Therapeutic potential of saponins for allergic rhinitis: Molecular mechanisms and clinical perspectives (Review)

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Abstract. Allergic rhinitis (AR) is a chronic inflammatory disorder of the nasal mucosa, often a comorbid condition with asthma, posing notable challenges for treatment. Current therapies, including corticosteroids and antihistamines, primarily target nasal symptoms but exhibit limited efficacy against concurrent asthma and systemic inflammation. Saponins, a class of bioactive plant-derived compounds, have garnered attention for their pleiotropic effects, including immunomodulation, anti-inflammatory activity and antioxidant properties. Saponins, such as ginsenosides, notoginsenosides, astragalosides, saikosaponins and platycodins, modulate key molecular pathways in AR, including T helper 1/2 cell balance, mast cell stabilization and NF-κB signaling. Their multi-target action and low toxicity profile give them advantages such as metabolic compatibility, reduced polypharmacy risks and mucosal protection. The present review highlighted the mechanistic insights into saponin-mediated alleviation of AR and asthma, focusing on their molecular targets, signaling pathways and potential for clinical translation. The present review also discussed current limitations and future directions for the development of saponin-based therapeutics, providing a potential foundation for novel strategies in allergic airway diseases in the future.

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Abbreviations: AR, allergic rhinitis; AS-IV, astragaloside IV; A549 cell, adenocarcinoma human alveolar basal epithelial cell; BEAS-2B cell, bronchial epithelioid cell; CCL, C-C motif chemokine ligand; CHM, Chinese herbal medicine; IgE, immunoglobulin E; ILC2, type 2 innate lymphoid cell; INCS, intranasal corticosteroids; MAPK, mitogen-activated protein kinase; MC, mast cell; NF-κB, nuclear factor κ-light-chain-enhancer of activated B; OVA, ovalbumin; PLD, platycodin D; SSA, saikosaponin A; SSD, saikosaponin D; STAT3, signal transducer and activator of transcription 3; TCM, Traditional Chinese Medicine; Th0, naive T cell; Th2, T helper 2 cell; TNF-α, tumor necrosis factor-α; Treg, regulatory T cell

Key words: allergic rhinitis, saponins, ginsenoside, notoginsenoside, astragaloside, saikosaponin, platycodin

Contents

1. Introduction

Allergic rhinitis (AR) is a type I hypersensitivity reaction mediated by immunoglobulin (Ig)-E, driven by T helper 2 (Th2) cells and induced by allergen exposure in susceptible individuals (1). The prevalence of AR is increasing annually due to increasing environmental pollution. Currently, its global prevalence is 5-50%, affecting ~500 million individuals and exhibiting a constant upward trend (2). As a global health issue, AR is a burdensome condition with a notable socioeconomic impact due to its high prevalence, direct medical costs (3) and reduced productivity of affected individuals (4,5). Typical AR symptoms include profuse watery rhinorrhea, paroxysmal sneezing, nasal obstruction and itching of the eyes and nose, with olfactory impairment also noted in certain cases (6). AR involves more than the classic symptoms, which are associated with daily functioning impairments (1). Inadequately controlled AR markedly impacts the sleep, daily activities and

work productivity of affected individuals, leading to psychological stress and economic burden (7). It has been reported that 10-20% of individuals in the United States are affected by AR, posing a burden on the healthcare system. Indirect costs that are associated with lost work time, missed diagnosis, over-prescription and secondary effects further increase this burden (8).

Chronic and extensive occurrence of AR leads to various complications and coexistence of multiple diseases, including asthma (1,9), sleep disorders (10), chronic sinusitis (11) and olfactory dysfunction (12). Asthma has become a notable concern in recent years (1). Several studies support the 'one airway, one disease' concept, emphasizing the interrelation and co-occurrence of diseases affecting the upper and lower respiratory tracts due to their anatomical continuity and similarity in disease mechanisms (13-15). The World Health Organization and other notable guidelines have highlighted the importance of combined treatment strategies for such conditions (16-18).

AR can be treated both pharmacologically and non-pharmacologically. Environmental control minimizing allergen exposure is theoretically optimal (19). Various interventions, such as those controlling dust mites, pets, air quality and humidity, reduce allergen exposure (20,21). However, comprehensive and sustained environmental control is often expensive and difficult to maintain, particularly in patients with multiple allergies who may not be able to completely prevent allergen exposure (22). Therefore, pharmacological interventions are often required to control symptoms of AR. Current first-line treatments include intranasal corticosteroids (INCSs), antihistamines and leukotriene receptor antagonists. INCSs, which reduce nasal inflammation, are typically recommended as topical monotherapies for moderate-to-severe AR (23). However, despite providing temporary symptom relief, INCSs can induce dependence, resistance and adverse effects, including epistaxis (4-8% incidence with short-term use and 20-28% incidence with 1-year use) (24). Further concerns include potential growth suppression in children and increased risk of osteopenia, osteoporosis, glaucoma and cataracts (25). Although immunotherapy exhibits long-term efficacy, multiyear treatment limits its extensive use (26).

Considering its high morbidity and limitations of current treatments, novel therapies are urgently needed for AR (26). Natural active ingredients derived from medicinal plants have garnered notable interest for their multi-target pharmacological activities and favorable safety profiles (27-29). Specifically, saponins, a class of bioactive plant-derived compounds present in herbs such as ginseng, *Panax notoginseng* and *Platycodon grandiflorus*, exert promising anti-allergic and immunomodulatory effects (30-32). Their efficacies and mechanisms of action have been extensively investigated *in vivo* and *in vitro* (27-32). However, to the best of our knowledge, the latest advancements in the use of saponins for AR treatment have not yet been comprehensively reviewed.

In the present review, the therapeutic potential of saponins for AR was comprehensively evaluated, particularly in cases of asthma comorbidity. The underlying pathophysiology was systematically analyzed, the multi-target mechanisms for AR pathway modulation were elucidated and translational challenges and future research directions were assessed, thereby providing a scientific foundation for the development of next-generation AR therapeutics.

2. Pathogenic mechanisms of AR and concurrent asthma

Pathogenic mechanisms of AR. AR pathogenesis involves complex immunoregulatory processes that are broadly categorized into sensitization and elicitation phases. During sensitization, allergens are presented to naive T (Th0) cells by antigen-presenting cells, such as epithelial and dendritic cells, driving their differentiation into Th2 cells (33). These Th2 cells release cytokines (for example, IL-4, IL-5 and IL-13) stimulating B cells to produce allergen-specific IgE antibodies (34), which bind to mast cells (MCs) and basophils, priming the immune system (35). Elicitation involves both immediate- and late-phase reactions. The immediate phase is characterized by MC degranulation, release of mediators, such as histamine and bradykinin, and triggering of symptoms, such as nasal itching, sneezing and congestion (34). The late phase, driven by mediators (for example, TNF-α, leukotriene B4 and IL-5) released from MCs, involves eosinophil and basophil infiltration, leading to further tissue damage and worsening symptoms such as nasal congestion and rhinorrhea (34,35). Dysregulation of the immune system, including an imbalance in Th1/Th2 responses (increased Th2 cell proportions), impaired regulatory T cell (Treg)/Th17 balance (decreased Treg cell proportions and increased Th17 cell proportions and IL-17 levels) (36-39) and activation of type 2 innate lymphoid cells (ILC2s), contributes to inflammation. ILC2s are activated by cytokines, such as thymic stromal lymphopoietin, IL-25 and IL-33 from epithelial cells, which release IL-5 and IL-13 and promote Th2 cell differentiation and eosinophil recruitment, linking innate and adaptive immunity (40-42). These dysregulated immune responses collectively contribute to the development of AR (Fig. 1).

Potential mechanisms of AR complicated by asthma. AR and asthma frequently coexist and exhibit a bidirectional relationship, often conceptualized under the 'one airway, one disease' paradigm (20-22). Uncontrolled AR exacerbates asthma (42) and asthma worsens upper airway inflammation (43). The present review focuses on the mechanistic pathways by which AR is complicated by asthma, a disease involving multiple interconnected mechanisms (Fig. 2).

Anatomically, the respiratory tract, from the nose to the bronchi, is a continuous mucosal surface. Inflammation initiated in the nasal mucosa leads to systemic dissemination of inflammatory mediators and cells, which subsequently affect the lower airways, thereby inducing or worsening asthma (44). Physiologically, the nasobronchial reflex provides a neural association and nasal irritation or inflammation enhances reflex-mediated bronchoconstriction (45). Emerging evidence suggests that dysbiosis of the nasal microbiome influences the lung microenvironment via the circulation of immune cells or mediators, potentially exacerbating asthmatic inflammation in AR (46,47).

AR and asthma share a core pathogenic mechanism driven by Th2-type immune responses (19). Systemic inflammation in AR, characterized by elevated Th2 cytokine levels in the circulation, primes the lungs for inflammation, providing

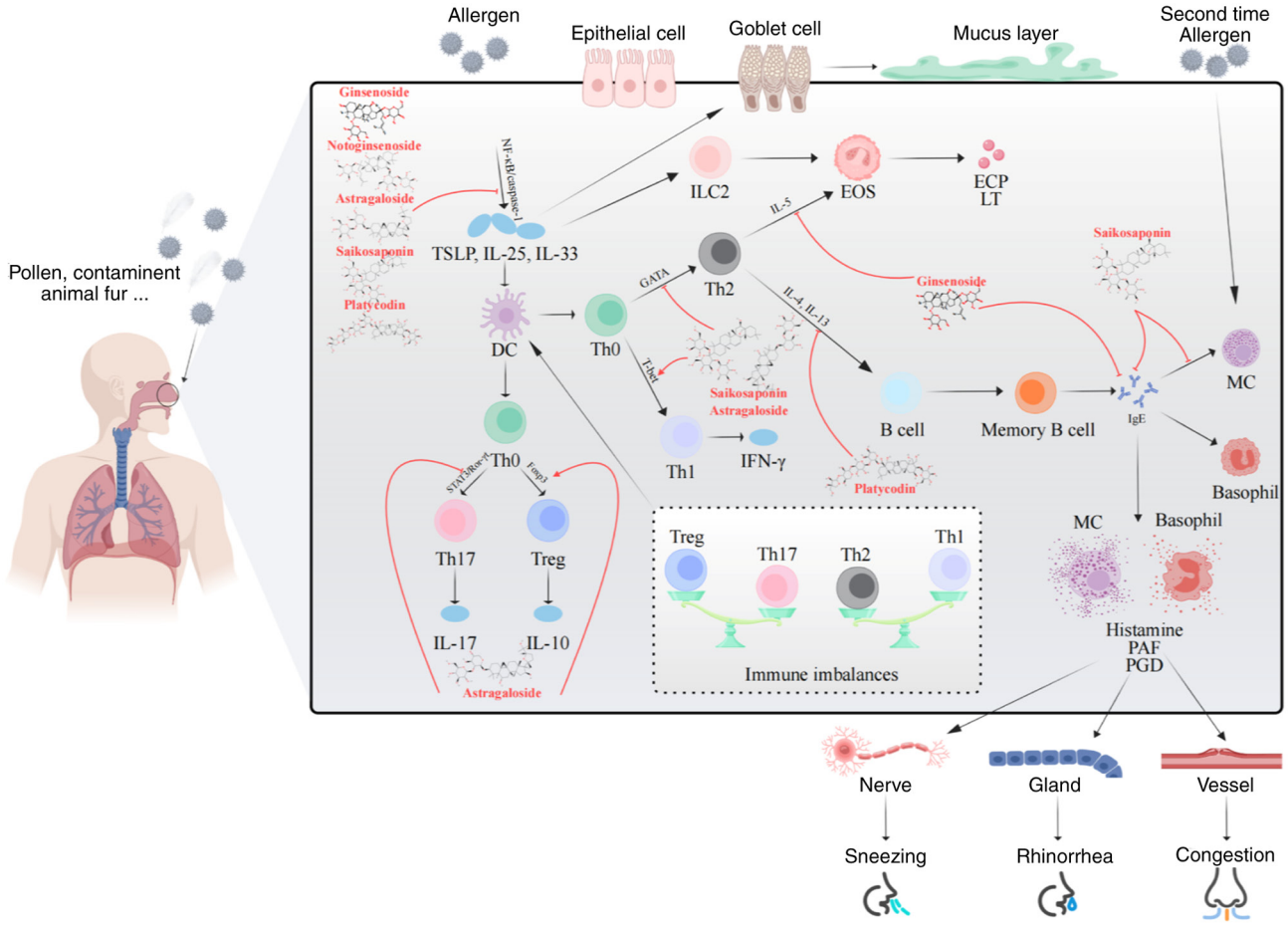

Figure 1. Pathogenesis of allergic rhinitis: Immune cell interactions and intervention points for saponins. Allergen exposure triggers nasal epithelial cells to release alarmins (TSLP, IL-25 and IL-33). These alarmins activate DCs and ILC2s. DCs promote the differentiation of Th0 cells into Th2 cells, which produce IL-4, IL-5 and IL-13. ILC2s also produce Th2-type cytokines. IL-4 and IL-13 drive B cells to produce allergen-specific IgE, which sensitizes MCs and basophils. Upon subsequent allergen exposure, cross-linking of IgE triggers the degranulation of MCs and basophils, releasing mediators (for example, histamine, prostaglandin D2 and leukotrienes) that cause immediate symptoms (sneezing, rhinorrhea, congestion). IL-5 recruits EOS, which release mediators such as ECP, contributing to late-phase inflammation and tissue damage. Saponins (for example, ginsenosides, astragalosides, saikosaponins and platycodin D) counteract this process by: Inhibiting alarmin release; promoting Th1/Treg differentiation; suppressing inflammatory cell activation and degranulation; and reducing the production of key cytokines (IL-4, IL-5, IL-13 and IgE). Red lines indicate the targeting action of the specific saponin on the depicted pathways. Black lines represent the signaling cascades/ cell-cell interaction. Arrows (→) denote activation, promotion or upregulation, while T-bars (-|) signify inhibition, suppression or downregulation. DC, dendritic cell; EOS, eosinophil; ECP, eosinophil cationic protein; IgE, immunoglobulin E; IL, interleukin; ILC2, innate lymphoid cell type 2; LT, leukotriene; MC, mast cell; PAF, platelet-activating factor; PGD2, prostaglandin D2; Th, T helper cell; Treg, regulatory T cell; TSLP, thymic stromal lymphopoietin.

a fundamental association with comorbidity (48). Even subclinical nasal inflammation in patients with AR can signify generalized airway susceptibility (49). This shared pathophysiology is the reason for asthma being the most common comorbidity among patients with AR, affecting >80% of cases (1) and highlights the necessity of concurrently managing both conditions (50,51).

3. Therapeutic mechanisms of action of saponins against AR

Saponins are a class of amphipathic glycosides extensively distributed in various plants, marine organisms and certain lower animals, such as ginseng, starfish and soft corals (27-29). Their structure comprises a hydrophobic aglycone (genin) coupled to ≥1 hydrophilic sugar moieties via glycosidic bonds (52). Based on the aglycone structure, saponins are primarily classified into two major types: Steroids and triterpenoids (52). They exhibit various pharmacological activities, including immunomodulatory, anti-inflammatory, antifungal and antiviral activities (30-32). The present review focuses on the therapeutic effects and mechanisms of action of saponins derived from five Chinese herbal medicines (CHMs) against AR (Figs. 1-3; Table SI).

Ginsenosides. Ginseng (the root of *Panax ginseng* C.A.Mey.), an extensively used and valuable CHM (53), contains ginsenosides, which exert diverse anti-allergic effects (54-56). Ginsenosides, particularly Rg5, Rg1, Rh2, Rd, Rg3, Rb1 and Rh1, effectively mitigate allergic airway inflammation via multiple mechanisms (30,54-62).

One mechanism involves the inhibition of the release of inflammatory mediators. For example, ginsenoside Rg3 reduces cyclooxygenase-2 expression in IL-1β-stimulated adenocarcinoma human alveolar basal epithelial (A549) cells and reduces C-C motif chemokine ligand (CCL)-24, CCL11,

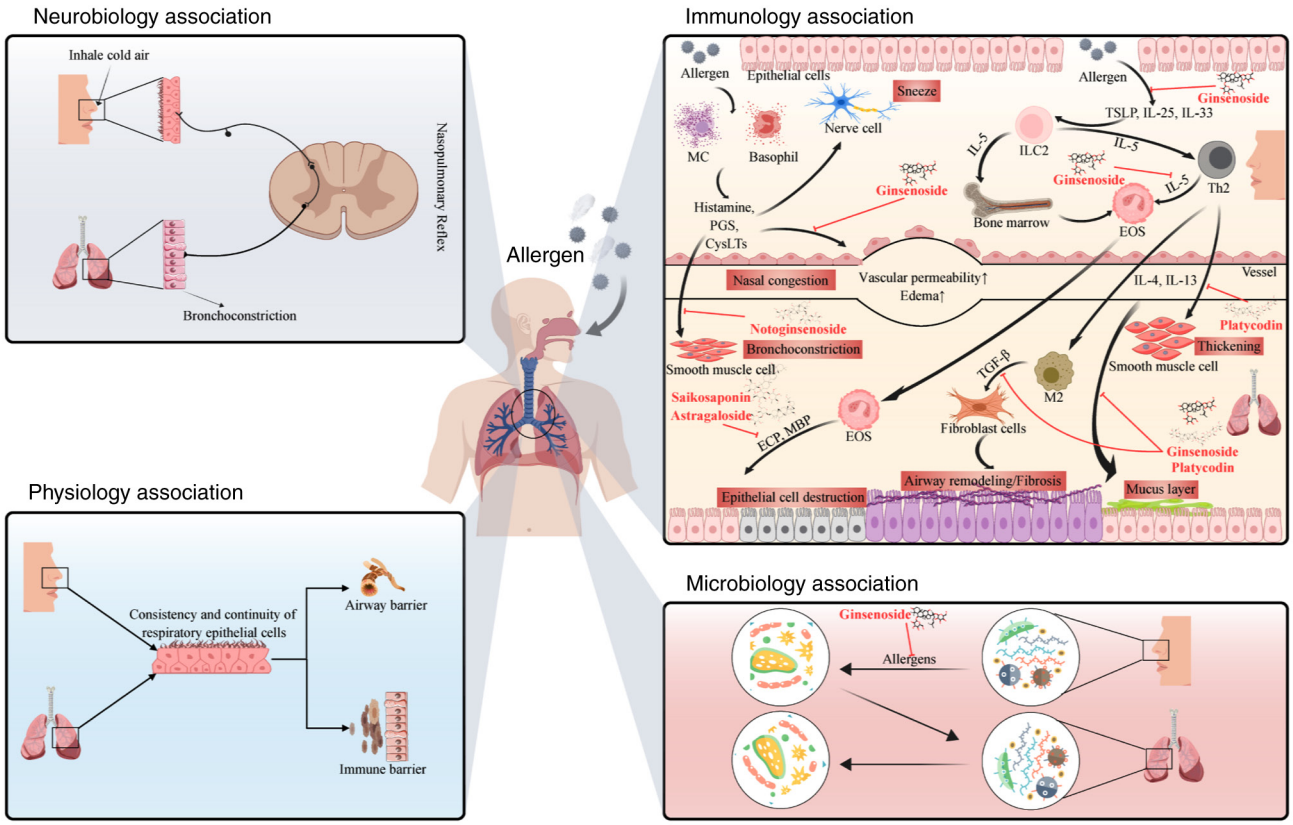

Figure 2. Pathogenic associations between allergic rhinitis and comorbid asthma and the therapeutic mechanisms of saponins. Associations between upper and lower airway inflammation in the context of AR with comorbid asthma. The neurobiology component shows nasal inflammation stimulating trigeminal afferents associated with bronchoconstriction, with saikosaponin A acting on this pathway. The immunology section depicts the IgE-mediated mast cell activation cascade, Th2-driven inflammation and the targeting of this pathway by multiple saponins including ginsenosides and platycodin D. Physiology highlights the anatomical continuity of airways and downward spread of inflammation, while microbiology indicates nasal barrier disruption and dysbiosis influencing lung environment, modulated by ginsenoside. Red lines indicate the targeting action of the specific saponin on the depicted pathways. Black lines represent the signaling cascades/cell-cell interaction. Arrows (→) denote activation, promotion or upregulation, while T-bars (-l) signify inhibition, suppression or downregulation. AHR, airway hyperresponsiveness; CysLTs, cysteinyl leukotrienes; DC, dendritic cell; ECP, eosinophil cationic protein; Eos, eosinophil; IgE, immunoglobulin E; IL, interleukin; ILC2, innate lymphoid cell type 2; LT, leukotriene; MBP, major basic protein; MC, mast cell; MUC5AC, mucin 5AC; PG, prostaglandin; Th, T helper cell; TNF-α, tumor necrosis factor-α; TSLP, thymic stromal lymphopoietin.

CCL5, monocyte chemoattractant protein-1, IL-6, IL-8, intercellular cell adhesion molecule-1 and reactive oxygen species production in human bronchial epithelioid (BEAS-2B) cells stimulated by IL-4 and TNF-α (57-59). Kim *et al* (60) reported that fermented red ginseng and ginsenoside Rd alleviate ovalbumen (OVA)-induced AR in mice by inhibiting IgE, IL-4 and IL-5 expression. Ginsenosides also alleviate allergic reactions by inhibiting the activation of inflammatory cells. Treatment of inflammatory BEAS-2B cells with ginsenoside Rg3 reduces the expression levels of CCL and pro-inflammatory cytokines and adhesion of monocytes to BEAS-2B cells (58), thereby markedly reducing eosinophil infiltration, oxidative stress, airway inflammation and airway hyperresponsiveness in the lungs of asthmatic mice. Ginsenosides also modulate key signaling pathways. For example, Rg1 reduces the expression levels of receptor-interacting serine/threonine-protein kinase 2 and inhibitor of κB kinase β and accumulation of NF-κB, thereby inhibiting the production of thymic stromal lymphopoietin in AR model mice (61). Li *et al* (62) revealed that ginsenoside Rh2 alleviates allergic airway inflammation by modulating NF-κB activation and p38 mitogen-activated protein kinase (MAPK) phosphorylation. Overall, ginsenosides act on multiple targets and affect multiple pathological pathways to improve AR symptoms. This has been validated by an *in vivo* study integrating metabolomics and transcriptomics (63), which reported the downregulation of the expression levels of three AR-related pro-inflammatory genes are downregulated and upregulation of the expression levels of nine anti-inflammatory genes. These expression patterns have also been validated by other studies and revealed to be closely associated with asthma (64-69). These studies revealed the potential cause of AR with asthma and highlighted the therapeutic mechanisms of ginsenosides via multi-target anti-AR and asthma effects. A previous study identified the upregulation of COP9 signalosome subunit 3 is potentially associated with *Lactobacillus helveticus* and microbiome modulation (70). Collectively, these findings underscore the potential of ginsenosides to treat both AR and concurrent asthma via multitarget therapeutic effects (Fig. 2; Table SI).

Notoginsenosides. Notoginsenosides, the active compounds in *Panax notoginseng*, exert diverse pharmacological effects, including anti-inflammatory, antioxidant, neuroprotective and immunomodulatory effects (71-73). Clinically, they are used to treat thrombotic, inflammatory and cardiovascular conditions (73,74). Notoginsenoside R1, a key saponin

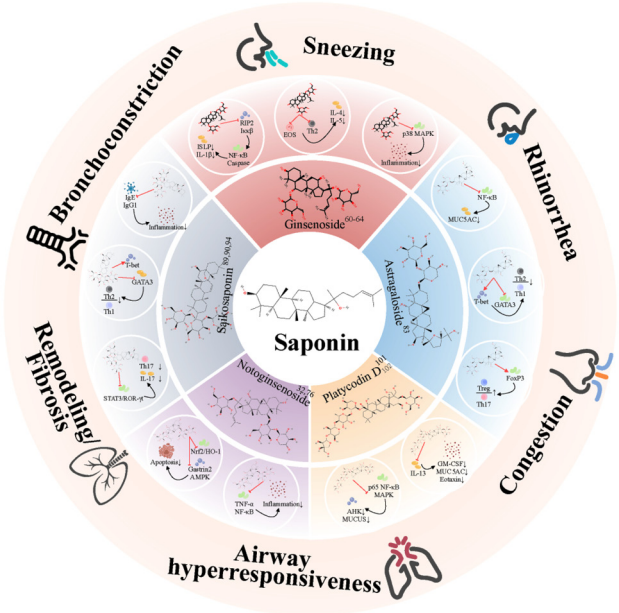

Figure 3. Molecular mechanisms of various saponins in alleviating allergic rhinitis and comorbid asthma. Different saponins (ginsenoside, astragaloside, platycodin D, notoginsenoside and saikosaponin) modulate key signaling pathways and cellular responses involved in the pathogenesis of allergic rhinitis and asthma, leading to the amelioration of associated symptoms (outer ring). The figure illustrates the key signaling pathways modulated by different saponins (ginsenoside, astragaloside, platycodin D, notoginsenoside and saikosaponin) and the resulting amelioration of symptoms (outer ring). Ginsenoside inhibits the RIP2/IκBβ/NF-κB axis, eosinophil activity, Th2 differentiation and the p38 MAPK pathway. Astragaloside suppresses NF-κB activation, modulates the T-bet/GATA3 balance to inhibit Th2 responses and enhances Treg function via FoxP3. Platycodin D inhibits p65 NF-κB and MAPK pathways, reducing IL-13, GM-CSF, MUC5AC and eotaxin. Notoginsenoside activates Nrf2/HO-1 and AMPK pathways, while inhibiting TNF-α/NF-κB signaling. Saikosaponin reduces IgE/IgG1 production, inhibits Th2 and Th17 differentiation via T-bet/GATA3 and IL-6/STAT3/ROR-γt pathways, and blocks NF-κB. The specific mechanisms of action of these saponins are explained in the article. Red lines indicate the targeting action of the specific saponin on the depicted pathways. Black lines represent the signaling cascades. Arrows (→) denote activation, promotion or upregulation, while T-bars (-|) signify inhibition, suppression or down-regulation. Upward arrows (↑) indicate an increase and downward arrows (↓) indicate a decrease in the respective molecule or process. AHR, airway hyperresponsiveness; AMPK, AMP-activated protein kinase; caspase-1, caspase-1; EOS, eosinophil; FoxP3, forkhead box P3; GATA3, GATA binding protein 3; GM-CSF, granulocyte-macrophage colony-stimulating factor; HO-1, heme oxygenase-1; IgE, immunoglobulin E; IgG1, immunoglobulin G1; IκBβ, nuclear factor of κ light polypeptide gene enhancer in B-cells inhibitor, β; IL, interleukin; MAPK, mitogen-activated protein kinase; MUC5AC, mucin 5AC, oligomeric mucus/gel-forming; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; Nrf2, nuclear factor erythroid 2-related factor 2; p38 MAPK, p38 mitogen-activated protein kinase; RIP2, receptor-interacting serine/threonine-protein kinase 2; ROR-γt: related orphan receptor γt; T-bet, T-box transcription factor TBX21; Th, T helper cell; TNF-α, tumor necrosis factor-α; Treg, regulatory T cell.

present in this plant, is currently being investigated for its potential to treat AR (32,75,76). Notoginsenosides possibly alleviate AR- and asthma-related airway inflammation by modulating key signaling pathways. Xue *et al* (75) and Zhang *et al* (76) demonstrated that notoginsenoside R1 reduces allergic airway inflammation in asthma models by influencing the TNF-α/NF-κB pathway and attenuating glucocorticoid-induced apoptosis of airway epithelial cells (activate nuclear factor erythroid 2-related factor 2/heme oxygenase-1 and sestrin 2/AMP-activated protein kinase signaling pathways) (32,75,76). Furthermore, notoginsenoside R1 mitigates AR symptoms by inhibiting AMP-activated protein kinase/dynamin-related protein 1-mediated mitochondrial division and regulating the Th1/Th2 balance (75). However, further studies are key to fully elucidating the action mechanisms and efficacy of notoginsenosides for AR treatment (Fig. 2; Table SI).

Astragaloside (AS). Astragalus is the root of *Astragalus membranaceus* (Mongolian milkvetch) and *A. propinquus*, leguminous plants commonly used in China to treat several diseases, including AR (31,77,78). AS-IV, its main bioactive component, exerts various pharmacological effects, including anticancer, antiviral, anti-allergic and immunomodulatory effects (79,80). It regulates the differentiation of key immune cells in AR. Li *et al* (81) demonstrated that AS-IV reduces the secretion of the pro-inflammatory cytokines IL-4 and IL-17 and increases the production of interferon-γ by regulating the expression levels of transcription factors, such as GATA-binding protein 3 (GATA3), retinoic acid-related orphan receptor (ROR)-γt, T-box protein (T-bet) and forkhead box P3, which promote the conversion of Th0 cells to the Th1 phenotype and reduce inflammatory responses, nasal symptoms and mucosal remodeling in AR mice (81). Notably, these mechanisms have also been reported in the spleen, a key immune organ in mice, suggesting that AS-IV regulates systemic immune responses. A previous study using a histamine-induced AR mouse model reported that AS-IV exerts anti-allergic effects by regulating the expression levels of inflammatory genes (for example, IL-6, C-X-C motif chemokine ligand 8 and Mucin 5AC) and reducing the release of inflammatory factors and mucin (82) (Fig. 2; Table SI).

Saikosaponin. Bupleuri Radix (Chaihu), derived from the plant *Bupleurum chinense* DC. or *Bupleurum scorzonerifolium* Willd, is an herb commonly used in Traditional Chinese Medicine (TCM) (83). Saikosaponin, the main active component of Bupleurum, exerts neuroprotective (83), anti-atherosclerotic (84), antipyretic (85), anti-inflammatory (85), lung-protective (86), liver-protective (85) and antidepressant (83). Previous studies have demonstrated the potential of saikosaponins A (SSA) and D (SSD) to treat allergic airway diseases (87-89).

NF-κB signaling pathway serves a key role in inflammatory responses by regulating the expression levels of various inflammatory genes (such as *IL6, IL1B* and *TNF*) (90). Saikosaponins markedly inhibit the activation of inflammatory pathways. A previous study demonstrated the ability of saikosaponin to inhibit NF-κB activation and reduce the expression levels of target genes in macrophages (87). Saikosaponins exert therapeutic effects against AR by inhibiting inflammatory cell activation in the nasal mucosa and pro-inflammatory factor production. Piao *et al* (88) reported that SSA inhibits the activation of the IL-6/ STAT3/ROR-γt/IL-17 and NF-κB pathways, thereby alleviating rhinitis symptoms, including nose rubbing and sneezing, and suppressing nasal mucosal remodeling in an OVA-induced AR mouse model. STAT3/ROR-γt pathway is closely associated with Th17 cell differentiation and IL-17 production, whereas T-bet/GATA3 pathway is associated

with the balance of Th2 and Th1 cells (91,92). SSD alleviates inflammatory reactions by modulating the T-bet/GATA3 and NF-κB pathway and restoring the Th1/Th2 balance in AR model mice (89). SSD also alleviates allergic reactions by downregulating IgE and IgG1 production in AR model mice. Furthermore, SSA inhibits MC activation by targeting the MC activation targets (for example, zyxin and A-23187), thereby alleviating allergic asthma (93,94) (Fig. 2; Table SI).

Platycodin. Platycodin D (PLD), a triterpenoid saponin isolated from *Platycodon grandiflorus*, exhibits various pharmacological activities, including antidiabetic (95), anti-inflammatory (96), anticancer (97), anti-infectious and immunomodulatory activities (98). Although clinical trials on PLD for AR are currently lacking, previous *in vivo* mouse studies suggested that PLD effectively mitigates AR symptoms (99-101). Specifically, PLD inhibits inflammatory factor release, regulates allergic asthma (and by implication, AR) symptoms, such as airway hyperresponsiveness and remodeling and reduces systemic inflammation by modulating the NF-κB signaling pathway and inhibiting IL-13 (99-101) (Fig. 2; Table SI).

4. Potential therapeutic mechanisms of saponins against AR complicated by asthma

Previous studies have suggested the potential therapeutic mechanisms of saponins against AR and asthma involve multiple immunomodulatory pathways (including NF-κB, MAPK, Th1/Th2 and Th17/Treg pathways). Although relevant research on combined treatment strategies for concurrent AR and asthma is currently lacking, to the best of our knowledge, existing research suggests that saponin components, with their multi-pathway and multi-target immunomodulatory characteristics, synergistically regulate the complex comorbid mechanisms of AR and concurrent asthma, facilitating the unified treatment of the upper and lower respiratory tracts and alleviating inflammation and symptoms of AR and its complications (32,59,63,75,88,93,100,101) (Fig. 2; Table SI). Consistently, He *et al* (102) reported that Jieyu Gubentang, a herbal formula containing saponin-based drugs, simultaneously inhibits inflammatory cell infiltration and damage in the nasal mucosa and lung tissues, reducing the overall allergic reaction in the respiratory tract of rats, highlighting its potential for the synergistic regulation of comorbidities. However, further studies, including in-depth mechanistic studies and clinical trials, are necessary to validate the efficacy and safety of saponin-based therapies for AR complicated by asthma in the future.

5. Future prospects and challenges of AR treatment with saponins

Saponins offer unique advantages over traditional multiherbal Chinese medicinal formulas and conventional pharmacotherapies for AR. There has been a resurgence of interest in TCM, with increased research on the use of CHMs to treat complex diseases, including AR (54-56,102,103). However, treatment often faces challenges, such as complex herbal compositions, variable efficacy and dependence on clinician expertise. The notable success of artemisinin derived from *Artemisia annua* in treating malaria provided a novel avenue for CHMs (104,105), with reduced safety concerns associated with complex herbal mixtures and markedly enhanced efficacy. Complex TCM formulas, for example, Biminne (106), Yu Ping Feng San (composed of *Astragalus membranaceus*, *Atractylodis macrocephalae rhizoma and Saposhnikoviae radix*) (107), antiasthma simplified herbal medicine intervention (composed of *Ganoderma lucidum*, *Radix Sophorae flavescentis* and *Radix Glycyrrhiza*) (108) and Jieyu Gubentang (composed of *Bupleurum chinense*, *Angelica sinensis*, *Paeonia lactiflora*, Radix Glycyrrhiza, *Magnolia biondii*, *Cryptotympana pustulata*, *Perilla frutescens*, *Citrus reticulata*, *Astragalus membranaceus*, *Atractylodes macrocephala*, *Saposhnikoviae Radix* and *Xanthium strumarium*) (102) exhibit variable efficacies, multifaceted yet unclear mechanisms and standardization limitations (36,55,102,109,110). By contrast, isolated saponins (for example, ginsenosides, AS-IV, SSA, SSD and PLD) exhibit defined chemical structures, facilitating improved standardization, quality control, targeted mechanistic studies (for example, modulation of NF-κB and MAPK pathways and Th1/Th2 and Treg/Th17 balance), potentially more predictable pharmacokinetics and a reduced risk of toxicity or unknown interactions compared with whole extracts or multi-herb mixtures. Unlike several pharmaceutical drugs [for example, INCSs and antihistamines (23,24,103)], antileukotrienes (111-113), which often focus on single targets primarily for symptomatic relief and possibly lead to side effects (such as epistaxis and growth concerns) or dependency on long-term use (114), saponins exert pleiotropic effects. Their potential to simultaneously modulate multiple inflammatory and immune pathways (including NF-κB, MAPK, Th1/Th2 and Th17/Treg pathways) offers a more holistic approach to manage the complex pathophysiology of AR and concurrent asthma, addressing systemic inflammation and neuroimmune interactions more effectively compared with single-target agents, while also possessing a favorable safety profile inherent to natural products (Table SII).

The potential of saponins in more holistic and multi-faceted approaches arises directly from their ability to inhibit the occurrence and development of AR and its complications, such as asthma, through multiple mechanisms. Unlike single-target conventional drugs, they regulate Th1/Th2 and Th17/Treg imbalance, reduce inflammatory factor levels in the serum, alleviate systemic inflammation caused by AR and potentially improve gut microbiota dysbiosis. In addition to regulating immune mechanisms, saponins potentially alleviate AR and asthma symptoms by regulating neuroimmune interactions. The nasobronchial reflex is a key neural pathway connecting the upper and lower respiratory tracts (45); attenuation of local inflammation in the nasal mucosa reduces its sensitivity, thereby alleviating the lung symptoms resulting from this reflex. SSA exerts neuroprotective effects, such as inhibiting neuronal apoptosis, attenuating oxidative stress and suppressing neuroinflammation (83). And by inhibiting neuroinflammation, it possibly also reduces airway hyperreactivity. Notably, pathological mechanisms of AR are heterogeneous, with effective treatment requiring individualized approaches based on specific biomarkers. Different saponins improve AR symptoms through distinct therapeutic mechanisms, providing the option of selecting suitable drugs

for individualized and precise treatment. For example, saponins inhibiting ILC2 activity (for example, ginsenoside Rg1) can be selected for patients with primary ILC2 activation, whereas those regulating the Th17/Treg balance (for example, SSA) can be used for patients with primary Th17 cell activation (61,89). Furthermore, compared with conventional treatments, saponins are typically derived from natural resources, are renewable and offer various advantages in terms of drug economics (27-29).

Despite promising preclinical findings, therapeutic application of saponins for AR remains challenging. Low bioavailability, resulting from their high molecular weight, high glycosylation, poor water solubility and low oral absorption hinder their effectiveness (115). Nanotechnology offers a potential solution by enhancing bioavailability via encapsulation (37,116-119). However, extensive application of nanotechnology has limitations and research on the majority of nanodrug formulations for AR treatment remains in the animal experimental and *in vitro* research stages (37,119). Therefore, further research is key to clarifying their safety and efficacy after application. Furthermore, the existing research on saponins for AR treatment is limited to animal experiments. Animal experimental results cannot be used to accurately predict drug efficacy in humans (120). The majority of AR and asthma mouse models are induced using histamine or OVA, with no comorbid models for concurrent AR and asthma currently available. Therefore, study results cannot be generalized to patients with simple AR or AR complicated by asthma who are allergic to specific allergens (for example, dust mites and pollen) (121). Therefore, development of suitable comorbidity models and promotion of clinical studies are key research directions for the future.

6. Conclusions

Currently, various drugs are used to treat AR; however, their limited efficacy and adverse reactions pose major concerns. Natural active ingredients, particularly saponins, exhibit notable potential for individualized treatment of complex AR because of their multi-target multi-pathway effects. Furthermore, saponins from different sources provide therapeutic advantages via distinct mechanisms. Additionally, nanotechnology-based drug delivery systems exhibit the potential to overcome the bioavailability limitations of saponins, further enhancing their efficacy and targeting capacity. However, clinical translation of saponins is limited by various challenges, including low bioavailability, complex action mechanisms and a lack of clinical evidence. Therefore, future studies should conduct in-depth analyses of the mechanisms of action of saponins, develop novel delivery systems and perform high-quality clinical trials to potentially identify more effective and safer natural drug options for AR treatment.

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Authors' contributions

YCL, BYL, ZYF and PTZ designed the present review. FFL, KH, ZHX, YXH, YZ and SWC contributed to data collection, analysis and interpretation. YHL, HFP and YCL supervised the project and revised the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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