Phytochemicals in Food and Medicine

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Phytochemicals in Asthma Management: Mechanism, Translational Gap and Clinical Integration

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ABSTRACT

Asthma is a chronic inflammatory airway disease characterized by oxidative stress, immune dysregulation, and airway remodeling. Conventional therapies such as corticosteroids and bronchodilators provide symptomatic relief but are limited by adverse effects and incomplete efficacy in heterogeneous phenotypes. Phytochemicals, including flavonoids, alkaloids, terpenoids, saponins, and coumarins, have emerged as promising adjuncts due to their molecular mechanisms targeting key inflammatory pathways. A systematic review was conducted following PRISMA guidelines across PubMed, Scopus, and Web of Science (2004–2026). Studies reporting asthma-related outcomes of phytochemicals in preclinical or clinical settings were included. Evidence quality was assessed using the GRADE framework to distinguish randomized controlled trials (RCTs) from observational and preclinical studies. Quercetin modulates PI3K/Akt/mTOR signaling and suppresses Th2 cytokines, reducing airway inflammation. Glycyrrhizin inhibits NF-κB activation and enhances corticosteroid responsiveness, with derivatives such as SHR-1905 currently in Phase III trials for severe asthma. Piperine, a bioenhancer, is under evaluation in inhalable formulations. Other phytochemicals, including saponins from *Bacopa monnieri* and coumarins from *Amburana cearensis*, remain at preclinical stages but demonstrate immunomodulatory and bronchodilatory potential. Despite these advances, translational gaps persist. Clinical adoption is hindered by poor bioavailability, limited randomized controlled trials, and safety concerns such as hepatotoxicity with glycyrrhizin. Integrating phytochemicals into current therapeutics offers a pathway toward personalized, safer, and more effective asthma management. This review synthesizes molecular mechanisms, highlights translational gaps, and proposes strategies for clinical integration, bridging bench discoveries to bedside applications of phytochemicals in asthma management.

1 | Introduction

Asthma affects more than 300 million people worldwide, with prevalence expected to rise significantly by 2025 (GINA 2024). In India alone, over 34 million individuals suffer from asthma, contributing disproportionately to global disability-adjusted life years (Abdurrahman et al. 2020). Conventional therapies, including corticosteroids and biologics, have improved disease control but remain limited by side effects, high costs, and incomplete efficacy (Agache et al. 2021). These challenges have prompted interest in phytochemicals as adjunct therapies. Numerous medicinal plants have been reported to be used for the treatment of asthma (Table 1). Various phytochemicals reported to have a direct impact in asthmatic conditions. Natural, plant-based, nontoxic anti-inflammatory medications are crucial for the treatment of several inflammatory illnesses (Aich et al. 2012). Understanding the mechanism of action and possible therapeutic advantages of the phytochemicals requires knowledge of the doses that target the immunopathology of asthma and the pharmacological effects in pulmonary disorders.

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TABLE 1 | Medicinal plants used in asthma management.

Name of the plant	Family	Chemical composition	Reference
Aerva lanta L.	Amaranthaceae	β-sitosteryl palmitate, α- amyrin and β-sitosterol (triterpenoids), Canthin - 6-one and β-Carboline, Hentriacontane, D-glucoside (alkaloids), betulin, campesterol, Chrysin (flavonoid glycosides)	Zapesochnaya et al. (1992)
Ageratum conyzoides L.	Asteraceae	Tannins, quercetin, isoquercetin, alkaloids, and mainly flavonoids, oleoresin, resin, ceryl alcohol, ailanthin, ceryl palmitate, and saponins	Kundu and Laskar (2010) and X. L. Yang et al. (2014)
Asystasia gangetica T. Adams	Acanthaceae	Sugars, phenolics, saponins, steroids, tannins and amino acids, alkaloids, flavonoids, terpenoids, quinines, carbohydrates and phenolics	Bouabdallah et al. (2023)
Bacopa monnieri L.	Scrophulariaceae	Brahmine, nicotinine, herpestine, bacosides A and B, saponins A, B and C (Alkaloids), triterpenoid saponins, stigmastanol, β-sitosterol, betulinic acid, D-mannitol, stigmasterol, α-alanine, aspartic acid, glutamic acid, and serine and pseudojujubogenin glycoside	Jeyasri et al. (2020)
Cassia sophera	Caesalpiniaceae	Ascorbic acid, dihydroascorbic acid and β-sitosterol. Anthraquinone sopheranin β-sitosterol, chrysophenol, physcion and emodin	Rahman et al. (2017)
Casuarina equisetifolia L.	Casuarinaceae	Alkaloids, steroids, triterpenoids, proteins, saponins, phenolics, glycosides, tannins and flavonoids, reducing sugars	Muthuraj et al. (2020)
Clerodendrum Serratum L.	Verbenaceae	D-mannitol, hispidulin, cleroflavone, apigenin, scutellarein, serratagenic acid, acteoside, verbascoside, oleanolic acid, clerodermic acid, γ-sitosterol, β-sitosterol, cholestanol, clerosterol, campesterol and 24-ethyl cholesterol	Praveen Kumar and Nishteswar (2013)
Eclipta alba Linn	Asteraceae	β-amyrin, hentriacontanol, Wedololactone, demethylwedelolactone, desmethyl-wedelolactone-7glucoside and other constituents are ecliptal, demethylwedelolactone, β-amyrin, luteolin-7-O-glucoside, hentriacontanol, heptacosanol, stigmasterol	Timalsina and Devkota (2021)
Hemidesmus indicus R. Br.	Asclepiadaceae	Hemidesmol, hesmidesmine, hemidesmin-1, hemidesmin-2, lupeol, 13- amyrins, 11-sitosterol, lupeol, α-amyrin, lupeol acetate, þamyrin acetate, hexane triconate acid and lupeol octacosonate, a coumarino lignoid, resin, glucoside, tannin	Nagat et al. (2016)
Amburana cearensis	Fabaceae	Coumarins, flavonoids, phenolic glycosides, phenolic acids, phenylpropanoid derivatives, and triterpenoids	Silveira et al. (2022)
Lepidium sativum L.	Cruciferae	Protein, lipids, carbohydrates, fiber, ash, moisture, alkaloids, flavonoid, saponin, tannin and phenol	Al-Snafi (2019)
Myrica esculenta Buch. Ham.	Myricaceae	Tannins, phenolic acids, flavonoids, terpenes, glycosides, steroids, volatile oils, and amino acids	Kabra et al. (2019)
Olea europea	Oleaceae	Oleic acid, phenolic constituents, and squalene	Bouftira et al. (2019)
Kaempferia parviflora	Zingiberaceae	5-hydroxy-7-methoxyflavone, 5,7-dimethoxyflavone, 5-hydroxy-7,40-dimethoxyflavone, 5,7-dimethoxyflavone, 5,7,40-trimethoxyflavone, 5,7,30,40-tetra dimethoxyflavone, 5-hydroxy-3,7-dimethoxyflavone, 5-hydroxy-3,7,40-heptamethoxyflavone, 5,3,7-trimethoxyflavone, and 5-hydroxy-3,7,30,40-trimethoxyflavone. Found 3,5,7,30,40-heptamethoxyflavone, 5,3,7,40-tetramethoxyflavone, 5-hydroxy-7,40-dimethoxyflavone, 20-hydroxy-40,60-dimethoxy chalcone, and 20-hydroxy-4,40,60-trimethoxychalcone-hydroxypanduratin A, panduratin A, sakuranetin, pinostrobin, pinocembin, and dihydro-5,6-dehydrokawain	Pripdeevech et al. (2012)
Pistacia integerrima	Anacardiaceae	Carotenoids, triterpenoids, alcohol, catechins and flavonoids. Tannins, essential oil, resin, carotenoids, pistacienoic acid, triterpene alcohol and triterpenoic acid catechins	Rauf (2013)

Although numerous reviews have described their mechanisms (Gautam et al. 2024), few have addressed the translational hurdles that prevent clinical adoption. This review aims to bridge that gap by critically analyzing phytochemicals not only for their pharmacological actions but also for their potential integration into clinical practice, focusing on bioavailability, drug interactions, formulation strategies, and regulatory considerations.

1.1 | Asthma Pathophysiology and Immune-Mediated Airway Hyperresponsiveness

Asthma pathophysiology involves mast cell activation, IgE-mediated responses, eosinophilic infiltration, and release of pro-inflammatory mediators such as histamine, leukotrienes, and cytokines (Al-Snafi 2019). Body's mast cells coated with IgE antibodies, T cells and eosinophils are primarily activated by foreign or antigenic substances that are recognized by mast cells. This results in the release of proinflammatory mediators like histamine, leukotrienes, interleukins (IL-2, IL-3, IL-4, IL-5), tumor necrosis factor-α (TNF-α), GM-CSF, prostaglandins, and others. Such cell degranulation increases vascular permeability, which causes pulmonary edema and exudate. On the other hand, selectins (signal-transducing receptors) and integrins (adhesion receptors) influenced neutrophilic migration via chemotaxis to the inflammatory site. By increasing the expression of the C3b opsonin, this migration causes oxidative stress and tissue damage by triggering the release of leukotrienes LTB4 and LOX-5, which are responsible for the generation of ROS. Increase smooth tissue/muscle bronchoconstriction, mucus production, and cellular endothelial vasodilation all at once. These processes are regulated by PGD-2 (Figure 1). It is a condition when respiratory infections or inhaled particles trigger an immune response through IgG antibodies. The process of tissue destruction was initiated by an increase in the input of inflammatory cells, which in turn generated inflammatory mediators (Al-Snafi 2019). These processes drive airway hyperresponsiveness, mucus overproduction, and tissue remodeling. Although conventional drugs target these pathways, phytochemicals offer complementary mechanisms, including modulation of NF-κB signaling, suppression of

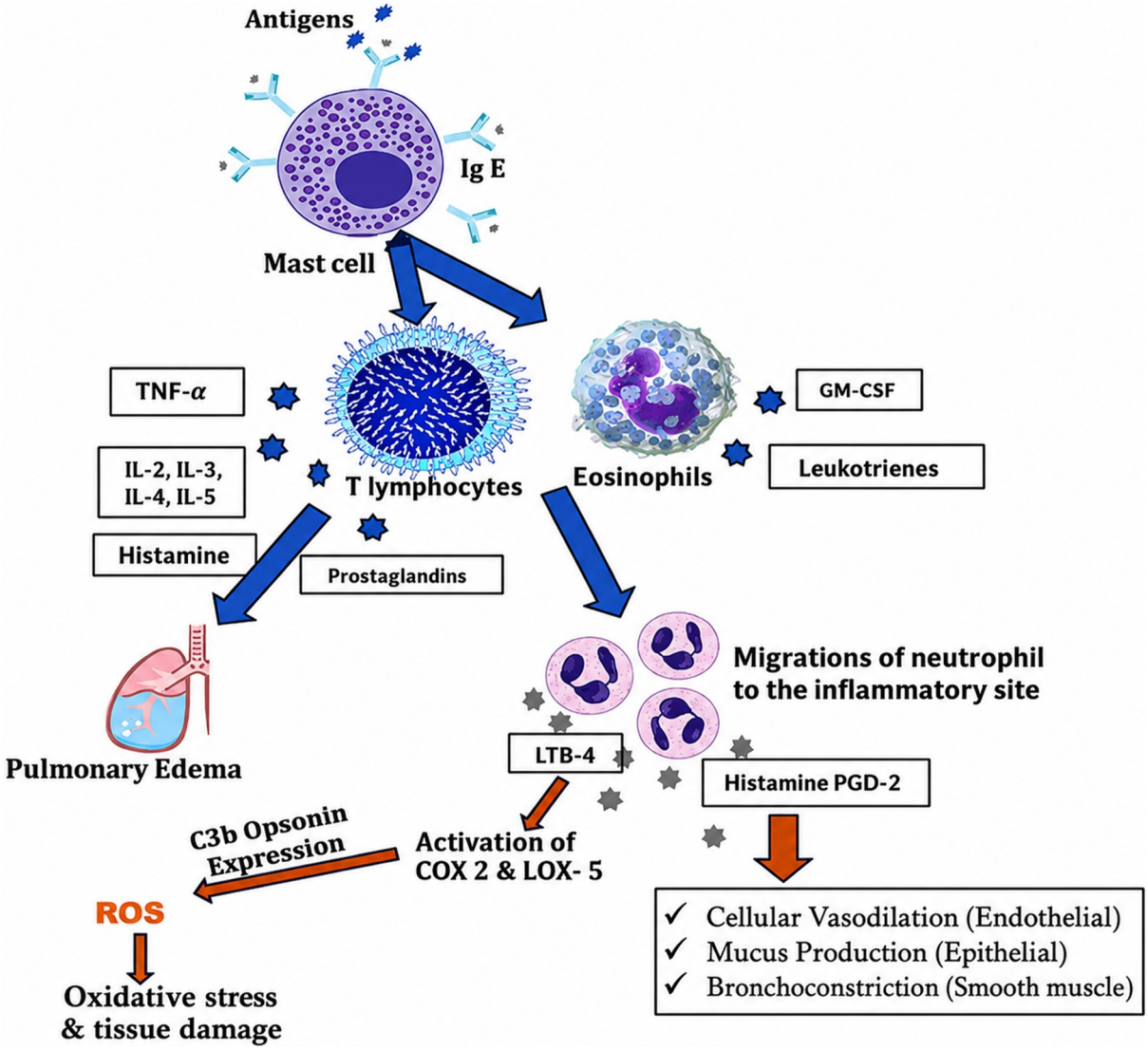


FIGURE 1 | Schematic representation of the biological process of asthma (antigenic stimulation). C3b, opsonin; COX-2, Cyclooxygenase type 2; GM-CSF, granulocyte-macrophages colony-stimulating factor; IL, interleukin; LOX-5, lipoxygenase type 5; LTB4, Leukotriene type B; PGD-2, prostaglandin type D; ROS, Reactive oxygen species; TNF-α, Tumor necrosis factor-α.

oxidative stress, and regulation of Th2 cytokines (S. Chen 2012). Emerging evidence also suggests novel roles for phytochemicals in epigenetic modulation and microbiome regulation (Tanaka and Takahashi 2013b).

2 | Methodology

This review adopted a systematic approach following PRISMA guidelines. Literature searches were conducted across PubMed, Scopus, and Web of Science from 2004 to 2024 using keywords including "asthma", "phytochemicals", "alkaloids", "flavonoids", "terpenoids", “clinical trials", and "mechanisms". Inclusion criteria were peer-reviewed studies in English reporting asthma-related outcomes in preclinical or clinical settings. Exclusion criteria included nonpeer-reviewed sources and studies lacking asthma-specific endpoints. Screening was performed independently by two reviewers, and evidence quality was assessed using the GRADE framework (Guyatt et al. 2011) which evaluates risk of bias, inconsistency, indirectness, imprecision, and publication bias. This allowed us to distinguish between high-quality randomized controlled trials and lower-quality observational studies, ensuring transparency in evidence grading. A PRISMA flow diagram (Figure 2), summarizes the study selection process. This methodology ensures transparency and rigor, distinguishing this review from narrative approaches. Records were identified through database searches, screened for eligibility, and assessed for inclusion in qualitative and quantitative synthesis.

3 | Results/Molecular Mechanistic Insights of Phytochemicals

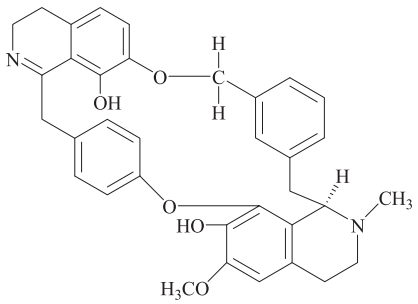
The main therapeutic agents in the anti-asthmatic regime widely employed were alkaloids, flavonoids, triterpenoids and coumarins, etc. having a significant impact on the pharmacology of asthma management.

3.1 | Alkaloids

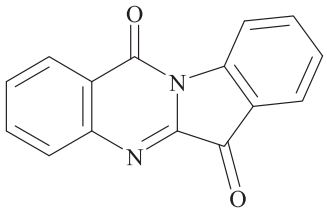
Alkaloids are the naturally occurring bioactive compounds having basic nitrogenous structure with distinct pharmacological potentials in asthma pharmacology. It can notably reduce eosinophilic inflammation in the pleural cavities and bronchoalveolar lavage which could be developed by activated eosinophils producing cysteinyl leukotrienes and lipid bodies. It also suppresses the synthesis of exotoxins, which eosinophils use as a chemoattractant.

The bisbenzylisoquinoline alkaloids (*Cissampelos sympodialis*) significantly reduced eosinophil migration and modulated Th2 cytokine production, resulting in a reduction of IL-5 levels in the bronchoalveolar lavage, while presenting high levels of the anti-inflammatory cytokine IL-10 (Tereza Cerqueira-Lima et al. 2010). Alkaloids affect inflammatory leukocytes by altering mast cell activation in many ways. In vitro investigations have also evidenced the inhibitory role in mast cell degranulation induced by pharmacological or immunological stimuli. Furthermore, through IgE-dependent pathways, warifteine, an alkaloid from *Cissampelos sympodialis* was found to lower the incidence of acute allergic events, such as thermal hyperalgesia and anaphylactic shock (Dey et al. 2020). Apart from it, various classes of alkaloids possess various mechanisms of action against the clinical asthma as described in Table 2 and also depicted in Figure 3.

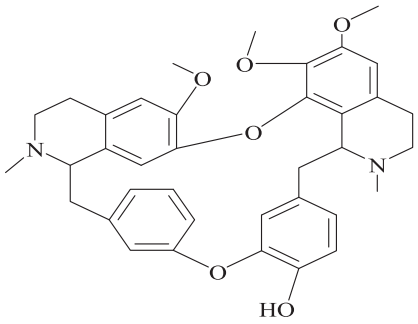
As per the existing knowledge, asthma inflammation begins when allergens trigger immune cell activation, particularly macrophages and dendritic cells. Certain bioactive natural phytochemicals such as berbamine (*Berberis* species) and eripatrin (*Orthosiphon aristatus*) act at this early stage to suppress immune activation. Once activated, phospholipase A2 releases arachidonic acid, which feeds into two major inflammatory pathways: the COX-2 pathway producing prostaglandins, and the lipoxygenase pathway producing leukotrienes, both of which drive inflammation and bronchoconstriction. Several inhibitors, including chelerythrin (*Chelidonium majus*), quinolone (Rutaceae plants), and isoquiline (Papaveraceae and Berberidaceae families), block lipoxygenase activity and reduce leukotriene formation. Parallel to this, the TAK1 pathway stimulates IL-1β, which activates fibroblast-like synoviocytes to increase NF-κB, COX-2, and CCR7 expression; tryptathrin (*Indigofera tinctoria*) and piperine (*Piper nigrum, Piper longum*) counteract this signaling, thereby dampening inflammatory gene expression. Dendritic cell migration further amplifies inflammation, but magnoflorine (Magnoliaceae and Berberidaceae families) and isoquathrin (*Mangifera indica*, *Camellia sinensis*) inhibit PI3K/Akt signaling to block this process, whereas colchicine (*Colchicum autumnale*) reduces neutrophil activity and CCR7 expression. Altogether, these phyto alkaloids act at multiple checkpoints in immune activation, arachidonic acid metabolism, signal transduction, and cell migration to reduce inflammation, bronchoconstriction, and immune overactivation, highlighting their therapeutic potential in asthma management. The below Figure 2 described the phytochemicals and their active role in asthma pathology.



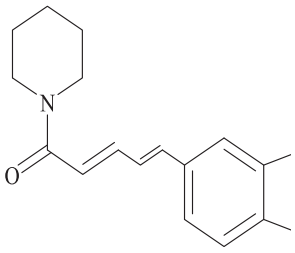
Warifteine



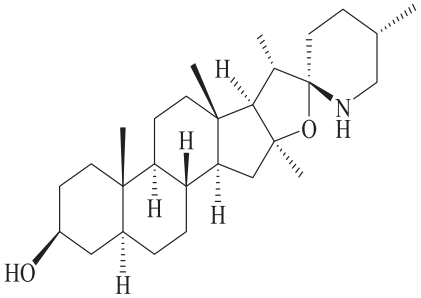
Tryptathin



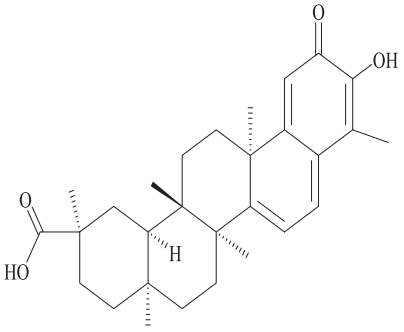
Berbamine



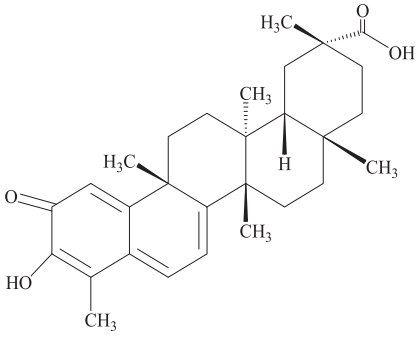
Piperine



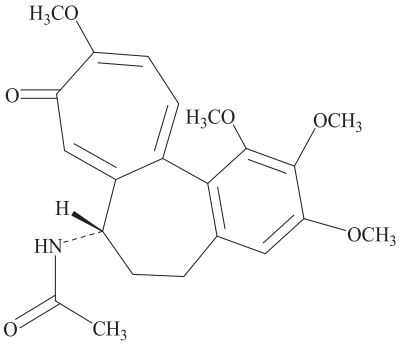
Tomatidine



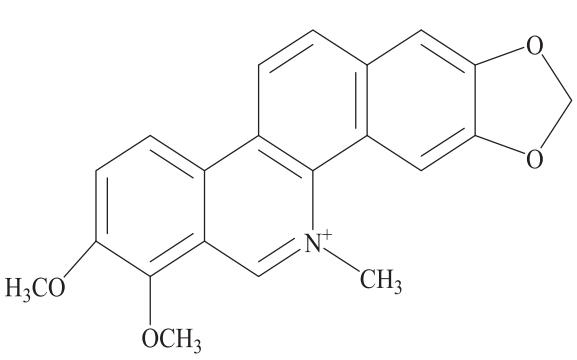
Triptolide



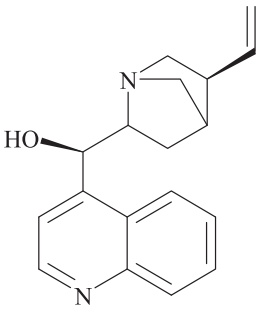
Celastrol



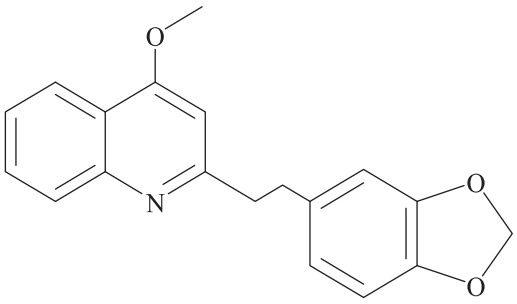
Colchicine



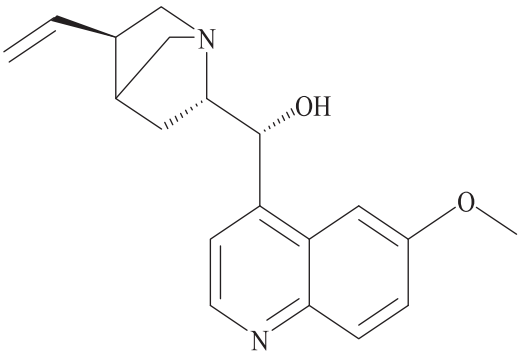
Chelerythrin



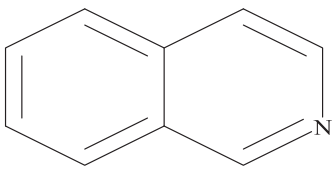
Cinchonine



Cusparine



Quinine



Isoquinoline

3.1.1 | *Piperine*

Piperine, an alkaloid containing the piperidine nucleus, have monoclinic needles that have a strong, pungent flavor and are partially soluble in water. Piperine has a number of well-established health advantages and beneficial therapeutic properties (Mohapatra et al. 2015).

In asthma, production of pro-inflammatory mediators (i.e., IL-1β, IL-8, TNF-α, LTB-4, and NE) exhibited notably higher concentrations of oxidative stress indicators, including Malondialdehyde (MDA), Myeloperoxidase (MPO), Nitric Oxide (NO), and Matrix Metalloproteinase-9 (MMP9), in comparison to the normal conditions. It also raised the number of inflammatory cells, neutrophils, and macrophages (Ashokkumar et al. 2021). Piperine reduced the release of cytokines, oxidative stress indicators, and enhanced lung function when combined with other drugs (P. Saha et al. 2022; S. Saha, Ghosh, et al., 2022; S. Saha, Mukherjee, et al. 2022). Moreover, piperine's favorable binding affinity for the MMP-9, IL-8, human neutrophil elastase, and MPO receptors was well established. The protective function of piperine in inflammatory cells increased oxidative stress and pro-inflammatory mediator synthesis (Vani et al. 2019). Reduction of airway hyperresponsiveness improves bronchial airflow and antioxidant properties protects against oxidative stress and airway remodeling (Figure 4).

3.1.2 | *Colchicine*

Structured (-) -(aS, 7S)- Colchicine is a naturally occurring alkaloid that is obtained from *Colchicum autumnale*, and *C. luteum* (Kefi 2018). Whereas the synthetic drug indomethacin also exhibits a similar mechanism of action. Cells switch the arachidonic acid (AA) in a different way in the presence of colchicine. They focused on alveolar macrophages, a subpopulation of immune cells that release a range of substances when they get activated. The administration of colchicine to these immune cells led to a significant reduction in the production of some compounds (metabolites) from arachidonic acid by the 5-lipoxygenase enzyme (5-LO). This enzyme is also involved in the process of inflammation. Colchicine also decreased the overall release of arachidonic acid and other inflammatory compounds, but to a lower degree. Cell internal microtubule structure is disrupted by colchicine's effects on arachidonic acid metabolism. Colchicine further stopped the cells from generating 5-LO products in response to zymosan, a substance that activates the immune system. Colchicine, like other drugs such as nocodazole and vinblastine, also modify the way immune cells respond to arachidonic acid, particularly by reducing the production of inflammatory chemicals (Downing et al. 2020).

3.1.3 | *Tomatidine*

Tomatidine, a tetra-saccharide glycoalkaloid or steroid alkaloid found naturally in leaves of tomatoes has come to light with the development of novel bioengineered tomatoes (Zrieq et al. 2021). Tomatidine greatly reduced the infiltration of eosinophils into the lung tissue as well as goblet cell hyperplasia. It also inhibited airway hyper responsiveness (AHR) and decreased Th2-associated cytokine and chemokine levels in bronchoalveolar lavage fluid (BALF). However, low doses of tomatidine suppressed the production of OVA-IgE and Th2 cytokines (IL-4, IL-5, and IL-13) as observed in the splenocyte culture. Tomatidine dramatically decreased the levels of proinflammatory cytokines (IL-6), cell adhesion molecules (ICAM-1), and chemokines (IL-8 and CCL11) in human tracheal epithelial cells. It appears to reduce lung inflammation and the pathogenic presentation of asthma (Kuo et al. 2017).

3.1.4 | *Pharmacokinetics and Integration Challenges of Alkaloids*

The alkaloids all show strong pharmacological promise but suffer from pharmacokinetic drawbacks such as poor solubility, rapid metabolism, low oral bioavailability, narrow therapeutic windows, and systemic toxicity, which hinder their clinical integration. Such as Tryptanthrin, an indoloquinazoline alkaloid, suffers from poor aqueous solubility and rapid hepatic metabolism, resulting in low oral bioavailability (Bhambhani et al. 2021). Berbamine, a bisbenzylisoquinoline alkaloid, undergoes extensive first-pass metabolism and demonstrates poor systemic exposure, requiring high doses to achieve therapeutic effects (Pereira et al. 2023). Liensinine and magnoflorine, isoquinoline alkaloids from lotus, display weak absorption and rapid clearance, limiting their systemic efficacy (Bhambhani et al. 2021). Piperine, although widely recognized for enhancing the bioavailability of other drugs, itself exhibits poor solubility and rapid metabolism, reducing its stability in clinical use (Pereira et al. 2023). Triptolide, a diterpenoid alkaloid-like compound, is constrained by a narrow therapeutic window, systemic toxicity, and rapid clearance, with hepatotoxicity being a major concern (Bhambhani et al. 2021). Colchicine, a tropolone alkaloid, is similarly limited by its narrow therapeutic index and extensive metabolism, which increases the risk of toxicity even at therapeutic doses (Pereira et al. 2023). Chelerythrin, a benzophenanthridine alkaloid, suffers from poor solubility and rapid metabolism, and its cytotoxicity restricts systemic application. Isoquinoline alkaloids in general are characterized by poor oral bioavailability, significant first-pass metabolism, and narrow therapeutic windows, whereas quinolone-like alkaloids show variable absorption, rapid metabolism, and potential hepatotoxicity (Bhambhani et al. 2021). Collectively, these pharmacokinetic limitations such as low solubility, poor bioavailability, rapid metabolism, and toxicity, underscore the need for advanced formulation strategies such as nanoparticles, prodrugs, and targeted delivery systems to enable their safe and effective clinical translation.

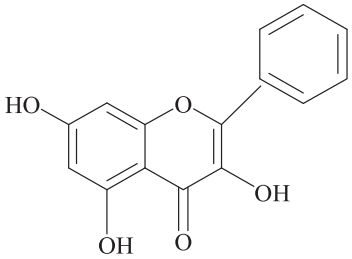
3.2 | Flavonoids

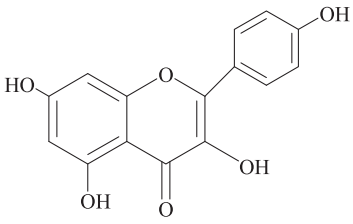
Flavonoids are powerful antioxidants and anti-allergic nutrients that stop the production of Th2 type cytokines (like IL-4 and IL-13), the release of chemical mediators, cellular CD40 ligand resulted seize the high-affinity immunoglobulin E (IgE) receptors, such mast cells and basophils. Flavonoids also have an impact on the maturation of naive CD4+ T cells into effector T-cells and inhibit the activation of the aryl hydrocarbon receptor, which stops IL-4-induced signal transduction (Figure 5) (Seder and Paul 2003). Several studies have demonstrated the beneficial effects of flavonoids in asthma pharmacology (Tanaka and Takahashi 2013a).

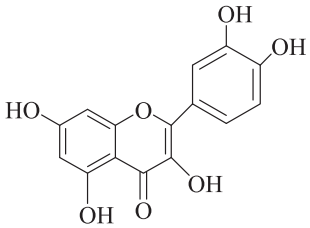
A wide variety of flavonoids are found in fruits, vegetables, and leaves and belong to the class of polyphenolics. Fundamentally this group of biomolecules have a heterocyclic structure with an oxygen molecule, joined by two phenyl rings. Although flavonoids are specifically defined as polyhydroxy polyphenol (non-ketonic) compounds, bioflavonoids are described as flavonoids that contain a ketonic group, such as neoflavonoids and isoflavonoids. They have a plethora of well-studied medicinal benefits, including as potent anti-inflammatory, immune-modulating, anti-allergic, and antioxidant qualities. Flavonoids have a great therapeutic potential for the treatment of asthma, even though their functions diverge, notwithstanding the lack of human clinical trials and epidemiological studies at this time (Tanaka and Takahashi 2013b; Toledo et al. 2013). Various flavonoids such as Galangin, Kaempferol, Quercetin, Buddledin A, Chrysin, etc. possess diverse mechanisms as listed in Table 3 in therapeutics of asthma.

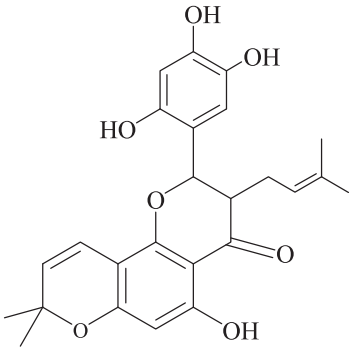
Asthma pathogenesis begins with allergen exposure that polarizes Th2 cells, which secrete IL-4 and IL-13 to drive B-cell class switching to IgE and airway hyperresponsiveness, and IL-5 to recruit eosinophils; flavonoids such as quercetin, resveratrol, luteolin, and kaempferol suppress these cytokines, with quercetin reducing IgE and luteolin inhibiting mast cell activation (Tanaka and Takahashi 2013a, 2013b; X. Li et al. 2021). Intracellular signaling cascades amplify inflammation through the PI3K/Akt/mTOR pathway, modulated by quercetin and inhibited by wogonin, and the MAPK/ERK pathway, suppressed by wogonin, chrysin, and apigenin; transcription factors NF-κB and STAT6 further drive inflammatory gene expression, with apigenin blocking NF-κB and wogonin suppressing IL-4/STAT6 (X. Li

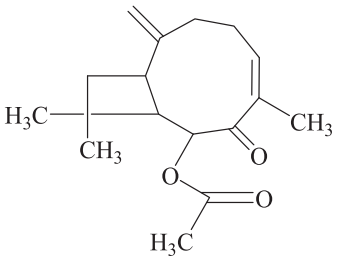
et al. 2021; Y. Zhang et al. 2020). Oxidative stress worsens tissue damage via ROS, countered by the Nrf2/SIRT1 axis, which resveratrol activates while upregulating PTEN to inhibit PI3K, and by antioxidants such as quercetin, silibinin, and kaempferol that neutralize ROS and reduce macrophage activation (Y. Zhang et al. 2020; A. Singh et al. 2022). In the effector phase, chronic inflammation causes airway smooth muscle hyperplasia and mucus hypersecretion, with wogonin inducing ASM apoptosis, chrysin reducing proliferation via ERK1/2 inhibition, and kaempferol and chrysin decreasing remodeling and mucus secretion; additionally, Artonin E (Artocarpus genus), though not yet tested in asthma models, shows cytotoxic and anti-inflammatory potential likely targeting effector cells (A. Singh et al. 2022). Whereas Apigenin, Wogonin, Chrysin, Eriodictyol targets overlapping pathways (NF-κB, MAPK, STAT6), reducing cytokine cascades and oxidative stress. Similarly, Silibinin enhances Nrf2, boosts antioxidant enzymes, and suppresses NF-κB to counteract inflammation.

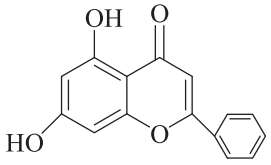

Galangin

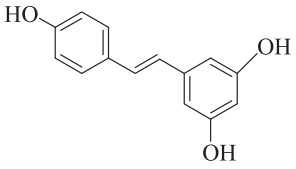

Kaepferol

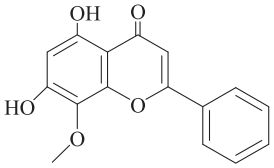

Quercetin

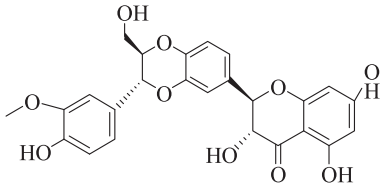

Artonin E

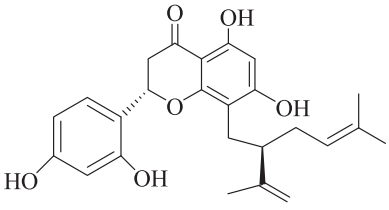

Buddledin A

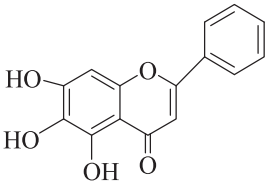

Chrysin

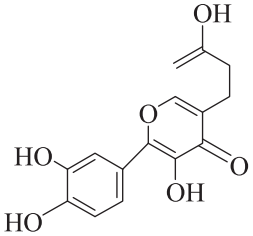

Resveratol


Wogonin


Silibinin


Sophora-flavanone G


Baiacalein


Fisetin

3.2.1 | *Quercetin*

Quercetin is a naturally occurring polyphenol flavonoid with three rings and five hydroxyl groups similar to the structure in terms of disodium cromoglycate, a synthetic anti-allergic drug. It is naturally present as glycone or carbohydrate conjugates in plants. The main foods that include quercetin are apples, tomatoes, grapes, brassica, tea, and other typical fruits and vegetables. After ingesting such fruits and vegetables, a substantial amount of quercetin stays in the plasma, despite the fact that it is mostly metabolized in the liver and stomach.

Quercetin suppresses mast cell IgE/Anti-IgE activation, which in turn decreases the generation of inflammatory mediators such as histamine and leukotrienes. Recent studies suggest quercetin may have the ability to lower the periostin content in bronchoalveolar lavage fluid. The fasciclinian protein periostin, contributes significantly to asthma through allergic inflammation. This protein primarily binds with other ECM proteins to generate subepithelial fibrosis in bronchial asthma. Since IL-13-mediated periostin expression is known to be corticosteroid-sensitive, periostin expression is frequently virtually downregulated in asthma patients on corticosteroids. The mechanistic approach discovered that blocking transforming growth factor-β1 TGF-β1 might exacerbate asthmatic symptoms. By suppressing the TGF-β1/Smad pathway in lung tissues, the flavonoid quercetin had the most protective impact against asthma (Bidian et al. 2020).

3.2.2 | *Wogonin*

Wogonin, a flavone derivative with the molecular formula 5,7-dihydroxy-8-methoxyflavone, is derived from *Scutellariae* species. The whole herb of *S. radix*., *S. rivularis* Wall, the roots of *S. baicalensis* Georgi, the leaves of *Andrographis paniculata* (Burm. F.) Nees, and the stems of *Anodendron affine* Druce are among the herb parts that can be used to extract wogonin (Alsharairi 2021). Wogonin inhibits inflammation, by reducing the generation of Th2-type inflammatory cytokines and the number of eosinophils in the nasal mucosa (Figure 5). It also decreased OVA-specific IgE, IL-4, IL-5, and IL-13 levels in NALF, as well as OVA-induced eotaxin and Regulated upon Activation, Normal T cell Expressed and Secreted (RANTES) levels. The number of eosinophils infiltrated during asthma conditions. Wogonin had significantly decreased eosinophil levels and also stopped the invasion of eosinophils (K. A. Kim et al. 2018).

3.2.3 | *Chrysin*

Chrysin, a bioactive component obtained from fruit, vegetable, and even mushrooms that possesses the typical flavone backbone of 15 carbons. It shares a similar chemical structure, consisting of two fused rings and a phenyl ring attached to the second position. It contains the same flavone structure but for an additional hydroxyl group at positions five and seven. The amino acid that is converted to chrysin is phenylalanine (Mani et al. 2018).

The anti-inflammatory and immunoregulatory properties of chrysin flavonoid, have an impact on the immune system. They appear to possess a variety of potential biological roles, immune-regulating traits, and antioxidant qualities. NF-kB is known to be antagonistic to cChrysin and regulates a variety of proinflammatory cytokines, including IL-1, IL-2, IL-6, and TNF-a, inducible enzymes, COX-2 and iNOS, adhesion molecules, chemokines, and other acute phase proteins (Figure 5). They are all necessary for regulating the majority of inflammatory processes of the immune system and those associated with neurodegenerative illnesses. Moreover, Chrysin can lower airway inflammatory cells, IgE levels, and the ratio of (Th1) T-beta in allergic responses such as asthma (Th2) GATA-3 (A. Siddiqui et al. 2018).

3.2.4 | *Pharmacokinetics and Integration Challenges of Flavonoids and Polyphenols*

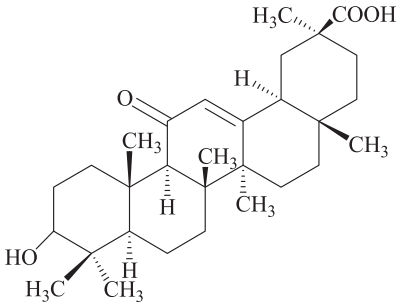
The prominent problem of most flavonoids and polyphenols such as quercetin, resveratrol, luteolin, apigenin, kaempferol, wogonin, chrysin, silibinin, and artonin E, etc. suffer from poor oral bioavailability, rapid metabolism (glucuronidation, sulfation, and methylation), instability in plasma, and short half-lives. These pharmacokinetic drawbacks limit their therapeutic translation despite strong in vitro activity. These pharmacokinetics limitations are given in the Table 4.

3.3 | Terpenoids

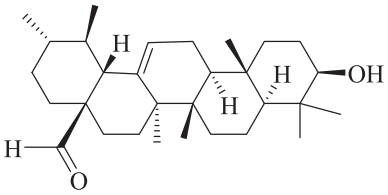
Terpenoids and terpenes present in the plants inhibit the distinct phases of the inflammatory process which mitigate a range of inflammatory symptoms. Many in vitro studies have demonstrated the anti-asthmatic effects of terpenoids and volatile terpenes. Strong anti-asthmatic properties are found in d-limonene (a monoterpene) and reduce the generation of reactive oxygen species (ROS) (Bai et al. 2020). Moreover, various terpenoids such as glycyrrhizin, ursolic acid, butanoic acid, celastrol, parthenolid, aethiopinone, triptoloid, irisolidone and inuviscolide are well explored plant chemicals therapeutically active against asthma. All those chemicals possess a numerous mechanism against asthma therapeutics (Table 4) by modulating the arachidonic acid cascade, inhibiting NF-κB signaling, and suppressing cytokine production. These mechanisms collectively reduce bronchoconstriction, oxidative stress, and airway inflammation (Figure 6). The inflammatory cascade in asthma is initiated by the release of arachidonic acid from membrane phospholipids via *phospholipase A2 (PLA2)*. Glycyrrhizin (A triterpenoid saponin glycoside) and aethiopinone (A diterpenoid quinone) inhibit PLA2, thereby blocking the precursor supply for both the *cyclooxygenase (COX)* and *lipoxygenase (LOX)* pathways (D. K. Semwal et al. 2025). Triptoloid (Diterpenoid epoxide) from *Tripterygium wilfordii* specifically targets the *5-LOX* pathway, reducing leukotriene synthesis, which are potent bronchoconstrictors. Glycyrrhizin and irisolidone also inhibit *COX-1* and *COX-2*, reducing prostanoid production, whereas inuviscolide (Sesquiterpene lactone) acts downstream to suppress *prostaglandin E2 (PGE2)*. In the *NF-κB signaling pathway*, butanoic acid (short-chain fatty acid) from gut microbiota and also found in butter inhibits the *IKK complex* and *p65 phosphorylation*, preventing NF-κB nuclear translocation. Celastrol (Quinone methide triterpenoid) suppresses NF-κB, enhancing *TNF-induced apoptosis* and reducing inflammatory cell invasion. Irisolidone (Isoflavone) further downregulates NF-κB expression. Once NF-κB is activated, it

induces pro-inflammatory cytokines. Parthenolid (Sesquiterpene lactone) from *Tanacetum parthenium* suppresses *IL-6*, *TNF-α*, and *IL-1β*, whereas irisolidone reduces *TNF-α* and *IL-6*. Ursolic acid (Pentacyclic triterpenoid) inhibits *inducible nitric oxide synthase (iNOS)*, reducing nitric oxide production and oxidative stress.

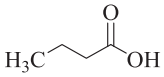
inflammation



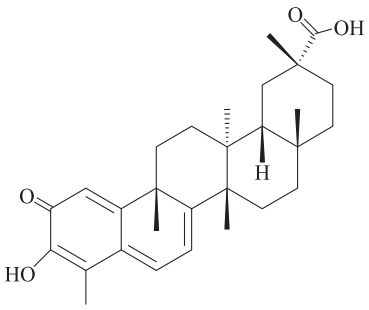
Glycerrhizin



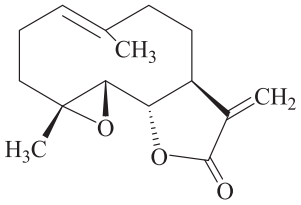
Ursolic acid



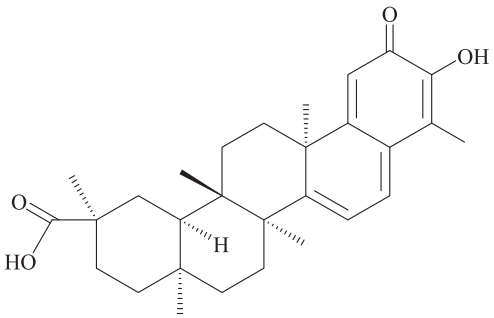
Butanoic acid



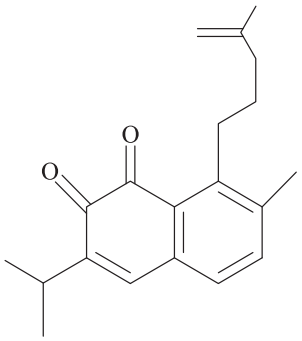
Celastrol



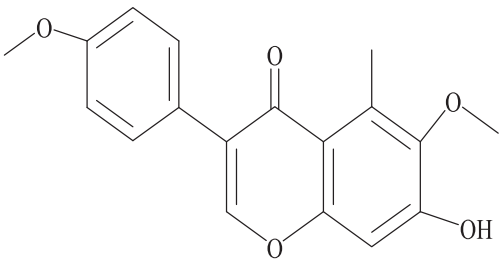
Parthenolide



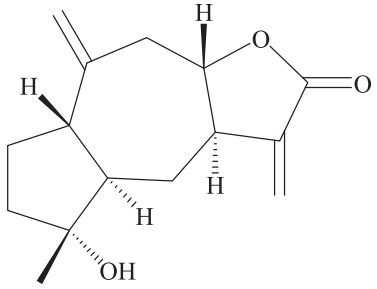
Triptoloid



Aethiopinone



Irisolidone



Inuviscolide

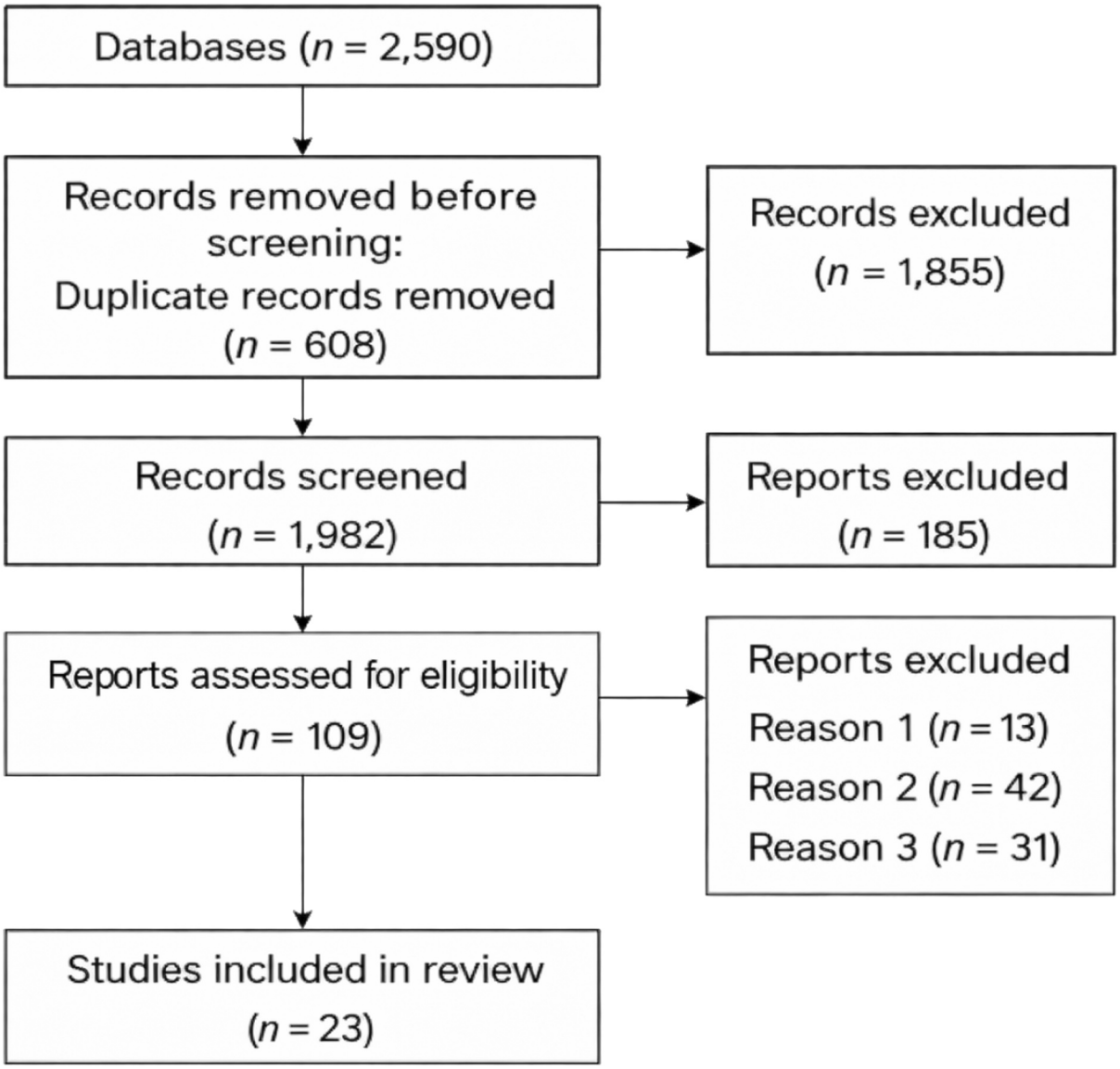


FIGURE 2 | PRISMA 2020 flow diagram illustrating the study selection process for the systematic review of phytochemicals in asthma management.

TABLE 2 | Plant alkaloids role as anti-asthmatic agents.

Mechanism of action	Alkaloids	Reference
1. Cyclooxygenase-2 inhibitor	Tryptathrin	Alsultan et al. (2021)
2. Targets phospholipase A_2 enzyme and implicated in the pro-inflammatory process	Berbamine	Z. Chen et al. (2021)
3. Inhibited the TAK1-induced NF-κB activation	Liensinine and magnoflorine	Danielewski et al. (2022)
4. Effects on IL1β-stimulated FLSs	Piperine	Huang et al. (2021)
5. Reduction of DC migration via PI3-K/Akt and NF-κB signal pathways-mediated downregulation of COX-2 and CCR7 expression	Triptolide	Lan et al. (2022)
6. Inhibit leukotriene synthesis in neutrophils	Colchicine	Obafemi et al. (2021)
7. Inhibition of 5-lipoxygenase product synthesis	Chelerythrin	Danielewski et al. (2022)
8. 12-lipoxygenase (12-LOX) enzyme inhibition	Isoquinoline	Alsultan et al. (2021)
9. Lipoxygenase inhibition rather than nonspecific reactivity	Quinolone	S. Siddiqui et al. (2023)

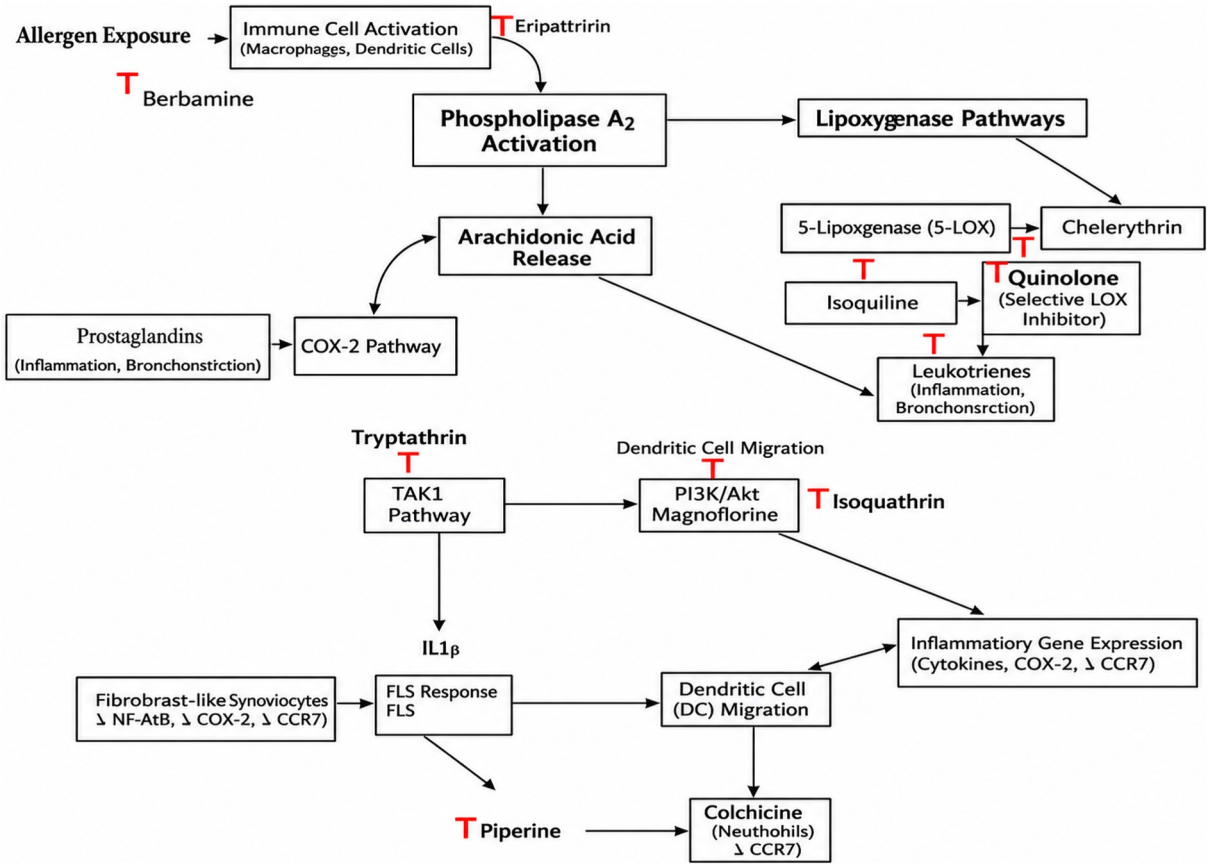


FIGURE 3 | Mechanistic inside of alkaloids in asthma management.

3.3.1 | *Glycyrrhizin*

Glycyrrhizin, also known as glycyrrhizic acid, is a triterpenoid saponin found in the root and rhizome extracts of *Glycyrrhiza glabra* (licorice). CBX is a derivative of glycyrrhetinic acid that resembles steroids and is related to compounds that are present in licorice plant roots (Bharathala et al. 2020).

In asthma, glycyrrhizin acts as an anti-inflammatory and immunomodulatory agent by blocking NF-κB activation and MAPK pathways, which lowers pro-inflammatory cytokines (TNF-α, IL-1β, IL-6). It reduces Th2 cytokines (IL-4, IL-5, IL-13), limiting eosinophil recruitment and IgE production, while stabilizing mast cells to prevent histamine and leukotriene release (Figure 4). Additionally, glycyrrhizin enhances antioxidant enzymes such as superoxide dismutase and glutathione peroxidase, protecting bronchial epithelium from oxidative stress. These combined effects decrease airway hyperresponsiveness and inflammation, with evidence of synergistic benefit when combined with β2-agonists such as salbutamol, though long-term use may cause pseudoaldosteronism. The course of therapy restored normal levels of IL-4 and IL-5 and stopped the decline in IFN-γ levels (Qi et al. 2023; D. K. Semwal et al. 2025; X. Li et al. 2019; L. Chen et al. 2022).

3.3.2 | *Ursolic Acid*

Ursolic acid, a pentacyclic triterpenoid, found in plants is used in human diets. It can be found as free acid or as the aglycones of triterpenoid saponins (Nguyen et al. 2021). Ursolic acid helps with breathing in allergic asthma (Figure 4) by inducing PPARγ (Peroxisome Proliferator-Activated Receptor Gamma), a special cell regulator that decreases inflammation, widens airways, and decreases the generation of allergen-causing molecules (S. H. Kim et al. 2013). PPARγ agonists mainly work by inhibiting inflammation and oxidative stress, most likely via having a protective effect on the mitochondria. It is a ligand-dependent transcription factor that belongs to the nuclear receptor superfamily. It regulates glucose metabolism and adipocyte growth and is mostly expressed in adipose tissue. Recent research has shown that PPAR-γ, which functions on immune and nonimmune cells, is essential for controlling inflammatory responses, including lung inflammation (C. Li et al. 2020).

3.3.3 | *Inuviscolide and Tomentosin*

A methyl group at Position 5, a hydroxy group at Position 5, and a sesquiterpene lactone known as inuviscolide are replaced by methylidene groups at Positions 3 and 8 (the 3aR, 4aR, 5R, 7aS, and 9aS stereoisomer) in addition to a hydroxy group at Position 5. It possesses anti-inflammatory qualities and was isolated from the aerial portions of *Inula hupehensis* (Paço et al. 2022). Tomentosin and inuviscolide, two pure sesquiterpene lactone compounds, were extracted from the leaves of *Inula viscosa* (Tom).

Inuviscolide and tomentosin, sesquiterpene lactones derived from *Inula viscosa*, share mechanistic similarities with other anti-inflammatory agents studied in human PBMCs, such as

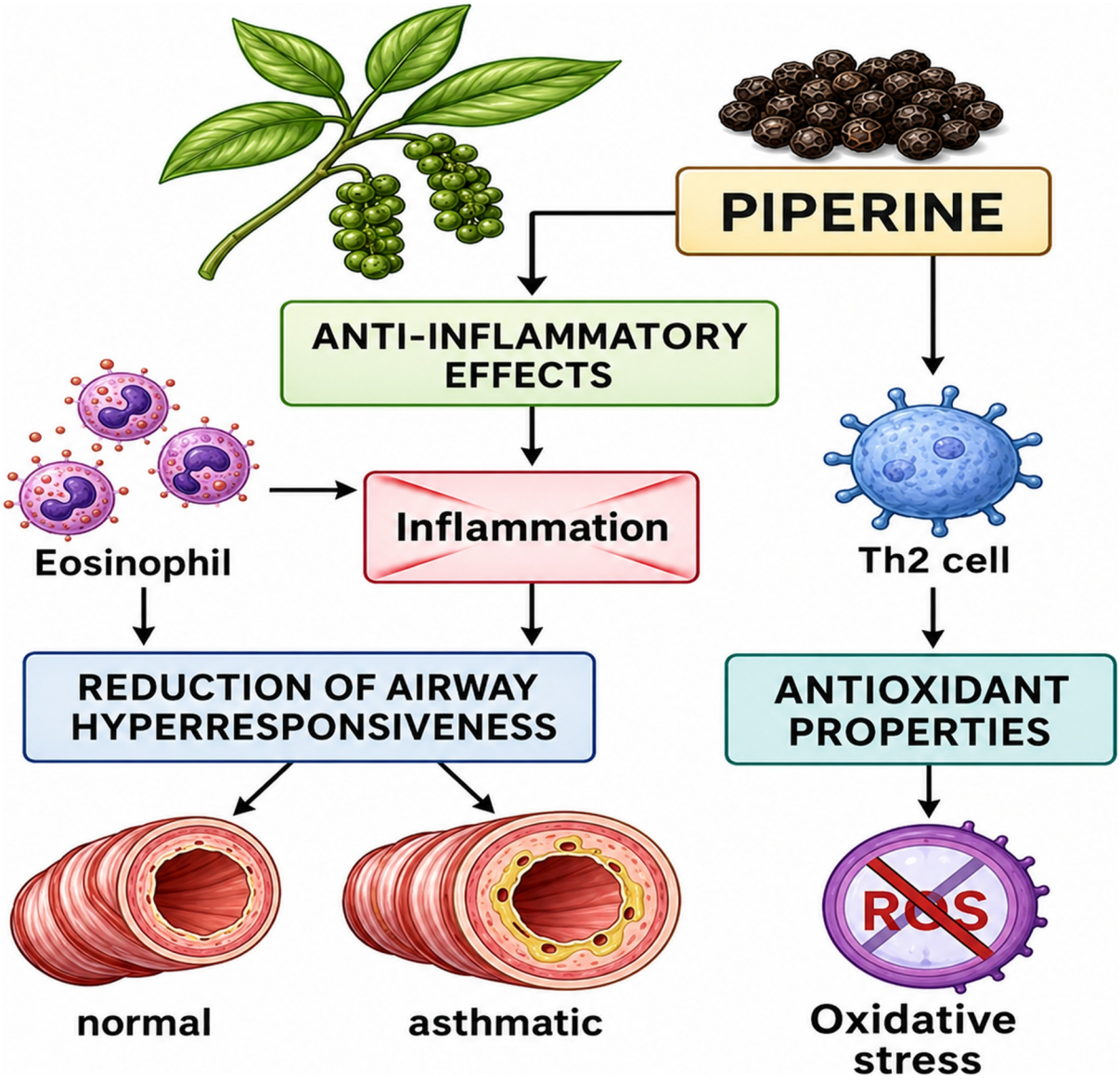


FIGURE 4 | Suppression of Th2 cytokines (IL-4, IL-5, IL-13) reduces eosinophilic infiltration. Immunomodulation balances Th2 cell activity.

those described by Abrham et al. (2010). Both compounds exert their effects in asthma by inhibiting NF-κB and MAPK signaling, leading to reduced transcription of pro-inflammatory cytokines (IL-1β, IL-2, IFNγ) and Th2 cytokines (IL-4, IL-5, IL-13), while modulating oxidative stress through suppression of iNOS and enhancement of antioxidant defenses. Tomentosin additionally promotes apoptosis of activated immune cells, thereby dampening chronic airway inflammation. These actions parallel the findings that certain medications decrease NF-κB p65/RelA and STAT1 protein levels via proteasomal degradation, selectively modulating cytokine release without affecting PBMC viability (Abrham et al. 2010). Taken together, this correlation highlights how both synthetic and plant-derived agents converge on transcription factor regulation to rebalance immune responses, suggesting potential therapeutic applications in asthma and other inflammatory conditions (Bouyahya et al. 2019; El Omari et al. 2021).

3.3.4 | Pharmacokinetics and Integration Challenges of Terpenoids

The main pharmacokinetic drawbacks of terpenoids and terpenes are their poor oral bioavailability, rapid metabolism, low aqueous solubility, and instability, which limit their therapeutic use despite strong biological activity. The details of pharmacokinetics limitations are tabulated below (Table 5).

4 | Mechanistic Approaches and Clinical Trials of Plant Chemicals in Asthma

Glycyrrhizin, ursolic acid, celastrol, parthenolide, triptolide, etc., are tested in murine asthma models (Table 6) with clear mechanistic outcomes such as cytokine suppression, Th17 inhibition, airway remodeling reduction, etc. Butanoic acid (butyrate) acts indirectly via the gut–lung axis and is promising in metabolomics

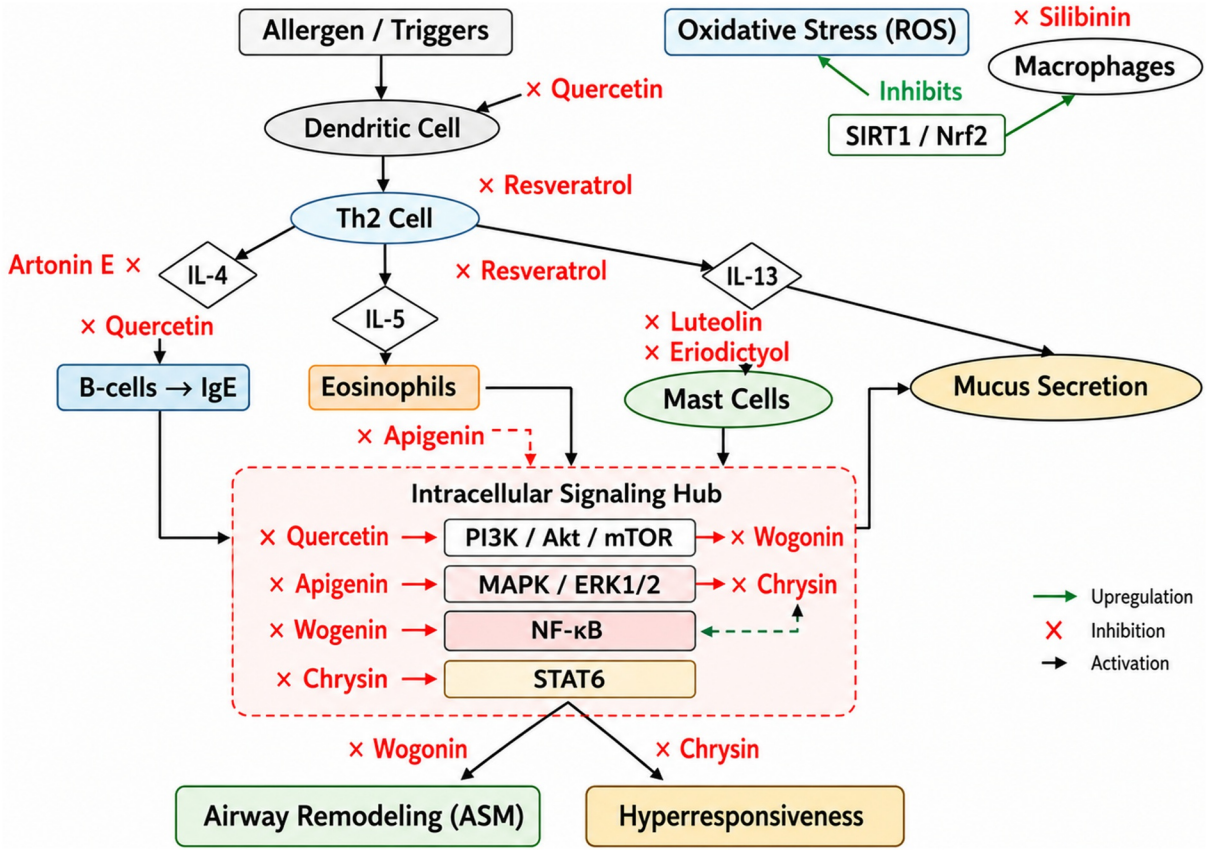


FIGURE 5 | Flavonoids and polyphenols interactions with the immune and oxidative stress pathways in airway inflammation and remodeling.

TABLE 3 | Plant flavonoids role as anti-asthmatic agent.

Compound	Mechanism of action	Experimental model	Key findings	Reference
Quercetin	Suppresses IL-4, IL-5, IgE; modulates PI3K/Akt/mTOR; antioxidant	OVA-induced asthma in mice	Reduced airway inflammation, improved autophagy regulation	Y. Zhang, Liu, et al. (2021)
Wogonin	Induces apoptosis in airway smooth muscle cells; inhibits MAPK/Akt; suppresses IL-4/STAT6	Neutrophilic asthma model	Reduced airway remodeling and inflammation	J. Zhang, Chen, et al. (2020)
Chrysin	Inhibits ERK1/2 pathway; reduces ASM proliferation and allergic inflammation	Guinea pig and human ASM cell models	Decreased airway remodeling and inflammation	Kandasamy, Kumar, et al. (2022)
Resveratrol	Activates SIRT1/Nrf2 axis; upregulates PTEN; suppresses Th2 cytokines	OVA-induced asthma in mice	Improved lung function, reduced oxidative stress and inflammation	S. Saha, Ghosh, et al. (2022)
Silibinin	Potent antioxidant; suppresses inflammatory cytokines	ASD-induced airway inflammation in mice	Reduced macrophage activation and airway inflammation	H. Lee, Kim, Kim, et al. (2021)
Artonin E	Prenylated flavonoid; cytotoxic and anti-inflammatory potential	No direct asthma model yet	Inferred potential from flavonoid bioactivity	Abdullah et al. (2020)
Luteolin	Inhibits mast cell activation; suppresses IL-4, IL-13	OVA-induced asthma in mice	Reduced airway inflammation and mucus secretion	Y. Jia, Li, et al. (2015)
Apigenin	Anti-inflammatory; inhibits NF-κB and MAPK pathways	OVA-induced asthma in mice	Reduced eosinophilic infiltration and cytokine release	X. Li et al. (2010)
Kaempferol	Antioxidant; suppresses Th2 cytokines and airway remodeling	OVA-induced asthma in mice	Reduced airway hyperresponsiveness and inflammation	Park et al. (2017)

TABLE 4 | Pharmacokinetic drawbacks of flavonoids and polyphenols.

Compound	Pharmacokinetic limitations	Reference
Quercetin	Very low oral bioavailability (< 5%), extensive first-pass metabolism, poor solubility, rapid clearance	Xiong et al. (2024)
Wogonin	Limited absorption, rapid metabolism, poor systemic exposure; instability in vivo	X. Wang et al. (2024)
Chrysin	Extremely poor bioavailability due to rapid conjugation (glucuronidation/sulfation), low plasma levels	Kurkiewicz et al. (2025)
Resveratrol	Rapidly absorbed but bioavailability < 1% due to extensive metabolism; unstable in plasma	Yu et al. (2024)
Silibinin	Poor solubility, low oral bioavailability, variable absorption; rapid metabolism limits systemic exposure	Ray et al. (2024)
Artonin E	Limited pharmacokinetic data; poor solubility and bioavailability reported; prenylation improves lipophilicity but systemic exposure remains low	Etti et al. (2024)
Luteolin	Poor solubility, rapid conjugation, short half-life; low systemic bioavailability	Jayawickreme et al. (2024)
Apigenin	Low oral bioavailability, rapid metabolism, poor aqueous solubility; limited clinical translation	Siddiquee et al. (2024)
Kaempferol	Poor absorption, extensive metabolism, low plasma concentrations; dietary matrix influences uptake	Saranya and Sudha (2024)

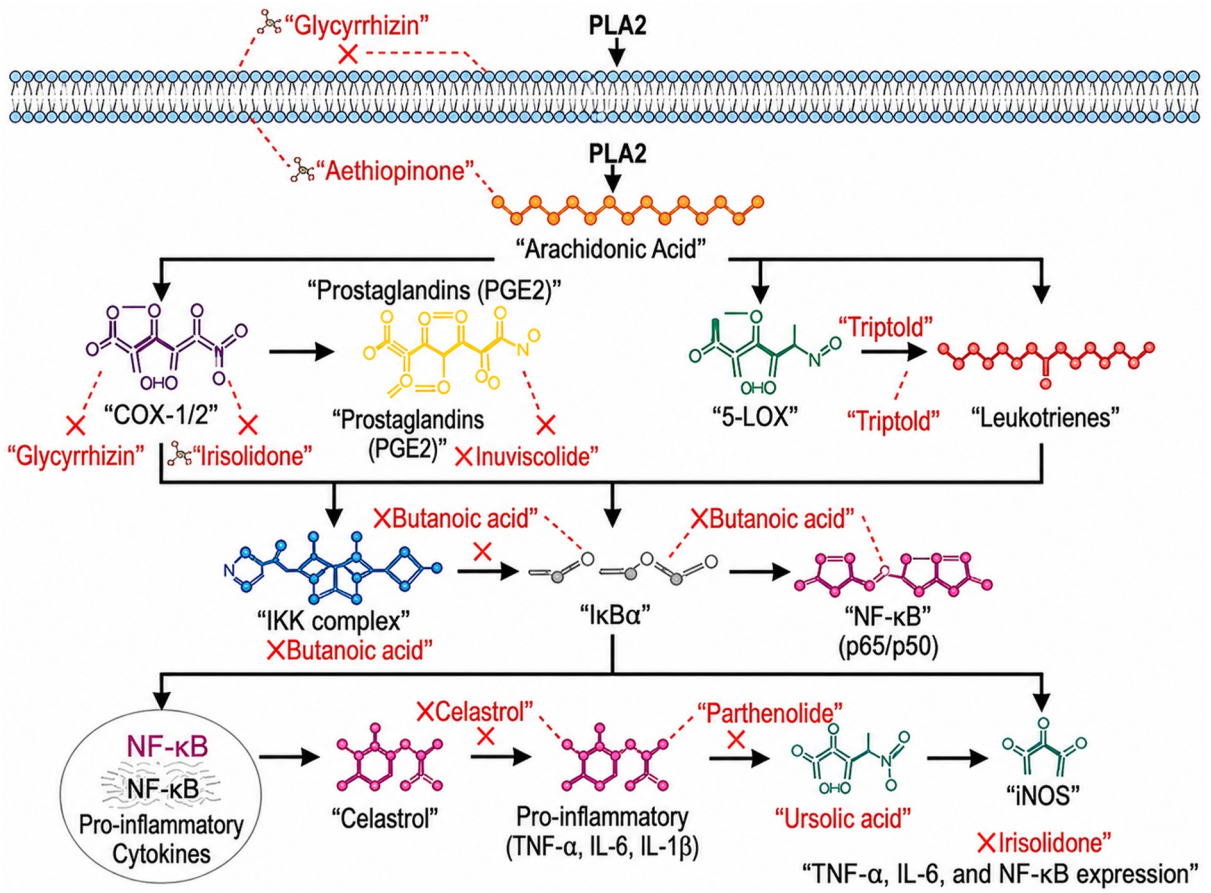


FIGURE 6 | Impact of terpenoids in modulating the arachidonic acid cascade in allergic airway inflammation.

studies, whereas irisolidone, inuviscolide, aethiopinone, etc. are some of the chemicals mentioned in reviews, although direct asthma-specific experimental data are scarce. Monoterpenes and sesquiterpenes show anti-inflammatory and antioxidant activity, supporting their potential as adjunct therapies.

A clear correlation emerges between the type of evidence (pilot studies, mechanistic reviews, preclinical models, and ongoing trials) and the strength of clinical validation. Quercetin shows the most consistent trajectory, with registry-based pilot data in asthma patients complemented by mechanistic and

TABLE 5 | Pharmacokinetic drawbacks of terpenoids and terpenes.

Compound	Pharmacokinetic limitations	Reference
Ursolic acid	Very low oral bioavailability (< 1%) due to poor aqueous solubility and extensive first-pass metabolism	Fatima et al. (2023)
Oleanolic acid	Poor solubility and rapid hepatic metabolism, leading to short half-life and weak systemic exposure	Didigwu and Nnadi (2024)
Limonene, pinene	Volatile and chemically unstable; prone to oxidation and degradation during storage and formulation	Didigwu and Nnadi (2024)
Parthenolide, tomentosin	Lipophilic with nonspecific distribution; accumulate in fatty tissues, reducing targeted efficacy	Bouyahya et al. (2019)
Triptolide, Celastrol	Narrow therapeutic window; rapid metabolism and systemic toxicity limit clinical translation	El Omari et al. (2021)

TABLE 6 | Pharmacological actions of phytochemicals in asthma models.

Compound	Mechanism	Model	Reference
Glycyrrhizin	Anti-inflammatory; reduces airway remodeling and cytokine release; improves lung histopathology	Murine chronic asthma	Babayigit et al. (2011)
	Systems pharmacology shows modulation of NF-κB and MAPK pathways	Computational and experimental validation	Qi et al. (2023)
Ursolic acid	Potent anti-inflammatory and antioxidant; suppresses NF-κB, reduces cytokines, protects airway epithelium	Systematic review of preclinical models	Zhao et al. (2023)
Butanoic acid (butyrate)	Short-chain fatty acid; modulates gut–lung axis; enhances Treg activity; reduces airway inflammation	Metabolomics in asthma models	Barosova et al. (2024)
Celastrol	Inhibits Th17 responses; reduces airway hyperresponsiveness in obese asthma	OVA-induced obese asthma in mice	Zeng et al. (2018)
Parthenolide	Active sesquiterpene lactone from *Tanacetum parthenium*; reduces IL-4, IL-5; improves lung histopathology	Murine chronic asthma	Arıkan-Ayyıldız et al. (2016)
Irisolidone (isoflavone)	Reported anti-inflammatory potential; limited direct asthma data	Mentioned in reviews of anti-asthmatic screening	S. Singh et al. (2025)
Inuviscolide (sesquiterpene lactone)	Anti-inflammatory potential; cited in reviews of anti-asthmatic screening	Review of animal models	S. Singh et al. (2025)
Triptolide	Potent immunosuppressive diterpenoid; reduces airway inflammation; modulates Treg/Th17 balance	Nebulized inhalation in murine asthma	Miao et al. (2023)
Aethiopinone (quinone derivative)	Anti-inflammatory potential; limited direct asthma data	Mentioned in reviews of anti-asthmatic screening	S. Singh et al. (2025)
Other terpenoids (e.g., volatile monoterpenes, sesquiterpenes)	Broad anti-inflammatory and antioxidant effects; reduce airway inflammation and oxidative stress	Experimental asthma models and reviews	T. Kim et al. (2020)

immunomodulatory reviews. This suggests a promising but still under-validated clinical role, particularly in reducing airway inflammation and IgE-mediated responses. On other hand, glycyrrhizin demonstrates synergy with conventional bronchodilators in limited clinical settings, whereas mechanistic reviews emphasize its NF-κB suppression and antioxidant activity. However, hepatotoxicity risks and the absence of robust RCTs temper its translational potential. Another phytochemical Piperine remains largely preclinical, with mechanistic overviews highlighting anti-inflammatory pathways. Notably, its derivative PF-07275315 is under active clinical investigation, marking a transition from bench to bedside. The correlation across these entries underscores a progressive evidence gradient: from hypothesis-driven mechanistic insights to early clinical validation, and finally to structured clinical trials. Various clinical trials details are listed in Table 7. These gradients highlight both the

TABLE 7 | Clinical trial of phytochemicals in asthma management (2010–2026): Current status and gaps.

Compound	Study design and population	Outcomes	Limitations	Reference
Quercetin	Pilot registry study (Italy, 2019) with quercetin phytosome in mild-to-moderate asthma patients	Improved asthma control scores; reduced airway inflammation	Small sample size; registry design	Cesarone et al. (2019)
	Mechanistic review (India, 2025)	Potent antioxidant, anti-inflammatory, immunomodulatory effects; potential adjunct in asthma	Mostly mechanistic; limited clinical validation	P. Patel et al. (2025)
	Review of immunomodulatory effects (Iraq, 2025)	Reduced IgE-mediated inflammation; potential role in asthma and nasal allergies	Review only; lacks trial data	R. J. Mohammed et al. (2025)
	Mechanistic overlap with post-COVID pulmonary syndrome (2023)	Suggested therapeutic overlap in asthma and PF syndrome	Hypothesis-driven; not clinical	B. Wang et al. (2025)
Glycyrrhizin	Preclinical and clinical synergy study (China, 2010) with salbutamol	Synergistic anti-asthmatic effects; reduced airway hyperresponsiveness	Preclinical and small clinical data; limited replication	Y. Yang et al. (2010)
	Pharmacological review (India, 2025)	Anti-inflammatory via NF-κB suppression; antioxidant activity	No asthma-specific RCTs; hepatotoxicity risk	R. Gore et al. (2025)
	Molecular mechanisms review (India, 2024)	Highlighted pharmacological pathways relevant to asthma	Review only; lacks trial data	R. Semwal et al. (2024)
Piperine	Mechanistic overview	Demonstrated anti-inflammatory and immunomodulatory effects in bronchial asthma models	Preclinical; no RCTs	Tripathi et al. (2022)
	Technical overview (BenchChem 2025)	Potent anti-inflammatory and immunomodulatory properties	Preclinical; no published RCTs	BenchChem Technical Report (2025)
Piperine derivative (PF-07275315)	Ongoing clinical trial (Pfizer, 2026, NCT06977581) in moderate-to-severe asthma	Investigating safety and efficacy; aims to reduce airway inflammation	Trial ongoing; results not yet available	ClinicalTrials.gov (2026)

TABLE 8 | Comparative evidence matrix.

Phytochemical	Mechanism of action	Evidence level	Translational stage	Limitation
Quercetin	Suppresses IL-4/IL-5, modulates PI3K/Akt/mTOR, antioxidant	Preclinical (mouse OVA models)	Early clinical exploration	Poor bioavailability
Luteolin	Inhibits mast cell activation, reduces mucus secretion	Preclinical (OVA mice)	No clinical trials	Limited human data
Chrysin	ERK1/2 inhibition, reduces ASM proliferation	Preclinical (guinea pig, ASM cells)	No clinical trials	Weak absorption
Resveratrol	Activates SIRT1/Nrf2, suppresses Th2 cytokines	Preclinical (OVA mice)	Nutraceutical trials	Rapid metabolism
Silibinin	Potent antioxidant, suppresses macrophage activation	Preclinical (PM-induced mice)	No clinical trials	Solubility issues
Piperine	Inhibits NF-κB, enhances drug bioavailability	Preclinical and formulation studies	Inhalable formulations under evaluation	Narrow therapeutic window
Colchicine	Inhibits 5-LO, reduces neutrophil activity	Approved for gout; tested in airway inflammation	Repurposing potential	Toxicity, narrow index
Triptolide	Suppresses NF-κB, CCR7, COX-2	Preclinical (mouse asthma models)	No clinical trials	Hepatotoxicity
Coumarins (Amburana)	Bronchodilatory, immunomodulatory	Preclinical	No clinical trials	Limited pharmacokinetics

promise and the limitations of phytochemicals in asthma therapy, where mechanistic plausibility is strong, but large-scale clinical validation remains scarce.

A comparative evidential metrix (Table 8) provides a summarizing phytochemical mechanisms, evidence levels, translational stages, and limitations. This synthesis highlights both the

promise and the challenges of integrating phytochemicals into asthma management. It can indicate the current situation of phytochemicals in asthma care and its lacunas.

5 | Clinical Translation of Phytochemicals in Asthma Management

5.1 | Translational Barriers/Landscape

Clinical translation of phytochemicals in asthma is an exciting but challenging frontier. Although many flavonoids and polyphenols (quercetin, resveratrol, wogonin, chrysin, silibinin, luteolin, apigenin, kaempferol, etc.) show strong preclinical efficacy in animal models, their movement into human trials and therapeutic use faces several hurdles. Strong preclinical evidence exists for multiple phytochemicals, especially in eosinophilic asthma (quercetin, luteolin, apigenin, kaempferol) and neutrophilic/steroid-resistant asthma (wogonin, chrysin). Resveratrol and silibinin stand out for broad-spectrum antioxidant and immune-modulatory effects, making them candidates for mixed or oxidative stress-driven asthma phenotypes. Clinical translation is limited by poor bioavailability, lack of standardized formulations, and insufficient large-scale trials. Nanomedicine approaches (nanoformulations and phytosomes) are actively being explored to overcome pharmacokinetic barriers.

The clinical translation pathway, that is, preclinical validation through formulation development to clinical potential, illustrates both the promise and complexity of phytochemical integration in asthma management. These phytochemicals embody a paradigm shift toward multi-target, low-toxicity interventions capable of complementing existing therapies. However, their successful translation demands rigorous pharmacokinetic optimization, standardized dosing, and large-scale clinical validation. The graphical representation of this pathway (Figure 7) encapsulates the continuum of discovery, emphasizing how natural molecules, once confined to experimental models, are gradually advancing toward precision-based adjuncts in respiratory medicine.

In the preclinical stage, compounds such as quercetin, resveratrol, curcumin, luteolin, and silibinin demonstrate strong anti-inflammatory and antioxidant effects, suppressing Th2 cytokines (IL-4, IL-5, IL-13), reducing airway remodeling, and modulating oxidative stress through NF-κB and Nrf2 pathways (Y. Zhang, Liu, et al. 2021; Y. Zhang, Li, et al. 2021; P. Saha et al. 2022; S. Saha, Ghosh, et al., 2022; S. Saha, Mukherjee, et al. 2022). Early clinical trials have begun to test resveratrol, quercetin, and curcumin, showing safety but limited efficacy due to poor bioavailability (Subali, Kumar, et al. 2024; Subali, Kurniawan, et al., 2024). Formulation development using nanoparticles, liposomes, and phytosomes has improved solubility and lung delivery, with luteolin and quercetin phytosomes showing enhanced pharmacokinetics (Sharma et al. 2026). Yet, translational barriers remain rapid metabolism, lack of large randomized controlled trials, regulatory ambiguity, and patient heterogeneity between eosinophilic and neutrophilic asthma (H. Lee, Kim, Kim, et al. 2021; H. Lee, Kim, Park, et al. 2021; Y. Jia, Li, et al. 2015; Y. Jia, Chen, et al. 2015). Finally, the clinical potential stage envisions these phytochemicals as adjuncts to corticosteroids and biologics, particularly in oxidative stress-driven and steroid-resistant asthma, with wogonin and chrysin highlighted for neutrophilic asthma and airway remodeling (J. Zhang, Chen, et al. 2020; J. Zhang, Liu, et al. 2020; Y. Zhang et al., 2020; Kandasamy, Subramanian, et al. 2022).

5.2 | Bioavailability and Formulation Strategies for Integration of Phytochemicals

Despite potent bioactivity, many phytochemicals suffer from poor bioavailability. Quercetin, for instance, has limited solubility and rapid metabolism. Formulation strategies such as phytosomes, nanoemulsions, and liposomal carriers have shown promise in enhancing absorption and stability (Cesarone et al. 2019). Piperine, known for its bioenhancing properties, is being evaluated in inhalable formats (PF-07275315, ClinicalTrials.gov 2026). Berberine, an alkaloid, suppresses NF-κB and MAPK signaling to reduce airway inflammation, yet its poor oral absorption necessitates nanoparticle and liposomal formulations to improve systemic exposure (Subali, Kumar, et al. 2024; Subali, Kurniawan, et al., 2024). Ephedrine, another alkaloid, has long been used as a bronchodilator, though modern controlled-release inhalables are being developed to minimize cardiovascular toxicity (Shivakumar et al. 2025). Among flavonoids, quercetin demonstrates potent antioxidant and anti-inflammatory effects but suffers from limited solubility and rapid clearance; phytosomes, nanoemulsions, and liposomal carriers have been shown to enhance its stability and pulmonary deposition (Tanaka and Takahashi 2013a, 2013b). Similarly, luteolin inhibits mast cell activation and cytokine release, with nanoemulsion-based delivery improving solubility and lung targeting (Pentu et al. 2025), whereas kaempferol modulates Th2 cytokines and reduces airway hyperresponsiveness, with inhalable nanoparticle formulations under investigation (Xu et al. 2022). Triterpenoids such as boswellic acids inhibit 5-lipoxygenase, thereby reducing leukotriene-mediated bronchoconstriction, and phytosome formulations enhance their absorption (Noushahi et al. 2022). Glycyrrhizin from licorice root exhibits immunomodulatory effects, with liposomal encapsulation improving systemic stability (Sergazy et al. 2024), whereas oleanolic acid shows bronchodilatory and anti-inflammatory properties, with nano-formulations improving solubility and bioavailability (Patil et al. 2025). Advanced nanomedicine approaches such as inhalable dry powders, nanobodies, and computational docking studies are increasingly being explored to bridge the translational gap, enabling these phytochemicals to move from molecular promise toward clinical integration in asthma management (Ashique et al. 2025; Khatoon et al. 2025; Waghmare et al. 2025).

5.3 | Drug Interactions and Safety Considerations

Phytochemicals may interact with conventional asthma medications. Glycyrrhizin can potentiate corticosteroid effects and alter hepatic metabolism, necessitating caution in long-term use (Y. Yang et al. 2010; P. S. Gore et al. 2025; R. Gore et al. 2025). Quercetin inhibits CYP3A4, potentially affecting antihistamine metabolism (R. J. Mohammed et al. 2025; S. Mohammed et al. 2025). Piperine may enhance drug absorption but also modulate cytochrome P450 enzymes. Safety profiles must be established through rigorous toxicological studies and stratified clinical trials. Over the past 15 years, multiple studies have documented drug–phytochemical interactions in asthma management, highlighting both therapeutic promise and safety concerns.

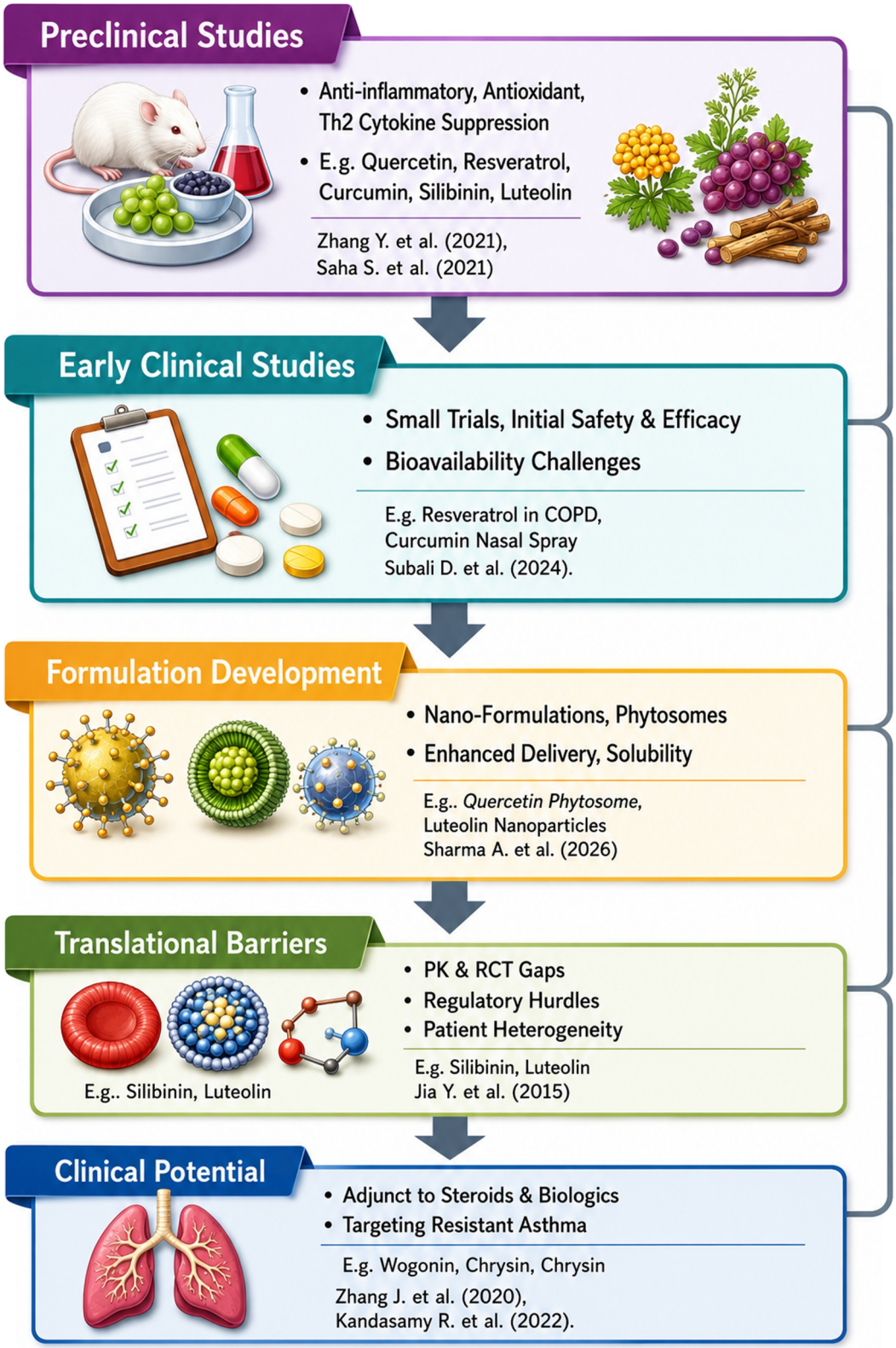


FIGURE 7 | Clinical translation pathway for phytochemicals in asthma treatment.

Glycyrrhizin, has been shown to potentiate corticosteroid activity by inhibiting 11β-hydroxysteroid dehydrogenase, thereby enhancing glucocorticoid effects but also increasing risks of hepatotoxicity and cardiovascular complications when combined with β2-agonists such as salbutamol (Y. Yang et al. 2010; Qi et al. 2023; P. S. Gore et al. 2025; R. Gore et al. 2025). Flavonoids like quercetin and luteolin demonstrate antioxidant and anti-inflammatory benefits, yet they modulate CYP3A4 metabolism, which can alter clearance of corticosteroids and leukotriene modifiers, raising concerns about unpredictable immune suppression (Tanaka and Takahashi 2013a, 2013b; El-Hosni et al. 2021; R. Semwal et al. 2024). Reports also indicate that

polyphenols and alkaloids interfere with CYP-mediated metabolism of antibiotics commonly prescribed during asthma exacerbations, potentially affecting plasma drug levels (ESCOP 2019; Gamil et al. 2025; R. J. Mohammed et al. 2025; S. Mohammed et al. 2025). Although some studies suggest synergistic effects, of luteolin and quercetin enhancing montelukast efficacy, these interactions remain underexplored in randomized controlled trials, wherever most evidence derived from preclinical or observational studies (Neighbour and McIvor 2010; Gupta et al. 2025; P. Patel et al. 2025; R. Patel et al. 2025). Overall, these findings emphasize the need for biomarker-guided clinical trials, long-term toxicology monitoring, and regulatory frameworks that mandate herb–drug interaction studies to ensure safe integration of phytochemicals into asthma therapy.

5.4 | Clinical Evidence (2010–2025): Current Status and Gaps

Between 2010 and 2026, only a limited number of clinical trials have evaluated phytochemicals in asthma management. Among all, Glycyrrhizin derivatives (e.g., SHR-1905) have progressed to Phase III trials for severe asthma, whereas piperine has been explored in inhalable formulations with preliminary safety data. Resveratrol and quercetin have been tested in small nutraceutical studies, showing modest improvements in oxidative stress markers but inconsistent clinical outcomes (Table 7). Overall, these trials remain underpowered, heterogeneous in design, and insufficient to establish efficacy. Safety concerns, including hepatotoxicity and narrow therapeutic windows, further constrain translation. This sparse clinical evidence underscores the translational gap between robust preclinical promise and clinical adoption, reinforcing the need for well-designed randomized controlled trials.

6 | Future Research Priorities/Directions

To bridge existing gaps, future research should prioritize integrated and translational approaches that enhance both efficacy and clinical applicability of phytochemicals in asthma management. Emphasis should be placed on advanced formulation strategies such as nanoemulsions, phytosomes, and inhalable delivery systems to overcome poor bioavailability and enable targeted pulmonary delivery. At the clinical level, biomarker-guided trials are essential, where patients are stratified based on cytokine signatures including IL-4, IL-5, and IL-13, along with oxidative stress markers, to align specific phytochemicals with defined asthma phenotypes and improve therapeutic precision. In parallel, combination therapies involving phytochemicals and standard bronchodilators or corticosteroids, such as glycyrrhizin with salbutamol, should be explored to harness synergistic effects and potentially reduce corticosteroid dependence. Rigorous safety and toxicological evaluations are also critical, particularly focusing on long-term hepatotoxicity, cytochrome P450-mediated drug interactions, and unintended immunomodulatory consequences. Finally, establishing clear regulatory and commercialization pathways under frameworks such as AYUSH, EFSA, and FDA will be necessary to facilitate standardization, ensure quality control, and improve global accessibility of these phytochemical-based interventions. Phytochemicals can be integrated into current asthma therapeutics through adjunctive therapy, preventive nutraceuticals, personalized medicine and with next-generation inhalable for direct airway delivery.

7 | Conclusion

Phytochemicals such as flavonoids (quercetin, luteolin, apigenin), alkaloids (glycyrrhizin derivatives), terpenoids (lupeol, oleanolic acid), and saponins (bacosides, triterpenoid saponins) have demonstrated diverse molecular mechanisms that complement conventional asthma therapies, targeting oxidative stress, immune dysregulation, and airway remodeling. Although preclinical evidence is robust, clinical translation remains hindered by poor bioavailability, systemic toxicity, and limited randomized trials. Addressing these challenges through nanomedicine, prodrug design, and inhalable delivery systems, alongside rigorous clinical validation and regulatory oversight, is essential. Integrating phytochemicals into asthma management has the potential to advance personalized, safer, and more effective therapeutic strategies, bridging the gap between experimental promise and clinical reality. Their clinical adoption requires metabolite standardization, advanced formulations to overcome bioavailability, and well-designed Phase II/III trials. Furthermore, asthma's heterogeneity, particularly the distinction between eosinophilic and neutrophilic phenotypes necessitates biomarker-guided phytochemical selection to ensure therapeutic relevance. Positioned as adjuncts to corticosteroids and biologics, phytochemicals offer a pathway toward personalized, safer, and cost-effective asthma management.

Author Contributions

Pulak Majumder: conceptualization, methodology, supervision, writing – review and editing, validation, data curation, visualization, project administration, formal analysis **Trisita Majumder:** methodology, resources, investigation, formal analysis, data curation, software, writing – original draft.

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Ethics Statement

This review is based solely on previously published peer-reviewed literature and did not involve new studies with humans or animals; hence, ethical approval was not required. The analysis followed PRISMA guidelines, with evidence quality assessed using the GRADE framework. No personal or confidential data were accessed.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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