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Targeting PI3K/AKT signaling pathway to treat allergic asthma: Pathogenesis, mechanism, and treatment with traditional Chinese medicine and its components

Jiamao Wang, Qitong Zheng, Yiqing Shi, Mengyao Chen, Xia'nan Sang*, Gang Cao*

School of Pharmacy, Zhejiang Chinese Medical University, Hangzhou, China

Abstract

Traditional Chinese medicine and its bioactive components have garnered increasing attention as potential therapeutic options for allergic asthma. By targeting the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway, these natural compounds exhibit unique advantages in multilevel immunomodulation and inflammation suppression compared with single-target synthetic drugs. Accumulating pharmacological evidence supports their capacity to restore pathway homeostasis, positioning them as promising candidates for complementary strategies in asthma management. Allergic asthma, a heterogeneous respiratory disorder affecting approximately 150 million individuals worldwide, arises from a complex interplay of genetic predisposition, environmental exposures, and lifestyle factors. Its pathological progression is marked by aberrant activation of the PI3K/AKT signaling cascade, with the mechanistic target of rapamycin serving as a key downstream regulatory node. This evolutionarily conserved pathway orchestrates fundamental cellular processes that contribute to three hallmark pathological features of allergic asthma: chronic airway inflammation, structural remodeling of the bronchial architecture, and airway hyperresponsiveness. This review has 3 primary objectives: (1) to evaluate the role of the PI3K/AKT pathway in allergic asthma pathogenesis, (2) to analyze the molecular mechanisms of representative traditional Chinese medicine preparations and their active ingredients, and (3) to identify novel bioactive inhibitors derived from natural products. Collectively, these investigations provide a conceptual framework for the development of next-generation targeted therapies and for optimizing clinical management strategies for allergic asthma.

Key words: AKT; Allergic asthma; Inflammation; PI3K; Traditional Chinese medicine

1. Introduction

Allergic asthma represents the most prevalent clinical phenotype of asthma, with epidemiological data consistently showing a long-term upward trend in both incidence and prevalence.[1] Its complex etiopathogenesis, encompassing numerous immunological and structural alterations, continues to pose significant challenges to therapeutic development. Consequently, patients often face substantial treatment-related clinical and economic burdens. Current guidelines recommend corticosteroids, phosphodiesterase-4 inhibitors, and β2-agonists as cornerstone therapies. However, their clinical use is frequently limited by off-target effects, including iatrogenic bone loss, gastrointestinal dysfunction, and cardiovascular autonomic dysregulation.[2-4] Therefore, the development of safer and more effective interventions is imperative.[5] The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway plays a central role in regulating diverse physiological processes across multiple tissue types and has emerged as a critical focus in the study of allergic asthma pathophysiology and pharmacology.[6] Traditional Chinese medicine (TCM), composed primarily of natural plant–derived products, has a long history of use in asthma management. Its holistic, multitarget approach makes it a promising avenue for novel drug development. Numerous TCM-derived compounds targeting the PI3K/AKT pathway have been identified and applied therapeutically.[7–10] To advance the development of more effective therapies for allergic asthma, this review searched PubMed, Web of Science, and China National Knowledge Infrastructure for studies related to the targeting of PI3K/AKT signaling pathway by TCM and its active ingredients for the treatment of allergic asthma. The search period is concentrated from 2010 to 2025. Keywords included "allergic asthma," "asthma," "PI3K," with "herbal medicine," "herbs," "traditional Chinese medicine," and "active ingredients of Chinese medicine." All the collected information was then summarized to analyze the pathomechanisms and therapies for targeting the PI3K/AKT signaling pathway for the treatment of allergic asthma. Furthermore, from the perspective of integrated treatment, particularly the integration of conventional and traditional approaches, this work offers a comprehensive evaluation of the PI3K/AKT pathway in allergic asthma, addressing its etiology, underlying mechanisms, and treatment strategies.

*Corresponding Author: Xia'nan Sang, School of Pharmacy, Zhejiang Chinese Medical University, 548 Binwen Road, Hangzhou 310053, China. E-mail: xnsang881014@163.com (X. Sang). Gang Cao, School of Pharmacy, Zhejiang Chinese Medical University, 548 Binwen Road, Hangzhou 310053, China. E-mail: caogang33@163.com (G. Cao).

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Jiamao Wang and Qitong Zheng contributed to the work equally and should be regarded as co-first authors.

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2. Characteristics of allergic asthma

Asthma is a chronic respiratory disease driven by airway inflammation. This inflammatory environment contributes to a range of interconnected pathophysiological abnormalities, including airway hyperresponsiveness (AHR), eosinophilic infiltration, mucus hypersecretion accompanied by goblet cell hyperplasia, subepithelial fibrosis, and other features of airway remodeling, as well as partially reversible airflow obstruction.[11] Major allergic triggers, or allergens, include pollen, dust mites, microorganisms (bacteria and viruses), and certain drugs or foods. Collectively, these factors contribute to disease development as integral components of its pathogenic process.[12] In allergic asthma, genetic and environmental triggers coordinate the activation and regulation of the immune system, serving as central drivers of disease pathophysiology. Key cellular contributors include dendritic cells (DCs), T cells, B cells, innate lymphoid type-2 cells (ILC2s), T-helper (Th) cell subsets such as Th1/Th2 and Th17/regulatory T (Treg), eosinophils, basophils, neutrophils, and mast cells (MCs) infiltrating the bronchial submucosa. These cells are primarily responsible for chronic airway inflammation.[13,14] In turn, they secrete various cytokines and growth factors that promote goblet cell proliferation, airway smooth muscle (ASM) hypertrophy, and deposition of collagen and fibronectin (Fig. 1).[15,16]

3. Molecular mechanisms of the PI3K/AKT

Functioning as a pivotal cellular signaling cascade, PI3K regulates a broad spectrum of critical processes involved in cell-cycle control and pathophysiological mechanisms.[17] The canonical PI3K/AKT pathway is initiated by PI3K-mediated phosphorylation of phosphatidylinositol lipids, leading to the recruitment and activation of AKT at the plasma membrane. Activated AKT regulates diverse cellular processes, including phosphorylation of cyclic adenosine monophosphate response element-binding protein (CREB), inhibition of p27, cytosolic retention of forkhead box O (FOXO) transcription factors, generation of phosphatidylinositol 3-phosphate, and activation of the mechanistic target of rapamycin (mTOR).[18,19] In the context of asthma pathogenesis, PI3K orchestrates inflammatory responses through direct activation by focal adhesion kinase. This activation occurs via receptor tyrosine kinase dimerization, phosphorylation, and growth factor-mediated signaling, which promotes interactions with the SH2 domain of the p85 regulatory subunit. As a result, PI3K triggers downstream signaling cascades involving transforming growth factor-beta (TGF-β), nuclear factor-κB (NF-κB), rat sarcoma/rapidly accelerated fibrosarcoma pathways, and epithelial–mesenchymal transition (EMT), while also facilitating the recruitment and activation of AKT and phosphoinositide-dependent kinase.[20,21]

The PI3K/AKT/mTOR axis is a central regulator of metabolic processes in both immune and nonimmune cells. Within this pathway, the mTOR, a serine/threonine (Ser/Thr) kinase, functions as a key downstream effector. Specifically, the mTOR signaling network exerts regulatory control over the differentiation and functional programming of innate and adaptive immune cells.[22] This pathway integrates diverse intracellular and extracellular cues, including growth factors, cytokines, nutrient availability, adenosine 5'-triphosphate levels, cellular stress, and inflammatory signals, translating these inputs into metabolic and functional adaptations.[23,24] Mechanistic studies indicate that mTOR complex 1 (mTORC1) activation depends on upstream PI3K signals, which converge primarily

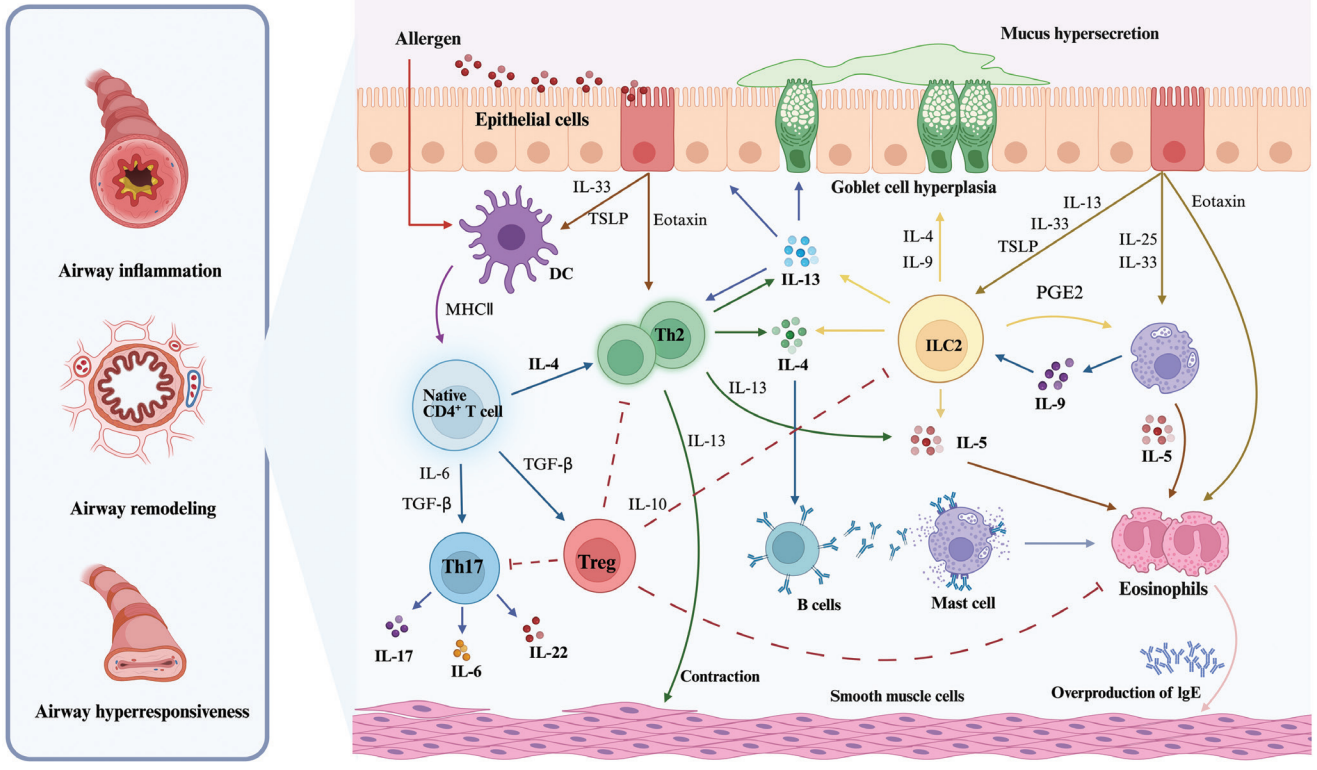

Figure 1. Immunomodulatory mechanisms in allergic asthma (Figure created using BioRender.com). Asthma is a chronic inflammatory airway disease characterized by airway and blood eosinophilia, mucus hypersecretion, goblet cell hyperplasia, and AHR. The airway epithelium, a key component of the innate immune system, initiates airway remodeling by releasing cytokines such as thymic stromal lymphopoietin (TSLP), IL-33, IL-25, and eotaxin upon injury or activation. These mediators recruit and activate dendritic cells to present allergens, coordinating the activity of various immune cells in asthma. Solid lines indicate promotion, whereas dashed lines indicate inhibition.

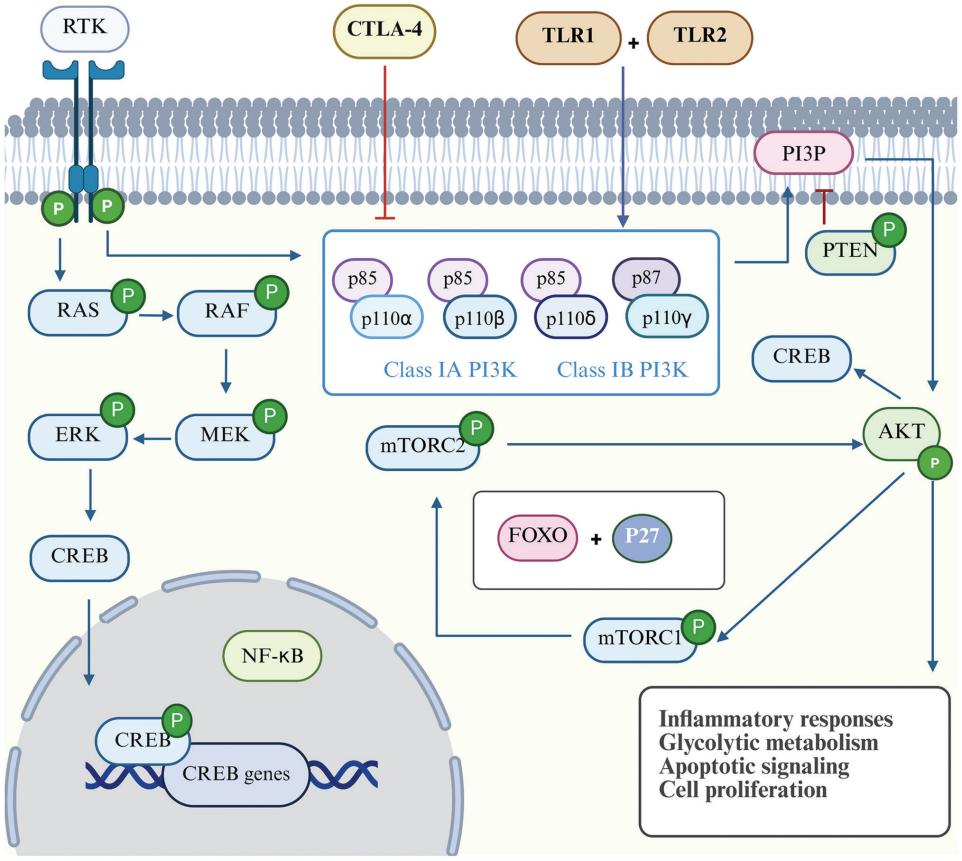

Figure 2. PI3K/AKT signaling pathway and its upstream and downstream influences (Figure created using BioRender.com). Activation of receptors such as RTK, CTLA-4, and TLR initiates PI3K signaling (class IA and IB), leading to phosphorylation and activation of AKT. AKT regulates downstream effectors, including mTORC1, mTORC2, FOXO, P27, CREB, and NF-κB, thereby modulating cellular processes such as inflammation, glycolytic metabolism, apoptosis, and cell proliferation. Furthermore, RTK can activate CREB through the RAS-RAF-MEK-ERK pathway, influencing CREB-mediated transcription. PTEN serves as a negative regulator by dephosphorylating the lipid second messenger PI3P. Solid lines indicate promotion, and dashed lines indicate inhibition. RAS-RAF, rat sarcoma-rapidly accelerated fibrosarcoma.

through the PI3K/AKT axis. mTOR operates through 2 discrete multiprotein complexes, mTORC1 and mTOR complex 2 (mTORC2), which serve as critical hubs within the downstream PI3K signaling network.[25] The coordinated phosphorylation of mTORC1 and mTORC2 is regulated by phosphoinositide-dependent kinase-1, which facilitates AKT phosphorylation at Ser308 and Thr473 residues. Notably, mTORC1 contributes to partial AKT activation and indirectly modulates mTORC2 activity, whereas mTORC2-mediated phosphorylation fully activates AKT.[26] This hierarchical regulation influences multiple cellular processes, including inflammatory responses, glycolytic metabolism, apoptotic signaling, and proliferation, largely through suppression of FOXO1/3a transcription factors.[27] Moreover, AKT-mediated upregulation enhances PI3K lipid kinase activity via RAS-guanosine triphosphate-binding protein interactions.[28] As a central downstream effector of the PI3K/AKT pathway, mTOR plays a pivotal role in asthma pathogenesis by modulating both immune cell activity and structural pulmonary cells, thereby contributing to airway inflammation and remodeling. Specifically, mTOR integrates upstream signals through mTORC1 and mTORC2 to coordinate cellular proliferation, metabolism, survival, and protein synthesis.[29] Studies have demonstrated that hyperactivation of mTORC1 in airway epithelium enhances fibroblast growth factor-binding protein 1 expression via upregulation of signal transducer and activator of transcription 3, promoting angiogenesis and extracellular matrix reorganization, which exacerbates airway remodeling.[30]

The PI3K pathway engages in extensive crosstalk with multiple molecular mechanisms. Immune checkpoint receptors, including cytotoxic T-lymphocyte-associated protein 4 and programmed death protein 1, inhibit the PI3K/AKT/mTOR axis, thereby reducing interleukin (IL)-2 production.[31] In contrast, metabolic reprogramming induced by Toll-like receptor (TLR)-driven PI3K/AKT/mTORC1 signaling enhances the expansion of Treg cells in the tumor microenvironment.[32] Beyond immune modulation, Sirtuin 1 (SIRT1) counteracts *Toxoplasma gondii*-induced FOXO1 activation through PI3K/AKT-mediated mechanisms.[33] In asthma pathogenesis, the OX40/OX40L interaction modulates helper T-cell differentiation through coordinated engagement of the PI3K/AKT and p38 mitogen-activated protein kinase (MAPK) signaling cascades. Therapeutic blockade of this costimulatory pathway suppresses $CD4^+$ T-cell proliferation and alters Th polarization profiles.[34] Additionally, accumulating evidence implicates the PI3K/AKT pathway in regulating the proliferation of ASM cells (ASMCs) in asthma, highlighting its potential as a therapeutic target (Fig. 2, Table 1).[35]

4. Influence factors of inflammatory response in allergic asthma

In allergic asthma, the well-established role of PI3K in modulating inflammatory processes extends to multiple downstream cellular signaling cascades. A comprehensive understanding of the disease, therefore, requires systematic investigation of the broader cellular network influenced by allergic asthma. This includes elucidating the roles of key immune effectors that interact with PI3K through synergistic or feedback mechanisms,

Table 1

Roles and functions of the PI3K/AKT signaling pathway in allergic asthma.

Signaling pathway	Function	Result
PI3K/AKT/FOXO1	Activate the pathway, inhibit FOXO1 activity, inhibit Dendritic cells maturation, reduce IL-12 secretion	Reduce fiber inflammation[36]
PI3K/AKT/mTOR	Blocking the pathway, saving autophagy, and reducing the accumulation of p62 and LC3	Increased autophagy and anti-inflammatory effects[37]
PI3K/AKT/eNOS	Activate the pathway and inhibit the gene expression of IL-1β, IL-6, and TNF-α, and the expression of VEGF	Anti-inflammation[38]
PI3K/AKT/NF-κB	Activation of the blocking pathway in ILC2 recruitment	Inhibit allergic airway inflammation[39]
TLR2/PI3K/AKT	The expression of PI3K, p-AKT, Beclin-1, and LC3-II was down-regulated, which alleviated inflammatory cell infiltration and IL-13/IFN-γ imbalance	Regulate related autophagy. Blocking the pathway reduces inflammation[40]
AMPK/PI3K/AKT/p38/NF-κB	Blocking the pathway and inhibiting the expression of TGF-β	Reduced airway inflammation and increased bronchial hyperresponsiveness[41]
p-AKT/p-PI3K/HIF-1α/VEGF	Downregulation pathway	Reduce airway inflammation[42]

VEGF, vascular endothelial growth factor.

including, but not limited to, MCs, ILC2s, Th2 cells, eosinophils, and DCs.[43]

4.1. Mediated mechanisms of DCs in allergic asthma

As professional antigen-presenting cells, conventional DCs, derived from progenitor cells of the macrophage-DC lineage in the bone marrow, play a pivotal role in bridging innate and adaptive immunity by capturing and presenting antigens to T lymphocytes. These immune sentinels reside in peripheral, non-lymphoid tissues, where they continuously monitor their environment by internalizing both self and foreign antigens via endocytic mechanisms.[44] Upon antigen capture, DCs degrade internalized proteins into peptide fragments, which are then loaded onto major histocompatibility complex (MHC) class II molecules for surface presentation—an essential step for T-cell activation. While immature DCs are relatively inefficient at antigen presentation, they undergo maturation upon encountering danger signals, such as pathogen-associated molecular patterns or damage-associated molecular patterns. This transition enhances the assembly and transport of MHC–peptide complexes to the plasma membrane,[45] establishing DCs as the most efficient antigen-presenting cells, outperforming macrophages in this function. Concurrently, they migrate from peripheral tissues to secondary lymphoid organs, where they prime naive T and B cells through MHC class II-mediated antigen presentation, thereby initiating a specific adaptive immune response.[46] Owing to their central role in immune regulation, DCs are important therapeutic targets in diseases characterized by immune dysregulation. Evidence indicates that PI3K-δ modulates TLR4 signaling in DCs by facilitating its internalization from the cell membrane. This activity restrains excessive pro-inflammatory cytokine production, highlighting a homeostatic function for PI3K-δ in DCs.[47] Furthermore, PI3K-δ is implicated in DC-mediated allergic inflammation. For example, in patients with allergic rhinitis, inhibition of PI3K-δ markedly reduces levels of the DC-derived chemokines C-C motif chemokine ligand 17 (CCL17) and CCL22, which are critical for Th2 cell recruitment, suggesting that PI3K-δ modulates allergic inflammation via DC-dependent pathways.[48]

4.2. Functions of the MC degranulation in allergic asthma

MC degranulation, a central event in allergic reactions, can be initiated via 2 principal mechanisms. The first is immunoglobulin (Ig) E-independent, involving stimulation of the Mas-related G protein-coupled receptor X2 (MRGPRX2). The second is IgE-dependent and requires binding of allergen–IgE complexes to the high-affinity IgE receptor (FcεRI) on MCs.[48,49]. Secreted by plasma cells, IgE belongs to one of the five canonical Ig classes, distinguished by the structure of its constant Fc domains. The Fc domain determines effector functions and cellular specificity, whereas the variable Fab region confers antigen-binding diversity, enabling adaptive immune responses.[50]

Upon initial allergen exposure, MC activation through FcεRI engagement induces phosphorylation of phospholipase C-γ1 (PLC-γ1), resulting in elevated intracellular calcium levels and subsequent degranulation. The PI3K/AKT pathway contributes to MC regulation, in part through its interplay with PLC-γ1. Signaling via MRGPRX2 has also been shown to modulate calcium mobilization and degranulation through coordinated activation of the PI3K/AKT and PLC-γ1 pathways.[51] Additionally, silibinin suppresses MC degranulation, calcium influx, and cytokine release in a dose-dependent manner by inhibiting both the PLC-γ1 and PI3K/AKT pathways.[52]

Beyond its role in inflammatory mediator secretion, PI3K/AKT activation regulates cytoskeletal dynamics in MCs. The binding of IL-33 to its cognate receptor ST2 triggers MC activation and promotes the production of pro-inflammatory cytokines. This response depends on the integrated activation of multiple signaling pathways, notably NF-κB, p38 MAPK, and the MK2/3–PI3K/AKT axis. Within this network, NF-κB functions as a master transcriptional regulator driving the expression of inflammation-related genes. Simultaneously, p38 MAPK and its downstream effectors MK2/3 enhance inflammatory signaling by modulating mRNA stability and translational control. Meanwhile, these effectors engage in functional crosstalk with the PI3K/AKT pathway, which is crucial for cellular metabolism and survival. Notably, the phytopolyphenol resveratrol exerts a targeted inhibitory effect on this signaling cascade by suppressing the MK2/3–PI3K/AKT axis downstream of p38. This intervention effectively reduces both IL-33/ST2- and IgE-mediated MC degranulation and subsequent release of inflammatory mediators.[53]

4.3. PI3K plays an essential role in adaptive immune responses involving T cells and B cells

Different isoforms of PI3K regulate distinct cellular processes. Among these, PI3K-δ is the predominant isoform in T cells and has been extensively studied using both genetic mouse models and selective inhibitors. The p110δ catalytic subunit of PI3K-δ

is highly expressed in leukocytes and plays critical roles in both cellular and humoral immune responses. In the thymus, p110δ and p110γ cooperate to promote T-cell development through key developmental checkpoints. Beyond thymic development, p110δ regulates the differentiation of peripheral $CD4^+$ T cells into Th1 and Th2 subsets and modulates Treg cell function.[54]

The PI3K signaling pathway plays a critical role in orchestrating the expansion, differentiation, and spatial distribution of helper T cells. It supports T-cell activation, differentiation, and trafficking, and is essential for T-cell adhesion and migratory behaviors. Specifically, the PI3K-δ isoform modulates T-cell trafficking into and out of lymph nodes and regulates their recruitment and persistence at sites of inflammation. This precise control of cell movement is primarily mediated through PI3K-dependent modulation of integrin activation in T cells.[55] Activation of p110δ downstream of the T-cell receptor is also required for proper localization of T cells to antigen-rich tissues in murine models.[56] Beyond T cells, the PI3K pathway is a key regulator of multiple aspects of B lymphocyte function, including development, proliferation, differentiation, antibody class switching, and secretion. The PI3K-δ isoform, predominantly expressed in hematopoietic cells, exerts distinct immunomodulatory effects. In allergic settings, both genetic ablation and pharmacological inhibition of PI3K-δ enhance Ig class switching to IgE *in vivo*, despite concurrently reducing type 2 cytokine secretion and IgG antibody levels. This apparent paradox highlights a previously underappreciated homeostatic role of PI3K-δ in limiting IgE responses by negatively regulating signals that promote IgE class switching in B cells. These findings underscore the complex role of PI3K-δ in allergic inflammation and emphasize its dual potential as a therapeutic target for IgE-mediated allergic disorders, providing a basis for more precise immunomodulatory strategies.[57]

4.4. Th2 immunity and ILC2 cooperate with PI3K to affect asthma

In susceptible individuals, exposure to harmless environmental antigens triggers a classical adaptive immune response orchestrated by Th2 cells, which differentiate in lymphoid tissues and subsequently secrete type 2 cytokines.[58] The pathophysiology of type 2 inflammation is driven by the interplay between innate immune mechanisms and adaptive immune responses initiated by allergen-specific Th2 cell differentiation.[59] Both ILC2s and Th2 cells secrete type 2 cytokines (IL-4, IL-5, and IL-13), which exert distinct yet complementary effects in promoting inflammatory responses. In classical allergic airway inflammation, DC-primed Th2 cells coordinate eosinophil infiltration and AHR through the production of these cytokines. Specifically, IL-4 and IL-13 mediate B-cell class switching to IgE, stimulate the release of pro-inflammatory mediators, disrupt epithelial barrier integrity, and drive tissue remodeling. IL-13 additionally induces goblet cell hyperplasia and mucus hypersecretion. Collectively, these cytokines facilitate eosinophil recruitment to tissues, contributing to the hallmark pathology of chronic airway inflammatory diseases.[60]

Notably, IL-13 plays a predominant role in mucus overproduction and AHR, whereas IL-5 is critical for eosinophil activation, survival, and migration into the respiratory tract, contributing to eosinophilic bronchitis. IL-4 has a dual function in allergic sensitization: it promotes IgE class switching in B cells and enhances FcεRI expression on MCs and other effector cells. Subsequent allergen-mediated cross-linking of IgE bound to FcεRI triggers MC activation, resulting in the rapid release of histamine and other preformed mediators responsible for immediate hypersensitivity reactions.[61]

The modulatory role of PI3K in type 2 immunity indicates that PI3K-δ may substantially influence Th2-polarized responses at the airway epithelial barrier.[62] The engagement of pattern recognition receptors triggers the release of alarmins, which in turn activate DCs, ILC2s, and basophils, promoting DC migration to draining lymph nodes and the initiation of adaptive immune responses. Furthermore, IL-33-mediated activation of Th2 cells and ILC2s has been shown to rely on PI3K-δ signaling within these cell populations.[63]

Emerging evidence indicates that airway epithelial PI3K-δ regulates mitochondrial reactive oxygen species production, thereby promoting Th2-type eosinophilic inflammation. Additionally, PI3K contributes to vasodilation, increased vascular permeability, and plasma extravasation—hallmark processes of allergic airway inflammation. For instance, studies indicate that PI3K-δ in epithelial cells drives the development of allergic lung pathology by modulating the production of inflammatory mediators, including hypoxia-inducible factor (HIF)-1α and vascular endothelial growth factor.[64]

Although ILC2s do not recognize antigens via classical adaptive immune mechanisms, they respond to microenvironmental cues derived from epithelial and immune cells. Unlike classical adaptive immune cells, group 2 ILC2s are directly activated by cytokines released from epithelial cells, rapidly secreting type 2 cytokines in response. Notably, ILC2 activation occurs independently of antigen presentation and T-cell receptor engagement, highlighting their role as effector cells in nonallergic asthma exacerbations and virus-induced asthma attacks.[65] These cells are now recognized as key effectors in allergic airway inflammation. Allergen-derived proteases or environmental insults, such as pollutants and viruses, induce epithelial damage and trigger the release of alarmins, which in turn stimulate ILC2s to secrete Th2-type cytokines.[66] Furthermore, ILC2s are responsive to lipid mediators, including prostaglandin D_2 and cysteinyl leukotrienes.

Collectively, Th2 cytokines orchestrate the hallmark features of allergic asthma, including pronounced eosinophilic infiltration of mucosal tissues, epithelial barrier dysfunction, and the release of cytotoxic granules by eosinophils, which further amplify alarmin production and sustain a chronic inflammatory loop. Airway eosinophilia, defined as ≥3% eosinophils in sputum,[67] serves as a key biomarker of this response. The resulting pathophysiological consequences include variable airflow obstruction, bronchial hyperresponsiveness, and mucus hypersecretion. Accordingly, targeting regulatory nodes that disrupt this self-amplifying cycle—such as the PI3K pathway, which modulates both adaptive Th2 responses and eosinophilic inflammation—represents a promising therapeutic strategy for type 2-mediated allergic diseases.[68]

4.5. PI3K pathway in the epithelium affects airway remodeling

Airway remodeling, a hallmark structural change in asthma, results in airway wall thickening and impaired airflow. Its manifestations include upregulation of angiogenic factors, goblet cell chemotaxis, hyperplasia and hypertrophy of ASM, subepithelial deposition of matrix proteins and fibrosis, and accumulation of extracellular matrix proteins within the reticular basement membrane, lamina propria, and submucosa.[69] As a central component of the innate immune response, the airway epithelium plays an initiating role in this remodeling process. Exposure to harmful exogenous or endogenous agents triggers a cascade that begins with epithelial disruption and activation, ultimately leading to cytokine-mediated recruitment and activation of immune cells that drive airway remodeling and AHR.[70]

Multiple molecular mechanisms underlie the close association between PI3K signaling and endoplasmic reticulum (ER) stress. Moreover, due to the tight functional coupling between the ER and mitochondria, PI3K signaling may also affect

mitochondrial function, thereby modulating oxidative stress and impacting various lung pathophysiological processes. For example, studies indicate that PI3K can mitigate glucocorticoid (GCS)-resistant eosinophilic pneumonia induced by fungi by reducing ER stress and mitochondria-related oxidative stress—particularly in airway epithelial cells—resulting in reduced airway wall thickening and improved airflow.[71]

Studies show that in the airway epithelium, PI3K-δ partially regulates the NOD-LRR (a large number of Nods contain leucine-rich repeats, hence referred to as NOD-LRR proteins) and pyrin domain-containing protein 3 (NLRP3) activation via mitochondrial reactive oxygen species, thereby playing a significant role in the development of GCS-resistant eosinophilic lung inflammation.[72] These findings reveal that cytoplasmic complexes involving ER stress, PI3K-δ, and NLRP3 activation provide novel mechanistic insights into PI3K-driven asthma pathogenesis, with important implications for the treatment of severe disease.[73]

5. Regulation of the PI3K/AKT for treating allergic asthma

The PI3K/AKT pathway serves as a central regulator of numerous cellular processes and is widely recognized as a promising therapeutic target for various human diseases. Over recent decades, growing evidence has highlighted its critical involvement in allergic asthma, prompting the development and clinical investigation of multiple therapeutic agents targeting this pathway, including natural products derived from TCM. Research on PI3K/AKT-targeted therapies for allergic asthma is promising and warrants further exploration (Fig. 3).

5.1. Natural products for regulating the PI3K/AKT

The successful clinical application of artemisinin, recognized by the 2015 Nobel Prize in Physiology or Medicine, has revitalized scientific and clinical interest in natural products, particularly Chinese herbal compounds, as promising sources for therapeutic development. A growing body of research suggests that natural products, including Chinese herbal compounds, can inhibit multiple signaling pathways associated with inflammatory responses, many of which are closely linked to the PI3K/AKT pathway.[74]

5.1.1. Alpinetin

Alpinetin, a natural flavonoid derived from the Zingiberaceae family, has been widely used in Chinese patent medicines. It exhibits multiple biological activities, including antitumor, anti-inflammatory, and hepatoprotective effects, largely through the regulation of various signaling pathways.[75] Studies have shown that alpinetin significantly alleviates ovalbumin (OVA)-induced pulmonary pathology. Administration of alpinetin markedly reduces levels of Th2 cytokines, suppresses IgE-mediated phosphorylation of NF-κB p65, phosphorylated AKT (p-AKT), and phosphorylated PI3K (p-PI3K), and inhibits heme oxygenase-1 activity.[76] Further investigations reveal that alpinetin effectively downregulates the production of pro-inflammatory mediators, such as tumor necrosis factor-α (TNF-α), IL-6, and IL-1β, by inhibiting the PI3K/AKT/NF-κB signaling pathway. As a result, alpinetin prevents the accumulation of inflammatory cells in alveolar spaces, demonstrating potent anti-inflammatory efficacy in allergic asthma models.[77,78]

5.1.2. Luteolin

Luteolin (3′,4′,5,7-tetrahydroxyflavone), a common flavonoid present in numerous vegetables and medicinal herbs, possesses notable medicinal value due to its broad spectrum of biological activities.[79] Studies have indicated that low concentrations of luteolin do not significantly affect the PI3K/AKT/mTOR pathway, whereas higher doses significantly upregulate the expression of key pathway proteins. This upregulation correlates with reduced airway inflammation, evidenced by decreased levels of IL-5 and IL-13, lower eosinophil counts in bronchoalveolar lavage fluid (BALF), and reduced OVA-specific IgE in serum.[80] High-dose luteolin treatment also significantly inhibits pulmonary autophagy, as indicated by reduced Beclin-1 protein expression. In asthmatic mice, luteolin administration improves lung function, mitigates excessive mucus production in the airways, and reduces collagen deposition in pulmonary tissue. These therapeutic effects are attributed to luteolin's dual action of inhibiting the Beclin-1–PI3KC3 autophagy-promoting complex while activating the PI3K/AKT/mTOR pathway.[81]

5.1.3. Vitex negundo leaf extract (VNLE)

V. negundo, a medicinally valuable shrub commonly found on uncultivated lands, serves as a source of bioactive compounds.[82] Its extract (VNLE) exhibits antibacterial, antioxidant, and anti-inflammatory properties and mitigates allergic inflammation through modulation of effector cell activity and immune cell activation.[83] Experimental studies have demonstrated that VNLE significantly inhibits the activation of PI3K, AKT, p38, and MAPK pathways in murine models. Treatment with VNLE downregulates the PI3K/AKT/p38/NF-κB axis, where reduced PI3K/AKT phosphorylation contributes to suppression of p38 activation and subsequent NF-κB signaling pathway. Further research indicates that VNLE alleviates airway remodeling and allergic inflammation by inhibiting TGF-β/PI3K/AKT/NF-κB signaling pathway. Additionally, VNLE reduces inflammatory cell infiltration and attenuates allergic airway inflammation through modulation of TGF-β and gap junction proteins in alveolar macrophages.[41]

5.1.4. Paeoniflorin

Paeoniae Radix Alba, a traditional Chinese medicinal herb, contains active constituents with well-documented anti-inflammatory properties. Recent studies have identified the dichloromethane fraction of Paeoniae Radix Alba as the most effective component against allergic asthma. The extract is characterized by elevated levels of paeoniflorin and its structurally analogous compounds, and it significantly reduces serum levels of IL-4, IL-17, and IgE, while suppressing phosphorylation of PI3K and AKT.[84] These studies indicate that paeoniflorin, a major bioactive compound in Paeoniae Radix Alba, attenuates the production of pro-inflammatory mediators through inhibition of MAPK signaling pathway and inhibits the proliferation and migration of ASMCs via suppression of the PI3K/AKT pathway.

5.1.5. Bixin

Bixin, a natural apocarotenoid derived from the seeds of *Bixa orellana*, exhibits anti-inflammatory, antioxidant, and anticancer properties.[85] Studies have demonstrated that bixin administration reduces phosphorylation of PI3K, AKT, and mTOR in the lungs across multiple murine asthma models. Concurrently, bixin treatment significantly decreases levels of key inflammatory cytokines, including IL-17, IL-6, interferon-γ (IFN-γ), and TNF-α, and attenuates neutrophil infiltration in the airways of GCS-resistant asthmatic mice, highlighting its protective role against allergic asthma through anti-inflammatory activity.[86,87] Furthermore, in TGF-β1-stimulated airway epithelial cells, bixin inhibits PI3K/AKT activation and markedly suppresses TGF-β1-induced EMT, a critical process in airway remodeling. Collectively, these findings demonstrate that bixin functions

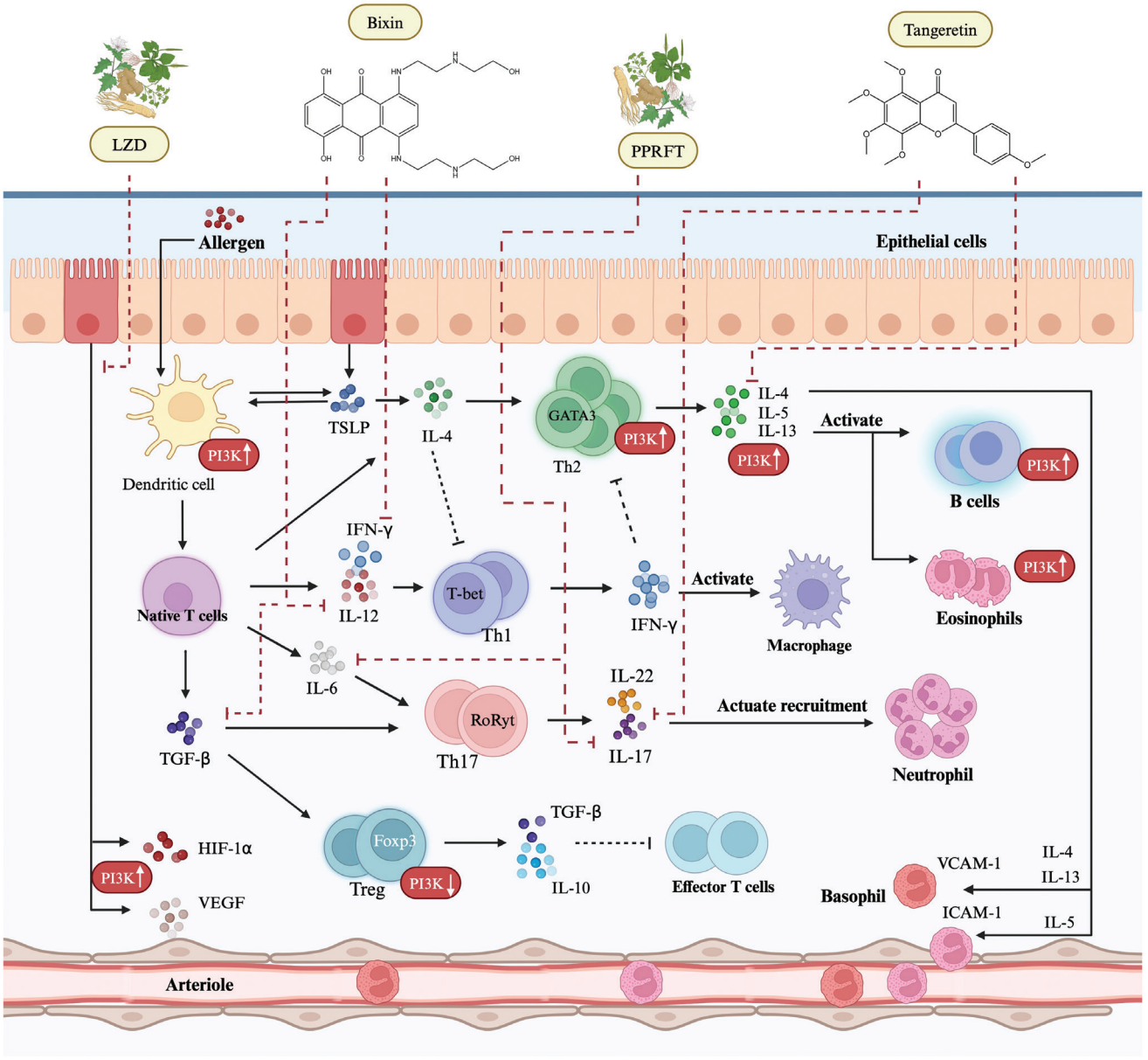

Figure 3. Effects of drugs targeting PI3K on cellular immunomodulatory mechanisms in allergic asthma (Figure created using BioRender.com). Allergen stimulation of epithelial cells and dendritic cells triggers the production of cytokines such as IL-4 and IL-6, promoting the differentiation of naïve T cells into Th1, Th2, Th17, and Treg subsets. T-helper cells mediate adaptive immunity, recruit and activate neutrophils and eosinophils, and initiate eosinophilic inflammation, which influences vascular microcirculation by regulating vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) expression. Allergen-induced epithelial activation also engages the HIF-1α/VEGF axis, resulting in vasodilation, protein extravasation, AHR, and elevated IgE levels—hallmarks of asthma. Regulatory T cells exert immunosuppressive effects via IL-10 and TGF-β, while downregulating Th2 and Th17 responses through IL-12 and IFN-γ, thereby limiting class switching associated with asthma. Traditional Chinese medicines and their bioactive compounds targeting PI3K modulate these pathways. Solid lines indicate promotion; dashed lines indicate inhibition.

as a potent PI3K/AKT inhibitor with anti-inflammatory, anti-EMT, and GCS-sensitizing effects, ultimately mitigating allergic inflammation, airway remodeling, and AHR in experimental asthma models.[88]

5.1.6. Resveratrol

Resveratrol (3,4,5-trihydroxystilbene), a phenolic compound originally isolated from *Veratrum grandiflorum* and abundantly present in grapes, wine, peanuts, soy, berries, and other dietary sources, demonstrates significant antioxidative and anti-inflammatory properties. It inhibits cyclooxygenase (COX)-1, COX-2, and 5-lipoxygenase enzymes.[89] Studies have shown that resveratrol treatment in allergic mice effectively alleviates oxidative stress and restores mitochondrial function, as evidenced by enhanced cytochrome oxidase activity and reduced cytochrome C levels.[90] Moreover, resveratrol inhibits calpain activity and normalizes the expression of inositol polyphosphate 4-phosphatase type I A in the bronchial epithelium. These effects decrease AKT kinase activity and phosphorylation, thereby suppressing the PI3K/AKT signaling pathway.[91]

5.1.7. Emodin

Emodin (1,3,8-trihydroxy-6-methylanthraquinone) functions as a protein tyrosine kinase inhibitor and exhibits a broad

spectrum of pharmacological activities, including anti-inflammatory, hepatoprotective, neuroprotective, and immunosuppressive effects.[92,93] Studies have demonstrated that emodin reduces inflammatory cell infiltration, suppresses the secretion of Th2 cytokines such as IL-4, IL-5, and IL-13, and attenuates chronic OVA-induced AHR and α-smooth muscle actin overexpression. Furthermore, emodin inhibits the proliferation and differentiation of human embryonic lung fibroblasts, indicating its potential therapeutic role in mitigating airway remodeling.[94] Additionally, emodin suppresses MC activation and subsequent allergic responses by blocking spleen tyrosine kinase-dependent signaling pathways. This inhibition reduces intracellular Ca^{2+} mobilization and downregulates multiple downstream effectors, including MAPKs, PI3K, and NF-κB signaling cascades.[95]

5.1.8. Curcumin

Histone deacetylase inhibitors (HDACi) are emerging therapeutic agents that modulate post-translational modifications of proteins involved in asthma-related signaling pathways and have demonstrated efficacy in diseases such as arthritis, cancer, and asthma. Curcumin, the bioactive component of *Curcuma longa*, exhibits anti-inflammatory and anticancer properties and functions as a natural pan-HDACi with low toxicity.[96] Sodium butyrate, a short-chain fatty acid and a metabolic product of gut microbiota, is a well-characterized class I and II HDAC inhibitor.[97] Studies have shown that the PI3K/AKT pathway can modulate airway inflammation and AHR by activating HIF-1α/vascular endothelial growth factor signaling via upregulation of mucus-associated HDACi. Both HDACi and curcumin reduce inflammation, suppress mucus hypersecretion, and attenuate hypoxia-induced responses by inhibiting PI3K/AKT axis activation.[98,99]

5.1.9. Bee venom (BV)

BV, a complex secretion produced by *Apis cerana* Fabr., contains a diverse array of bioactive constituents, such as peptides, enzymes, biogenic amines, and non-peptide molecules.[100,101] To investigate its protective role in asthma, studies examined BV's effect on IL-13-induced signaling. IL-13 stimulation increased phosphorylation of both signal transducer and activator of transcription 6 (STAT6) and AKT in A549 cells. Treatment with BV significantly suppressed AKT phosphorylation without affecting STAT6 activation. Furthermore, the PI3K/AKT inhibitor LY294002 selectively blocked AKT phosphorylation while leaving STAT6 phosphorylation unchanged, indicating that AKT functions downstream of STAT6 within this signaling cascade.[102]

Further analysis revealed that forkhead box A2 expression is regulated by PI3K/AKT activation, whereas the transcription factor SPDEF, a critical regulator of mucus production, is unaffected by this pathway. BV treatment mitigated IL-13-induced upregulation of mucin 5AC by modulating these transcription factors. It restored forkhead box A2 levels while suppressing SPDEF expression.[103] Thus, BV alleviates IL-13-mediated mucus metaplasia in airway epithelium by inhibiting the PI3K/AKT, reducing SPDEF expression, and normalizing mucin 5AC overproduction, providing a mechanistic basis for its therapeutic potential in asthma.

5.1.10. Artesunate

Artesunate, a semi-synthetic derivative of artemisinin and a well-established antimalarial agent, exerts potent inhibitory effects on the PI3K/AKT signaling pathway.[104,105] Specifically, artesunate suppresses OVA-induced phosphorylation of AHR, AKT, and downstream signaling molecules, including p70 ribosomal S6 kinase (p70S6K) and 4E-binding protein 1 (4E-BP1), as well as NF-κB transactivation, by blocking the PI3K/AKT cascade. This inhibition attenuates ASM contraction.[106,107] Moreover, artesunate targets ASMC proliferation via the PI3K/p70S6K/AKT signaling pathway, thereby mitigating airway wall remodeling in asthma (Fig. 4).[108]

5.1.11. Tangeretin

Tangeretin is an *O*-polymethoxylated flavonoid found in citrus peel, lime peel, and the leaves and stems of citrus plants. It exhibits anticancer, anti-inflammatory, and antioxidant activities in various animal disease models.[109] Experimental studies have shown that tangeretin treatment upregulates OVA-induced phosphatase and tensin homolog (PTEN) and p27kip1 expression while downregulating AKT, glycogen synthase kinase-3β (GSK-3β), and their phosphorylated forms. In addition, tangeretin reduces the release of IL-6, IL-17A, IL-4, IL-5, and IL-13. Through modulation of the PI3K/AKT and Notch signaling pathways, as well as rebalancing Th1/Th2 and Th17 cytokine levels, tangeretin effectively attenuates AHR and other asthma-related pathological indicators.[110]

5.2. TCM with regulatory effects on the PI3K/AKT signaling pathway

TCM has long been used to treat asthma through a holistic, multitarget approach, offering promise for drug development.[111] However, its complex formulations contain numerous bioactive compounds, making mechanistic studies challenging with conventional methods. Nevertheless, advances in high-throughput screening and network pharmacology have enabled the identification of active components and molecular targets, providing key insights into TCM's therapeutic mechanisms in allergic asthma.[112,113]

5.2.1. Loke Zupa Decoction (LZD)

LZD is a traditional medicine widely used in Xinjiang Uyghur medicine in China. It is composed of *Hyssopus officinalis* L. (Lamiaceae) and the roots of *Iris halophila* Pall. (Iridaceae).[114] Experimental studies demonstrated that LZD effectively suppresses TGF-β1-induced proliferation and migration of BEAS-2B human bronchial epithelial cells without affecting normal cellular viability. Furthermore, mechanistic investigations revealed that LZD downregulates EMT-related markers and inhibits the PI3K/AKT/HIF-1α signaling pathway, as evidenced by decreased phosphorylation of PI3K and AKT, accompanied by reduced HIF-1α expression.[115] Additionally, LZD attenuated recurrent inflammatory responses in airway epithelial cells, suppressed EMT progression and differentiation into myofibroblasts, thereby mitigating subepithelial fibrosis and airway remodeling in experimental asthma.[116]

5.2.2. Mahuang Decoction (MHD)

MHD, a classical and effective TCM prescription, has long been used to alleviate allergic reactions and inflammatory conditions by reducing airway inflammation.[117] Specific protein 1 (SP1) binds to the promoter region of fibroblast growth factor receptor 3 and enhances its transcriptional activation. MHD downregulates SP1 expression, thereby suppressing fibroblast growth factor receptor 3 transcription and subsequently inhibiting the PI3K/AKT signaling pathway.[118] Western blot analyses from multiple studies have demonstrated that both MHD treatment and SP1 silencing suppress PI3K/AKT pathway activation in the lung tissues of asthmatic mice.[119] Through this mechanism, MHD inhibits the proliferation of ASMCs, leading to attenuation of airway inflammation and remodeling. Furthermore, combined use of Ephedrae Herba

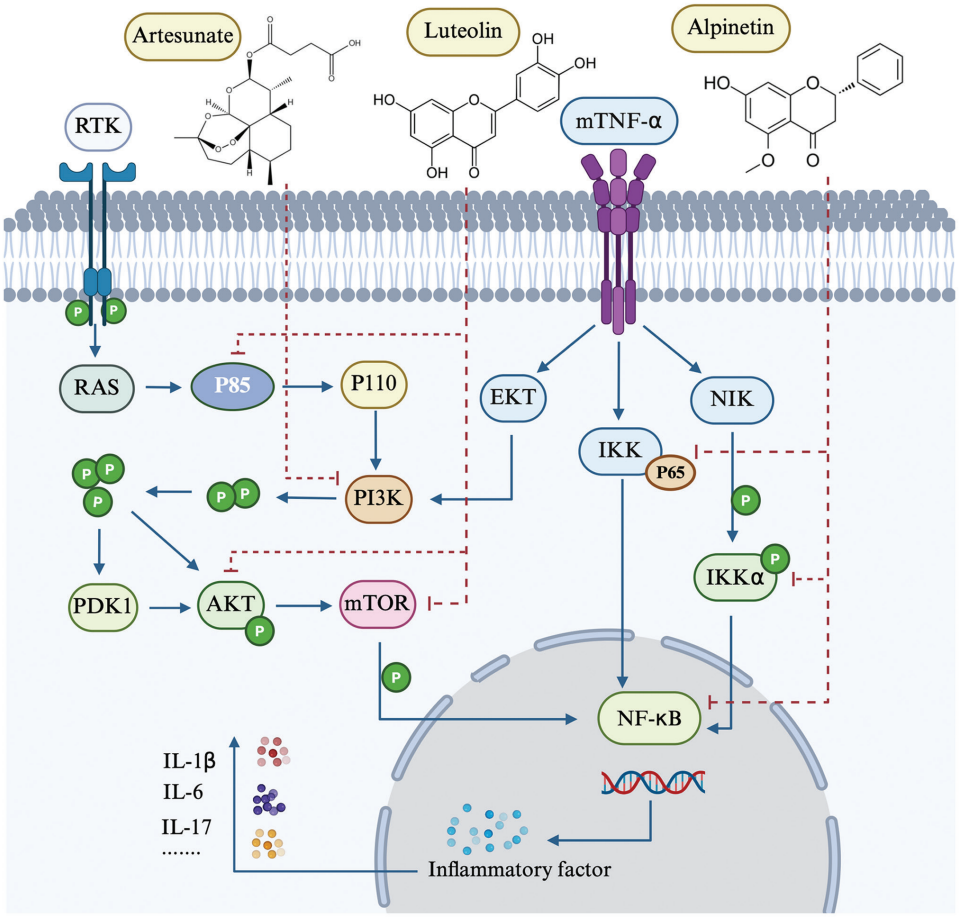

Figure 4. The PI3K/AKT/mTOR/NF-κB signaling axis and its modulation by relevant inhibitors (Figure created using BioRender.com). Drugs such as artesunate, luteolin, and galangin, commonly used in the treatment of allergic asthma, exert therapeutic effects by targeting key nodes within this pathway. Solid lines indicate activation or promotion, while dashed lines indicate inhibition.

and Schisandrae Chinensis Fructus has been shown to synergistically alleviate OVA-induced airway inflammation and remodeling in asthmatic rats by inhibiting the PLC/TRPC1/PI3K/AKT/NF-κB signaling cascade, supporting their therapeutic potential in mitigating airway pathology in asthma models.[120]

5.2.3. Bushen Yiqi *Decoction (BYD)*

BYD is a modern TCM formulation composed of Epimedii Folium, Astragali Radix, Schisandrae Chinensis Fructus, and Salviae Miltiorrhizae Radix et Rhizoma. Clinical evidence indicates that BYD markedly improves asthma-related symptoms.[121] Experimental studies have reported that this prescription significantly decreases inflammatory cell infiltration and cytokine levels in both BALF and serum samples from asthmatic mice, highlighting its modulatory effects on airway inflammation.[122] Furthermore, western blot analysis confirmed that phosphorylated PI3K and AKT protein levels were significantly reduced in the lung tissues of BYD-treated mice. Additionally, bioactive compounds within BYD, such as quercetin and lignans, are proposed to act on specific molecular mediators, including IL-6 and epidermal growth factor receptor, thereby inhibiting the PI3K/AKT signaling pathway to alleviate asthma-associated inflammation (Fig. 5).

5.2.4. Baihe Qingjin *Decoction (BHQJ)*

BHQJ, a TCM formulation composed of seven herbs—Stemonae Radix, Chebulae Fructus, Ephedrae Herba, Asteris Radix et Rhizoma, Pheretima, Mori Cortex, and Agrimoniae Herba—is commonly used in the treatment of cough and asthma. Experimental studies have shown that BHQJ alleviates airway pathological damage in asthmatic mice and significantly reduces the secretion of pro-inflammatory cytokines. Histopathological examination revealed pronounced inflammatory cell infiltration and excessive mucin secretion by airway epithelial cells before treatment, both of which were markedly attenuated after BHQJ administration. Furthermore, Western blot analyses demonstrated that BHQJ downregulated the phosphorylation of PI3K, AKT, and P65 proteins in lung tissues.[123] Therefore, inhibition of the PI3K/AKT/NF-κB signaling pathway and P65 may constitute a principal mechanism by which BHQJ exerts its anti-inflammatory effects.[124]

5.2.5. *Pipa Runfei Decoction (PPRFD)*

PPRFD is a traditional prescription consisting of 8 medicinal herbs historically used in asthma management.[125] Experimental studies have shown that PPRFD exerts protective effects on the lungs by attenuating OVA-induced oxidative stress, airway inflammation, and lung tissue damage in murine models. Specifically, it reduces inflammatory cell infiltration, lowers the levels of IL-6, IL-1β, and TNF-β in BALF, and decreases serum IgE concentrations. Furthermore, PPRFD treatment downregulates the expression of multiple signaling molecules.[126] These findings indicate that PPRFD not only alleviates clinical asthma symptoms but also modulates systemic metabolic processes. Its anti-asthmatic effects are likely mediated through the

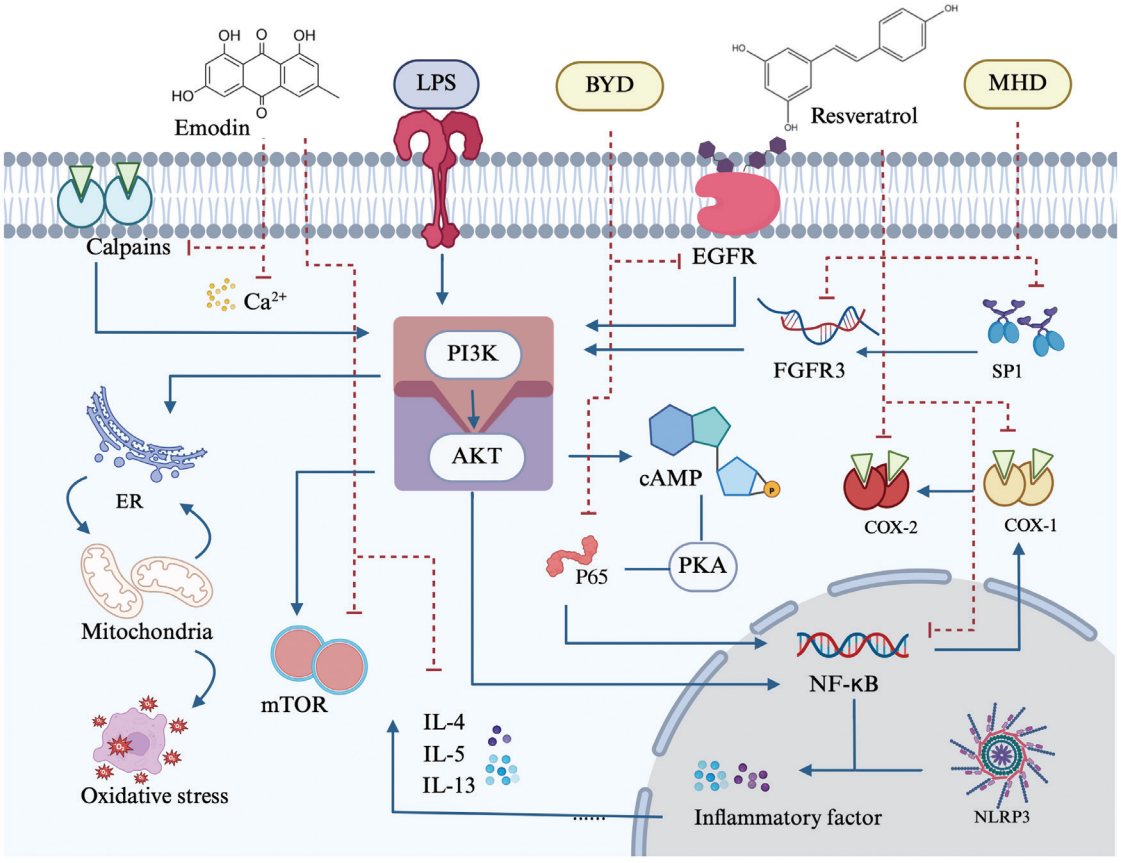

Figure 5. Upstream and downstream mechanisms of the PI3K/AKT signaling pathway and the effects of relevant inhibitors (Figure created using BioRender.com). Activation of the PI3K/AKT system is initiated by RTK stimulation, with contributions from upstream factors such as RAS proteins. In the PI3K/AKT/mTOR axis, signals from EGFR, calpains, and mitochondrial oxidative stress influence PI3K activation in airway epithelial cells, modulating endoplasmic reticulum (ER) stress and NLRP3 inflammasome activity. AKT subsequently regulates downstream effectors, including cAMP and p65, and coordinates with compensatory signaling pathways such as NF-κB/iNOS/COX-2. Drugs including emodin, BYD, resveratrol, and MHD, commonly used in allergic asthma treatment, exert therapeutic effects by targeting this signaling network. Solid lines indicate promotion, while dashed lines indicate inhibition. RAS, rat sarcoma.

coordinated regulation of the PI3K/AKT/NF-κB and IL-6/JAK2/STAT3/IL-17 signaling pathways.

5.2.6. Zisuzi Decoction (ZSD)

ZSD, particularly Perillae Fructus, has long been recognized for its potent antitussive and anti-asthmatic properties.[127] The formulation comprises Perillae Fructus, Citri Exocarpium Rubrum, Pinelliae Rhizoma, Magnoliae Officinalis Cortex, Peucedani Radix, Cinnamomi Cortex, and Glycyrrhizae Radix et Rhizoma. ZSD is commonly employed in the treatment of cough and asthma, including cough-variant asthma, a subtype characterized by cough as the sole or primary symptom and typically associated with AHR.[128] Experimental studies have shown that ZSD inhibits the release of pro-inflammatory mediators and attenuates AHR and remodeling via modulation of the PI3K/AKT1/mTOR, JAK2/STAT3, and HIF-1α/NF-κB signaling pathways. These effects contribute to significant improvements in cough-variant asthma, including suppression of cough symptoms and enhancement of lung function in rat models.[129] However, a limitation of current research is that pharmacological analyses of the prescription cannot directly correlate the bioactive components of ZSD to individual herbs, nor can they fully clarify the contributions of specific chemical constituents within the boiled mixture at varying doses and ratios.

5.2.7. Jiawei Bushen Yiqi Formula (JWBSYQF)

JWBSYQF, a formula comprising six medicinal herbs, has been shown to attenuate AHR by reducing airway resistance and enhancing lung compliance.[130] In JWBSYQF-treated mice, inflammatory responses were significantly ameliorated, as evidenced by decreased leukocyte counts in BALF, reduced Th2 cytokine levels in BALF, and lower serum IgE concentrations. Mechanistic studies suggest that these effects may involve modulation of the MAPK and NF-κB signaling pathways downstream of IL-17. Recent evidence also indicates that JWBSYQF decreases PI3K and p-AKT levels in fibrotic lung tissue, highlighting its potential role in ameliorating pulmonary fibrosis via the PI3K/AKT pathway.[131] Pulmonary fibrosis is considered a progressive outcome within the continuum of asthma, airway remodeling, and fibrotic changes.[132]

6. Conclusions

As a critical signaling pathway regulating cell growth, proliferation, metabolism, survival, and angiogenesis, the PI3K/AKT pathway plays a central role in coordinating chronic inflammation and airway structural remodeling in asthma. Increasing clinical evidence has highlighted the significant role of PI3K/AKT in allergic asthma and the potential of related pharmacological interventions.[133,134] Nevertheless, targeting the PI3K/AKT pathway for asthma therapy remains challenging. First, due to its complexity, with numerous regulators and effectors, fully elucidating the therapeutic mechanisms of PI3K/AKT in allergic asthma is difficult. Limitations in current research techniques hinder a comprehensive understanding, and optimizing and evaluating the clinical efficacy of novel

Table 2

Key TCM treatments related to the PI3K/AKT signaling pathway in allergic asthma.

Therapeutic products	Categories	Mechanism of action
Alpinetin	Flavonoid	Effectively reduces the production of TNF-α, IL-6, and IL-1β, inhibits the activity of PI3K/AKT/NF-κB signaling pathway, prevents inflammatory cells from infiltrating the alveoli, and shows strong anti-inflammatory activity against allergic asthma
Luteolin	Flavonoid	The high-dose of luteolin significantly up-regulated the PI3K, p-AKT, and p-mTOR protein levels in lung tissues and alleviated the airway inflammation by downregulation of the levels of IL-5, IL-13, eosinophils in BALF, and OVA-specific IgE in serum
VNLE	Mixture	Reduce allergic inflammation by regulating effector cells and regulating the activation of immune cells
Paeoniflorin	Monoterpene	Inhibits MAPK metabolism and reduces arterial smooth muscle cell (ASMC) proliferation and migration by inhibiting PI3K/AKT metabolism
Bixin	Carotenoids	As an effective PI3K/AKT antagonist
Resveratrol	Phenol	Inhibits calpain activity and restores the normal expression of INPP4A in bronchial epithelium, thereby reducing AKT kinase activity and AKT phosphorylation, and decreasing PI3K/AKT signaling
Emodin	Anthraquinone	Inhibits the proliferation of MASMC *in vitro* and attenuates airway smooth muscle remodeling *in vivo* and proliferation of airway smooth muscle cells *in vitro* via the PI3K/AKT signaling pathway *in vitro* and *in vivo*
Curcumin	Phenol	Reduces inflammation mucus hyper-secretion and attenuates hypoxic response by inhibiting activation of PI3K/AKT axis
Bee venom	Mixture	Inhibits IL-13-induced AKT phosphorylation through the PI3K/AKT signaling pathway and inhibits mucus metaplasia by inhibiting the enhanced SPDEF in airway epithelial cells to prevent FOXA2 from regulating MUC5AC production
Artesunate	Terpene	Targets ASM cell proliferation through the PI3K/AKT/p70(S6K) pathway to contribute to airway wall remodeling in asthma
Tangeretin	Flavonoid	Alleviates the chronic response of allergic asthma by upregulating the expression of PTEN and inhibiting EMT through the PI3K/AKT signaling pathway.
LZD	Formula	Reduces the levels of EMT-related molecules and significantly downregulates the PI3K/AKT/HIF-1α signaling pathway
MHD	Formula	Downregulates the expression of SP1 and inhibits the transcription of FGFR3, which leads to the inactivation of the PI3K/AKT signaling pathway
BYD	Formula	Inhibits phosphorylation of PI3K and AKT, thereby inhibiting the activation of PI3K/AKT signaling pathway
BHQJ	Formula	Downregulates the expression of P65 protein and inhibits the PI3K/AKT signaling pathway.
PPRFT	Formula	Regulates the PI3K/AKT/NF-κB and IL-6/JAK2/STAT3/IL-17 mechanistic pathways
ZSD	Formula	Inhibits the release of inflammatory factors and reduces airway hyperresponsiveness and airway remodeling through the PI3K/AKT1/mTOR, JAK2/STAT3, and HIF-1α/NF-κB signaling pathways
JWBSYQF	Formula	Reduces pulmonary fibrosis and reduces the level of inflammatory factors in asthma by inhibiting PI3K/AKT signaling pathway and affects the activation of MAPK and NF-κB signaling pathways by IL-17

FOXA2, forkhead box A2; MUC5AC, mucin 5AC.

subtype-specific PI3K inhibitors remains an ongoing concern. Second, these challenges are compounded when applying TCM strategies. Although studies of individual TCM-derived compounds targeting PI3K/AKT have provided valuable mechanistic insights, it remains difficult to correlate the chemical constituents in complex decoctions—with varying doses and ratios—with their pharmacological effects. Moreover, analyses based solely on pharmacological outcomes cannot readily link the active ingredients of a finished prescription to each individual herb. Such limitations present a challenge for network pharmacology in elucidating mechanistic strategies for multi-herb formulations in practice. Nonetheless, these limitations do not conflict with the holistic and systemic approach emphasized in TCM. To advance therapeutic research, it is necessary to re-examine the role of PI3K/AKT targeting in allergic asthma based on etiology, pathophysiology, and clinical interventions. Addressing these key issues and integrating insights from plant-derived compounds offer promising opportunities for the development of novel treatments for respiratory diseases (Table 2).[135,136]

Statement of ethics

Not applicable.

Conflict of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

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Data availability statement

All data generated or analyzed during this study are included in this published article.

Author contributions

Jiamao Wang: Writing—original draft preparation. Qitong Zheng: Writing—original draft preparation. Yiqing Shi: Formal analysis. Mengyao Chen: Project administration. Xia'nan Sang: Writing—review & editing. Gang Cao: Writing—review & editing.

References

[1] Huang K, Yang T, Xu J, et al. China Pulmonary Health (CPH) Study Group. Prevalence, risk factors, and management of asthma in China: a national cross-sectional study. *Lancet* 2019;394:407–418.
[2] Holley AD, Boots RJ. Review article: management of acute severe and near-fatal asthma. *Emerg Med Australas* 2009;21:259–268.
[3] Hawkins PT, Stephens LR. PI3K signalling in inflammation. *Biochim Biophys Acta* 2015;1851:882–897.
[4] Barnes PJ. Drugs for asthma. *Br J Pharmacol* 2006;147(Suppl 1):S297–S303.
[5] Abbott-Banner KH, Page CP. Dual PDE 3/4 and PDE 4 inhibitors: novel treatments for COPD and other inflammatory airway diseases. *Basic Clin Pharma Tox* 2014;114:365–376.
[6] Caesar LK, Cech NB. Synergy and antagonism in natural product extracts: When 1 + 1 does not equal 2. *Nat Prod Rep* 2019;36:869–888.
[7] Papadopoulos NG, Megremis S, Kitsioulis NA, Vangelatou O, West P, Xepapadaki P. Promising approaches for the treatment and prevention of viral respiratory illnesses. *J Allergy Clin Immunol* 2017;140:921–932.
[8] Sprouse AA, Van Breemen RB. Pharmacokinetic interactions between drugs and botanical dietary supplements. *Drug Metab Dispos* 2016;44:162–171.
[9] Vivier E, Artis D, Colonna M, et al. Innate lymphoid cells: 10 years on. *Cell* 2018;174:1054–1066.
[10] Saravia J, Raynor JL, Chapman NM, Lim SA, Chi H. Signaling networks in immunometabolism. *Cell Res* 2020;30:328–342.
[11] Athari SS, Athari SM, Beyzay F, Movassaghi M, Mortaz E, Taghavi M. Critical role of Toll-like receptors in pathophysiology of allergic asthma. *Eur J Pharmacol* 2017;808:21–27.
[12] Gans MD, Gavrilova T. Understanding the immunology of asthma: pathophysiology, biomarkers, and treatments for asthma endotypes. *Paediatr Respir Rev* 2020;36:118–127.
[13] Yin J, Yan F, Zheng R, Wu X, Athari SS. Immunomodulatory effect of IL-2 induced bone marrow mononuclear cell therapy on control of allergic asthma. *Allergol Immunopathol (Madr)* 2023;51:110–115.
[14] Komlósi ZI, Van De Veen W, Kovács N, et al. Cellular and molecular mechanisms of allergic asthma. *Mol Aspects Med* 2022;85:100995.
[15] Fruman DA, Chiu H, Hopkins BD, Bagrodia S, Cantley LC, Abraham RT. The PI3K pathway in human disease. *Cell* 2017;170:605–635.
[16] Boulet LP, Sterk PJ. Airway remodelling: the future. *Eur Respir J* 2007;30:831–834.
[17] Boulet LP, Chakir J, Dubé J, Laprise C, Boutet M, Laviolette M. Airway inflammation and structural changes in airway hyper-responsiveness and asthma: an overview. *Can Respir J* 1998;5:16–21.
[18] Abbastabar M, Kheyrollah M, Azizian K, et al. Multiple functions of p27 in cell cycle, apoptosis, epigenetic modification and transcriptional regulation for the control of cell growth: a double-edged sword protein. *DNA Repair (Amst)* 2018;69:63–72.
[19] Hamamdzic D, Fenning RS, Patel D, et al. Akt pathway is hypoactivated by synergistic actions of diabetes mellitus and hypercholesterolemia resulting in advanced coronary artery disease. *Am J Physiol Heart Circ Physiol* 2010;299:H699–H706.
[20] Xie Y, Shi X, Sheng K, et al. PI3K/Akt signaling transduction pathway, erythropoiesis and glycolysis in hypoxia (Review). *Mol Med Rep* 2019;19:783–791.
[21] Yokota J, Chosa N, Sawada S, et al. PDGF-induced PI3K-mediated signaling enhances the TGF-β-induced osteogenic differentiation of human mesenchymal stem cells in a TGF-β-activated MEK-dependent manner. *Int J Mol Med* 2014;33:534–542.
[22] Lu J, Xie L, Liu C, Zhang Q, Sun S. PTEN/PI3K/AKT regulates macrophage polarization in emphysematous mice. *Scand J Immunol* 2017;85:395–405.
[23] Conciatori F, Ciuffreda L, Bazzichetto C, et al. mTOR cross-talk in cancer and potential for combination therapy. *Cancers (Basel)* 2018;10:23.
[24] Conciatori F, Bazzichetto C, Falcone I, et al. Role of mTOR signaling in tumor microenvironment: an overview. *Int J Mol Sci* 2018;19:2453.
[25] Powell JD, Pollizzi KN, Heikamp EB, Horton MR. Regulation of immune responses by mTOR. *Annu Rev Immunol* 2012;30:39–68.
[26] Huang K, Fingar DC. Growing knowledge of the mTOR signaling network. *Semin Cell Dev Biol* 2014;36:79–90.
[27] Xiong X, Tao R, DePinho RA, Dong XC. Deletion of hepatic FoxO1/3/4 genes in mice significantly impacts on glucose metabolism through downregulation of gluconeogenesis and upregulation of glycolysis. *PLoS One* 2013;8:e74340.
[28] Bossler F, Hoppe-Seyler K, Hoppe-Seyler F. PI3K/AKT/mTOR signaling regulates the virus/host cell crosstalk in HPV-positive cervical cancer cells. *Int J Mol Sci* 2019;20:2188.
[29] Manning BD, Toker A. AKT/PKB signaling: navigating the network. *Cell* 2017;169:381–405.
[30] Chen X, Miao M, Zhou M, et al. Poly-L-arginine promotes asthma angiogenesis through induction of FGFBP1 in airway epithelial cells via activation of the mTORC1-STAT3 pathway. *Cell Death Dis* 2021;12:761.
[31] Parry RV, Chemnitz JM, Frauwirth KA, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. *Mol Cell Biol* 2005;25:9543–9553.
[32] Gerriets VA, Kishton RJ, Johnson MO, et al. Foxp3 and Toll-like receptor signaling balance Treg cell anabolic metabolism for suppression. *Nat Immunol* 2016;17:1459–1466.
[33] Lee J, Kim J, Lee JH, et al. SIRT1 promotes host protective immunity against *Toxoplasma gondii* by controlling the FoxO-autophagy axis via the AMPK and PI3K/AKT signalling pathways. *Int J Mol Sci* 2022;23:13578.
[34] Huang L, Wang M, Yan Y, et al. OX40L induces helper T cell differentiation during cell immunity of asthma through PI3K/AKT and P38 MAPK signaling pathway. *J Transl Med* 2018;16:74.
[35] Hu S, Wang R, Zhang M, et al. BAFF promotes T cell activation through the BAFF-BAFF-R-PI3K-Akt signaling pathway. *Biomed Pharmacother* 2019;114:108796.
[36] Xiang M, Liu T, Tian C, et al. Kinsenoside attenuates liver fibroinflammation by suppressing dendritic cells via the PI3K-AKT-FoxO1 pathway. *Pharmacol Res* 2022;177:106092.
[37] Li F, Li J, Wang PH, et al. SARS-CoV-2 spike promotes inflammation and apoptosis through autophagy by ROS-suppressed PI3K/AKT/mTOR signaling. *Biochim Biophys Acta Mol Basis Dis* 2021;1867:166260.
[38] Duan MX, Zhou H, Wu QQ, et al. Andrographolide protects against HG-induced inflammation, apoptosis, migration, and impairment of angiogenesis via PI3K/AKT-eNOS signalling in HUVECs. *Mediators Inflamm* 2019;2019:6168340.
[39] Zhu G, Cai H, Ye L, et al. Small proline-rich protein 3 regulates IL-33/ILC2 axis to promote allergic airway inflammation. *Front Immunol* 2022;12:758829.
[40] Jiang X, Fang L, Wu H, et al. TLR2 regulates allergic airway inflammation and autophagy through PI3K/Akt signaling pathway. *Inflammation* 2017;40:1382–1392.
[41] Tirpude NV, Sharma A, Joshi R, Kumari M, Acharya V. *Vitex negundo* Linn. extract alleviates inflammatory aggravation and lung injury by modulating AMPK/PI3K/Akt/p38-NF-κB and TGF-β/Smad/Bcl2/caspase/LC3 cascade and macrophages activation in murine model of OVA-LPS induced allergic asthma. *J Ethnopharmacol* 2021;271:113894.
[42] Islam R, Dash D, Singh R. An antioxidant ameliorates allergic airway inflammation by inhibiting HDAC1 via HIF-1α/VEGF axis suppression in mice. *Sci Rep* 2023;13:9637.
[43] Boonpiyathad T, Sözener ZC, Satitsuksanoa P, Akdis CA. Immunologic mechanisms in asthma. *Semin Immunol* 2019;46:101333.
[44] Xi Y, Upham JW. Plasmacytoid dendritic cells and asthma: a review of current knowledge. *Expert Rev Respir Med* 2020;14:1095–1106.
[45] Datler H, Vogel A, Kerndl M, et al. PI3K activity in dendritic cells exerts paradoxical effects during autoimmune inflammation. *Mol Immunol* 2019;111:32–42.
[46] Chinn AM, Insel PA. Cyclic AMP in dendritic cells: a novel potential target for disease-modifying agents in asthma and other allergic disorders. *Br J Pharmacol* 2020;177:3363–3377.

[47] Thummar K, Rathinam CV. Class I PI3K regulatory subunits control differentiation of dendritic cell subsets and regulate Flt3L mediated signal transduction. *Sci Rep* 2022;12:12311.
[48] Yamaki K, Tamura Y, Suzuki T, Uesaki Y, Dougan A, Koyama Y. PI3K/mTOR inhibitor dactolisib attenuates allergic response through inhibitions of the sensitization and mast cell activation. *Pharmazie* 2023;78:128–133.
[49] Zhang F, Hong F, Wang L, Fu R, Qi J, Yu B. MrgprX2 regulates mast cell degranulation through PI3K/AKT and PLCγ signaling in pseudo-allergic reactions. *Int Immunopharmacol* 2022;102:108389.
[50] Banafea GH, Bakhashab S, Alshaibi HF, Natesan Pushparaj P, Rasool M. The role of human mast cells in allergy and asthma. *Bioengineered* 2022;13:7049–7064.
[51] Xu H, Gu LN, Yang QY, Zhao DY, Liu F. MiR-221 promotes IgE-mediated activation of mast cells degranulation by PI3K/Akt/PLCγ/Ca^{2+} pathway. *J Bioenerg Biomembr* 2016;48:293–299.
[52] Wang Y, Hu S, Dang B, et al. Silibinin attenuated pseudo-allergic reactions and mast cell degranulation via PLCγ and PI3K/Akt signaling pathway. *Phytother Res* 2023;37:3572–3582.
[53] Nakajima S, Ishimaru K, Kobayashi A, et al. Resveratrol inhibits IL-33–mediated mast cell activation by targeting the MK2/3–PI3K/Akt axis. *Sci Rep* 2019;9:18423.
[54] Patton DT, Garçon F, Okkenhaug K. The PI3K p110delta controls T-cell development, differentiation and regulation. *Biochem Soc Trans* 2007;35(Pt 2):167–171.
[55] Johansen KH, Golec DP, Thomsen JH, Schwartzberg PL, Okkenhaug K. PI3K in T cell adhesion and trafficking. *Front Immunol* 2021;12:708908.
[56] Jarmin SJ, David R, Ma L, et al. T cell receptor–induced phosphoinositide-3-kinase p110δ activity is required for T cell localization to antigenic tissue in mice. *J Clin Invest* 2008;118:1154–1164.
[57] Jeong JS, Kim JS, Kim SR, Lee YC. Defining bronchial asthma with phosphoinositide 3-kinase delta activation: towards endotype-driven management. *Int J Mol Sci* 2019;20:3525.
[58] Maggi L, Mazzoni A, Capone M, Liotta F, Annunziato F, Cosmi L. The dual function of ILC2: from host protection to pathogenic players in type 2 asthma. *Mol Aspects Med* 2021;80:100981.
[59] Emami Fard N, Xiao M, Sehmi R. Regulatory ILC2—role of IL-10 producing ILC2 in asthma. *Cells* 2023;12:2556.
[60] Akdis CA, Arkwright PD, Brüggen MC, et al. Type 2 immunity in the skin and lungs. *Allergy* 2020;75:1582–1605.
[61] Athari SS. Targeting cell signaling in allergic asthma. *Signal Transduct Target Ther* 2019;4:45.
[62] Matsuyama T, Matsuyama H, Dotake Y, Takagi K, Machida K, Inoue H. The therapeutic potential for targeting group 2 innate lymphoid cells in asthma. *Front Immunol* 2022;13:930862.
[63] Spits H, Mjösberg J. Heterogeneity of type 2 innate lymphoid cells. *Nat Rev Immunol* 2022;22:701–712.
[64] Wang L, Zhang YL, Wang XF, Song Z, Wang W. Expression and significance of mTOR/4EBP1/HIF-1α/VEGF signaling pathway in lung tissues of asthmatic mice. *Chin J Contemp Pediatr* 2017;19:104–110. [in Chinese].
[65] Bal SM, Bernink JH, Nagasawa M, et al. IL-1β, IL-4 and IL-12 control the fate of group 2 innate lymphoid cells in human airway inflammation in the lungs. *Nat Immunol* 2016;17:636–645.
[66] Jiang Y, Pan Q, Zhu X, et al. Knockdown of CCR3 gene inhibits proliferation, migration and degranulation of eosinophils in mice by down-regulating the PI3K/Akt pathway. *Int Immunopharmacol* 2022;113(Pt B):109439.
[67] McBrien CN, Menzies-Gow A. The biology of eosinophils and their role in asthma. *Front Med (Lausanne)* 2017;4:93.
[68] Southworth T, Plumb J, Gupta V, et al. Anti-inflammatory potential of PI3Kδ and JAK inhibitors in asthma patients. *Respir Res* 2016;17:124.
[69] Varricchi G, Brightling CE, Grainge C, Lambrecht BN, Chanez P. Airway remodelling in asthma and the epithelium: on the edge of a new era. *Eur Respir J* 2024;63:2301619.
[70] Varricchi G, Ferri S, Pepys J, et al. Biologics and airway remodeling in severe asthma. *Allergy* 2022;77:3538–3552.
[71] Jeong JS, Kim SR, Lee YC. Can controlling endoplasmic reticulum dysfunction treat allergic inflammation in severe asthma with fungal sensitization? *Allergy Asthma Immunol Res* 2018;10:106–120.
[72] Kim RY, Pinkerton JW, Essilfie AT, et al. Role for NLRP3 Inflammasome–mediated, IL-1β–dependent responses in severe, steroid-resistant asthma. *Am J Respir Crit Care Med* 2017;196:283–297.
[73] Jeong JS, Kim SR, Cho SH, Lee YC. A novel insight on endotyping heterogeneous severe asthma based on endoplasmic reticulum stress: beyond the "type 2/non-type 2 dichotomy." *Int J Mol Sci* 2019;20:713.
[74] Sharma S, Naura AS. Potential of phytochemicals as immune-regulatory compounds in atopic diseases: a review. *Biochem Pharmacol* 2020;173:113790.
[75] Zhao G, Tong Y, Luan F, et al. Alpinetin: a review of its pharmacology and pharmacokinetics. *Front Pharmacol* 2022;13:814370.
[76] Abdureyim S, Amat N, Umar A, Upur H, Berke B, Moore N. Anti-inflammatory, immunomodulatory, and heme oxygenase-1 inhibitory activities of Ravan Napas, a formulation of Uighur traditional medicine, in a rat model of allergic asthma. *Evid Based Complement Alternat Med* 2011;2011:725926.
[77] Possa SS, Leick EA, Prado CM, Martins MA, Tibério IFLC. Eosinophilic inflammation in allergic asthma. *Front Pharmacol* 2013;4:46.
[78] Wu D, Li S, Liu X, et al. Alpinetin prevents inflammatory responses in OVA-induced allergic asthma through modulating PI3K/AKT/NF-κB and HO-1 signaling pathways in mice. *Int Immunopharmacol* 2020;89:107073.
[79] Imran M, Rauf A, Abu-Izneid T, et al. Luteolin, a flavonoid, as an anticancer agent: a review. *Biomed Pharmacother* 2019;112:108612.
[80] Almatroodi SA, Almatroudi A, Alharbi HOA, Khan AA, Rahmani AH. Effects and mechanisms of luteolin, a plant-based flavonoid, in the prevention of cancers via modulation of inflammation and cell signaling molecules. *Molecules* 2024;29:1093.
[81] Wang S, Wuniqiemu T, Tang W, et al. Luteolin inhibits autophagy in allergic asthma by activating PI3K/Akt/mTOR signaling and inhibiting Beclin-1-PI3KC3 complex. *Int Immunopharmacol* 2021;94:107460.
[82] Sharma RL, Prabhakar A, Dhar KL, Sachar A. A new iridoid glycoside from *Vitex negundo* Linn (Verbenacea). *Nat Prod Res* 2009;23:1201–1209.
[83] Gill BS, Mehra R, Navgeet, Kumar S. *Vitex negundo* and its medicinal value. *Mol Biol Rep* 2018;45:2925–2934.
[84] Sang X, Ying J, Wan X, et al. Screening of bioactive fraction of Radix Paeoniae Alba and enhancing anti-allergic asthma by stir-frying through regulating PI3K/AKT signaling pathway. *Front Pharmacol* 2022;13:863403.
[85] De Oliveira Júnior RG, Bonnet A, Braconnier E, et al. Bixin, an apocarotenoid isolated from *Bixa orellana* L., sensitizes human melanoma cells to dacarbazine-induced apoptosis through ROS-mediated cytotoxicity. *Food Chem Toxicol* 2019;125:549–561.
[86] Soond DR, Bjørgo E, Moltu K, et al. PI3K p110δ regulates T-cell cytokine production during primary and secondary immune responses in mice and humans. *Blood* 2010;115:2203–2213.
[87] Zhang H, Xue L, Li B, Tian H, Zhang Z, Tao S. Therapeutic potential of bixin in PM2.5 particles-induced lung injury in an Nrf2-dependent manner. *Free Radic Biol Med* 2018;126:166–176.
[88] Zhu Y, Sun D, Liu H, et al. Bixin protects mice against bronchial asthma though modulating PI3K/Akt pathway. *Int Immunopharmacol* 2021;101:108266.
[89] Hou Y, Wang K, Wan W, Cheng Y, Pu X, Ye X. Resveratrol provides neuroprotection by regulating the JAK2/STAT3/PI3K/AKT/mTOR pathway after stroke in rats. *Genes Dis* 2018;5:245–255.
[90] Anekonda TS, Adamus G. Resveratrol prevents antibody-induced apoptotic death of retinal cells through upregulation of Sirt1 and Ku70. *BMC Res Notes* 2008;1:122.
[91] Aich J, Mabalirajan U, Ahmad T, et al. Resveratrol attenuates experimental allergic asthma in mice by restoring inositol polyphosphate 4 phosphatase (INPP4A). *Int Immunopharmacol* 2012;14:438–443.
[92] Semwal RB, Semwal DK, Combrinck S, Viljoen A. Emodin—a natural anthraquinone derivative with diverse pharmacological activities. *Phytochem* 2021;190:112854.
[93] Dong X, Fu J, Yin X, et al; Huyiligeqi. Emodin: a review of its pharmacology, toxicity and pharmacokinetics. *Phytother Res* 2016;30:1207–1218.
[94] Guan R, Zhao X, Wang X, et al. Emodin alleviates bleomycin-induced pulmonary fibrosis in rats. *Toxicol Lett* 2016;262:161–172.
[95] Lu Y, Yang JH, Li X, et al. Emodin, a naturally occurring anthraquinone derivative, suppresses IgE-mediated anaphylactic reaction and mast cell activation. *Biochem Pharmacol* 2011;82:1700–1708.
[96] Jaiswal A, Dash D, Singh R. Intranasal curcumin and dexamethasone combination ameliorates inflammasome (NLRP3) activation in lipopolysachharide exposed asthma exacerbations. *Toxicol Appl Pharmacol* 2022;436:115861.
[97] Islam R, Dash D, Singh R. Intranasal curcumin and sodium butyrate modulates airway inflammation and fibrosis via HDAC inhibition in allergic asthma. *Cytokine* 2022;149:155720.
[98] Kim SR, Lee KS, Park HS, et al. HIF-1a inhibition ameliorates an allergic airway disease via VEGF suppression in bronchial epithelium. *Eur J Immunol* 2010;40:2858–2869.

[99] Choi YH, Jin GY, Li LC, Yan GH. Inhibition of protein kinase C delta attenuates allergic airway inflammation through suppression of PI3K/Akt/mTOR/HIF-1 alpha/VEGF pathway. *PLoS One* 2013;8:e81773.
[100] Kim W. Bee venom and its sub-components: characterization, pharmacology, and therapeutics. *Toxins* 2021;13:191.
[101] Vazquez-Revuelta P, Madrigal-Burgaleta R. Death due to live bee acupuncture apitherapy. *J Investig Allergol Clin Immunol* 2018;28:45–46.
[102] Shin D, Choi W, Bae H. Bee venom phospholipase A2 alleviate house dust mite-induced atopic dermatitis-like skin lesions by the CD206 mannose receptor. *Toxins* 2018;10:146.
[103] Kim S, Kim HW, Chang SH, Leem KH, Park HJ. Bee venom prevents mucin 5AC production through inhibition of AKT and SPDEF activation in airway epithelia cells. *Toxins* 2021;13:773.
[104] Woodrow CJ, Haynes RK, Krishna S. Artemisinins. *Postgrad Med J* 2005;81:71–78.
[105] Efferth T, Romero MR, Wolf DG, Stamminger T, Marin JJG, Marschall M. The antiviral activities of artemisinin and artesunate. *Clin Infect Dis* 2008;47:804–811.
[106] Nashed BF, Zhang T, Al-Alwan M, et al. Role of the phosphoinositide 3-kinase p110δ in generation of type 2 cytokine responses and allergic airway inflammation. *Eur J Immunol* 2007;37:416–424.
[107] Cheng C, Ho WE, Goh FY, et al. Anti-malarial drug artesunate attenuates experimental allergic asthma via inhibition of the phosphoinositide 3-kinase/Akt pathway. *PLoS One* 2011;6:e20932.
[108] Tan SS, Ong B, Cheng C, et al. The antimalarial drug artesunate inhibits primary human cultured airway smooth muscle cell proliferation. *Am J Respir Cell Mol Biol* 2014;50:451–458.
[109] Shu Z, Yang B, Zhao H, et al. Tangeretin exerts anti-neuroinflammatory effects via NF-κB modulation in lipopolysaccharide-stimulated microglial cells. *Int Immunopharmacol* 2014;19:275–282.
[110] Liu LL, Li FH, Zhang Y, Zhang XF, Yang J. Tangeretin has anti-asthmatic effects via regulating PI3K and Notch signaling and modulating Th1/Th2/Th17 cytokine balance in neonatal asthmatic mice. *Braz J Med Biol Res* 2017;50:e5991.
[111] Chan HHL, Ng T. Traditional Chinese medicine (TCM) and allergic diseases. *Curr Allergy Asthma Rep* 2020;20:67.
[112] Yuan H, Ma Q, Cui H, et al. How can synergism of traditional medicines benefit from network pharmacology? *Molecules* 2017;22:1135.
[113] Suo T, Wang H, Li Z. Application of proteomics in research on traditional Chinese medicine. *Expert Rev Proteomics* 2016;13:873–881.
[114] Wei Y, Abduwaki M, Li M, et al. Loki zupa (Luooukezupa) decoction reduced airway inflammation in an OVA-induced asthma mouse model. *Chin Med* 2016;11:22.
[115] Liu J, Li L, Han X, Chen Y, Diao J. Loke zupa decoction attenuates bronchial EMT-mediated airway remodelling in chronic asthma through the PI3K-Akt/HIF-1α signaling pathway. *Pharm Biol* 2023;61:1332–1342.
[116] Gosens R, Grainge C. Bronchoconstriction and airway biology: Potential impact and therapeutic opportunities. *Chest* 2015;147:798–803.
[117] He Y, Zhu Y, Zhang R, Ge L, Wan H. Simultaneous quantification of nine major active components in traditional Chinese prescription Mahuang decoction and the influence of herbal compatibility on their contents. *Pharmacogn Mag* 2014;10(Suppl 1):S72–S79.
[118] McEwen DG, Ornitz DM. Regulation of the fibroblast growth factor receptor 3 promoter and intron I enhancer by Sp1 family transcription factors. *J Biol Chem* 1998;273:5349–5357.
[119] Wei L, Gou X, Su B, et al. Mahuang Decoction attenuates airway inflammation and remodeling in asthma via suppression of the SP1/FGFR3/PI3K/AKT axis. *Drug Des Devel Ther* 2022;16:2833–2850.
[120] Zhuo Z, Nie J, Xie B, et al. A comprehensive study of *Ephedra sinica* Stapf-*Schisandra chinensis* (Turcz.) Baill herb pair on airway protection in asthma. *J Ethnopharmacol* 2024;322:117614.
[121] Zhong Y, Hu L, Chen W, Wang B, Sun J, Dong J. Exploring the comorbidity mechanisms between asthma and idiopathic pulmonary fibrosis and the pharmacological mechanisms of Bu-Shen-Yi-Qi decoction therapy via network pharmacology. *BMC Complement Med Ther* 2022;22:151.
[122] Qin Z, Chen Y, Liu N, et al. Mechanisms of Bushenyiqi decoction in the treatment of asthma: an investigation based on network pharmacology with experimental validation. *Front Pharmacol* 2024;15:1361379.
[123] Yan X, Tong X, Jia Y, et al. Baiheqingjin formula reduces inflammation in mice with asthma by inhibiting the PI3K/AKT/NF-κB signaling pathway. *J Ethnopharmacol* 2024;321:117565.
[124] Devi K, Soni S, Tripathi V, Pandey R, Moharana B. Ethanolic extract of *Tridax procumbens* mitigates pulmonary inflammation via inhibition of NF-κB/p65/ERK mediated signalling in an allergic asthma model. *Phytomedicine* 2022;99:154008.
[125] Jie XL, Tong ZR, Xu XY, et al. Mechanic study based on untargeted metabolomics of Pi-pa-run-fei-tang on pepper combined with ammonia induced chronic cough model mice. *J Ethnopharmacol* 2024;326:117905.
[126] Jie XL, Luo ZR, Yu J, et al. Pi-Pa-Run-Fei-Tang alleviates lung injury by modulating IL-6/JAK2/STAT3/IL-17 and PI3K/AKT/NF-κB signaling pathway and balancing Th17 and Treg in murine model of OVA-induced asthma. *J Ethnopharmacol* 2023;317:116719.
[127] Liu S, Jin X, Shang Y, et al. A comprehensive review of the botany, ethnopharmacology, phytochemistry, pharmacology, toxicity and quality control of Perillae Fructus. *J Ethnopharmacol* 2023;304:116022.
[128] Antoniu SA, Mihaescu T, Donner CF. Pharmacotherapy of cough-variant asthma. *Expert Opin Pharmacother* 2007;8:3021–3028.
[129] Nguyen V, Zhang Q, Pan F, et al. Zi-Su-Zi decoction improves airway hyperresponsiveness in cough-variant asthma rat model through PI3K/AKT1/mTOR, JAK2/STAT3 and HIF-1α/NF-κB signaling pathways. *J Ethnopharmacol* 2023;314:116637.
[130] Shi H, Deng L, Zhou Y, et al. Network pharmacology and experiments in vivo and in vitro reveal that the Jia-Wei-Bu-Shen-Yi-Qi formula (JWBSYQF) and its active ingredient baicalein ameliorate BLM-induced lung fibrosis in mice via PI3K/Akt signaling pathway. *J Ethnopharmacol* 2023;315:116691.
[131] Qin J, Wuniqiemu T, Wei Y, et al. Proteomics analysis reveals suppression of IL-17 signaling pathways contributed to the therapeutic effects of Jia-Wei Bu-Shen-Yi-Qi formula in a murine asthma model. *Phytomedicine* 2022;95:153803.
[132] Savin IA, Zenkova MA, Sen'kova AV. Bronchial asthma, airway remodeling and lung fibrosis as successive steps of one process. *Int J Mol Sci* 2023;24:16042.
[133] Wang W, Yao Q, Teng F, Cui J, Dong J, Wei Y. Active ingredients from Chinese medicine plants as therapeutic strategies for asthma: overview and challenges. *Biomed Pharmacother* 2021;134:111383.
[134] Jasemi SV, Khazaei H, Morovati MR, et al. Phytochemicals as treatment for allergic asthma: therapeutic effects and mechanisms of action. *Phytomedicine* 2024;122:155149.
[135] Jiang W, Qi J, Li X, et al. Post-infectious cough of different syndromes treated by traditional Chinese medicines: a review. *Chin Herb Med* 2022;14:494–510.
[136] Li X, Wen Z, Si M, et al. Exploration of Hanshi Zufei prescription for treatment of COVID-19 based on network pharmacology. *Chin Herb Med* 2022;14:294–302.

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