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REVIEW

Exploring Advances in Natural Plant Molecules for Allergic Rhinitis Immunomodulation in Vivo and in Vitro

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Abstract: Allergic rhinitis (AR) is a prevalent allergic disease that imposes significant economic burdens and life pressures on individuals, families, and society, particularly in the context of accelerating globalization and increasing pathogenic factors. Current clinical therapies for AR include antihistamines, glucocorticoids administered via various routes, leukotriene receptor antagonists, immunotherapy, and several decongestants. These treatments have demonstrated efficacy in alleviating clinical symptoms and pathological states. However, with the growing awareness of AR and rising expectations for improvements in quality of life, these treatments have become associated with a higher incidence of side effects and an elevated risk of drug resistance. Furthermore, the development of AR is intricately associated with dysregulation of the immune system, yet the underlying pathogenetic mechanisms remain incompletely understood. In contrast, widely available natural plant molecules offer multiple targeting pathways that uniquely modify the typical pathophysiology of AR through immunomodulatory processes. This review presents a comprehensive analysis of both in vivo and in vitro studies on natural plant molecules that modulate immunity for treating AR. Additionally, we examine their specific mechanisms of action in animal models to provide new insights for developing safe and effective targeted therapies while guiding experimental and clinical applications against AR.

Keywords: natural plant molecules, allergic rhinitis, immunomodulation, therapeutic mechanism, research progress

Introduction

Allergic rhinitis (AR), a prevalent chronic inflammatory disease that affects the nasal mucosa of the upper respiratory tract, is categorized into two types: perennial and seasonal. This condition is characterized by recurrent episodes of sneezing, rhinorrhea, nasal congestion, and pruritus. In some patients, it may progress to allergic conjunctivitis, idiopathic dermatitis, allergic pharyngitis or eosinophilic esophagitis.[1–3] The rapid advancement of the global economy coupled with accelerated industrialization and continuous changes in climate and environment has led to an increase in allergens and a rise in related risk factors, resulting in higher incidence rates of AR.[4] Reports suggest that the global annual cost associated with AR is approximately $20 billion, with prevalence rates ranging from 10% to 40% worldwide and between 20% and 30% among adults; it exceeds 8.5% in school-age children and reaches up to 14% in adolescents in the Americas and Europe.[5,6] The World Health Organization Working Group has recognized AR as a global health problem. This increasing prevalence poses a significant challenge to global health, having extensive implications for individuals as well as society at large. Therefore, there is an urgent need to identify safe and effective prevention methods along with control measures.

The pathogenesis of AR remains incompletely understood as it involves a variety of biological pathways primarily associated with regulating the immune system. The entry of allergens disrupts existing immune mechanisms and stimulates allergic reactions that damage the nasal mucosal structure and trigger an inflammatory response.[7] Concurrently, it induces

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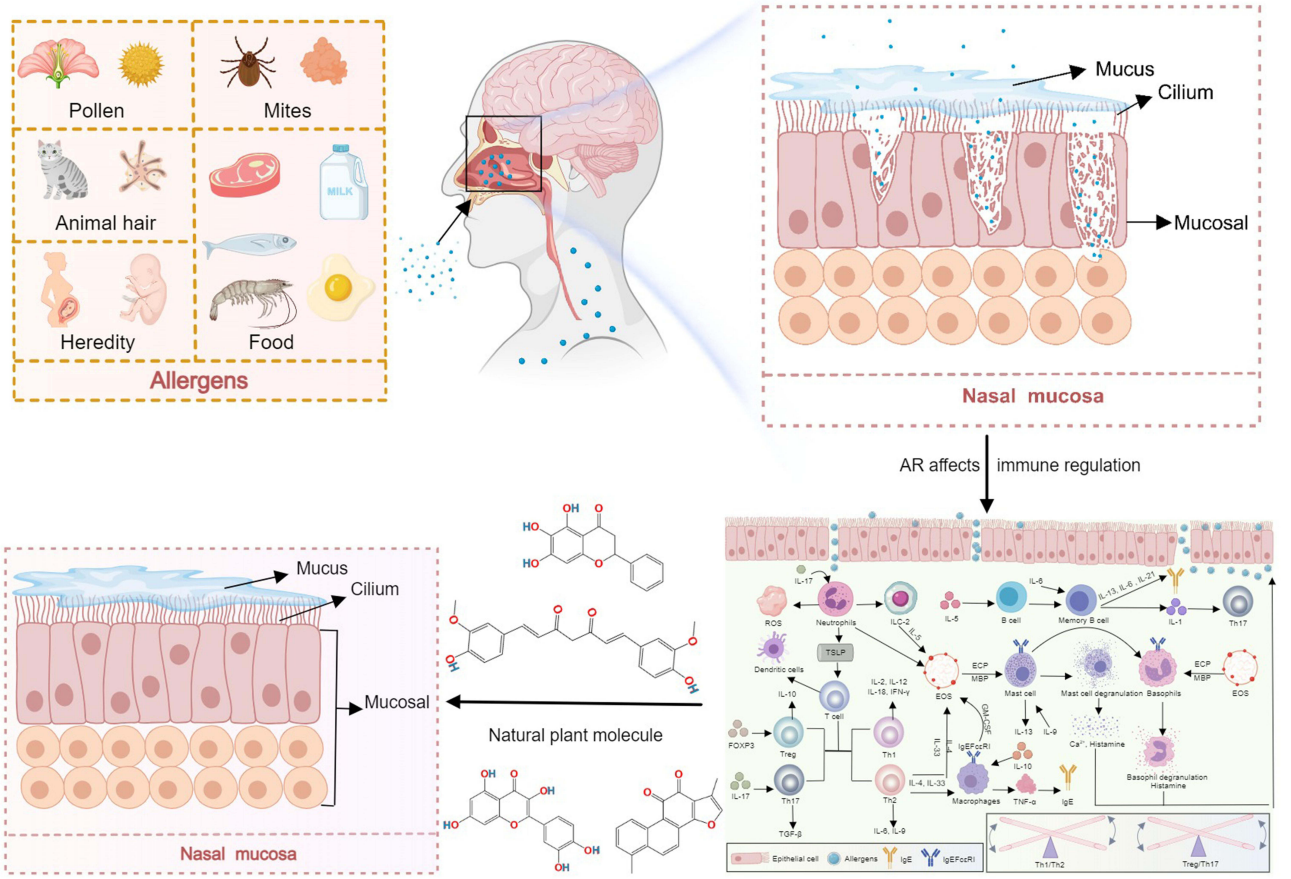
Graphical Abstract



abnormal cellular secretion while compromising capillary integrity and impairing circulatory function. These processes can initiate various pathological reactions that may lead to allergic diseases through multiple pathways.[8] Furthermore, studies have shown that the immune system transmits inflammatory signals to the central nervous system via both neuro-reflex and non-neuro-reflex mechanisms, activating specific brain regions and altering brain function. This understanding paves the way for targeted pharmacological interventions.[9] Currently, in clinical practice, there are 15 commonly utilized antihistamines in Western medicine, including diphenhydramine, levocetirizine, desloratadine, and others; 6 types of glucocorticoids such as budesonide nasal spray, mometasone furoate, and fluticasone propionate; 4 varieties of decongestants including pseudoephedrine, oxymetazoline, and cylozolin; 8 different anti-leukotriene drugs like pranlukast, zafirlukast, and montelukast; along with 3 distinct forms of specific immunotherapy encompassing subcutaneous administration as well as sublingual and nasal immunotherapy.[10] Since alternative therapies are excluded from these guidelines, treatment options remain limited. Additionally, other medications with targeted mechanisms are either undergoing clinical trials or have not yet reached the market. To date, many modern therapeutic strategies have failed to intervene effectively in the disease process and merely manage symptoms. As a result, identifying safe and effective drug-targeting pathways and developing multifunctional, multi-targeted drugs for AR within complex biological pathways present both challenges and opportunities.

In recent years, extensive studies have increasingly highlighted the unique therapeutic advantages of natural plant molecules in the treatment of AR. These molecules are characterized by their ability to target multiple pathways and channels while exhibiting minimal side effects, allowing them to influence relevant cells and mediators involved in immune regulation. Notably, the combination of specific monomers and components from Traditional Chinese Medicine

(TCM) facilitates the development of personalized and precise therapeutic strategies. The herbs commonly utilized for the treatment of AR encompass Astragalus, Atractylodes macrocephala, Xanthium sibiricum, Divaricate saposhnikovia root, Mentha haplocalyx, Dark plum, and Magnoliae Flos. Their active constituents are frequently observed in curcumin, quercetin, as well as other polyphenols, flavonoids, and saponins.

However, due to the complexity of their pathways and mechanisms of action, the precise role of natural plant molecules in immunomodulation remains ambiguous. This paper aims to comprehensively explore the role of natural plant molecules in immunomodulating AR by systematically addressing the relationship between immunomodulation and the pathogenic aspects of AR, elucidating the specific mechanisms that affect its progression, and detailing the pathways through which natural plant molecules exert their immunomodulatory effects. The findings from this study will help identify new therapeutic targets for combating AR and provide valuable insights for future experimental studies and clinical applications.

Pathogenesis of AR

The pathogenesis of AR, a non-infectious disease, involves the activation of type 2 helper T cells (Th2 cells), which drive the IgE-mediated degranulation of mast cells and subsequent release of inflammatory mediators.[11] Dendritic cells and macrophages within the body uptake allergens and inhibit Th1-type cytokine activity through antigenic Th2-type cytokines such as IL-4, IL-5, and IL-13, thereby inducing a series of immune responses. Additionally, cytokines such as IL-2 and INF-γ are involved in further contributing to these immune responses.[12] AR progresses through two stages: sensitization and excitation.[13] During the sensitization stage, initial exposure to allergens triggers a latency period of 1–2 weeks, during which protease activity compromises the barrier function of nasal mucosa and accelerates the production of pro-inflammatory factors. Concurrently, the nasal mucosal epithelium acts as the primary defense mechanism by extending dendritic cell projections beneath the mucosa upon invasion by allergens. This process exposes antigenic determinants to local lymph nodes, which synergistically stimulate signaling to naïve helper T cells (Th0 cells) and nasal mucosa CD4 cells, leading to their activation as Th2 cells and promoting the secretion of Th2 cytokines. Additionally, this activation results in increased expression of ICAM-1 by vascular endothelial cells. This activation sequence involves eosinophils, mast cells, and cytokines such as IL-4, IL-5, and IL-13. Cytokines play a pivotal role in the subsequent immune response by facilitating the differentiation of B cells into plasma cells and the synthesis of immunoglobulins that convert into specific IgE. This IgE binds to the surfaces of effector cells, such as mast cells and basophils, through the high-affinity receptor FcεRI in a sensitized state. Upon re-exposure to the same allergen, a patient with sensitized AR enters an excitation phase during which the allergen immediately binds to specific IgE, disrupting immune regulation. This phase consists of a rapid-onset and a delayed-onset phase. The rapid-onset phase occurs within seconds to six hours after allergen re-exposure and primarily involve effector cells like mast cells and basophils. During this phase, the allergen bridges two neighboring IgE molecules on effector cell surfaces, prompting cell degranulation and releasing numerous inflammatory mediators, including histamine, leukotrienes, prostaglandins, and platelet-activating factors. These mediators induce clinical symptoms such as nasal itching, sneezing, and a runny nose by binding to various receptors. The delayed phase occurs 12 to 24 hours after re-exposure primarily involving eosinophils as effector cells. Activated eosinophils release inflammatory mediators, including leukotrienes and eosinophil cationic proteins that contribute to symptoms like nasal congestion and a runny nose. During the activation phase, upon re-exposure to the allergen, it immediately binds to specific IgE on the surfaces of mast cells, triggering a pathological immune response (Figure 1).

Immunomodulatory Structure and Function

The concept of immunity can be categorized into two main types: physiological and pathological types. Animals are capable of distinguishing between two distinct categories of antigens: “self” and “non-self”. The body develops immune tolerance towards self-antigens while mounting rejection responses against non-self antigens. In healthy individuals, physiological immunity effectively detects and responds to pathogenic microorganisms through mechanisms such as phagocytosis, anti-inflammatory actions, and anti-infective responses, thereby maintaining physiological homeostasis.[14] However, despite the immune system’s complex structure and numerous components, it can occasionally cause harm by

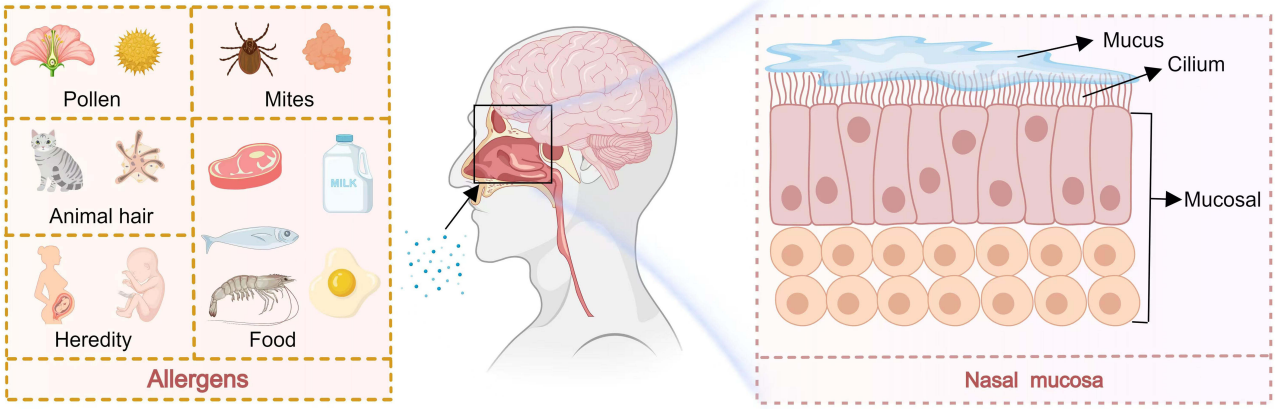


Figure 1 The pathogenesis of allergic rhinitis is that the allergen enters the nasal cavity. The allergen mainly comes from pollen, mites, animal fur, food and heredity, the mucosal cells produce pathological changes.

triggering autoimmune diseases, hypersensitivity reactions, and inflammation in response to pathogen invasion. Upon encountering such invasion, the immune system rapidly mobilizes by differentiating immune cells that secrete and release molecules to activate the immune response.[15] Subsequently, these immune cells secrete additional molecules that activate other bodily systems in a collaborative effort to eliminate pathogens and restore physiological stability. Modern immunology posits that the immune system of a healthy organism typically maintains stability through self-regulatory mechanisms. Nevertheless, when immune regulation is compromised, this can disrupt physiological balance and lead to disease. In Western medicine, immune-related diseases are addressed by administering exogenous substances to control disease factors, employing various drugs or surgical interventions to modulate the immune response and influence disease progression. Although these interventions often provide rapid relief, they primarily target symptoms rather than addressing the underlying causes of diseases, which may result in relapses and increased difficulty in managing the disease due to developed self-tolerance. As a result, Chinese medicine has gained attention from immunologists for its distinctive diagnostic and treatment approaches (Figure 2).

Granulocytes

Neutrophil

After differentiating and maturing in the bone marrow, neutrophils are released into either peripheral blood or tissues. In these locations, they carry out phagocytosis and degranulation functions that serve as the first line of innate immune defense.[16] Stimulation by allergens on nasal mucosa results in a significant increase in mucosal neutrophils count along with T cells activation and enhanced migratory capacity for eosinophils.[17] During the initial phase of AR, neutrophils, which are recruited prior to eosinophils, induce Th2-type inflammation in the airways through the formation of neutrophil extracellular traps (NETs), releasing inflammatory mediators.[18] As AR progresses, the response to allergens is characterized by increased neutrophil chemotaxis, phagocytosis, and reactive oxygen species (ROS) production that contribute to oxidative stress. Furthermore, eosinophil cationic proteins (ECPs) are produced via an IgE-dependent mechanism, which further activates eosinophils and exacerbates inflammation.[19]

Basophil Granulocytes

Basophils, which mature in the bone marrow and are released into the peripheral blood, constitute only 0.5–1.0% of leukocytes.[20] Despite their limited abundance, they rapidly synthesize Th2-type cytokines, thereby effectively supporting the immune response in AR.[21] Basophils share several characteristics with mast cells and function as both Th2-inducing cells and antigen-presenting cells (APCs), primarily through the expression and engagement of the IgE receptor FcεRI on their cell surfaces.[22] Upon exposure to allergens, allergen-specific IgE binds to basophils and cross-links with them,

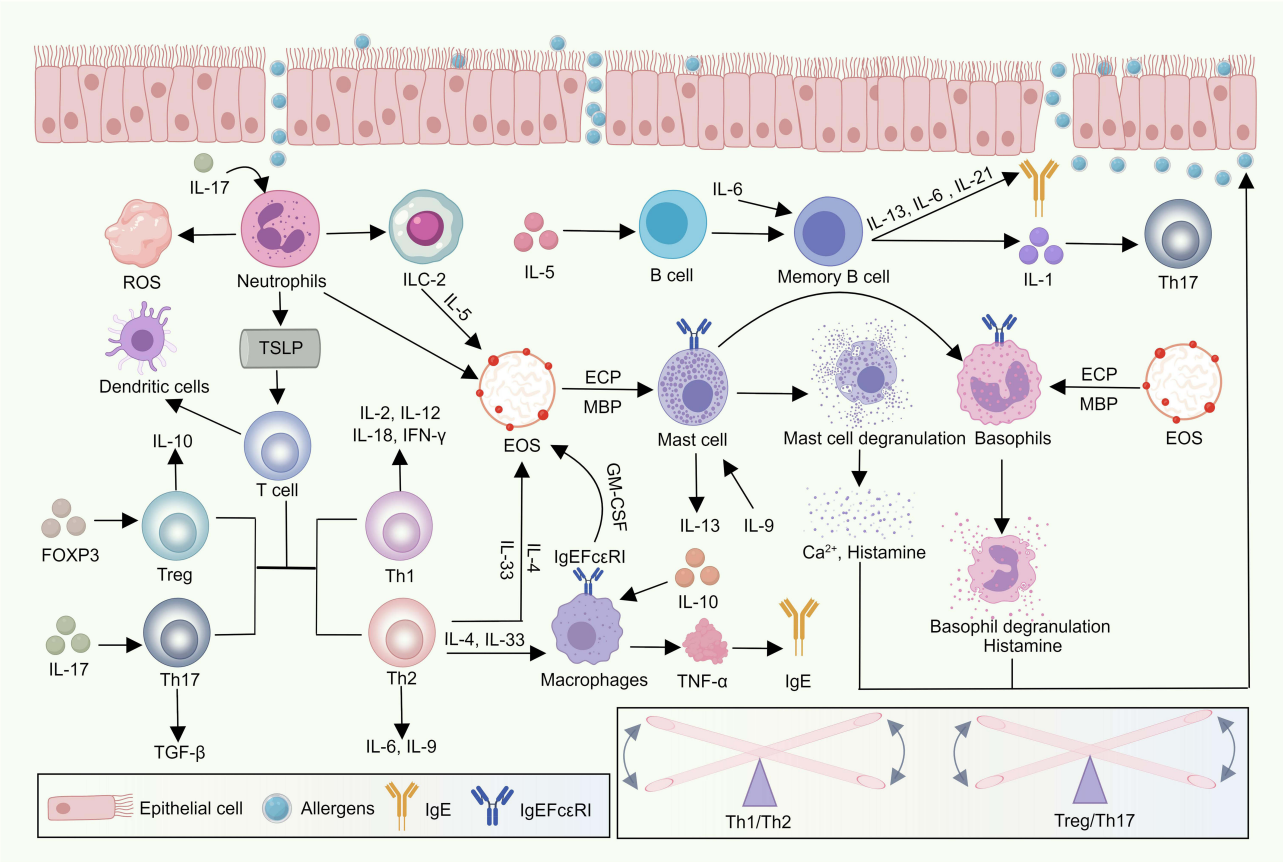


Figure 2 The Allergen invades the nasal mucosa, first into the neutrophil, triggering an oxidative stress response. It affects TSLP and releases Ilc-2. Ilc-2 release IL-5 factor under the activation of Allergen, make it act on B cells, and form memory B cells under the influence of IL-6, igE production and IL-1 cytokine production affect Th17 cell secretion. TSLP leads to imbalance of Th1, Th2, Treg and Th17 cells in T cells, and stimulates dendritic cell. Th2-releasing factors and IgE receptors act on macrophages to release IgE and other factors, il-33 and IL-4 factors released by Th2 Act together with IL-5 factors released by Ilc-2 on eosinophil granulocyte. The Eosinophil granulocyte release ECP, MBP and IgE receptors, which act on mast cells and basophil granulocyte. The mast cells degranulate to release calcium and histamine, and the basophil granulocyte degranulate to release histamine, which reacts with the nasal mucosa, initiate the corresponding inflammatory response.

triggering the release of effector molecules such as histamine and leukotrienes. Notably, basophil activation is initiated by FcεRIα-mediated cross-linking via IgE antibodies independent of their presence on the basophil membrane. Basophils play a crucial role in the onset, development, and maintenance of AR as major effector cells that are highly sensitive to IgE-mediated activation.[23] Research has demonstrated that basophils contribute to the pathogenesis of various allergic diseases, including AR. Clinically, the basophil activation test (BAT) aids in diagnosing AR and monitoring patient responses to therapy.[24] However, the role of basophils in AR remains controversial, and further research is required to elucidate and clarify their involvement in the development and onset of AR.

Eosinophils

Eosinophils (EOS), derived from bone marrow hematopoietic stem cells, undergo differentiation and maturation within the bone marrow prior to being released into the peripheral blood.[25] The development of EOS is influenced by various cytokines, including IL-5, IL-33, and granulocyte-macrophage colony-stimulating factor (GM-CSF).[26] EOS serve as effector cells in natural immunity, along with neutrophils, participate in antibody-dependent cell-mediated cytotoxicity, resulting in tissue damage and inflammation. In allergic diseases, EOS go through multiple stages of development, adhesion, migration, and activation before being recruited to the site of inflammation.[27] Mature EOS, regulated by IL-5, migrate from the bone marrow into the bloodstream. Following allergen stimulation, mast cells and endothelial cells at the site of inflammation secrete various cytokines that activate surface integrins (such as β1, β2, and β7) on EOS, thereby promoting their aggregation at the site. Once EOS adhere to epithelial cell ligands via integrins, a signaling cascade is activated, leading to the release of cytotoxic particles specific to EOS as they migrate toward the inflammation site,

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guided by the synergistic effects of chemokines.[28] Additionally, activation products of eosinophils, including ECP and major basic protein (MBP), stimulate mast cells and basophils to release histamine, which increases vascular permeability and mucus secretion.[29,30] This process ultimately damages the epithelium of respiratory mucosa and exacerbates local inflammatory responses.

Macrophages

Macrophages function as pivotal bridge cells between innate and adaptive immunity, playing a crucial role in coordinating immune responses. Upon pathogen invasion, macrophages present in the blood or tissues phagocytose and eliminate pathogens, induce cellular immune responses, and facilitate tissue repair and remodeling.[31] Additionally, due to their inherent plasticity, macrophages exposed to diverse microenvironmental stimuli can differentiate into various subpopulations, predominantly M1 and M2-type macrophages.[32] The roles of macrophages include: 1) providing antigenic information to lymphocytes; 2) producing oxygen free radicals and lymphokines, such as IL-1, which modulate inflammatory responses; 3) generating inflammatory mediators like arachidonic acid and platelet-activating factor; 4) modulating lymphocyte activation; and 5) exhibiting limited affinity for the IgE Fcε surface receptor. Macrophages play a crucial role in balancing Th1/Th2-type immune responses in AR.[33] Cytokines and chemokines secreted by M2-type macrophages facilitate the differentiation of Th2 cells and the recruitment of EOS. Th2-type cytokines, such as IL-4 and IL-13, promote macrophage polarization towards the M2 phenotype through STAT6 activation. Conversely, M2 macrophages secrete various cytokines and chemokines including Arginase-1 (Arg-1), CCL17, and CCL24 to regulate eosinophil recruitment and mediate allergic inflammation.[34] Furthermore, increased TGM2 expression in M2 macrophages enhances eosinophilic infiltration. Additionally, macrophages and classic T-lymphocyte immune mechanisms complement each other and regulate the progression and resolution of allergic diseases while also influencing the course of AR.[35,36]

Mast Cells

Mast cells (MCs) are the primary effector cells in type I hypersensitivity reactions, playing a crucial role in the activation and aggregation of neutrophils and EOS. Originating from the bone marrow, MCs circulate in the bloodstream in an immature form before migrating to various tissues.[37] The degranulation of MCs is central to the pathophysiology of AR, with the secretory response varying significantly based on the size and distribution of FcεRI clusters.[38] Immature MCs undergo maturation through IgE-induced histamine synthesis and cytokine release. Upon maturation, they produce and store numerous dense cytoplasmic granules, which are released in response to specific stimuli.[39] The most common stimulus for this release is cross-linking of IgE molecules via multivalent antigen binding to the high-affinity IgE receptor, FcεRI. The binding of IgE to multiple FcεRI on the cell membrane initiates the phosphorylation of downstream proteins, activating signaling molecules and generating second messengers.[40,41] This cascade results in the release of Ca^{2+} from the MC's endoplasmic reticulum, leading to subsequent MC degranulation. Degranulation through the IgE-dependent pathway results in various symptoms, including damage to epithelial tissue, thickening of the basement membrane, hypertrophy of airway smooth muscles, and increased respiratory mucus.[42,43]

Dendritic Cells (DCs)

Dendritic cells (DCs) are derived from hematopoietic stem cells in the bone marrow. In the human nasal mucosa, DCs predominantly reside in the epithelium and lamina propria. They traverse the tightly connected epithelium through dendritic projections.[44] Based on their origin, DCs can be classified into plasma cell-like dendritic cells (pDCs) and myeloid dendritic cells (mDCs).[45] The two principal types of DCs found in blood and lymphoid tissues are conventional DCs (cDCs) and pDCs. Functioning as "transmitters" in the pathogenesis of AR, DCs by capture and present allergens to naive T cells, subsequently initiating a cascade of immune responses.[46–48] Together with macrophages and B cells, DCs form the three primary populations of APCs. Unlike macrophages, which do not migrate to lymph nodes or activate T cells ex vivo, DCs possess the ability to transport antigens to draining lymph nodes, thereby initiating T cell activation. Only live, mature, and fully functional DCs that migrate to the lymph nodes can effectively stimulate a T cell response.[49,50]

B-Cells

B cells, which are essential for humoral immune defense and effective antigenic recognition, migrate back to local lymph nodes and serve as sources of allergen-specific IgE in AR.[51] They can either mediate an immediate immune response by producing IgG or act as regulatory B cells in the absence of pathogenic entities.[52] AR is categorized into two phases: sensitization and stimulation. During the sensitization phase, the initial exposure of the nasal mucosa to allergens involves a latency period of 1–2 weeks. During this time, protease activity impairs the barrier function of the nasal mucosa upon contact with the allergen and accelerates the production of pro-inflammatory factors. Patients with AR exhibit a significant increase in memory B cells, plasma cells, and CD19+CD24hiCD27+ Bregs, while naïve B cells are substantially reduced compared to healthy individuals.[53] The initial increase in serum allergen-specific IgE characterizes the B cell response, likely representing a memory response triggered by exposure to allergens. Memory B cells, which become activated upon encountering antigens, maintain long-term sensitization or tolerance to allergens through rapid proliferation, somatic mutations, and class-switch recombination.[54] Treg cells inhibit the functions of B cells and influence their proliferation, activation, and apoptosis. In AR patients, B cells have a notable impact on the magnitude, duration, and affinity of IgE production. The IL-21 receptor signaling in B cells is crucial for regulating IgE.[55]

T-Cells

T lymphocytes, crucial regulators of the cellular immune response, mature into two primary types: CD4+ T cells and CD8+ T cells. CD4+ T cells can be further subdivided into three subtypes based on their secretion of cytokines: Th0, Th1, and Th2.[56] Th1 cells secrete cytokines such as IL-2, IL-12, and INF-γ that play a role in in humoral immunity and regulate the differentiation of cytotoxic T helper cells, thereby contributing to the pathogenesis of AR. In contrast, Th2 cells produce cytokines like IL-4 and IL-5, which activate MCs, EOS, and basophils. These immune cells accumulate at sites of inflammation where they degranulate and release inflammatory mediators to modulate AR.[57] Regulatory T cells (Tregs), a specialized subtype of T lymphocytes characterized by the expression of CD4+, CD25+, and the transcription factor Foxp3, possess immunoregulatory functions exerting suppressive effects on immune responses. Thymic Treg cells (tTregs) interact with DCs to promote immune tolerance. Tregs can be categorized into two groups based on their origin: tTregs and induced Treg cells (iTregs), each playing distinct roles in immune regulation.[58] In vivo, Tregs either differentiate directly in the thymus or develop from conventional CD4+ T cells in the periphery. Foxp3, a crucial regulator of Treg development and function, is essential for inducing and maintaining the Treg cell phenotype. Foxp3+ Treg cells sustain their suppressive functions both in vivo and in vitro after expansion, presenting potential therapeutic avenues for AR.[59] The acetylation, phosphorylation, and ubiquitination of Foxp3 are integral to the development and functional maintenance of tTreg cells by influencing protein stability and DNA-binding capacity. Foxp3 collaborates with other transcription factors and proteins to shape the transcriptional profile and effector functions of Treg cells. Disrupting specific protein interactions with Foxp3 diminishes Treg cell functionality. Under specific environmental conditions, Treg cells can modulate the components of the Foxp3 protein complex to regulate inflammation associated with AR.[60] The expression and stability of Foxp3 are crucial in maintaining the functionality of Treg cells. Treg cells exhibit both plasticity and instability, as activated Tregs can inhibit the interaction between T-cell responses and DCs. Post-translational modifications, including hyperacetylation, play a crucial role in regulating the plasticity and stability of Treg cells by modifying Foxp3. IL-2, a key cytokine for promoting T cell proliferation and differentiation, plays an indispensable role in the development, survival, and function of Foxp3+ Treg cells. Studies have demonstrated that naturally occurring Treg cells are characterized by their expression of Foxp3. The suppressive function of Treg cells is influenced not only by their expression of Foxp3 but also by the microenvironment. Tregs exert immunosuppressive effects through cell-contact mechanisms and secretion of inhibitory cytokines, while also influencing T cell function by regulating APCs.[61] Foxp3 is currently recognized as the most reliable molecular marker for natural Treg cells, elucidating the mechanisms underlying Treg cell differentiation. Foxp3 collaborates with various transcription factors and proteins to shape the transcriptional profile and effector functions of regulatory T (Treg) cells.[62] Disruption of specific protein interactions with Foxp3 impairs the functionality of Treg cells. Under certain environmental conditions, Treg cells can modulate the components of the Foxp3 protein complex to regulate inflammation associated with AR. The expression and stability of Foxp3 are crucial for maintaining Treg cell functionality. Treg cells exhibit both plasticity and instability; activated Tregs can inhibit

the interaction between T-cell responses and DCs.[63–65] Post-translational modifications of Foxp3, including hyperacetylation, play significant roles in regulating the plasticity and stability of Treg cells. Interleukin-2 (IL-2), a key cytokine for T-cell proliferation and differentiation, is indispensable for the development, survival, and function of Foxp3+ Treg cells. Numerous studies have demonstrated that naturally occurring Treg cells are characterized by the expression of Foxp3.[66] The suppressive function of Treg cells is not only influenced by Foxp3 expression but also by the surrounding microenvironment. In addition to regulating APCs, Tregs exert their immune-suppressive effects through both cell-contact mechanisms and secretion of inhibitory cytokines. Currently recognized as the most reliable molecular marker for natural Treg cells, Foxp3 elucidates the underlying mechanisms involved in Treg cell differentiation.[67] However, the instability in Foxp3 expression can significantly diminish their suppressive capacity, potentially disrupting immune tolerance and contributing to AR. The mechanisms governing Foxp3 stability and Treg cell integrity remain incompletely understood.[68] Furthermore, understanding these regulatory mechanisms is crucial due to the impact of specific Treg cell populations on the severity of AR when exposed to allergens. Clinical trials have investigated the therapeutic potential of Treg cells for immune disorders, suggesting their prospective application in managing AR.[69,70]

Inflammatory Factor

IL-1

Interleukin-1 (IL-1), a lymphocyte-stimulating factor commonly found in the forms of IL-1α and IL-1β, is predominantly produced by macrophages.[71] Additionally, almost all nucleated cells, including B cells and DCs, can produce IL-1. IL-1 plays a role in negative regulation of the inflammatory signaling pathway mediated by the IL-1 receptor/Toll-like receptor.[72] Research indicates that IL-1R8 significantly negatively regulates Th17 cell differentiation, proliferation, and function by directly inhibiting the IL-1 signaling pathway.[73] Immunomodulatory effects of IL-1 include: 1) synergistic effects with antigens to activate CD4+ T cells; 2) promotion of B cell growth and differentiation, enhancing CD4+ T cell activation and expression of the IL-2 receptor, leading to a 100-fold increase in the number of hemolytic vacuoles in splenocytes (PFC), indicating the role of IL-1 in promoting antibody production; 3) enhancement of antigen-presenting capacity for monocytes, macrophages, and other APCs; 4) synergy with IL-2 or interferon to enhance NK cell activity; and 5) attracting neutrophils, which subsequently release inflammatory mediators.[74–76]

IL-2

Interleukin-2 (IL-2), a cytokine produced by activated Th1 cells, primarily promotes the proliferation of killer T cells and NK cells, enhances the differentiation and proliferation of B cells, stimulates antibody production, and induces lymphokine-activated killer cells.[77] IL-2 is crucial for the immune response; nonetheless, aging and various diseases can diminish IL-2 production, subsequently impacting the entire immune system. In order for IL-2 to exert its immunomodulatory effects, it must bind to the activated membrane interleukin-2 receptor (mIL-2R).[78] The soluble interleukin-2 receptor (sIL-2R), a polypeptide released into the bloodstream by activated Th1 cells, competes with mIL-2R for IL-2 binding and inhibits the clonal expansion of activated T cells. The IL-2/IL-2R system plays a central role in regulating the body's immune response.[79]

IL-3

Interleukin-3 (IL-3), an important member of the interleukin family and also referred to as multi-directional colony-stimulating factor (multi-CSF), is a cytokine produced by T lymphocytes.[80] It stimulates the proliferation in the immune response-associated cells, including Th2 cells that secrete pivotal cytokines. IL-3 is crucial in the pathogenesis of AR as it stimulates the proliferation and differentiation of multipotent hematopoietic stem cells, MCs, EOS, and basophils.[81,82] Furthermore, IL-3 induces not only multipotent hematopoietic stem cell and MCs proliferation and differentiation but also that of EOS and basophils.[83] Due to its broad impact on various cell types, IL-3 is also referred to as a multi-colony stimulating factor. Under normal circumstances, IL-3 concentration is tightly regulated through negative feedback. However, in allergic conditions, activation of the IL-3 gene leads to abnormally high concentrations of this cytokine.[84]

IL-4

Interleukin-4 (IL-4) is a cytokine secreted by type II helper T cells (Th2 cells). As a hallmark of Th2 cells, IL-4 promotes the proliferation of activated B and T cells and facilitates the differentiation of CD4+ T cells into type II helper T cells.[85] Additionally, it regulates humoral and adaptive immunity, induces class switching to IgE in B cell antibody production, and upregulates the expression of type II major histocompatibility complex.[86] IL-4 plays critical roles in metabolic responses such as promoting the differentiation of type 2 helper T lymphocytes, inducing IgE production, upregulating cellular adhesion molecule 1 expression via the IgE receptor, facilitating eosinophil migration to the lungs, inhibiting apoptosis in T lymphocytes and promoting mucus hypersecretion.[87] Furthermore, IL-4 enhances the adhesion of EOS and basophils to endothelial cells and inhibits the production of γ-interferon.[88] Additionally, IL-4 prompts the proliferation, differentiation, and maturation of MCs. Upon activation, MCs release IL-4 into the extracellular microenvironment, which in turn activates T cells to produce more IL-4 and further initiates recruitment of inflammatory cells.[89] The documented impact of IL-4 on MC proliferation, differentiation, and maturation is well-established. Moreover, it has been shown that IL-4 inhibits TGF-β-mediated FoxP3 expression, thereby preventing the conversion of naive T cells into Tregs. Allergenic individuals exhibit increased secretion of IL-4 following allergenic stimulation.[90,91]

IL-5

The multifunctional cytokine Interleukin-5 (IL-5) is produced by cells of the immune system. It is primarily produced by activated T cells and is particularly abundant in the Th2 cell subpopulation.[92] IL-5, secreted by activated Th2 helper cells, possesses proliferative, chemotactic, and activating functions for EOS.[93] When EOS infiltrate the nasal mucosa, they can release ECP and MBP, both of which are cytotoxic and neurotoxic.[94] These proteins can damage the nasal mucosa and enhance glandular secretion, leading to symptoms such as nasal congestion, itching, runny nose, and sneezing. IL-5 stimulates the proliferation and differentiation of B cells while also promoting antibody production to enhance the humoral immune response. On one hand, IL-5's activation of EOS synergizes with other cytokines to enhance their inflammatory infiltration and increase the expression of adhesion molecules.[95] On the other hand, IL-5 prolongs the lifespan of EOS and alters their density from normal to low. While IL-5 activates EOS, these cells can also produce more IL-5 themselves, creating a feedback loop that exacerbates and prolongs AR.[96,97]

IL-6

Interleukin-6 (IL-6), a cytokine secreted by Th2 cells, is also produced by MCs, epithelial cells, and endothelial cells within the body. IL-6 exerts regulatory effects on the growth and differentiation of various cell types.[98] The cytokine induces T-cell activation, growth, and differentiation, as well as promoting the differentiation of Th0 cells into Th17 cells and MC proliferation.[99,100] In response to IL-6 stimulation, B-cells differentiate into mature plasma cells that subsequently secrete IgE. IL-6 plays a crucial role in the cascade of inflammatory mediators contributing to fibrosis and airway remodeling. The effects of IL-6 are dose-dependent: normal levels have beneficial effects, while excessive production leads to various inflammatory damages. Serum levels of IL-6 increase under conditions such as inflammation, infection, and certain tumors.[101]

IL-9

Interleukin-9 (IL-9), produced by Th2 cells, serves as an important factor in immune regulation and the inflammatory response.[102] By enhancing MC survival and function, IL-9 promotes inflammation and triggers the release of additional inflammatory mediators. IL-9 acts on effector Th2 cells and memory T cells of the Th2 phenotype, which directly differentiate from them.[103] In IL-9 cells, the transcription factor PU.1 activates Th9 cell differentiation while inhibiting Th2 cell differentiation. As a result, cytokine expression in Th2 cells is significantly reduced, whereas IL-9 expression is markedly increased.[104,105]

IL-10

Interleukin-10 (IL-10), derived from multiple cell types, is a multifunctional cytokine that regulates cellular growth and differentiation and plays a crucial role in inflammatory and immune responses.[106] IL-10 exerts its influence on key

functions of monocyte macrophages, including the release of immune mediators and antigen presentation. In brief, IL-10 inhibits the ability of monocyte macrophages to promote natural and specific immunity functions while enhancing cytostatic, immune tolerance-inducing, and scavenging activities.[107] Indeed, IL-10 suppresses the secretion of inflammatory mediators by monocyte macrophages, thereby reducing the levels of TNF-α, IL-1β, IL-6, IL-8, G-CSF, and GM-CSF in response to LPS and IFN-γ.[108] Furthermore, IL-10 promotes the release of anti-inflammatory factors, including IL-1 receptor antagonists and soluble TNF-α receptors. Thus, IL-10 significantly reduces the levels of key cytokines involved in innate immunity and inhibits antigen presentation by monocyte macrophages.[109] Moreover, IL-10 suppresses the synthesis of IL-12, thereby hindering the Th1 immune response. The inhibitory effect of IL-10 on cellular factor production and antigen presentation is further enhanced by CD4+ T cell suppression. Additionally, IL-10 hampers IFN-γ production by Th1 cells, while a deficiency in IFN-γ enhances APC inactivation. IL-10 also decreases macrophage secretion of essential cytokine IL-23 required for Th17 cell-mediated immunity.[110]

IL-12

Interleukin-12 (IL-12), produced mainly by activated macrophages and DCs, is a significant immunomodulatory cytokine.[111] This cytokine is crucial in promoting the secretion of Th1 cytokines, such as IFN-γ, which enhance immune responses of Th cells. Simultaneously, it inhibits the production of Th2 cytokines, like IL-4, that suppress immune responses of Th2 cells.[112]

IL-13

Interleukin-13 (IL-13), an immunomodulatory protein with inhibitory properties, shares both functional and structural similarities with IL-4. It is primarily produced by Th2 cells and MCs. As members of the Th2 gene family, they both utilize the same receptor chain and signaling system. In the absence of IL-4, IL-13 serves as a critical factor in inducing Th2 responses and is a major mediator of Th2 cell production.[113] During the development of allergic diseases, such as AR, levels of IL-13 are significantly elevated. IL-13 induces mitosis in B-lymphocytes activated by IgM or anti-CD40 monoclonal antibody, contributing to their differentiation and antibody class switching. Additionally, it enhances the production of IgE, IgM, and IgG, while inhibiting apoptosis in B-cells.[114] In the presence of activated CD4+ T cells or anti-CD40 monoclonal antibody, IL-13 autonomously induces B cells to synthesize IgE. IL-13 functions as a TH2 cell effector by inducing the synthesis and extracellular secretion of IgE by activated B lymphocytes. Additionally, it enhances the body's response to mutagens, promotes cuprocyte proliferation and gland secretion, and exacerbates nasal cicatrization in AR.[115,116] As a TH2 effector, IL-13 plays a pivotal role in the pathogenesis of AR through its regulation of Th1 and Th2 cell functions, promotion of IgE secretion by B cells, and localization of the response to mutagens.[117]

IL-17

Interleukin-17 (IL-17), a subset of pro-inflammatory cytokines, is mainly synthesized by activated CD4+ lymphocytes and stimulates T lymphocytes, particularly during the initial stages of inflammation, affecting a variety of cells and tissues.[118] It induces mesenchymal stromal cells to secrete inflammatory and hematopoietic cytokines, such as IL-6 and IL-8. Furthermore, it prompts fibroblasts to facilitate the proliferation and differentiation of CD34+ hematopoietic progenitors, a process closely related to autoimmunity and tumorigenesis.[119] Additionally, IL-17 amplifies inflammation by inducing the release of neutrophil chemokines.[120]

IL-18

Interleukin-18 (IL-18), a member of the serum IL-1 family, is a widely distributed pro-inflammatory factor with diverse biological activities. It is expressed in various cells including B-cells, T-cells, macrophages, osteoblasts, and keratinocytes.[121] In AR patients, IL-18 can up-regulate IgE production and activate Th2 cells to produce cytokines. It synergizes with IL-12 to produce IFN-γ, which inhibits IL-4-induced IgE synthesis. This ultimately reduces serum IgE levels, decreased eosinophil aggregation in the nasal mucosa, and suppressed proliferation of Th2 cells. These actions result in decreased release of inflammatory mediators and airway hyperresponsiveness (AHR), ultimately reducing

airway inflammation.[122,123] Simultaneously, IL-18 promotes the secretion of IL-4 and IL-13 from T cells, MCs, and basophils, playing a dual regulatory role in Th1 and Th2 cytokine production as well as IgE synthesis. Furthermore, IL-18 enhances IFN-γ production through synergistic and autocrine effects during AR progression, inhibiting the synthesis of IgE induced by IL-4 while promoting Th1 differentiation and suppressing Th2 cells to affect the immune balance between Th1/Th2.[124,125] It also activates Th2 cells to produce cytokines, contributing to the immune imbalance between Th1/Th2 associated with AR.[126]

IL-22

Interleukin-22 (IL-22), a member of the IL-10 cytokine family, is primarily synthesized by various immune cells, including Th17 and Th22 cells. IL-22 is crucial in maintaining the barrier function of the respiratory mucosa by promoting epithelial cell survival and repair, thereby enhancing resistance to mechanical and chemical damage.[127] In AR, this function helps mitigate mucosal damage and strengthens defenses against external allergens.[128] It collaborates with cytokines like IL-17 and may also be implicated in releasing inflammatory mediators that exacerbate the nasal mucosa's inflammatory response, characterized by mucosal swelling and increased secretions.[129]

IL-33

The cytokine Interleukin-33 (IL-33), recently identified as tissue-derived, connects natural and adaptive immunity and promotes mucosal Th2 inflammatory responses; it is also referred to as an epithelial-derived alerting hormone. The ST2 receptor, specific to IL-33, becomes activated when IL-33 binds to ST2 on the surfaces of MCs, various immune cells (including Th2 and ILC2s), and DCs.[130] This interaction recruits downstream signaling molecules that activate nuclear factor (NF)-κB and mitogen-activated protein kinase (MAPK), which mediate the release of inflammatory mediators from Th2 cytokines and promote allergic diseases.[131] The ST2 receptor is prevalent among a variety of immune cells, including Th2 cells. Binding of IL-33 to the ST2 receptor forms an immune complex expressed in Th2 cells, promoting the release of inflammatory mediators such as IL-4, IL-5, and IL-13 while regulating the functions of basophils, MCs, EOS, and intrinsic lymphocytes.[132]

IFN-γ

Interferon-γ (IFN-γ), a characteristic cytokine secreted by Th1 cells, activates macrophages and neutrophils, inhibits the differentiation of Th0 cells into Th2 cells, and suppresses secretion, proliferation, and activation of Th2 cells. Consequently, it indirectly hampers type I allergic reactions.[133] Inherently inflammatory in nature, Th1 cells can elicit an associated inflammatory response when allergen-specific Th1 cells are transferred to a patient's lungs. Although this transfer does not directly induce AHR that exacerbates asthma and allergic reactions, IFN-γ is frequently detected at sites of allergic inflammation where it promotes inflammatory responses.[134] Additionally, IFN-γ induces inducible nitric oxide synthase (iNOS) production in macrophages and promotes NO synthesis. It also stimulates microglial astrocytes to produce iNOS, potentially contributing to the development of certain allergic diseases.

TNF-α

Tumor necrosis factor-α (TNF-α), primarily produced by macrophages and monocytes, plays a crucial role in the pathogenesis of allergic diseases.[135] In patients with AR, the nasal mucosa exhibits high levels of macrophages, monocytes, polymorphonuclear leukocytes, and MCs, all secreting TNF; consequently, elevated TNF concentrations are observed in their serum.[136] TNF-α is produced and released by IgE-dependent activation of monocyte-macrophages, inducing the expression of adhesion molecules in epithelial cells. This cytokine also promotes the infiltration and activation of inflammatory cells, stimulates monocytes and T-cells to secrete IL-6 and IL-8, and directs Th cell differentiation towards Th2 phenotype. This cascade leads to an IgE-mediated type I hypersensitivity reaction, causing immune damage.[137,138]

TGF-β

Transforming growth factor-β (TGF-β) belongs to a superfamily that regulates cellular growth, differentiation, and metabolism. Secreted by various cells, TGF-β primarily governs the healing process of injuries and influences cell proliferation, differentiation, immune responses, and fibrosis.[139] In terms of immune regulation, TGF-β1 has been discovered to chemotactically attract and regulate neutrophils, EOS, monocytes, and other inflammatory cells. This prompts their accumulation at the site of inflammation and triggers an inflammatory response.[140] Additionally, TGF-β1 inhibits the differentiation of CD4+CD25− T cells into Treg cells while promoting a bias towards Th17 cell differentiation.[141] These highly effective pro-inflammatory effectors enhance the recruitment of inflammatory cells through the release of mediators, thereby expanding and sustaining acute inflammatory responses in the body. Concerning immunosuppression mechanisms, TGF-β1 inhibits the maturation and differentiation processes in immune cells such as Th1 cells, Th2 cells, B cells, as well as innate lymphocytes, while reducing associated cytokine releases like IFN-γ and IL-2.[142] The involvement of TGF-β1 further enhances the expression in the nasal mucosa, induces histopathological changes, and potentially leads to tissue remodeling within the nasal mucosa.[143]

T-Cell Levels

During the immune response, CD4+ T helper (Th) cells undergo several stages of differentiation. Initially, upon stimulation by external antigens and under the influence of various inducing factors, CD4+ T cells can differentiate into diverse subpopulations, including Th1, Th2, Th17, Th9, and Tregs. This process of differentiation is guided by the cytokines produced and the physiological functions of these cells. While operating independently as distinct T cell subpopulations, they also demonstrate interconnections.

Th1/Th2

When allergens invade the body, APCs process and present allergenic peptides to Th0 cells, initiating their differentiation into Th2 cells and resulting in a Th1/Th2 immune imbalance.[144] Th2 cells facilitate the synthesis and secretion of IgE by MCs and promote IgE release from B cells through various cytokines. Concurrently, Th2 cells secrete cytokines such as IL-4 and IL-13, with IL-4 playing a crucial role in driving further differentiation from Th0 to Th2 and directly stimulating B cell production of IgE antibodies.[145] In contrast, Th1 cells secrete IL-2 and interferon-γ (IFN-γ), both of which inhibit in vivo IgE production by blocking IL-4-induced IgE synthesis.[146] In patients with AR, IgE binds to the IgE-FcεRI receptor on MCs, macrophages, and epithelial cells' surfaces, sensitizing these cells. Upon re-exposure to the allergen, it crosslinks two adjacent surface-bound IgEs, triggering the release of inflammatory mediators, cytokines, and neuropeptides that affect the nasal mucosa, leading to various clinical symptoms of AR.[147]

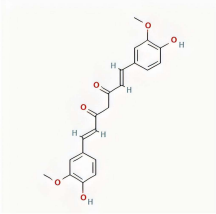
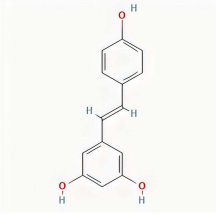
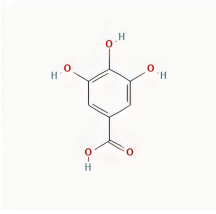
Treg/Th17

Under normal physiological conditions, there is a dynamic equilibrium between the number and function of Th17 and Treg cells. Disruption of this balance can lead to the onset and exacerbation of various diseases, typically characterized by an increase in Th17 cells and a decrease in Treg cells. Th17 cells primarily contribute to tissue damage and inflammatory cell infiltration through secretion of IL-17, which induces the expression of metalloproteinases, chemokines, and pro-inflammatory cytokines.[148] Treg cells, as a subset of T cells, inhibit and regulate the proliferation and activation of T lymphocytes, thereby exhibiting anti-inflammatory activity and maintaining immunological homeostasis. It is worth noting that a reduction in Treg cells is associated with several autoimmune diseases. In AR patients, Th17 cells exhibit enhanced pro-inflammatory effects compared to healthy individuals, resulting in elevated levels of cytokines such as IL-17, IL-25 (also known as IL-17E), and TNF-α.[149] Additionally, Th17 cells stimulate other cell types to produce significant amounts of inflammatory cytokines, including IL-6, IL-8, and GM-CSF. Collectively, these cytokines exacerbate the inflammatory response, further worsening the clinical symptoms observed in AR.[150]

Natural Plant Molecules Modulate Pathways Associated With AR Immunomodulation

This paper initially discusses recent advancements in the immunomodulatory mechanisms associated with AR. Subsequently, we summarize and analyze experimental studies, recent reviews, and web-based pharmacological analyses pertaining to the

utilization of natural plant molecules for AR treatment. We also provide a summary of the effectiveness and corresponding pathways by which these plant compounds modulate immunomodulation. The chemical structures of these plant compounds are shown in Figure 3.

Polyphenols		
		
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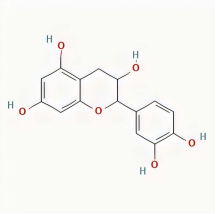	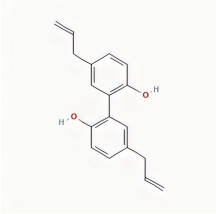	
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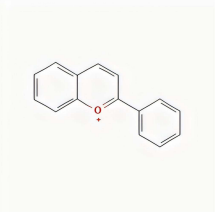	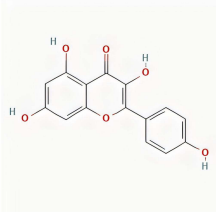	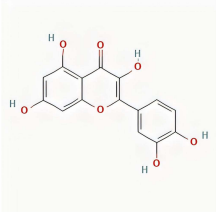
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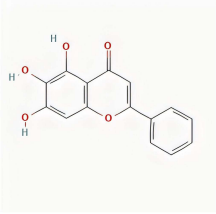	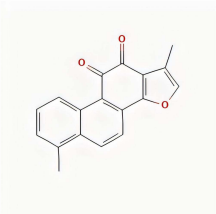	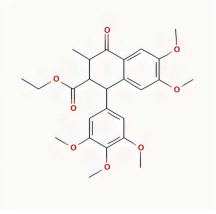
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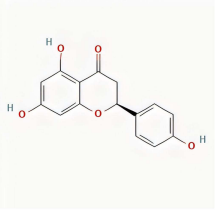	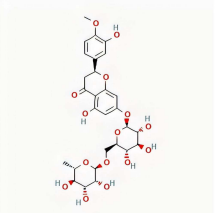	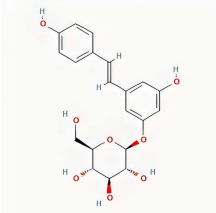
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Figure 3 Continued.

https://doi.org/10.2147/IJGM.S493021

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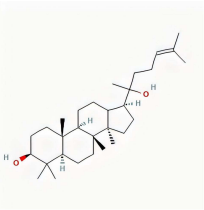	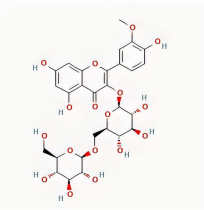	
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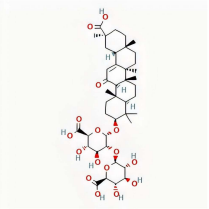	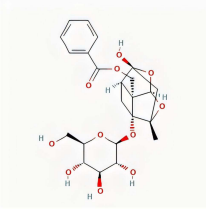	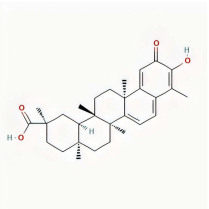
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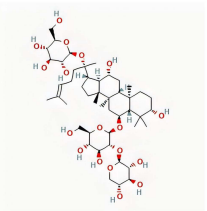		
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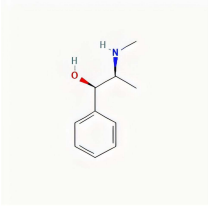	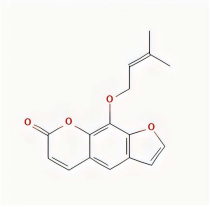	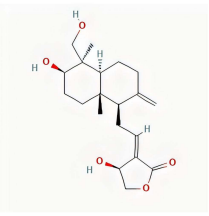
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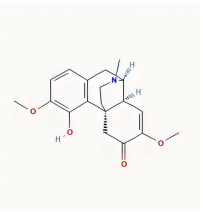		
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Figure 3 Chemical structure of natural plant molecules.

Polyphenols (Table 1)

Curcumin

Curcumin (Cur), the primary active compound found in turmeric, is a natural polyphenol with a medicinal history spanning over 4000 years. It is derived from the Curcuma longa plant and has been widely utilized in traditional Chinese medicine. In the past decade, there has been a surge in research focusing on the pharmacological activities and mechanisms of action of curcumin, attracting growing attention from the scientific community.[162,163] Numerous studies have confirmed that curcumin possesses diverse properties, including anti-inflammatory, antioxidant, antibacterial, antifungal, antiprotozoal, antiviral, hepatic and renal protective, anti-fibrotic, anticancer, and anti-carcinogenic effects. Additionally, it exhibits anti-fibrotic and anticancer effects without causing significant toxic side effects.[164,165] Recent findings suggest that curcumin can inhibit histamine release in animal models of type I and type IV allergic reactions, highlighting its potential as an anti-allergic agent. In a study conducted by Zhang Ning et al,[151] curcumin was administered to OVA-sensitized mice, resulting in a reduction of immune cytokine levels through the inhibition of histamine release and specific IgE production in MCs. Furthermore, curcumin demonstrated its efficacy in alleviating nasal symptoms and improving the morphology of damaged nasal mucosa by attenuating histamine and specific IgE levels, reducing TNF-α expression, and inhibiting the release of inflammatory mediators through the stabilization of I-κBα in the cytosol, thus preventing PM-stimulated nuclear translocation of NF-κB in MCs. Under physiological conditions, the human body maintains redox homeostasis. Nevertheless, disruption of this balance caused by internal or external factors that increase free radical concentrations can lead to oxidative damage to biological macromolecules and various diseases.[166] Furthermore, a study on human nasal fibroblasts demonstrated that curcumin reduced the levels of ROS induced by urban particulate matter (UPM), achieving this through the activation of the Nrf2/HO-1 pathway.[152] It was observed that curcumin activated Nrf2 and inhibited extracellular signal-regulated kinase (ERK) in UPM-exposed

Table 1 The Immunomodulatory Effects and Mechanisms of Natural Plant Polyphenols on AR Were Summarized

Natural Plant Molecules	Experiment Object	Mechanism of Action	Reference
Curcumin	Female Balb/C and C57BL/6 mice	NF-κBp65↓, Iκ-Bα↓, mast cell↓, EPK1/P38MAPK↓, JNK↓	[151]
	The inferior turbinate tissues were obtained from 6 patients with turbinate hypertrophy	Nrf2↑, HO-1↑, SOD 2↑, ROS↓, Nrf2/HO-1↑	[152]
Resveratrol	Female Balb/C mice	IL-4↓, IL-13↓, OVA-sIgE↓, B-cell↓	[153]
	Guinea pigs	HA↓, INF-γ↓, IL-4↓, eosinophil↓	[154]
	Female Balb/C mice	IgE↓, PGD 2↓, LTC 4↓, ECP↓, IL-4↓, IL-5↓, IL-6↓, IL-33↓, TNF-α↓, TXNIP↓, SOD↓, ROS↓, TXNIP-oxidative stress pathway↓	[155]
Gallic acid	Male Balb/C mice	IgE↓, IgG1↓, IgG2a↑, eosinophil↓, mast cell↓, IFN-γ↑, IL −12 ↑, IL −4 ↓, IL-13↓, Nrf2/NF-κB pathway↓	[156]
	Male ICR mice and male SD rats	mast cell↓, TNF-α↓, IL-6↓, Iκ-Bα↓, NF-κBp65 ↓, p38 MAPK↓	[157]
Catechins	Female Balb/C mice	IL 4↓, IL-5↓, IL-13↓, TNF-α↓, TSLP↓, NF-κBp65↓, NF-κB/TSLPpathways↓	[158]
	Female Balb/C mice	RORγtmRNA↓, Foxp3mRNA↑, MCP-1↓, RANTES↓	[159]
	Balb/c mice	HDC↓	[160]
Magnolol	Balb/c mice	IL-2↓, IL-4↓, ORA11 /ANO1 pathways↓	[161]

Notes: ↑ represents upregulation, ↓ represents downregulation.

fibroblasts, significantly increasing antioxidant enzymes like heme oxygenase-1 (HO-1) and superoxide dismutase (SOD2). Consequently, this alleviated oxidative stress and mitigated allergic nasal symptoms.

Resveratrol

Resveratrol is a naturally occurring polyphenol found in various herbs and foods, including tiger nuts, grapes, and soybeans. Currently, it is marketed as both a nutritional supplement and food additive. Due to its broad pharmacological effects, resveratrol exhibits potent properties in terms of anti-inflammatory, antioxidant, antiviral, hypolipidemic, hypoglycemic, and anticancer activities.[167,168] It is anticipated to emerge as a novel therapeutic agent for disease prevention and treatment. Experiments conducted on different animal models have confirmed that resveratrol can repair damaged nasal mucosa cells by regulating the release of inflammatory factors and alleviating allergy symptoms through the reduction of oxidative stress.[160,169] In a randomized controlled trial focusing on AR, it was demonstrated that resveratrol has the ability to regulate serum levels of inflammatory factors and T-lymphocyte subpopulations.[170] This study further revealed that modifying the stoichiometry of resveratrol resulted in reduced infiltration of inflammatory cells,[153] decreased serum levels of Th2 cytokines IL-4, IL-13, and OVA-sIgE; inhibited polarization of Th2 cells; regulated immune function; and altered Th2 polarization, while modifying the inflammatory response. Resveratrol not only suppresses the elevation of peripheral blood INF-γ but also mitigates histopathological changes in the nasal turbinate mucosa.[154] It reduces eosinophil infiltration and inhibits glandular secretion. Additionally, resveratrol was found to decrease SOD activity by inhibiting the TXNIP-oxidative stress pathway,[155] subsequently reducing MDA and ROS production. As a result, this led to the down-regulation of inflammatory mediators in splenic mononuclear cells and decreased levels of PGD2, LTC4, ECP, IL-4, IL-5, IL-6, IL-33, and TNF-α. However, further large-scale animal and human studies are necessary to elucidate and refine the mechanisms of action of resveratrol for potential therapeutic enhancement.

Gallic Acid

Gallic acid (GA) is a key constituent of several traditional Chinese herbal plants, including Pentaphyllum, Pawpaw Rhubarb, Cornu Cervi, and Myrtus communis. Previous studies have demonstrated that GA exhibits a range of properties, including antioxidant, anti-inflammatory, anti-allergic, antibacterial, antiviral, and antitumor effects with minimal toxicity to normal cells.[171,172] These findings suggest the significant potential of GA in the field of medicine.[173] Recently, Shenna et al conducted an experimental study on the effects of GA in mice with AR.[156] The results revealed that GA modulates the Nrf2/NF-κB pathway which influences immunoglobulin levels (IgE, IgG1, and IgG2a), as well as alters nasal mucosa thickness. These outcomes indicate that GA can enhance immune function and augment resistance against pathogens in nasal mucosa while also modulating inflammatory responses. Sang-Hyun Kim et al demonstrated that GA reduces histamine release from MCs induced by compound 48/80 or immunoglobulin E (IgE),[157] regulates cAMP and intracellular calcium levels, inhibits nuclear factor kB and p38 mitogen-activated protein kinase, and contributes to blocking the expression of pro-inflammatory factors. These actions mitigate in vivo allergic reactions, restore and enhance local immune function, strengthen the nasal mucosa's resistance to pathogens, thereby reducing the incidence of AR.

Catechins

Catechins, classified as flavanols within the flavonoid family, are natural polyphenolic compounds found in various plants. Ongoing research has unveiled that catechins possess a range of pharmacological effects, including anti-inflammatory, antibacterial, antiviral, and antioxidant properties.[174,175] Recent experimental studies utilizing catechins to treat AR in mice have demonstrated significant improvements in behavioral responses, reductions in leukocyte counts, inhibition of inflammatory cell infiltration, and alleviation of local inflammation symptoms.[158] Furthermore, catechins have been shown to inhibit the NF-κB pathway and reduce the degradation of IκBα proteins while influencing upstream regulators of TSLP in epithelial cells. This modulation leads to decreased levels of TSLP and NF-κB p65 protein,[176] suggesting that catechins can modify the response of nasal mucosa epithelial cells and provide protection to the nasal mucosa. Yan Yajie et al discovered that catechins reduce the levels of MCP-1 and nasal mucosa RORγt mRNA, while simultaneously increasing Foxp3 mRNA levels.[159] This is associated with a decrease in inflammatory cell infiltration in the nasal mucosa. Additionally, catechins not only alleviate inflammatory symptoms and protect the nasal mucosa in

mice with AR, but also restore the disrupted Th17/Treg balance, correct immune imbalances, and accelerate recovery from AR. Mohamed A. Morsy et al's study demonstrated that catechins can inhibit histamine expression and reduce histidine decarboxylase (HDC) activity.[160] Molecularly, catechins have been shown to exhibit greater activity than the standard HDC inhibitor, histidine methyl ester, positioning them as an effective alternative treatment.[177]

Magnolol

Magnolol (MG), a novel oleuropein compound derived from the traditional Chinese medicine magnolia, has been found to possess anti-inflammatory potential in previous in vivo and in vitro studies.[178] The current study suggests that MG inhibits the nuclear translocation of activated NF-κB by reducing glial activation, peripheral blood cell infiltration, and the production of pro-inflammatory cytokines.[179] It is now recognized that NF-κB, a protein with multiple transcriptional regulatory roles, serves as a central component in the complex network structure of allergic diseases such as AR and asthma. By regulating cytokines associated with inflammation, immunity, and inflammatory mediators, NF-κB plays a crucial role in inflammation and immune responses. Hong Thi Lam Phan et al conducted a study on AR treatment using MG,[161] which demonstrated that MG (30 μM) inhibited anti-CD3-induced cell proliferation. Furthermore, it suppressed IL-2 production via ORAI1 channels in T lymphocytes and reduced IL-4 secretion through ATP-induced electrolyte transport mediated by ANO1 channels to correct the Th1/Th2 imbalance.

Flavonoids (Table 2)

Anthocyanin

Anthocyanin belongs to the class of polyphenolic flavonoids, which are secondary metabolites synthesized by higher plants. Anthocyanins are widely found in the kernels, skins, or seeds of various plants and contribute to the coloration of most angiosperm flowers, fruits, and leaves, ranging from orange-red to dark blue. Different plants exhibit varying sensitizing properties for anthocyanins. Being the most abundant and widely distributed flavonoid pigments, they absorb the longest wavelengths of light. Extensive studies on quercetin, catechins, and isoflavones with similar structures as anthocyanins may provide a basis for evaluating anthocyanins' biological activities.[207] Previous studies have demonstrated that anthocyanins possess anti-inflammatory, antibacterial, antioxidant, and anticancer properties.[208] Recently, Hongli Hua et al examined the effects of anthocyanins in AR rats exposed to PM2.5.[180] The researchers discovered that anthocyanins could restore the damaged epithelial structure of the nasal mucosa, resulting in a higher number of cilia, a

Table 2 To Summarize the Immunomodulatory Effects and Mechanisms of Flavonoids Natural Plant Molecules on AR

Natural Plant Molecules	Experiment Object	Mechanism of Action	Reference
Anthocyanin	SD rats	Eosinophil↓, IgE↓, IgE↓, IL-6↓, IL-8↓, TNF-α↓, NF-κBp65↓, p38MAPK↓	[180]
	Balb/c mice	Mast cell↓	[181]
Kaempferol	Female Balb/C mice	EOL-1cell↓, IL-32↓, IL-8↓, caspase-1↓, IFN-γ↑, TSLP↓, IL-32/TSLP/caspase-1 signalling pathway↓	[182]
Quercetin	SD rats	IL-2↑, IFN-γ↑, IL-4↓, IL-5↓, Tim1↓, Tim3↓	[183]
	Balb/c mice	IgE↓, IgG1↓, IgG2↑, IL-10↑, FOXP3↑, IL-17↑, TGF-β, IL-6↑, TNF-α↑, NF-κB signalling pathway↓	[184]
	SD rats	Neuropeptides substance P, calcitonin gene-related peptide and NGF↓	[185]
	SD rats	CC10↑	[186]
	Human nasal epithelial cells	IL-4↓, NO↓	[187]

(*Continued*)

Table 2 (Continued).

Natural Plant Molecules	Experiment Object	Mechanism of Action	Reference
Baicalin	Male guinea pig	IL-1b↓, IL-6↓, IL-8↓, TNF-α↓, NF-κB/ STAT3 / ERK signalling pathways↓	[188]
	SD rats	IgE↓, HA↓, IL-1b↓, IL-4↓, IL6↓, TNF-α↓	[189]
	Balb/c mice, Human nasal mucosa	IL-17A↓, Foxp3↑, Beclin1↓, Lc3-II/Lc3-I↓, p62↑	[190]
	SD rats	IL-6↓, IL-1β↓, TNF-α↓, STAT3 signalling pathway↓	[191]
	Balb/c mice	IL-12↓, TNF-α↓, IL-6↓, IgE↓, IgG1 ↓, eosinophil↓, neutrophil↓, lymphocyte↓, macrophage↓, NF-κB/ STAT3 / ERK signalling pathway↓	[192]
Tanshinone	C57BL/6 mice	TNF-α↓, IL-4↓, NF-κB signalling pathway↓	[193]
	Female Balb/C mice	IL-4↓, IL-5↓, IL-1↓, PLCγ1/PKC/IP3R signalling pathway↓	[194]
	Balb/c mice	HA↓, IgE↓, IgG1↓, TNF-α↓, IL-4↓, IL-5↓	[195]
Lignan	Balb/c mice	IL-4↓, IL-5↓, IL-13↓, NF-κB signalling pathway↓	[196]
	Balb/c mice	IgE↓, IL-4↓, IL4/STAT6/GATA3 signalling pathway↓	[197]
	SD rats	IL-4↓, IL-5↓, IL-13↓, OVE-sIgE↓, IFN-γ↑, IL-2↑, TLR4/NF-κB↓	[198]
	Balb/c mice	IgG2a↓, IL-10↑	[199]
	SD rats	Th1↑, T-bet↑, IFN-γ↑, IL-4, IL-13, OVA-sIgE↓, PI3K/Akt/mTOR signalling pathway↓	[200]
Naringenin	SD rats	IgE↓, IL4↓, IL5↓	[201]
	SD rats	IgE↓, IL-17↓, IL-18↓, CD19↓, CD23↓, TLR4/NF-κB/TNF-α signalling pathway↓	[202]
Hesperidin	SD rats	Ig-E↓, IL-5↓, IL-13↓, ROS↓, TNF-α↓	[203]
	Balb/c mice	TSLP↓, GATA3↓, OX40L↓	[204]
Polydatin	Balb/c mice	Pro-apoptotic proteins Bax↓, caspase-3↓, cleaved-caspase-3↓, Apoptosis protein Bcl-2↑	[205]
	Balb/c mice	IgE↓, IL-6↓, TNF-α↓, IL-17↓, IL-10↑, Occludin↑, Claudin–1↑, SOD↓, CAT↓, MDA↑, ROS/NLRP3/Caspase–1↓	[206]

Notes: ↑ represents upregulation, ↓ represents downregulation.

more organized arrangement, and reduced infiltration of inflammatory cells as well as chemotaxis of goblet cells in the lamina propria. Additionally, anthocyanins were shown to decrease the levels of IgE, IL-6, IL-8, and TNF-α, while also reducing the expression of NF-κB p65 and phosphorylated p38MAPK proteins in the nasal mucosa, thus altering allergic behavioral symptoms in rats. Katsunori Yamaura et al found that anthocyanins alleviated itching symptoms in mice by inhibiting MC degranulation.[181] Moreover, a separate investigation showed the potential therapeutic benefits of anthocyanins in restoring the Th17/Treg balance in autoimmune diseases.

Kaempferol

Kaempferol, a naturally occurring edible flavonoid derived primarily from the rhizome of the Kaempferia spp. ginger plant, is found in various vegetables and fruits and is renowned for its anti-inflammatory, antioxidant, and anticancer properties.[209,210] Current studies indicate that EOS are immunomodulatory cells that interact with T and B lymphocytes. GM-CSF, in particular, serves as a critical survival and activating factor for hematopoietic cells, supporting the maturation of macrophages, EOS, and neutrophils. It is recognized as a pleiotropic cytokine with pro-inflammatory effects. Hyun-Aoh et al conducted an experimental study on the effects of kaempferol in an allergic rhinitis mouse model

by assessing spleen weights,[182] spleen indices, as well as changes in serum and nasal mucosal tissues. The results revealed that kaempferol demonstrated anti-allergic efficacy by inhibiting levels of new mediators such as IL-32 and TSLP, along with major mediators like IgE. Additionally, it was hypothesized that kaempferol could down-regulate histamine production while reducing inflammation-related protein levels and diminishing the infiltration of inflammatory cells. As a result, it may regulate both local and systemic allergic reactions while improving clinical allergy symptoms.

Quercetin

Quercetin is present in various parts of plants, including the stem bark, flowers, leaves, buds, seeds, and fruits. It mainly exists as glycosides and acts as a flavonol compound with a variety of biological activities.[211] These activities encompass free radical scavenging antioxidant properties and antiallergenic effects that stimulate the immune system, exhibit antiviral activity, inhibit histamine release, and reduce pro-inflammatory cytokines.[212] Extensive research has been conducted on quercetin's role in multiple diseases from a pathogenesis perspective, and existing studies have shown that quercetin modulates Th1/Th2 and Treg/Th17 cytokine levels to alleviate AR pathogenesis.[213] Peng et al demonstrated that quercetin can restore the cytokine balance of Th1/Th2 by activating the release of IL-2 and IFN-γ in Th1 cells and inhibiting the abnormal secretion of IL-4 and IL-5 in Th2 cells.[183] Additionally, it can regulate Th1/Th2 cytokines at the gene level by suppressing the expression of Tim1 and Tim3 in the nasal mucous membrane tissues to change the original immune balance. Xia Ke et al demonstrated that quercetin reduced the serum levels of IgE,[184] IgG1, and histamine, while increasing the level of IgG2. It also increased the percentage of Th17 cells, IL-10, and FOXP3, as well as elevated levels of IL-17, transforming growth factor-β, IL-6, and tumor necrosis factor-α. In addition, quercetin down-regulated COX-2, p-Tim3, and p-Tim2 cytokines in ovarian cancer cells, and it was also found to inhibit the expression of Tim1 and Tim3 in nasal mucosal tissues at the gene level to regulate Th1/Th2 cytokines and alter the original immunological balance state. Quercetin inhibited COX-2 expression along with p-IkBα and nuclear p65 expression, but upregulated ovalbumin-induced IkBαand cytoplasmic-65 levels, suggesting its inhibition on the nuclear transcription factor-κB pathway. The anti-allergic aspect of quercetin has been demonstrated by many scholars. As a plant extract, it serves as the main ingredient in many potential anti-allergic drugs, supplements, and fortified products. MisakoKashiwabara et al conducted a study to explored the modulatory effects of quercetin on neuropeptides from a neuroimmunological perspective. They administered quercetin through gavage using the distilled water purification technique.[185] Their findings revealed that modulation of quercetin administration concentration inhibited changes in axon terminal calcium ion content after nasal stimulation. This inhibition subsequently reduced the release of neuropeptide substance P, calcitonin gene-related peptide, and nerve growth factor from nasal lavage fluid. Moreover, it simultaneously inhibited eosinophil degranulation and altered the ability of EOS to produce chemokines while modifying allergic responses. In a recent study, Amane Otaki et al utilized TNF-α derived from human nasal epithelial cells (HNEPCs) to stimulate the nasal mucosa of SD rats.[186] The observation showed that quercetin enhances the upregulated ability of nasal cells to produce CC10, which effectively inhibits the chemotactic effects of phospholipase A2 and inflammatory cells, while downregulating the differentiation of Th2 cells. Consequently, this blocks allergen induction and reduces the inflammatory response, thus controlling the severity of AR. In addition, Nachi Ebihara et al[187] employed nanotechnology to demonstrate that quercetin significantly inhibited IL-4-induced NO production in nasal mucosal epithelial cells by modulating their immune function. This inhibition is achieved through blocking STAT6 activation and iNOS mRNAs expression, leading to improved clinical symptoms of AR.

Baicalein

Baicalin, an active ingredient in the dried root extract of the traditional Chinese medicine plant Scutellaria baicalensis, is an antiviral, anti-inflammatory, and antiplatelet-coagulant agent with proven therapeutic efficacy in a variety of inflammation-induced diseases.[214] In addition, baicalein can inhibit the generation of ROS by increasing the expression of Nrf2 protein. This protein plays an antioxidant role and inhibits oxidative damage; at the same time, it acts as an antagonist of 12-LOX's specific target and reduces the programmed death of neuronal cells. It also attenuates overexpression of c-jun protein, and modulates the inflammatory state in AR distress syndrome, and mitigates response to oxidative stress.[215] In animal cell experiments conducted by Yun-jiang Zhou, it was found that baicalin inhibited compound 48/80-induced release of histamine and b-hexosidase from HMC-1 MCs,[188] demonstrating its protective effect on metamorphosis. Furthermore, it targeted the

JAK2-STAT5 signaling pathway and inhibited the activation of JAK2, which subsequently suppressed the phosphorylation of downstream molecule STAT5. Consequently, STAT5 translocated to the nucleus where it regulated transcription of target genes encoding inflammatory mediators. These downstream molecules also translocated to the nucleus, regulated the transcription of target genes encoding inflammatory mediators, and blocked the production of IL-1β, IL-6, IL-8, and TNF-α by lipopolysaccharide (LPS)-stimulated HMC-1 MCs. In addition, baicalin was found to markedly attenuate the activation of IKKB and inhibit the phosphorylation of IkBα in the cytosol, thereby blocking nuclear translocation and suppressing NF-kB signaling in the lipopolysaccharide-stimulated HMC-1 MCs. This leads to inhibition of inflammation mediator production. Saizhen Chen et al, analyzed from a metabolomics perspective,[189] discovered that baicalin intervention resulted in the alignment of the nasal mucosa and the reduction of eosinophil infiltration, as well as the inhibition of immunoglobulin E (IgE), histamine, IL-1β, IL-4, IL6, and TNF-α, which plays a protective role in preserving the integrity of the nasal mucosa. Jing Li et al through the human nasal mucosa and animal models, observed that baicalin decreased IL-17A expression,[190] increased Foxp3 expression, reduced Beclin1 and Lc3-II/Lc3-I expression levels while increasing p62 expression level. They also found alterations in Treg/Th17 cell ratio due to baicalin treatment, leading to inhibition of Treg/Th17 cells' activity. Meanwhile, they found that baicalin inhibited the release of toxic protein ECP from EOS cells, down-regulated cellular autophagy levels, which promoted the proliferation of Th17 cells while inhibiting Treg cell growth. These effects improved AR immune system response and controlled AR incidence. Liu Tao et al investigated the STAT3 signaling pathway and determined that baicalin inhibited p-STAT3 expression at inflammatory sites to reduce the secretion of serum IL-6, IL-1β and TNF-α.[191] Also, they observed attenuated splenic injury during inflammation with baicalin treatment. In a recent study, Hu Qing et al,[192] found that baicalein inhibited the activation of NF-κB/STAT3/ERK signaling pathway proteins, reduced the phosphorylation levels of ERK, NF-κBp65, and STAT3, inhibited inflammatory cell activity, alleviated inflammatory responses, accelerated the recovery of nasal mucosal tissues in mice, and improved the symptoms of AR.

Tanshinone

Tanshinone is a fat-soluble constituent of the dried roots and rhizomes of Salvia miltiorrhiza, which belongs to the Labiatae family. It exhibits a wide range of biological activities, with tanshinone being the most active fat-soluble constituent of Salvia miltiorrhiza. It possesses antioxidant, anti-inflammatory, anti-angiogenic, and anti-tumor properties.[-216] Recent domestic and international studies have also shown that tanshinone TIIA regulates the development, activation, and function of immune cells. It can participate in both innate and acquired immune response. TIIA promotes the reverse migration of neutrophils by inducing apoptosis and accelerating their loss of sensitivity to chemotaxis environments. This facilitates inflammation resolution and tissue repair. Additionally, it significantly reduces lipopolysaccharide-induced inflammation and tissue repair damage by reducing lipoprotein (TI) levels.[217] In mice with acute lung injury induced by lipopolysaccharide, it effectively decreases neutrophil infiltration, myeloperoxidase activity, expression of inflammatory cytokines in bronchoalveolar lavage fluid while mitigating inflammatory factor-induced lung tissue damage. Earlier studies have shown that macrophages can be induced to polarize into the M1 type by up-regulating the P-STAT1/NF-KB signaling pathway, whereas TIIA effectively activates P-STAT6 phosphorylation and induces macrophages to polarize into the M2 type, thereby reducing the inflammatory response.[218] It has been found that IgE-induced MC activation is negatively regulated by the Sirt1.LKB1.AMPK pathway. In vitro and ex vivo experimental studies have revealed that TIIA could inhibit IgE receptor (FcεRI)-mediated MC activation in vitro and MC-mediated allergic responses in vivo by activating the Sirt1.LKB1.AMPK pathway. Therefore, TIIA may become a new drug for allergic diseases mediated by MCs.[219] Currently, it is believed that allergen-induced IgE antibodies binding to high-affinity FcεRI on the surface of MCs activate them, which triggers an intracellular signaling cascade reaction. Thus, targeting MCs may hold potential for treating AR. Huang Fuse et al investigated the effect of TIIA on MC-mediated AR through in vivo and ex vivo experiments.[193] The results showed that TIIA could alleviate AR responses such as histamine release, IgE production, and vasodilatation in model mice. Additionally, it inhibited the degranulation of MCs and suppressed the activation of the NF-κB pathway to down-regulate the expression of inflammatory factors TNF-α and IL-4. These findings suggest that TIIA alleviates MC-mediated AR responses by inhibiting the activation of the NF-κB pathway and prevents immune diseases by regulating dendritic cell maturation. Research has also found that TIIA can slow down autoimmune diseases by inhibiting DC function and maturation, thereby affecting T-cell differentiation and leading to

increased secretion of anti-inflammatory factors and decreased secretion of inflammatory factors in the body. TIIA can weaken the development of immune diseases by inhibiting DC-mediated adaptive immunity and acquired immunity. TIIA can regulate T lymphocytes in various immune diseases by inhibiting the activation of the NFκB pathway, thereby alleviating MC-mediated AR. TIIA is involved in the immune mechanism of many diseases by regulating T lymphocytes. By inhibiting inflammation, TIIA can regulate the balance of Th1/Th2 by significantly downregulating the levels of Th1 cytokines and upregulating the expression of Th2 cytokines in mice, thus regulating the balance of Th1/Th2. TIIA increases the ratio of CD3+, CD4+, and CD8+ T-lymphocyte subsets while decreasing inflammatory cytokine levels (IL-2, IL-4, INF-γ, TNF-α), and it also enhances the expression of anti-inflammatory cytokine IL-10 to boost immune response. In addition, Shouye Li found that Tan IIA could effectively inhibit the activation of the PLCγ1/PKC/IP3R pathway induced by IgE/Has in the nasal mucosa of mice with follicle-stimulated AR.[194] It downregulated the expression of downstream inflammatory factors IL-4, IL-5, IL-1β, and α, as well as decreased intracellular calcium ion release and MC degranulation. Additionally, it inhibited tissue swelling, small blood vessel dilation, glandular hyperplasia, and acid granulocyte infiltration in mice. In a recent study conducted by Qing Chen et al, TIIA significantly reduced histamine,[195] OVA-IgE, and OVA-IgG1 levels while inhibiting Th2 cytokine release (TNF-α, IL-4, and IL-5) in OVA-induced AR mice. Furthermore, it counteracted C48/80-induced histamine release and promoted MC degranulation. These findings suggest that TIIA could be used as a treatment for allergic diseases.

Lignan

Lignan is a natural compound of plant origin, typically a flavonoid, which is considered an effective anti-allergic component of Perilla frutescens. It plays an important role in various aspects of anti-inflammatory, antioxidant, and immune function enhancement by altering signaling pathways such as NF-κB, MAPK/AP-1, and JAK-STAT.[220] Early studies have shown that it can improve the Th2 response in patients with allergic diseases by lowering the levels of IL-4, IL-5, and IL-13, with less infiltration of inflammatory cells in the upper respiratory tract (nasal mucosa).[196] In addition, lignans can inhibit the release of mediators like leukotrienes and the expression of intercellular adhesion molecules induced by tumor necrosis factor-α in endothelial cells. They also inhibit the nuclear transcription factor-κB pathway and its related genes. The study conducted by Kai-Li Liang et al demonstrated that lignans effectively alleviate allergic symptoms,[197] reduce serum IgE levels and mucus production, as well as suppress local and systemic IL-4 production in allergy-experienced mice. These findings suggest that lignans possess the ability to inhibit both TH2 polarization and TH2 cytokine production in human peripheral blood mononuclear cells (PBMCs); furthermore, lignans exhibit inhibitory effects on the release of mediators, such as tumor necrosis factor-α, from endothelial cells, along with their ability to suppress the nuclear transcription factor-κB pathway and its associated genes. Moreover, lignocaine treatment inhibited the IL4/STAT6/GATA3 signaling pathway in naïve CD4+ cells, leading to reduction in the expression of pSTAT6 and GATA3 and thereby alleviating nasal allergy symptoms. Lignans also inhibited ICaCC in CALU-3 cells, which are responsible for calcium-activated chloride currents but not CFTR currents in human respiratory epithelial CALU-3 cells. Additionally, inhibition of ANO1 activity reduced electrolytic secretion at the parietal membrane and helped alleviate the hypersecretory state of the nasal cavity in individuals with AR. Jin Huidong et al, in their study targeting the TLR4/NF-κB pathway,[198] demonstrated that lignans could restore the imbalance of Th1/Th2 cytokines and ameliorate nasal mucosal inflammation by promoting the down-regulated levels of Th1-type cytokines IFN-γ and IL-2, while inhibiting the up-regulated Th2-type cytokines IL-4, IL-5, IL-13, OVE-sIgE, TLR4, and p65. Yuping Yang et al, from an AR pathogenesis perspective,[199] found that it could enhance anti-OVA-IgE levels, autophagy-related factors (Beclin1, LC3II/LC3I), helper T-cells IL-17A expression, as well as flavic acid receptor-associated orphan nuclear receptor γt (RORγt) expression. These factors were shown to regulate h17 and Treg cell percentages while suppressing anti-OVA-IgG2a levels along with IL-10 and Foxp3 expression to improve inflammation levels. In a recent study, Wang Hui-Hui et al found that lignocaine intervention resulted in reduced eosinophil infiltration,[200] orderly epithelial arrangement, decreased nasal mucosal cell exfoliation, and suppression of P-PI3K/PI3K, P-AKT/AKT, and mTOR protein levels. This suggests that it may reduce IL-4, IL-13, and OVA-sIgE by down-regulating PI3K/AKt/mTOR pathways. Furthermore, it reduces IL-4, IL-13, and OVA-sIgE levels, while significantly decreasing Th2 levels and GATA-3 protein levels. Conversely, it

increases Th1 levels and T-bet protein level. These findings suggest that Lut may alleviate AR by suppressing inflammation through the regulation of Th1/Th2 balance.

Naringenin

Naringenin, a natural flavonoid derived from the seed coats of plants in the Lacertaceae family, exhibits anti-inflammatory, antioxidant, and antitumor properties. It is involved in regulating numerous metabolic and signaling pathways, including nuclear factor and inflammatory vesicle activation pathways. Ongoing research has increasingly brought naringenin to public attention in recent years.[221,222] Earlier studies have demonstrated that naringenin enhances immunity and anti-inflammatory capacity by suppressing both inflammation and T-cell-mediated immune responses.[223] Utilizing MC degranulation models and network pharmacological techniques, Yixuan Niu et al found that naringenin modulates AR through multiple targets (eg, AKT1, MAPK3, VEGFA) and pathways (eg, cancer, VEGF signaling).[224] It significantly reduces P815 MC degranulation, increases IL-4 levels, decreases tumor necrosis factor-α levels, and improves inflammatory responses in AR. Furthermore, Abdulkadir Şahin et al discovered that naringenin improves the condition of damaged nasal mucosa in sensitized rats by realigning nasal mucosal epithelial cells,[201] reducing inflammatory cell infiltration, and lowering serum total IgE levels as well as IL-4 and IL-5 levels to modify the inflammatory state. In cell experiments conducted by Niu Jinming et al, the TLR4/NF-κB/TNF-α signaling pathway was observed. It was demonstrated that naringenin inhibits the nuclear translocation of NF-κBp65 and suppresses TNF-α expression by downregulating TLR4 expression. This inhibition led to a reduction in the production of inflammatory mediators, such as IgE, and decreased the release of IL-17 and IL-18. Furthermore, naringenin attenuated CD1, CD9, and CD23 expression in the nasal mucosa, thereby interfering with the inflammatory response and mitigating pathological damage and symptoms in rats.[202]

Hesperidin

Hesperidin, a bioactive compound found in Chenpi, has demonstrated multiple pharmacological effects, including anti-cancer, cardiovascular and neuroprotective properties, anti-allergic asthma activity, anti-inflammatory actions, and immune regulation.[225] In a previous study conducted by Korhan Kilic et al on OVA-sensitized AR rats,[203] it was observed that hesperidin reduced serum levels of Ig-E, IL-5, IL-13, and total oxidative status (TOS), decreased the expression of TNF-α while enhancing the release of total antioxidant capacity (TAC). These findings underscore the antioxidant and anti-inflammatory characteristics of hesperidin along with its ability to regulate oxidative stress and improve allergic reactions. Li Wei et al investigated the signaling pathways influenced by hesperidin[204] and noted its potential to regulate the Th2 immune response in AR. Hesperidin improved the pathological conditions of nasal mucosa and alleviated allergic reactions in mice by inhibiting the expression of TSLP, GATA3, and OX40L proteins and blocking the activation of the TSLP/OX40L/OX40 signaling pathway.

Polydatin

Polydatin, extracted from its rhizome, is a natural herbal component known for its anti-inflammatory, antioxidant, and antimotile effects. Reports suggest that polydatin has the potential to effectively treat allergic inflammatory diseases by inhibiting allergic inflammatory responses through targeting the Nrf2/HO-1 pathway, modulating the inflammatory responses of nasal mucosal epithelial cells, and reducing the release of inflammatory factors.[226] In a study on mitochondrial autophagy conducted by Liu Siqi et al, it was observed that polydatin suppressed the expression of pro-apoptotic proteins (Bax, caspase-3, cleaved-caspase-3, and Cytochrome C) while enhancing the expression of anti-apoptotic protein Bcl-2 in AR model mice.[205] This regulation resulted in upregulated mitochondrial kinases PINK1 and E3-ubiquitin ligase Parkin activation, leading to improved nasal mucosa thickness reduction in eosinophil secretion and alteration of allergy symptoms. Gao Qiong et al,[227] in their study on oxidative stress responses, found that polydatin reduced serum IgE levels and pro-inflammatory factors (IL-6, TNF-α, IL-17), while increasing IL-10 levels and regulating the Th1/Th2 balance. Additionally, significant upregulation of polydatin and Claudin-1 in nasal mucosal tissues suggested enhanced barrier function and mucosal remodeling. Increases in SOD and CAT activities, along with decreased MDA levels, indicated a reduction in oxidative stress. The mode of action was linked to the modulation of the cellular pyroptosis pathway induced by ROS/NLRP3/Caspase-1, thereby alleviating the disease in AR model mice.[206]

Saponins (Table 3)

Ginsenoside

Ginsenoside, a ginseng extract, exhibits anti-inflammatory, immunomodulatory, anti-tumor, and anti-viral effects. Ginsenosides can be classified into three main types: proto-ginsenoside diols (eg, Rb1, Rb2, Rc, Rd, Rh2), proto-ginsenoside triols (eg, Re, Rf, Rg1, Rg2, Rh1), and oleanolic acid derivatives (eg, Ro, Rh3).[235] Oh et al investigated the therapeutic effects of ginsenoside Rg1 using an ovalbumin-induced AR mouse model.[228] They found that Rg1 potentially mitigates inflammation by decreasing levels of factors such as TSLP, IL-1β, IL-4, histamine, IgE, IgG1, EOS, and MC infiltration, while also inhibiting caspase-1 activity, receptor-interacting protein 2, IκB kinase-β, and NF-κB/RelA expression in activated human MCs-1 (HMCs-1), thereby alleviating allergy symptoms. Utilizing transcriptomics and metabolomics, Liu et al demonstrated that ginsenoside Rg3 exerted protective effects in mice by reducing the levels of IL-4, IL-13, IgE, IL-5, and MDA while increasing superoxide dismutase (SOD) in serum.[229] Moreover, Rg3 influenced the expression of 12 genes and 8 metabolites, enhancing the protein expression of Nrf2 and HO-1 in the nasal mucosa of AR mice. In contrast, ML385 significantly inhibited the regulatory effects of the Nrf2/HO-1 pathway on oxidative stress modulation and protection in AR mice.

Astragaloside

Astragaloside, a highly purified compound extracted from the legume species Astragalus membranaceus and Astragalus myrtillus, is renowned for its potent biological activity. It exhibits more than twice the effectiveness of standard astragaloside and over thirty times greater potency than Astragalus polysaccharides in terms of antiviral effects, despite its lower content. Astragaloside exhibits a wide range of pharmacological effects, including anti-inflammatory, anti-fibrotic, and immunomodulatory properties.[230,236] In mitochondrial research conducted by Chen Xuqing et al, it was found that astragaloside reduced serum IL-4 and IL-5 levels.[237] Furthermore, in OVA-sensitized mice models, it decreased the ratio of NKp46 cells expressing IL-4 and p-Drp1 (Ser616). Additionally, astragaloside inhibited NK2 differentiation in nasal mucosa NK cells, which restored mitochondrial morphology and substantially increased mitochondrial length. As a result, this alleviated nasal allergy symptoms as well as mucosal inflammation in mice. Further research by Ma Wenling on the mechanisms of astragaloside in treating AR revealed its ability to inhibit the TLR4/MyD88/NF-κB signaling pathway.[231] In addition, it was found that astragaloside could modulate Th2 cytokine release and reduce pro-inflammatory factors such as IL-4 and TNF-α, thereby improving symptoms in AR rats. Observations of nasal mucosa tissue showed a more intact structure of the nasal mucosa epithelium in AR rats, with less shedding of cilia, fewer abnormal cup cells, and reduced eosinophil infiltration. Studies on nasal mucosa and spleen tissues in AR mice demonstrated that astragaloside intervention led to reduced levels of p-JAK2 and p-STAT6-positive cell counts, as well as ROS levels. Furthermore, it downregulated the ratios of p-JAK2/JAK2 and p-STAT6/STAT6, thus suppressing the JAK2/

Table 3 The Immunomodulatory Effects and Mechanisms of Saponins From Natural Plants on AR Were Summarized

Natural Plant Molecules	Experiment Object	Mechanism of Action	Reference
Ginsenoside	Mice	TSLP↓, IL-1β↓, IL-4↓, HA↓, IgE↓, IgG1↓, eosinophil ↓, mast cell↓, caspase-1↓, NF-κB/RelA↓	[228]
	Balb/c mice	IL-4↓, IL-13↓, IgE↓, IL-5↓, MDA↓, SOD↑, Nrf2↑, HO-1 ↑	[229]
Astragaloside	C57/BL6 mice	IL-4↓, IL-5↓, p-Drp1 (Ser616) ↓	[230]
	Wistar Male rats	IL-4↓, TNF-α↓, IgE↓, TLR4↓, NF-κBp65↓, MyD88↓	[231]
	C57/BL6 mice	P-JAK2↓, p-STAT6↓, ROS↓	[232]
	C57/BL6 mice	Eosinophil↓, IL-4↓, IL-6↓, IL-1β↓, IgE↓, ICAM-1↓, VCAM-1↓, IL-10↑, HMGB1/TLR4/NF-κB signalling pathway↓	[233]
	C57BL/6 mice	IL-6↓, IL-17↓, IgE↓, TGF-β1↓, IL-10↑, Treg cell↑	[234]

Notes: ↑ represents upregulation, ↓ represents downregulation.

STAT6 signaling pathway and ameliorating AR inflammation.[232] These findings suggest a potential target for precise treatment strategies for AR. Ying Tian et al discovered that a dose of 50.0 mg/kg of astragaloside modulated the HMGB1/TLR4/NF-κB signaling pathway,[233] resulting in decreased protein expression and levels of inflammatory factors such as IL-4, IL-6, IL-1β, IgE, TNF-α, ICAM-1, and VCAM-1, while increasing IL-10 concentrations. From the perspective of T cell pathogenesis, Zhang Fei et al observed that astragaloside reduced the expression of IL-17, IL-6, and IL-1β in peripheral blood T17 cells and inhibited the proliferation of effector T cells through cytokine activation (eg, IL-10, TGF-β), thereby maintaining Th17/Treg cell balance and reducing AR severity.[234]

Monoterpenes (Table 4)

Glycyrrhizic Acid

Glycyrrhizic acid, a pentacyclic triterpene derivative, is a major active component of licorice with pharmacological effects that include anti-inflammatory, anti-allergic, and antioxidant activities. It inhibits oxidative stress and ROS release, reduces pro-inflammatory cytokine levels, and exhibits corticosteroid-like effects.[250] Early studies have indicated that GA suppresses Th2-type cytokines (IL-4, IL-5, IL-13) and up-regulates the Th1-type cytokine interferon-γ (IFN-γ) in OVA-sensitized asthma and AR mouse models. This mechanism helps maintain a balance Th1/Th2 responses while mitigating inflammatory cell infiltration and airway inflammation.[251] 18 β-Glycyrrhetinic acid, an important metabolite derived from glycyrrhizic acid through hydrolysis, is also a pentacyclic triterpene with notable anti-inflammatory and antioxidative effects.[238] Zhou Liuqing et al observed that glycyrrhizic acid reduced intestinal metaplasia effects by decreasing eosinophil counts in the intestinal walls of AR model rats.[252] Dong Ming et al demonstrated that glycyrrhizic acid improved mitochondrial count,[253] reduced cristae degradation, and decreased swelling, vacuolization, and autophagosome appearance in nasal mucosal epithelial cells. Research has demonstrated that 18β-Glycyrrhizic acid (18β-GA) can delay or even reverse pathological changes in nasal mucosal cilia,[239] reduce OVA-sIgE levels, and inhibit the release of inflammatory mediators such as IL-1β, IL-6, IL-8, and TNF-α in AR rats, thereby alleviating allergy symptoms. Furthermore, 18β-GA downregulates proteins like CCL11, AQP1, AQP5, and TSLP in the nasal mucosa,[240] thereby attenuating inflammation and allergic reactions. It also decreases MUC5AC expression to restore normal function of the

Table 4 The Immunomodulatory Effects and Mechanisms of Monoterpenoid Natural Plant Molecules on AR Were Summarized

Natural Plant Molecules	Experiment Object	Mechanism of Action	Reference
Glycyrrhetinic acid	Wistar rats	eosinophil↓	[238]
18 β-Glycyrrhetinic acid	Wistar rats	mitochondrion↑	[239]
	SD rats	sIgE↓, IL-1β↓, IL-6↓, IL-8↓, TNF-α↓, AQP1↓, AQP5↓, TSLP↓	[240]
	Wistar rats	AQP5↑, MUC5AC↓, IL-4↓, sIgE↓, IFN-γ↑	[241]
	SD rats	IL-2↑, IFN-γ↑, IgE↓, IL-4↓, IL-5↓, ICAM-1↓, AQP5↓, NF-κB /PI3K-Akt signalling pathways↓	[242]
Paeoniflorin	Human mast cells	TNF-α↓, IL-1β↓, caspase-1↓, NF-κB/MAPK signalling pathway↓	[243]
	SD rats	IFN-γ↑, IL-4↓, IgE ↓, TGF-β1↓, ICAM-1↓, IL-33/ST2 signalling pathway↓	[244]
Celastrol	Mouse mast cells	SP↓, PI3K/AKT/GSK3P signalling pathway↓	[245]
	SD rats	Eotaxin↓, NF-κB↓	[246]
	SD rats	SOD↑, GSH-PX↑, MDA↓, NRF2↑, GCLC↑	[247]
Notoginsenoside	Balb/c mice	WBC↑, GAR↑, LYM↑, MON↑, IL-6↑, TNF-α↑, TLRs/NF-κB signalling pathway↑	[248]
	Balb/c mice	IgE↓, NLF↓, IL-4↓, IL-6 ↓, IL-8↓, IL-13↑, ROS↓	[249]

Notes: ↑ represents upregulation, ↓ represents downregulation.

ciliary transport system.[241] Additionally, 18β-GA ameliorates ER expansion, vacuolization, and degranulation in the nasal mucosal cells of AR model rats.[254] Research has investigated the mechanisms underlying AR and identified a direct involvement of the p50 subunit in Th2 cell differentiation.[255] By inhibiting NF-κB activity and downregulating p50 expression, 18β-GA limits Th0 to Th2 differentiation while reducing IL-4 levels. It also suppresses transcription of genes associated with inflammatory factors via NF-κB inhibition, thus mitigating the inflammatory response in the nasal mucosa and demonstrating anti-inflammatory effects.[256] In a pathway study, 18-β-glycyrrhizic acid sodium ameliorated nasal mucosal tissue lesions in young AR rats.[242] It inhibited the secretion of IL-2 and IFN-γ, reduced the levels of IgE, IL-4, and IL-5, and restored Th1/Th2 cytokine ratios. Furthermore, it down-regulated ICAM-1 and AQP5 protein expression while inhibiting the activation of NF-κB and PI3K-AKt signaling pathways, demonstrating a significant protective efficacy in young AR rats. This treatment also conferred protective effects against AR in young mice.

Paeoniflorin

Paeoniflorin, a monoterpene glycoside, is the primary bioactive compound found in Paeonia lactiflora. It is well-known for its anti-inflammatory, immunomodulatory, antioxidant, hepatoprotective, and lipid-lowering properties.[257] In initial studies conducted by Guanghui Wang et al, it was observed that paeoniflorin effectively reduced the production of tumor necrosis factor-α and IL-1β by inhibiting the NF-κB/MAPK signaling pathway in PMACI-induced HMC-1 cells.[243] This inhibition gave rise to a reduction in MC-mediated allergic inflammation and improvement in clinical symptoms. Furthermore, recent research conducted by Li Feng et al demonstrated that paeoniflorin modulated cellular immunity through the inhibition of the IL-33/ST2 pathway,[244] leading to increased levels of IFN-γ and decreased levels of IL-4 and IgE. These actions also contributed to reduced expression of TGF-β1 and ICAM-1, thereby attenuating AR pathology and promoting nasal mucosal health.

Celastrol

Celastrol, a pentacyclic triterpenoid monomer, is an active ingredient itself, appearing as red crystals that are chemically stable and physiologically active in vivo. It is insoluble in water and possesses immunomodulatory and anti-inflammatory effects.[258] Studies have shown that celastrol regulates the PI3K/AKT/GSK3β pathway to inhibit substance P-induced MC degranulation,[245] thereby enhancing the survival of sensitized MCs, reducing cellular death, boosting immune response, and modulating symptoms of body metamorphosis. Li Ying et al investigated an OVA-sensitized AR rat model[246] and discovered that celastrol modulates eotaxin expression by inhibiting NF-κB in the nasal mucosa, subsequently reducing EOS aggregation and activation to mitigate allergic pathogenesis. Cui Jing et al reported that pretreatment with celastrol increased SOD and GSH-PX levels,[247] decreased MDA levels in the respiratory zone of nasal mucosa, elevated nuclear NRF2 expression and plasma GCLC protein levels, thus enhancing GSH content and antioxidant capacity of nasal mucosa in AR rats, while significantly improving the symptoms of metamorphic reactions.

Notoginsenoside

Notoginsenoside, the predominant chemical component in Panax ginseng, is primarily a dammarane-type tetracyclic triterpenoid saponin, comprising up to twelve percent of the plant's content. It is known for its involvement in immune regulation, antitumor activity, antioxidant and anti-inflammatory effects, as well as cardiovascular protection.[259,260] Gao Min's initial study on cyclophosphamide-induced immunosuppressed mice demonstrated that notoginsenoside enhances immune cell defense by activating peripheral blood immune cells (WBC, GAR, LYM, MON),[248] promoting lysozyme and cytokine (IL-6, TNF-α) secretion, and stimulating lymphocyte proliferation. Furthermore, it activates and regulates the TLRs/NF-κB signaling pathway by targeting proteins such as TLR-2, TLR-4, TRAF-6, TAK-1, IKKα, NF-κBp65, thereby enhancing macrophage vitality and phagocytosis, while increasing expression of NO, IL-6, and TNF-α, resulting in improved local and systemic immunoregulation. In a recent study, Zhang Yalin et al discovered that notoginsenoside reduced mitochondrial fission,[261] inhibited serum OVA-specific IgE levels, and decreased cytokine (IL-4, IL-6, and IL-8) production in nasal lavage fluid (NLF). It also suppressed the expression of mitochondrial fission proteins DRP1 and ROS, hence reducing mitochondrial fission by inhibiting the TXNIP/NLRP3 signaling axis, enhancing mitochondrial integrity, and alleviating AR symptoms.

Other (Table 5)

Ephedrine

Ephedrine, an alkaloid derived from various ephedra plants, functions as a classical α- and β-adrenergic agonist, stimulating the central nervous system, elevating blood pressure, and dilating bronchi.[266] Research has indicated that ephedrine modulates inflammation by upregulating the anti-inflammatory cytokine IL-10 while downregulating pro-inflammatory cytokines IL-1β, IL-6, IL-12, and TNF-α through the PI3K/Akt signaling pathway.[249] In a mouse model of lipopolysaccharide-induced endotoxic shock, ephedrine was shown to promote immune homeostasis and exert anti-inflammatory effects by balancing cytokine production via TLR4 signaling. Recent studies have emphasized the enhanced therapeutic effects of combining ephedrine with other medications for the treatment of AR.[267] In 1995, research revealed that ephedrine elicits a vasoconstrictive effect on nasal mucosal vessels, thereby optimizing the inspiratory flow rate.[268] Additionally, Yang Ling et al observed that ephedrine suppresses COX2 expression in the nasal mucosa and downregulates mRNA and protein levels of thymic stromal lymphopoietin (TSLP) and OX40L, thus modulating the Th2 immune response in AR rats via the TSLP/OX40L pathway.[262] This intervention significantly attenuated serum levels of IgE, IL-4, and IL-13, consequently modulating the inflammatory response in the nasal mucosa.

Imperatorin

Imperatorin is a principal pharmacological component in commonly utilized traditional Chinese medicines such as Serpentine, Angelica dahurica, Fenghuang, Angelica sinensis, Ming Dangshen, and Duhuo. It exhibits a broad spectrum of pharmacological effects, including analgesic, anti-inflammatory, antibacterial, and anti-tumor properties.[269] Research has shown that imperatorin effectively inhibits MC activation and degranulation, thereby exerting a therapeutic effect on allergic inflammation.[270] Imperatorin has been shown to significantly inhibit the degranulation of RBL-2H3 cells and reduce the release of histamine and various inflammatory markers, including IL-3, IL-4, IL-6, TNF-α, and COX-2, while promoting the expression of IFN-γ, thus modulating the cellular inflammatory response.[271] In both in vivo and in vitro experiments using an OVA-induced AR mouse model, Hyun-AOh et al observed that ouabain effectively attenuated the elevated levels of IgE and histamine, while concurrently increasing interferon-γ levels.[263] In addition, it substantially reduced the protein expression of IL-1β, macrophage inflammatory protein-2, intercellular adhesion molecule-1, and cyclooxygenase-2. Furthermore, imperatorin was found to inhibit the activation of MC, receptor-interacting protein 2 (RIP2), IκB kinase (IKK-β), NF-κB, and caspase-1, consequently leading to a significant reduction in IL-4 levels within splenic tissues. This mechanism ultimately enhances the body's anti-inflammatory response.

Andrographolide

Andrographolide, a natural occurring active compound, is abundant in the plant Andrographis paniculata. It demonstrates potent anti-inflammatory and antioxidant properties by inhibiting the inflammatory response through blocking IKKγ phosphorylation, thereby preventing NF-κB activation and its subsequent nuclear translocation.[272,273] In a study conducted by He Li et al, it was found that the administration of Andrographolide drops combined with Danxi Yupingfeng granules effectively reduced elevated serum levels of total immunoglobulin (Ig)E while also regulating the Th1/Th2 ratio to enhance immune function.[264]

Table 5 The Immunomodulatory Effects and Mechanisms of Other Natural Plant Molecules on AR Were Summarized

Natural Plant Molecules	Experiment Object	Mechanism of Action	Reference
Ephedrine	SD rats	COX2↓, TSLP↓, OX40L↓	[262]
Imperatorin	Balb/c mice	IgE↓, HA↓, INF-γ, IL-4 ↓, caspase-1↓	[263]
Andrographolide	Children with AR	IgE↓	[264]
Sinomenine	Balb/c mice	IL-4 ↓, IFN-γ↓, T-bet↑, GATA3↓, IgE↓, IL-4↓, TGF-β↑	[265]

Notes: ↑ represents upregulation, ↓ represents downregulation.

Sinomenine

Sinomenine, a natural phytochemical derived from Cymbopogon, has been shown to possess anti-inflammatory and immunosuppressive properties.[274] Initial studies have indicated that sinomenine inhibits the production of Th1 and Th2 cytokines, such as IL-4 and INF-γ, while simultaneously enhancing T-bet expression and attenuating GATA3 expression.[275] This modulation alters the balance between Th1 and Th2 cells in the body, thereby regulating the overall Th1/Th2 equilibrium. Zhechen et al investigated the immunosuppressive effects of sinomenine in an OVA-induced AR model.[265] Their findings revealed that this treatment reduced eosinophil infiltration, cuprocyte proliferation, and ciliated cell loss in the nasal epithelium. Additionally, it inhibited the expression of OVA-specific IgE and IL-4 levels while enhancing TGF-β secretion,[276] ultimately regulating the expression of T-bet-a transcription factor critical for Th1 and Th2 differentiation, resulting in decreased overall inflammation along with an enhanced capacity for immune regulation.

Conclusion

Natural plant molecular sources of a wide range of medicinal ingredients mentioned above widely exist in the daily diet of vegetables and fruits. However, they are most abundant in many plants and herbs, and their extraction processes are more advanced. With the continuous advancement of research and the progress of science and technology, previously extracted components from food and medicinal herbs can now be isolated and purified into various forms such as volatile oils, capsules, and liquid injections, enabling diverse routes of administration into the human body. This facilitates enhanced absorption into the bloodstream, achieving optimal drug concentrations while minimizing inefficient utilization by the body's metabolic processes. Although natural plant analysis has been extensively explored and studied, numerous undiscovered plant molecules persist due to technological limitations and limited understanding. For comprehensively investigated plant molecules, in-depth research should be conducted throughout disease onset and progression stages. Currently, traditional Chinese herbal medicine, particularly the focus of current research, exhibits significant potential in modern investigations into its active components. For thousands of years, the therapeutic effects of these natural products have been recognized through human medical experience, encompassing the use of natural animals and plants for medical treatment and diet therapy. Returning to their origins, our present emphasis lies on these plants and animals, especially herbs. These medicinal materials not only come from diverse sources, but also possess a wealth of medicinal ingredients. Some are even referred to as natural antioxidants that serve as crucial sources for novel drug development and effective means for disease prevention and treatment. In recent years, an increasing number of natural plant molecules have been found to exert important effects on AR, with immune regulation being a key underlying mechanism. Previous studies have unequivocally demonstrated a close association between AR pathogenesis and immune regulation. Several studies have suggested that changes in immune regulation within the body may influence the onset and progression of AR in a given population.[277] If this hypothesis holds true, targeting immune cells and factors could potentially enhance the management of AR. Despite extensive research efforts and experimental evidence supporting the underlying mechanisms, limited attention has been directed towards pharmacological interventions specifically aimed at modulating immunity. Consequently, recent focus has shifted towards immunotherapy, gut microbiota intervention, and physical exercise.[278] However, it is important to note that these approaches necessitate longer durations of treatment and patience for optimal benefits. At present, extensive research has been conducted in the field of nanotechnology to achieve targeted drug delivery and improve drug bioavailability, leading to significant advancements in nanomedicine and intranasal dosing.[279–281] Nonetheless, breakthrough results are still lacking, bringing about a gradual shift of focus towards natural molecules.[282] Although there is a lack of specific reports on the immunomodulatory effects of these plant molecules mentioned above, our study on their treatment of AR reveals that they alter disease progression by modulating the body's immune capacity. These results suggest their potential for treating AR. Therefore, using natural plant molecules to regulate AR from an immune regulatory perspective may provide a new way to interfere the progression of AR and enhance cognitive function. In conclusion, it is indisputable that natural plant molecules have strong targeting abilities as AR therapeutic drugs. They can effectively penetrate the blood-brain barrier and provide inherent advantages in maintaining their integrity while regulating their functionality. Moreover, they effectively suppress the secretion of inflammatory factors and cells, modulate the allergic reactions, and ameliorate the pathological characteristics of AR by anti-inflammatory, anti-allergic mechanisms, and signal pathway regulation. These effects have been substantiated in

animal models and cell-based experiments. Nevertheless, comprehensive investigations on the potential toxicological side effects associated with these plant molecules are lacking. Despite their relative reliability, toxicological assessments remain imperative. Moreover, further validation of the multi-pathway targeting effects of natural plant molecules on AR necessitates subsequent clinical trials. Furthermore, it is imperative to investigate the synergistic effects of multiple plant molecules rather than focusing solely on individual compounds. In addition, comprehensive considerations such as pharmacology, pharmacokinetics and pharmacogenetics should be taken into account when addressing issues related to dosage forms and metabolic timing. This multifaceted task presents various challenges, including trial design, trial period definition, ethical review and technical financial support. Therefore, concerted efforts are necessary to optimize the biological activity of natural plant molecules for AR immunoregulation and develop more efficacious therapeutic drugs.

Data Sharing Statement

All data are available in the manuscript and they are shown in the figures and tables.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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