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REVIEW

Exploring the Therapeutic Role of Natural Products in Allergic Rhinitis Based on Pathophysiology and Signaling Pathways

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Abstract: Allergic rhinitis (AR) is a prevalent chronic inflammatory allergic disease, characterized by paroxysmal nasal congestion, itching, sneezing, and rhinorrhea, which affects mental health in severe cases. Western medical treatments primarily rely on glucocorticoids and antihistamines, which, while providing symptomatic relief, are associated with varying degrees of side effects and fail to ensure long-term efficacy. The pathogenesis of AR is intricately related to immune system dysregulation, and the treatment of AR has not yet been fully clarified. Natural products, having co-evolved with humans over millennia, boast structural diversity and rich biological activity, and they can precisely interact with intracellular targets such as enzymes, receptors, and ion channels, positioning them as a vital resource for therapeutic interventions. Notably, validated natural products often contain multiple active constituents, which confer broader therapeutic effects compared to single-component compounds. These constituents also exhibit lower acute toxicity than synthetic drugs, ensuring superior long-term. The synergistic interactions among their components endow them with dual potential for both prevention and treatment. Natural products modulate AR pathogenesis through various signaling pathways, addressing key etiological factors such as immune dysregulation, inflammatory responses, as well as oxidative stress. These developments will drive research and application of natural products in AR management, unlocking their untapped potential. This review systematically examines the mechanisms by which natural products regulate AR pathogenesis through signaling pathways, drawing on both animal studies and laboratory research, though clinical data are still relatively limited. By elucidating their specific mechanisms of action, this work not only provides novel insights for developing effective, long-term AR management drugs but also offers scientific guidance for experimental research and clinical application in AR therapeutics.

Keywords: allergic rhinitis, natural products, pathogenesis, signaling pathways, therapeutic mechanism

Introduction

AR is a chronic, non-infectious inflammatory condition of the nasal mucosa, typically triggered by allergen exposure that activates the body's immune response, resulting in allergic symptoms, and the primary allergens causing AR include animal dander, pollen, molds, and dust mites. Typical clinical symptoms encompass paroxysmal nasal congestion, itching, runny nose, frequent sneezing, and in severe cases, can escalate to allergic asthma, atopic dermatitis, affective disorders, or attention deficit hyperactivity disorder.[1] Surveys indicate that the global annual cost of AR is around $20 billion, with a prevalence rate of 10–30% among adults and up to 40% in children.[2] As globalization accelerates, the prevalence of AR is rising rapidly. The World Health Organization Working Group has identified AR as "a global health problem". This increasing prevalence poses a significant global health challenge, impacting both individuals and society at large.

Modern medicine posits that the pathogenesis of AR is intricately linked to immune dysregulation, inflammatory responses, and oxidative stress, though its exact mechanisms remain under investigation. Currently, scholars widely acknowledge that numerous biological pathways contribute to AR's onset and progression, most of which are related to

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the body's humoral immune regulation. When allergens infiltrate the body, they disrupt the original immune regulatory mechanisms, triggering allergic reactions that damage the nasal mucosa's structure, incite inflammation, and stimulate abnormal cellular secretion, and this, in turn, impairs capillary and circulatory functions, processes that can be initiated through various allergic pathways.[3] According to clinical treatment guidelines, modern medical therapy for AR predominantly employs combination therapy with drugs such as glucocorticosteroids (eg, fluticasone propionate, trimethoprim, and fluticasone furoate), antihistamines (eg, benadryl, loratadine, and levocetirizine), and leukotriene receptor antagonists (eg, zalustat, prilostat, and montelukast).[4] While these treatments effectively suppress nasal symptoms in the short term, they fail to prolong disease remission. Prolonged drug use raises concerns about potential drug dependence and adverse reactions, impacting patients' physical and mental well-being and potentially leading to doctor-patient conflicts. Immunotherapy, on the other hand, stands as the only potential causal treatment capable of altering AR's natural course and achieving long-term efficacy.[5] Currently, subcutaneous and sublingual immunotherapy are the most prevalent clinical routes. These involve repeatedly exposing patients to standardized allergen extracts at escalating doses, fostering immune tolerance. Consequently, subsequent exposure to the same allergen significantly reduces symptoms.[6] However, this therapy requires at least three years of continuous use, with some patients requiring extended treatment before observing initial benefits. This financial burden may strain some families, while long-term adherence demands high self-management skills from patients, as interruptions may compromise treatment efficacy.[7] In summary, despite advancements in AR treatment options, no curative drug therapy currently exists. Current approaches primarily focus on managing acute symptoms, all of which entail non-negligible side effects. Given AR's high prevalence and the limitations of existing treatments, there is an urgent imperative to identify novel, effective therapies.

Natural products, the result of millions of years of natural selection and evolution, originate from vast natural resources such as plants, microorganisms, and marine organisms, and these products boast unique structures and potent biological activities, positioning them as primary resources for drug discovery.[8] With the continuous advancement of technology and deepening research, it has been confirmed that natural products possess a wealth of pharmacological effects. These compounds can simultaneously target multiple stages of disease progression and address various conditions, making them particularly suitable for use as adjunctive therapies or in long-term symptom management. Their strong efficacy, synergistic effects, and low resistance development potential have garnered significant research attention, making them ideal for adjunctive therapies and long-term symptom management.[9] Currently, research on natural products primarily focuses on preclinical studies, such as animal experiments and in vitro models. However, significant variations in concentration, purity, and bioavailability among natural products pose considerable challenges to their application. Therefore, extensive toxicological and clinical studies are crucial. There is an urgent need for a standardized system to ensure the development of natural products with well-defined constituents, consistent quality, proven safety, and scientifically validated efficacy.[10] Signaling pathways represent molecular mechanisms for information transfer within and outside cells. Through a series of biochemical reactions, they convert external signals, such as hormones, growth factors, and environmental stimuli, into specific responses within the cell, thereby regulating cellular physiological functions.[11] So far, systematic summaries of natural product interventions in the pathogenesis and signaling pathways for treating AR are lacking. To address this gap, this paper conducted a systematic literature search using databases like PubMed, Web of Science, and Google Scholar. Keywords such as "AR", "hay fever", or "nasal allergy", and "natural products", "natural compounds", "biological products", "plant extracts", "naturally derived products" or "natural resources" were employed to retrieve relevant literature. Original studies focusing on AR were selected, while duplicates and other irrelevant literature were excluded, enabling a comprehensive review and compilation of existing research. This review centers on the current understanding of AR pathogenesis and the regulatory mechanisms by which various natural products modulate its pathology through specific signaling pathways. These insights will facilitate the identification of effective pathways for natural products to combat AR, enabling more precise and effective selection of natural compounds for targeted therapeutic outcomes. Additionally, they will provide valuable references for future experimental research and clinical applications.

Pathogenesis of AR

Current research on the pathogenesis of AR focuses on seven key areas: immune regulation, inflammation, mitochondrial function, intestinal flora, oxidative stress, cellular autophagy, and pyroptosis (Figures 1–3).

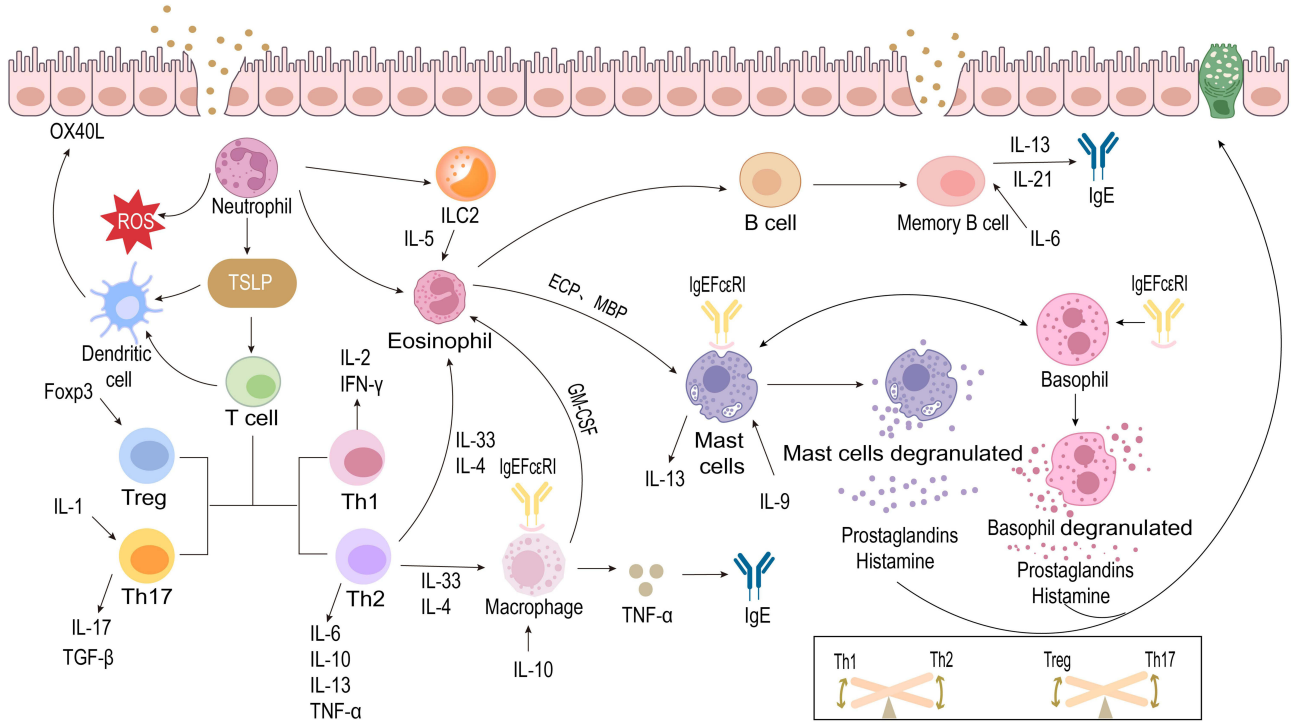

Figure 1 Immunomodulation and the inflammatory response. Nasal mucosa contact with allergens, destroying the original mucosal structure, when the violation of neutrophils, triggering oxidative stress, stimulating TSLP so that it affects the DC and T cells, resulting in the release of dendritic cells to destroy the mucosal immune function of OX40L; at the same time so that the T cells in the Th1, Th2, Treg and Th17 cells in the imbalance, the release of a large number of inflammatory factors, the counteracts the dendritic cells. Th2 cells release inflammatory factors (IL-33, IL4, IL-10) that act in conjunction with the IgE receptor on macrophages, causing them to release IgE and other inflammatory factors (TNF-α). GM-CSF released by macrophages, IL-5 released by ILC2 cells and Th2 cytokines together stimulate eosinophils. Factors in eosinophils (IL-5) stimulate B cells to become memory B cells with inflammatory factors to stimulate a large amount of IgE; ECP, MBP and inflammatory factors in eosinophils act on mast cells and basophils, causing them to degranulate and produce a large number of compounds, such as histamine, which stimulate the mucous membranes of the nasal cavity and aggravate the inflammatory response. https://www.adobe.com/.

Immunomodulation

Organismal Immunomodulation

The pathogenesis of AR is characterized by immune dysregulation triggered by allergen exposure. During the sensitization phase, inhaled allergens breach the mucosal epithelial barrier and are captured by dendritic cells (DCs). These DCs process and present antigens via MHC class II molecules to CD4+ T lymphocytes, disrupting the Th1/Th2 balance and Treg/Th17 homeostasis. This immune polarization results in an overproduction of Th2 cytokines, including IL-4, IL-5, and IL-13, and these cytokines, in turn, drive B cell differentiation into plasma cells, leading to the generation of allergen-specific IgE antibodies.[12] Upon re-exposure to the same allergen, the effector phase is initiated. IgE antibodies bind to high-affinity FcεRI receptors on mast cells and basophils, triggering rapid degranulation. This process releases preformed inflammatory mediators, such as histamine and tryptase, and newly synthesized ones, including leukotrienes and prostaglandins. These mediators act on the nasal vasculature, sensory nerve endings, and glands, producing characteristic early-phase symptoms like sneezing and rhinorrhea.[13] Allergen exposure also activates the NADPH oxidase system in granulocytes, prompting airway epithelial cells to secrete thymic stromal lymphopoietin (TSLP). This cytokine is pivotal in promoting DC migration to draining lymph nodes and upregulating OX40L expression, thereby amplifying Th2-mediated immune responses and establishing a self-perpetuating inflammatory loop.[14] Aberrant Th2 cell differentiation is of particular pathophysiological significance, as it sustains the overproduction of IL-4 and IL-13, leading to functional impairment of macrophages and monocytes. Furthermore, engagement of FcεRI receptors on these myeloid cells by IgE complexes further exacerbates the release of inflammatory mediators. This "IgE-FcεRI-cytokine" tripartite axis not only perpetuates nasal mucosal damage but may also contribute to central sensitization through neuroimmune cross-talk mechanisms.[15]

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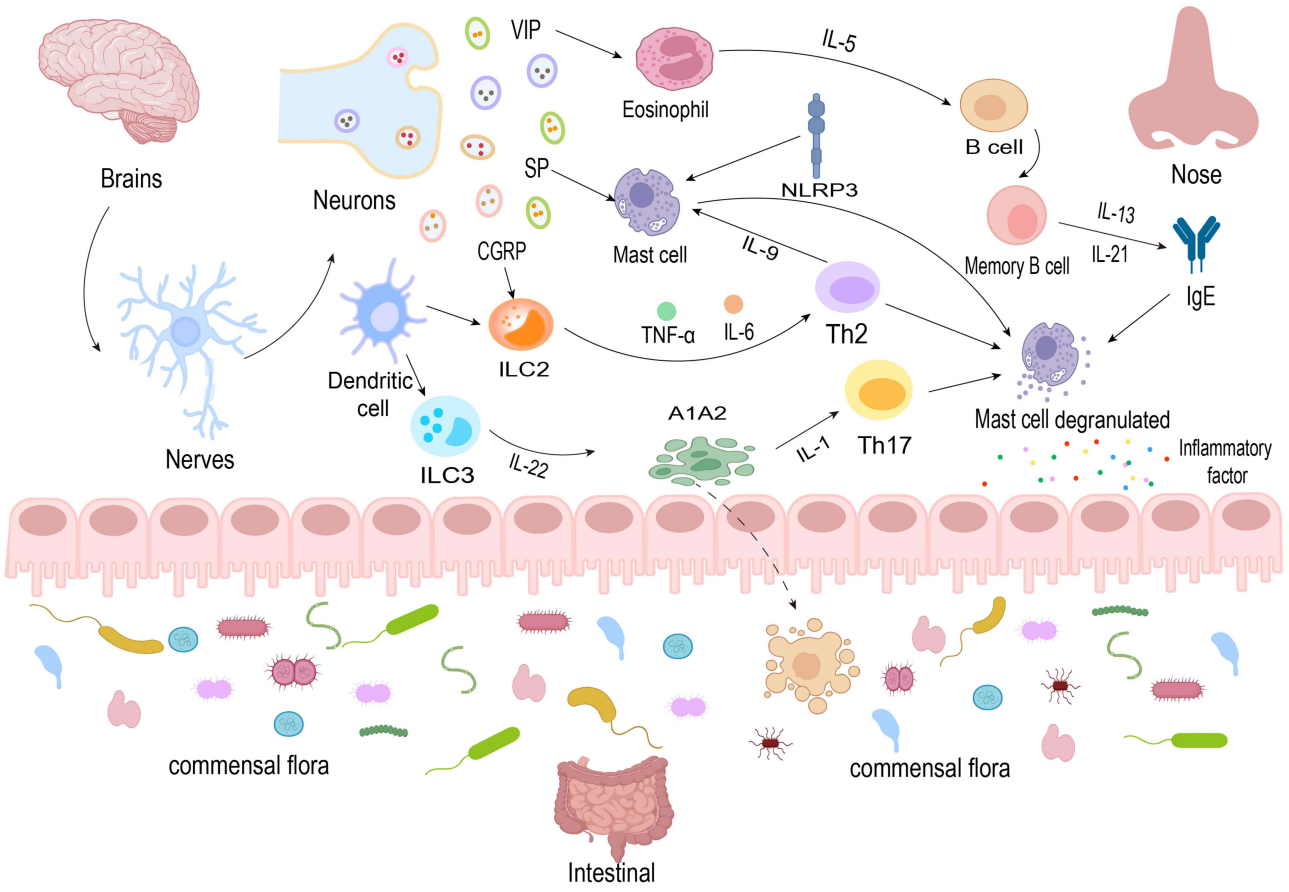

Figure 2 Neuroimmunity and intestinal flora. Allergens enter the nasal cavity, contact the nasal mucosa, stimulate the sensory nerves, parasympathetic nerves and sympathetic nerve endings of the nasal mucosa, and the signals from the nerve endings are transmitted to the ganglia of the brain, which cause the neurons to release a large number of neurotransmitters (SP, VIP and VGRP), and the neurotransmitters activate the immune cells to trigger an inflammatory response, producing a large number of inflammatory factors, which fight against the mucous membranes of the nasal cavity and destroy mucous membrane tissues. SFB induces ILC3 to produce IL-22, which induces the production of serum amyloid A1 and A2, altering the intestinal flora. https://www.adobe.com/.

Neuroimmunomodulation

In recent years, significant progress has been made in understanding the neuroimmune regulatory networks involved in the pathogenesis of AR. Research on the central-peripheral bidirectional regulatory mechanism and the peripheral nerve-immune network in AR has intensified.[16] Studies reveal that the nasal mucosa is innervated by a complex network of sensory, parasympathetic, sympathetic, peripheral sensory, and non-adrenergic non-cholinergic nerves. Transient receptor potential (TRP) channel ion channels, such as TRPV1, TRPA1, and TRPM8, are present on the surface of submucosal sensory nerve terminals.[17] When the nasal mucosa responds to external stimuli through a neuroimmune cascade, the parasympathetic nervous system becomes dominant, exciting sensory nerves and triggering the release of large amounts of neuropeptides from peripheral neurons. Abnormally released neuropeptides, including substance P, neuropeptide Y, and vasoactive intestinal peptide, not only accelerate the recruitment and activation of eosinophils (EOSs) and other core immune cells but also promote the release of inflammatory mediators, and these inflammatory signals are then transmitted throughout the body via nerves.[18,19] Building on the "lung-brain axis" hypothesis, the "nose-brain axis" theory has been proposed. According to this concept, nerve terminals innervating the nasal mucosa transmit external stimuli to the central nervous system (CNS), which integrates and relays signals to peripheral target organs, thereby modulating immune responses.[20] Focusing on the trigeminal nerve, studies suggest that it conveys stimulatory signals to the brainstem, inducing the release of neuropeptides that act on the CNS. Through hypothalamic-pituitary-adrenal (HPA) axis regulation, this process enhances efferent CNS signaling and lowers the threshold to external stimuli. Additionally, it modulates immune responses via the cholinergic anti-inflammatory pathway, ultimately reducing the body's sensitivity during the

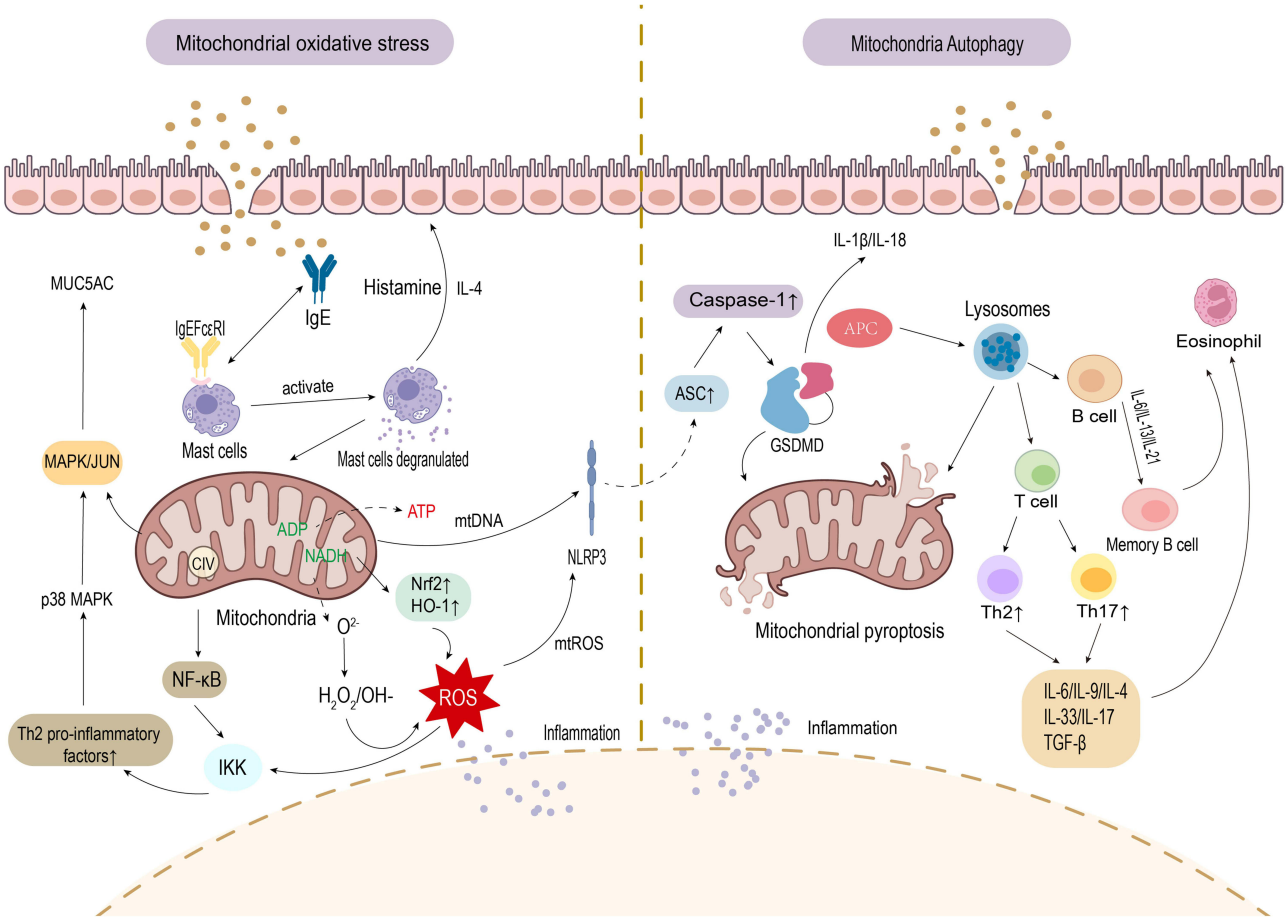

Figure 3 Mitochondrial oxidative stress and autophagy. Allergen destroys the original mucosal structure, IgE receptor binds to mast cells, causing mast cells to degranulate and release histamine and inflammatory factors, causing mitochondria to release O^{2-} and H_2O_2 to form oxidative damage, mitochondria down-regulate Nrf2, and up-regulate HO-1, which provokes oxidative stress, and at the same time, activate NF-κB, which promotes the inflammatory factors of Th2 cells, and activates the downstream MAPK/JUN signalling pathway. In addition, redox response and mitochondrial stimulation of NLRP3 inflammatory vesicles, up-regulation of ASC, activation of GSDMD initiated caspase-1-mediated pyrolysis pathway, which led to the release of inflammatory factors (IL-1β, IL-18) from GSDMD, and caused inflammatory response into the nucleus. The output of antigen-presenting cells (APC) to lysosomes causes B cells to transform into memory B cells in response to inflammatory factors (IL-6, IL-13 and IL-21), and lysosomes cause abnormal secretion of inflammatory factors by Th2 and Th17 cells in T cells, which activate eosinophils and exacerbate the metamorphic response. ↑ represents upregulation, ↓ represents downregulation. https://www.adobe.com/.

initial phase of allergic reactions while promoting their progression. This exacerbates symptoms such as nasal congestion and rhinorrhea and may even damage the olfactory nerve, leading to olfactory dysfunction.[21,22]

Inflammatory Response

Inflammation plays a pivotal role in the initiation, progression, and resolution of allergic diseases, including AR. AR disrupts cytokine homeostasis, leading to dysregulated immune responses. Upon allergen exposure, T lymphocytes exhibit aberrant secretion of intracellular cytokines, including those from Th1, Th2, Treg, and Th17 subsets. Notably, Th2 cells release excessive inflammatory mediators such as IL-4, IL-5, and IFN-γ, while Th17 cells produce elevated levels of IL-17 and TGF-β, each contributing distinctly to subsequent inflammatory cascades.[23] IL-4 is a pivotal cytokine in Th2 cell differentiation, particularly in vitro, where it stimulates B-cell and T-cell proliferation, enhances IgE secretion, and exacerbates inflammatory responses.[24] IL-5 promotes EOS proliferation, chemotaxis, and activation, triggering the release of cytotoxic proteins, including eosinophil cationic protein (ECP) and major basic protein (MBP). These proteins damage the nasal mucosa, increase glandular secretion, and induce clinical symptoms such as nasal congestion, pruritus, rhinorrhea, and sneezing.[25] Moreover, EOS-derived IL-5 establishes a self-perpetuating feedback loop, perpetuating chronic inflammation and contributing to the refractory nature of AR. IL-17, a pro-inflammatory cytokine secreted by activated CD4+T cells, plays a crucial role in early-phase inflammation by stimulating

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T-cell activation and promoting neutrophil recruitment through chemokine induction. It further amplifies inflammatory responses by enhancing the secretion of hematopoietic and pro-inflammatory cytokines from stromal cells.[26,27] Conversely, TGF-β suppresses Treg cell differentiation while favoring Th17 cell polarization. As a potent pro-inflammatory effector, Th17 cells exacerbate inflammation by recruiting inflammatory cells, sustaining acute-phase responses, and impairing immune cell maturation. This process not only increases inflammatory mediator expression in the nasal mucosa but also drives tissue remodeling.[28,29] Growing evidence suggests that minimal persistent inflammation (MPI) underlies AR recurrence. Whether mediated by Th17, Th1/Th2 imbalance, or type 2 innate lymphoid cells (ILC2s), MPI sustains a Th2-dominant microenvironment. This latent Th2 bias may facilitate the premature accumulation of allergen-responsive cells in the nasal mucosa, priming the tissue for rapid and exaggerated reactions upon re-exposure to allergens, thereby intensifying symptom severity.[30,31]

Intestinal Flora

The gut represents the primary site for host-microbiome interactions, with the host immune system continuously shaped by intestinal flora throughout life. Under normal conditions, the gut microbiota maintains a dynamic balance, fortified by the mucus barrier, epithelial barrier, and immune barrier. The immune barrier encompasses gut-associated lymphoid tissues (GALT), the lamina propria, and intraepithelial lymphocytes (IELs), involving key immune cells such as intestinal epithelial cells (IECs), DCs, regulatory T cells (Tregs), Th17 cells, and ILC2s.[32] Emerging evidence suggests that gut microbial antigens can be transported to the thymus via DCs, facilitating interactions between microbes and T cells within the thymic microenvironment. This indicates that alterations in gut microbiota can disrupt the balance between effector T cells and Tregs.[33] Disruptions in microbial colonization, such as delayed colonization, reduced diversity, or structural dysbiosis, may impair intestinal metabolism and compromise mucosal immune tolerance. Through the "gut-organ axis", pathogenic microbes can dysregulate innate and adaptive immune responses, modulate immune mediators, and contribute to the pathogenesis of allergic diseases. The crosstalk between T/B cells and the gut microbiota stimulates mucosal immunity, which defends against exogenous pathogens while maintaining immune tolerance and homeostasis. For instance, segmented filamentous bacteria (SFB) colonizing the ileal epithelium induce interleukin-22 (IL-22) secretion by ILC3s. IL-22. This, in turn, upregulates intestinal epithelial production of serum amyloid A1/A2, driving Th17 cell differentiation and disrupting the Th17/Treg equilibrium.[34,35] Furthermore, proteobacteria-stimulated IECs secrete IL-25, IL-33, and TSLP, activating ILC2s and enhancing TNF-α secretion. This cascade promotes type 2 inflammatory mediators, shifts IgA-to-IgE class switching, and recruits EOSs, polarizing the immune response toward a Th2 phenotype and exacerbating allergic manifestations, including nasal congestion and rhinorrhea.[36]

Mitochondria

Mitochondria, double-membrane-bound organelles with outer and inner lipid bilayers, serve as the metabolic hub of eukaryotic cells, and they orchestrate critical physiological processes, including energy production, redox balance, calcium signaling, and cellular homeostasis. Mitochondria generate most cellular adenosine triphosphate (ATP) through oxidative phosphorylation, a process that also produces reactive oxygen species (ROS). Beyond their metabolic roles, mitochondria have emerged as key regulators of inflammatory responses. Pathological mitochondrial alterations lead to the extracellular release of mitochondrial components, which act as damage-associated molecular patterns (DAMPs) to drive innate immune activation through multiple mechanisms. Notably, overproduction of mitochondrial ROS (mtROS) induces oxidative stress through free radical accumulation, causing mitochondrial and cellular damage. This triggers the expression of proinflammatory cytokines, enhances cellular sensitivity to inflammatory stimuli, and promotes inflammasome activation, a pivotal mechanism in various inflammatory disorders.[37] Oxidative stress bidirectionally regulates mitochondrial physiology, inducing structural and functional alterations that compromise mitochondrial integrity. Current evidence implicates ROS as a central signaling molecule in NLRP3 inflammasome activation. In AR, damaged mitochondria exhibit increased mtROS production, which potently activates the NLRP3 inflammasome and exacerbates disease progression. Conversely, mitochondria possess quality control mechanisms, notably mitophagy, which is the selective clearance of damaged organelles via autophagosome-lysosome pathways. This protective mechanism limits

excessive ROS generation and suppresses inflammatory cascades, highlighting the dual role of mitochondria in both promoting and resolving inflammatory responses.[38,39]

Oxidative Stress

Redox imbalance is a defining characteristic in the pathogenesis of numerous diseases, including AR, where airway inflammation is accompanied by a disruption in the oxidation-antioxidant balance.[40] Allergen exposure triggers a cascade of immune responses, creating a pro-inflammatory environment marked by excessive generation of oxygen-free radicals. When generated in excess, these reactive species can exert cytotoxic effects across various organ systems. Under physiological conditions, endogenous antioxidant defenses maintain redox homeostasis by neutralizing free radicals. However, persistent inflammatory stimulation tips the balance towards oxidative dominance, leading to a state of oxidative stress.[41,42] This condition initiates two interconnected pathological cycles: (1) the activation of inflammatory pathways that promote cell-mediated immunity within an oxidative microenvironment, and (2) increased production of ROS that induces tissue damage and aberrant pathophysiology. Notably, oxidative stress and inflammation mutually reinforce each other. The oxidative environment activates inflammatory cells and their signaling pathways, resulting in heightened production of pro-inflammatory mediators.[43,44] This positive feedback loop rapidly escalates inflammatory responses, thereby worsening disease progression in AR.

Autophagy and Pyroptosis

Autophagy-related regulatory proteins are crucial in modulating key cellular processes, including inflammatory responses, immune function, cell proliferation, and apoptosis.[45] Under normal physiological conditions, basal autophagy maintains cellular homeostasis and supports cell survival. However, excessive autophagy, triggered by intracellular or extracellular stimuli such as infection, oxidative stress, or nutrient deprivation, can lead to uncontrolled degradation of cellular components, resulting in autophagic cell death and contributing to disease pathogenesis.[46] Emerging evidence links autophagy to the development of AR. Upon allergen exposure, antigen-presenting cells (APCs) employ autophagy to engulf and degrade antigens in lysosomes. Autophagosomes facilitate the delivery of exogenous antigens to lysosomes, serving as a vital source of MHC class II antigens. In naïve T cells, autophagy levels influence differentiation pathways, suggesting a regulatory role in T cell development and selection. In mature T cells, autophagy is essential for maintaining homeostasis, survival, and effector functions. Autophagy modulates the quality and magnitude of T cell responses; for instance, T cell receptor (TCR) stimulation upregulates autophagy activity, while deficiencies in autophagy genes impair T cell generation and proliferation in response to antigenic challenge. These disruptions further alter T helper (TH) cell polarization, which is closely linked to AR pathogenesis. Additionally, autophagy affects nasal mucosal epithelial cells, vascular permeability, and glandular secretions, collectively exacerbating AR symptoms.[47,48]

In recent years, pyroptosis has become a focal point of research across various disciplines, particularly in the study of allergic, inflammatory, and immune-related diseases. Accumulating evidence suggests that activation of the NLRP3 inflammasome in nasal mucosal epithelial cells triggers both canonical (caspase-1-dependent) and non-canonical (caspase-4/5/11-mediated) pyroptotic pathways. This activation leads to the cleavage of gasdermin proteins (GSDMD or GSDME), resulting in pore formation in the plasma membrane, cellular lysis, and subsequent release of pro-inflammatory cytokines. These events collectively amplify the inflammatory cascade and cause tissue damage. Furthermore, caspase-3 and caspase-8 have been implicated in promoting allergic responses through alternative pyroptotic mechanisms. The release of interleukin-1β (IL-1β) during pyroptosis enhances dendritic cell activation and drives Th2 cell polarization, thereby exacerbating allergic inflammation. Additionally, high-mobility group box 1 (HMGB1) released from pyroptotic cells activates sensory nerve endings via toll-like receptor 4 (TLR4) signaling, further aggravating neurogenic inflammation.[49,50]

Cell Signaling Pathways

The signaling pathways targeted by natural products in the treatment of AR predominantly include the NF-κB pathway, TLR4/NF-κB pathway, MAPK pathway, PI3K/Akt pathway, IL-33/ST2 pathway, JAK/STAT pathway, AMPK pathway, Notch pathway, TGF-β/Smads pathway, and Nrf2/HO-1 pathway (Figure 4).

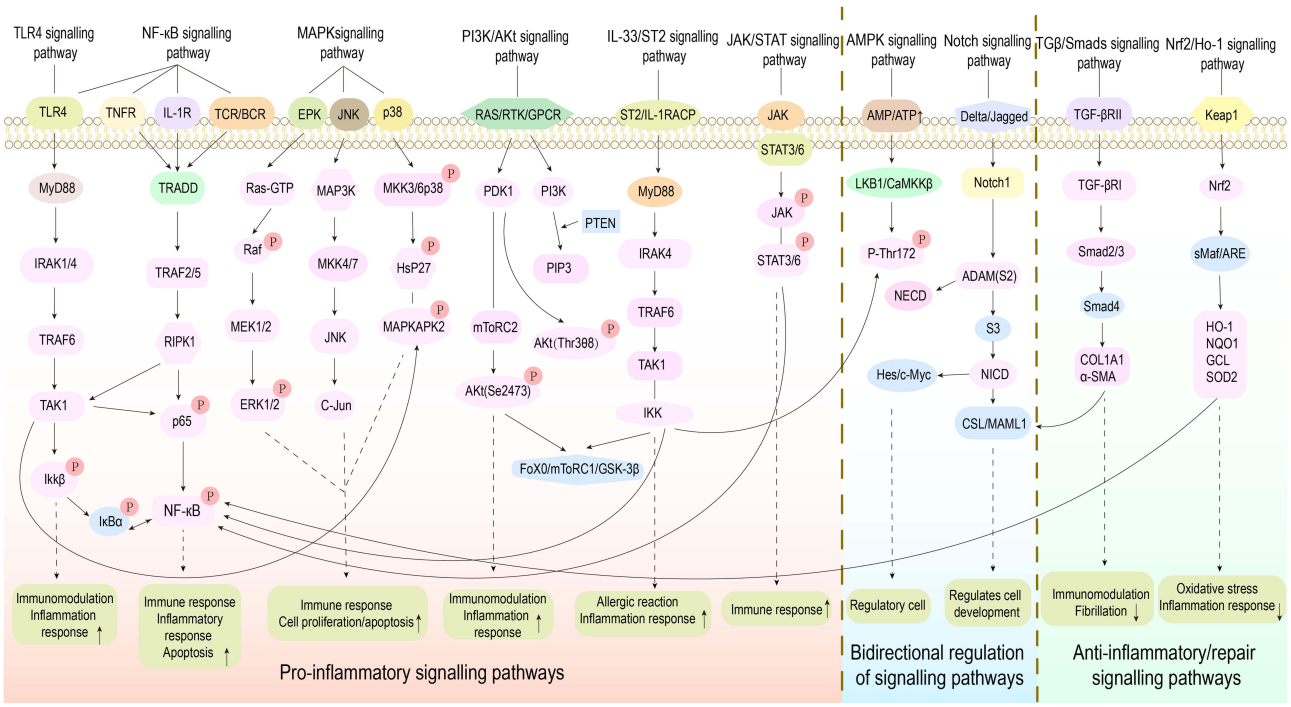

Figure 4 Signalling pathways associated with AR. Pink: Indicates that the protein stability/activity or gene expression level of this molecule is upregulated or enhanced following pathway activation. Blue: Indicates that the protein stability/activity or gene expression level of this molecule is downregulated, degraded, or inactivated following pathway activation. Other colours: indicates that the molecule serves as a key scaffold, structural component, or DNA element, with its expression levels remaining largely unchanged. ↑ represents upregulation, ↓ represents downregulation. https://www.adobe.com/.

NF-κB Signaling Pathway

NF-κB Signaling Pathway in Relation to AR

The NF-κB pathway is a pivotal regulator in chronic inflammation, playing key roles in physiological and pathological processes such as inflammation, immunity, cell survival, and proliferation. In a resting state, NF-κB dimers bind to the inhibitory protein IκBα, forming inactive trimeric complexes stored in the cytoplasm. Upon exposure to allergens like dust mite Der p1 or stimulation by pro-inflammatory factors and oxidative stress, the original equilibrium between the resting and activation states is disrupted, resulting in the phosphorylation and proteasomal degradation of the IκB kinase (IKK) complex, allowing NF-κB to translocate into the nucleus, accelerating the inflammatory signaling, triggering a cascade that over-releases inflammatory factors (IL-4, IL-6, IL-10, and TNF-α), creating an inflammatory response environment, while interfering with the maturation and migration of DCs, affecting the dynamic balance among T cells, and exacerbating the immune cell imbalances in AR.[51] Studies have confirmed that activation of the NF-κB pathway alters the immunogenicity and tolerance of DCs, up-regulates GATA3 expression, and over-expresses pro-inflammatory factors in Th2 and Treg cells, thereby triggering inflammation and immune responses that affect the development of AR.[52]

Natural Products Modulate the NF-κB Signaling Pathway for the Treatment of AR (Table 1)

Astragalus Polysaccharide (APS), the main active ingredient extracted from Astragalus, is a heteropolysaccharide with various pharmacological activities, including immunomodulation, anti-inflammation, and antioxidant effects.[67] In OVA-induced AR model mice, APS down-regulated the overexpression of NF-κB, inhibited the levels of immunity factors sIgE, sIgG1, and Th2 cytokines TNF-α and IL-6 in serum, thus restoring the imbalanced CD25Foxp3Treg/CD4IL17Th17 ratio, altering T-cell differentiation, and effectively blocking allergen induction, reducing the inflammatory response, controlled AR severity, and reducing the number of sneezing and nasal rubbing in rats.[53]

Table 1 Natural Products Treats AR by Interfering with the NF-κB Signalling Pathway

Natural Products	Causality	Subjects	Dose	Mechanisms of Action	References
Astragalus Polysaccharide	Polysaccharides	Guinea pig	400mg/kg/d	OVA-sIgE↓, OVA-sIgG1↓, TNF-α↓, IL-6↓, IL-17↓, TGF-β↓, IL-10↓, Foxp3↓, CD25Foxp3Treg↑, CD4IL17Th17↓, NF-κB p65 mRNA↓	[53]
Baicalin	Flavonoids	BALB/c mice, Mast Cells	50mg/kg/d, 200mg/kg/d	Histamine↓, β-hexokinase↓, JAK2↓, p-JAK2↓, STAT5↓, p-STAT5↓, IKKβ↓, p-IKKβ↓, IκBα↓, p-IκBα↓, NF-κB p65↓, ECP↓, IL-1β↓, IL-6↓, IL-8↓, TNF-α↓	[54]
Tripterine	Furan hydroxyketones	SD rats	120mg/kg/d	Eotaxin↓, NF-κBp65↓	[55]
Tanshinone IIA	Fat-soluble phenanthrenequinone	C57BL/6 mice, RBL-2H3 cell	2mg/kg/d, 10mg/kg/d, 50mg/kg/d	Histamine↓, Ca^{2+}↓, IL-4↓, TNF-α↓, GATA3↓, IgE↓	[56]
Saikosaponin A	Triterpenoid saponin	BALB/c male mice	2mg/kg/d, 10 mg/kg/d	IgE/IgG1↓, ROR-γt↓, STAT3↓, NF-κB p65↓, IL-6↓, IL-17↓	[57]
Piperine	Alkaloid	BALB/c mice	50mg/kg/d, 100mg/kg/d, 200mg/kg/d	NF-κB p65↓, IκBα↓, TNF-α↓, IL-1β↓, STAT3↓, RORc↓, IL-17A↓, IL-5↓, IL-13↓, IL-6↓, IL-10↑, IFN-γ↑, IL-12↑, macrophage↓, neutrophil↓	[58]
Rosmarinic acid	Phenolic acid	Sprague Dawley rats	20mg/kg/d	sIgE↓, NF-κB p65↓, IκBα↓, T-bet mRNA↑, INF-γ↑, IL-4↓, IL-13↓, GATA-3 mRNA↓	[59]
Chimonanthus nitens Oliv	Alkaloid	Sprague Dawley rats	10mg/kg/d	IL-6↓, NF-κB↓, STAT6↓, GATA-3↓, p-p65↓, STAT4↑, T-bet↑	[60]
Fructus Amomi extract	Flavonoids	BALB/c male mice	200mg/kg/d	Mast cell↓, B cell↓, IL-6↓, TNF-α↓, IgE ↓, IgG_1 ↓, IFN-γ↑, NF-κB↓, p-NF-κB↓, p-IκB↓, NF-κB ↓, Histamine↓	[61]
Fucoxanthin	Carotenoids	BALB/c male mice	10mg/kg/d, 20mg/kg/d	NF-κB p65↓, IκBα↓, STAT-3↓, IL-17A↓, IL-5↓, IL-6↓, IL-12↓	[62]
Manoalide	Sesquiterpenoids	HMC-1 cell	20mg/kg/d	Caspase-1↓, IL-1β↓, Thymic stromal lymphopoietin↓, NF-κB↓, IL-6↓, IL-8↓	[63]
Glycyrrhizin	Dihydroflavone monomers	Human nasal epithelial cells(HNEpCs)	20μM/d, 40μM/d	p-NF-κB p65↓, p-IκBα↓, MUC5AC↓, AQP5 ↓	[64]
Curcumin	Diketones	Human nasal epithelial cells(HNEpCs), BALB/c mice	100mg/kg/d, 200mg/kg/d	Mast cell↓, IgE↓, TNF-α↓, I-KBα↓, p-NF-κB p65↓	[65]
Catechin	Flavanols	Human nasal epithelial cells(HNEpCs), BALB/c mice	75mg/kg/d, 150mg/kg/d, 300mg/kg/d	IL-5↓, IL-13↓, IgE↓, IκBα↓, NF-κBp65↓	[66]

Notes: ↑ represents upregulation, ↓ represents downregulation.

Baicalin, a flavonoid extracted from the root of *Scutellaria baicalensis*, exhibits anti-inflammatory and anti-metamorphic effects, showing good therapeutic potential for inflammation-induced diseases.[68] In vitro and in vivo studies have demonstrated that baicalin regulates the transcription of target genes encoding inflammatory mediators by blocking the phosphorylation of IκBα and the nuclear translocation of the NF-κBp65 subunit in LPS-stimulated human mast cells, and it reduces the levels of OVA-induced guinea pig serum ECP, IL-1β, IL-6, IL-8, TNF-α, and IgE, prevents histamine and β-hexosaminidase release, inhibits tissue swelling, dilates small blood vessels, and reduces gland proliferation in mice, thereby alleviating allergic symptoms. This suggests that baicalin may be able to treat AR by inhibiting the NF-κB signaling pathway.[54]

Tripterine, a furan hydroxyketone compound extracted from *Radix et Rhizoma Polygoni Multiflori*, is a pentacyclic triterpenoid monomer with antioxidant, anti-inflammatory, and immune-suppressive activities.[69] It reduces the expression

of EOS chemokines and inhibits the overexpression of the NF-κB subunit in mice, thereby decreasing EOS aggregation and activation caused by Eotaxin and reducing allergic reaction pathogenesis, and this alleviates nasal mucosa swelling and reduces inflammatory cell infiltration, suggesting that tripterine may serve as a new drug to regulate the NF-κB signaling pathway.[55]

Tanshinone IIA, a fat-soluble constituent of the dried roots and rhizomes of *Salvia miltiorrhiza*, exhibits a wide range of biological activities, including improving microcirculation and scavenging oxygen-free radicals.[70] In AR mice, tanshinone IIA reduced histamine and Ca2+ release, down-regulated GATA3 expression, and decreased levels of downstream inflammatory factors IL-4 and TNF-α by inhibiting mast cell degranulation induced by dinitrophenylated human serum albumin (DNP-HSA), suggesting that mast cells may be a potential target for AR treatment, and tanshinone IIA alleviates mast cell-mediated AR by inhibiting the NF-κB pathway.[56]

Saikosaponin A (SSA), the active ingredient of silver chaihu, possesses sedative, antiviral, immunomodulatory, hepatoprotective, renal, and anti-tumor effects.[71] In vivo studies have confirmed that SSA inhibits the expression of NF-κB p65 protein and the activation of transcription factors ROR-γt and phosphorylated STAT3 in the nasal cavity and lungs of AR model mice, resulting in a reduction in the level of inflammatory factors in pro-inflammatory cells Th2 and Th17 (IL-6 and IL-17). Additionally, it alleviates allergic symptoms such as nasal rubbing and sneezing, reduces nasal mucosa thickness, cup-shaped cell proliferation, and EOS and mast cell infiltration, thereby decreasing the inflammatory response.[57]

Black pepper is a globally popular spice, rich in volatile oils, oleoresins, and alkaloids. Piperine, its key active component, exhibits antioxidant and anti-inflammatory properties.[72] Studies show that piperine reduces neutrophil and macrophage accumulation in the nasal mucosa, alleviating swelling, fibrosis, and epithelial thickening, and it also decreases nose rubbing and sneezing in mice.[73] Piperine inhibits the phosphorylation of NF-κB p65 and IκBα in the cytoplasm, preventing their nuclear translocation and reducing the stimulation of pro-inflammatory cytokines like TNF-α and IL-1β. Additionally, it blocks the tyrosine phosphorylation of STAT3, suppressing signaling to Th17-associated (RORc and IL-17A) and Th2-associated cytokines (IL-5, IL-13, and IL-6).[58]

Rosmarinic acid, a water-soluble phenolic acid derived from rosemary, possesses anti-inflammatory, antibacterial, antiviral, and antitumor activities.[74] Research indicates that rosmarinic acid mitigates nasal irritation and down-regulates OVA-sIgE expression, easing allergic reactions in AR-modeled mice, and it inhibits IκBα phosphorylation, ubiquitination, and degradation, reduces NF-κB p65 protein expression, up-regulates Th1-associated cytokines and T-bet mRNA, and down-regulates Th2-associated cytokines and GATA-3 mRNA, thereby alleviating AR symptoms, suggesting that rosmarinic acid may reverse AR damage by inhibiting the NF-κB signaling pathway.[59]

Chimonanthus nitens Oliv (CLO), commonly used for upper respiratory tract infections, boasts antioxidant, anti-inflammatory, and antiviral properties.[75] Recent studies highlight CLO's potential in AR treatment by inhibiting NF-κB signaling pathway activation. CLO reduces eosinophil counts in AR mouse serum, suppresses STAT6, GATA-3, and p-p65 expression, and increases STAT4 and T-bet expression in the nasal mucosa, which shifts the immune balance, restoring nasal cavity structure.[60]

Fructus Amomi extract, from the ginger family, contains various active ingredients, notably volatile oils. Modern pharmacology reveals its anti-inflammatory, immunomodulatory, and antioxidant properties.[76] In vivo and in vitro studies show that the extract inactivates NF-κB signaling pathway proteins, alters naïve T-cell differentiation towards Th1 cells, down-regulates the Th2 immune response, and inhibits histamine, IgE, and IgG1 production by mast cells and B-cells, and blocks the allergic reaction chain, improving nasal allergy symptoms in model mice.[61]

Fucoxanthin, a carotenoid from algae and marine phytoplankton, exhibits anti-tumor, anti-inflammatory, antioxidant, and neuroprotective properties.[76] Cytological analysis reveals that fucoxanthin prevents NF-κB p65 activation and subsequent IκBα phosphorylation in vivo, directly inhibiting inflammatory mediator release (IL-5, IL-6, and IL-12), and it also down-regulates STAT-3, controlling the expression of IL-17A and alleviating the progression of AR.[62]

Manoalide, a marine natural product derived from *Luffariella variabilis* as an antibacterial metabolite, functions as a calcium channel blocker.[77] By inhibiting caspase-1, manoalide diminishes the production of inflammatory cytokines IL-1β and TSLP, which, in turn, reduces mast cell-induced NF-κB activation, mitigates mitogen-activated protein kinase (MAPK) signaling in HMC-1 cells, and suppresses the secretion of tumor necrosis factor-α, IL-6, and IL-8.

Pharmacotoxicological studies confirm that manoalide exhibits no cytotoxicity in activated HMC-1 cells,[63] suggesting its potential as a novel therapeutic agent for AR.

Glycyrrhizin (GL), an oleanane-type triterpenoid found in liquorice, encompasses glycyrrhizic acid (GA) and its salts. Renowned for its antiviral, anti-inflammatory, neuroprotective, and hepatoprotective properties, it finds widespread application in medicine, food, and the chemical industry.[78] Haixia Li et al employed histamine-induced human nasal epithelial cells (HNEpCs) to investigate GL's effects. GA was found to inhibit histamine-induced phosphorylation of NF-κB p65 and p-IκBα, reverse MUC5AC expression, curb inflammatory cytokine production, and restore AQP5 expression, thereby reinstating the nasal mucous membrane's barrier function, and this positions GL as a promising alternative treatment for AR.[64]

Curcumin, a low molecular weight polyphenolic compound initially isolated from turmeric (Curcuma longa), exhibits anti-inflammatory and antioxidant properties.[79] Recent studies demonstrate curcumin's ability to block histamine release, conferring anti-allergic effects in type I and type IV allergic reaction animal models. It inhibits the activation of transcription factors such as NF-κB and activator protein-1, suppresses cell proliferation, attenuates inflammatory factor release, and reduces oxidative damage through immunomodulation.[80] Zhang Ning et al administered curcumin to OVA-sensitized mice, revealing that it reduced immune cytokine levels by decreasing histamine, specific IgE, and TNF-α release from mast cells. Curcumin improved nasal symptoms and nasal mucosa morphological changes by reducing histamine and specific IgE release, lowering TNF-α levels, and inhibiting inflammatory mediator release through the suppression of cytosolic I-KBα degradation and PM-stimulated NF-κB nuclear isomerization in mast cells.[65]

Catechin, a naturally occurring polyphenolic flavanol within the flavonoid family, is found in a variety of plants. Ongoing research has unveiled catechin's diverse pharmacological functions, including anti-inflammatory, antibacterial, antiviral, and antioxidant effects.[81] An experimental study utilizing HNEpC and AR model mice confirmed that catechins reduced serum IL-5 and IL-13 levels, corrected Th1/Th2 cell imbalance, and improved allergic mouse behavior. Catechins attenuated leukocyte proportions and alleviated local inflammatory symptoms. In addition, as an upstream regulator of TSLP, catechin treatment in model mice resulted in reduced levels of phosphorylated NF-κBp65 and NF-κBp65, along with decreased nuclear translocation of IκBα degradation.[66]

TLR4/NF-κB Signaling Pathway

TLR4/NF-κB Signaling Pathway in Relation to AR

Toll-like receptors (TLRs), pivotal pattern recognition receptors (PRRs) in the innate immune system, exert a dual role in the pathogenesis of AR by mediating allergen recognition, immune regulation, and inflammatory responses. Widely expressed on DCs and mucosal epithelial cells within the respiratory nasal mucosa, TLRs act as natural immune receptors. Specifically, TLR4, a key TLR family member, is intricately involved in inflammatory and immune processes. Upon exposure to external immune stimuli, TLR4 becomes abnormally activated, binding to cellular receptors and triggering a cascade of events, including the phosphorylation of IRAK4, activation of NF-κB, disruption of the Treg/Th17 balance, and upregulation of pro-inflammatory factors, culminating in an immune response.[82] Activated TLR4 initiates two myeloid differentiation factor 88 (MyD88) signaling pathways: the MyD88-dependent pathway, which results in excessive release of pro-inflammatory cytokines such as IL-6, IL-1β, IL-25, and IL-33; and the MyD88-dependent pathway, which drives Th2/ILC2-mediated inflammatory responses. NF-κB, situated downstream of TLR4, is induced to translocate to the nucleus upon TLR4 activation, which accelerates downstream inflammatory signaling, exacerbates inflammatory cell infiltration, promotes GATA3 expression, inhibits the Th1 transcription factor (T-bet), and disrupts immune polarization. Notably, studies have demonstrated that inhibition of TLR4/NF-κB activation significantly ameliorates the pathology of AR.[83]

Natural Product Modulation of the TLR4/NF-κB Signaling Pathway for the Treatment of AR (Table 2)

Resveratrol, a naturally occurring polyphenol abundant in herbs and foods like tiger nuts, grapes, and soybeans, is marketed as a nutritional supplement or additive. With its broad pharmacological effects, resveratrol exhibits anti-inflammatory, antioxidant, antiviral, hypolipidemic, hypoglycemic, and anticancer properties, positioning it as a promising candidate for disease prevention and treatment.[95] Animal model studies have demonstrated that resveratrol

Table 2 Natural Products Treats AR by Interfering with the TLR4/NF-κB Signalling Pathway

Natural Products	Causality	Subjects	Dose	Mechanisms of Action	References
Resveratrol	Non-flavonoid polyphenols	SD rats	100mg/kg/d	T-bet↓, GATA-3↓, IL-4↓, IgE↓, IFN-γ↑, IL-2↑, TLR4↓, NF-κB↓	[84]
Thymol	Phenolics	SD rats	10mg/kg/d, 20mg/kg/d, 30mg/kg/d	TLR4/GAPDH↓, p-NF-κB p65↓, NF-κB p65↓, Eosinophil↓, INF-γ↑, IL-2↑, TNF-α↓, IL-4↓, IL-13↓, Th1/Th2↑, T-bet mRNA↑, T-bet/GATA-3↑	[85]
Quercetin	Flavonols	SD rats	17.5mg/kg/d, 35mg/kg/d	Th17↓, Treg/Th17↑, IL-17↓, IL-10↑, p-IRAK4/IRAK4↓, p-NF-κB p65/NF-κB p65↓, TLR4↓	[86]
Tretinoin	Epoxy diterpene lactones	SD rats	100μg/kg/d	IgE↓, HIS↓, IFN-γ↑, IL-4↓, CD3+ CD4+ IFN- γ + Th1↑, CD3+ CD4+ IL-4+ Th2↓, TLR4↓, NF-κB mRNA↓	[87]
Berberine	Quaternary ammonium alkaloids	Guinea pig	25mg/kg/d, 50mg/kg/d, 100mg/kg/d	IL-6↓, IL-1β↓, IL-17↓, TNF-α↓, IgE↓, TLR4↓, PTGS2↓, NF-κB↓	[88]
Kaempferol	Flavonoids	SD rats	20mg/kg/d	Caspase-1p20/p45↓, GSDMD-N/GSDMD↓, IL-18↓, IL-1β↓, TLR4↓, p-NF-κB↓, NLRP↓	[89]
Apigenin	Flavonoids	BALB/c mice	20mg/kg/d	TLR4↓, MyD88↓, NF-κB↓, Th1(CD4IFN-γ)/Th2(CD4IL-4)↑, IgE↓, IgG1↓, IgG2a↓, β-hexosaminidase↓, Histamine↓, ECP↓, IFN-γ↑, IL-4↓, IL-5 ↓, IL-13↓, T-bet↑, GATA-3↓, mast cell↓	[90]
Luteolin	Flavonoids	BALB/c mice	20mg/kg/d, 40mg/kg/d	sIgE↓, IFN-γ↑, IL-2↑, IL-4↓, IL-5↓, IL-13↓, TLR4↓, p65↓	[91]
Radix Saposhnikoviae Extract	Chromones	BALB/c mice	16mg/kg/d	NF-κB↓, p-STAT3↓, TLR4↓, TRAF6↓, p-IκBα/IκBα↓, IgE↓, Histamine↓, IL-4↓, IL-5↓, TNF-α↓, IL-6↓, IL-17↓, IL-2 ↑, IL-10↑, IFN-γ↑, TGF-β 1↑	[92]
Naringenin	Flavonoids	SD rats	1.0mg/mL/d, 2.0mg/mL/d	CD19↓, CD23↓, TLR4↓, NF-κBP65↓, IL-17↓, IL-18↓, IgE↓	[93]
Astragaloside	Saponins	C57BL/6 mice	12.5mg/kg/d, 25mg/kg/d, 50mg/kg/d	HMGB↓, ICAM-1↓, VCAM-1↓, IL-6↓, TNF-α↓	[94]

Notes: ↑ represents upregulation, ↓ represents downregulation.

modulates inflammatory factor release, thereby altering damaged nasal mucosa cells and alleviating allergy symptoms by mitigating oxidative stress.[96] Focusing on the TLR4/NF-κB signaling pathway, resveratrol was found to reduce TLR4 and NF-κB protein expression, inhibit the downstream T-bet and GATA-3 secretion, decrease IL-4 and IgE levels, elevate IFN-γ and IL-2 levels, and promote T cell conversion to Th1 cells in AR model mice.[84] This suggests resveratrol's therapeutic potential through TLR4/NF-κB pathway inhibition and Th1/Th2 cell balance regulation.

Thymol, a fragrant phenolic compound extracted from traditional Chinese medicine, exhibits antioxidant, anti-inflammatory, anti-allergic, antibacterial, antiviral, and antitumor effects with low toxicity to normal cells.[97] Experimental studies on thymol intervention in AR mice revealed that thymol regulates EOS infiltration by decreasing TLR4/GAPDH and p-NF-κB p65/NF-κB p65 protein expression, up-regulates INF-γ and IL-2 levels in Th1 cells, and down-regulates TNF-α, IL-4, and IL-13 levels in Th2 cells, thereby improving nasal mucosa pathological changes.[85] This indicates thymol's ability to ameliorate AR by inhibiting TLR4/NF-κB signaling pathway-mediated immunomodulation.

Quercetin, a flavonol compound found in the stem bark, flowers, leaves, buds, seeds, and fruits of various plants, predominantly in glycoside form, possesses a broad spectrum of bioactivities, including anti-inflammatory, antioxidant, and anti-allergic properties.[98] By comparing AR model mice with controls, researchers found that quercetin, through TLR4/NF-κB signaling pathway regulation, down-regulates p-IRAK4/IRAK4 and p-NF-κB p65/NF-κB p65 ratios and TLR4 protein expression, regulates Th17/Treg ratios, inhibits Th17/Treg imbalance, elevates Treg ratio and IL-10 level, suppresses in vivo inflammatory responses, and alters severe nasal mucosa tissue damage with partial epithelial cell

shedding and goblet cell proliferation.[86] This may represent quercetin's primary therapeutic pathway for slowing down the process of AR.

Tretinoin, a diterpene lactone compound extracted from plants with significant biological activity for autoimmune disease treatment, is clinically available as tretinoin polyglucoside tablets.[99] By interfering with the TLR4/NF-κB pathway, tretinoin reduces total IgE and HIS levels in serum, increases the ratio of CD3+CD4+IFN-γ+Th1 cells, decreases the ratio of CD3+CD4+IL-4+Th2 cells, and regulates the balance of the Th1/Th2 ratio, thereby exerting an anti-allergic effect and alleviating nasal mucosa damage and the reduction of nasal cilium cells.[87]

Berberine, an isoquinoline alkaloid isolated from traditional Chinese medicine Huanglian, possesses antimicrobial and vital organ-protective effects and has been extensively studied in metabolic diseases and chronic inflammation.[100] Berberine inhibits NLRP3 inflammatory vesicle activation through mitochondrial autophagy.[101] Bioinformatic analysis and animal experiments have shown that different doses of berberine reduce serum TNF-α, IL-6, IL-1β, IL-17, and IgE levels in AR model mice, inhibit in vivo inflammatory response exacerbation, and decrease TLR4 and PTGS2 expression. Berberine exhibits strong binding affinity to Alb, Il6, Il1b, Tlr4, and Ptgs 2, suggesting the TLR4/NF-κB signaling pathway as a potential therapeutic mechanism for berberine in AR treatment.[88]

Kaempferol, a natural edible flavonoid derived mainly from the rhizome of the ginger plant, Kaempferia spp. and widely found in vegetables and fruits, possesses anti-inflammatory, antioxidant, and anticancer properties.[102] Studies indicate that EOSs, as immunomodulatory cells, interact with T and B lymphocytes. Granulocyte-macrophage colony-stimulating factor (GM-CSF), a major hematopoietic cell survival and activation factor, provides the basis for mature macrophages, EOSs, and neutrophils and is considered a pleiotropic and pro-inflammatory cytokine.[103] Observing cellular pyroptosis, different doses of kaempferol were found to inhibit pyroptosis-related protein Caspase-1p20/p45, GSDMD-N/GSDMD, IL-18, and IL-1β expression, reduce the release of inflammatory cytokines, improve the damage of the nasal mucous membrane, decrease the expression of TLR4, p-NF-κB, and NLRP protein expression, promote downstream Th1 cell secretion, accelerate nasal mucosal remodeling, and alter behavior in mice.[89]

Apigenin, a flavonoid widely found in plants and vegetables, exhibits antioxidant, sedative, and tranquilizing effects with low toxicity and non-mutagenicity compared to other flavonoids (quercetin, kaempferol flavonoids).[104] Taking multiple signaling pathways as the base of observation, apigenin blocked LPS-induced mast cell viability and apoptosis by inhibiting the activity of the TLR4/MyD88/NF-κB pathway, decreased the serum levels of IgE, IgG1, and IgG2a, β-hexosaminidase, histamine, as well as ECP in mice, declined the levels of Th2 cytokines (IL-4, IL-5, and IL-13) and transcription factor GATA-3 levels, increased Th1 cytokine (IFN-γ) and transcription factor T-bet levels, and attenuated the level of metamorphic response in mice with AR.[90]

Luteolin, a natural flavonoid found in many plants as glycosides, exhibits pharmacological effects on chronic airway inflammation.[105] Investigating AR inflammatory response pathogenesis, Dong J et al found that luteolin intervention in OVA-induced model mice promoted Th1-type cytokine levels (IFN-γ and IL-2) in vivo, inhibited Th2-type cytokines (IL-4, IL-5, and IL-13), improved Th1/Th2 cytokine imbalance, controlled OVE-sIgE, TLR4, and P65 levels, and reversed allergic symptoms in model mice. These results suggest luteolin's potential as a TLR4/NF-κB pathway inhibitor in the treatment of AR.[91]

Radix Saposhnikovia divaricata (also known as *Ledebouriella divaricata*), a plant in the Umbelliferae family, has its dried root used in traditional Chinese medicine. The extract contains active ingredients such as chromones, coumarins, and polysaccharides with anti-inflammatory, immunomodulatory, anti-allergic, and neuroprotective effects, widely used in the treatment of colds, arthritis, and allergic diseases.[106] It reduces cell and mucosa dense arrangement, blocks immune cell activation, inhibits NF-κB, p-STAT3, TLR4, TRAF6, and p-IκBα/IκBα protein expression, and reduces downstream inflammatory factor signaling activation to induce inflammatory responses. Analyzed from the intestinal flora perspective, *Radix Saposhnikoviae* Extract altered intestinal flora abundance, providing a new direction for the treatment of AR.[92]

Naringenin, a natural flavonoid from the seed coat of plants in the Lacertaceae family, regulates various metabolic and signaling pathways, such as the nuclear factor signaling pathway and inflammatory vesicle activation pathway.[107] With continuous research, naringenin has gained public attention. Early studies showed that naringenin enhances immunity and anti-inflammatory ability by suppressing inflammation and T cell-mediated immune response.[108] A recent study on rat nasal mucosa histopathology found that naringenin changes the proportion of IgE receptor CD19 and CD23 positive cells in nasal mucosa, down-regulates the expression of TLR4, inhibits the nuclear translocation of NF-κBP65 protein

and the expression of TNF-α, reduces the release of inflammatory mediators such as IgE, IL-17, and IL-18, interferes with the onset and progression of inflammatory response, and restores the inflammation in the tissue pathology of the nasal mucosa. Typical nasal allergy symptoms such as nasal congestion, nasal itching, and sneezing are brought about by histopathological damage of the nasal mucosa.[93]

Astragaloside, a high-purity drug extracted from Astragalus membranaceus and Astragalus myrtillus, exhibits superior biological activity and efficacy compared to APS, with over 30 times the antiviral effect. It possesses anti-inflammatory, anti-fibrosis, and immunomodulatory pharmacological effects.[109] By regulating astragaloside administration dose in AR model mice, it was found that astragaloside prevents HMGB from binding to TLR4, inhibits NF-κB transcriptional activation, down-regulates signaling provoked by high expression of IL-6 and TNF-α, reduces the secretion of ICAM-1 and VCAM-1, inhibits inflammatory response, improves the role of vascular endothelial dysfunction, and enhances the immunity and allergen recognition of nasal mucosa.[94]

MAPK Signaling Pathway

MAPK Signaling Pathway in Relation to AR

The MAPK signaling pathway stands as a pivotal regulator of inflammatory responses and immune cell activation. The three core subfamilies of the MAPK signaling pathway are ERK12 (extracellular signal-regulated kinase), JNK (C-jun n-terminal kinase), and p38 MAPK.[110] In the pathogenesis of AR, ERK12 disrupts the epithelial cell barrier, upregulates MMP-9, degrades ZO-1, prolongs EOS granulocyte survival, activates GATA3, exacerbates mast cell degranulation, promotes Th2 cell differentiation, and thereby exacerbates AR. Meanwhile, the p38 isoform enhances MUC5AC production through STAT6, promotes VEGF release, increases Vascular permeability, and stimulates excessive mucus secretion. Existing studies have demonstrated that U0126, a MEK1/2 inhibitor, effectively alleviates clinical symptoms in AR patients, downregulates histamine components, and inhibits H1R gene expression in vivo.[111]

Natural Product Modulation of the MAPK Signaling Pathway for the Treatment of AR (Table 3)

Bergapten, a naturally occurring furanocoumarin compound found in the legume psoralea corylifolia and other plants such as figs and celery, exhibits anti-inflammatory, antioxidant, and antidepressant-like pharmacological effects. Currently, nanocarriers are employed to enhance the targeting of psoralen and mitigate side effects.[120] To assess the

Table 3 Natural Products Treats AR by Interfering with the MAPK Signalling Pathway

Natural Products	Causality	Subjects	Dose	Mechanisms of Action	References
Bergapten	Furanocoumarins	BALB/c mice	10mg/kg/d, 30mg/kg/d	IL-6↓, IL-1β↓, IgE↓, IgG1 ↓, STAT3↓, MAPK↓, IL-12↑, INF-γ↑, IL-4↓, IL-5↓, IL-13↓	[112]
Chlorogenic acid	Phenylpropanoid	BALB/c mice, RAW264.7 cell	15mgkg/d	NO↓, TNF-α↓, IL-6↓, Tlr4↓, p-p38MAPK↓, p-p65NF-κB↓, p-IκB↓,	[113]
Hyperforin	Flavonol glycosides	Human nasal epithelial cells(HNEpCs)	0.1μM/d, 1μM/d, 10μM/d	p38 MAPK/CCL11↓	[114]
Paeoniflorin	Monoterpene bicyclic glycosides	BALB/c mice	10mg/kg/d, 20mg/kg/d	p38 MAPK↓, IL-1β↓, TNF-α↓, caspase-1↓, Histamine↓	[115]
Ursolic acid	Triterpenoids	BALB/c mice	150mg/mL/d, 300mg/mL/d	MAPK↓, ERK↓, IL-17↓, IL-33↓, TNF-α↓	[116]
Asarum sieboldii Miq. essential oil extract	Methyl eugenol	BALB/c mice	20μM/d	TNF-α↓, IL-4↓, IL-13↓, ROS↓, claudin-1↓, occludin↓, mitochondria↓, eosinophil↓, neutrophil↓, macrophage↓	[117]
Capsaicin	Capsaicinoids	BALB/c mice	25μg/mL/d, 50μg/mL/d, 75μg/mL/d, 100μg/mL/d	IL-6↓, TNF-α↓, NO↓, EPK1/2↓, p65↓, macrophage↓	[118]
(2′S,7′S)-O-(2-methylbutanoyl)-columbianetin	Flavonoids	HMC-1 cell, BALB/c mice	10μg/mL/d	L-1β↓, IL-6↓, IL-8↓, TNF-α↓, ERK↓, JNK↓, p38MAPK↓, IκB-α↓, NF-κB↓, Histamine↓, caspase-1↓, MIP-2↓, ICAM-1↓, IFN-γ↑	[119]

Notes: ↑ represents upregulation, ↓ represents downregulation.

impact of psoralen in the AR model mice exposed to PM2.5, psoralen reduced the levels of pro-inflammatory factors IL-6 and IL-1β, thereby inhibiting MAPK signaling pathway activation. Additionally, psoralen increased the secretion of IL-12 and INF-γ in Th1 cells while reducing the secretion of IL-4, IL-5, and IL-13 in Th2 cells, thereby regulating the Th1/Th2 ratio, which alleviated the inflammatory responses in the nasal mucosa and lungs, strengthening immune cell protection. These findings suggest that psoralen holds potential as a therapeutic agent for AR.[112]

Chlorogenic acid, a natural polyphenolic compound widely found in plants, such as coffee, honeysuckle, Chrysanthemum, apple, and potato,[121] was studied for its effects on AR from the perspective of macrophages. Chlorogenic acid reduced LPS-induced macrophage activity in AR model mice, leading to decreased secretion of NO, TNF-α, and IL-6. Although its direct effect on AR was not significant, chlorogenic acid down-regulated TLR4, P-P38, p-p65, and p-IκB expression, thereby inhibiting MAPK pathway activity and reducing the activation of the downstream transcription factor NF-KB, ultimately alleviating allergic symptoms. These results suggest that chlorogenic acid's modulation of inflammatory responses in AR may be related to the inhibition of the MAPK/NF-κB signaling pathway.[113]

Hypericin, a natural naphthalene dianthrone compound extracted from *Hypericum perforatum L*, enhances immunity and exhibits anti-inflammatory effects.[122] Hypericin activated BCL6 expression to control p38 MAPKCL11 expression, reversed the release of inflammatory cytokines from the nasal epithelium caused by IL-13 downstream, restored the structure of the damaged nasal mucosa epithelium, and resulted in more numerous and regularly arranged cilia. Inflammatory cell infiltration and goblet cell metaplasia were rarely observed in the lamina propria. This study confirms that hypericin may represent a novel therapeutic target for AR.[114]

Paeoniflorin, one of the main active ingredients in Paeonia lactiflora and Paeonia suffruticosa, possesses anti-tumor, anti-inflammatory, and anti-allergic properties.[123] Paeoniflorin prevented the phosphorylation of p38 MAPK in HMC-1 cells within activated mast cell lines, inhibiting downstream transcription factor NF-KB release and attenuating IL-1β and TNF-α production. Moreover, paeoniflorin inhibited the activation of HMC-1 cells, histamine release, and Caspase-1 activation.[115] The results suggest that paeoniflorin attenuates mast cell-mediated allergic inflammation by inhibiting the MAPK signaling pathway.

Ursolic acid, an active ingredient in Hedyotis diffusa, gardenia, Prunella vulgaris, and other plants, exhibits anti-inflammatory and antibacterial effects.[124] In a recent experiment involving mice with AR, different doses of ursolic acid were observed to inhibit MAPK and ERK protein phosphorylation levels in the nasal mucosa and reduce the concentrations of IL-17, IL-33, and TNF-α in serum.[116] These results suggest that ursolic acid may alter the inflammatory state of AR by regulating the activation of the MAPK/ERK signaling pathway.

The roots and rhizomes of *Asarum sieboldii Miq*. are rich in chemical components, including lignans, flavonoids, steroids, polysaccharides, and volatile oils (terpenes, aromatics, and aliphatics), which exhibit antiviral, antibacterial, antioxidant, antidepressant, and carcinoma cell inhibitory effects.[125] Combining bioinformatics with in vivo experiments, it was found that extracts of the essential oil of *Asarum sieboldii Miq*. controlled the tightness of nasal epithelial claudin-1 and occludin in model mice, reducing nasal epithelial thickness hyperplasia and inflammatory cell infiltration, and they inhibited the activation of pro-inflammatory cytokines (TNF-α, IL-4, and IL-13) to the MAPK/NF-κB signaling pathway, blocking the exacerbation of oxidative stress and restoring the mitochondrial membrane potential, thereby improving symptoms of rubbing and sneezing in AR mice.[117]

Capsaicin, a vanilloid alkaloid and the main active ingredient in chili peppers, has been shown by modern pharmacology to stimulate sympathetic excitation, exhibit antioxidant and analgesic effects.[126] Capsaicin was found to inhibit the secretion of inflammatory cytokines (IL-6 and TNF-α) and carbon monoxide production in mice with lipopolysaccharide-induced AR, reducing the protein expression of EPK (extracellular signal-related kinase) 1/2 and p65, thus preventing macrophage activation and the subsequent inflammatory response. This reduced cell death, enhanced the immune response, and regulated allergic reaction symptoms.[118]

(2′S,7′S)-O-(2-methylbutanoyl)-columbianetin (OMC), a novel secondary metabolite extracted from Corydalis heterocarpa and long used as a folk medicine for various inflammatory disorders in South Korea, was studied by Sun-Young Nam et al. Treatment of HMC-1 cells with OMC altered cell morphology, stretched cell membrane folds, decreased histamine and trypsin-like levels, and reduced MAPK signaling pathway stimulation by inflammatory cytokines IL-1β, IL-6, IL-8, and TNF-α. OMC inhibited the phosphorylation of ERK, JNK, and p38, blocking signaling to IκB-α and NF-κB

while decreasing cellular caspase-1 expression in vitro. In a mouse model of OVA-induced AR, OMC reduced serum Th2 cytokine release, as well as MIP-2 and intercellular adhesion molecule 1 (ICAM-1) protein levels, EOSs, and mast cells in nasal mucosal tissues, and it also reduced spleen weight and increased IFN-γ levels in splenic tissues. This study demonstrated that (2'S, 7'S)-O-(2-methylbutanol)-columbianetin is a potent anti-AR compound that acts through inhibition of the MAPK/NF-κB signaling pathway, suppression of pro-inflammatory and Th2 cytokines, and enhancement of Th1 cytokines.[119]

PI3K/Akt Signaling Pathway

PI3K/Akt Signaling Pathway in Relation to AR

PI3K, or phosphatidylinositol 3-kinase, is an intracellular enzyme comprising a regulatory subunit and a catalytic subunit in a heterodimeric configuration. Akt, also known as protein kinase B or PKB, is a serine/threonine kinase that plays a pivotal role in glucose metabolism and the regulation of cell proliferation, differentiation, and apoptosis. The PI3K/Akt signaling pathway is a central route in immune regulation. Activation of the PI3K/Akt signaling pathway primarily stems from PI3K activation, which leads to the production of phosphatidylinositol triphosphate (PIP3), which, in turn, activates the downstream molecule Akt through phosphorylation. PIP3 specifically binds to the PH domain of Akt, prompting a conformational change that enables Akt to translocate from the cytoplasm to the cytosolic membrane. Once there, phosphorylated Akt targets various downstream proteins, such as gluconeogenic synthase kinase 3β (GSK3β) and NF-κB, initiating gene transcription. This cascade of events culminates in the activation of cellular processes, including metabolism, proliferation, apoptosis, and inflammatory responses. In AR, triggers such as IgE-FcεRI, TLRs, or cytokine receptors (IL-4R) can activate PI3K, and the phosphorylation of Akt serves as a marker for the activation of downstream components in the PI3K/Akt signaling pathway.[127] Phosphorylated Akt then phosphorylates STAT6, promoting GATA3 expression and driving Th2 differentiation, which in turn induces inflammatory responses. Additionally, Akt enhances FcεRI signaling, accelerating mast cell degranulation, inhibiting EOS apoptosis, and promoting the release of histamine and leukotrienes, and it can also activate TRPV1 channels, heightening sensory nerve sensitivity and resulting in nasal itching and sneezing.[128]

Natural Products Modulate the PI3K/Akt Signaling Pathway for the Treatment of AR (Table 4)

Coptisine is an extract derived from Coptis chinensis, renowned for its anti-cancer and immune-regulatory properties. Extensive research has explored its effects on immune cells across various diseases.[133] Studies indicate that coptisine can block PI3K and Akt phosphorylation in vivo by reducing IgE levels, and this compound also exerts a protective effect on immune cells, as evidenced by decreased serum levels of IL-4 and TNF-α in mice. Meanwhile, coptisine inhibits the release of β-hexosamine and histamine from degranulating mast cells, suggesting its potential therapeutic role in AR.[129]

Dendrobium water extracts, primarily sourced from the Dendrobium genus, contain polysaccharides, alkaloids, phenols, amino acids, and other bioactive components, which exhibit immune-regulatory, antioxidant, and

Table 4 Natural Products Treats AR by Interfering with the PI3K/Akt Signalling Pathway

Natural Products	Causality	Subjects	Dose	Mechanisms of Action	References
Coptisine	Quaternary ammonium alkaloids	C57BL/6 mice	15mg/kg/d	IgE↓, PI3K↓, Akt↓, IL-4↓, TNF-α↓, mast cell↓, β-hexosaminidase↓, Histamine↓	[129]
Dendrobium water extracts	Alkaloid	BALB/c mice	20mgkg/d	Forkhead box↑, IL-2↑, IL-4↓, IFN-γ↑, IL-6↓, IL-10 ↑, IL-17↓	[130]
Luteolin	Flavonoids	BALB/c mice	10mg/kg/d	IL-4↓, IL-13↓, INF-γ↑, T-bet↑, GATA-3↓	[131]
Higenamine	Alkaloid	Human nasal epithelial cells(HNEpCs), BALB/c mice	30mg/kg/d, 60mg/kg/d, 120mg/kg/d	IgE↓, AKT1↓, EGFR↓, c-Jun↓, iNOS↓, JAK2↓, MUC5AC↓, NF-κB↓, Histamine↓, IL-4↓	[132]

Notes: ↑ represents upregulation, ↓ represents downregulation.

hepatoprotective functions, finding applications in health supplements, pharmaceuticals, and cosmetics.[134] Analyzing from the perspective of the "Lung-gut axis" theory, these extracts regulate the aberrant activation of the PI3K/Akt signaling pathway in AR mice, reducing the release of downstream inflammatory cytokines such as IL-2, IL-4, IFN-γ, IL-6, IL-10, and IL-17 in the lungs, while preserving diversity and abundance. This ameliorates lung inflammatory responses and mitigates AR severity.[130]

Luteolin, a natural flavonoid found in honeysuckle flowers, possesses anti-inflammatory and anti-allergic properties.[135] In AR model mice, luteolin reduces the expression of phosphorylated p-PI3K/PI3K and p-Akt/AKT markers, along with decreased levels of IL-4 and IL-13, thereby playing a role in inhibiting the inflammatory response. Moreover, luteolin elevates Th1 and T-bet protein levels while inhibiting ANO1 activity, thereby reducing electrolytic secretion from the apical membrane and alleviating nasal hypersecretion in AR.[131] These findings suggest that luteolin's therapeutic effects on AR may be related to the PI3K/Akt signaling pathway.

Higenamine (HG) is a plant alkaloid with a stable molecular structure, initially isolated from *Aconitum carmichaeli* and recognized as its cardiotonic active component. Numerous animal studies have demonstrated its anti-apoptotic, antioxidant, anti-inflammatory, and immunomodulatory effects.[136] Combining human nasal mucosa analysis with bioinformatics, higenamine was found to reduce IgE concentrations in AR model mice, inhibit mast cell degranulation and histamine release, and down-regulate cellular autophagy levels, and it also suppresses Th2 cell proliferation, modulates immune cell function, blocks the expression of AKT1, EGFR, c-Jun, iNOS, MUC5AC, and NF-κB signaling pathways, and inhibits the activity of inflammatory cells, thereby alleviating the inflammatory response. At the same time, higenamine was observed to reduce lung injury during inflammation.[132]

IL-33/ST2 Signaling Pathway

IL-33/ST2 Signaling Pathway in Relation to AR

The IL-33/ST2 signaling pathway is intricately linked to allergic diseases, autoimmune disorders, and cardiovascular conditions. IL-33, a member of the IL-1 family of alarmins, is released by epithelial cells and various human tissues and organs following injury, and its primary in vivo targets include inflammation-associated cells such as group 2 innate lymphoid cells (ILC2s), mast cells, and Tregs, ST2, a member of the IL-1 receptor superfamily, exists in two main isoforms: soluble (sST2) and transmembrane (ST2L). IL-33 is the sole known ligand for ST2 and exerts its effects on mast cells, neutrophils, subsets of regulatory T-cells, helper T-cells, natural killer cells (NK), and constant NK cells.[137] Activation of the IL-33/ST2 signaling pathway is primarily initiated by the upstream release of IL-33, which binds to and activates ST2. This interaction triggers homotypic protein-protein interactions with the adaptor molecule MyD88, subsequently recruiting IRAKs as well as TRAF6, and activating downstream NF-κB and MAPK pathways, thereby contributing to the release of various inflammatory mediators. In AR, ILC2s produce substantial amounts of IL-5 and IL-13 in response to IL-33 stimulation, promoting EOS infiltration and mucus secretion. Additionally, IL-33 downregulates tight junction proteins (ZO-1 and Occludin), increasing allergen penetration and forming a vicious cycle of inflammation and barrier disruption, and this pathway synergizes with the signaling of IgE/FcεRI, enhancing the release of histamine and tryptase and triggering the release of acute inflammatory mediators.[138] Together with IgE/FcεRI signaling, it enhances histamine and trypsin-like release, triggering acute allergic symptoms (sneezing and itchy nose).

Natural Product Modulation of IL-33/ST2 Signaling Pathway for the Treatment of AR (Table 5)

Fallopia japonica root extract (FJE) is rich in polyphenols such as resveratrol, flavonoids/flavonols, polydatin, and glycosides, which exhibit anti-inflammatory, antiviral, and oxidative stress-inhibiting effects.[142] In OVA-sensitized mouse models, FJE treatment reduced the recruitment of epithelial cells, macrophages, EOSs, neutrophils, and lymphocytes, modulating immune cell function, and it inhibited the activation of epithelial-derived cytokines TSLP and IL-33, thereby reducing the expression of the IL-33 receptor ST2 and controlling the levels of P-NF-κB and P-IκB, suggesting that FJE reduces inflammatory cell infiltration, regulates mucus accumulation, and accelerates immune cell recovery by modulating the IL-33/TSLP/NF-κB signaling pathway.[139]

Table 5 Natural Products Treats AR by Interfering with the IL-33/ST2 Signalling Pathway

Natural Products	Causality	Subjects	Dose	Mechanisms of Action	References
Fallopia japonica root extract	Saponins	CARAS mice	50mg/kg/d, 100mg/kg/d, 200 mg/kg/d	IgE↓, IgG1↓, IgG2a↑, IL-4↓, IL-5 ↓, IL-13↓, FOXP3↑, IL-10↑, P-NF-κB↓, P-IκB↓, IL-33↓, ST2↓	[139]
Hydrangea serrata extract	Isocoumarins	BALB/c mice	100mg/kg/d, 200mg/kg/d	Macrophage↓, neutrophil↓, eosinophil↓, mast cell↓, IgE↓, Histamine↓, IgG1↓, IL-33↓, IL-4↓, IL-5↓, ST2↓, MyD88↓, NF-κB↓, p-NF-κB↓, IκB↓, p-IκB↓	[140]
Chaenomeles sinensis	Flavonoids	BALB/c mice	50mg/kg/d, 100mg/kg/d, 200mg/kg/d	IgE↓, IgG2a↑, IL-33↓, ST2↓, IL-4↓, IL-5↓, IL-13↓, IFN-γ↑, IL-12↑, E-cadherin↑, occludin↑, ZO-1↑	[141]
Trans-resveratrol	Bisstyrene	Allergic rhinitis patients	100mg/kg/d	HIF-1α↓, IL33↓, ST2↓, EGLN3↑	[96]

Notes: ↑ represents upregulation, ↓ represents downregulation.

Hydrangea serrata extract (HSE), derived from a plant native to Korea and Japan, contains a unique natural compound called zeolanol. Research indicates that HSE possesses antifungal, allergy-reducing, and muscle growth-promoting properties.[143] In vivo studies have shown that HSE inhibits the activation of immune cells (macrophages, neutrophils, and EOSs), slows mast cell degranulation, and reduces the release of histamine, heparin, as well as prostaglandins, and other compounds that stimulate the nasal mucosa. This controls symptoms such as nasal rubbing caused by mucosal fibrosis; at the same time, HSE has also been shown to have anti-fungal properties, alleviate allergies, and promote muscle growth. At the same time, HSE strongly regulates IL-33 and ST2 levels, alters coupled Th2 cytokines (IL-4 and IL-5), and controls all components of the NF-κB signaling pathway (p-NF-κB and p-IκB), thereby inhibiting the inflammatory response of nasal mucosal epithelial cells. These findings suggest that HSE may serve as an effective complementary therapy for allergic airway inflammatory diseases.[140]

Chaenomeles sinensis (CSE), a deciduous shrub native to China, contains triterpenoids and phenolic bioactive compounds with pharmacological properties such as antimicrobial, anti-inflammatory, antihypertensive, neuroprotective, and anti-mutagenic effects, exhibiting low toxicity to normal cells.[144] CSE extract has been reported to increase IgG2a levels while inhibiting IgE levels in the serum of mice with OVA-induced AR, thereby blocking IL-33/ST2 signaling and regulating Th2 cytokine release. It also activates Th1 cytokine secretion and reverses epithelial permeability in model mice by enhancing E-cadherin, occludin, and ZO-1 expression, and these effects improve nasal allergy symptoms and alleviate the condition of AR.[141]

Trans-resveratrol (TR), a naturally occurring polyphenolic compound found in grapes, berries, and peanuts, possesses anti-inflammatory and immunomodulatory properties that may alleviate allergic disease symptoms.[145] Currently, marketed as a nutritional supplement or additive, TR has been shown in various animal models to modulate the release of inflammatory factors and counteract the effects of damaged nasal mucosal cells. Compared to resveratrol, TR exhibits greater stability under high temperature, light, and oxygen conditions. Through bioinformatics analysis and experimental validation, TR has been found to down-regulate HIF-1α and IL33/ST2 levels while increasing the expression of EGLN3, promoting mucosal repair, accelerating the remodeling of epithelial cells, reversing the hypoxic state of nasal mucosa, and inhibiting the development of AR.[96]

JAK/STAT Signaling Pathway

JAK/STAT Signaling Pathway in Relation to AR

The JAK/STAT signaling pathway serves as the central conduit for cytokine signaling, and the JAK family comprises JAK1, JAK2, JAK3, as well as TYK2, while the STAT family includes STAT1, STAT3, STAT5, and STAT6.

Upon cytokine binding to its receptor, receptor dimerization occurs, triggering phosphorylation at multiple sites on the JAK receptor. This, in turn, phosphorylates the STAT protein, which then binds to the receptor, forms a dimer, and translocates into the nucleus to regulate gene expression and induce an immune response. The dimer modulates the expression of target genes and inflammatory factors, with the activation of these inflammatory factors further exacerbating tissue damage and establishing a positive feedback loop within the JAK/STAT pathway.[146] Recent studies have confirmed that the JAK/STAT pathway can prolong EOS survival, inhibit T-bet (Th1) and FoxP3 (Treg) expression, promote Th2 and Th17 cell differentiation, and exacerbate immune imbalance. Consequently, inhibiting the JAK/STAT signaling pathway represents a potential therapeutic approach for AR.

Natural Product Modulation of JAK/STAT Signaling Pathway for the Treatment of AR (Table 6)

Cinnamaldehyde, a 3-phenyl-2-acrolein compound extracted from cinnamon bark, is a yellow oily liquid with a strong cinnamon aroma and exhibits various biological activities, including anti-inflammatory, antibacterial, and antioxidant properties.[153] Current research indicates that cinnamaldehyde can reduce the expression of p-JAK2, p-STAT3, as well as BCL-2 protein, and decrease IL-6 levels in AR model rats undergoing apoptosis, thereby increasing the apoptosis index (AI) and Bax protein expression, and promoting apoptosis in the nasal mucosa of AR rats. Additionally, cinnamaldehyde reduces nasal tissue edema and maintains normal cell proliferation and apoptosis.[147] By inhibiting the JAK/STAT signaling pathway, cinnamaldehyde may exert its anti-inflammatory effects by blocking inflammatory factors.

Malvidin, one of the most widely distributed anthocyanins, is a polyphenolic flavonoid and a secondary metabolite synthesized by vascular plants. Modern pharmacological studies have demonstrated that malvidin possesses dual properties: inhibiting inflammasome secretion and exhibiting antioxidant activity.[154] Observations of T cell and nasal mucosa changes in OVA-induced AR model mice revealed that malvidin inhibited STAT6 phosphorylation and GATA3 protein expression, reduced the Th2-mediated immune response, and enhanced the Treg population, which provides a theoretical basis for the development of AR. Furthermore, malvidin reduced pathological changes in the nasal mucosa,

Table 6 Natural Products Treats AR by Interfering with the JAK/STAT Signalling Pathway

Natural Products	Causality	Subjects	Dose	Mechanisms of Action	References
Cinnamaldehyde	Aldehydes	SD rats	20mg/kg/d, 40mg/kg/d, 80mg/kg	p-JAK2↓, p-STAT3↓, Bcl-2↓, IL-6↓, AI↑, Bax↑	[147]
Malvidin	Benzodiazepines	BALB/c mice	15mg/kg/d	STAT6↓, GATA3↓, IL-4↓, IL-5↓	[148]
Pulsatilla koreana Nakai	Alkaloid	Splenocyte, BALB/c mice	50μg/mL/d, 100μg/mL/d, 200μg/mL/d	JAK1/3↓, JAK1/2↓, STAT6↓, GATA3↓, IL-4↓, IL-13↓, IL-5↓, eosinophil↓, neutrophil↓, macrophage↓	[149]
Alpha-linolenic acid	Fatty acids	BALB/c mice	5mg/kg/d	Occludin↓, zonula occludens-1↓, IgE↓, Th1/Th2 ↑, IL-5↓, IL-13↓, TNF-β↓, IFN-γ↑, IL-25↓	[150]
Magnolin	Polyphenols	Guinea pig	20mg.kg^{-1}/d, 40mg.kg^{-1}/d, 80mg.kg^{-1}/d	FynmRNA↓, SCFmRNA↓, IL-10mRNA↓, STAT5↑,	[151]
Platycodin D	Saponins	Human nasal epithelial cells(HNEpCs), BALB/c male mice	30mg/kg/d	IFN-γ↑, IgE↓, IL-4↓, p-JAK2↓, p-STAT3↓,	[152]

Notes: ↑ represents upregulation, ↓ represents downregulation.

such as edema, EOS granulocyte infiltration, and goblet cell hyperplasia, suggesting that malvidin modulates Th1/Th2 and Treg/Th17 immune responses in vivo by suppressing the STAT signaling pathway.[148]

Pulsatilla Koreana Nakai (PKN), distributed in China, Korea, Japan, and the Far East Region of Russia, contains triterpenoid saponins as its main active component. Modern pharmacological studies have shown that PKN possesses immune-enhancing and anti-inflammatory pharmacological activities.[155] Studies on immune cells revealed that the aqueous extract of PKN inhibited the passive accumulation of immune cells, such as EOS granulocytes, neutrophils, macrophages, and lymphocytes, in AR model mice, reducing the secretion of histamine and IL-13, decreasing the level of inflammation in vivo, as well as inhibiting JAK1/3 or JAK1/2-mediated phosphorylation in splenocytes. Consequently, STAT6 dimerization and GATA3 expression were reduced, along with IL-13 expression in splenocytes, preventing Th2 cell activation and differentiation of naive CD4 T cells. PKN holds potential for AR treatment.[149]

Alpha-linolenic acid (ALA), a natural plant-derived unsaturated fat, exhibits pharmacological properties such as regulating blood lipids, inflammatory mediators, and interleukins.[156] From a serological perspective, ALA reduced serum IL-4 release in AR model mice. By activating the JAK2/STAT3 signaling pathway, ALA prevented the reduction of occludin and zonula occludens-1 (ZO-1) expression, altered CD3CD4 T cell differentiation in splenic lymphocytes, restored Th1/Th2 immune balance, and alleviated nasal symptoms, improving nasal inflammation and epithelial barrier damage, and strengthening epithelial barrier function to resist pathogen attacks.[150] Thus, ALA is a candidate for improving epithelial barrier function by restoring the Th1/Th2 ratio in AR.

Magnolol, a natural organic compound primarily found in magnolia and the main active ingredient of lignans, significantly inhibits the early onset of inflammation and suppresses allergy activation in vivo.[151] From the perspective of immune protein genes and nasal mucosa, a high dose of magnolol significantly changed the morphology of fibroblasts, reduced epithelial tissue shedding and necrosis, and gland overexpansion, which alleviated continuous rhinorrhea, reduced FynmRNA and SCFmRNA expression levels, upregulated STAT5 and IL-10 mrna expression, positively regulated mast cell degranulation, exerted a negative immunomodulatory effect, reduced T cell responses, enhanced B cell function, and improved immune response. The effects of magnolol were dose-dependent.[147]

Platycodin D, a triterpenoid monomer isolated from Platycodon grandiflorum, is the main effective component of this plant. Existing studies have confirmed that platycodin D promotes antigen differentiation of CONA protein, lipopolysaccharide, and spleen cells, enhances the antigenic activity of IGG1, IgG2a, and IgG2b in mouse serum, and boosts mouse immunity.[157] Recent studies using IL13-induced human nasal mucosal cells and AR model mice observed the therapeutic effect of platycodin D. Platycodin D regulated human nasal mucosal cells, improved the nasal mucosa of injured mice, arranged nasal mucosal epithelial cells neatly, inhibited goblet cell hyperplasia, altered T cell immune responses, increased IFN-γ levels, reduced serum IgE and IL-4 levels, inhibited p-JAK2 and P-STAT3 expression in vivo, and decreased serum IL-4 and IL-4 levels. This blocked the activation of the JAK/STAT signaling pathway, improved the pathological expression of the nasal mucosa, and alleviated the allergic reaction in the nasal mucosa of AR mice.[152]

AMPK Signaling Pathway

AMPK Signaling Pathway in Relation to AR

As a pivotal regulator of cellular energy metabolism, AMPK plays an essential role in sustaining cellular energy homeostasis and orchestrating metabolic processes. Beyond its metabolic functions, AMPK activation has been shown to mitigate oxidative stress and inflammatory responses, thereby safeguarding cellular integrity by maintaining mitochondrial homeostasis and promoting autophagy. The fundamental structure of AMPK comprises three subunits: α, β, and γ.[158] In the context of AR, AMPK activation exerts multifaceted therapeutic effects, and it inhibits mTORC1 activation, dampens NF-KB and STAT3 signaling pathways, and reduces Th2 cell differentiation; at the same time, it suppresses chemokine expression, such as CCL11 (Eotaxin), positioning it as a promising therapeutic target for AR. In addition, AMPK activation modulates TRPV1 expression in EOSs, desensitizes sensory nerve endings, and alleviates symptoms like nasal itching and sneezing.[157]

Table 7 Natural Products Treats AR by Interfering with the AMPK Signalling Pathway

Natural Products	Causality	Subjects	Dose	Mechanisms of Action	References
Panax ginseng saponin	Saponins	BALB/c mice	20mg/kg/d	IgE↓, IL-4↓, IL-6↓, IL-8↓, IL-13↓, TNF-α↓, Drp1↓, MFN2↑, TXNIP↓, NLRP3↓, Caspase-1↓, IL-1β↓, Ser 616↓	[159]
Tanshinone	Fat-soluble phenanthrenequinone	BALB/c mice, HMC-1 cell	20μg/mL/d	Mast cell↓, AMPK↑	[160]

Notes: ↑ represents upregulation, ↓ represents downregulation.

Natural Product Modulation of AMPK Signaling Pathway for the Treatment of AR (Table 7)

Panax ginseng saponin, a distinctive constituent of Panax notoginseng, represents the most abundant chemical component in this herb, primarily comprising dammarane-type tetracyclic triterpenoid saponins, which constitute up to 12% of its composition. This compound exhibits a broad spectrum of pharmacological activities, including immunomodulation, anti-tumor, antioxidant, anti-inflammatory, hemostatic, and cardiovascular protective effects.[161] From a mitochondrial perspective, Panax ginseng saponin R1 has been demonstrated to attenuate allergic symptoms in an AR mouse model, and it reduces serum levels of IgE, IL-4, IL-6, IL-8, IL-13, and TNF-α, while restoring Th1/Th2 cell balance. Notably, Panax ginseng saponin R1 down-regulates Drp1 phosphorylation (Ser 616) and translocation in an AMPK-dependent manner, promotes MFN2 expression, and decreases TXNIP, NLRP3, Caspase-1, and IL-1β expression to reduce mitochondrial oxidative stress and preserve mitochondrial integrity, suggesting its potential as a therapeutic agent for AR.[159]

Tanshinone, a lipophilic constituent derived from the dried roots and rhizomes of Salvia miltiorrhiza (Labiatae family), exhibits a wide array of biological activities. Among its various components, tanshinone stands out as the most biologically active lipophilic fraction, demonstrating antioxidant, anti-inflammatory, anti-angiogenic, and anti-tumor properties. Recent studies, both domestically and internationally, have highlighted tanshinone's regulatory role in immune cell development, activation, and function, participating in both innate and adaptive immune responses.[162] Specifically, IgE-induced mast cell activation is negatively regulated by Sirt1.LKB1. AMPK pathway. Li et al demonstrated through in vitro and ex vivo experiments that TIIA can inhibit IgE receptor (FcεRI)-mediated mast cell activation in vitro and mast cell-mediated allergic responses in vivo by activating Sirt1.LKB1. AMPK pathway; Therefore, TIIA holds promise as a novel therapeutic agent for mast cell-mediated allergic diseases.[160]

Notch Signaling Pathway

Notch Signaling Pathway in Relation to AR

The Notch signaling pathway represents an evolutionarily conserved pathway that regulates immune cell differentiation, epithelial barrier integrity, and inflammatory responses. In AR, the Notch signaling pathway is activated by the binding of ligands DLL and JAG to Notch1-4 receptor proteins, activating target genes such as HES/HEY, and participating in the regulation of T-cell function, which leads to the up-regulation of GATA3 to drive the differentiation of CD4þT cells to Th2. Concurrently, FcεRI signaling enhances mast cell degranulation, accelerating EOS recruitment and histamine release, which accelerates EOS recruitment, promotes histamine release, and exacerbates metaplasia.[163,164]

Natural Product Modulation of Notch Signaling Pathway for the Treatment of AR (Table 8)

Hesperetin, a flavonoid derived from citrus peels, exhibits anti-inflammatory, antioxidant, and neuroprotective properties.[166] Recent investigations into immune and inflammatory responses revealed that hesperetin suppresses NOTCH1 and Jagged1 gene expression while upregulating Foxp3. In an AR mouse model, hesperetin significantly increased the proportion of CD4 + CD25 + FOXP3 + Tregs in splenic tissue and reduced IL-6 and IL-

Table 8 Natural Products Treats AR by Interfering with the Notch Signalling Pathway

Natural Products	Causality	Subjects	Dose	Mechanisms of Action	References
Hesperetin	Phenols	BALB/c mice	30mg.kg^{-1}/d	Notch1↓, Jagged1↓, Foxp3↑, CD4+CD25+FOXP3+Treg↑, IL-6↓, IL-17A↓, IL-10↑	[165]

Notes: ↑ represents upregulation, ↓ represents downregulation.

17A levels. These findings suggest that hesperetin mitigates AR progression by inhibiting the Notch1/Jagged1 signaling axis.[165]

TGF-β/Smads Signaling Pathway

TGF-β/Smads Signaling Pathway in Relation to AR

The TGF-β/Smads signaling pathway plays a pivotal role in immune tolerance regulation. The TGF-β superfamily comprises three isoforms (TGF-β1, TGF-β2, and TGF-β3) that signal through a shared receptor complex. TGF-β1, the first fully cloned member of this family, is encoded by 33 distinct mammalian genes and secreted by Tregs, mast cells, and epithelial cells, and it exerts dual immunosuppressive and pro-fibrotic effects,[167] acting as a homeostatic regulator that coordinates tissue repair following injury or infection. Smads serve as the sole kinase substrates for TGF-β receptors. Upon TGF-β1 activation and binding to type II transforming growth factor-β receptor (TβRII), TβRI kinase becomes phosphorylated, triggering downstream Smads2/3 phosphorylation. The resulting trimeric complex induces FoxP3 expression, up-regulates MUC5AC, leading to mucus hypersecretion, and activates transcription factors Snail and Twist, which disrupt epithelial barrier integrity, increasing allergen penetration and exacerbating chronic inflammation.[168]

Natural Product Modulation of TGF-β/Smads Signaling Pathway for the Treatment of AR (Table 9)

18β-glycyrrhetinic acid, a pentacyclic triterpenoid derivative and hydrolytic metabolite of glycyrrhizin, shares pharmacological properties with glycyrrhizin, including inhibition of oxidative stress and ROS release, and it demonstrates corticosteroid-like anti-inflammatory, anti-allergic, and antioxidant effects.[171] Sodium 18β-glycyrrhetinate reduces serum IgE levels, suppresses TGF-β1 expression, inhibits vascular gland proliferation, and diminishes inflammatory cell infiltration to promote epithelial cell activation and mucosal tissue remodeling,[169] suggesting its potential as a novel AR therapeutic target.

Total paeoniflorin, a mixture of physiologically active compounds, including paeoniflorin, hydroxypaeoniflorin, benzoylpaeoniflorin, derived from *Paeonia lactiflora* roots, has been marketed since the 19th century. Modern pharmacological studies confirm its anti-inflammatory, analgesic, antioxidant, and anti-autoimmune diseases and other pharmacological effects.[172] In an OVA-induced AR mouse model, total paeoniflorin reduced serum IgE and inflammatory cytokine levels (IL-4, IL-5, IL-17, and IFN-γ). Mechanistically, it upregulated Smad7 expression, inhibited TGF-β signaling activation, and decreased malondialdehyde (MDA) and glutathione (GSH) concentrations while enhancing

Table 9 Natural Products Treats AR by Interfering with the TGF-β/Smads Signalling Pathway

Natural Products	Causality	Subjects	Dose	Mechanisms of Action	References
18β-glycyrrhetinic acid	Pentacyclic triterpenoids	SD rats	20mg.kg^{-1}/d	IgE↓, TGF-β1↓	[169]
Paeonia lactiflora total	Monoterpene bicyclic glycosides	BALB/c male mice	30mg/kg/d, 60mg/kg/d, 120mg/kg/d	IL-4↓, IL-5↓, IL-17↓, IFN-γ↑, Smad7↑, TGF-β↓, MDA↓, GSH↓, CAT↓, SOD↓	[170]

Notes: ↑ represents upregulation, ↓ represents downregulation.

superoxide dismutase (SOD) and catalase (CAT) activities. These effects improved oxidative stress responses, reduced apoptosis, and alleviated allergic severity in mice, positioning total paeoniflorin as a promising AR therapeutic agent.[170]

Nrf2/HO-1 Signaling Pathway

Nrf2/HO-1 Signaling Pathway in Relation to AR

The Nrf2/HO-1 signaling pathway serves as a pivotal cellular defense system against oxidative stress and inflammatory responses, and is frequently implicated in chronic inflammatory conditions, metabolic disorders, neurodegenerative diseases, and cancers. The Nrf2/HO-1 pathway typically encompasses components such as Nrf2, HO-1, Keap1, and the antioxidant response element (ARE). Activation of this pathway upregulates antioxidant enzymes such as HO-1, NQO1, and SOD, which scavenge ROS, reduce lipid peroxidation products (MDA), and decrease the expression of GATA-3 (a key transcription factor for Th2 cells), while upregulating Foxp3 to enhance the immunosuppressive function of Tregs; at the same time, Nrf2 activation boosts the expression of ZO-1 and Occludin, thereby reducing allergen penetration, The products of HO-1, including cholecystokinin and CO, exert anti-inflammatory effects, inhibit EOS chemokines, and alleviate symptoms such as itchy nose and sneezing.[173]

Natural Products Modulate the Nrf2/HO-1 Signaling Pathway for the Treatment of AR (Table 10)

Daphnetin, an active coumarin derivative extracted from the plant Rafflesia chinensis, is renowned for its diverse biological activities. It is also known as Zuishi Ma Methylin and represents the first novel drug in China with significant pharmacological effects, including anti-tumor, anti-inflammatory, anti-fungal, anti-viral, and anti-anxiety properties.[182] From the perspective of the pathogenesis of AR, Daphnetin intervention improved clinical nasal symptoms in OVA-induced mouse models, and it reduced the release of inflammatory factors, activated the Nrf2/HO-1 signaling pathway, inactivated the TLR4/NF-κB signaling in the nasal mucosa, prevented the formation of oxidative stress, and restored damaged nasal mucosal morphology.[174] However, further large-scale animal and human experimental studies are needed to elucidate the precise mechanism of action and enhance the acceptance of the use of Daphnetin.

Table 10 Natural Products Treats AR by Interfering with the Nrf2/HO-1 Signalling Pathway

Natural Products	Causality	Subjects	Dose	Mechanisms of Action	References
Daphnetin	Phenylpropanoid	BALB/c mice	10mg/kg/d	IL-4↓, IL-5↓, IL-13↓, IFN-γ↑, IL-12↑, TLR4↓, NF-κB↓, Nrf2↑, HO-1↑	[174]
Mangiferin	Flavonoids	BALB/c mice	5mg/kg/d	IL-4↓, IL-5↓, IL-13↓, IL-17↓, GATA-3↓, RORγ↓, IL-12↑, IFN-γ↑, T-bet↑, EOS↓, mast cell↓, Nrf2↑, HO-1↑, MDA↓, SOD↑	[175]
Piperine	Alcohols	BALB/c mice	20mg/kg/d, 100mg/kg/d	IgE↓, mast cell↓, EOS↓, E-Cadherin↑, ZO-1↓, occludin↓, Nrf2↑, HO-1↑	[176]
Caesalpinia sappan Linn. heartwood water extract	Thapsigargin	BALB/c mice	1μg/mL/d, 3μg/mL/d, 10μg/mL/d	Eosinophil chemotactic factor-3↓, Periostin↓, MUC5AC↓, IgE↓, Histamine↓, IL-5↓, IL-13↓, ERK1/2↓, Keap1↓, NQO1↓, SOD1↑, β-actin↓, Nrf2↑	[177]
Hydroxysafflor yellow A	Monochalcone glucosides	BALB/c mice	20ug/mL/d	MDA↓, SOD↑, GPx↑, CAT↑, GSH↑, STAT3↓, ROR-γ↓, Nrf2↑, HO-1↑	[178]
Alpha lipoic acid	Disulfide	BALB/c mice	2mg/kg/d, 10mg/kg/d, 50mg/kg/d	Nrf2↑, HO-1↑, TNF-α↓, IL-1β↓, IL-6↓, IL-8↓, COX-2↓, IL-10 ↑, Foxp3 ↑, STAT3↓, RORγ ↓, IgE↓, IgG1↓	[179]
Astragalus polysaccharide	Polysaccharides	Inferior turbinate tissue	10ug/mL/d	Nrf2↑, HO-1↑, ROS↓, MDA↓, IL-13↓, SOD↓, CAT↓, GSH-Px↓	[180]
Curcumin	Diketones	Inferior turbinate tissue	20ug/mL/d	ROS↓, ERK↓, Nrf2↑, HO-1↑, SOD2↑	[181]

Notes: ↑ represents upregulation, ↓ represents downregulation.

Mangiferin, a carbonyl glycoside of tetrahydroxypyrazone and a bis-phenylpyrazone flavonoid, is primarily derived from the dried rhizomes of Zhiqi, a perennial herb in the Liliaceae family, and exhibits a broad spectrum of pharmacological activities, including immune-anti-inflammatory, analgesic, anti-lipid peroxidation, and anti-viral effects.[183] Mangiferin has been reported to affect the activation or expression of several signaling cascades, such as NF-κB, Nrf2/HO-1, and mitochondria-dependent pathways, targeting various cytokines like IL-6 and antioxidant enzymes such as SOD and CAT.[184] In vivo studies have demonstrated that mangostin reduced nasal mucosal epithelial cell and goblet cell thickness, decreased inflammatory infiltration of EOSs and mast cells in OVA-induced AR mice, and alleviated symptoms like nose rubbing and sneezing; and at the same time, it also reduced the release of IL-4, IL-5, IL-13, IL-17, and GATA-3 from Th2 and Th17 cells, regulated downstream transcription factors RNA, IL-6, and GATA-3, and down-regulated RORγ content. Additionally, mangiferin increased the levels of IL-12, IFN-γ, and transcription factor T-bet in Th1 cells in vivo to restore the Th1/Th2/Th17 balance. Notably, mangiferin reduced MDA and elevated SOD levels by up-regulating Nrf2 and HO-1 expression, thereby inhibiting oxidative stress, restoring local immune function, and enhancing nasal mucosa resistance to pathogens.[175]

Piper nigrum fruit extract, derived from the dried near-ripe or ripe fruit of *Piper nigrum L*. of the Piperaceae family, primarily contains piperine, which exerts a protective effect on the CNS.[185] Studies have shown that Piper nigrum extract reduces IgE content in mice, blocks the recruitment of inflammatory cells such as mast cells and EOSs, prevents nasal mucosal epithelial cell detachment by decreasing permeability, and inhibits gland secretion; at the same time, it also enhances the expression of E-calcineurin tight junction proteins in cellular junctions and inhibits the degradation levels of ZO-1 and occludin. In addition, black pepper extract activates Nrf2 expression and increases the synthesis of the anti-inflammatory enzyme HO-1 to restore nasal mucosal epithelial barrier function and reduce the incidence of AR.[176]

Caesalpinia sappan Linn., a traditional medicinal plant found in South India and Southeast Asia, exhibits antioxidant, anti-inflammatory, anti-allergic, and vasorelaxant activities.[186] In vivo and in vitro studies revealed that *Caesalpinia sappan Linn*. heartwood water extract (CSLW) altered the accumulation of subepithelial infiltrating inflammatory cells in OVA-induced AR mouse models, regulated the expression of EOS chemotactic factor-3, osteoprotegerin, and MUC5AC, and improved partial epithelial swelling; at the same time, it accelerated oxidative repair by decreasing cytoplasmic Nrf2 levels and the expression of related factors HO-1 and NQO1, reducing SOD1 and 4-HNE1 accumulation, and increasing in vivo antioxidant formation. Thus, CSLW can serve as a therapeutic agent for AR to reduce nasal mucosal inflammation.[177]

Hydroxysafflor yellow A (HYA), a flavonoid compound and the active phytoconstituent of safflower (*Cardhamus tinctorius L)*., possesses antioxidant, anti-inflammatory, and cardiovascular protective effects.[187] Recent experimental studies on AR mice demonstrated that HYA delayed oxidative stress and reversed the oxidative environment by lowering MDA and increasing the levels of SOD, glutathione peroxidase (GPx), CAT, and GSH. By increasing the levels of nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxygenase-1 (HO-1), it also reduced the levels of Th2 cytokines and Th17 transcription factors, reversed the imbalance of T-cell differentiation, and improved the symptoms of nasal allergy and the inflammatory lesions in the lung tissues of the model mice.[178]

Alpha lipoic acid (LA), a fat-soluble and water-soluble antioxidant found in various plants, including spinach, broccoli, and tomatoes,[188] inhibited NF-κB/IκB activation in vivo studies. It upregulated the expression of the Treg cytokine IL-10 and the Treg transcription factor Foxp3 by activating the Nrf2/HO-1 signaling pathway, suggesting a crucial role in regulating NF-κB/IκB signaling, downregulating Th17 cytokine IL-17 and Th17 transcription factors STAT3 and RORγ levels, inhibiting pro-inflammatory factor production, controlling the Th17/Treg balance, and alleviating AR conditions.[179]

APS is a water-soluble heteropolysaccharide compound with antioxidant activity and immune regulation.[67] Studies have demonstrated that APSs downregulate IL-13-induced oxidative stress injury in hNECs by activating the Nrf2/HO-1 pathway to reduce apoptosis, ROS, and MDA levels. Furthermore, APS alleviated IL-13-induced oxidative stress injury in hNECs by knocking down the WTAP/FBXW7 axis, restoring damaged nasal mucosa. From the molecular point of view, it is proven that APS is an effective alternative to the standard AR inhibitor group, with high activity and temporary, non-toxic side effects.[180]

Curcumin (Cur), a primary active ingredient of turmeric, is a natural active polyphenol with over 4000 years of medicinal use, extracted from Curcuma longa and related to traditional Chinese medicines. In the past decade, pharmacological activity and mechanism studies on Cur have gained momentum.[79] Curcumin has been confirmed to possess anti-inflammatory, antioxidant, oxygen radical scavenging, anti-bacterial, anti-fungal, anti-protozoal, anti-viral, liver and kidney protection, anti-fibrotic, as well as anti-cancer effects, with no obvious toxic side effects.[189] From the perspective of AR pathogenesis, curcumin reduced UPM-mediated ROS, inhibited ERK activation, promoted the production of Nrf2, increased the expression of HO-1 and SOD2, altered the fibrosis of the nasal mucosa, as well as improved clinical symptoms.[181]

Potential Issues Confronting Natural Products

Natural products, widely regarded as a rich repository for drug discovery and traditional medicine, harbor immense potential, but their application is not without flaws. The notion that "Natural" equates to "safe" is a misconception. While the natural products discussed in this context typically maintain therapeutic concentrations within safe parameters during treatment,[190,191] certain constituents can be inherently toxic. Prolonged use at high doses may induce varying degrees of toxic side effects and adverse reactions, including ehepatotoxicity, nephrotoxicity, neurotoxicity, cardiotoxicity, and allergic reactions.[192] For instance, aconitine poisoning can occasionally be fatal. Studies indicate that the maximum lethal dose of aconitine administered orally to mice is 1.8 mg/kg, while the minimum lethal dose for humans ranges from 1 to 2 mg.[193] Similarly, animal experiments have revealed that high concentrations of green tea extract can induce acute toxicity in rat hepatocytes.[194] Compared to the toxicity observed in animal models, artemisinin has demonstrated a favorable safety profile in human clinical trials, likely due to the relatively low doses and limited treatment durations employed.[195] The route of administration also significantly influences the toxic side effects of natural products. Compounds such as sesquiterpenelactones, terpinene-4-ol, and lithospermin can act as allergens, causing skin sensitization whilst exerting therapeutic effects.[196] When selecting natural products for treating AR, it is advisable to avoid those prone to inducing mucosal allergic reactions, given that intranasal administration is the standard route for this condition. Another significant concern is the potential for drug resistance. The use of natural antimicrobial substances, such as berberine and flavonoids, at low concentrations and in a non-standardized manner can exert sublethal selective pressure on microorganisms.[197] Furthermore, most natural products lack evidence from large-scale, high-quality, randomized double-blind controlled trials, with their efficacy and safety evaluations predominantly based on preclinical research. Additionally, the chemical composition of natural products is influenced by geographical origin, harvesting season, processing methods, and storage conditions, posing a significant challenge for standardization and global industrialization.

Conclusion and Prospect

With increasing public emphasis on quality of life and enhanced global awareness of diseases, AR has garnered significant attention. Evolving climatic conditions, environmental factors, and changing living environments have contributed to diversified disease patterns, characterized by younger onset ages and shorter remission intervals. These shifts exacerbate the disease's impact on patients' quality of life, physical and mental health, and comorbid conditions. Advances in technology and scholarly research have continuously elucidated the pathogenesis of AR, fostering the exploration of novel etiological factors and deeper investigations into established mechanisms.

This article summarizes the proven and theoretically based pathogenesis of AR and the associated pathological changes. The pathogenesis of AR can be summarized at seven levels: organismal immune regulation, neuro-immune regulation, inflammatory response, oxidative stress, dysregulation of gut flora, cellular autophagy and apoptosis, and mitochondrial dysfunction. On this basis, natural products are explored for their potential to act on cell signaling pathways to regulate the pathogenesis of AR and alter the pathological state. These natural products encompass a variety of species, including flavonoids, phenols, alkaloids, triterpenoids, saponins, and polysaccharides. They act on the ten signaling pathways of NF-κB, TLR4/NF-κB, MAPK, PI3K/Akt, IL-33/ST2, JAK/STAT, AMPK, Notch, TGF-β/Smads, and Nrf2/HO-1, which play crucial roles in regulating immune responses, inhibiting inflammation and oxidative stress, altering autophagy and apoptosis, and promoting the restoration of mitochondrial function. By controlling the

activation of immune cells such as mast cells, EOSs, and macrophages, and regulating T-cell differentiation to correct the balance of Th1/Th2 and Th17/Treg cells, these natural products offer promising therapeutic avenues. Additionally, certain natural products can enhance the defense capacity of the nasal mucosa through signaling pathways, modify the microbial composition of intestinal flora, and accelerate recovery in patients with AR. These effects have been demonstrated in animal and cellular experiments.

In contrast to existing treatments such as antihistamines and glucocorticoids, a wide variety of natural products work synergistically to regulate the upstream, midstream, and downstream processes of allergic reactions.[198] For instance, antihistamines block histamine receptors, while nasal corticosteroids suppress inflammation.[199] Many natural products, such as flavonoids, polyphenols, and terpenes, exhibit multiple biological activities, including antihistamine, anti-inflammatory, immunomodulatory, and antioxidant effects. This "Combinatorial synergy" aligns more closely with the complex pathogenesis of AR.[200] It is important to note the potential risks associated with the long-term use of existing drug treatments. For example, long-term oral administration of first-generation antihistamines can cause side effects such as drowsiness and dry mouth, while some second-generation drugs may have potential cardiac effects. Prolonged use of nasal glucocorticoids may lead to dryness and bleeding.[201]

Currently, extensive research has been conducted in fields such as gene chip technology, RNA sequencing (RNA-seq) , drug affinity reaction target stability technology, and nanotechnology, and these advancements predict the binding mode and affinity of small molecules from natural products with potential proteins, aiming to improve drug bioavailability and apply precision therapy to the treatment of AR.[202,203] It is noteworthy that natural products can effectively cross the blood-brain barrier, thereby maximizing therapeutic efficacy.[204] Overall, analyzing the role of natural products in treating AR from the perspectives of signaling pathways and pathogenesis can broaden therapeutic options, enhance drug utilization, clarify treatment mechanisms and directions, and lay the groundwork for future research into combination therapies and drug toxicity. Concurrently, this provides theoretical support and novel approaches for in-depth studies into disease prevention and management. With the advancement of technologies such as nanoparticles, liposomes, and phospholipid complexes, natural products with sufficient experimental basis will demonstrate significant clinical translational potential.[205,206] For example, the multi-target mechanism of curcumin offers new ideas for treating complex diseases, and its low bioavailability is being addressed through nanotechnology and structural modification.[207] Triptolide exhibits both potent activity and toxicity, but targeted delivery strategies, such as antibody-drug conjugates, have significantly broadened its therapeutic window, with related drugs entering late-stage clinical trials.[208] These cases illustrate that the deep integration of traditional natural products with modern medicinal chemistry and pharmaceutical technology is essential to realize their "greater potential" and transition from a "natural treasure house" to a "modern medicine". This paper has clearly identified the specific signaling pathways through which natural products exert their therapeutic effects on AR. However, whether these pathways can be leveraged to regulate corresponding complications arising from the disease warrants further investigation. Concurrently, exploring how to enhance the utilization rate of natural products to provide novel avenues for clinical treatment remains a subject worthy of consideration and exploration.

Although natural products have shown progress in regulating signaling pathways to alter the pathogenesis of AR, these studies still have significant limitations: (1) While these molecules are relatively reliable and some toxicological tests suggest safety, pharmacogenetics should address issues such as dosage form, metabolic time, and duration of efficacy; (2) The absorption, distribution, excretion, and water solubility of most natural products are poor and require further study; (3) Current research has predominantly focused on animal studies and laboratory investigations, with clinical data remaining relatively limited; (4) Emphasis should be placed on the clinical translational research of natural products, focusing on improving the quality of clinical research evidence. Therefore, more efforts are needed to maximize the therapeutic effects of these natural products in AR and to develop more effective therapeutic drugs.

Abbreviations

AR, allergic rhinitis; DCs, dendritic cells; TSLP, thymic stromal lymphopoietin; CNS, central nervous system; HPA, hypothalamic-pituitary-adrenal; EOS, eosinophil; ECP, eosinophil cationic protein; MBP, major basic protein; MPI, minimal persistent inflammation; ILC2s, type 2 innate lymphoid cells; GALT, gut-associated lymphoid tissues; IELs,

intraepithelial lymphocytes; IECs, intestinal epithelial cells; SFB, segmented filamentous bacteria; ATP, adenosine triphosphate; ROS, reactive oxygen species; DAMPs, damage-associated molecular patterns; mtROS, mitochondrial ROS; APCs, antigen-presenting cells; TCR, T cell receptor; TH, T helper; HMGB1, high-mobility group box 1; TLR4, toll-like receptor 4; IKK, IκB kinase; DNP-HSA, dinitrophenylated human serum albumin; SSA, Saikosaponin A; CLO, Chimonanthus nitens Oliv; GL, Glycyrrhizin; GA, glycyrrhizic acid; HNEpCs, human nasal epithelial cells; TLRs, Toll-like receptors; PRRs, pattern recognition receptors; MAPK, Mitogen-activated protein kinase; OMC, (2′S,7′S)-O-(2-methylbutanoyl)-columbianetin; ICAM-1, intercellular adhesion molecule 1; GSK3β, gluconeogenic synthase kinase 3β; HG, Higenamine; NK, natural killer cells; FJE, Fallopia japonica root extract; HSE, Hydrangea serrata extract; CSE, Chaenomeles sinensis; TR, Trans-resveratrol; PKN, Pulsatilla Koreana Nakai; ARE, antioxidant response element; HYA, Hydroxysafflor yellow A; SOD, superoxide dismutase; GPx, glutathione peroxidase; APS, Astragalus polysaccharide; Cur, Curcumin; RNA-seq, RNA sequencing.

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