxidative capabilities by scavenging free radicals and mitigating oxidative damage markers like MDA and 8-OHdG. Furthermore, Chromenol inhibited MAPK activation (ERK and JNK), reduced the secretion of pro-inflammatory cytokines, such as IL-1β, IL-6, and IL-33, and attenuated the mRNA expression of TLR2, TLR4, and TLR7 [13].

The study focused on the phytosterol Fucosterol obtained from *Padina boryana* and its effects on RAW 264.7 cells. The treatment regimen involved exposure to a dosage range of 6.25–50 μg/mL for a duration of 1 h. The results indicated that Fucosterol exhibited significant anti-inflammatory properties. It effectively inhibited the production of inflammatory mediators and downregulated the expression of pro-inflammatory cytokines, including IL-6, IL-1β, and TNF-α. This anti-inflammatory action was achieved through multiple mechanisms, such as the inhibition of the MAPK pathway and the activation of the Nrf2/HO-1 pathway. Additionally, Fucosterol downregulated the expression of iNOS and COX-2, phosphorylation of the NF-κB pathway, and p38 MAPK. Furthermore, it disrupted the association between Keap1 and Nrf2, suggesting its potential as a therapeutic agent in mitigating inflammatory responses [14].

Polysaccharides, particularly Fucoidan derived from *Saccharina japonica*, were investigated for their impact on RAW 264.7 cells, with a treatment duration of 1 h and a dosage range of 3.125 to μg/mL. The study found that Fucoidan had significant anti-inflammatory properties, as it effectively inhibited the production of nitric oxide (NO) and pro-inflammatory cytokines. Furthermore, it was observed to modulate inflammation by suppressing the transcription of pro-inflammatory genes, ultimately leading to the suppression of key pro-inflammatory molecules like TNF-α, IL-1β, and IL-6. Fucoidan's anti-inflammatory effects were also demonstrated through the inhibition of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), as well as the inhibition of the MAPK and NF-κB pathways, highlighting its potential as a valuable agent in mitigating inflammatory responses [15].

The study investigated the effects of Chromenol, specifically Sargachromenol, derived from *Sargassum horneri*, on RAW 264.7 cells, with a treatment duration of 1 h and a dosage range of 7.8–62.5 μg/mL. Chromenol, in the form of Sargachromenol, displayed notable anti-inflammatory properties by reducing the production of nitric oxide (NO) and reactive oxygen species (ROS). It effectively inhibited various inflammatory properties and suppressed the activation of the NFκB and MAPK pathways, which are known to be involved in inflammatory processes. Furthermore, Chromenol demonstrated its anti-inflammatory effects by activating the Nrf2/HO-1

Table 1
In vitro studies of products in asthma treatment.

Classification	Compound/Extract	Source	Experimental Model	Dose; Duration	Efficacy	Mechanism	Reference
Chromenol	Mojobanchromanol	*Sargassum horneri*	MLE-12 cells	3.9–250 μg/mL; 3 h	Reducing oxidative stress	Scavenging free radicals and attenuating oxidative damage markers (MDA and 8-OHdG)	[13]
					Inhibiting MAPK signaling pathways	Inhibit MAPK activation (ERK and JNK)	
					Supressing the secretion of pro-inflammatory cytokines	Reduces secretion of IL-1β, IL-6, and IL-33	
					Modulating Toll-Like Receptors in alveolar epithelial cells	Attenuate the mRNA expression of TLR2, TLR4, and TLR7	
Phytosterol	Fucosterol	*Padina boryana*	RAW 264.7 cells	6.25–50 μg/mL; 1 h	Inhibition of inflammatory mediators	Downregulate the production of IL-6, IL-1β, and TNF-α	[14]
						Downregulate expression of iNOS and COX-2	
					Downregulation of pro-inflammatory cytokines	Downregulate the phosphorylation of NF-κB pathway	
						Downregulate p38 MAPK	
					MAPK pathway inhibition	Disrupted the association between Keap1 and Nrf2	
					Nrf2/HO-1 activation		
Polysaccharides	Fucoidan	*Saccharina japonica*	RAW 264.7 cells	3.125 to μg/mL; 1 h	Inhibition of NO production	Suppressing TNF-α, IL-1β, IL-6	[15]
					Inhibition of pro-inflammatory cytokines	Inhibition of iNOS and COX-2	
					Modulate	Inhibition of MAPK and NF-κB Pathways	
					Suppress the transcription of pro-inflammatory genes		
Chromenol	Sargachromenol	*Sargassum horneri*	RAW 264.7 cells	7.8–62.5 μg/mL; 1 h	Reduces the production of NO and ROS	Inhibition of iNOS and COX-2	[16]
					Inhibition of inflammatory properties inhibition of NFκB and MAPK	reduces the expression of inflammatory cytokines such as IL-1β, IL-6, and TNF-α	
					Activates the Nrf2/HO-1 pathway Inhibition of HO-1		

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Table 1 (*continued*)

Classification	Compound/Extract	Source	Experimental Model	Dose; Duration	Efficacy	Mechanism	Reference
Alkylresorcinol	(−)-1S-myrothecol (+)-1R-myrothecol	*Myrothecium* sp. BZO-L062	RAW 264.7	10–100 μg/mL; 2 h	Anti inflammatory properties Antioxidant activity	Inhibited NO production Scavenging free radicals	[17]
Sesquiterpene	Hirsutanol A	*Chondrostereum* sp. NTOU4196	THP-1 cells	0.5–10 μM; 15 min	Reduce tissue damage and inflammation Reduction of pro-inflammatory cytokines Modulation of signaling pathways	Inhibition and down regulate of MMP-9 Reduce production of TNF-α, IL-6, and IL-1β Attenuate the activation of STAT3 and NF-κB	[18]
Polysaccharides	Sulfated polysaccharide	*Saccharina japonica*	RAW 264.7 cells	50–400 μg/mL; 1 h	Inhibition of NO production Reduction in inflammatory cytokines Inhibition of MAPK and NF-κB Signaling Pathways	Reduction of PGE2, IL-1β, and TNF-α Inhibition of p38 MARK, JNK, and ERK and the activation of phosphorylation IKKα/β	[19]
Polysaccharide	Sulfated polysaccharide	*Sargassum fulvellum*	RAW 264.7 cells	25–100 μg/mL; 1 h	Inhibition of inflammatory mediators Inhibition of pro-inflammatory cytokines Suppression of iNOS and COX-2 expression	Reduce NO and PGE2 production Inhibit production of TNF-α, IL-1β, IL-6	[20]
Flavonoid	Quercetin	Not reported	BCi-NS1.1 cells line	25 μM; 24 h	Reduce the levels of pro-inflammatory	Reduce of IL-1β, IL-6 and IL-8 Attenuated the activation of NF-kB	[21]
Others	Apocynin	Not reported	A549 cells	0.5, 1, 3 mg/mL; 4 h	Decrease the mRNA expression of TNF-α and IL-6	Inhibit of NADPH oxidase	[22]
Fatty acid	*Arctoscopus japonicus* egg lipids	*Arctoscopus japonicus*	RAW 264.7 cells	1.0–2.0 % v/v; 1 h	Inhibition of inflammatory mediators Supression of immune-associated genes Inhibition of NF-κB and MAPK Signaling Interupted JNK protein signaling pathway	Reduce the production of NO and PGE2 Decrease the expression of iNOS, COX-2, IL-1β, IL-6, and TNF-α Inhibition of ERK1/2, JNK, and p38	[23]
Others (combination of herbal plants extract)	*Raphanus sativus* L. and *Codonopsis lanceolate* roots *Allium hookeri* whole plant *Acanthopanax sessiliflorum* stems *Dendropanax morbiferus*leaves	*R. sativus* L., *C. lanceolate A. hookeri*, *A.sessiliflorum*, and *D. morbiferus*	RAW 264.7 cells	10–100 μg/mL; 1 h	Anti-inflammatory effects Inhibition of allergic asthma	Inhibited the production of NO, IL-1β, IL-6, TNF-α Supression of NF-κB Activation	[24]
Others (leaves extract)	*Saurauia vulcani*	*S. vulcani leaves*	RAW 264.7 cells	12.5 and 25 μg/mL; 15 min	Anti-inflammatory effects	Inhibition of NO production Reducing TNF-α, IL-6, COX-2, IL-1β, and iNOS gene expression	[25]

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Table 1 (*continued*)

Classification	Compound/Extract	Source	Experimental Model	Dose; Duration	Efficacy	Mechanism	Reference
Carotenoids	Crocetin	*Crocus sativus*	RAW 264.7 cells	12.5–100 μg/mL; 24 h	Inhibition of inflammatory factors Reduction of excessive NO	Inhibition of COX-2, iNOS, IL-1β, IL-6, IL-10, and TNF-α	[26]
Others (aerial parts hydrodistillation)	Esential oil	*Inula viscosa*, *Inula graveolens*, and *Inula crithmoides*	RAW 264.7 cells	10–100 μg/mL; 2 h	Anti-inflammatory effects	Inhibition of NO production	[27]
Iridoid and flavonoid glycosides	Ethanolic extract	*Veronica persica*	Splenocytes isolated from HDM-exposed mice	Up to 300 μg/mL for 24 h	Reduced asthmatic inflammation induced by HDM	Limits Th2 cell activation by increased expression of IFN-ɣ Attenuation of Th1 and Th2 cytokine secretion, except IL-10 Inhibition of eosinophilic infiltration and the expression of T-cell activators Inhibition MCP-1 production and STAT3/6 activation in airway epithelial cells	[28]
Polyphenols	Phloroglucinol	*Dyropteris crassirhizoma*	HMC-1 cells	0.1–10 mg/mL for 30 min	Anti-allergic and anti-inflammatory	Inhibited production of inflammatory cytokines	[29]
Flavonoids	Aqueous extract	*Rosa laevigata* Michx.	A549 cells	500 and 1000 μg/mL for 1 h	Surpressed inflammatory pathway activity and COX-2 expression levels	Inhibition of MAPK and NF-κB signalling pathways.	[30]
Others	2-Furoic acid, 5-hydroxymethyllfurfural, Vanillic acid 4-beta-D-glucopyranoside	*Adenophora stricta*	Raw 264.7 cells	1 or 3 mg/mL for 1 h	Surpressed proinflammatory response	Inhibition of iNOS gene transcription, and nitric oxide production on LPS-exposed cell	[31]
Others	Essential Oils	Leaves of *C. camphora* (L.) J. Presl, *C. cassia* (L.) J. Presl, *C. japonicum* Siebold, *N. aciculata* (Blume) Koidz., *N. sericea* (Blume) Koidz., *L. obtusiloba* Blume and *M. japonica* Siebold & Zucc.	NCH–H292 cells	5 μg/mL; 24 h	Suppresed the expression of pro-inflammatory cytokines and mucin gen	Reduce of IL-1β, IL-6, MUC5AC and MUC5B	[32]

Table 2
In vivo studies of natural products in asthma treatment.

Classification	Compound/Extract	Source	Experimental Model	Dose; Duration	Efficacy	Mechanism	Reference
Shogaols (polyphenol)	6-shogaol	*Zingiber officinale* Roscoe	BALB/c mice (OVA induced)	10 mg/kg; three consecutive days (days 28, 29, and 30, 2 h before challenging the mice with OVA).	Reduce eosinophilia, mucus production, and Th2 cytokines levels	Interfere the production of ILs and TNF-α	[33]
Gingerols (polyphenol)	6-gingerol	*Zingiber officinale* Roscoe	BALB/c mice (OVA induced)	10 mg/kg; three consecutive days (days 28, 29, and 30, 2 h before challenging the mice with OVA).	Reduce eosinophilia, mucus production, and Th2 cytokines levels	Interfere the production of ILs and TNF-α Upregulates the expression of SOD1	[33]
Prenylated chalcones	Renifolin F	*Shuteria involucrata*	BALB/c mice (OVA induced)	1.5 mg/kg and 3.0 mg/kg; the treatment period started on the 21st day and continued until the 27th day, each dose administrated orally 1 h before each daily OVA aerosol challenge.	Reduced airway hyperresponsiveness and inhibited the levels of mucin and related inflammatory factors in the blood and BALF	Inhibit key cytokines (IL-4, IL-5, IL-9, and IL-13), associated with Th2 immune response Reduce the production of type 2 cytokines (IL-2 and IL-7) Downregulate the expression of microRNA-155 Reduce the levels of upstream cytokines (IL-25, IL-33, and TSLP)	[34]
Alkaloids	Ethanolic extract (erysotrine, erysotrine-N-oxide, hypaphorine)	*Erythrina mulungu* Benth.	BALB/c mice (OVA induced)	200–800 mg/kg; seven consecutive days (simultaneously challenged with OVA)	Reduced BHR, leukocytes, eosinophils, lymphocytes, IL-4, and IL-5 Increased IL-13 and INF-ɣ	Indirect Th2 response through Th1 stimulation. Suppression of inflammatory cytokines via TLR4 inhibition and (PPAR)-ɣ activation	[35]
Multifloral honey	*Apis melifera* honey	*Melaleuca* spp.	BALB/c mice (OVA induced)	10 %, 40 %, and 80 % v/v; all groups received respective treatments orally once a day for 5 days during the challenged period	Reduce inflammatory cell infiltration and beta-hexosaminidase levels in BALF Reduce number of mast cells	Antioxidant and scavenging properties of the honey (ellagic acid, quercetin, chrysin, and caffeic acid) contribute to anti-inflammatory effects.	[36]
Carotenoic acid	Bixin	*Bixa orellana* seeds	BALB/c mice (OVA induced)	50 mg/kg and 100 mg/kg; acute murine asthma model (on day 18 and continued to day 23), chronic asthma model (from day 45 to day 58), GCs-resistant asthma model (day 18 to day 23)	Reduction in airway inflamation, airway hyperresponsiveness reduction, inhibition of inflammatory signaling pathways	Suppress the production of pro-inflammatory cytokines and chemokines Inhibit the NF-κB signaling pathway Interfere TGF-β1 signaling pathway	[37]
Coumaric acid esters	Methyl P-coumarate	Flower of *Trixis michuacana* var. l*ongifolia,* roots and stems of *Comptonia peregrine,* bark of *Melicope latifolia*,	BALB/c mice (OVA induced)	Administered orally at 5 mg/kg; 5 days (from days 9–13)	Anti-inflammatory effects Inhibition of immune cell recruitment	Inhibited the secretion of inflammatory molecules (IL-6, IL-8, MCP-1, ICAM-1, TNF- α, IL- 1β, and IL-6)	[38]

(*continued on next page*)

Table 2 (*continued*)

Classification	Compound/Extract	Source	Experimental Model	Dose; Duration	Efficacy	Mechanism	Reference
		leaves of *Hainan morinda citrifolia*, fruit of *Ziziphus jujuba* Mill., *Aloe vera*			Regulation of Th2 cytokines and modulated MCP-1 and IgE secretion Inhibition of NF-κB activation	Inhibit the adhesion of airway cells and eosinophills	
Flavonoid	Tilianin	*Agastache rugosa,* Dracocephalum moldavica	BALB/c mice (OVA induced)	10 and 20 mg/kg body weight; administered orally in 1 h before the OVA challenge on 21st to 23rd day	Inhibition of Th2 cytokines, reduction in inflammatory cells, antioxidant activity, suppression of pro-inflammatory cytokines, and modulation of TGF- β1/Smad Signaling	Suppressed the levels of Th2 Reduced the numbers of inflammatory cells (eosinophills, neutrophils, macrophages, and lymphocytes) in BALF Reducing MDA leves and increasing the activities of SOD and GSH Reduce pro-inflammatory cytokines (TNF-α, IL-6, IL-12, and TBX2)	[39]
Polyphenols	Total glucosides of Paeonia (TGP)	Roots of *Paeonia lactiflore* Pall	Male BALB/c mice (OVA induced)	100 mg/kg (low dose), 200 mg/kg (medium dose), 400 mg/kg (high dose), starting on 23rd day	Reduced airway hyperresponsiveness Improved lung tissue pathology Decrease inflammatory cell infiltration and collagen deposition	Reduce of BALF leukosyte, eosinophil counts, chemokines and cytokines (eotaxin, TNF-α, IL-4, MIP-1α Decrease of β-hexosaminidase release Inhibition of Ca^{2+} influx in mast cell degranulation	[40]
Polysaccharides	Cordyceps polysaccharide	*Cordyceps militarisis*	Female BALB/c mice (OVA induced)	25, 50, 100 mg/kg; starting on 23rd day after the initial sensitization and then continued each dose for 8 weeks	Decrease inflammatory cell infiltration, goblet cell hyperplasia Increase of inflammatory cells in the mouse model of asthma	Suppressed the secretion of eotaxin, IL-4, IL-5, IL-13, IFN-γ Decrease IgE Inhibit s activation of transforming growth factor β1 (TGF-β1)	[41]
Alkaloids	Isorhyncophylline	*Uncaria rhynchophylla*	BALB/c mice (OVA induced)	40 mg/kg; 42 days	Attenuated the eosinophils recruitment in BALF Reduced collagen deposition in lung tissue Suppressed production of IgE and pro-inflammation cytokine	Inhibit proliferation and induced the apoptosis of ASMCs Increased the level of miR-200a Inhibit activation of FOXC1/NF-kB pathways	[42]
Alkaloids	Sinomenine	*Root of Sinomenium acutum*	Male BALB/c mice (OVA induced)	100 mg/kg; 75 days	Improved all histopathological changes of airway remodelling Modulating Th-2 derived cytokines Inhibition of apoptosis of airway epithelial cells	Decrease all cytokine levels (IL-4, IL-5, IL-13, Nitric oxide)	[43]
Flavonoids	Mangiferin	Leaves of *Mangifera indica* L.	Female BALB/c mice (OVA induced)	100 mg/kg and 200 mg/kg; 30 days	Modulating Th1/Th2 cytokines imbalance via STAT6 signaling pathway	Reduced of IL-9, IL-17A Inhibit the expression of PU.1 and ROR γt in lung	[44]

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Table 2 (*continued*)

Classification	Compound/Extract	Source	Experimental Model	Dose; Duration	Efficacy	Mechanism	Reference
					Attenuated the symptoms of asthma attacks Reduces the total number of leukocytes, EOS, and goblet cells infiltration in lung	Increase IL-10, TGF- β1 and Foxp3	
Anthraquinone	Ethanolic extract	*Cassia occidentalis* Linn.	BALB/c mice (OVA induced)	250, 500, 2000 mg/kg	Reduced eosinophil count, IL-4, IL-13, OVA-specific IgE	Reduced mRNA expression of type 2 cytokines (IL-4, IL-5, and IL-13)	[45]
Methylated flavonoid	Eupatilin	*Artemisia argyi*	Female BALB/c mice (OVA induced)	15 and 30 mg/kg body weight; from day 17 to day 23	Reduces number of inflammatory cells in BALF (neutrophils and eosinophils) Inhibits Th2 cytokines (IL-5, IL-13, and OVA-specific IgE) Reduces inflammatory cell infiltration and mucus hypersection	Inhibits the phosphorylation of NF-κB and its translocation to the nucleus Inhibits the phosphorylation of p38 MAPK, Erk, and JNK Eupatilin activates Nrf2 signaling	[46]
Others (phytochemical in general)	Leaf extract	*Eriobotrya japonica*	Female BALB/c mice (OVA induced)	50, 100, 200 mg/kg daily from day 13–18 on a 19 days experiment	Reduced amounts of IgE, IL-4, IL-13	Inhibition of inflammatory mediator	[47]
Flavonoids	Flavocoxid	Roots of *Scutellaria baicalensis* and *Acacia catechu*	Swiss albino mice (OVA induced)	20 mg/kg for 16 days	Negate allergen-induced airway inflammation	Inhibition of leukocytes, NO production, and IL-13 expression	[48]
Others (boiling extraction)	*Pimpinella anisum* aqueous seeds extract	*Pimpinella anisum*	Male BALB/c mice (OVA induced)	0.16 mg/kg; days 24–30, 15 min after the OVA challenge	Inhibition of inflammatory cytokines	Down regulation of Th2 cytokines (IL-5, IL-13, and IL-33) and the inhibition of eosinophil trafficking	[49]
Flavonoid	*Rutin*	-	Female pregnant BALB/c mice (OVA induced)	37.5 and 75 mg/kg; days 1–21	Antioxidant and anti-inflammatory effects	Inhibited cellular filtration in the airway Downregulated of NF- κB and iNOS Inhibit expression of matrix metalloproteinasi 9 Reduce of Th2 and Th17	[50]
Iridoid and flavonoid glycosides	Ethanol extract	*Veronica persica*	BALB/c mice (HDM induced)	50, 100 mg/kg	Attenuate inflammatory cell recruitment and activation in the inflammatory region initiating or developing airway inflammation	Decreased levels of Th1 & Th2 cytokines, but increased level of IL-10 Increased expression of IFN-γ Inhibition of STAT-3 & STAT-6	[28]
Flavonoids	Lonicerin	*Lonicera japonica*	BALB/c mice (HDM induced)	10, 30 mg/kg	Reduce airway inflammation, mucus hypersecretion, and AHR	Upregulation of Src/EFGR pathway	[51]
Flavonoids	Platycodi radix extracts	Roots of *Platycodon grandiflorum*	Female C57BL/10 mice (HDM induced)	50, 100, 200 mg/kg; from day 2–20	Suppressed allergic airway inflammation	Inhibit expression of inflammatory cytokines and mucin5AC Regulating Th2 response by IL-4 and IL-13 Increase ER stress and ROS with NF- κB signaling	[52]

(*continued on next page*)

Table 2 (*continued*)

Classification	Compound/Extract	Source	Experimental Model	Dose; Duration	Efficacy	Mechanism	Reference
Flavonoids and Tannins	Aqueous extract	*Cinnamomum* spp.	BALB/c mice LPS induced	20, 100, 500 mg/kg for 6 days	Reduced amounts of TNF-α and IL-6	Inhibition of TLR-mediated pathways NF-κB and MAP kinases	[53]
Flavonoids and Tannins	Aerial parts of *Euphorbia cuneata* extract	*E. cuneata*	Male BALB/c albino mice LPS induced	25 and 50 mg/kg body weight; given orally for 5 days before LPS injection	Inhibited the infiltration of inflammatory cells (neutrophils) Reduced the levels of LDH in BALF Enhancing the activities of antioxidant enzymes (catalase, SOD, and GSH) and reducing MDA and 4-HNE	Inhibition of NF-κB Blockade of Toll-Like Receptor 4 (TLR4)	[54]
Flavonoids and phenolic acids	Leaf hydroalcoholic extract	*Vitex negundo* Linn.	BALB/c mice LPS induced	150, 300 mg/kg	Inhibition of inflammatory cell influx, fibrosis, epithelial cell apoptosis or selective suppression of inflammatory mediators or attenuation of autophagy, connexin regulation or alleviation of Th2 cytokines as well as activation of AMs	Modulation of gap junction proteins, TGF-β/Smad/ LC3A/B/Caspases/Bax/Bcl2 and AMPK/PI3K/Akt/p38/ NF-κB related to alveolar macrophages.	[55]
Aqueous decoction and hydroalcoholic extract	*Waltheria indica* L. extract	*W indica* L. leafy stems	NMRI Mice & Wistar rats ACh & KCl induced	10–3000 μg/mL; not specifically stated	Bronchorelaxant effect	Inhibit concentration induced by ACh and KCl Block receptor-operated calcium channels Opening potassium channels	[56]
Caffeoylquinic acid, flavonoids, coumarins, and alkaloids	Active fraction extracted from *Matricaria chamomilla* L.	*M. chamomilla* L.	Sprague Dawley rats OVA induced	0.06 g/kg to 0.18 g/kg body weight; from day 43 to day 72	Reduces EOS count in BALF Reduces IgE levels Increased GSH-Px levels in serum and ameliorated lung injury	Neutralize ROS and reduce oxidative stress Inhibit the release of chemical mediators and synthesis of Th2-type cytokines	[57]
Cyclophilins	Cyclophilin A	pET21a-CypA transfected to *E. coli*	Sprague Dawley rats OVA induced	10.0 ng/kg body weight; 1 days, injected 10 min before OVA challenge	Reduction in airway resistance Inhibition of tracheal contraction Modulating cytokine and immunoglobulin levels	Improve airflow and alleviate air way constriction Inhibition of IL-2, IFN-γ, IL-4, IL-10, and IL-13 Supressed IgG, IgA, and IgM	[58]
m-methoxybenzoic	Vanilic acid	Oxidized vanilin (*Vanilla planifola*, *Vanilla tahitensis*, *Vanilla pompona*, *Vanilla odorata*)	Sprague Dawley rats OVA induced	20 and 50 mg/kg body weight; began on day 15 and continued once daily for 14 days	Inflammatory cell infiltration Decrease pro-inflammatory cytokines Enchancement of antioxidant defenses	Dependently reduce the infiltration of inflammatory cells (macrophages, eosinophils, neutrophils, and lymphocytes) in BALF Decrease pro-inflammatory cytokines (TNF-α, IFN-γ, IL-4, IL-5, and IL-13) Increase the levels of antioxidant enzyme and GSH, while reducing MDA and ROS levels	[59]

(*continued on next page*)

Table 2 (*continued*)

Classification	Compound/Extract	Source	Experimental Model	Dose; Duration	Efficacy	Mechanism	Reference
Others (combination of herbal plants extract)	*Raphanus sativus* L. and *Codonopsis lanceolate* roots *Allium hookeri* whole plant *Acanthopanax sessiliflorum* stems *Dendropanax morbiferus*leaves	*R. sativus* L., *C. lanceolate* *A. hookeri*, *A.sessiliflorum*, and *D. morbiferus*	Sprague Dawley rats OVA and LPS induced	100–400 mg/kg body weight; Orally from day 11 to day 16	Modulation of proinflammatory cytokines Reduction of inflammatory cytokines in BALF	Regulate the production of IL-1β, IL-6, and TNF-α Reduce IL-1β, IL-6, and TNF-α levels	[24]
Others	Spirulina powder	Filamentous alga	Sprague Dawley rats OVA and cigarette smoke induced	500 mg/kg body weight; 4 weeks	Anti-inflammatory properties Antioxidant effects Immunomodulation	Inhibit activation and infiltration of eosinophils and lymphocytes Reducint the levels of IL-4, IL-5, and IL-13 Scavenge free radicals and protect lung tissue from oxidative damage	[60]
Ethanol extract	*Euphorbia hirta* leaves	*E. hirta*	Sprague Dawley rats OVA induced	100 μg/100 μl and 200 μg/100 μl; orally for 5 consecutive weeks	Reduction of inflammatory markers Modulation of mRNA expression Anti-apoptotic effects	Reduced the levels of TNF-α, IL-6 and NO. Reduce mRNA expression levels of TNF-α, IL-6, iNOS, COX-2 Modulated the mRNA expression of caspase-3, proNGF, p53, Bax, and Bcl-2	[61]
Polyphenols	Carvacrol	-	Wistar rats OVA induced	15 mg/kg; 17 days	Anti-inflammatory and immunomodulatory effect	Reduced the values of AEC, IgE, IL-4, IL-5, IL-13, TNF-α, IFN-γ, iNOS and MDA Increased values of SOD and reduced level of GSH in lung tissue	[62]
Others	Estragole	*Ocimum basilicum*	Wistar rats OVA induced	0.75–3 mg/mL for 21 days	Anti-inflammatory and immunomodulatory effect	Balancing of Th1 and Th2 cytokines ratio, in this case increase of IFN-ɣ and IL-4 ratio.	[63]
Flavonoids	Stems and leaves extract	*Nasturtium officinale*	Wistar rats OVA induced	500 mg/kg for 7 days	Anti-inflammatory	Attenuated inflammation and alveolar injury and increased activity of GPX	[64]
Flavonoid	E Ethyl *p*-methoxycinnamate	Kaempferia galanga L.	Wistar rats OVA induced	200 and 400 mg/kg; from day 26–34	Antiasthma effect	Reducing the expression of TGF-β1 fibrosis	[65]

pathway while inhibiting HO-1. It also downregulated the expression of inflammatory cytokines, including IL-1β, IL-6, and TNF-α, and inhibited the expression of iNOS and COX-2, highlighting its potential as a valuable agent in mitigating inflammatory responses [16].

In a study involving Alkylresorcinol, including both (−)-1S-myrothecol and (+)-1R-myrothecol, obtained from *Myrothecium* sp. BZO-L062, the effects on RAW 264.7 cells were investigated. The treatment conditions included a dose range of 10–100 μg/mL for a duration of 2 h. These Alkylresorcinols exhibited promising properties, as they displayed both anti-inflammatory and antioxidant activities. Specifically, they were found to inhibit the production of nitric oxide (NO), indicating anti-inflammatory effects, and demonstrated antioxidant properties by scavenging free radicals. These findings suggest the potential of Alkylresorcinols as valuable agents for combating inflammation and oxidative stress [17].

A study focused on the sesquiterpene Hirsutanol A, derived from *Chondrostereum* sp. NTOU4196 and its impact on THP-1 cells. The treatment involved exposure to a dose range of 0.5–10 μM for a duration of 15 min. Hirsutanol A demonstrated notable potential in reducing tissue damage and inflammation. It achieved this by reducing the levels of pro-inflammatory cytokines, particularly TNF-α, IL-6, and IL-1β. Furthermore, the sesquiterpene exhibited its anti-inflammatory properties through modulation of signaling pathways, inhibition, and downregulation of MMP-9, and attenuation of the activation of STAT3 and NF-κB. These findings suggest that Hirsutanol A has promising therapeutic applications in mitigating tissue damage and inflammation [18].

A study investigated the effects of polysaccharides, particularly sulfated polysaccharides derived from *Saccharina japonica*, on RAW 264.7 cells. The treatment regimen included exposure to a dose range of 50–400 μg/mL for a duration of 1 h. The results indicated that these polysaccharides possessed significant anti-inflammatory properties. They effectively inhibited the production of nitric oxide (NO) and reduced the levels of inflammatory cytokines, including PGE2, IL-1β, and TNF-α. Furthermore, these sulfated polysaccharides exhibited their anti-inflammatory effects by inhibiting the MAPK and NF-κB signaling pathways, specifically the inhibition of p38 MAPK, JNK, ERK, and the activation of phosphorylation IKKα/β. This suggests that sulfated polysaccharides from Saccharina japonica have potential as anti-inflammatory agents, with the ability to modulate key pathways involved in the inflammatory response [19].

In a study conducted with sulfated polysaccharides derived from *Sargassum fulvellum* and their effects on RAW 264.7 cells, with treatment involving a dose range of 25–100 μg/mL for 1 h, several significant findings were observed. These sulfated polysaccharides demonstrated potent anti-inflammatory properties. They effectively inhibited the production of inflammatory mediators and pro-inflammatory cytokines, contributing to the suppression of iNOS and COX-2 expression. Additionally, these compounds successfully reduced the production of nitric oxide (NO) and prostaglandin E2 (PGE2), while also inhibiting the production of key pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6. These results indicate the potential of sulfated polysaccharides from Sargassum fulvellum as valuable agents for alleviating inflammation and its associated mediators [20].

A study involving the flavonoid Quercetin, utilized BCi-NS1.1 cells and a treatment of 25 μM for a duration of 24 h. The results indicated that Quercetin had anti-inflammatory properties as it effectively reduced the levels of pro-inflammatory cytokines, specifically IL-1β, IL-6, and IL-8. Moreover, it was found to attenuate the activation of the NF-kB pathway. These findings suggest that Quercetin has the potential to mitigate inflammation by reducing the expression of pro-inflammatory cytokines and modulating key signaling pathways like NF-kB [21].

In an investigation involving the compound Apocynin and the use of A549 cells, a treatment regimen of 0.5, 1, and 3 mg/mL for a duration of 4 h was employed. The results showed that Apocynin had notable anti-inflammatory effects. It led to a decrease in the mRNA expression of pro-inflammatory cytokines TNF-α and IL-6. Additionally, Apocynin exhibited inhibitory properties against NADPH oxidase, suggesting its potential in reducing oxidative stress, a common trigger for inflammation. These findings indicate that Apocynin may be a valuable agent for mitigating inflammation by modulating the expression of pro-inflammatory genes and inhibiting NADPH oxidase [22].

A study investigated the impact of fatty acids obtained from *Arctoscopus japonicus* egg lipids on RAW 264.7 cells, with a treatment regimen involving 1.0–2.0 % v/v for a duration of 1 h. The results revealed that these fatty acids exhibited significant anti-inflammatory properties. They effectively inhibited the production of inflammatory mediators and suppressed the expression of immune-associated genes. Furthermore, these fatty acids played a role in inhibiting the NF-κB and MAPK signaling pathways, particularly interrupting the JNK protein signaling pathway. This resulted in a reduction in the production of nitric oxide (NO) and prostaglandin E2 (PGE2). Additionally, these fatty acids decreased the expression of key inflammatory molecules, including iNOS, COX-2, IL-1β, IL-6, and TNF-α, while also inhibiting ERK1/2, JNK, and p38 signaling pathways. These findings suggest that fatty acids from Arctoscopus japonicus egg lipids have potential as valuable anti-inflammatory agents by modulating multiple inflammatory pathways and mediators [23].

A study investigated the potential anti-inflammatory effects of a combination of herbal plant extracts, including *Raphanus sativus* L. and *Codonopsis lanceolate* roots, *Allium hookeri* whole plant, *Acanthopanax sessiliflorum* stems, and *Dendropanax morbiferus* leaves, on RAW 264.7 cells. The treatment involved a dose range of 10–100 μg/mL for a duration of 1 h. The results revealed that this herbal combination exhibited significant anti-inflammatory properties. It effectively inhibited the production of key inflammatory molecules, including nitric oxide (NO), IL-1β, IL-6, and TNF-α. Additionally, the herbal combination suppressed the activation of the NF-κB pathway, suggesting its potential in mitigating inflammation. Furthermore, the study indicated that this combination of herbal plant extracts had the ability to inhibit allergic asthma, underlining its possible therapeutic applications in the treatment of allergic and inflammatory conditions [24].

In a study involving the leaves extract of *Saurauia vulcani* and its effects on RAW 264.7 cells, with treatment at concentrations of 12.5 and 25 μg/mL for 15 min, the results showed significant anti-inflammatory properties. The leaves extract effectively inhibited the production of nitric oxide (NO) and reduced the expression of key pro-inflammatory molecules, including TNF-α, IL-6, COX-2, IL-1β, and iNOS genes. These findings suggest that *Saurauia vulcani* leaves extract has the potential to mitigate inflammation by modulating the expression of pro-inflammatory genes and reducing the production of inflammatory mediators [25].

In a study focusing on carotenoids, specifically Crocetin derived from *Crocus sativus* and its effects on RAW 264.7 cells, the treatment regimen involved concentrations ranging from 12.5 to 100 μg/mL for 24 h. The results indicated that Crocetin exhibited remarkable anti-inflammatory properties. It effectively inhibited the production of inflammatory factors, reduced the expression of key pro-inflammatory molecules, including COX-2, iNOS, IL-1β, IL-6, IL-10, and TNF-α. These findings suggest that Crocetin, a carotenoid from *Crocus sativus*, has the potential to mitigate inflammation by modulating the expression of pro-inflammatory genes and reducing the production of inflammatory mediators [26].

In a study involving the essential oil extracted from the aerial parts of *Inula viscosa*, *Inula graveolens*, and *Inula crithmoides*, and its effects on RAW 264.7 cells, the treatment utilized a concentration of 5 μg/mL for 24 h. The results showed that the essential oil from these *Inula* species exhibited significant anti-inflammatory properties. It effectively inhibited the production of nitric oxide (NO), indicating its potential to mitigate inflammation by reducing the production of this pro-inflammatory mediator [27].

In a study exploring the impact of an ethanolic extract derived from *Veronica persica*, which contains iridoid and flavonoid glycosides, on splenocytes isolated from mice exposed to house dust mites (HDM), several promising findings were observed. The extract demonstrated substantial potential in mitigating asthmatic inflammation induced by HDM. It achieved this through multiple mechanisms, including the limitation of TH2 cell activation by increasing the expression of IFN-γ, which is indicative of a shift towards an anti-inflammatory response. Furthermore, the extract attenuated the secretion of both Th1 and Th2 cytokines, except for IL-10, suggesting a balanced and less inflammatory immune response. It also inhibited eosinophilic infiltration, a hallmark of allergic asthma, and reduced the expression of T-cell activators that contribute to the immune response. Additionally, the extract inhibited the production of MCP-1, a chemokine involved in recruiting immune cells, and STAT3/6 activation in airway epithelial cells, thereby offering potential for mitigating airway inflammation. These results highlight the therapeutic promise of the ethanolic extract of *Veronica persica* in the context of allergic asthma management, indicating its potential for further exploration and application as a natural remedy [28].

In a study involving polyphenols, specifically Phloroglucinol obtained from *Dyropteris crassirhizoma*, and its effects on HMC-1 cells, the treatment utilized a range of concentrations from 0.1 to 10 mg/mL for 30 min. The results indicated that Phloroglucinol demonstrated potent anti-allergic and anti-inflammatory properties. It effectively inhibited the production of inflammatory cytokines, suggesting its potential as a valuable agent for mitigating allergic reactions and inflammation [29].

In a study involving flavonoids from an aqueous extract of *Rosa laevigata* Michx. and their effects on A549 cells, the treatment included concentrations of 500 and 1000 μg/mL for a duration of 1 h. The results demonstrated that the flavonoids had significant anti-inflammatory properties. They effectively suppressed inflammatory pathway activity and reduced COX-2 expression levels. Furthermore, the flavonoids inhibited the MAPK and NF-κB signaling pathways, indicating their potential to mitigate inflammation by modulating key inflammatory pathways and reducing the expression of pro-inflammatory enzymes and molecules [30].

In a study involving 2-Furoic acid, 5-hydroxymethylfurfural, and Vanillic acid 4-beta-D-glucopyranoside derived from *Adenophora stricta* and their effects on Raw 264.7 cells, treatment at concentrations of 1 or 3 mg/mL for 1 h yielded significant results. These compounds effectively suppressed the proinflammatory response and inhibited the transcription of the iNOS gene, leading to a reduction in nitric oxide production in LPS-exposed cells. These findings indicate the potential of these compounds to modulate the immune response and mitigate inflammation, making them valuable candidates for further research and potential therapeutic applications [31].

In a study involving essential oils extracted from the leaves of various plants, including *Cinnamomum camphora* (L.) J. Presl, *Cinnamomum cassia* (L.) J. Presl, *Cinnamomum japonicum* Siebold, *Neolitsea aciculata* (Blume) Koidz., *Neolitsea sericea* (Blume) Koidz., *Lindera obtusiloba* Blume, and *Machilus japonica* Siebold & Zucc., the effects on NCH–H292 cells were examined. The treatment utilized a concentration of 5 μg/mL for 24 h. The results indicated that the essential oils effectively suppressed the expression of pro-inflammatory cytokines and mucin genes, resulting in a reduction in the levels of IL-1β, IL-6, MUC5AC, and MUC5B. These findings highlight the potential of these essential oils in mitigating inflammation and mucin production, making them promising candidates for further research and potential therapeutic applications [32], and the in vivo studies evidences of natural products for asthma are summarized in Table 2.

Chromenols: Compounds like Mojobanchromanol derived from *Sargassum horneri* exhibit significant potential in reducing oxidative stress, suppressing pro-inflammatory cytokines, and modulating Toll-Like Receptors, making them valuable anti-asthma agents.

Phytosterols: Substances such as Fucosterol from *Padina boryana* display anti-inflammatory properties by inhibiting inflammatory mediators and cytokines, modulating pathways like MAPK and Nrf2/HO-1, indicating their potential for asthma treatment.

Polysaccharides: Compounds like Fucoidan from *Saccharina japonica* possess anti-inflammatory effects by inhibiting nitric oxide production, suppressing pro-inflammatory cytokines, and modulating pathways like MAPK and NF-κB, suggesting their usefulness in asthma management.

Alkylresorcinols: Extracts containing Alkylresorcinols from *Myrothecium* sp. BZO-L062 exhibit both anti-inflammatory and antioxidant activities, making them promising candidates for alleviating inflammation and oxidative stress associated with asthma.

Sesquiterpenes: Compounds like Hirsutanol A from *Chondrostereum* sp. NTOU4196 demonstrate potential in reducing tissue damage and inflammation by suppressing pro-inflammatory cytokines and modulating signaling pathways like STAT3 and NF-κB.

Flavonoids and Polyphenols: Natural products such as Quercetin, Phloroglucinol, and flavonoids from various plant extracts show anti-inflammatory and anti-allergic properties by suppressing inflammatory cytokines and modulating pathways like NF-κB and MAPK, indicating their potential for asthma treatment.

Essential Oils: Extracts from plants like Inula species and *Rosa laevigata* Michx. demonstrate significant anti-inflammatory effects by inhibiting nitric oxide production and suppressing pro-inflammatory cytokines, suggesting their usefulness in mitigating

inflammation associated with asthma.

Herbal Plant Extracts: Combinations of herbal extracts, such as those from *Raphanus sativus* L. and *Codonopsis lanceolate* roots, exhibit anti-inflammatory properties by inhibiting nitric oxide and cytokine production, suggesting their potential for allergic asthma management.

Other Compounds: Various compounds like fatty acids from *Arctoscopus japonicus* egg lipids and carotenoids like Crocetin from *Crocus sativus* display anti-inflammatory effects by modulating multiple pathways and reducing the expression of inflammatory mediators, indicating their potential for asthma treatment.

3.2. In vivo or preclinical trial researches reveal potential evidence of natural products in the treatment of asthma

In-vivo studies of asthma treatments are done on mice and rats, particularly BALB/c and NMRI mice, and Sprague Dawley and Wistar rats. All of which are induced with allergen to exhibit asthmatic symptomps, such as airway inflammation, bronchoconstriction, mucus hypersecretion, and hyperresponsiveness of airways. Common allergens used in studies are ovalbumin (OVA), house dust mite (HDM), and lipopolysaccharide (LPS). Test subjects are sensitized and challenged with aforementioned allergens either by intraperitoneal, intranasal, or intratracheal injection, or instillation and some by aerosol inhalation.

Differences between types of allergens used on subjects resulted in similar phenotypic symptoms with key distinctions. OVA-induced subjects showed a more predominant eosinophilic response, LPS-induced subjects showed a more neutrophilic response, and HDM-induced subjects showed a mixed response of eusinophils and neutrophils.

Shogaols, a type of polyphenol found in *Zingiber officinale* Roscoe (ginger), were examined in a study involving BALB/c mice with OVA-induced inflammation. The mice were administered 6-shogaol at a dose of 10 mg/kg for three consecutive days (on days 28, 29, and 30), with treatment occurring 2 h before challenging the mice with OVA. The results demonstrated that 6-shogaol effectively reduced eosinophilia, mucus production, and levels of Th2 cytokines. It achieved this by interfering with the production of interleukins (ILs) and tumor necrosis factor-alpha (TNF-α), suggesting its potential as an anti-inflammatory agent with the ability to mitigate allergic inflammation and associated symptoms in the OVA-induced mouse model [33].

In a study involving BALB/c mice with OVA-induced inflammation, gingerols, a type of polyphenol found in *Zingiber officinale* Roscoe (ginger), were investigated. The mice were treated with 6-gingerol at a dose of 10 mg/kg for three consecutive days (on days 28, 29, and 30), with treatment occurring 2 h before challenging the mice with OVA. The results revealed that 6-gingerol effectively reduced eosinophilia, mucus production, and levels of Th2 cytokines, indicating its potential as an anti-inflammatory agent for mitigating allergic inflammation. Additionally, 6-gingerol interfered with the production of interleukins (ILs) and tumor necrosis factor-alpha (TNF-α), further supporting its anti-inflammatory properties. Notably, it upregulated the expression of SOD1, an antioxidant enzyme, suggesting its role in enhancing antioxidant defenses, which can be beneficial in reducing oxidative stress associated with inflammation [33].

In a study involving BALB/c mice with OVA-induced inflammation, prenylated chalcones, specifically Renifolin F derived from *Shuteria involucrata*, were examined. The treatment consisted of two doses, 1.5 mg/kg and 3.0 mg/kg, and was initiated on the 21st day, continuing until the 27th day. Each dose was administered orally 1 h before the daily OVA aerosol challenge. Renifolin F demonstrated significant anti-inflammatory effects, as it reduced airway hyperresponsiveness and inhibited the levels of mucin and related inflammatory factors in both the blood and BALF. Furthermore, it displayed the ability to inhibit key cytokines such as IL-4, IL-5, IL-9, and IL-13, which are associated with the Th2 immune response. Renifolin F also reduced the production of type 2 cytokines IL-2 and IL-7, indicating its potential to modulate the immune response. Additionally, it downregulated the expression of microRNA-155, which is involved in regulating immune responses, and reduced the levels of upstream cytokines including IL-25, IL-33, and TSLP. These findings suggest that Renifolin F has promising anti-inflammatory properties with the potential for mitigating allergic inflammation and its associated immune responses [34].

In a study involving BALB/c mice with OVA-induced inflammation, an ethanolic extract of *Erythrina mulungu* Benth., containing alkaloids such as erysotrine, erysotrine-N-oxide, and hypaphorine, was examined. The treatment ranged from 200 to 800 mg/kg and spanned seven consecutive days, with simultaneous challenge to OVA. The ethanolic extract exhibited significant anti-inflammatory effects, as it reduced bronchial hyperresponsiveness (BHR), as well as the levels of leukocytes, eosinophils, lymphocytes, IL-4, and IL-5. Notably, it increased the levels of IL-13 and IFN-ɣ, indicating an indirect Th2 response through Th1 stimulation. The extract also demonstrated its ability to suppress inflammatory cytokines by inhibiting TLR4 and activating PPAR-ɣ. These findings suggest that the alkaloid-rich ethanolic extract from *Erythrina mulungu* Benth. holds promise as a potent anti-inflammatory agent with the potential to modulate immune responses and mitigate allergic inflammation [35].

The examination of multifloral honey, derived from a combination of *Apis mellifera* honey and *Melaleuca* spp., in the context of OVA-induced inflammation in BALB/c mice revealed notable anti-inflammatory properties. Administered at concentrations of 10 %, 40 %, and 80 % v/v, with each group receiving their respective treatments orally once daily for 5 days during the challenge period, multifloral honey effectively reduced both inflammatory cell infiltration and beta-hexosaminidase levels in bronchoalveolar lavage fluid (BALF). Furthermore, it resulted in a reduction in the number of mast cells. These anti-inflammatory effects were attributed to the honey's antioxidant and scavenging properties, which encompass compounds such as ellagic acid, quercetin, chrysin, and caffeic acid. These findings highlight the potential of multifloral honey in alleviating inflammation and its associated cellular responses, establishing it as a valuable natural remedy for conditions like allergic asthma [36].

In various murine models of asthma, including acute, chronic, and GCs-resistant models, Bixin, a carotenoid acid derived from *Bixa orellana* seeds, demonstrated its potential as a potent anti-inflammatory agent. Administered at doses of 50 mg/kg and 100 mg/kg in these diverse models, Bixin exhibited several noteworthy effects. These included the reduction of airway inflammation and airway

hyperresponsiveness, as well as the inhibition of inflammatory signaling pathways. Furthermore, Bixin suppressed the production of pro-inflammatory cytokines and chemokines, while simultaneously inhibiting the NF-κB and TGF-β1 signaling pathways. These findings underscore the potential of Bixin as a therapeutic agent for mitigating airway inflammation, hyperresponsiveness, and other related inflammatory responses, positioning it as a promising candidate for further research and application in the treatment of asthma and similar conditions [37].

In an examination of coumaric acid esters within a study involving BALB/c mice with OVA-induced inflammation, it was Methyl P-coumarate sourced from various plants such as *Trixis michuacana* var. longifolia, *Comptonia peregrine*, *Melicope latifolia*, Hainan *Morinda citrifolia*, *Ziziphus jujuba* Mill., and *Aloe vera* that took the spotlight. Administered orally at 5 mg/kg for 5 days from days 9–13, this compound displayed significant anti-inflammatory effects. Methyl P-coumarate showed promise in inhibiting immune cell recruitment, regulating Th2 cytokines, and modulating the secretion of MCP-1 and IgE. It also demonstrated efficacy in inhibiting the activation of NF-κB and the secretion of various inflammatory molecules such as IL-6, IL-8, MCP-1, ICAM-1, TNF-α, IL-1β, and IL-6. Moreover, it successfully inhibited the adhesion of airway cells and eosinophils. These findings underscore the potential of Methyl P-coumarate as a candidate for mitigating inflammation, immune responses, and allergic reactions [38].

In the context of a study using BALB/c mice with OVA-induced inflammation, the flavonoid Tilianin, sourced from *Agastache rugosa* and *Dracocephalum moldavica*, was subjected to investigation. The treatment consisted of oral administration at doses of 10 and 20 mg/kg body weight, 1 h before the OVA challenge on days 21–23. The results were compelling, with Tilianin revealing inhibitory effects on Th2 cytokines, leading to a reduction in inflammatory cells and displaying antioxidant activity. Furthermore, Tilianin suppressed pro-inflammatory cytokines and modulated TGF-β1/Smad signaling. It successfully reduced the levels of Th2 cytokines, decreased the numbers of inflammatory cells in BALF, including eosinophils, neutrophils, macrophages, and lymphocytes, and resulted in the reduction of MDA levels. In addition, Tilianin increased the activities of SOD and GSH, indicative of enhanced antioxidant capacity. These findings suggest that Tilianin possesses substantial potential in mitigating inflammation, oxidative stress, and immune responses, positioning it as a valuable candidate for further research and potential therapeutic applications in related conditions [39].

Within a study involving male BALB/c mice and OVA-induced inflammation, the polyphenols Total Glucosides of Paeonia (TGP), extracted from the roots of *Paeonia lactiflora* Pall, were the subject of exploration. TGP was administered at varying doses: 100 mg/kg (low dose), 200 mg/kg (medium dose), and 400 mg/kg (high dose), commencing on the 23rd day of the study. The outcomes were substantial, with TGP showcasing its potential by reducing airway hyperresponsiveness and improving lung tissue pathology. This effect was further evidenced by a decrease in inflammatory cell infiltration and collagen deposition in the lung tissue. Moreover, TGP led to a reduction in several key parameters in bronchoalveolar lavage fluid (BALF), including leukocyte and eosinophil counts, as well as levels of chemokines and cytokines such as eotaxin, TNF-α, IL-4, and MIP-1α. TGP also exhibited a reduction in the release of β-hexosaminidase, a marker of mast cell degranulation, indicating its potential to inhibit mast cell activation. Furthermore, it was associated with the inhibition of $Ca2+$ influx in mast cell degranulation. These findings highlight the therapeutic potential of TGP in mitigating airway inflammation, improving lung function, and regulating immune responses, making it a promising candidate for further research and potential applications in the treatment of related conditions [40].

In an investigation involving female BALB/c mice with OVA-induced asthma, the potential of *Cordyceps* polysaccharide derived from *Cordyceps militaris* was explored. Administered at various doses, including 25 mg/kg, 50 mg/kg, and 100 mg/kg, starting on the 23rd day after the initial sensitization and continued for 8 weeks, *Cordyceps* polysaccharide exhibited substantial effects on the asthma model. These included reduced inflammatory cell infiltration, goblet cell hyperplasia, and subsequently decreased airway inflammation and mucus production. The polysaccharide also demonstrated the capacity to modulate immune responses by increasing inflammatory cells in the mouse model of asthma. It notably suppressed the secretion of key cytokines like eotaxin, IL-4, IL-5, IL-13, and IFN-γ, all closely associated with asthma's inflammatory response. Additionally, *Cordyceps* polysaccharide lowered IgE levels, a marker of allergic reactions, and inhibited the activation of transforming growth factor β1 (TGF-β1), which plays a significant role in asthma-related tissue remodeling and fibrosis. These findings underline the potential of *Cordyceps* polysaccharide as a valuable agent for mitigating airway inflammation, reducing mucus production, and regulating immune responses in the context of asthma and related conditions [41].

In a study conducted with BALB/c mice, specifically within an OVA-induced asthma model, the effects of Isorhyncophylline derived from *Uncaria rhynchophylla* were examined. The treatment consisted of a 40 mg/kg dosage administered over 42 days. Isorhyncophylline produced significant effects on the asthma model, including the attenuation of eosinophil recruitment in bronchoalveolar lavage fluid (BALF, indicating potential for reducing airway inflammation. It also played a role in reducing collagen deposition in lung tissue, contributing to the prevention of tissue remodeling and fibrosis. Isorhyncophylline was effective in suppressing the production of IgE, an antibody associated with allergic reactions, and pro-inflammatory cytokines, which play a pivotal role in asthma pathogenesis. Additionally, it induced the apoptosis of airway smooth muscle cells (ASMCs), potentially preventing airway hyperresponsiveness, while also increasing the level of miR-200a, a microRNA involved in cellular processes. Moreover, it inhibited the activation of the FOXC1/NF-kB pathways, which are central to inflammatory responses. These findings suggest that Isorhyncophylline holds therapeutic potential in mitigating airway inflammation, preventing tissue remodeling, and modulating immune responses in the context of asthma and related conditions [42].

In an exploration involving male BALB/c mice and their OVA-induced asthma, Sinomenine, derived from the root of *Sinomenium acutum*, was administered at a dosage of 100 mg/kg over 75 days. Sinomenine yielded several significant effects in the asthma model, including the notable improvement of all histopathological changes associated with airway remodeling, thereby suggesting its potential in preventing structural alterations in the airways. The compound was found to modulate Th-2 derived cytokines, which are central to allergic responses and asthma pathogenesis. It also effectively inhibited the apoptosis of airway epithelial cells, contributing to the preservation of airway integrity and function. Furthermore, Sinomenine reduced the levels of various cytokines, including IL-4,

IL-5, IL-13, and nitric oxide, all of which are key mediators of inflammation and airway hyperresponsiveness in asthma. These findings underscore the promise of Sinomenine as a therapeutic agent for mitigating airway remodeling, modulating immune responses, and reducing inflammation in the context of asthma and related conditions [43].

In a study involving female BALB/c mice with OVA-induced asthma, the effects of Mangiferin derived from the leaves of *Mangifera indica* L. were assessed. Administered at dosages of 100 mg/kg and 200 mg/kg over a 30-day period, the study revealed several significant effects of Mangiferin on the asthma model. Firstly, Mangiferin was found to modulate the Th1/Th2 cytokine imbalance via the STAT6 signaling pathway, addressing the immune system dysregulation commonly observed in asthma. Secondly, the treatment with Mangiferin attenuated the symptoms of asthma attacks, indicating its potential for symptom relief. Additionally, Mangiferin reduced the total number of leukocytes, eosinophils, and goblet cell infiltration in the lung, contributing to the alleviation of airway inflammation and mucus production. The compound further reduced the levels of specific pro-inflammatory cytokines, IL-9 and IL-17A, which play a role in asthma pathology. It also inhibited the expression of PU.1 and RORγt in the lung, factors involved in immune cell differentiation and inflammatory responses. Conversely, it increased the levels of anti-inflammatory cytokines, IL-10 and TGF-β1, as well as the regulatory T cell marker Foxp3, indicating a shift towards a more balanced and anti-inflammatory immune environment. These findings suggest that Mangiferin has potential as a therapeutic agent for addressing immune dysregulation, alleviating symptoms, reducing inflammation, and promoting immune balance in asthma and related conditions [44].

In a study utilizing BALB/c mice with OVA-induced asthma, an ethanolic extract of *Cassia occidentalis* Linn., containing Anthraquinone, was administered at various dosages (250 mg/kg, 500 mg/kg, and 2000 mg/kg). The study yielded several notable effects of the extract on the asthma model. Specifically, the extract reduced the eosinophil count, levels of pro-inflammatory cytokines IL-4 and IL-13, and OVA-specific IgE, indicating a reduction in eosinophilic inflammation and the allergic response. Additionally, it downregulated the mRNA expression of type 2 cytokines, namely IL-4, IL-5, and IL-13, which are associated with Th2 immune responses and asthma pathology. These findings suggest that the ethanolic extract of *Cassia occidentalis* Linn., enriched with Anthraquinone, has potential as a therapeutic agent for mitigating inflammation, alleviating allergy-related responses, and reducing the expression of asthma-associated pro-inflammatory cytokines [45].

In an exploration involving female BALB/c mice with OVA-induced asthma, Eupatilin, a methylated flavonoid extracted from *Artemisia argyi*, was administered at doses of 15 mg/kg and 30 mg/kg from day 17 to day 23. The study unveiled several significant effects of Eupatilin on the asthma model. Notably, Eupatilin reduced the number of inflammatory cells in bronchoalveolar lavage fluid (BALF), specifically neutrophils and eosinophils, indicating a reduction in airway inflammation. It also inhibited Th2 cytokines such as IL-5, IL-13, and OVA-specific IgE, suggesting a suppression of allergic and inflammatory responses. Moreover, Eupatilin reduced inflammatory cell infiltration and mucus hypersecretion, which are characteristic features of asthma. Mechanistically, it inhibited the phosphorylation and nuclear translocation of NF-κB, a key regulator of inflammation. Additionally, Eupatilin blocked the phosphorylation of p38 MAPK, Erk, and JNK, all of which are involved in inflammatory signaling pathways. Furthermore, Eupatilin activated the Nrf2 signaling pathway, which is associated with antioxidant and cytoprotective responses. These findings suggest that Eupatilin, derived from *Artemisia argyi*, holds promise as a therapeutic agent for mitigating airway inflammation, reducing allergic responses, and modulating various signaling pathways involved in asthma pathogenesis [46].

In a study involving female BALB/c mice with OVA-induced asthma, the administration of a leaf extract from *Eriobotrya japonica* at daily doses of 50 mg/kg, 100 mg/kg, and 200 mg/kg from day 13–18 in a 19-day experiment yielded noteworthy results, indicating the potential of the leaf extract in mitigating asthma symptoms. The extract led to a reduction in the amounts of IgE, IL-4, and IL-13, which are key markers of allergic and inflammatory responses in asthma. Furthermore, the leaf extract demonstrated an inhibitory effect on inflammatory mediators, further supporting its role in reducing airway inflammation. These findings suggest that phytochemicals in the leaf extract of *Eriobotrya japonica* possess anti-inflammatory and anti-allergic properties, making them promising candidates for asthma management and warranting further research and exploration [47].

In a study conducted with Swiss albino mice afflicted with OVA-induced asthma, a flavonoid combination known as Flavocoxid, derived from the roots of *Scutellaria baicalensis* and *Acacia catechu*, was administered at a dosage of 20 mg/kg for 16 days. The study demonstrated the potential of Flavocoxid in mitigating allergen-induced airway inflammation, presenting several key findings. Firstly, Flavocoxid effectively inhibited leukocyte infiltration, which is often associated with inflammation in the airways. It also reduced the production of nitric oxide (NO), a pro-inflammatory molecule, and lowered the expression of IL-13, a cytokine linked to asthma and allergic responses. These results suggest that Flavocoxid, a combination of flavonoids from *Scutellaria baicalensis* and *Acacia catechu*, possesses anti-inflammatory and anti-allergic properties, making it a promising candidate for the management of asthma and related conditions. Further research is warranted to explore its therapeutic potential fully [48].

In a study involving male BALB/c mice with OVA-induced asthma, an aqueous extract of *Pimpinella anisum* seeds was administered at a dosage of 0.16 mg/kg from days 24–30, 15 min after the OVA challenge. The study revealed significant results, as the *Pimpinella anisum* seed extract demonstrated an inhibitory effect on inflammatory cytokines. It downregulated the expression of Th2 cytokines, including IL-5, IL-13, and IL-33, which are closely associated with allergic and asthmatic responses. Moreover, the extract effectively inhibited eosinophil trafficking, a crucial process in the inflammatory mechanisms of asthma. These findings underscore the potential of *Pimpinella anisum* seed extract as an anti-inflammatory and anti-allergic agent, offering promise for the management of asthma and related conditions. Further research is warranted to unlock its full therapeutic potential [49].

Rutin, a flavonoid, was administered at doses of 37.5 mg/kg and 75 mg/kg to pregnant female BALB/c mice throughout pregnancy, from days 1–21. This study revealed significant effects of Rutin, positioning it as a potential antioxidant and anti-inflammatory agent in the context of asthma. Notably, Rutin effectively reduced cellular infiltration in the airways, indicative of its role in mitigating airway inflammation. Mechanistically, Rutin downregulated NF-κB and iNOS, key regulators of the inflammatory response, shedding light on its anti-inflammatory action. Additionally, it demonstrated the capacity to inhibit matrix metalloproteinase 9, associated with tissue

damage in asthma. Furthermore, Rutin reduced levels of Th2 and Th17 cytokines, further underscoring its anti-inflammatory properties, making it a promising candidate for the management of asthma and related conditions [50].

In a study involving BALB/c mice exposed to house dust mite (HDM)-induced airway inflammation, an ethanol extract of *Veronica persica* enriched with iridoid and flavonoid glycosides was administered at doses of 50 and 100 mg/kg. The results revealed promising effects on the mitigation of inflammatory responses within the airways. This extract effectively attenuated the recruitment and activation of inflammatory cells, thus preventing or hindering the development of airway inflammation. Moreover, it reduced levels of both Th1 and Th2 cytokines, signifying its anti-inflammatory properties, while concurrently elevating the expression of the anti-inflammatory cytokine IL-10, contributing to immune regulation. Furthermore, the extract displayed inhibitory effects on signaling pathways, specifically STAT-3 and STAT-6, offering insights into its anti-inflammatory action. An upregulation in IFN-γ expression was also noted, emphasizing its role in immune modulation. Collectively, these findings highlight the potential of the ethanol extract of *Veronica persica*, rich in iridoid and flavonoid glycosides, as a valuable candidate for managing airway inflammation and its associated immune responses [28].

In a study involving BALB/c mice with house dust mite (HDM)-induced airway inflammation, Lonicerin, a flavonoid naturally occurring in *Lonicera japonica*, was administered at doses of 10 mg/kg and 30 mg/kg. This study unveiled several noteworthy effects of Lonicerin on the HDM-induced model. Most prominently, Lonicerin effectively reduced airway inflammation, mucus hypersecretion, and airway hyperresponsiveness (AHR), all of which are hallmark features of asthma and allergic responses. Furthermore, it upregulated the Src/EGFR pathway, providing insights into the potential mechanisms through which Lonicerin exerts its anti-inflammatory and anti-allergic effects. These findings underscore Lonicerin's promise as a therapeutic agent for mitigating airway inflammation and alleviating symptoms associated with conditions like asthma, necessitating further research to fully comprehend its mechanisms of action and clinical applications [51].

In a study involving female C57BL/10 mice with house dust mite (HDM)-induced allergic airway inflammation, *Platycodi radix* extracts derived from the roots of *Platycodon grandiflorum* were administered at doses of 50 mg/kg, 100 mg/kg, and 200 mg/kg from day 2–20 of the study. The findings of the study revealed significant effects of these extracts on the allergic airway inflammation model. Notably, *Platycodi radix* extracts suppressed allergic airway inflammation, a hallmark of asthma and allergic responses. It also inhibited the expression of inflammatory cytokines and mucin5AC, which are associated with airway inflammation and mucus production. Additionally, the extracts regulated the Th2 response by modulating IL-4 and IL-13, two crucial cytokines linked to allergic reactions. Interestingly, they increased endoplasmic reticulum (ER) stress and the production of reactive oxygen species (ROS) through NF-κB signaling, suggesting a potential mechanism underlying their anti-inflammatory and anti-allergic properties. These findings highlight the potential of *Platycodi radix* extracts in managing allergic airway inflammation and warrant further research into their clinical applications and mechanisms of action [52].

In the research involving BALB/c mice subjected to lipopolysaccharide (LPS)-induced inflammation, the administration of an aqueous extract from *Cinnamomum* spp. at varying doses (20 mg/kg, 100 mg/kg, and 500 mg/kg) over a 6-day period revealed its potential to reduce the levels of pro-inflammatory cytokines TNF-α and IL-6, both of which play a pivotal role in the inflammatory response. The extract's anti-inflammatory effects were notably achieved by its inhibition of Toll-like receptor (TLR)-mediated pathways, specifically targeting NF-κB and MAP kinases, which are key signaling pathways in the immune response and inflammation. These findings suggest that the flavonoids and tannins present in the aqueous extract from *Cinnamomum* spp. show promise as anti-inflammatory agents, potentially offering applications in the management of inflammatory conditions, prompting further exploration into their underlying mechanisms of action [53].

In a controlled experimental study involving male BALB/c albino mice, oral administration of an extract derived from the aerial parts of *Euphorbia cuneata* at daily doses of 25 mg/kg and 50 mg/kg for five consecutive days prior to lipopolysaccharide (LPS) exposure resulted in remarkable outcomes. The treatment effectively suppressed the infiltration of inflammatory cells, particularly neutrophils, while simultaneously reducing the levels of lactate dehydrogenase (LDH) in bronchoalveolar lavage fluid (BALF), indicating the mitigation of lung tissue damage. Furthermore, the extract displayed the ability to enhance the activities of antioxidant enzymes, including catalase, superoxide dismutase, and glutathione, while concurrently reducing malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) levels, signifying robust antioxidant and cytoprotective properties. On a mechanistic level, the extract demonstrated its inhibitory effect on the NF-κB signaling pathway, a pivotal regulator of inflammatory processes, and disrupted the activity of Toll-Like Receptor 4 (TLR4), a fundamental component of the innate immune system. These findings collectively underscore the potential of *Euphorbia cuneata*'s flavonoids and tannins as potent agents in the realms of anti-inflammation and antioxidation, offering promise for the management of inflammatory conditions and diseases associated with oxidative stress. This research necessitates further exploration of their therapeutic applications and the precise underlying mechanisms behind these effects [54].

In an examination conducted with BALB/c mice subjected to lung inflammation induced by lipopolysaccharide (LPS), a leaf hydroalcoholic extract sourced from *Vitex negundo* Linn. was administered at varying doses of 150 mg/kg and 300 mg/kg. This comprehensive analysis highlighted the extract's multifaceted impact on the lung's inflammatory response and overall health. The extract effectively curtailed the influx of inflammatory cells, mitigated fibrosis, and shielded epithelial cells against apoptosis. Notably, it displayed specific suppression of inflammatory mediators and the moderation of autophagy, concomitantly regulating connexins and reducing Th2 cytokine levels. A remarkable observation was the activation of alveolar macrophages, essential components of the lung's immune defense. These diverse effects were attributed to the modulation of gap junction proteins and the intricate regulation of various signaling pathways, encompassing TGF-β/Smad, LC3A/B, caspases, Bax, Bcl2, AMPK, PI3K, Akt, p38, and NF-κB within alveolar macrophages. Cumulatively, this investigation underscores the intricate influence of flavonoids and phenolic acids in *Vitex negundo* Linn.'s leaf extract on lung health, offering anti-inflammatory, anti-fibrotic, and immunomodulatory properties. Consequently, it emerges as a promising candidate for addressing inflammatory lung conditions, demanding further research into its

therapeutic potential and the underlying molecular mechanisms at play [55].

Aqueous decoction and hydroalcoholic extracts derived from *Waltheria indica* L. leafy stems were investigated for their bronchorelaxant effects. The study involved NMRI mice and Wistar rats, utilizing acetylcholine (ACh) and potassium chloride (KCl) as inducers. The concentration range for the extracts was not specifically stated but spanned from 10 to 3000 μg/mL. The results demonstrated that the extracts exhibited bronchorelaxant properties by inhibiting the concentration induced by ACh and KCl. Mechanistically, they were found to block receptor-operated calcium channels and open potassium channels, highlighting their potential as agents for managing airway hyperresponsiveness and warranting further exploration of their therapeutic applications [56].

In a study utilizing Sprague Dawley rats with OVA-induced asthma, an active fraction extracted from *Matricaria chamomilla* L., containing caffeoylquinic acid, flavonoids, coumarins, and alkaloids, was administered at doses ranging from 0.06 g/kg to 0.18 g/kg of body weight from day 43 to day 72. The study demonstrated several significant effects of this active fraction on the asthma model. Notably, it led to a reduction in eosinophil (EOS) count in bronchoalveolar lavage fluid (BALF), indicating a decrease in airway inflammation. It also reduced IgE levels, suggesting the suppression of allergic responses. Additionally, the treatment increased the levels of glutathione peroxidase (GSH-Px) in serum, ameliorating lung injury. Mechanistically, the active fraction neutralized reactive oxygen species (ROS) and reduced oxidative stress, contributing to its anti-inflammatory and antioxidant properties. Furthermore, it inhibited the release of chemical mediators and the synthesis of Th2-type cytokines, further supporting its potential as a therapeutic agent for asthma management and oxidative stress-related conditions [57].

In a Sprague Dawley rat model of OVA-induced asthma, a single dose of 10.0 ng/kg body weight of Cyclophilin A (CypA) was administered, with the injection taking place 10 min before the OVA challenge. This treatment exhibited several significant effects within the asthma model. Firstly, it resulted in a notable reduction in airway resistance, indicating an improvement in airflow and the relief of airway constriction. CypA also displayed an inhibitory effect on tracheal contraction, providing further evidence of its capacity to relax the airways. Additionally, CypA demonstrated the modulation of cytokines and immunoglobulins, with the suppression of IL-2, IFN-γ, IL-4, IL-10, and IL-13, all of which play pivotal roles in asthma pathogenesis. Furthermore, CypA effectively reduced the levels of immunoglobulins IgG, IgA, and IgM, underlining its potential as a therapeutic agent for asthma management and the mitigation of airway inflammation through the regulation of immune responses and airway functionality [58].

In a Sprague Dawley rats with OVA-induced asthma, the administration of vanilic acid, a compound derived from oxidized vanillin present in various Vanilla species, was carried out at doses of 20 and 50 mg/kg body weight. Commencing on day 15 and extending for a duration of 14 days, this treatment resulted in a range of significant effects within the asthma model. Most notably, vanilic acid led to a marked reduction in the infiltration of inflammatory cells, including macrophages, eosinophils, neutrophils, and lymphocytes, within the bronchoalveolar lavage fluid (BALF), indicative of a substantial decrease in airway inflammation. Furthermore, it demonstrated the capacity to reduce the levels of pro-inflammatory cytokines, encompassing TNF-α, IFN-γ, IL-4, IL-5, and IL-13, all closely associated with asthma pathogenesis. Moreover, vanilic acid exhibited the strengthening of antioxidant defenses by increasing the levels of antioxidant enzymes and glutathione (GSH) while simultaneously decreasing malondialdehyde (MDA) and reactive oxygen species (ROS) levels. These findings underscore the potential of vanilic acid as a therapeutic agent for mitigating airway inflammation, alleviating allergic and inflammatory responses, and enhancing antioxidant mechanisms [59].

In a study using Sprague Dawley rats with OVA and LPS-induced lung inflammation, a combination of herbal plant extracts including *Raphanus sativus* L. and *Codonopsis lanceolate* roots, *Allium hookeri* whole plant, *Acanthopanax sessiliflorum* stems, and *Dendropanax morbiferus* leaves was administered at doses ranging from 100 to 400 mg/kg of body weight. This treatment regimen, initiated from day 11 to day 16, led to notable effects on the lung inflammatory response. The herbal plant extract combination effectively modulated proinflammatory cytokines, contributing to a reduction in inflammatory cytokine levels in bronchoalveolar lavage fluid (BALF). Specifically, it regulated the production of key cytokines, including IL-1β, IL-6, and TNF-α, and ultimately resulted in the reduction of these cytokines. These findings highlight the potential of this combined herbal extract in mitigating lung inflammation and warrant further exploration for its therapeutic applications [24].

In a study conducted on Sprague Dawley rats with lung inflammation induced by OVA and cigarette smoke, Spirulina powder, derived from a filamentous alga, was administered at a dosage of 500 mg/kg of body weight over a period of 4 weeks. This treatment revealed multifaceted effects on lung health and inflammation. Spirulina powder demonstrated anti-inflammatory properties by inhibiting the activation and infiltration of eosinophils and lymphocytes, key contributors to lung inflammation. Furthermore, it reduced the levels of crucial pro-inflammatory cytokines, including IL-4, IL-5, and IL-13, contributing to an overall reduction in lung inflammation. Spirulina's antioxidant effects were also evident as it scavenged free radicals and protected lung tissue from oxidative damage. These findings underscore the potential of Spirulina powder as a therapeutic agent for managing lung inflammation and its associated oxidative stress and warrant further research into its immunomodulatory properties [60].

In an experimental model employing Sprague Dawley rats with OVA-induced lung inflammation, oral administration of an ethanol extract obtained from *Euphorbia hirta* leaves, at dosages of 100 μg/100 μl and 200 μg/100 μl over the course of five consecutive weeks, resulted in a multitude of noteworthy outcomes. The extract effectively brought about a reduction in various inflammatory markers and the modulation of mRNA expression, indicative of its anti-inflammatory properties. Furthermore, it exhibited anti-apoptotic effects through the reduction of critical pro-inflammatory molecules, including TNF-α, IL-6, and NO, while concurrently decreasing mRNA expression levels of TNF-α, IL-6, iNOS, and COX-2. Additionally, the extract exerted a modulatory influence on the mRNA expression of essential apoptosis-related genes, encompassing caspase-3, proNGF, p53, Bax, and Bcl-2. These findings collectively indicate the potential of *Euphorbia hirta* leaves as a therapeutic agent for the management of lung inflammation and the intricate molecular pathways associated with it, underscoring the need for further research to unlock its complete therapeutic potential [61].

In a study conducted with OVA-induced inflammation in Wistar rats, the administration of carvacrol, a type of polyphenol, at a dose of 15 mg/kg for 17 days demonstrated significant anti-inflammatory and immunomodulatory effects. This treatment resulted in

reduced levels of several key markers of inflammation and immune response, including AEC (absolute eosinophil count), IgE, IL-4, IL-5, IL-13, TNF-α, IFN-γ, iNOS (inducible nitric oxide synthase), and MDA (malondialdehyde), indicating a suppression of allergic and inflammatory processes. Furthermore, carvacrol increased the levels of antioxidant enzymes, specifically SOD (superoxide dismutase) and GSH (glutathione), in lung tissue. These findings suggest that carvacrol has the potential to alleviate airway inflammation, modulate immune responses, and enhance antioxidant defenses in the context of allergic lung inflammation, supporting its candidacy as a therapeutic agent for conditions like asthma. Further research is warranted to explore its full therapeutic potential [62].

In a study involving Wistar rats with OVA-induced inflammation, the use of estragole, a compound found in *Ocimum basilicum*, at concentrations ranging from 0.75 to 3 mg/mL for 21 days, exhibited significant anti-inflammatory and immunomodulatory effects. One of the key findings was the balancing of the Th1 and Th2 cytokines ratio, leading to an increase in the IFN-γ and IL-4 ratio. This rebalancing of immune responses indicates a potential shift towards a more regulated and controlled immune reaction. These results suggest that estragole from *Ocimum basilicum* has the potential to modulate immune responses, making it a candidate for further exploration as a therapeutic agent for conditions involving immune dysregulation, including allergies and asthma. Further research is needed to fully understand its mechanisms and therapeutic potential [63].

In a study conducted on Wistar rats with OVA-induced inflammation, the administration of a stems and leaves extract from *Nasturtium officinale* at a dosage of 500 mg/kg for 7 days exhibited strong anti-inflammatory properties. The extract was found to attenuate inflammation and alveolar injury, suggesting its potential in mitigating lung inflammation and related conditions. Additionally, it increased the activity of glutathione peroxidase (GPX), an antioxidant enzyme that plays a key role in protecting cells from oxidative damage. These findings highlight the therapeutic potential of flavonoids present in *Nasturtium officinale* as a means to reduce inflammation and enhance antioxidant defenses in lung tissue. Further research is needed to explore its full range of applications and mechanisms of action [64].

In a study involving Wistar rats with OVA-induced asthma, the administration of E-ethyl *p*-methoxycinnamate, a flavonoid found in *Kaempferia galanga* L., at doses of 200 and 400 mg/kg from day 26–34, demonstrated potent anti-asthma effects. Notably, the treatment reduced the expression of TGF-β1, a cytokine associated with tissue fibrosis. These findings suggest that E-ethyl *p*-methoxycinnamate derived from *Kaempferia galanga* L. holds promise as a therapeutic agent for alleviating asthma symptoms and potentially preventing fibrotic changes in lung tissue. Further research is warranted to fully understand its mechanisms of action and clinical applications [65], and the human studies evidences of natural products for asthma are summarized in Table 3.

Polyphenols: Polyphenols such as shogaols and gingerols found in *Zingiber officinale* (ginger) demonstrate anti-inflammatory properties by reducing eosinophilia, mucus production, and levels of Th2 cytokines in OVA-induced inflammation models.

Prenylated Chalcones: Compounds like Renifolin F derived from *Shuteria involucrata* exhibit significant anti-inflammatory effects, reducing airway hyperresponsiveness and inhibiting mucin levels and inflammatory factors associated with asthma.

Alkaloid-Rich Extracts: Extracts containing alkaloids such as erysotrine, erysotrine-N-oxide, and hypaphorine from *Erythrina mulungu* Benth. demonstrate anti-inflammatory effects by reducing bronchial hyperresponsiveness, leukocyte levels, and key Th2 cytokines while increasing IFN-γ levels.

Honey: Multifloral honey exhibits anti-inflammatory properties, reducing inflammatory cell infiltration and beta-hexosaminidase levels in bronchoalveolar lavage fluid (BALF), thus alleviating inflammation in asthma.

Carotenoid Acids: Bixin derived from *Bixa orellana* seeds demonstrates anti-inflammatory effects by reducing airway inflammation, hyperresponsiveness, and inhibiting inflammatory signaling pathways.

Coumaric Acid Esters: Compounds like Methyl P-coumarate show promise in inhibiting immune cell recruitment, regulating Th2 cytokines, and modulating the secretion of various inflammatory molecules, offering potential for mitigating inflammation and allergic reactions.

Flavonoids: Tilianin, Mangiferin, and Lonicerin exhibit anti-inflammatory effects by reducing Th2 cytokines, inflammatory cell infiltration, and mucus hypersecretion in asthma models.

Polysaccharides: Cordyceps polysaccharide and Platycodi radix extracts modulate immune responses, reduce inflammatory cell infiltration, and inhibit key cytokines associated with asthma.

Miscellaneous Compounds: Rutin, Sinomenine, Eupatilin, Anthraquinone-rich extracts, and flavonoid combinations demonstrate potential in reducing airway inflammation, modulating immune responses, and inhibiting inflammatory pathways.

Flavonoids and Phenolic Compounds: Natural products such as flavonoids and phenolic acids found in plants like *Euphorbia cuneata*, *Vitex negundo* Linn., *Matricaria chamomilla* L., and vanilic acid from Vanilla species exhibit potent anti-inflammatory and antioxidant effects. These compounds modulate inflammatory pathways, reduce oxidative stress, and suppress allergic responses, making them valuable in asthma management.

Herbal Extracts and Plant Compounds: Extracts from plants like *Waltheria indica* L., *Raphanus sativus* L., *Codonopsis lanceolate* roots, *Allium hookeri*, *Acanthopanax sessiliflorum* stems, *Dendropanax morbiferus* leaves, and *Nasturtium officinale* possess bronchorelaxant, anti-inflammatory, and antioxidant properties. These herbal extracts regulate cytokine production, inhibit airway hyperresponsiveness, and enhance antioxidant defenses, offering potential therapeutic benefits for asthma.

Algal Products: Compounds derived from algae, such as Spirulina powder, demonstrate anti-inflammatory and antioxidant effects in asthma models. Spirulina powder inhibits eosinophil infiltration, suppresses pro-inflammatory cytokines, and scavenges free radicals, suggesting its usefulness in managing asthma-related inflammation and oxidative stress.

Specific Compounds: Certain compounds like Cyclophilin A (CypA) and E-ethyl *p*-methoxycinnamate show promise in asthma treatment by modulating immune responses and inhibiting fibrotic changes in lung tissue, respectively.

Other Polyphenols: Polyphenolic compounds like carvacrol from *Ocimum basilicum* exhibit anti-inflammatory, immunomodulatory, and antioxidant properties, indicating their potential in alleviating airway inflammation and oxidative stress associated with asthma.

3.3. Human researches claim clinical evidences of natural products for asthma medication

In the past decade, there had been little number of human clinical trials on the usage of natural product to ameliorates asthma symptoms had been presented, all within the experimental model of double-blind randomized placebo-controlled trials. Extracts of natural products in clinical trials were prepared by its solubility in either ethanol or distilled water or was readily available in forms of capsules of certain commercial products. Observation done on its effect within the clinical trials were limited to patients physiological behaviour upon receiving treatments on a regular interval. Efficacies and pathophysiologies of said extracts were derived from in-vitro and in-vivo research and was corelated with the results of the clinical trials.

The study about *Punica granatum* (pomegranate) extracts, given at 500 mg/day for 8 weeks showed significant decreased levels of neutrophil and eosinophil and improved levels of clinical symptoms in patients with allergic asthma. The research presented that pomegranate extract improved breath shortness and limitation of asthma-related activities. Improvements toward clinical symptomps could be attributed to the decreased levels of neutrophil and eosinophil as they are involved in the pathogenesis of asthma.

In a clinical trial involving the use of herbal mixture (ASMATUS) of *Matricaria chamomilla*, *Althaea officinalis*, *Malva sylvestris*, *Hyssopus officinalis*, *Glycyrrhiza glabra*, *Ziziphus jujuba* on children showed significant decrease on severity of coughs and increase sleep quality compared to control groups. However, further studies should be done on interaction of active compounds between components of mixture, dose, duration of treatment, and ints effectiveness on different age groups.

Clinical trial conducted with *Curcuma longa* on moderate and severe asthma resulted in increase quality of sleep through less frequent nighttime awakenings, less frequent use of SAβAA, and better disease control after 3 and 6 months. Its improvement of clinical symptoms could be attributed to its anti-inflammatory and anti-oxidant effects tested of the bioactive compound curcumin. Other clinical trial showed that curcumin lowered patients nasal symptoms, airflow resistance, and lower levels of IL-4, IL-8, TNF-α, while increasing the number of IL-10 and ICAM.

Fruit Extracts: Extracts from fruits like *Punica granatum* (pomegranate) have shown efficacy in reducing levels of neutrophils and eosinophils, improving clinical symptoms such as breath shortness and limitation of asthma-related activities in patients with allergic asthma.

Herbal Mixtures: Herbal mixtures like ASMATUS, containing ingredients such as *Matricaria chamomilla*, *Althaea officinalis*, *Malva sylvestris*, *Hyssopus officinalis*, *Glycyrrhiza glabra*, and *Ziziphus jujuba*, have demonstrated a significant decrease in cough severity and improvement in sleep quality in children with asthma.

Curcuma longa (Turmeric): Clinical trials involving *Curcuma longa* have shown improvements in asthma symptoms, including better disease control, increased quality of sleep, reduced nasal symptoms, and airflow resistance. These effects are attributed to the anti-inflammatory and antioxidant properties of its bioactive compound, curcumin.

4. Discussion

Understanding the inflammatory processes involved in asthma is crucial for tailoring effective treatment strategies. Asthma triggers

Table 3
Clinical studies in human trials verify the efficacy of natural products in the treatment of asthma.

Classification	Compound/ Extract	Source	Experimental Model	Dose; Duration	Efficacy	Mechanism	Reference
Polyphenols	Ellagic acid and punicalagin	*Punica granatum*	Double-blind randomized placebo-controlled trial	250 mg twice per day (500 mg total)	anti-oxidant and anti-inflammatory	Inhibition of NF-κB	[66]
Others	Aqueous extract of mixture	*Matricaria chamomilla* *Althaea officinalis* *Malva sylvestris* *Hyssopus officinalis* *Glycyrrhiza glabra* *Ziziphus jujuba*	Double-blind randomized placebo controlled trial	5 mL 3x/day for 5 days	anti-asthma and anti-inflammatory	Regulation of IL-4, IL-6, IL-17, and IFN-ɣ secretion and balancing of Th1/Th2 cytokines.	[67]
Polyphenols	Curcumin	*Curcuma longa* L.	Double-blind randomized placebo controlled trial	20, 30, or 40/ mg/kg/day for 6 months	anti-inflammatory and anti-oxidant	Inhibition of COX-2, LOS, and iNOS Decreased levels of inflammatory cytokines Regulation of MAPKinase activation and prostaglandin D2 release Inhibition of NF-κB activation	[68]

initiate a cascade of events, releasing proinflammatory cytokines like tumor necrosis factor-α (TNF-α), interleukins (IL-2, IL-3, IL-4, IL-5), GM-CSF, prostaglandins, histamine, and leukotrienes from mast cells [69]. These molecules initiate airway inflammation and increase vascular permeability, leading to exudate and edema formation. Chemotaxis, mediated by selectins and integrins, brings leukocytes to the inflamed tissue, followed by neutrophils releasing LTB4, activating enzymes like COX-2 and LOX-5, leading to tissue damage via reactive oxygen species (ROS). This understanding informs tailored asthma treatments addressing both symptoms and underlying inflammation [70,79].

4.1. Inflammation and asthma

In asthma, airway epithelial cells play a pivotal role, responding to inflammatory triggers via specialized epithelial Toll-like receptors (TLRs). Antigen-presenting cells (APCs) internalize allergens, presenting them to naive T cells. Mast cells release bronchoconstrictor mediators upon IgE crosslinking. Myeloid dendritic cells process allergens, releasing chemokines attracting TH2 cells, which produce crucial cytokines. Eosinophils, NK cells, and ILC2s regulate inflammation and immune responses, impacting asthma pathogenesis [71].

The orchestration of allergic asthma pathogenesis involves various immune components. TH2 cells generate cytokines crucial for inflammation. Eosinophils contribute to inflammation resolution via lipid mediators and impact by several compounds. TGF-β regulates airway remodeling, while PDGF stimulates fibroblast and ASM proliferation. Airway epithelial cell injury triggers structural alterations, including angiogenesis and extracellular matrix degradation, underscoring inflammation's multifaceted nature in asthma [72].

Multiple compounds have shown promise in anti-asthma effects by targeting inflammatory mechanisms. They influence TLRs, prostaglandin, IgE, TH2 responses, cytokines like IL-4, IL-5, IL-9, eosinophils, TGF-β1, ASM, MMPs, offering potential avenues for asthma management by modulating immune responses and inflammation [73,74].

Eosinophils, in addition to their other roles, actively partake in the resolution of inflammation by generating pro-resolving lipid mediators such as PD1 and RvE3, which may also activate macrophages. Notably, patients with asthma may exhibit deficiencies in regulatory T (TReg) cells, potentially leading to an increased proliferation of TH2 cells. In this intricate landscape, TGF-β emerges as a central regulator of airway remodeling among individuals with asthma. Similarly, platelet-derived growth factor (PDGF) takes center stage as it stimulates the proliferation of fibroblasts and airway smooth muscle (ASM) in the context of asthmatic lung inflammation [73].

Furthermore, when airway epithelial cells sustain injury, they release stem-cell factor (SCF), which effectively promotes the differentiation of myofibroblasts and thus instigates structural alterations throughout airway-wall remodeling. These alterations encompass heightened angiogenesis, involving pro-angiogenic factors such as vascular endothelial growth factor (VEGF) and its receptors. Additionally, the dysregulation in the production of extracellular matrix metalloproteinases (MMPs) emerges as a pivotal factor in the degradation of the extracellular matrix during tissue remodeling within asthmatic airways. Collectively, these intricate mechanisms underscore the multifaceted nature of inflammation in asthma and its integral role in the pathogenesis of this disease [74].

Through the literature studies conducted, several products and compounds have undergone testing, either in vivo or in vitro, or through human clinical trials. The results indicate that these products or compounds can provide anti-asthma effects by targeting the inflammatory mechanisms that may occur during the asthma pathogenesis process. Mojobanchromanol, the aerial parts of *Euphorbia cuneata* extract, an ethanolic extract containing erysotrine, erysotrine-N-oxide, and hypaphorine, and *Cinnamomum* spp. Aqueous extract have shown promise in influencing Toll-Like Receptors (TLRs), crucial for recognizing and initiating defenses against pathogens. In the context of asthma, curcumin impacts Prostaglandin, which is essential for inflammation and various physiological processes, with potential implications for reducing airway inflammation.

Several compounds, such as Methyl P-coumarate, *Cordyceps* polysaccharide, Isorhyncophylline, *Cassia occidentalis* Linn. Ethanolic extract, Eupatilin, *Eriobotrya japonica* Leaf extract, an active fraction extracted from *Matricaria chamomilla* L., and Carvacrol, play a role in influencing IgE, a key player in allergic responses associated with asthma. Multiple compounds affect TH2 responses, pivotal in the adaptive immune response (Fig. 1). Interleukins IL-4 and IL-13, central to immune regulation and airway inflammation, are influenced by compounds like Renifolin F and *Cordyceps* polysaccharide. IL-5, involved in eosinophil activation, is influenced by compounds like Renifolin F and *Cordyceps* polysaccharide. IL-9 is affected by Renifolin F and Mangiferin. Eosinophils, central to allergies and asthma, are impacted by a range of compounds, including *Veronica persica* Ethanolic extract, ethanolic extract containing erysotrine, erysotrine-N-oxide, and hypaphorine, Isorhyncophylline, Eupatilin, Vanilic acid, Spirulina powder, 6-shogaol, 6-gingerol, Methyl P-coumarate, Tilianin, Total glucosides of Paeonia (TGP), and *Cassia occidentalis* Linn. Ethanolic extract*, and Pimpinella anisum* aqueous seeds extract.

Compounds like Bixin, Tilianin, *Cordyceps* polysaccharide, Mangiferin, *Vitex negundo* Linn. hydroalcoholic extract, and E Ethyl *p*-methoxycinnamate exert their effects on TGF-β1, which is critical in airway remodeling and inflammation in asthma. Isorhyncophylline affects Airway Smooth Muscle (ASM), relevant for airway constriction in asthma. Rutin influences Matrix Metalloproteinases (MMPs), which are linked to tissue remodeling and inflammation. These compounds collectively offer potential avenues for anti-asthma strategies by modulating immune responses and inflammation central to asthma pathogenesis and symptom management (Fig. 1).

4.2. ROS and asthma

Reactive oxygen species (ROS) significantly impact asthma, contributing to inflammation, airway remodeling, and

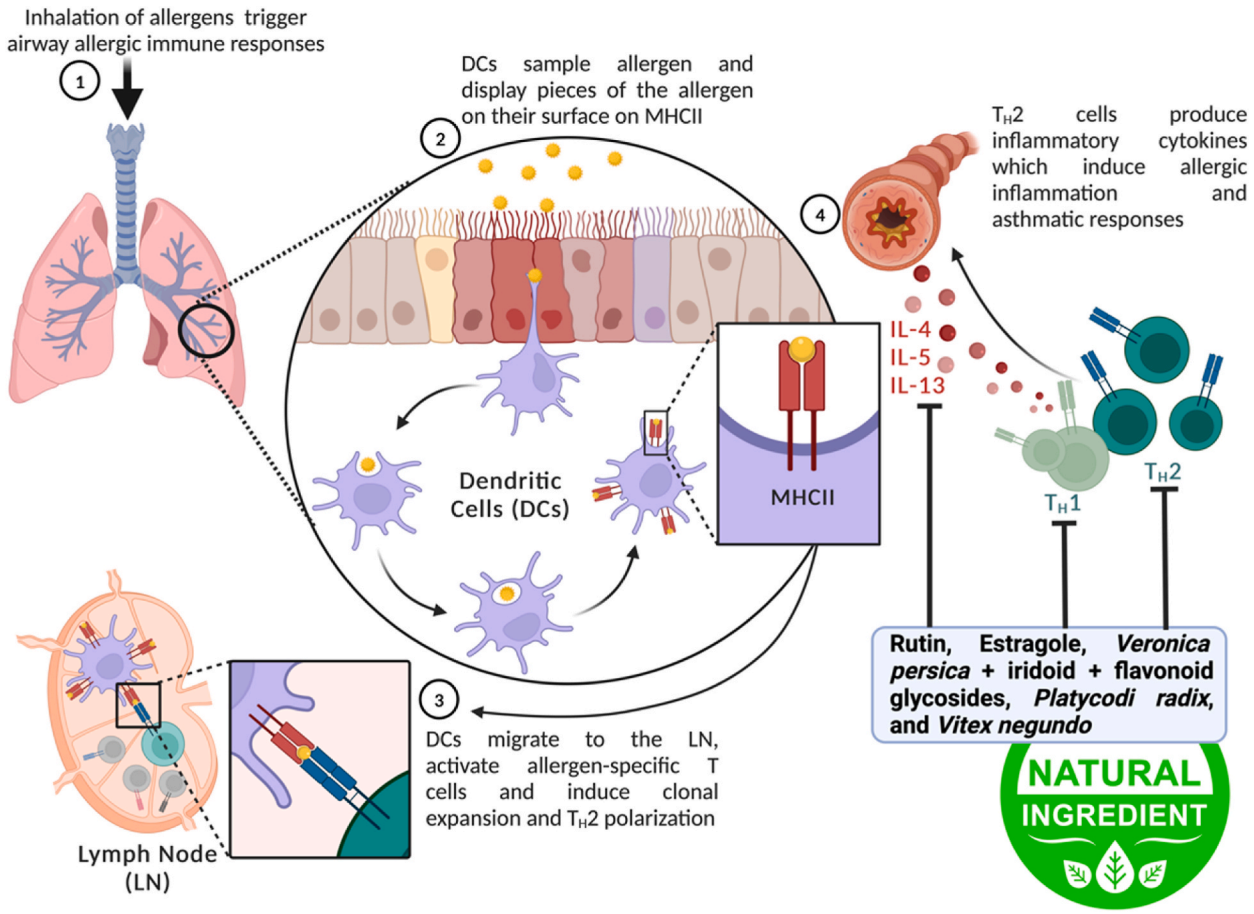

Fig. 1. The modulation and regulation of Inflammation-asthma by the natural products and their derivatives compounds.

hyperresponsiveness. Asthma-related inflammation is associated with oxidative stress (OS), driven by multiple pathways involving cytokines, lipid mediators, and granulocyte proteins. Redox-sensitive pathways and allergens play roles in ROS production, impacting inflammatory mediators, lung function, and airway hyperresponsiveness in asthma [75].

Literature suggests several products or compounds influence ROS-related mechanisms, attenuating oxidative stress. Chromenols like mojobanchromanol and sargachromenol exhibit antioxidant activities, lowering ROS levels by scavenging free radicals or upregulating antioxidant pathways. Other compounds also show antioxidant activities, offering potential in managing asthma symptoms by mitigating ROS effects.

Studies demonstrate ROS's critical role in asthma, affecting inflammation, airway remodeling, and hyperresponsiveness (Fig. 2). Both eosinophils and neutrophils are essential for ROS production via the oxidative burst, primarily through NOX-2. The imbalance in redox activity is also observed in airway epithelial cells, where DUOX-1, DUOX-2, and NOX-4 are overexpressed. These enzymes mediate ROS production in the lungs. Oxidation and nitration of manganese-superoxide dismutase (MnSOD) in asthmatic airways correlate with disease severity and hinder antioxidant defenses. Redox imbalance and mechanisms are central to asthma, impacting inflammatory mediators, epithelial damage, lung function, and airway hyperresponsiveness [76].

Redox-sensitive pathways such as NF-κB, AP-1, PI3K/Akt, JAK/STAT, and MAPKs are involved in asthma. Allergens can promote ROS production indirectly through immune and structural cell activation or directly via intrinsic mechanisms. For example, pollens contain NOX enzymes that contribute to airway ROS production. IL-4 and IL-13 activate non-canonical autophagy, leading to DUOX-2 trafficking and ROS production in airway epithelial cells. NOX-1 and NOX-2 also promote immunological cell responses in asthma. Redox-dependent mechanisms contribute to inflammatory mediators, epithelial damage, lung function reduction, and airway hyperresponsiveness in asthma [77].

Based on the literature review conducted, there are several products or compounds that can have an effect on mechanisms related to ROS, indirectly influencing the symptoms of asthma pathogenesis. Two studies on chromenols, particularly mojobanchromanol and sargachromenol, showed activities that could be attributed to attenuation of oxidative stress. Their antioxidant activities are derived from the chromanol ring ability to scavenge free radicals, lowering MDA levels and 8-OHdG on test subjects exposed to particulate matter [13,16]. Similar studies done indicated an upregulation of Nrf2/HO-1 resulting in downregulation of ROS on a transcriptional level through antioxidant response element [14,26]. Other studies showed antioxidant activities through SOD1, SOD2, GPx-1/2,

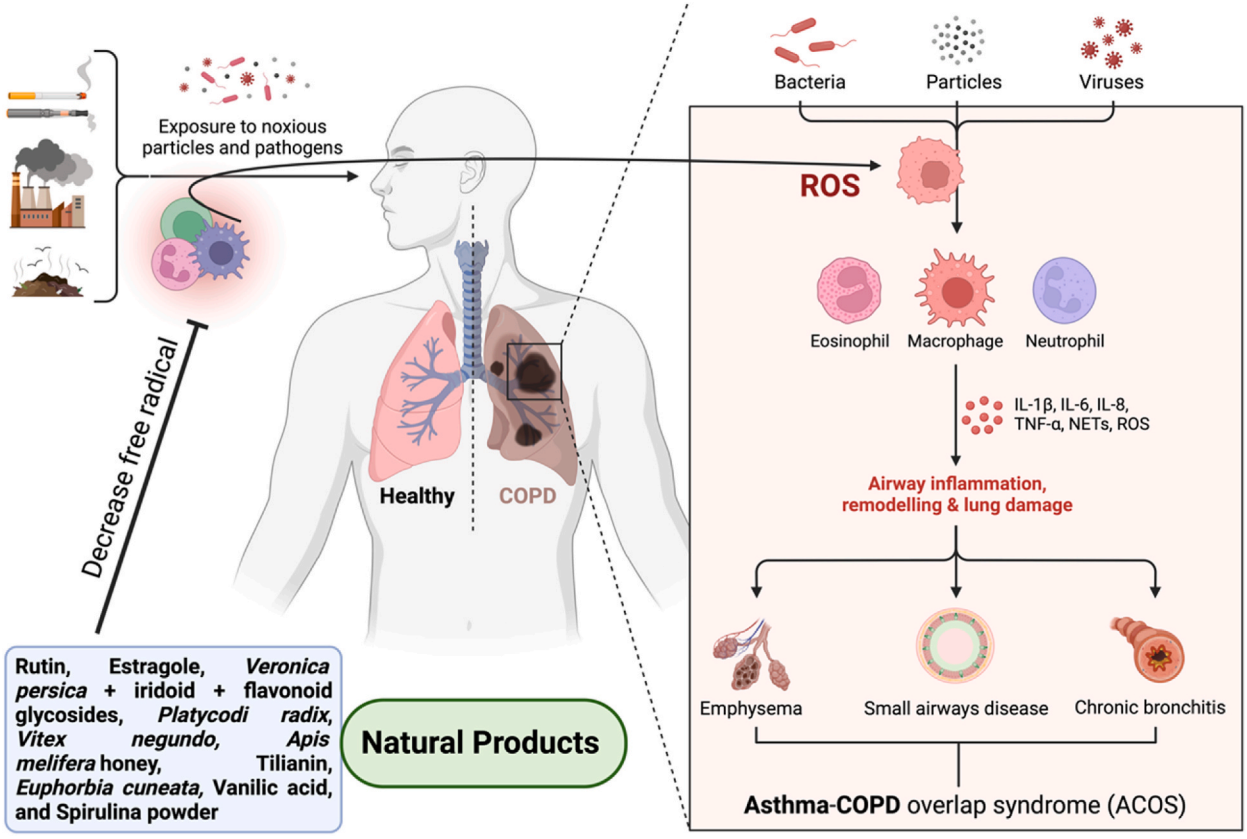

Fig. 2. Schematic diagram of ROS inhibitory activities in ACOS by natural product derivatives compounds. ACOS, Asthma-COPD overlap syndrome (ACOS).

or/and catalase [33,39,52,54,59,60,62,64]. Although unspecified, other studies also showed downregulation of ROS through its antioxidant activities [19–21,36,50,57,78]. All in all, antioxidant activities have direct effect on lowering the level of ROS through upregulation of Nrf2/HO-1, SOD1/2, GPx-1/2, and catalase, or through certain structural capabilities of certain group of compounds to bind free radicals.

5. Conclusions

This review discussed and highlighted the therapeutic benefits of several natural products on asthma comprehensively. Natural products were categorized using experimental methods such as in vivo, in vitro, and others. Interestingly, latest 59 studies on natural products with the potential to control asthma were examined. The results indicate that various products or compounds can provide anti-asthma effects by targeting the inflammatory mechanisms that may occur during the asthma pathogenesis process involving TLRs, Prostaglandin, Interleukins, IgE, TGF-β1, and MMPs. Then, there are several natural products or compounds that can have an effect on mechanisms related to ROS production, indirectly influencing the symptoms of asthma pathogenesis. It is exciting that natural remedies may one day be used to treat asthma via modern drug discoveries. More clinical studies on the use of such natural compounds are needed.

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Data availability statement

There is no data related to this review article or the data were only sourced from the literature listed in this article (Data included in

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CRediT authorship contribution statement

Dionysius Subali: Writing – original draft, Investigation, Conceptualization. **Rudy Kurniawan:** Writing – original draft, Investigation. **Reggie Surya:** Writing – original draft, Investigation. **In-Seon Lee:** Writing – review & editing, Formal analysis. **Sanghyun Chung:** Writing – review & editing, Formal analysis. **Seok-Jae Ko:** Writing – review & editing, Formal analysis. **Myunghan Moon:** Writing – review & editing, Formal analysis. **Jinwon Choi:** Writing – review & editing, Formal analysis. **Moon Nyeo Park:** Writing – review & editing, Supervision. **Nurpudji Astuti Taslim:** Writing – review & editing, Supervision. **Hardinsyah Hardinsyah:** Writing – review & editing, Supervision. **Fahrul Nurkolis:** Writing – original draft, Visualization, Supervision, Software, Investigation, Conceptualization. **Bonglee Kim:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Kwan-il Kim:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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