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Natural products modulating interleukin-mediated pathways for anti-allergic and immunomodulatory effects

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The increasing prevalence of allergic diseases and immunological disorders is a significant public health issue requiring the development of novel therapeutic approaches. Interleukins are prime therapeutic targets because they are crucial for immune control and allergic aetiology. Naturally occurring bioactive compounds show tremendous promise for altering interleukin signalling, providing therapeutic advantages with potentially fewer adverse effects than those of synthesised drugs. This review highlights key bioactive substances that influence interleukin pathways, including flavonoids, polyphenols, terpenoids, alkaloids, and plant extracts. These compounds exhibit multiple mechanisms of action, including enhanced anti-inflammatory responses and reduced production of pro-inflammatory cytokines. Controlling several interleukin-mediated pathways, including IL-6 and IL-17, IL-1β and IL-10, as well as IL-4 and IL-13, has shown promise, thus showing substantial anti-allergic properties. These compounds exert modulatory effects by reducing Th2-mediated allergic reactions. This review examined their binding affinities to important interleukins to support the therapeutic potential of these bioactive metabolites. Although the results are encouraging, some issues remain, including variations in compound bioavailability, formulation issues, and insufficient clinical validation. This review addresses these challenges and highlights the potential use of bioactive compounds in innovative approaches aimed at interleukin-mediated pathways in immunological control and allergies.

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1. Introduction

Allergic diseases, including atopic dermatitis, asthma, allergic rhinitis, and food allergies, primarily arise from complex immune responses. The prevalence of allergies worldwide is significant and has increased in recent decades. It affects

approximately 20–30% of the global population. Specific allergies, such as asthma, affect approximately 262 million people globally, allergic rhinitis around 400 million, atopic dermatitis 171 million, and food allergies affect over 200 million people.[1–4] Allergies remain a major global health concern, affecting hundreds of millions worldwide. The prevalence differs by region and allergy type, with environmental factors significantly contributing to the rising rates. The economic burden is

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considerable, thus emphasising the importance of effective management and prevention strategies.

These complex responses typically result from the overexpression of immune cells and the increased release of pro-inflammatory cytokines, particularly interleukins (ILs). ILs are signalling molecules that play a vital role in initiating and perpetuating the immune system by facilitating communication between cells.[5,6] There are two main types of ILs: pro-inflammatory and anti-inflammatory. Pro-inflammatory ILs are cytokines (small signalling proteins that play a crucial role in the immune system) that play a central role in the immune response to infections and tissue damage. ILs activate immune cells, promote inflammation, and aid in the fight against pathogens. However, overexpression of these ILs results in chronic inflammation and tissue damage.[7] These pro-inflammatory ILs include IL-1, IL-4, IL-5, IL-6, IL-12, IL-13, IL-17, IL-18, IL-23, IL-33, interferon-gamma (IFN-γ), and tumour necrosis factor-alpha (TNF-α).

IL-1 comprises two ILs, IL-1α and IL-1β. Both are strong pro-inflammatory ILs that play vital roles in host response to different stimuli. The main functions of IL-1 include inflammation and immune responses,[8] innate and adaptive immunity,[9] pathogenesis of diseases,[10] vascular diseases,[11] and tumorigenesis.[12] IL-4 is a versatile cytokine that plays a crucial role in the immune system, including the regulation of immunological responses such as Th2 cell development and immunoglobulin E (IgE) isotype switching, as well as participating in cellular mechanisms such as receptor binding and signal transduction.[13] It also has therapeutic implications, such as antagonists,[14] disease regulation,[15] and a significant impact on allergic illnesses,[13] autoimmunity, and cancer,[16] while also exhibiting anti-inflammatory properties, as seen in arthritis.[17] Along with this, IL-4 facilitates M2 macrophage polarisation and contributes to tissue repair processes. It modulates immune responses and supports regeneration, thereby suppressing pro-inflammatory pathways and contributing to healing and homeostasis.[18] IL-5 is a haematopoietic cytokine primarily responsible for the control of eosinophils, which are implicated in numerous allergic and inflammatory responses. The primary functions include the regulation of eosinophils, such as their proliferation, differentiation, survival, activation, and degranulation.[19,20] In addition, another significant role of IL-5 is the migration and recruitment of eosinophils to tissue sites, particularly during allergic reactions.[21] Another primary function of IL-5 relates to its clinical implications in disorders, its potential as a therapeutic target, and its larger biological roles.[22,23] Likewise, the remaining pro-inflammatory ILs, IL-6, IL-12, IL-13, IL-17, IL-18, IL-23, IL-33, IFN-γ, and TNF-α also play a significant role in immune regulation and allergic treatment.[24–30] For instance, IL-12 is a heterodimeric cytokine mainly synthesised by phagocytic and antigen-presenting cells. It activates natural killer and T cells, leading to the induction of IFN-γ production, cellular proliferation, and increased cytotoxic activity. IL-12 is essential for host defence against infections by promoting Th1 differentiation and innate immune responses; however, it may also contribute to pathological inflammation and autoimmune disorders.[31] IL-13 is a multifunctional cytokine primarily involved in Th2-polarized immune responses, allergic reactions, and the regulation of immunoglobulin production. IL-13 exhibits dual roles, providing protective effects that maintain metabolic and immune functions while also contributing to pathological processes, such as fibrosis and mucosal barrier dysfunction, especially in metabolic liver diseases like MASH.[32,33] In addition to this, IL-18, belonging to the IL-1 cytokine family, effectively stimulates IFN-γ production and has diverse functions in both mucosal and systemic inflammation. The dysregulation of IL-18 is associated with autoinflammatory diseases, as well as cancer, positioning it as a potential target for precision diagnostics, disease monitoring, and therapeutic intervention.[34] IL-23 is a proinflammatory cytokine primarily synthesised by macrophages and antigen-presenting cells, playing a crucial role in the modulation of both innate and adaptive immune responses. The IL-23/Th17

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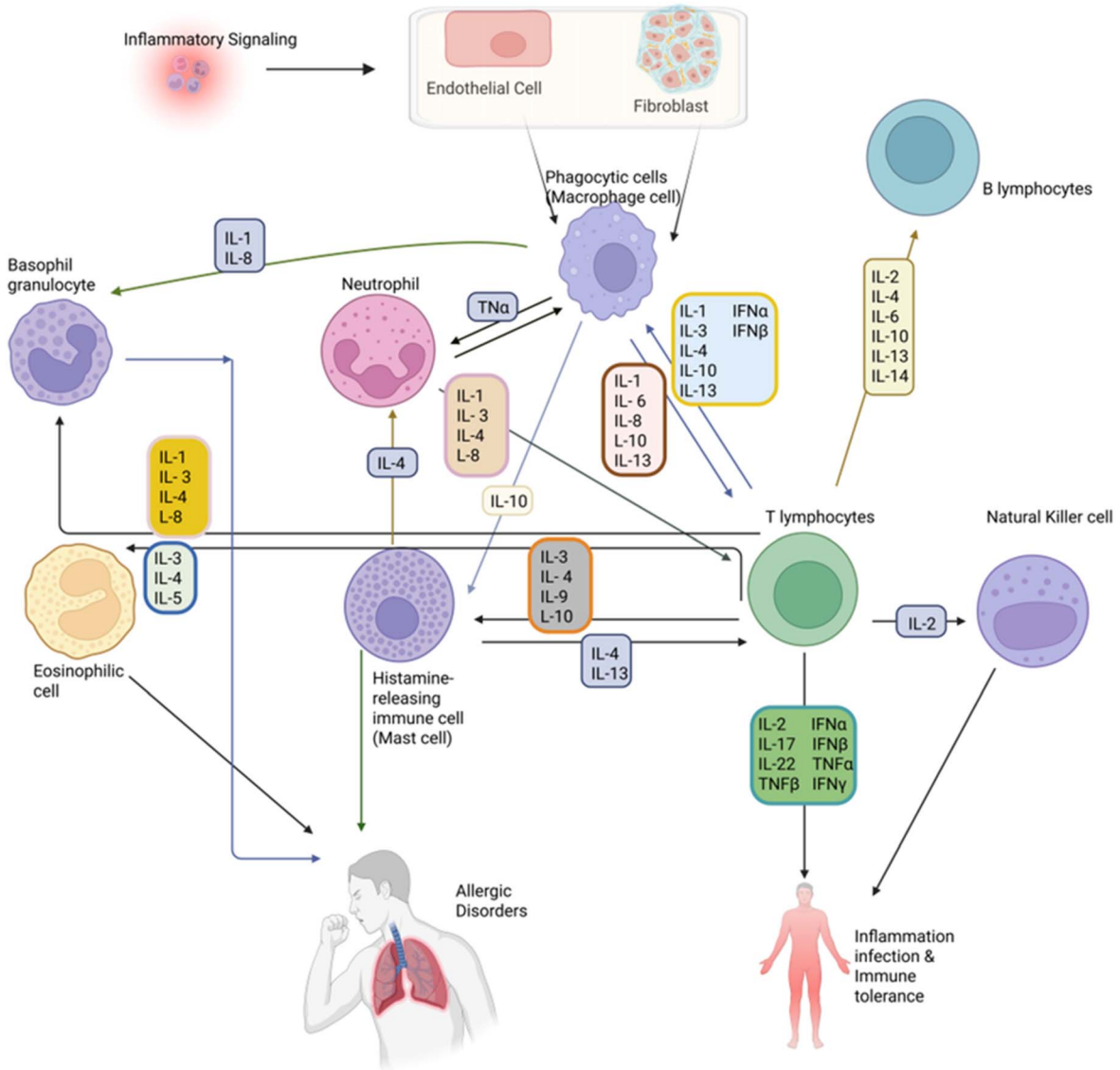

Fig. 1 The interleukin network shows interactions between immune cells (T cells, B cells, macrophages, NK cells, neutrophils, mast cells, eosinophils, basophils, monocytes, fibroblasts, and endothelial cells) and the cytokines they produce, highlighting their roles in inflammation, infection, allergy, asthma, and immune tolerance.

axis is crucial for immune regulation and is associated with allergic and chronic inflammatory disorders, indicating its potential as a therapeutic target.[35] IL-33, belonging to the IL-1 family, primarily stimulates type 2 immune responses through the activation of TH2 cells, mast cells, and group 2 innate lymphoid cells (ILC2s). The pleiotropic activity modulates Treg, TH1, $CD8^+$ T, and NK cells, thereby contributing to immune regulation in inflammation, infection, tissue homeostasis, and various diseases, which may have therapeutic implications.[36]

In contrast, anti-inflammatory ILs play a vital role in suppressing inflammation and promoting tissue repair by counteracting pro-inflammatory responses. Anti-inflammatory ILs include IL-1Ra, IL-4, IL-6, IL-10, IL-19, and IL-35. The IL-1 receptor antagonist (IL-1Ra) is primarily recognised as an anti-inflammatory cytokine. Its key functions include the inhibition of IL-1 activity, regulation of inflammation, and therapeutic applications.[37,38] IL-4 has both anti- and pro-inflammatory functions, as discussed previously. Further anti-inflammatory functions include the inhibition of pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1α, from activated monocytes. It also plays a vital role in the suppression of autoimmune inflammation.[39,40] IL-6 is mainly known as a pro-inflammatory cytokine but also has anti-inflammatory properties depending on the context and specific immune response involved. As an anti-inflammatory agent, it plays a vital role in the early infection response, metabolic regulation, and protective effects.[41–43] Despite the careful regulation of its expression through transcriptional and post-transcriptional pathways, the unregulated and persistent production of IL-6 has shown an impact on chronic inflammation.[44] IL-10 is primarily recognised for its significant anti-inflammatory properties. It suppresses the expression of pro-inflammatory cytokines, chemokines, and other molecules that

play a role in inflammation.[45,46] IL-10 is a key IL in preventing tissue damage caused by excessive inflammation.[47] Similarly, IL-19 and IL-35 function as anti-inflammatories by regulating immune responses and inhibiting excessive inflammation, which is beneficial in inflammatory bowel disease and maintaining tolerance to autoimmune diseases.[48–50]

In recent years, biological medicines targeting interleukins have emerged as effective treatments for allergic disorders, focusing on underlying immunological dysregulation rather than alleviating symptoms. These types of biologics include monoclonal antibodies that target IL-4Rα (dupilumab), IL-5 (mepolizumab), and IL-13 (tralokinumab), which have shown clinical effectiveness in severe asthma and atopic dermatitis.[51–53] The complex relationship between pro-inflammatory and anti-inflammatory ILs plays a vital role in the pathogenesis of allergic diseases. Certain pro-inflammatory ILs can be overproduced or dysregulated, which can worsen allergic reactions, cause tissue damage, and lead to chronic inflammation. However, anti-inflammatory ILs may not reverse these effects because of their lack of activity. Therefore, the inhibition or modulation of specific pro-inflammatory ILs and the strategic enhancement of anti-inflammatory pathways have emerged as promising therapeutic strategies for managing allergic disorders. In such a context, natural compounds, especially those isolated from medicinal plants, marine organisms and traditional herbal medicines, have emerged as promising modulators of IL activity. These bioactive molecules include polyphenols, flavonoids, alkaloids, terpenoids, lignans, and the target ILs.

In recent studies, numerous plant-derived compounds have been found to selectively inhibit the IL-33 and IL-25 pathways. This discovery, achieved through omics-based and systems biology approaches, represents a significant advancement in allergy suppression. For example, signalling through dectin-1 suppresses IL-33 secretion and type 2 immune responses, providing a protective mechanism against allergy development.[54] Genomic and transcriptomic analyses have further revealed how compounds affect the expression of IL genes, including IL-1β and IL-6, which are implicated in both Th1 and Th2 immune polarisation, as seen in the case of luteolin,[55] baicalin,[56] and glycyrrhizin.[57] These results suggest that natural compounds stop allergic inflammation from spreading and have wider effects on the immune system by changing how cytokine networks work at the transcriptional level. Given these advancements, this review comprehensively explores recent progress in identifying bioactive natural compounds that target interleukins involved in allergic and immune disorders. We highlight the mechanisms of action, therapeutic relevance, and prospects for immune modulation and allergy treatment. Fig. 1 shows the IL network, which displays the interactions between immune cells and their roles in different diseases.[58–60]

2. Bioactive flavonoids as modulators and inhibitors of interleukin signalling

Flavonoids are a diverse group of polyphenolic compounds that are found in various plants. They possess many biological activities that make them important candidates for the prevention of various diseases. They are known for their antioxidant activities, which enable them to scavenge reactive oxygen species (ROS) and reactive nitrogen species, reducing oxidative stress, and redox-sensitive pathways, which help treat many chronic diseases, such as cancer, neurodegenerative diseases, and cardiovascular diseases, *etc.*[61,62] In the context of inflammation, flavonoids have been shown to modulate or inhibit many ILs and enzymes related to the expression of immune responses and allergic diseases.

TNF-α is primarily secreted by activated macrophages and monocytes and can also enhance the production of other pro-inflammatory cytokines. Thus, it has been targeted in numerous diseases such as septic shock, chronic inflammatory diseases, and rheumatoid arthritis. In this context, *Amorpha fruticosa* extract containing amoradicin was isolated and found to significantly inhibit TNF-α production in RAW264.7 cells. This activity was comparable to or higher than that of standard flavonoid compounds such as genistein and silybin.[63] In the same year, Kotani *et al.* studied atopic dermatitis in mice. High-performance liquid chromatography (HPLC) was used to measure the extract content and its inhibitory effect on histamine release in KU812 cells. Oral intake of persimmon leaf extract and astragalin inhibited passive cutaneous reactions in mice with atopic dermatitis in a dose-dependent manner. This results in the suppression of dermatitis, scratching behaviour, and elevated serum IgE levels. Histological analyses revealed reduced infiltration of inflammatory cells and downregulation of splenic T-cell production of IL-4 and IL-13. This study highlights the novel activity of astragalin and its dramatic effect on atopic dermatitis-model mice.[64] The flavonoids astragalin, fisetin, kaempferol, myricetin, quercetin, and rutin were found to inhibit cytokine expression and synthesis by human basophils. The results displayed that fisetin suppressed the induction of IL-4, IL-13, and IL-5 mRNA expression in A23187-stimulated KU812 cells and basophils in response to cross-linking with the IgE receptor. Fisetin reduced IL-4, IL-13, and IL-5 synthesis, but not IL-6 and IL-8 production in KU812 cells. It also inhibited IL-4 and IL-13 synthesis by anti-IgE antibody-stimulated human basophils, and IL-4 synthesis by allergen-stimulated basophils from patients with allergies. Kaempferol and quercetin showed substantial inhibitory activities on cytokine expression but were less potent than fisetin. The results provide evidence that fisetin suppresses the expression of T(H)2-type cytokines by basophils.[65] The same group studies the inhibition of IL-4 and IL-13 production by basophils by other flavonoids and aims to determine the fundamental structure of flavonoids related to inhibition. Approximately 18 flavones and flavonols were studied, and three flavonoids (luteolin, fisetin, and apigenin) showed the strongest inhibition of IL-4 and IL-13 production by basophils, although they did not influence leukotriene C4 synthesis. When administered at high doses, these flavonoids inhibit IL-4 production in T-cells. Based on this study, it was found that the amount and quality of flavonoids may either alleviate allergic symptoms or prevent the development of allergic disorders.[66] This group further studied that luteolin can suppress cluster of differentiation 40 (CD40) ligand

expression by basophils. Luteolin and other flavonoids were tested in the human basophilic cell line KU812. The expression of the CD40 ligand was analysed by fluorescence-activated cell sorting (FACS) and semi-quantitative reverse transcription PCR. The results showed that CD40 ligand expression was enhanced by A23187 and was significantly enhanced by A23187 plus phorbol 12-myristate 13-acetate (PMA). Luteolin inhibits CD40 ligand mRNA expression in stimulated KU812 cells. The expression of CD40 ligand was significantly inhibited by luteolin, apigenin, fisetin, and quercetin at a concentration of 30 μM. CD40 ligand expression is increased by incubating purified basophils with A23187 and PMA.[67] The findings showed the significant anti-allergic and immunomodulatory effects of flavonoids, specifically fisetin, luteolin, and apigenin, by inhibiting key T(H)2 cytokines and CD40 ligand expression in basophils. Dietary or therapeutic supplementation with specific flavonoids may serve as an effective approach to mitigate allergic symptoms and inhibit the onset of allergic disorders.

In 2005, a group of researchers from the Tufts University School of Medicine and Tufts-New England Medical Center, USA, showed that flavonoids inhibited histamine and cytokine release from rodent basophils and mast cells. However, their effect on pro-inflammatory mediator release and their mechanism of action in human mast cells have not been well defined. Therefore, they studied human umbilical cord blood-derived cultured mast cells (hCBMCs) pre-incubated with the flavonols quercetin, kaempferol, myricetin, and morin. The release of IL-6, IL-8, and TNF-α was inhibited by 82–93% at 100 μM quercetin and kaempferol and by 31–70% at myricetin and morin. Flavonols suppress intracellular calcium ion elevation and inhibit phosphorylation of calcium-insensitive protein kinase C theta (PKCθ). Based on this study, it was concluded that flavonols could be appropriate candidates against allergy and inflammatory disorders.[68] Flavonoid apigenin was studied for its effect on IL-4 production in activated T-cells. Apigenin significantly inhibited IL-4 production in EL4 T thymoma and primary lymph node cells. It also inhibited IL-4 promoter activity in EL4 cells transiently transfected with the IL-4 promoter construct. However, this effect was impaired in EL4 cells transfected with an IL-4 promoter construct that lacked NF-AT-binding sites. This study concluded that apigenin inhibits IL-4 production in activated T-cells by down-regulating NF-AT DNA binding activity.[69] Apigenin was also studied for its ability to inhibit cytokine expression, nitric oxide production, and phosphorylation of mitogen-activated protein kinase (MAPK) signal molecules in RAW264.7 cells. It also induced the expression of filaggrin, loricrin, aquaporin-3, hyaluronic acid, hyaluronic acid synthase (HAS)-1, HAS-2, and HAS-3, the main components of the physical barrier of the skin, in HaCaT cells. These studies showed that apigenin could improve the function of physical and chemical skin barriers and alleviate psoriasis, acne, and atopic dermatitis by enhancing protein levels at skin barriers, while also suppressing inflammatory and immune-mediated responses involved in these chronic skin conditions.[70] Kaempferol was further studied for its effect on STAT6 activation. This compound inhibits STAT6 activation by IL-4 in haematopoietic cells. Kaempferol blocked JAK3 activity without affecting JAK1 expression. In addition to preventing mixed lymphocyte culture growth, it blocks IL-2-mediated responses, but not IL-3-mediated responses. These results indicate that kaempferol could be used to selectively regulate cell responses to IL-4 and responses that depend on JAK3.[71]

Park *et al.* compared the effects of six flavonoids on MC-mediated allergic inflammation. The six flavonoids tested were astragalin, fisetin, kaempferol, myricetin, quercetin, and rutin. Except for myricetin, the other five compounds reduced histamine release and calcium levels in the mast cells. Fisetin, quercetin, and rutin were most effective in lowering inflammatory cytokines and blocking the nuclear factor-kappa B (NF-κB) pathway. Myricetin attenuated TNF-α and IL-6, but not IL-1β or IL-8. Myricetin likely exhibits this differential behaviour due to its unique structural characteristics, which selectively influence mast-cell signalling pathways, leading to partial rather than extensive cytokine suppression. Taken together, this study further suggests that flavonoids may help treat allergic inflammatory diseases by suppressing mast cell activation.[72]

In the same year, another group studied the protective effects of *Kalanchoe pinnata* on fatal anaphylactic shock in mice, a Th2-driven immunopathology. Mice treated daily with oral *Kalanchoe pinnata* during hypersensitisation with ovalbumin were protected against death when challenged with the allergen, compared with 100% mortality in the untreated group. Eosinophilia, reduced formation of ovalbumin-specific IgE antibodies, and impaired production of IL-5, IL-10, and TNF-α cytokines were observed alongside oral protection. However, 75% of mice were protected from deadly anaphylaxis by quercitrin extracted from this plant.[73]

An *in vivo* study on morin was performed using mast cells. The results showed that morin suppressed IgE-mediated passive cutaneous anaphylaxis (PCA) in mice and inhibited the degranulation and production of TNF-α and IL-4 in antigen-stimulated mast cells. This flavonoid blocked the phosphorylation of Syk and LAT in RBL-2H3 cells and mast cells generated from bone marrow. RBL-2H3 and LAT-positive T-cells were used. Furthermore, it was also shown that morin inhibits Akt, MAP kinases, p38, extracellular signal-regulated kinase (ERK)1/2, and c-Jun N-terminal kinase (JNK). However, an *in vitro* study indicated that it inhibited Fyn kinase in mast cells but not Lyn and Syk. These results suggested that morin suppresses IgE-mediated allergic responses by inhibiting Fyn kinase activity in mast cells.[74]

In 2010, two studies investigated the anti-allergic properties of flavonoids. In the first study, luteolin derived from *Lonicera japonica* flower was shown to suppress the induction of many inflammatory cytokines, such as TNF-α, IL-8, IL-6, and granulocyte-macrophage colony-stimulating factor (GM-CSF), by PMA combined with A23187. Furthermore, it was also shown that it lowered the expression of COX-2 and the concentration of Ca^{2+}, suggesting a reduction in inflammation and cellular activation. It suppressed PMA- and A23187-induced NF-κB activation, inhibitor of kappa B (IκB) degradation, and luciferase activity. Lowering intracellular Ca^{2+} levels also prevents the expression of TNF-α, IL-8, IL-6, GM-CSF, and COX-2. This finding indicates that luteolin can modulate mast cell-

mediated inflammatory conditions in many allergic diseases.[75] Another study showed the effect of two other well-known flavonoids, quercetin and kaempferol, on the suppression of IgE-mediated allergic responses and intestinal epithelial barrier function in RBL-2H3 and Caco-2 cells. These *in vitro* studies showed that flavonoids decreased allergen production in RBL-2H3 cells, IL-4-stimulated Caco-2 cell CD23 mRNA expression, p38 MAPK activation, and IgE-ovalbumin-induced ERK activation and chemokine release. This study found that the tested flavonoids significantly suppressed the development of IgE-mediated allergic inflammation in intestinal cell models, showing they have anti-allergic properties by altering critical inflammatory pathways and cellular responses involved in allergic reactions.[76]

Luteolin, which has been extensively studied, affects allergic diseases. In 2012, a study investigated the effect of luteolin on dermal fibroblasts, which are major targets of photoaging. It protects the epidermis from UV-induced damage *via* its UV-absorbing, antioxidant, and anti-inflammatory properties. This study found that luteolin inhibited the production of pro-inflammatory cytokines such as IL-20, IL-6, matrix metalloproteinase-1 (MMP-1), and hyaluronidase in keratinocytes irradiated with solar radiation. Furthermore, it reduced the expression of IL-6 and MMP-1 in the fibroblasts. These findings were confirmed by ex vivo experiments using skin explants treated with luteolin before UV irradiation. These results confirmed that luteolin can modulate the production of soluble inflammatory mediators induced by simulated solar radiation in keratinocytes. By regulating these mediators, this compound can reduce the skin inflammatory response to UV exposure, which is associated with photoaging. Because keratinocytes play a key role in initiating and amplifying cutaneous immune reactions, such as contact and atopic dermatitis, the ability of luteolin to suppress these responses represents its potential as a defensive agent not only against photoaging but also in the inhibition or mitigation of UV-induced allergic skin conditions.[77] Another study found that luteolin inhibited the secretion of inflammatory cytokines from human mast cells and reduced histamine release from rat peritoneal mast cells. In addition, it inhibited the scratching behaviour and vascular permeability induced by pruritogens in ICR mice. This study also confirmed that luteolin may be a promising agent to treat inflammation and itch-related skin diseases, as it effectively targets key pathological features. Atopic dermatitis, contact dermatitis, urticaria, and other inflammatory skin disorders characterised by chronic scratching and immunological dysregulation may be controlled by luteolin, which has therapeutic potential for modulating these mechanisms.[78]

Yoo *et al.* isolated 23 compounds from *Sophora tonkinensis* and tested their effects on IL-6 production in PMA-stimulated HMC-1 cells in conjunction with the ionophore A23187. Among the 23 compounds examined, four specifically—2′-hydroxyglabrol, glabrol, maackiain, and bolusanthin IV—demonstrated a significant ability to inhibit IL-6 production. Screening of compounds against IL-6 production suggests that they can help to suppress the inflammatory cascade, reducing tissue damage and alleviating symptoms linked to chronic inflammatory and autoimmune diseases.[79] Astragalin, a natural flavonoid, has been found to treat allergic diseases. Li *et al.* investigated the molecular mechanism of astragalin in lipopolysaccharide (LPS)-induced primary cultures of mouse mammary epithelial cells. They studied the expression of pro-inflammatory cytokines, such as TNF-α and IL-6, and the production of nitric oxide. The expression of these cytokines was dose-dependently decreased by astragalin, according to the western blot measurements. In addition, astragalin effectively reduced the expression of Toll-like receptor 4 (TLR4) in response to LPS, activation of NF-κB, degradation of IκBα, and phosphorylation of p38, a kinase controlled by extracellular signals, in BMECs. This study concluded that astragalin exhibited anti-inflammatory activities based on the inactivation of the TLR4-mediated NF-κB and MAPK signalling pathways in LPS-stimulated mouse mammary epithelial cells. Accordingly, astragalin may reduce the production of inflammatory mediators during the pathogenesis of mastitis, indicating its potential as a therapeutic agent for the prevention and treatment of bovine mastitis.[80]

Vitamins A and E, along with catechins and epigallocatechin gallate flavonoids, have the potential to serve as vaccine adjuvants and therapeutic agents. Therefore, researchers have attempted to develop safer and more effective vaccines. Research has demonstrated that the amalgamation of catechin, epigallocatechin gallate, and vitamins A and E within a vegetable-oil-in-water emulsion synergistically improved adaptive B-cell and CD4(+) and CD8(+) T-cell responses after the induction of diminished local and systemic innate TNF-α, IL-6, and IL-17, while eliciting moderately raised initial systemic IL-15 responses. The study also showed that the mechanism of action of nutritive immune-enhancing delivery depends on antioxidant activity and IL-15 but is independent of IL-1β and inflammasome formation. This nutritive vaccine adjuvant design approach holds promise to develop safer and more effective vaccines. This approach holds potential for designing safer and more effective nutritive vaccine adjuvants by utilising natural bioactive compounds to modulate immune responses without causing unnecessary inflammation, providing a safer alternative to traditional adjuvants.[81] Epigallocatechin gallate, a catechin found in tea, was examined for its possible immunotherapeutic effects on nicotine-induced dysfunction of alveolar macrophages. Nicotine treatment of MH-S macrophages enhanced *Legionella pneumophila* proliferation and decreased the production of IL-6, IL-12, and TNF-α, although IL-10 levels remained unchanged. Epigallocatechin gallate administration restored macrophage resistance to infection and alleviated nicotine-induced suppression of cytokine production. This study indicates that epigallocatechin gallate may restore the anti *L. pneumophila* activity, diminished by nicotine, by reinstating TNF-α and IFN-γ production in macrophages.[82] The concurrent use of vitamins A and E with catechins, especially epigallocatechin gallate, underlines an innovative nutritional strategy for vaccine adjuvant development and immunological regulation. These natural chemicals improve the adaptive immune responses and reduce excessive inflammation, providing safer alternatives to traditional adjuvants. Moreover,

their capacity to restore macrophage activity during nicotine-induced immune suppression highlights their potential as both a preventive and therapeutic immunological approach.

Another flavonoid, pinocembrin, is found in propolis, as well as in certain plants, such as *Lippia graveolens* and *Alpinia mutica*. This compound has been studied for its ability to inhibit histidine decarboxylase and pro-inflammatory mediators. This study confirmed that pinocembrin inhibits histidine decarboxylase activity and histamine production in IgE-sensitised RBL-2H3 cells in response to dinitrophenol-bovine serum albumin stimulation. Furthermore, pinocembrin has been shown to reduce the levels of pro-inflammatory mediators, such as IL-6, nitric oxide, TNF-α, nitric oxide synthase (iNOS), COX-2, prostaglandins, and phosphorylation of inhibitory κB. This study suggests that pinocembrin is a natural anti-allergic compound that can inhibit histidine decarboxylase and lower histamine levels, emphasising its dual action of reducing histamine production and suppressing key inflammatory pathways. It could be a safer alternative to traditional anti-allergic medicines with fewer side effects.[83] As previously shown in numerous studies, fisetin has demonstrated its effect in allergic diseases. A study published in 2017 demonstrated that the anti-inflammatory properties of fisetin reduced allergic responses in rat basophilic leukaemia cells. It inhibited β-hexosaminidase release and decreased IL-4 and TNF-α mRNA levels in IgE/antigen (IgE/Ag)-stimulated RBL-2H3 cells. In addition, it lowered the levels of Grb2-associated binder 2 (Gab2) proteins, linker of activated T-cells, extracellular signal-related kinase 1/2, NF-κB, and STAT3 proteins in the ear tissue of mice with PCA, along with a decrease in the high-affinity immunoglobulin E receptor (FcεRI) α-subunit mRNA expression. These results suggest that fisetin may be useful as a treatment for allergic diseases because it not only changes how mast cells respond to allergies in the early stages but also disrupts signalling pathways and transcription factors that are important for continuing inflammation, offering a multi-targeted approach to allergy management.[84]

Fisetin treatment in 2D and 3D psoriasis-like disease models induced differentiation, inhibited proliferation, and activated the phosphoinositide 3-kinase (PI3K)/Akt/mechanistic target of rapamycin (mTOR) pathway, along with inhibiting the activation of p38 and JNK, but had an enhanced effect on ERK1/2. Its treatment also reduced the secretion of pro-inflammatory cytokines (Th1/Th17), mainly IFN-γ and IL-17A. Fisetin significantly ameliorated psoriasis-like disease features and decreased the production of IL-17 in $CD4^+$ T lymphocytes co-cultured with a full-thickness human skin model of psoriasis. Based on this study, the findings indicated that fisetin is an effective and inexpensive agent for treating psoriasis and other related inflammatory skin diseases, displaying a potential strategy that targets both keratinocyte dysfunction and immune dysregulation, even though the fact that it modulates the main signalling pathways involved in disease development.[85] Dihydromyricetin, which is found in numerous plants, has been studied for various biological activities, including anti-allergy. One study showed that this flavonoid could regulate rectal temperature, treat diarrhoea, decrease serum IgE levels, and promote the production of IL-10 *in vivo*. Dihydromyricetin also upregulates regulatory T-cells in the spleen, blocks FcεRI–IgE interaction, inhibits β-hexosaminidase and histamine release, and alleviates PCA reactions. These findings suggest that dihydromyricetin may have potential for improving food hypersensitivity or allergic diseases by modulating immune tolerance mechanisms and suppressing IgE-mediated allergic responses.[86] In an *in vitro* study, quercetin was administered to immortalised human HaCaT keratinocytes treated with IL-4, -13, and TNF-α to treat model atopic dermatitis. The results showed that quercetin significantly reduced the expression of IL-1β, IL-6, IL-8, and thymic stromal lymphopoietin (TSLP), while enhancing the expression of superoxide dismutase-1, SOD2, catalase, glutathione peroxidase, and IL-10. Quercetin also inhibited extracellular signal-regulated kinase 1/2/mitogen-activated protein kinase (ERK1/2 MAPK) and the expression of NF-κB but did not alter STAT6 phosphorylation. This study suggests that quercetin may be a potential bioactive compound to treat atopic dermatitis-associated symptoms by modulating key inflammatory signalling pathways and oxidative stress responses without interfering with STAT6-mediated IL-4 or IL-13, thus presenting a targeted yet balanced therapeutic approach for managing immune-driven skin inflammation.[87] Among flavonoids, 3,5,6,7,3′,4′-hexamethoxyflavone (quercetogetin) inhibited the production of prostaglandin E2 and nitric oxide by suppressing the expression of cyclooxygenase-2 and inducible nitric oxide synthase. It also reduced the production of IL-6, IL-1β, and TNF-α; reduced NF-κB nuclear translocation; and inhibited the phosphorylation of ERK protein expression in LPS-induced RAW264.7, indicating its strong anti-inflammatory effects. This study suggested that quercetogetin acts as a promising therapeutic agent against many inflammatory diseases such as emphysema, thus potentially preventing tissue damage, lowering chronic inflammation, and resulting in improved respiratory function.[88] Naringenin, a plant-based flavonoid, reversed the injury of primary chondrocytes induced by IL-1β by inhibiting the TLR4/TNF receptor-associated factor 6 (TRAF6)/NF-κB pathway. In an *in vivo* osteoarthritis model, naringenin alleviated pathological symptoms, lowered TLR4 and TRAF6 expression, and NF-κB phosphorylation in knee cartilage tissue. It also inhibits inflammatory factors, prevents extracellular matrix degradation, and decreases the protein expression of caspase-3. These findings show that naringenin can be a potent therapeutic agent against osteoarthritis by protecting the cartilage, preserving extracellular matrix integrity, and inhibiting chondrocyte apoptosis by modulating the TLR4/TRAF6/NF-κB signalling pathway.[89] Another study showed that naringenin increased the secretion of IL-6, TNF-α, and COX-2 in primary chondrocytes, increased matrix metalloproteinase expression, and reduced collagen II protein expression. It reversed the injury to primary chondrocytes and inhibited the TLR4/TRAF6/NF-κB pathway. This compound alleviated pathological symptoms in an *in vivo* study and reduced TLR4 and TRAF6 expression along with NF-κB phosphorylation in the knee cartilage tissue.[90]

Betuletin, a flavonoid found in Brazilian green propolis (BGP), suppresses the expression of the allergy-sensitive gene

IL-33 and reduces eosinophilia. This study demonstrated the anti-allergic properties of this compound in PMA-induced upregulation of IL-33 gene expression in Swiss 3T3 cells. The outcome of this study showed that both BGP and betuletol suppressed IL-33 gene expression and reduced ERK phosphorylation, suggesting that they could be effective in suppressing IL-33-mediated eosinophilic chronic inflammation.[91] Recently, our group isolated compounds from *Canavalia gladiata* pods and studied their biological activity against IL-33. These compounds include 3α-friedelinol, β-sitosterol, medicarpin, formononetin, sophorophenolone, 7-hydroxy-6-methoxy dihydroflavonol, 2′-hydroxy biochanin A, β-adenosine, 5-methoxydaidzein, rutin, and myricetin 3-*O*-rutinoside. Among these, formononetin, 7-hydroxy-6-methoxy dihydroflavonol, 2′-hydroxy biochanin A, β-adenosine, 5-methoxydaidzein, rutin, and myricetin 3-*O*-rutinoside showed significant IL-33/ST2 inhibitory activity. This work was further substantiated by molecular docking and dynamic simulation analyses, which indicated these compounds may serve as therapeutic candidates that require further *in vivo* experiments.[92]

Rutin modulated ROS production and mast cell function. Enhanced ROS production was observed in IgE-challenged murine mast cells, which reduced elevated ROS levels and significantly inhibited histamine release from activated mast cells. These findings suggest that rutin affects mast cell effector function by reducing intracellular ROS levels.[93]

The genus *Wikstroemia* has traditionally been used in Asia for numerous treatments. A recent study identified 42 compounds in the methanolic extract of *Wikstroemia trichotoma,* including flavonoids. These compounds significantly inhibited β-hexosaminidase release and IL-4 mRNA expression, suggesting their potential in treating allergic diseases.[94] Another recent study investigated the effects of aspalathin, a flavonoid found in rooibos, on mast cell-mediated allergic inflammation. *In vivo* experiments showed that aspalathin suppresses IgE-mediated passive cutaneous anaphylactic responses in a dose-dependent manner. Compared with another compound, nothofagin, from a similar source, aspalathin was more effective. It also reduced pro-inflammatory cytokine expression by inhibiting two major transcription factors: nuclear factor of activated T-cells and nuclear factor-κB. This study suggests that aspalathin might be a promising candidate to be used against mast cell allergic diseases.[95] Fig. 2 depicts the chemical structures of flavonoids used in the management of allergic diseases.

A study conducted in 2024 indicated that *Oroxylum indicum* (Phe Kaa) possesses anti-allergic properties. HPLC analysis of this plant revealed elevated flavonoid concentrations. It demonstrated a dose-dependent suppression of nitric oxide and greatly decreased the expression levels of inflammatory genes, perhaps helping to treat allergies.[96]

After listing most flavonoids from natural sources used in the management of allergic diseases, these compounds have the potential for use in this context. Although most of these compounds have not been fully studied *in vivo* models, their potential remains significant. Some compounds, such as luteolin, have emerged as the most extensively studied

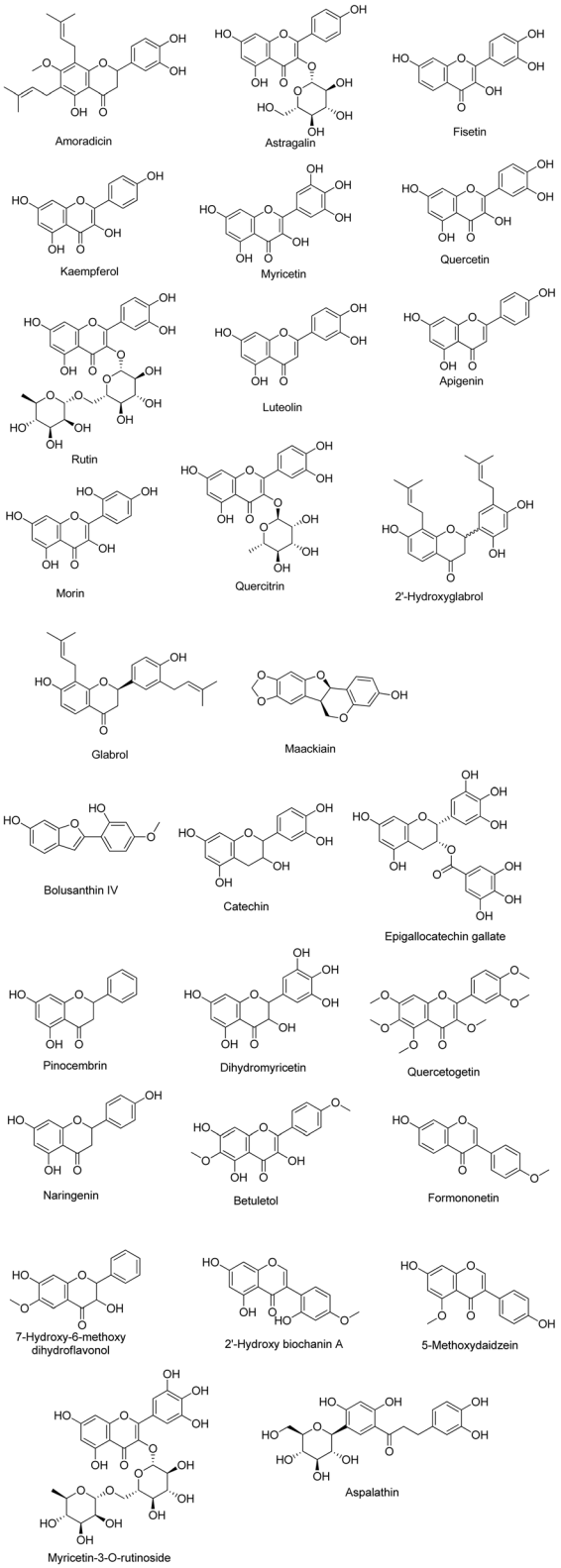

Fig. 2 Structure of flavonoids as modulators and inhibitors of interleukin signaling.

flavonoids in the context of inflammation and allergies. Numerous studies have documented its effect on pro-inflammatory cytokines, such as IL-6, IL-20, IL-1β, and TNF-α,

Table 1 Summary of flavonoids evaluated for their roles in immune modulation and allergic disease management, including their molecular targets and supporting *in vitro* and *in vivo* evidence

No	Compound	Targeted in immune modulation and allergic treatment	Study model (*in vitro*/*in vivo*)
1	Amoradicin	TNF-α	*In vitro* (RAW264.7)
2	Astragalin	IL-4, IL-13. TNF-α, IL-6, NO. TLR4, NF-κB	*In vitro* (mast cell, BMECs)/*in vivo* (mice), ex vivo
3	Fisetin	IL-4, IL-13, IL-5, IL-17A, IL-17	*In vitro* (KU812, mast cell, RBL-2H3)/*in vivo* (mice), 2D and 3D model
4	Kaempferol	IL-4, IL-13, IL-5, IL-6, IL-8, TNF-α, STAT6	*In vitro* (KU812, hCBMCs, hemopoietic cells, mast cell, RBL-2H3, Caco-2)
5	Myricetin	IL-6, IL-8, TNF-α	*In vitro* (hCBMCs)
6	Quercetin	IL-4, IL-13, IL-5, IL-6, IL-8, TNF-α, IL-10	*In vitro* (KU812, hCBMCs, mast cell, RBL-2H3, Caco-2, HaCaT)
7	Rutin	IL-33, IL-13, IL-10, IL-6, IFN-γ, TNF-α	*In vitro* (mast cell)
8	Luteolin	IL-4, IL-13, CD40 ligand, TNF-α, IL-8, IL-6, GM-CSF, IL-20, IL-6, IL-1β, IL-6, TNF-α	*In vitro* (KU812, keratinocyte, fibroblast, mast cell, ARPE-19)/*in vivo*, ex vivo (mice, rat)
9	Apigenin	IL-4, IL-13, CD40	*In vitro* (KU812, T-cells, EL4, primary lymph node, RAW264.7, HaCaT)
10	Morin	IL-6, IL-8, TNF-α, IL-4	*In vitro* (hCBMCs)/*in vivo* (mice)
11	Quercitrin	IL-5, IL-10, TNF-α	*In vivo* (mice)
12	2′-Hyrdoxyglabrol	IL-6	*In vitro* (HMC-1)
13	Glabrol	IL-6	*In vitro* (HMC-1)
14	Maackiain	IL-6	*In vitro* (HMC-1)
15	Bolusanthin IV	IL-6	*In vitro* (HMC-1)
16	Catechin	TNF-α, IL-6, IL-17 IL-15	*In vitro* (MH-S macrophage)
17	Epigallocatechin gallate	TNF-α, IL-6, IL-17, IL-15, IL-12, TNF-α, IFN-γ	*In vitro* (MH-S macrophage)
18	Pinocembrin	IL-6, NO, TNF-α, iNOS, COX-2	*In vitro* (RBL-2H3)
19	Dihydromyricetin	IL-10	*In vivo* (mice)
20	3,5,6,7,3′,4′-hexamethoxyflavone (quercetogetin)	IL-6, IL-1β, TNF-α	*In vitro* (RAW 264.7)
21	Naringenin	IL-6, TNF-α, COX-2	*In vitro* (chondrocyte)/*in vivo* (mice)
22	Betuletol	IL-33	*In vitro* (Swiss 3T3)
23	Formononetin	IL-33	*In vitro* (ELISA)
24	7-Hydroxy-6-methoxy dihydroflavonol	IL-33	*In vitro* (ELISA)
25	2′-Hydroxy biochanin A	IL-33	*In vitro* (ELISA)
26	5-Methoxydaidzein	IL-33	*In vitro* (ELISA)
27	Myricetin 3-*O*-rutinoside	IL-33	*In vitro* (ELISA)
28	Aspalathin	NF-κB	*In vivo* (mice)

as well as enzymes, such as MMP-1 and hyaluronidase. It suppresses mast cell activation and reduces histamine release, both of which are directly associated with allergic diseases. Along with this, fisetin exhibits significant anti-allergic and anti-inflammatory effects by inhibiting key T(H)2 cytokines, mast cell activation, and various inflammatory signalling pathways. The effects on keratinocytes, T-cells, and basophils underscore its ability to modulate immune responses and restore tissue homeostasis. The findings indicate that fisetin may serve as a multi-targeted agent for the management of allergic and inflammatory disorders, such as psoriasis and atopic dermatitis. Other flavonoids also exhibit promising biological activities. In addition, the natural origin of these flavonoids gives them a favourable safety profile, and their antioxidant activities further support their promising therapeutic effects. Collectively, these flavonoids are valuable candidates for the prevention and treatment of allergic diseases. The flavonoids used in this study are summarised in Table 1.

3. Non-flavonoid polyphenols and their impact on interleukin pathways

Non-flavonoid polyphenols modulate IL pathways by reducing pro-inflammatory cytokines and increasing anti-inflammatory ILs, which helps to treat allergies and other inflammatory conditions by controlling immune responses. In the previous section, we discussed the significance of flavonoids in modulating immune responses and highlighted the importance of other polyphenols and their therapeutic potential. Polyphenols

other than flavonoids comprise a wide range of compounds that contribute to immune regulation through diverse molecular mechanisms. Recent studies have shown that these polyphenols exert notable effects on interleukin (IL) signalling pathways, influencing allergic reactions, inflammatory processes, and immune modulation. Their ability to regulate cytokine production and balance pro- and anti-inflammatory responses makes them promising candidates for the development of novel strategies to treat allergies and immune-related disorders. Most flavonoid polyphenols have been identified. Here, we aimed to highlight other non-flavonoid polyphenols and their role in allergy treatment and immune modulation.

Chlorogenic acid modulates ROS generation and mast cell function. In antigen–IgE-challenged murine mast cells, chlorogenic acid reduced the elevated ROS levels and significantly inhibited histamine release from activated mast cells. Moreover, it augmented the expression of inducible cytokines, such as IL-13, IL-10, IL-6, IFN-γ, and TNF-α, in IgE-sensitised mast cells after antigen challenge. These results indicated that chlorogenic acid regulates mast cell effector functions by quenching intracellular ROS and modulating cytokine-mediated responses.[93]

Gingerol is the principal pungent component of fresh ginger rhizomes, and is recognised for its anti-inflammatory, antioxidant, and other pharmacological properties. One study examined the effects of 6-gingerol, a polyphenol derived from ginger, on IL-1beta-induced MUC5AC gene expression in human airway epithelial cells (NCI-H292). IL-1β elevated MUC5AC mRNA expression, but pre-treatment with 6-gingerol markedly inhibited this elevation at both the mRNA and protein levels. The research found that 6-gingerol inhibited IL-1β-induced MUC5AC gene expression through the ERK and p38 MAPK pathways, indicating its potential as an anti-hypersecretory drug.[97] Another important non-flavonoid polyphenol is resveratrol, which is a stilbene with health-promoting properties like antioxidant and anti-inflammatory effects, and is found in plants like grapes and peanuts. We examined the effect of *trans*-resveratrol on the activation of human eosinophils, which is a critical element in inflammatory and allergic disorders. Research demonstrated that *trans*-resveratrol at doses below 100 μM did not promote eosinophil apoptosis. It efficiently suppressed eosinophil activation and degranulation, including peroxidase release with an IC_{50} value in the range of 2.9–3.9 μM, leukotriene C4 synthesis, and chemotaxis, while concurrently diminishing p38 and ERK1/2 phosphorylation.[98] Another study showed the impact of resveratrol on cytokines and apoptosis in the epithelium of mice with atopic dermatitis-like lesions. Mice treated with 2,4-dinitrofluorobenzene developed lesions and were divided into the control, vehicle control, and resveratrol treatment groups. Resveratrol administration (30 mg kg^{-1} per day) during the sixth week significantly reduced epithelial thickness and the expression of IL-25, IL-33, and TSLP in the epithelium compared to the vehicle control group. In addition, resveratrol treatment significantly decreased the number of caspase-3-positive cells, indicating reduced epithelial apoptosis.[99] Collectively, these data highlight the therapeutic significance of non-flavonoid polyphenols, including gingerol and resveratrol, in modulating airway and dermal inflammation. By altering critical pathways, such as ERK and p38 MAPK signalling, inhibiting pro-inflammatory cytokines, and diminishing epithelial apoptosis, these compounds show significant promise in mitigating allergic and inflammatory diseases. The varied modes of action underscore the adaptability of polyphenols as natural agents for immune modulation and disease management.

Tannins are a class of plant-derived polyphenolic compounds that confer astringency to various substances, including tea, coffee, wine, and fruit. Tannic acid demonstrates immunomodulatory effects and can alleviate allergic reactions by reducing the levels of inflammatory mediators, decreasing Th2 cytokine production, inhibiting NF-κB activation, and limiting mast cell activity. Studies using animal models of asthma and allergic rhinitis have suggested that tannic acid may alleviate airway inflammation, reduce mucus hypersecretion, and inhibit airway remodelling, indicating its potential as an anti-allergic therapy. Tannic acid can diminish the production of inducible nitric oxide synthase (iNOS) and COX-2, which are essential enzymes involved in the inflammatory cascade. It also inhibits Th2 cytokines, including IL-4, IL-5, and IL-13, which play pivotal roles in allergic responses. Tannic acid can inhibit the NF-κB signalling pathway, an essential modulator of inflammatory and immunological responses. Tannic acid reduces immunoglobulin E (IgE) and histamine levels, which are critical indicators of allergic inflammation, in allergic rhinitis models. Tannic acid has demonstrated a reduction in mast cell quantities and mucus hyper-secretion in asthmatic animals.[100–103] Apple-condensed tannins, abundant in phenolic compounds, were assessed for their impact on collagen-induced arthritis in DBA1/J mice, a model for human rheumatoid arthritis. An oral dose of apple-condensed tannins delayed the onset of rheumatoid arthritis and markedly decreased the clinical rating relative to that of the control group. *In vitro* investigations using splenocytes demonstrated that apple-condensed tannins reduced the elevation of IL-17 expression and production induced by collagen type II.[104] Together, these data underscore the substantial immunomodulatory and anti-inflammatory capabilities of tannins in allergy and autoimmune disorders. By targeting critical pathways, such as NF-κB signalling and Th2 cytokine generation, tannic acid and condensed tannins mitigate allergy-related inflammation and confer advantages for chronic conditions such as rheumatoid arthritis. This further underscores the significance of non-flavonoid polyphenols as potential natural therapeutics for modulating immune responses and addressing inflammatory disorders.

Oleuropein is a naturally occurring phenolic secoiridoid glycoside prevalent in the leaves and fruits of olive trees (*Olea europaea*). It has multiple potential health benefits, including antioxidant, anti-inflammatory, anti-atherosclerotic, anticancer, and neuroprotective effects. One study investigated the effect of oleuropein on IL-1β-induced inflammation in ARPE-19 cells, which served as a model for retinal disorders. IL-1β induced the release of inflammatory cytokines IL-6, MCP-1, and sICAM-1 and enhanced monocyte adhesion to ARPE-19

cells. Oleuropein markedly suppressed these inflammatory responses. Oleuropein mechanistically decreased cyclooxygenase-2 levels, augmented anti-inflammatory protein HO-1 expression, and inhibited JNK1/2 and p38 MAPK signalling pathways, suggesting a role in the regulation of NF-κB. These findings demonstrate that oleuropein possesses significant anti-inflammatory properties by inhibiting pro-inflammatory mediators and regulating essential signalling pathways such as MAPK and NF-κB. Its capacity to inhibit cytokine release and augment protective proteins underscores its potential as a natural polyphenol to manage inflammation-related illnesses, including allergies and immune-mediated diseases.[105]

Dietary polyphenols, specifically curcumin and the flavonoid epigallocatechin gallate (EGCG), exhibit anti-allergic and anti-inflammatory properties by inhibiting mast cell degranulation and releasing key inflammatory mediators. Both compounds inhibited the release of β-hexosaminidase, IL-4, and TNF-α in an IgE/antigen-stimulated mast cell model. Lipidomic analysis demonstrated that curcumin and epigallocatechin gallate significantly altered the cellular lipidome, with curcumin exhibiting a pronounced effect on lipid metabolism. Polyphenols modulated 78% of the differential lipids observed upon stimulation, and LPC-O 22 : 0 was identified as a sensitive biomarker. Changes in diacylglycerols, fatty acids, and bismonoacylglycerophosphates affect cell signalling pathways, offering insights into the anti-anaphylactic mechanisms of these dietary compounds. These findings indicate that curcumin and epigallocatechin gallate suppress mast cell activation and the release of inflammatory mediators while also modulating lipid metabolism, contributing to their anti-allergic and anti-inflammatory effects. Their dual roles in immune regulation and cellular lipid metabolism underscore their potential as natural dietary agents for preventing and managing allergic disorders.[106]

Punicalagin, a polyphenol derived from pomegranates, mitigates inflammation in HaCaT cells triggered by TNF-α and IFN-γ by upregulating SIRT1 expression, subsequently leading to downregulation of STAT3 and activation of the nuclear factor erythroid 2-related factor 2 (Nrf2)/HO-1 pathway. This dual mechanism suppresses inflammation by inhibiting inflammatory pathways and enhancing the antioxidant response. Its mechanism of action involves enhancement of SIRT1 expression, an enzyme crucial for cellular health and ageing. Increased SIRT1 levels subsequently inhibit the activation of STAT3, a protein that plays a role in inflammatory signalling. The Nrf2/HO-1 pathway is also activated and serves as a vital cellular defence mechanism against oxidative stress. This activation aids in safeguarding cells from damage induced by inflammation.[107]

Fig. 3 shows the structure of the studied polyphenols.

Panduratin A, isolated from *Boesenbergia pandurata*, was evaluated for its anti-allergic effects on calcium influx, degranulation, and inflammatory mediators in calcium ionophore A23187-and PMA-stimulated rat basophilic leukaemia cells. This study showed that panduratin A inhibited the secretion of β-hexosaminidase, histamine, and Ca^{2+} influx and reduced the production of prostaglandin E2, leukotriene B4, and mRNA expression of cyclooxygenase-2, 5-lipoxygenase, interleukin (IL)-4, IL-13, and tumour necrosis factor-α. Furthermore, the phosphorylation levels of important signalling molecules such as Akt, ERK, p38, and JNK were markedly decreased by treatment. This compound may disrupt the signalling cascades involved in mast cell degranulation and cytokine release, as evidenced by the downregulation of their activation. This implies that it shows great promise as a treatment for immediate-type hypersensitivity reactions such as those observed in allergic diseases.[108]

Solanum tuberosum cv. Jayoung (JY) is a purple-fleshed potato cultivar known for its high polyphenol content, which includes anthocyanins and phenolic acids. These compounds give it a deep purple colour and exhibit antioxidant and anti-inflammatory properties. Studies have suggested that JY extract may be beneficial for treating atopic dermatitis by suppressing inflammatory responses and improving skin health. The extract ameliorated the severity of dermatitis, reduced serum levels of IgE and thymus- and activation-regulated chemokines, and decreased mast cell infiltration into the skin. It also suppressed the expression of type 2 helper T-cell cytokines (IL-4, IL-5, IL-13), reduced the induction of TSLP, decreased the nuclear translocation of nuclear factor-κB p65, and restored filaggrin protein expression in AD-like skin lesions. These data suggest that the JY extract has significant anti-inflammatory and immunomodulatory properties, making it a viable natural alternative for the prevention and treatment of atopic dermatitis. Similar to other polyphenols, including resveratrol and catechins, their capacity to modulate cytokine signalling and restore skin barrier function underscores the therapeutic promise of polyphenols in allergy management and immunological regulation.[109]

Collectively, these findings highlight how a wide range of dietary polyphenols, including resveratrol, oleuropein, punicalagin, curcumin, tannins, and gingerol, exert potent anti-inflammatory and immunomodulatory effects through diverse complementary mechanisms. By regulating key cytokines, signalling pathways such as NF-κB, MAPK, STAT3, and Nrf2/HO-1, and stabilising immune cells, these natural compounds collectively demonstrate a strong potential for preventing and managing allergic and immune-mediated disorders. Their ability to balance pro- and anti-inflammatory responses underscores the therapeutic value of polyphenols as safe and natural alternatives to conventional treatments. Although these polyphenols have beneficial effects, they also possess limitations; for instance, curcumin has had a favourable influence on pro-inflammatory cytokines, particularly IL-6. Clinical research with curcumin indicates safety, tolerance, and non-toxicity. Nonetheless its significant pharmacological potential, the therapeutic efficacy of curcumin remains little acknowledged, and this polyphenol has yet to receive approval for clinical application in humans. Additional research involving larger cohorts is necessary to determine which patients are most appropriate for curcumin supplementation and which formulation should be prioritized to enhance its anti-inflammatory properties. The bioavailability of curcumin is a critical

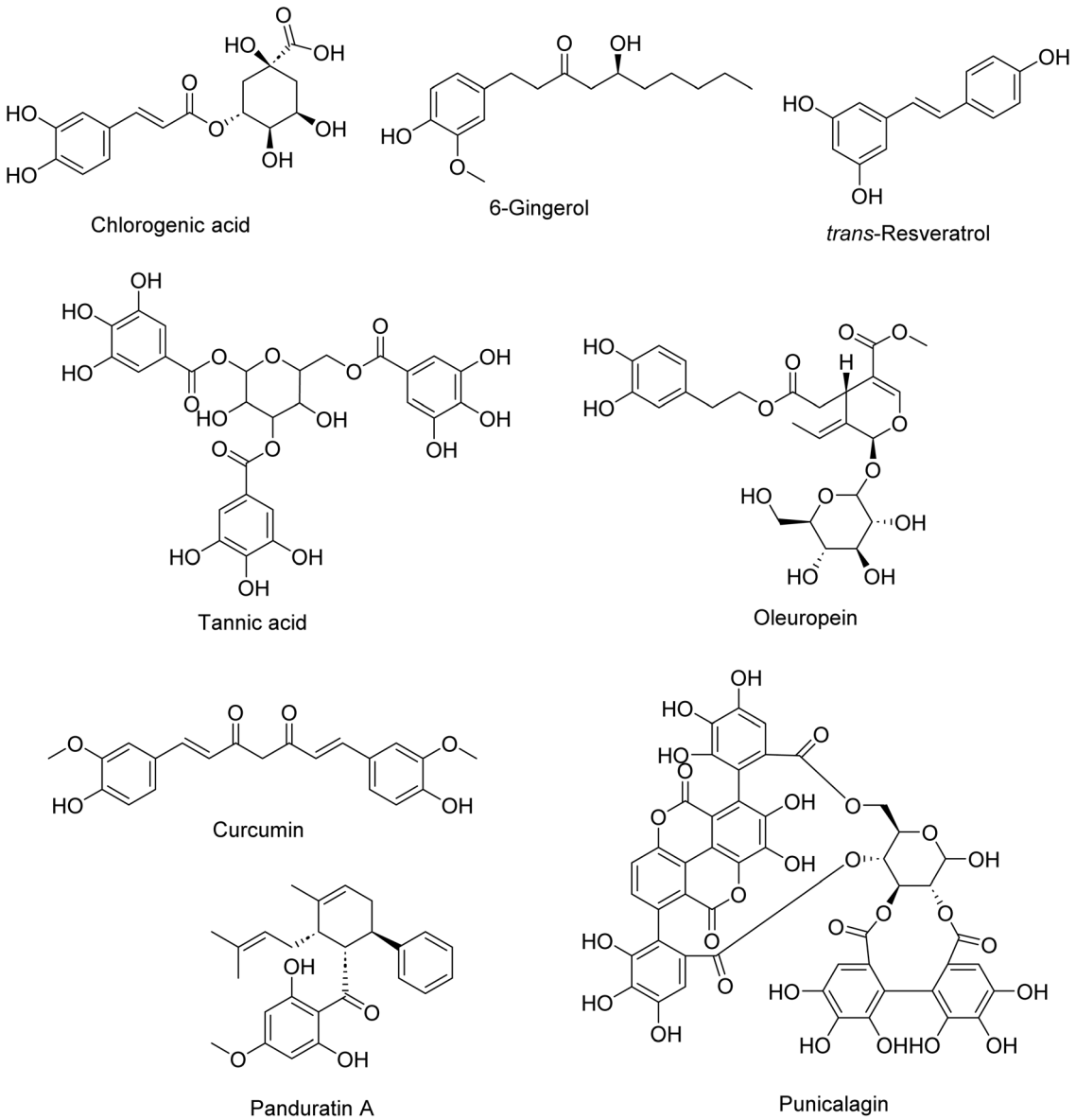

Fig. 3 Structures of polyphenols used in allergic responses and immune modulation. Structure of non-flavonoid polyphenols used in allergic responses and immune modulation.

consideration that should ideally be substantiated by pharmacokinetic studies to facilitate the translation of dosages.[110,111] A recent review article highlights that over the past two decades, 104 randomized controlled trials involving more than 4800 participants have been conducted on resveratrol interventions. However, the evidence is limited due to several factors:

Table 2 Summary of non-flavonoid polyphenols used for immune modulation and allergic treatment

No	Compound	Targeted in immune modulation and allergic treatment	Study model (*in vitro*/*in vivo*)
1	Chlorogenic acid	IL-13, IL-10, IL-6, IFN-γ, TNF-α	*In vitro* (mast cell)
2	6-Gingerol	IL-1β	*In vitro* (NCI–H292)
3	*Trans*-resveratrol	IL-25, IL-33	*In vitro* (eosinophil)/*in vivo* (mice)
4	Tannic acid	IL-4, IL-5, IL-13, NF-κB	*In vivo*
5	Oleruopein	IL-6, MCP-1, sICAM-1	*In vitro* (ARPE-19)
6	Curcumin	IL-4, TNF-α	*In vitro* (mast cell)
7	Panduratin A	IL-4, IL-13, TNF-α	*In vitro* (RBL-2H3)
8	Punicalagin	Nrf2/HO-1 pathway	*In vitro* (HaCaT)

heterogeneous study designs, short intervention durations, and inconsistent formulations impacting bioavailability. Additionally, many studies fall short in methodological reporting and often utilize surrogate markers instead of clinically relevant endpoints. These limitations highlight the necessity for larger, well-designed clinical studies utilizing standardized formulations, strong randomisation techniques, and validated clinical outcomes. Additionally, research into metabolomic variability and possible drug interactions is essential to elucidate the therapeutic potential of resveratrol.[112] Numerous polyphenols require meticulously structured clinical trials utilizing standardized formulations and verified immunological endpoints to definitively determine their effectiveness in allergic responses and immune regulation. The major polyphenols identified are listed in Table 2.

4. Terpenoids in interleukin regulation

Terpenoids modulate interleukins (ILs) by regulating inflammatory pathways, particularly *via* inhibition of the NF-κB signalling pathway, which governs the production of pro-inflammatory ILs, including IL-1β, IL-6, and TNF-α.

Isomeric phenolic monoterpenes thymol and carvacrol have been shown to modulate Th cell responses in ovalbumin-immunised mice. Both compounds reduced the delayed-type hypersensitivity (DTH) responses and splenocyte proliferation. They also decreased Th1 (IL-2, IFN-γ), Th2 (IL-4), and Th17 (IL-17A) cytokine levels while increasing IL-10 and TGF-β levels. Gene expression analysis revealed significantly reduced levels of T-bet, GATA-3, and RORγc transcription factors in splenocytes treated with thymol or carvacrol. These results indicate that thymol and carvacrol exert broad immunomodulatory effects by suppressing Th1, Th2, and Th17 responses, while enhancing regulatory cytokines, suggesting their potential to restore immune balance in allergic inflammation.[113]

Specific monoterpenes, including D-limonene, terpinen-4-ol, and linalool, have been shown to decrease the expression of these interleukins in various *in vitro* and *in vivo* models. Terpenoids inhibit the translocation and activation of NF-κB, preventing the transcription of pro-inflammatory cytokines, suggesting a potential therapeutic approach for inflammatory conditions.[114] Geraniol, a monoterpenoid alcohol with a rose-like scent present in plants such as geranium and lemon, exhibited notable anti-asthmatic activity in a mouse model by decreasing airway hyper-responsiveness and eosinophil infiltration. The modulation of immune responses involves a reduction in Th2 cytokines and an elevation of the Th1 cytokine IFN-γ, along with a decrease in IgE and a shift in gene expression towards a Th1 profile. Furthermore, geraniol increased Nrf2 protein expression and activated Nrf2-mediated antioxidant pathways, leading to an enhanced antioxidant status in the lungs. These findings indicated that geraniol mitigates allergic airway inflammation by enhancing the Th1-skewed immune response and activating Nrf2-mediated antioxidant pathways, making it a potential candidate for asthma therapy.[115]

Geniposide, a bioactive iridoid glucoside isolated from *Gardenia jasminoides*, has demonstrated therapeutic potential similar to that of dexamethasone in a mouse model of ovalbumin-induced allergic airway inflammation. Geniposide treatment in ovalbumin-sensitised mice mitigated airway hyper-responsiveness, eosinophilic pulmonary infiltration, mucus hyper-secretion, and elevated levels of Th2-associated cytokines (IL-4, IL-5, IL-13), chemokines (eotaxin), vascular cell adhesion molecule 1 (VCAM-1), and serum ovalbumin-specific IgE.[116] Geniposide exhibits strong anti-inflammatory and immunomodulatory effects, highlighting its potential as a natural therapeutic agent for allergic asthma.

Paeoniflorin, a monoterpenoid glycoside, has anti-inflammatory and immunomodulatory effects, and its anti-asthmatic properties have been studied in an ovalbumin-induced mouse model. The study demonstrated that paeoniflorin reduced ovalbumin-induced elevations in airway resistance and eosinophil count, while also modulating cytokine levels in bronchoalveolar lavage fluid, specifically restoring IL-4 and IgE levels and elevating IFN-γ levels. Histological analysis demonstrated a decrease in eosinophilia within the lung tissue, whereas flow cytometry indicated a modulation of the Th1/Th2 balance. These findings indicated that paeoniflorin effectively mitigated asthma progression and may serve as a potential treatment for allergic asthma.[117]

Gentiopicroside, a secoiridoid glycoside derived from a monoterpene skeleton, was tested in a mouse model of OVA-induced allergic asthma. Gentiopicroside lowered lung wet-to-dry weight ratio, inflammatory cell infiltration, and goblet cell hyperplasia at various doses. It also reduced inflammatory cell recruitment and T-helper type 2 cytokines (IL-4, IL-5, and IL-13) in the bronchoalveolar lavage fluid. In addition, gentiopicroside treatment reduced ovalbumin-specific IgE and TNF-α levels. GPS was found to increase SIRT1 and decrease NF-κB p65, and SIRT1 inhibition partially reversed the effects of gentiopicroside. These findings indicate that gentiopicroside may be a viable treatment for allergic asthma by modulating the SIRT1/NF-κB p65 pathway.[118]

Artemisinin, a widely used antimalarial compound, modulates the lymphocytic response from Th1 to Th2 cells. Artemisinin has been tested in the treatment of experimental autoimmune encephalomyelitis (EAE). The results showed that artemisinin-treated mice had significantly higher weights and lower EAE scores than those in the untreated group ($p < 0.05$). Histological analysis of the artemisinin-treated brain tissue revealed no plaque development. Low-dose artemisinin treatment significantly reduced IFN-γ levels ($p < 0.05$) compared to those in the untreated group. The treated groups showed significantly higher IL-4 levels ($p < 0.05$) than the control group. These results indicate that artemisinin shifts immune responses towards a Th2 profile, reducing IFN-γ production and EAE severity, highlighting its potential as a therapeutic agent for autoimmune disorders.[119]

Atractylenolide III is a sesquiterpenoid and eudesmanolide derivative present in the rhizomes of medicinal plants such as *Atractylodes macrocephala* and *Atractylodes japonica*. Its effects were examined in IL-4-induced 16HBE cells and in OVA-induced

asthmatic mice. The results indicated that IL-4 stimulation considerably reduced the proliferation and apoptosis of 16HBE cells, whereas atractylenolide III treatment restored proliferation and attenuated apoptosis. In 16HBE cells, the application of atractylenolide III markedly inhibited IL-4-induced elevation in the expression of cleaved caspase-1, apoptosis-associated speck-like protein containing a caspase recruitment domain, nucleotide-binding domain, and leucine-rich repeat protein 3 (NLRP3). These findings demonstrate that atractylenolide III diminishes NLRP3 inflammasome activation and modulates the Th1/Th2 balance in IL-4 stimulated 16HBE cells and ovalbumin-induced asthmatic mice, implying its potential protective role in paediatric asthma treatment.[120]

Zerumbone, a monocyclic sesquiterpenoid found in the rhizomes of bitter ginger plants, such as *Zingiber zerumbet*, known for its anticarcinogenic, anti-inflammatory, and antioxidant properties, was investigated for its anti-allergic effects. *In vitro* studies have shown that zerumbone activates dendritic cells to enhance T-cell proliferation and Th1 cell polarisation. In a mouse model of ovalbumin-induced Th2-mediated asthma, the oral administration of zerumbone resulted in lower ovalbumin-specific IgE and higher IgG2a antibody levels. It also attenuates airway hyper-responsiveness, reduces eosinophilic infiltration in the lungs, and ameliorates mucus hypersecretion. Furthermore, zerumbone treatment decreased the production of IL-4, IL-5, IL-10, IL-13, eotaxin, and keratinocyte-derived chemokines while promoting the Th1 cytokine interferon-γ. These findings suggest that zerumbone effectively shifts the immune balance towards a Th1 response, reduces Th2-driven airway inflammation, and holds promise as a natural therapeutic candidate for allergic asthma.[121]

Similarly, ovatodiolide, a distinct macrocyclic diterpenoid derived from *Anisomeles indica*, has potential therapeutic effects against allergic asthma. Mice immunised with ovalbumin exhibit Th2 cytokine production in the bronchoalveolar lavage fluid, along with airway inflammation and hyper-responsiveness, and serve as a model for allergic inflammation. Ovatodiolide diminished airway hyper-responsiveness and Th2 activation, including cell proliferation and cytokine production (IL-4, IL-5, IL-13, IL-33, and eotaxin). In a murine asthma model, ovatodiolide reduced Th2 responses, mitigating allergic asthma.[122]

For instance, the diterpenoid excavatolide B has been studied for its potential in the treatment of atopic dermatitis. Excavatolide B was chemically modified to produce excavatolide B-61 and B-79 salts. The *in vitro* findings indicated that these compounds markedly suppressed the expression of inflammatory proteins and cytokines in LPS-induced RAW 264.7 cells. *In vivo*, they mitigated symptoms in atopic dermatitis mice by decreasing serum IgE and various cytokines, while restoring skin barrier proteins and reducing angiogenesis-related proteins. This study indicated that these compounds may serve as viable candidates for novel AD treatments.[123] Fig. 4 shows the structure of the studied terpenoids.

In a murine sensitisation model, high-dose vitamin A (isoprenoid derivatives, such as retinol, retinal, and retinoic acid) increased inflammatory responses and inhibited Th1 responses, whereas vitamins C and E (tocopherols containing an isoprenoid side chain) did not affect immune function in young, healthy adult mice. This study indicated that supplementation in older, stressed, or nutritionally deficient animals could produce varying results, possibly mirroring outcomes in at-risk human populations. The key findings of this study indicate that high-dose vitamin A supplementation in mice results in increased inflammation and decreased Th1 responses, which are critical for cell-mediated immunity.[124] In an ovalbumin-exposed mouse model, vitamin A deficiency correlated with Th1 bias, whereas a high dietary intake of vitamin A (250 IU g^{-1}) facilitated Th2 bias. Vitamin A deficiency decreases serum IgE and IgG1 levels, pulmonary eosinophilia, and IL-4 and IL-5 concentrations, inhibiting pulmonary hyper-responsiveness. In contrast, a high-vitamin A diet elevated serum IgE levels and worsened pulmonary hyper-responsiveness. These findings suggest that vitamin A deficiency reduces and that high levels of vitamin A increase the development of experimental asthma. This indicates that excessive vitamin A intake may elevate asthma risk or severity in industrialised nations, whereas vitamin A deficiency presents risks in developing countries.[125] These studies indicate that vitamin A, an isoprenoid compound, has a dose-dependent, bidirectional effect on immune regulation; deficiency reduces allergic inflammation, whereas high intake increases Th2 responses and exacerbates asthma-like symptoms. In contrast, vitamins C and E did not exhibit notable immunomodulatory effects. These findings highlight the importance of maintaining a balanced intake of vitamin A, as both vitamin A deficiency and excess can adversely affect immune function and allergic outcomes.

Bruceine D is a tetracyclic triterpene quassinoid. A previous study investigated the impact of elevated doses of bruceine D on airway hyper-responsiveness, Th1-/Th2-associated cytokines, and inflammatory cell infiltration in mice with ovalbumin-induced allergic asthma. Bruceine D reduced OVA-induced inflammatory cell infiltration and bronchial hyper-responsiveness in peribronchial and perivascular tissues. Following ovalbumin stimulation, animals administered bruceine D exhibited a significant reduction in Th2-associated cytokines (IL-4, IL-5, and IL-13) and elevation in Th1-associated cytokines (IFN-γ and IL-2). Treatment with bruceine D markedly diminished OVA-induced activation of the NOTCH signalling pathway, whereas exposure to ovalbumin elevated the expression of pulmonary NOTCH receptors. These transmembrane proteins transmit signals by interacting with ligands on neighbouring cells. Bruceine D may protect against allergic asthma by modifying the Th1/Th2 cytokine equilibrium and inhibiting NOTCH pathway activation.[126] In recent years, other triterpenoids have been investigated.

Lupeol is a naturally occurring triterpenoid found in numerous fruits, vegetables, and medicinal plants, with established pharmacological effects, including anti-inflammatory, antioxidant, and anti-cancer properties. Lupeol exhibits anti-arthritic properties, presumably through suppression of the immune system. Studies have indicated that it suppresses macrophage phagocytosis and cytokine production in $CD4^+$ T-cells. In BALB/c mice, oral treatment with lupeol (12.5–200 mg kg^{-1}) decreased $CD4^+$ and $CD8^+$ T-cell populations and

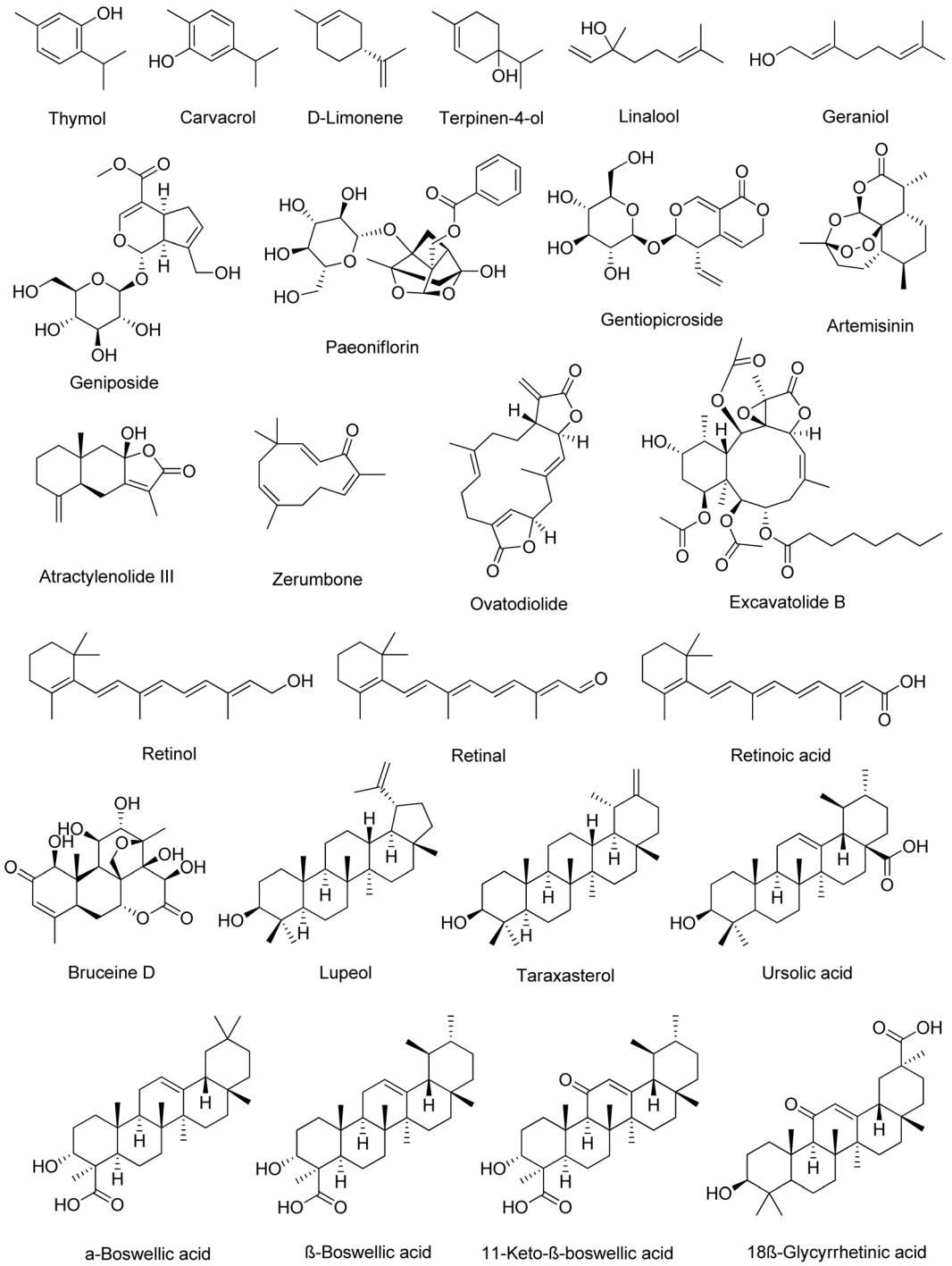

Fig. 4 Structure of terpenoids used in interleukin regulation.

inhibited the intracellular cytokines IL-2, IFN-γ (Th1), and IL-4 (Th2), as evaluated by flow cytometry. Cytometric bead array (CBA) was used for multiplexed quantification of serum cytokines. These findings indicate that lupeol has significant immunosuppressive and anti-inflammatory effects through the modulation of T-cell responses and cytokine production, underscoring its potential as a therapeutic triterpenoid for immune-mediated inflammatory disorders.[127]

Similarly, another terpenoid isolated from *Taraxacum officinale*, taraxasterol, was investigated *in vivo* for its effects on ovalbumin-induced allergic asthma in mice. The findings demonstrated that taraxasterol markedly decreased both total and specific inflammatory cell counts in the bronchoalveolar lavage fluid (BALF), inhibited the production of Th2 cytokines (IL-4, IL-5, and IL-13) in the BALF, and reduced ovalbumin-specific IgE levels in the serum in a dose-dependent manner. Histological analysis of lung tissues indicated that taraxasterol

inhibited ovalbumin-induced inflammatory cell infiltration and goblet cell hyperplasia. In addition, taraxasterol inhibited airway hyper-responsiveness to inhaled methacholine. These findings demonstrate that taraxasterol significantly reduces airway inflammation and hyper-responsiveness by modulating Th2 cytokine production and IgE levels, underscoring its potential as a therapeutic agent for allergic asthma.[128]

Ursolic acid, a terpenoid, exhibits antitumour, anti-inflammatory, and antibacterial properties. It demonstrated anti-asthmatic properties in a murine model of allergic asthma. BALB/c mice were sensitised with ovalbumin and subsequently challenged to induce asthma. Ursolic acid and cyclosporine A were administered to evaluate their effects on the enhanced pause (Penh), pulmonary eosinophil infiltration, immune cell morphology, Th2 cytokines, IL-17, and ovalbumin-specific IgE. These findings demonstrated that ursolic acid inhibits eosinophil infiltration, allergic airway inflammation, and Penh in BALB/c mice. This suppression was accomplished by diminishing the synthesis of IL-5, IL-13, IL-17, and ovalbumin-specific IgE, presumably *via* inhibition of the GATA-3 and STAT6 pathways. The therapeutic mechanism of ursolic acid in asthma appears to involve the reduction of Th2 cytokines (IL-5 and IL-13), ovalbumin-specific IgE, and eosinophil infiltration through the Th2-GATA-3, STAT6, and IL-17-NF-κB pathways. These findings indicated that ursolic acid may serve as a viable therapeutic option for asthma by addressing critical inflammatory pathways and reducing Th2-mediated airway inflammation.[129]

Boswellic acids, a series of pentacyclic terpenoid molecules derived from *Boswellia serrata*, were investigated for their anti-asthmatic effects in a murine model of ovalbumin-induced asthma. Boswellic acid suppresses allergic airway inflammation, airway hyper-responsiveness, ovalbumin-specific IgE, and Th2 cytokine secretion. Furthermore, boswellic acid inhibited phosphorylated pSTAT6 and GATA3 expression in a dose-dependent manner. These findings suggest that boswellic acid alleviates asthma by reducing Th2 cytokine levels through the inhibition of pSTAT6 and GATA3 expression.[130]

18β-Glycyrrhetinic acid, a pentacyclic triterpenoid derived from *Glycyrrhizaa uralensis*, was examined for its immunological adjuvant effects in BALB/c mice. BALB/c mice were intraperitoneally immunised on days 1 and 22 using an emulsion of *Candida albicans* surface mannan extract (SM) combined with either Incomplete Freund's adjuvant (SM/IFA), Complete Freund's adjuvant (SM/CFA), or 18β-glycyrrhetinic acid mixed with IFA (SM/18β-glycyrrhetinic acid/IFA). The results indicated that SM/18β-glycyrrhetinic acid/IFA enhanced T-cell proliferation by 85% compared with SM/IFA ($p < 0.05$). Furthermore, SM/GA/IFA enhanced IgG synthesis, with an IgG2a/IgG1 ratio of 1.31, and increased IFN-γ secretion, suggesting a predominant Th1 immune response. In contrast, SM/CFA exhibited an IgG2a/IgG1 ratio of less than 1, whereas SM/IFA primarily produced IL-4 with minimal IFN-γ. Testing for DTH corroborated these results, with SM/18β-glycyrrhetinic acid/IFA exhibiting the greatest footpad oedema, signifying a predominant Th1 immune response. The results demonstrate that 18β-glycyrrhetinic acid serves as an effective Th1-skewing adjuvant, promoting T-cell proliferation, increasing IFN-γ production, and elevating IgG2a/IgG1 ratios, indicating its potential application in the treatment of Th1-disordered infections like *Candida albicans*.[131]

As of 2025, terpenoids constitute a diverse class of bioactive natural compounds that significantly modulate immune responses by regulating interleukins and associated signalling pathways, positioning them as promising candidates to treat allergic diseases. Their mechanisms of action primarily involve the inhibition of NF-κB signalling and associated transcription factors (*e.g.* GATA-3 and STAT6), leading to the suppression of Th2 cytokines (IL-4, IL-5, and IL-13) and IgE production while also restoring Th1 cytokines (IFN-γ and IL-2), thus re-establishing immune homeostasis. Compounds such as geraniol, zerumbone, and ovatodiolide demonstrate the capacity to inhibit pro-allergic cytokines (TSLP and IL-33), suppress STAT3/ROR-γt pathways, activate antioxidant Nrf2 pathways, and promote a shift from a Th2-dominant profile to a Th1- or Treg-favouring immune response, which is essential for achieving long-term immune tolerance. Certain terpenoids, such as vitamin A derivatives and artemisinin, exhibit dose-dependent and bidirectional immunoregulatory effects, highlighting the need for accurate dosing to prevent the exacerbation of Th2 responses. Compounds such as gentiopicroside, taraxasterol, and ursolic acid have demonstrated efficacy in ovalbumin-induced asthma models by decreasing airway hyper-responsiveness, reducing eosinophilic infiltration, attenuating goblet cell hyperplasia, and down-regulating inflammatory cytokines, preventing airway remodelling. 18β-Glycyrrhetinic acid serve as an effective Th1-skewing adjuvant, promoting IFN-γ production, increasing IgG2a/IgG1 ratios, and facilitating T-cell proliferation, indicating its potential utility in vaccines and immunotherapy. These findings highlight the complex role of terpenoids in modulating interleukins and immune signalling, providing a comprehensive, multi-targeted therapeutic strategy for allergic conditions, including asthma, allergic rhinitis, and contact dermatitis. Recent advances in elucidating molecular mechanisms, particularly the modulation of the Th1/Th2/Treg/Th17 balance and suppression of key inflammatory pathways, have facilitated the development of safe, effective, and natural immunotherapeutic agents. Compared to flavonoids, terpenoids have been studied mainly *in vivo* models; however, future research should prioritise clinical validation, optimisation of bioavailability, and exploration of potential synergistic formulations. Table 3 summarises the terpenoids used for immune regulation and allergy treatment.

5. saponins targeting cytokines for allergy relief

Saponins are naturally occurring compounds having diverse biological activities, including immunomodulatory, anti-inflammatory, and hypoglycemic effects. They regulate both innate and adaptive immune responses by promoting immune organ development, modulating immune cell activity, and enhancing cytokine secretion and antigen-specific antibody

Table 3 Summary of terpenoids investigated for immune modulation and allergic disease management, highlighting their molecular targets, and supporting *in vitro* and *in vivo* evidence

No	Compound	Targeted in immune modulation and allergic treatment	Study model (*in vitro*/*in vivo*)
1	Thymol	IL-2, IL-4, IL-17a, IFN-γ	*In vivo* (mice)
2	Carvacrol	IL-10, TGF- β	
3	D-limonene	IL-1β, IL-6, TNF-α	*In vitro*/*in vivo* (mice, rats)
4	Terpinen-4-ol		
5	Linalool		
6	Geraniol	IFN-γ	*In vivo* (mice)
7	Geniposide	IL-4, IL-5, IL-13	*In vivo* (mice)
8	Paeoniflorin	IL-4, IgE, IFN-γ	*In vivo* (mice)
9	Gentiopicroside	IL-4, IL-5, IL-13, TNF-α	*In vivo* (mice)
10	Artemissin	IFN-γ	*In vivo* (mice)
11	Atractylenolide III	IL-4	*In vitro* (16HBE cells)/*in vivo* (mice)
12	Zerumbone	IL-4, IL-5, IL-10	*In vivo* (mice)
13	Ovatodiolide	IL-4, IL-5, IL-13, IL-33	*In vivo* (mice)
14	Excavatolide B	IgE	*In vitro* (RAW 264.7)
15	Vitamin A	IgE, IgG1, IL-4, IL-5	*In vivo* (mice)
16	Bruceine D	IL-4, Il-5, IL-13, IL-2, IFN-γ	*In vivo* (mice)
17	Lupeol	IL-2, IFN-γ, IL-4	*In vivo* (mice)
18	Taraxasterol	IL-4, IL-5, IL-13, IgE	*In vivo* (mice)
19	Ursolic acid	IL-5, IL-13, IL-17, IgE	*In vivo* (mice)
20	Boswellic acid	Th2 cytokines, pSTAT6, GATA3	*In vivo* (mice)
21	18β-glycyrrhetinic acid	IFN-γ	*In vivo* (mice)

production. Despite the potential haemolytic and cytotoxic effects associated with their chemical structure, technological advancements have facilitated the mitigation of these drawbacks, positioning saponins as promising agents for immune modulation and therapeutic applications.[132,133]

Astragaloside IV, a cycloartane-type triterpene glycoside isolated from *Astragalus membranaceus*, is an immunoregulatory, anti-inflammatory, and antifibrotic compound. AS-IV significantly reduced eosinophilic airway inflammation, hyperresponsiveness, BALF IL-4 and IL-13 levels, and serum total IgE levels. It prevents airway remodelling, including subepithelial fibrosis, smooth muscle hypertrophy, and goblet cell hyperplasia. Astragaloside IV decreases lung TGF-β1 expression. AS-IV demonstrates potent immunoregulatory and anti-inflammatory activities by reducing Th2 cytokine levels, IgE production, and airway remodelling. This finding supports its use as a natural treatment for asthma.[134] astragaloside IV has also been investigated for its anti-asthmatic effects in mouse models. The study found that it significantly reduced ovalbumin-induced eosinophil counts in the BALF, normalised IL-4 levels, and increased IFN-γ and IL-10 levels. Histological analysis confirmed its ability to inhibit eosinophilic infiltration into the lung tissue. Flow cytometry revealed a substantial increase in CD4 + CD25 + Foxp3 T-cells (Tregs), and qPCR data indicated enhanced Foxp3 mRNA expression in lung tissue. These results suggest that astragaloside IV may be a viable therapeutic agent for ameliorating airway inflammation in allergic conditions.[135] In a mouse model, astragaloside IV administered during sensitisation reduced allergic contact dermatitis symptoms. Its capacity to block pro-allergic cytokines, including TSLP and IL-33, which are elevated during sensitisation, may explain its anti-allergic effects. AS-IV reduced TSLP, IL-33, type 2 ILC2s, and pro-allergic cytokine production *in vitro* and significantly reduced allergic inflammation-related ear oedema, Th2 cytokine production, and histological changes *in vivo*. These data indicate that AS-IV may prevent and treat allergic contact dermatitis by targeting critical initiating factors such as TSLP and IL-33, which are potential therapeutic targets for allergic diseases.[136]

Twelve saponins were isolated from the leaves of *Acanthopanax koreanum.* The anti-inflammatory activity of the isolated saponins was assessed in LPS-stimulated bone marrow-derived dendritic cells (BMDCs) using ELISA. Among these compounds, 3α,11α-dihydroxylup-23-al-20(29)-ene-28-oic acid 28-*O*-β-D-glucopyranosyl ester, 3-*O*-β-D-glucopyranosyl-3α,11α-dihydroxylup-20(29)-en-28-oic acid, 3α,11α,23-trihydroxylup-20(29)-en-28-oic acid 28-*O*-[α-L-rhamnopyranosyl-(1 → 4)-β-D-glucopyranosyl-(1 → 6)-β-D-glucopyranosyl] ester, acantrifoside A, acankoreoside D, acankoreoside E, acankoreoside F, and acankoreoside H exhibited significant inhibition of IL-12 production.[137]

Ginsenosides are triterpenoid saponins, a class of chemical compounds that are recognised for their medicinal properties, and are primarily found in the *Panax* genus. They modulate allergic reactions through the reduction of pro-inflammatory cytokines, inhibition of the NF-κB signalling pathway, and regulation of T-helper cells, thereby alleviating symptoms associated with asthma and allergic rhinitis. They enhance the immune system by activating immune cells, improving barrier function, and inhibiting excessive inflammation.[138] One study investigated the adjuvant effects of ginsenoside Rg1 and aluminium hydroxide on immune responses to ovalbumin in mice. The results indicated that alum predominantly enhanced Th2 responses (IgG1 and IL-5), whereas Rg1 improved both Th1 (IgG2a, IFN-γ, and DTH) and Th2 (IgG1 and IL-5) responses. Significant immune responses were observed in mice administered ovalbumin along with, aluminium hydroxide, and Rg1.

The haemolytic activity of Rg1 was lower than that of Quil A, indicating its potential for further investigation into the modulation of mixed Th1/Th2 immune responses. The results suggest that ginsenoside Rg1, particularly in conjunction with aluminium hydroxide, enhances Th1- and Th2-mediated immune responses while exhibiting lower toxicity, indicating its potential as a viable adjuvant candidate for vaccine development.[139] ginsenoside Rd from *Panax ginseng* acts as an effective immunoadjuvant for *Candida albicans* surface mannan extract (CASM), inducing a protective antibody response against candidiasis in mice. Mice immunised with CASM and ginsenoside Rd showed significantly enhanced survival (4/5 survived for 110 days) compared with the control groups. This protection was transferable *via* the antiserum and correlated with a Th1-dominant immune response, as indicated by a higher IgG2a/IgG ratio and confirmed by cytokine profiles and DTH. Ginsenoside Rd did not cause haemolysis and effectively enhanced the Th1 response to CASM, leading to protection against disseminated candidiasis. Both 18β-glycyrrhetinic acid and ginsenoside Rd act as potent Th1-skewing adjuvants, enhancing IFN-γ production, IgG2a/IgG1 ratios, and DTH responses, highlighting their potential for developing immunotherapies against *Candida albicans*.[140] 20-*O*-β-D-glucopyranosyl-20(S)-protopanaxadiol, the principal metabolite of ginsenosides, has demonstrated anti-allergic and anti-pruritic properties. A previous study examined the immunomodulatory effects of 20-*O*-β-D-glucopyranosyl-20(S)-protopanaxadiol-enriched ginseng extract on atopic dermatitis-like symptoms in mice. The results indicated a significant reduction in dermatitis score, ear thickness, scratching duration, and severity of skin lesions generated by *Dermatophagoides farinae* body extract. It also diminished the concentration of macrophage-derived chemokines in the serum, infiltration of eosinophils and mast cells, and cytokine synthesis in the splenocytes. Thus, 20-*O*-β-D-glucopyranosyl-20(S)-protopanaxadiol-enriched ginseng extract effectively alleviates atopic dermatitis-like symptoms by modulating immune responses and suppressing inflammatory mediators.[141]

Quillaja saponins have been examined for their ability to inhibit ovalbumin (OVA)-induced IgE-mediated allergic reactions. The study included BALB/c mice sensitised with ovalbumin and treated with saponins for 35 days. The mice were subsequently immunised intraperitoneally with ovalbumin on days 14 and 21. Following the observation of allergic symptoms, Quillaja saponin elevated IL-12 and IFN-γ levels, although IL-4 levels were diminished. Quillaja saponins inhibit total and ovalbumin-specific IgE production in the spleen cells, leading to reduced levels of total and ovalbumin-specific IgE and IgG secretion. Therefore, Quillaja saponin demonstrates a promising immunomodulatory potential for mitigating IgE-mediated allergic responses by promoting a Th1-skewed immune profile.[142]

One study investigated the immunoregulatory and anti-asthmatic effects of glycyrrhizic acid from liquorice (*Glycyrrhiza glabra*) in an ovalbumin-induced asthmatic mouse model. Glycyrrhizic acid significantly inhibited ovalbumin-induced increases in airway resistance and eosinophil count, whereas it reduced Th2 cytokines (IL-4, IL-5, IL-13) and increased IFN-γ levels in the BALF. Histological analysis showed that glycyrrhizic acid reduced airway eosinophilia and flow cytometry indicated an enhancement in Tregs. These findings indicate that glycyrrhizic acid may exert a protective effect by rebalancing Th1/Th2 immune responses and enhancing Treg-mediated immunoregulation, positioning it as a potential candidate for asthma therapy.[143] Glycyrrhizic acid also exhibits therapeutic effects on ovalbumin-induced allergic asthma in mice by regulating Th1/Th2 balance. Treatment with glycyrrhizic acid inhibited adverse alterations in cytokine levels (IFN-γ, IL-4, IL-5, and IL-13) in the BALF, decreased serum IgE levels, and diminished the expression of OX40 and OX40L in lung tissues and immune cells. Furthermore, glycyrrhizic acid suppressed p38 MAPK activation in lung tissues and influenced T-cell proliferation and the Th1/Th2 balance in $CD4^+$ T-cells. The mechanisms involved in the suppression of OX40-OX40L signalling and p38 MAPK activity indicate that glycyrrhizic acid may serve as a promising treatment for asthma.[144]

The anti-allergic properties of dried fruits of *Kochia scoparia* have been evaluated in animal models of type I–IV allergies. The 70% ethanol extract exhibited inhibitory effects on 48-hours homologous PCA in rats and 1.5-hours heterologous PCA in mice. In the type III allergy paradigm, it suppresses the direct passive Arthus reaction in rats. In an animal model of type IV allergy, it suppressed the effector phase of picryl chloride-induced contact dermatitis. The antipruritogenic constituent of *K. scoparia*, momordin Ic (a triterpenoid saponin), demonstrated inhibitory effects on PCA and picryl chloride-induced contact dermatitis. *K. scoparia* should be acknowledged as a prospective anti-allergic agent.[145]

Saikosaponin A, a principal triterpenoid saponin extracted from the roots of *Bupleurum chinense*, a traditional Chinese herb, was examined for its effects on nasal inflammation and related signalling pathways in an ovalbumin-induced allergic rhinitis rat model. Research has shown that exposure to ovalbumin heightens nasal symptoms and numerous signalling markers, whereas treatment with saikosaponin A markedly diminishes these symptoms by reducing mucosal thickness and inflammatory cell infiltration. Saikosaponin A also reduced the serum concentrations of ovalbumin-specific IgE/IgG1 and Th2/Th17 cytokines including IL-6 and IL-17. Moreover, it suppressed critical signalling pathways such as ROR-γt, STAT3, and NF-κB. These findings indicate that saikosaponin A could be a viable treatment candidate for allergic rhinitis by modulating inflammatory signalling pathways.[146]

Platycodin D is a natural triterpenoid saponin derived from the root of *Platycodon grandiflorum*, commonly called balloon flower. In this study, we investigated the anti-asthmatic properties of platycodin D in a murine model. Histological analysis revealed that platycodin D inhibited eosinophilic inflammation and mucin synthesis. It also suppresses Th2 cytokines (IL-4, IL-5, and IL-13) and decreases GATA3 and IRF4 protein levels. These results suggested that platycodin D may alleviate airway inflammation and could function as a prospective treatment for allergic asthma.[147] Fig. 5 shows the structures of the studied saponins.

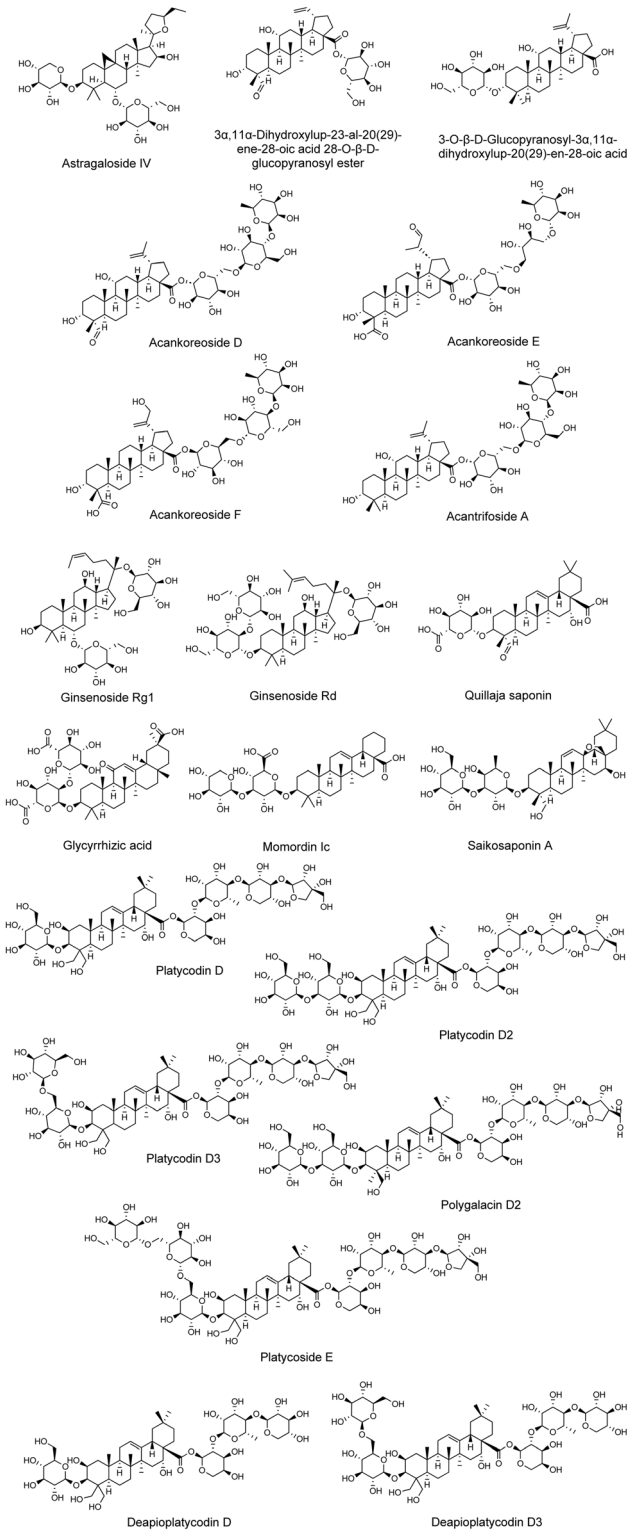

Fig. 5 Structure of saponins used for interleukin regulation.

One study examined the anti-allergic properties of changkil saponins (deapioplatycoside E, platycoside E, deapioplatycodin D3, platycodin D3, polygalacin D2, platycodin D2, deapioplatycodin D, and platycodin D) derived from the roots of *Platycodon grandiflorum* in mice and mast cells. Oral administration of changkil saponins suppressed the systemic PCA reaction induced by dinitrophenyl (DNP)-IgE antibodies in mice, diminished the release of β-hexosaminidase and histamine from anti-DNP-IgE-sensitised RBL-2H3 cells, and inhibited IgE antibody-induced elevation of IL-4 and TNF-α production and expression in RBL-2H3 cells. Changkil saponins inhibit the phosphorylation of Akt and MAP kinases, suggesting possible therapeutic applications in allergic disorders by inhibiting inflammatory cytokine production and Syk-dependent signalling pathways.[148]

Research on triterpenoid saponins, including astragaloside IV, glycyrrhizic acid, ginsenosides, saikosaponin A, and platycodin D, underscores their notable immunoregulatory, anti-inflammatory, and anti-allergic effects, suggesting their potential as therapeutic agents for allergic conditions such as asthma, allergic rhinitis, and contact dermatitis. These compounds are effective in modulating Th1/Th2 immune responses, enhancing Treg activity, and inhibiting pro-inflammatory cytokines and signalling pathways including NF-κB, p38 MAPK, and OX40-OX40L. Their capacity to diminish airway inflammation, eosinophilia, IgE production, and tissue remodelling highlights their therapeutic potential. Future studies should focus on clarifying the specific molecular mechanisms governing their immunomodulatory effects, enhancing their delivery methods, and performing clinical trials to assess their safety and efficacy in humans. Furthermore, investigating the synergistic effects of current therapies and creating new formulations may improve the efficacy of natural treatments for allergic and inflammatory diseases. Table 4 summarises the saponins used for immune regulation and allergy treatment.

6. Alkaloids as interleukin modulators

Alkaloids represent a significant and varied class of naturally occurring nitrogenous compounds predominantly found in plants, fungi, and certain microorganisms and are recognised for their strong physiological and pharmacological effects. In addition to their recognised functions as analgesics, antimalarials, and anti-cancer agents, numerous alkaloids have been identified as modulators of immune responses by regulating interleukins and inflammatory pathways. They can reduce pro-inflammatory cytokines, including IL-1β, IL-6, IL-17, and TNF-α, while increasing anti-inflammatory cytokines, such as IL-10, thus restoring the immune equilibrium. The immunomodulatory effects of alkaloids make them potential candidates for managing allergic diseases, such as asthma and allergic rhinitis, through mechanisms that reduce airway inflammation, suppress Th2 cytokine production, and restore the balance in Th1/Th2 immune responses.[149,150]

Collectively, these findings highlight the significant therapeutic potential of alkaloids as multifunctional modulators of the immunological and inflammatory pathways. Structural classes of alkaloids, such as quinolizidine, isoquinoline, protoberberine, and benzoylmesaconine derivatives, exhibit substantial experimental evidence to support their ability to reduce pro-inflammatory cytokine production (*e.g.* IL-1β, IL-6, IL-17, and TNF-α) while promoting anti-inflammatory

Table 4 Summary of saponins investigated for immune modulation and allergic disease management, highlighting their molecular targets and supporting *in vitro* and *in vivo* evidence

No	Compound	Targeted in immune modulation and allergic treatment	Study model (*in vitro*/*in vivo*)
1	Astragaloside IV	IL-4, IL-13, IL-33	*In vitro* (HaCaT cells)/*in vivo* (mice)
2	3-*O*-β-D-Glucopyranosyl-3α,11α-dihydroxylup-20(29)-en-28-oic acid	IL-12	*In vitro* (BMDCs)
3	3α,11α-dihydroxylup-23-al-20(29)-ene-28-oic acid 28-*O*-β-D-glucopyranosyl ester		
4	Acankoreoside D		
5	Acankoreoside E		
6	Acankoreoside F		
7	Acantrifoside A		
8	Ginsenoside Rg1	IL-5, IFN-γ	*In vivo* (mice)
9	Ginsenoside Rd	IFN-γ	*In vivo* (mice)
10	Quillaja saponin	IL-4, IL-12, IgE, IgG, IFN-γ	*In vivo* (mice)
11	Glycyrrhizic acid	IL-4, IL-5, IL-13, IFN-γ	*In vivo* (mice)
12	Momordin Ic	Alleviation of allergic symptoms	*In vivo* (mice)
13	Saikosaponin A	IL-6, IL-17, IgE, IgG	*In vivo* (mice)
14	Platycodin D	IL-4, IL-5, IL-13, TNF-α	*In vitro* (RHL-2H3)/*in vivo* (mice)
15	Platycodin D2	IL-4, TNF-α	*In vitro* (RHL-2H3)/*in vivo* (mice)
16	Platycodin D3		
17	Platycoside E		
18	Polygalacin D2		
19	Deapioplatycodin D		
20	Deapioplatycodin D3		

mediators, thus restoring immune homeostasis under various pathological conditions. These include asthma, allergic rhinitis, rheumatoid arthritis, atopic dermatitis, neuroinflammatory diseases, and cancer.

Herbal medicines from *Sophora flavescens* contain matrine, a major quinolizidine alkaloid. According to one study, matrine-treated rats exhibited significantly fewer clinical symptoms, inflammatory cell infiltration ($CD4^+$ and $CD8^+$ T-cells and macrophages), and demyelination than untreated controls. After therapy, the blood IL-23 and IL-17 levels markedly decreased, especially at higher matrine doses. The powerful immunomodulatory and neuroprotective activities of matrine suggest that it can treat neuroinflammatory illnesses by lowering inflammation, modulating T-cell-mediated immune responses, and demyelination.[151] Another study found that matrine treatment suppressed the proliferation of chronic myeloid leukaemia cells, induced apoptosis, and increased the accumulation of G0/G1 cells, while reducing the expression of Bcl-xL, Cyclin D1, and c-Myc. Matrine treatment reduced the phosphorylated STAT3 and JAK2 levels without altering their protein expression, as confirmed by western blotting. Matrine significantly reduced IL-6, a potent upstream activator of STAT3.[152] These findings indicate that matrine modulates immune responses, diminishes neuroinflammation, and inhibits cancer cell proliferation by regulating key signalling pathways, such as JAK2/STAT3, making it a promising multi-target candidate to treat neuroinflammatory disorders and malignancies, including chronic myeloid leukaemia.

Inflammation of the pulmonary airways is a characteristic feature of numerous lung disorders, and is often linked to increased levels of cytokines that promote inflammation, particularly TNF-α and IL-1β. Berberine, a protoberberine alkaloid commonly found in plants, efficiently inhibits cytokine production induced by inflammatory agents in various cell types in a dose-dependent manner. The degradation of inhibitory κB-α and blockade of its phosphorylation are integral components of the suppression mechanism. These findings indicate that berberine exerts anti-inflammatory effects through stabilisation of inhibitory κB-α and inhibition of its phosphorylation. This mechanism prevents the activation of pro-inflammatory signalling pathways and reduces cytokine production, making berberine a promising therapeutic candidate for managing airway inflammation in lung disorders.[153] A meta-analysis indicated that berberine supplementation significantly reduced IL-6, TNF-α, and serum C-reactive protein (CRP) levels, based on a review of 18 randomised controlled trials involving 1600 participants. The results reveal a weighted mean difference of IL-6 (-1.18 pg mL^{-1}), TNF-α (-3.72 pg mL^{-1}), and CRP (-1.33 mg L^{-1}). A notable dose-dependent effect was observed, particularly at doses less than 1000 mg day^{-1}, during interventions shorter than 5 weeks. Despite these findings, limitations such as low study quality and considerable heterogeneity remain. These findings suggest that berberine may serve as an adjunct therapy for inflammation management, warranting further investigation to provide stronger evidence.[154]

Isoquinoline alkaloids may alleviate asthma associated with prolonged airway inflammation and hyper-responsiveness. The protective effects and underlying mechanisms of protopine in asthma have been studied using historical, biochemical, and molecular approaches, including real-time reverse transcription-quantitative polymerase chain reaction, molecular docking, western blotting, and metabolomic analyses.

Protopine administration significantly reduced inflammatory cell counts (eosinophils, leukocytes, and monocytes) and lung histopathology and decreased IgG and histamine levels in BALF. Protopine suppressed TLR4/NF-κB signalling by interacting with MyD88 and TNF-α, as demonstrated by molecular docking and western blotting analyses. Protopine also regulates NLRP3 inflammasome and pyroptosis-related proteins to attenuate inflammation. *In vitro* studies have shown decreased cell viability, ROS, and pro-inflammatory cytokines (IL-1β and IL-18) following protopine treatment. Immunofluorescence analysis revealed decreased TLR4 and MyD88 expression and reduced NF-κB p65 nuclear translocation. Serum metabolomic analysis revealed 21 biomarkers associated with phenylalanine, tryptophan, glucose, and sphingolipid metabolism. These findings indicate that protopine alleviates asthma symptoms by modulating TLR4/NF-κB signalling, suppressing NLRP3 inflammasome-mediated pyroptosis, and regulating metabolic pathways, making it a promising therapeutic candidate for airway inflammation and hyper-responsiveness.[155]

Norisoboldine, the principal isoquinoline alkaloid derived from the dried roots of *Lindera aggregata* (*L. strychnifolia*), is used in traditional Chinese medicine to treat rheumatic diseases. One study assessed the effect of norisoboldine on IL-6 production in fibroblast-like synoviocytes, which are pivotal effector cells in the pathogenesis and progression of rheumatoid arthritis. Upon stimulation with IL-1β *in vitro*, fibroblast-like synoviocytes derived from rats with adjuvant arthritis produce elevated levels of IL-6. The production of IL-6 decreased in a concentration-dependent manner after norisobold treatment. Furthermore, it reduced phosphorylation of MAPKs, PKC, NF-κB (ser 276), and CREB in fibroblast-like synoviocytes. Studies using inhibitors have revealed that PKC and p38 MAPK act upstream of MAPKs and cAMP response element-binding proteins. Norisoboldine inhibited the PKC/MAPKs/p65/cAMP signalling pathway and suppressed IL-6 synthesis in fibroblast-like synoviocytes, potentially exerting anti-RA effects. These results confirm that norisoboldine possesses significant anti-inflammatory and anti-arthritic properties by inhibiting the PKC/MAPKs/p65/cAMP signalling pathway, leading to a concentration-dependent reduction in IL-6 production in fibroblast-like synoviocytes, underscoring its potential as a therapeutic agent for the treatment of rheumatoid arthritis.[156] A separate investigation examined the effect of norisoboldine on the activation of the nuclear factor of activated T-cells and its potential therapeutic use in atopic dermatitis. These findings demonstrate that norisoboldine markedly suppressed nuclear factor of activated T-cells reporter gene expression in a dose-dependent manner and inhibited nuclear factor of activated T-cells dephosphorylation in both K562-luc and Jurkat cells. This inhibition decreased IL-2 expression in Jurkat cells. In a murine model, norisoboldine significantly alleviated DNCB-induced dermatitis, leading to reduced ear swelling and infiltration of inflammatory cells. Norisoboldine treatment led to substantial reductions in the mRNA levels of IFN-γ, TNF-α, IL-4, and IL-6 by 78.4%, 77.8%, 72.3%, and 73.9%, respectively, compared with untreated controls. These data indicate that norisoboldine significantly modulates immune responses by limiting the activation of activated T-cells and decreasing pro-inflammatory cytokine production, underscoring its potential as a viable therapeutic agent for atopic dermatitis.[157]

Portulacatone A, a novel alkaloid isolated from *Portulaca oleracea*, showed significant inhibitory effects on the inflammatory mediator interleukin-1β (IL-1β) in RAW 264.7 cells. Other compounds isolated from *P. oleracea*, such as oleracein E and N-*trans*-*p*-coumaroyltyramine (NCPA), have also been reported to exhibit interleukin-modulating activity. Oleracein E decreased the levels of inflammatory cytokines such as IL-1β, IL-6, and TNF-α in a TNCB-induced ulcerative colitis rat model. It also increases the expression of antioxidant enzymes by activating the NRF2 signalling pathways.[158] NCPA alleviates the clinical symptoms of atopic dermatitis in a DNCB-induced mouse model. In addition, the levels of immunoregulatory cytokines, such as IL-4, IL-5, IL-13, IFN-γ, and TNF-α were decreased by NCPA treatment. Furthermore, *in vitro*, NPCA treatment downregulated the transcriptional levels of IL-2, inhibiting both Th1 and Th2 cytokines expression, indicating that NCPA has potential as a treatment for allergic disease.[159] These alkaloids have significant anti-inflammatory activity, principally by inhibiting IL-1β production in LPS-stimulated macrophages, suggesting their promise as therapeutic agents for inflammation-related illnesses.[160]

Higenamine, a benzyl-tetrahydroisoquinoline alkaloid, exhibits anti-inflammatory properties. It mitigates IL-1β-induced apoptosis in human nucleus pulposus cells (HNPCs) in a dose-dependent manner, affecting apoptosis-related biomarkers such as Bcl-2, Bax, and cleaved caspase-3. While higenamine does not directly alter ROS levels or PI3K/Akt signalling, it counteracts IL-1β-induced ROS production and restores PI3K/Akt pathway activity. Inhibition of PI3K/Akt signalling reverses the protective effects of higenamine, indicating its potential as a therapeutic agent for intervertebral disc degeneration by modulating ROS and enhancing PI3K/Akt pathway activation.[161]

The main alkaloids of *Stephania tetrandra*, fanchinoline, and tetrandrine, have been used to treat inflammatory diseases in East Asian countries such as Korea. Fangchinoline and tetrandrine reduce croton oil-induced ear oedema in mice. Fangchinoline and tetrandrine were also tested *in vitro* against cyclooxygenase, mIL-5, and hIL-6 to determine their anti-inflammatory properties. Fangchinoline inhibited cyclooxygenase activity by 35% at 100 μM, whereas tetrandrine showed no inhibition. In contrast, 12.5 μM tetrandrine inhibited mIL-5 activity by 95%, whereas fangchinoline had no such effect. Fangchinoline (4 μM) and tetrandrine (6 μM) inhibited hIL-6 activity by 63% and 86%, respectively. Although structurally similar, fangchinoline and tetrandrine have diverse anti-inflammatory effects, highlighting their potential for tailored therapeutic use by targeting various inflammatory pathways.[162] Tetrandrine has also been investigated for its immunosuppressive effect on autoreactive peripheral blood T-cells, which play a key role in autoimmune disorders. It also reduced PMA/ionomycin-induced T-cell proliferation and interleukin-2 and CD71 expression. Moreover, tetrandrine inhibited the protein kinase C-dependent interleukin-2 receptor α-chain and CD69 but not the Ca^{2+}-dependent CD40 ligand. The combination of

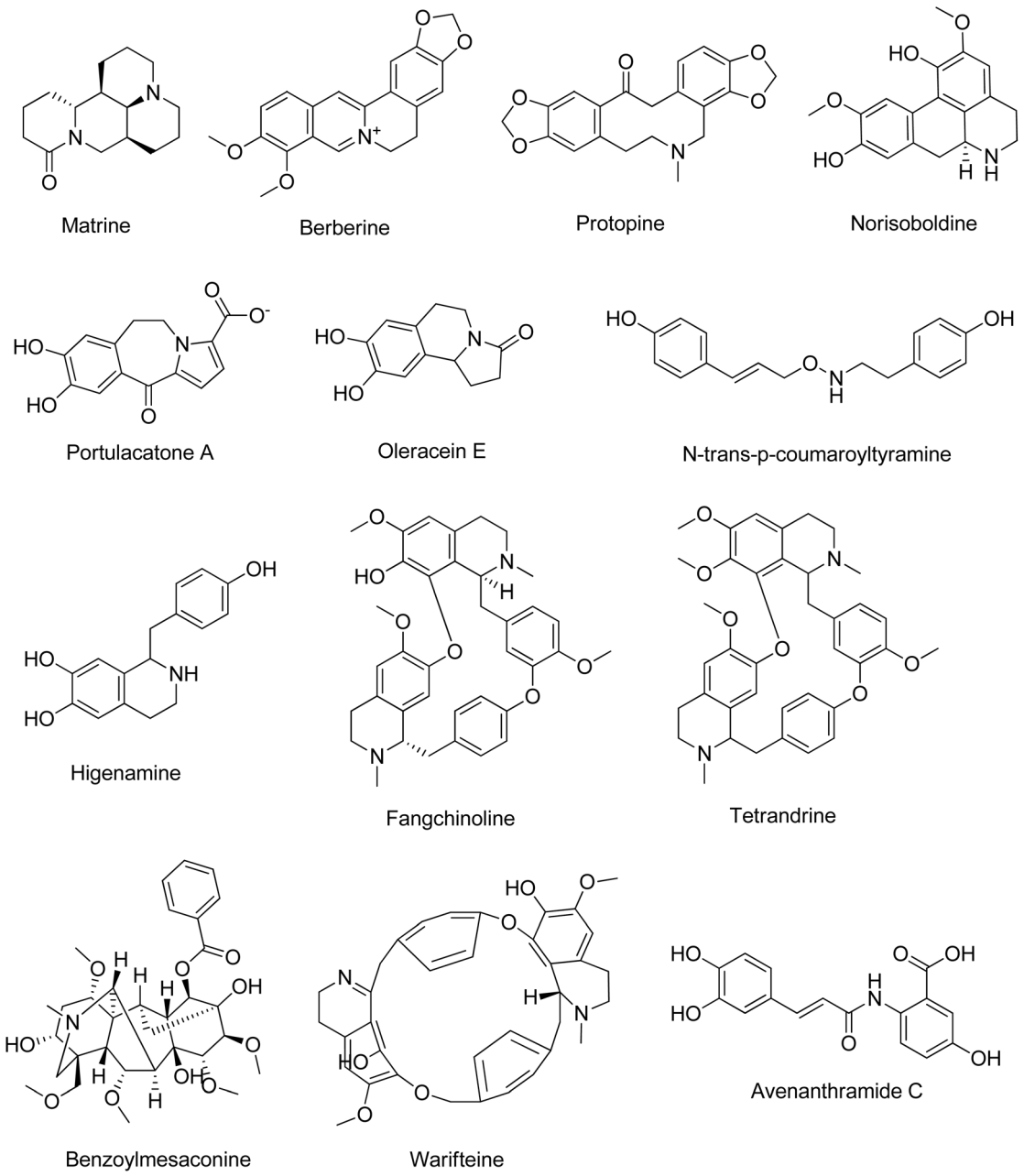

Fig. 6 Structure of bioactive alkaloids against interleukins.

tetrandrine and cyclosporine A inhibited T-cell activation. Among tetrandrines, hernandezine most effectively inhibited protein kinase C signalling. These data suggest that inhibition of protein kinase C by tetrandrine and its analogues may not involve Ca^{2+} channel blockage. Finally, tetrandrine and its analogues have been shown to induce cell death at therapeutic concentrations, which may mechanistically differ from their effects on autoimmune disorders. The molecular mechanisms underlying the immunosuppressive effects of tetrandrine and its analogues on human peripheral blood T-cells have been elucidated. Tetrandrine and its analogues block protein kinase C and induce T-cell apoptosis, suggesting their potential as therapeutic agents for autoimmune disease.[163]

Recently, the anti-inflammatory alkaloid benzoylmesaconine from *Aconitum carmichaeli* was investigated for its therapeutic potential against metabolic diseases associated with NLRP3 inflammasome activation. The effects of benzoylmesaconine on upstream and downstream protein expression and pyroptosis in NLRP3-activated bone marrow-derived macrophages were evaluated. The anti-inflammatory effects of benzoylmesaconine have been confirmed in animal models of monosodium urate-induced gouty arthritis and dextran sulphate sodium (DSS)-induced colitis. Benzoylmesaconine was found to inhibit NLRP3 inflammasome activation by reducing IL-1β production and GSDMD-N protein expression, which blocks intracellular potassium efflux and preventing NLRP3 assembly. *In vivo*

Table 5 Summary of alkaloids evaluated for their roles in immune modulation and allergic disease management

No	Compound	Targeted in immune modulation and allergic treatment	Study model (*in vitro*/*in vivo*)
1	Matrine	IL-6, IL-17, IL-23	*In vitro* (CML cells)/*in vivo* (rats)
2	Berberine	IL-6, TNF-α	*In vivo* (A-549, HFL1, U-937 cells)/clinical trials
3	Protopine	IL-1β, IL-18, TNF-α	*In vivo* (mice)
4	Norisoboldine	IL-2, IL-4, IL-6, INF-γ, TNF-α	*In vitro* (K562-luc, Jurkat cells)/*in vivo* (mice)
5	Portulacatone A	IL-1β	*In vitro* (RAW 264.7)
6	Oleracein E	IL-1β, IL-6, TNF- α	*In vitro* (RAW 264.7)/*in vivo* (rats)
7	N-trans-*p*-coumaroytyramine	IL-2, IL-4, IL-5, IL-13, INF-γ, TNF-α	*In vitro* (Jurkat cells)/*in vivo* (mice)
8	Higenamine	IL-1β	*In vitro* (HNPCs)
9	Fanchinolin	IL-6	*In vivo* (mice)
10	Tetrandrine	IL-6, IL-5	*In vivo* (mice)
11	Benzoylmesaconine	IL-1β	*In vivo* (mice)
12	Warifteine	IL-13	*In vivo* (mice)
13	Avenanthramide C	TNF-α, IL-25, IL-33	*In vitro* (mast cell)/*in vivo* (mice, rats)

testing revealed that benzoylmesaconine reduces inflammation in an animal model. *In vivo*, benzoylmesaconine reduced NLRP3 inflammasome activation and pyroptosis, reducing inflammation, suggesting its potential as a treatment for metabolic and inflammatory diseases associated with NLRP3.[164] Fig. 6 displays the structure of the alkaloids studied in the context of ILs.

Cissampelos sympodialis and its alkaloid warifteine have been evaluated to treat asthma related to allergen-induced airway hyperreactivity and pulmonary remodelling. In bronchoalveolar lavage, pre-treatment with *C. sympodialis* or warifteine diminished allergen-induced airway hyperreactivity and IL-13 levels. The post-treatment effects of warfarin were also significant. Both treatments reduced eosinophil infiltration, mucus production, and subepithelial fibrosis to the non-allergic levels. These findings indicate that *C. sympodialis* and its alkaloid warifteine possess significant anti-inflammatory and anti-remodelling properties, making them promising candidates for innovative asthma therapies to mitigate and reverse allergen-induced airway hyperreactivity and structural alterations in the lungs.[165]

Avenanthramides, which are naturally occurring phenolic alkaloids in oats, have demonstrated beneficial effects on allergic responses by inhibiting mast cell activation and degranulation, reducing inflammatory cytokines, and improving intestinal barrier integrity in food allergy models. Their anti-inflammatory properties, particularly those associated with avenanthramide C, together with their similarity to the anti-allergic drug tranilast, highlight their potential as therapeutic alternatives to treat mast cell-mediated food allergies. They diminish the secretion of histamine and β-hexosaminidase, which are essential mediators of allergic responses, from mast cells. They can reduce the synthesis of pro-inflammatory cytokines, including TNF-α, IL-25, and IL-33, and regulate Hsp70-NF-κB signalling, thereby alleviating intestinal inflammation in food allergies.[166,167] Based on these findings, avenanthramides demonstrate diverse anti-allergic properties *via* the stabilisation of mast cells, inhibition of pro-inflammatory cytokines, and enhancement of intestinal barrier integrity. Their structural resemblance to tranilast and proven effectiveness in food allergy models renders them attractive natural options for the treatment of mast cell-mediated gastrointestinal allergic conditions.

Alkaloids exert their bioactivity by inhibiting critical signalling pathways, including NF-κB, MAPK, PKC, and TLR4, suppressing NLRP3 inflammasome activation, modulating the Th1/Th2 cytokine balance, and regulating programmed cell death pathways such as apoptosis and pyroptosis. Several alkaloids, including protopines and benzoylmesaconines, have been shown to regulate metabolic and oxidative stress-related pathways, enhancing their multifaceted anti-inflammatory properties.

Despite these encouraging results, the transition of these molecules from laboratory to clinical application remains a challenge. Future research must emphasise thorough pharmacokinetic and pharmacodynamic assessments, clarification of structure–activity correlations, and stringent toxicity and safety evaluations. The incorporation of high-throughput screening, systems pharmacology, and computational modelling may enhance the identification of optimised lead candidates with superior bioavailability and target specificity. Ultimately, these endeavours may facilitate the development of therapeutically feasible, multi-target, alkaloid-based therapies, thus enhancing precision medicine strategies to treat immune-mediated and inflammatory disorders. Table 5 shows the major alkaloids studied for immune modulation and allergic treatments.

7. Mechanisms of action of bioactive compounds in modulating interleukins pathways

ILs are essential signalling molecules within the immune system that facilitate communication between immune cells and initiate an immunological cascade in response to infections, allergies, and tissue damage. These cytokines orchestrate both innate and adaptive immune responses, and are essential for the genesis, propagation, and resolution of inflammation. The pro-inflammatory cytokines discussed in the Introduction are crucial for the immediate immunological response, facilitating leukocyte recruitment, macrophage activation, and fever onset.[168,169]

Conversely, anti-inflammatory cytokines, such as IL-10 and TGF-β, contribute to the regulation of the immune response,

facilitate tissue repair, and re-establish immunological equilibrium. Dysregulation of interleukin has been observed in numerous diseases, including allergies, asthma, inflammatory bowel disease, autoimmune disorders, and chronic inflammatory conditions. For instance, excessive synthesis of IL-4, IL-5, and IL-13 contributes significantly to Th2-mediated allergies, whereas elevated IL-17 levels exacerbate tissue damage in autoimmune disorders. Consequently, medications that precisely modulate interleukin signalling are essential for re-establishing the immunological equilibrium and preventing widespread immunosuppression.[170,171]

Natural bioactive compounds, including flavonoids, polyphenols, terpenoids, and alkaloids, have demonstrated the capacity to modulate these cytokine pathways at various levels. These compounds suppress cytokine gene expression, influence receptor binding, inhibit cellular signalling pathways (such as NF-κB or JAK/signal transducer and activator of transcription (STAT)), and enhance the production of anti-inflammatory cytokines. This complex activity renders them appealing candidates to treat immunological disorders, with fewer adverse effects than conventional synthetic medications. The following sections delineate several principal mechanisms of action by which bioactive substances exert their effects. These processes demonstrate how these compounds influence interleukin pathways, regulate immunological responses, and help prevent and treat inflammation-related illnesses.

7.1. Imbalance of innate cytokines in diseases

Chronic inflammatory and allergic disorders frequently result in an imbalance in the expression of innate cytokines, which exacerbates the disease pathology. Both pro-inflammatory cytokines and anti-inflammatory cytokines are important to understand how the balance between these two types can regulate the immune system. Pro-inflammatory cytokines, including IL-1, IL-6, and TNF-α, provoke an initial immune response against harmful stimuli but can also be detrimental to surrounding cells and tissues when secreted excessively. Under infectious conditions, the IL-1 family activates the adaptive immune system by promoting T-cell differentiation and maturation. The IL-6 family plays a pivotal role in innate immune defence against viral infections. Anti-inflammatory cytokines, comprising the IL-1Rα, IL-4, and IL-10 families, play a pivotal role in the innate immune defence against parasitic or bacterial infections. IL-1Rα blocks pro-inflammatory cytokine production by preventing IL-1 from binding to its receptor IL-1R. IL-4 has a dual function in modulating the differentiation of Th cells. It induces the differentiation of naïve T-cells into Th2 cells, enhancing humoral immunity, and suppresses the differentiation of Th1 cells, leading to inflammation. IL-4 also regulates the immunity against parasitic infections by activating B cells to produce IgE. IL-10 is a potential candidate for treating infectious diseases, and ongoing attempts have been made to create an immune system that mimics the structure of IL-10. The crosstalk between these two types of cytokines regulates the immune system balance. Therefore, understanding interleukin homeostasis can be an effective therapeutic approach.[172,173]

7.2. Modulation of NF-κB and JAK/STAT pathways

The predominant focus of research on bioactive substances is their influence on the NF-κB pathway, which initiates the transcription of pro-inflammatory cytokines. In the resting state, NF-κB resides in the cytoplasm as a heterodimer that binds to the inhibitory subunit IκBα. Upon activation, IκBα is phosphorylated and degraded by IKK. Subsequently, the released NF-κB complex translocate to the nucleus and mediates the transcription of inflammatory cytokines, such as IL-1β, IL-6, and TNF-α. Compounds such as curcumin, resveratrol, and berberine inhibit nuclear translocation of the p65 subunit of NF-κB, leading to diminished synthesis of inflammatory cytokines.[174,175] Likewise, JAK/STAT signalling is initiated by cytokine receptor activation. Activated Janus kinase (JAK) phosphorylates the cytoplasmic domain of the receptor, and the STAT proteins bind to this domain. Subsequently, STATs are phosphorylated by JAK, form dimeric complexes *via* their SH2 domains, and translocate to the nucleus. It binds to specific DNA elements and initiates transcription of various cytokine genes. The JAK/STAT pathway can be suppressed by bioactive substances, reducing the levels of IL-17 and IL-23, which play crucial roles in autoimmune and chronic inflammatory diseases.[176,177] Various compounds previously discussed modulate the NF-κB and JAK/STAT pathways. For instance, flavonoids inhibit NF-κB-mediated transcription while also affecting JAK/STAT signalling, resulting in reduced Th2-type cytokine production and allergic inflammation. The situation is analogous for other classes of compounds; however, it is difficult to assert that flavonoids specifically target the NF-κB pathway, whereas others target the JAK/STAT pathways.

7.3. Effects on MAPK and PI3K/Akt pathways

The MAPK pathway plays a pivotal role in the inflammatory response. Cytokine receptors are activated by the binding of inflammatory factors, such as IL-1β, IL-6, IL-8, and TNF-α, which induces the sequential phosphorylation of MAPKs, including ERK, JNK, and p38. Phosphorylated MAPKs initiate the transcription of pro-inflammatory cytokines, leading to severe inflammation. Flavonoids, such as quercetin and luteolin, impede the phosphorylation of MAPKs, attenuating pro-inflammatory gene expression.[178,179] Moreover, the regulation of PI3K and Akt, upstream signalling molecules of NF-κB, is important for cytokine production. When cytokine receptors are activated, two downstream kinases, PI3K and Akt, are sequentially phosphorylated, inducing NF-κB activation and the production of inflammatory cytokines. The PI3K/Akt pathway can also alter macrophage polarisation towards the M2 anti-inflammatory phenotype, facilitating tissue repair and resolution of inflammation.[180]

7.4. Restoration of Th1/Th2/Th7 and Treg balance

$CD4^+$ T-cells control immune cell activity and differentiate into various types of T-helper cells. Type 1 T-helper (Th1) cells, modulating cell-mediated immunity, secrete Th1 cytokines such as IL-2 and IFN-γ. Type 2 T-helper (Th2) cells are involved in humoral immunity and secrete Th2 cytokines such as IL-4, IL-5, IL-13, and

IgE. Type 17 T-helper (Th17) cells contribute to chronic inflammation by producing IL-17 and IL-22. In contrast, regulatory T (Treg) cells inhibit Th17-mediated inflammation and maintain immune homeostasis. Moreover, IFN-γ, a Th1-type cytokine, inhibits IgE production, suppressing the Th2-type immune response.[181,182] Therefore, restoring the balance between Th cells and Treg cells is crucial for the regulation of interleukin production. Several studies have shown that plant-derived compounds help restore the Th1/Th2 balance. For example, luteolin and apigenin suppressed Th2 cytokine production and increased Th1 cytokine production, reducing allergic responses. Similarly, curcumin and resveratrol inhibit Th17 cell differentiation and increase the number and function of regulatory T-cells, which are important for controlling autoimmune diseases.[183,184]

7.5. Oxidative stress and antioxidant defence system

Oxidative stress promotes interleukin dysregulation and persistent inflammation. ROS generated during cellular metabolism can cause cellular damage. Pro-inflammatory cytokines, such as IL-1, IL-6, and TNF-α, also stimulate ROS production *via* multiple cellular mechanisms. ROS act as secondary messengers, activating the NF-κB signalling pathway. This amplifies the inflammatory response by inducing various cytokines.[182] A natural antioxidant system exists that can reduce ROS levels to protect the endogenous system from oxidative stress. Catalase (CAT), glutathione reductase (GR), glutathione peroxidase (GPx), and superoxide dismutase (SOD) are enzymes that regulate oxidative stress. Moreover, the Nrf2 signalling pathway counteracted oxidative stress. Under stress conditions, Nrf2 translocates to the nucleus and promotes the transcription of antioxidant enzymes such as GPx. Polyphenols reduce ROS production and enhance antioxidant enzyme levels by activating the Nrf2 pathway. This leads to reduced oxidative damage and the regulation of cytokine overproduction.[185,186] Fig. 7 depicts the mechanisms by which bioactive compounds modulate interleukin-mediated immune pathways.

7.6. Future directions and clinical significance

Bioactive compounds collectively regulate interleukin-mediated signalling at several levels, leading to reduced inflammation and the re-establishment of immunological equilibrium. In the future, multi-omics methodologies (transcriptomics, metabolomics, and proteomics) and meticulously structured clinical trials will enhance our understanding of these pathways and identify specific biomarkers for personalised therapy. Consequently, these compounds may serve as adjuvants or principal therapies for chronic allergic and autoimmune conditions, cancers, and metabolic disorders.

8. clinical evidence and applications of bioactive compounds in allergic treatments and immune modulation

In recent years, an increasing number of clinical studies have highlighted the therapeutic relevance of bioactive compounds, such as flavonoids, alkaloids, terpenoids, and polyphenols, in the management of allergic disorders and immune dysregulation. These compounds have shown promising results in reducing the levels of pro-inflammatory cytokines and modulating the production of Th2 cytokines, which are often elevated in allergic asthma, rhinitis, and atopic dermatitis. Randomised controlled trials have reported that plant-derived compounds can significantly improve the clinical outcomes of certain diseases.

Although quercetin is a well-studied dietary flavonoid, its poor oral absorption limits its clinical applications. Quercetin Phytosome™ (Quercefit™) is a new delivery technology that uses a lecithin-based phospholipid matrix to disperse quercetin. This breakthrough food-grade phytosome technology boosts quercetin solubility by approximately 11-fold, improving absorption, stability, and tolerance and increasing systemic availability. Compared with its unformulated counterpart, the quercetin phytosome formulation showed significantly increased plasma levels and bioavailability in healthy individuals. Numerous clinical trials have explored the therapeutic potential of quercetin phytosomes in allergic, inflammatory, and metabolic conditions. Supplementation improved respiratory metrics, symptom ratings, and quality of life in patients with allergic asthma and rhinitis, with higher doses being more beneficial. Further research has shown that quercetin phytosomes reduce capillary permeability, aid recovery, and decrease oxidative stress in athletes.[187–190]

A systematic review and meta-analysis of 13 randomised controlled trials (823 patients) indicated that polyphenolic compounds, such as catechins and quercetin, may help in the treatment of allergic rhinitis. In seasonal allergic rhinitis, these compounds improved total nasal symptom scores (SMD = 0.75, $p = 0.0001$), reduced sneezing (SMD = 0.58, $p = 0.0042$), and alleviated nasal itching (SMD = 0.54, $p = 0.011$). Perennial allergic rhinitis also showed significant improvement, although symptom consistency varied. The pooled analyses indicated significant reductions in nasal symptoms; however, evidentiary confidence was low owing to trial heterogeneity. Quality of existence did not improve noticeably. Although polyphenolic compounds may serve as adjunctive therapies, further high-quality trials are required to confirm these findings and determine the optimal dosage.[191]

Fermented red ginseng has potential advantages for the management of perennial allergic rhinitis. A 4-weeks, double-blind, placebo-controlled trial involving 59 patients demonstrated that supplementation with fermented red ginseng significantly improved nasal congestion ($p < 0.005$), enhanced quality of life scores pertaining to activity and emotion ($p < 0.05$), and reduced skin reactivity to perennial allergens ($p < 0.05$), whereas placebo exhibited no effect. Although no significant difference was observed in total nasal symptom scores (TNSS) overall, the results suggest that fermented red ginseng may provide targeted relief, especially for nasal congestion, and demonstrate good tolerability.[192]

A recent interventional, perspective, multicentre, randomised, open-label, controlled clinical trial assessed the efficacy of Respicure® (a phytotherapeutic formulation containing

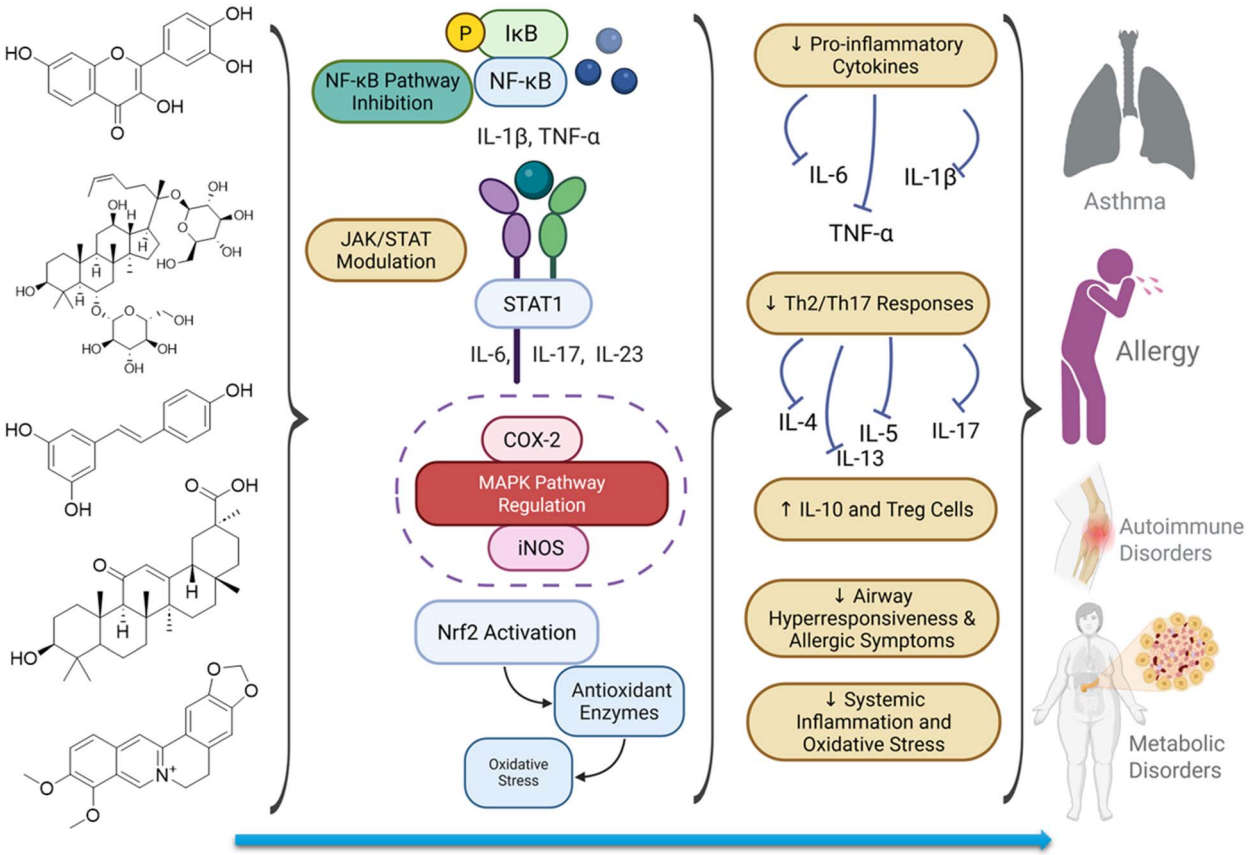

Fig. 7 Schematic representation of the mechanisms by which bioactive compounds modulate IL-mediated immune pathways. Flavonoids, non-flavonoid polyphenols, terpenoids, saponins and alkaloids act on key signalling cascades, including NF-κB, JAK/STAT, MAPK, and Nrf2, leading to the suppression of pro-inflammatory cytokines (IL-1β, IL-6, IL-17, and TNF-α) and enhancement of anti-inflammatory mediators (IL-10 and Treg activation). These actions collectively reduce oxidative stress, restore immune homeostasis, and mitigate inflammation-related conditions such as asthma, allergy, autoimmune disorders, and metabolic syndromes.

0.38% resveratrol and 0.38% quercetin) as an adjunct treatment for respiratory conditions, including partially controlled asthma, chronic obstructive pulmonary disease (COPD; stages A–D), and long COVID in Algerian adults. The trial enrolled 480 patients from eight centres who were randomised into two parallel groups: a control group receiving standard care and an intervention group receiving normal care plus Respicure®. The participants underwent five scheduled visits over 180 days, accompanied by regular safety evaluations and the ongoing provision of the research product for the intervention group. The results demonstrated improvements in the respiratory symptoms, inflammatory markers, and comprehensive disease management. This study underscores the potential clinical significance of bioactive substances such as resveratrol and quercetin as adjunctive treatments for chronic inflammatory respiratory disorders.[193]

Nickel (Ni)-induced allergic contact dermatitis (ACD) is a common hypersensitivity disorder characterised by symptoms, such as epidermal barrier disruption, urticaria, itching, and inflammation triggered by nickel exposure. A recent study explored the immunomodulatory effects of polyphenols from red grape seeds (Nero di Troia cultivar, marketed as NATUR-OX®) in patients with Ni-induced ACD. *In vitro* studies have shown that polyphenol supplementation reduces pro-inflammatory cytokines, including Th1-derived IFN-γ and Th2-derived IL-4, as well as decreases IL-17 and nitric oxide production. In contrast, levels of the anti-inflammatory cytokine IL-10 were significantly elevated. This study aimed to further validate these findings through the oral administration of polyphenols in a placebo-controlled trial to assess their ability to restore immune homeostasis. These results suggest that grape seed polyphenols mitigate Ni-induced inflammatory responses by modulating cytokine production and oxidative stress, indicating their potential role as dietary adjuncts in the management of ACD.[194]

Emerging clinical evidence supports the therapeutic potential of bioactive compounds to treat allergic diseases and modulation of the immune system. Here, several representative examples are highlighted. Clinical investigations suggest that these substances may help reduce pro-inflammatory cytokine levels, restore Th1/Th2/Th17 equilibrium, and enhance immunological coordination. However, contemporary research continues to disclose only a fraction of the potential inherent to this domain. Most investigations are preclinical or involve small-scale clinical trials, necessitating the completion of large-scale randomised controlled clinical trials. Moreover, issues

such as limited bioavailability, inter-individual heterogeneity in responses, and optimal dosage are significant concerns. Consequently, whereas the present findings are promising, additional well-designed and rigorously conducted clinical studies are required to validate the efficacy and safety of these compounds and to integrate them into established treatment protocols for allergic and immunological disorders.

9. Future directions of bioactive compound development for allergy treatment

Current evidence indicates that naturally occurring flavonoids, such as quercetin and luteolin, may have significant potential in the treatment of allergic and inflammatory disorders. Numerous investigations of these compounds suggest that they diminish pro-inflammatory cytokine levels, including IL-6, IL-1β, and TNF-α, while inhibiting histamine release from mast cells, thereby alleviating allergic symptoms. Nonetheless, comprehensive clinical trials are limited, highlighting the need for extensive and high-quality studies to ascertain efficacy and optimal dosage. Polyphenols, including resveratrol, curcumin, and epigallocatechin gallate (flavonoid), have been shown to significantly modulate the immune system by influencing signalling pathways, such as NF-κB, MAPK, and Nrf2. These compounds mitigate inflammation and protect cells from oxidative damage through antioxidant mechanisms. Future studies should investigate new methodologies, such as nanoformulations or phytosome technology, to enhance the bioavailability of these compounds, augmenting their efficacy in clinical practice.

Terpenoids, including astragaloside IV, ursolic acid, glycyrrhizic acid, and ginsenosides, have been shown to transition the immune system from a Th2-dominant profile to a Th1 or Treg response in allergic and asthma models, facilitating long-term immunological tolerance. These compounds can be integrated into vaccine adjuvants or immunotherapies to provide novel therapeutic strategies for enduring outcomes in patients with allergic diseases and asthma. Alkaloids, such as protopine and benzoylmesaconine, attenuate inflammation by blocking the NF-κB and TLR4 signalling pathways and suppressing activation of the NLRP3 inflammasome. These compounds also diminish metabolic and oxidative stress, rendering them promising candidates for multi-targeted therapies. Before they are introduced as pharmaceuticals, extensive research on their toxicological effects, dosage safety, and pharmacokinetic profiles is essential. These natural bioactive compounds represent promising advances in the treatment of allergic and immunological disorders. With a focus on extensive clinical trials, systematic pharmacological investigations, and advanced drug delivery systems, these compounds may be integrated into clinical practice as safe and effective therapeutics, serving as reliable alternatives or complements to traditional treatments.

This review highlights that bioactive compounds from natural sources offer a robust scientific foundation for the treatment of allergic- and immune-related disorders. These compounds not only inhibit key inflammatory cytokines (IL-4, IL-5, IL-13, TNF-α, *etc.*) but also facilitate the restoration of the Th1/Th2/Th17 equilibrium, diminish mast cell degranulation, and modulate signalling pathways, including NF-κB, MAPK, and STAT3. Their antioxidant and immunomodulatory properties make them safe and effective alternatives or complementary approaches to conventional therapies. Nonetheless, most research in this domain remains preclinical or limited to clinical trials. Thus, extensive randomised controlled clinical studies, pharmacokinetic and pharmacodynamic assessments, improved bioavailability, and precise dosing are required for the translation of these natural compounds into dependable and clinically feasible therapies.

Moreover, subsequent research should concentrate on AI-driven technologies and computational approaches to accelerate the discovery and clinical application of these bioactive molecules. Predictive modelling using machine learning, network pharmacology, and systems biology can examine multi-target interactions, identify synergistic combinations, and predict patient-specific responses in allergies and immune-mediated disorders. Molecular docking, molecular dynamics simulations, and *in silico* ADMET screening can enhance compound selection and prioritize those with favourable pharmacokinetic and safety characteristics before *in vivo* testing. The design of AI-assisted drug delivery, including the development of nanoformulations, phytosomes, and targeted delivery systems, can markedly enhance the bioavailability and therapeutic efficacy of flavonoids, polyphenols, terpenoids, and alkaloids. The integration of computational metabolomics and transcriptomics elucidates individual variations in immune responses and enhances precision medicine methodologies. These methods, in conjunction with rigorous clinical trials, standardized formulations, and comprehensive toxicity evaluations, can significantly facilitate the progression of natural substances as clinically reliable therapies for allergic and immunological disorders.

10. Conclusions

We carefully documented most bioactive compounds, such as flavonoids, polyphenols, terpenoids, and alkaloids, which present a significant opportunity to influence interleukin-mediated pathways in the treatment of allergic diseases and immunological disorders. These compounds exhibit anti-inflammatory and Th2-suppressive effects, potentially providing enhanced safety compared with synthetic options. Targeting key interleukins, these natural metabolites exhibit significant therapeutic potential, as evidenced by their binding affinity and efficacy in preclinical models. However, achieving complete clinical potential necessitates addressing challenges, such as inadequate bioavailability, formulation instability, and the requirement for comprehensive human trials. Future research should focus on optimising delivery systems and conducting translational studies to utilise these compounds as novel, nature-inspired approaches for immune regulation and allergy treatment.

11. Author contributions

KYL and ABS originally proposed the highlight and jointly wrote the manuscript; YJK and KSL collated references and jointly

wrote the manuscript; SHH and YB commented on and enhanced the manuscript.

12. Conflicts of interest

There are no conflicts to declare.

13. Data availability

No primary research results, software or code have been included, and no new data were generated or analyzed as part of this review.

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