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Asthma in the 21st Century – Unexpected Applications of Ancient Treatments

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1. Introduction

Asthma comes from the Greek word for “panting” and has been described as a pathological condition for centuries. It is a chronic inflammatory disorder of the airways in which many immunological cells play a role, including mast cells and eosinophils. In susceptible individuals, this inflammation causes symptoms which are usually associated with widespread variable airflow obstruction that is often reversible, either spontaneously or with treatment, and causes an associated airway hyperresponsiveness (AHR) to a variety of stimuli. The clinical features of asthma include dyspnea, wheezing and coughing.

During the last forty years there has been an increased understanding of the wide spectrum of this disease and as a result a number of effective treatments have been developed. Despite these advances, however, the mortality continues to increase and approximately 500 Canadians and 3500 Americans die each year from asthma. It remains a major cause of morbidity, as the leading cause of school absenteeism and the third leading cause of work absenteeism. The prevalence of asthma in North America has been on a constant rise over the last 25 years and it is estimated that currently over 3 million Canadians and 25 million Americans suffer from asthma. Worldwide the prevalence rates of asthma are rising on average by 50% each decade and developing a better understanding of the risk factors associated with this trend is critical. These may be broadly classified as either host genetic factors or environmental factors (Table 1).

One of the marked risk factors of asthma associated with the westernized lifestyle is our changing diet and/or nutritional status. It has been hypothesized that the significant change in our diet plays a dominant role in the etiology of asthma. Seaton *et al.* have proposed that

Genetic Factors	Environmental Factors
Atopy	Smoking
Gender	Allergens
Genetic predisposition	Occupational sensitizers
Race/ethnicity	Respiratory infections
	Parasitic infections
	Perinatal risk factors
	Diet and nutrition

Table 1. Risk factors associated with asthma

asthma prevalence has increased in UK because of an alteration in diet associated with industrialization [1]. This has lead to a substantial decline in the consumption of fresh fruits, green vegetables, fish and red meat, and as a result decrease in pulmonary antioxidant defences and an increase in susceptibility to inhaled irritants and allergens [1]. These foods are the main sources of antioxidants, substances that protect cells against the effects of free radicals generated during oxidative stress.

Oxidative stress is important in the pathophysiology of asthma [2] and development of AHR [3]. A large number of epidemiologic studies have reported the protective effects of dietary antioxidants such as micronutrients vitamin A, C, and E, polyphenol, and carotenoids against the development of asthma and decline of lung function. In a study on American children higher levels of antioxidants beta-carotene and Vitamin C, along with antioxidant trace mineral selenium is associated with a lower risk of asthma [4]. Dietary vitamin C intake is positively associated with 1 Second Forced Expiratory Volume (FEV₁) in children and adults [5-8] but less frequently with asthma or wheeze in children and adults [4, 9-11]. Dietary vitamin E intake is positively associated with ventilatory function [5, 6, 12] but negatively associated with asthma and wheeze in children [13], adult-onset wheeze [11] and the likelihood of atopic sensitization in adults [14]. Fresh fruits intake is inversely associated with wheeze [15] and chronic lung disease onset [16] and is positively associated with FEV₁ [17]. Total fruit and vegetable intake is inversely related to asthma prevalence [18] but not to FEV₁ [19] or airway obstruction [20]. Vegetables may protect against chronic bronchitis, asthma [21], and wheeze [22]. Moreover, dietary polyphenols intake are associated with lower disease risk with beneficial clinical outcomes attributed to both the antioxidants and anti-inflammatory properties of polyphenols [23]. Polyphenols consist of a large group of natural antioxidants extracted from plants and flavonoids comprise the most studied group.

In addition to antioxidants, intake of fats, particularly the changing composition of polyunsaturated fatty acids (PUFA) in westernized diets, has been implicated in the etiology of asthma. There has been a reduced intake of saturated fat accompanied by an increase in n-6 PUFA consumption, particularly linoleic acid and arachidonic acid. In addition, there has been a decrease in consumption of n-3 PUFA such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Thus, it has been postulated that the increased ratio of n-6:n-3 PUFA in diets of industrialized countries may also contributed to the increased asthma incidence.

Ancient Egyptian papyrus writings contain prescriptions for asthma that include several herbs suggesting that naturally occurring bioactive compounds may been used to effectively treat asthma. This chapter summarizes the current knowledge on the effects of dietary compounds and nutrients on allergy and asthma, with a focus on the mechanisms involved, wherever possible.

2. Pathogenesis of asthma

Airway inflammation in asthma is a complex process involving the interactions between immunological mediators produced by inflammatory cells such as mast cells, eosinophils, basophils, neutrophils, dendritic cells and lymphocytes [24]. This inflammation leads to structural and architectural changes in the airways of asthmatic patients including collagen and fibronectin deposition, wall thickening, subepithelial fibrosis and hypertrophy, goblet and airway smooth muscle cell hyperplasia, and angiogenesis, all of which collectively contribute to the phenomenon known as airway remodeling [25].

Allergic inflammation is often classified into four phases [26]:

- a. Induction of allergic reaction involving antigen uptake, processing and presentation (Figure 1),
- b. Early-phase asthmatic reaction (EAR, Figure 2),
- c. Late-phase asthmatic reactions (LAR, Figure 3), and
- d. Chronic allergic inflammation (Figure 4)

3. Common molecular targets used in current asthma therapy

Inspite of the advances made in the field of asthma treatments, some patients remain less responsive to conventional therapies than others. Current treatment strategy includes the combinations of bronchodilators, particularly short or long acting β_2 -adrenergic agonists (SABA, LABA), and inhaled and oral corticosteroids. The current approach to the management of asthma includes the addition of drugs in a stepwise fashion based on the severity of symptoms, however the stronger drugs include more severe side effects. The treatment aims to reverse airflow obstruction and reduces asthma exacerbations thus improving quality of life. However, long-term use of high dose inhaled corticosteroids therapy may lead to detrimental effects, such as cataracts [46], osteoporosis in elderly patients [47], and stunting of growth in children [48]. Moreover, the combination therapy may not modify the disease progression and are not curative.

The limited efficacy and side effects associated with conventional treatments has lead to the introduction of nutraceuticals as a “safer” alternative therapy and for those whom symptoms

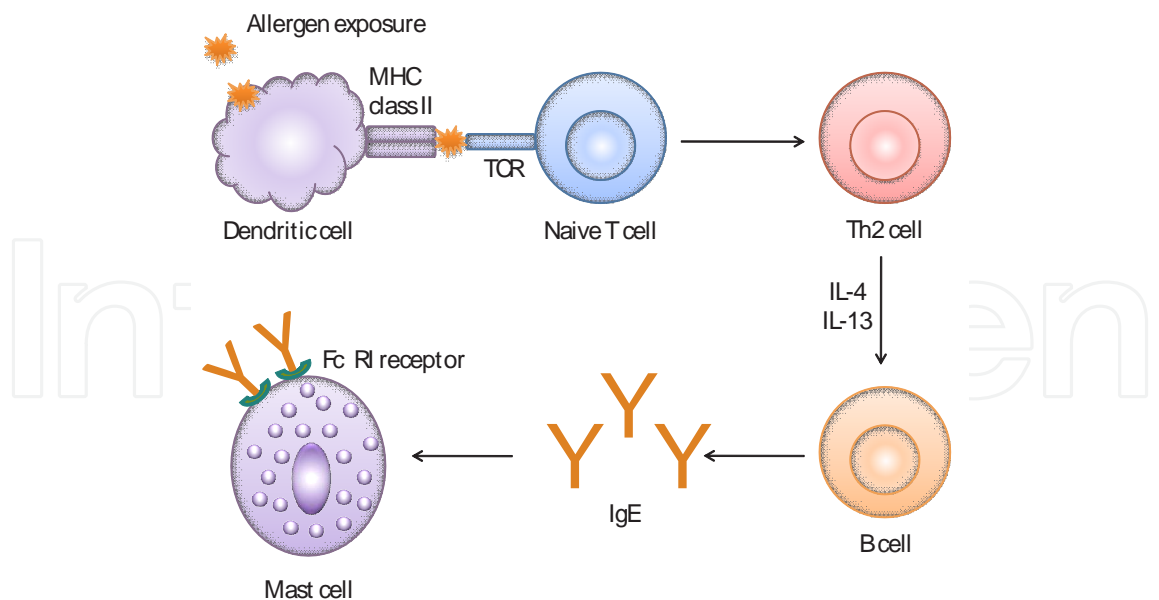


Figure 1. AHR and bronchial inflammation starts with the inhalation of an allergen. The allergen enters tissues through disrupted epithelium. It is then captured by antigen-presenting cells (APCs), usually dendritic cells (DCs), but also alveolar macrophages and B cells [27]. Allergen-loaded DCs migrate to regional lymph nodes where they present peptides to naïve T cells [28]. Presentation of processed allergen in the form of peptide fragments on MHC class II molecules to naïve T cells signals activation and clonal expansion of T cells [27]. In the presence of interleukin (IL)-4, naïve T cells acquire the characteristic of T helper 2 (Th2) cells [29]. Activated Th2 cells secrete greater amounts of IL-4 and IL-13 which triggers the isotype switch to immunoglobulin (Ig)E synthesis [29, 30]. IgE produced by B cells diffuses locally, enters the blood and is then distributed systemically. Allergen-specific or non-specific IgE binds to the high-affinity receptor for IgE (FcεRI) on the surface of tissue-resident mast cells and peripheral blood basophils, thereby sensitizing them to future allergen exposures [30].

are not improved with current therapies. Nutraceuticals is a very general term which encompasses many classifications of food products and derivatives that have the potential to either prevent or treat pathological conditions in humans or animals. For example, micronutrients such as vitamins and minerals and non-nutritive components of plant products such as polyphenols have some anti-inflammatory activity and have been used to supplement some foods to improve their health benefits. Table 3 summarizes some of the major nutraceuticals used to treat allergy and asthma currently.

The following sections discuss the current knowledge on the effects of nutraceuticals on inflammation associated with asthma with a focus on the cellular and molecular mechanism involved.

3.1. Anti-mediator agents

Anti-mediator agents are a group of drugs that antagonize the release of granule-associated preformed mediators, lipid mediators, cytokines, chemokines, and growth factors released by allergen-activated inflammatory cells. Several important groups of specific inhibitors against many of these inhibitors have been developed.

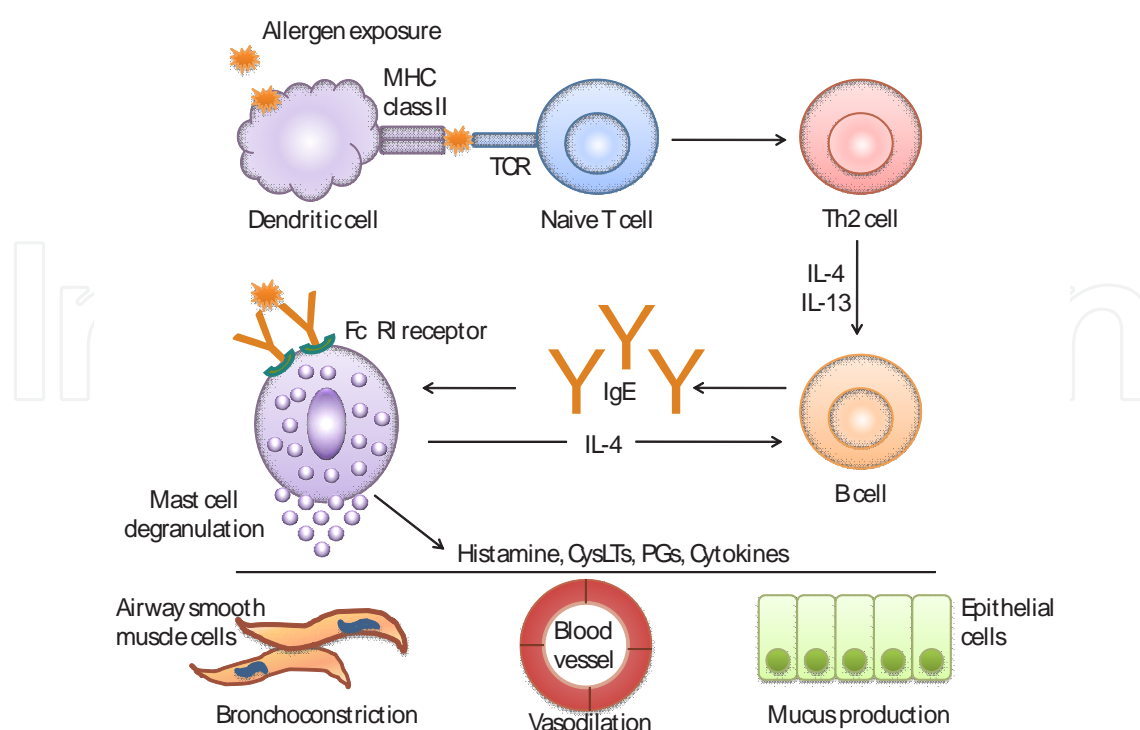


Figure 2. The EAR occurs within 30 min of allergen exposure and is principally initiated by mast cell and basophil activation [26]. Mast cells are widely distributed throughout the human respiratory tract and are found in large numbers in the walls of the alveoli and airways [31]. Asthmatics have allergen-specific IgE bound to the FcεRI receptors on mast cell surface. Upon cross-linking of adjacent IgE molecules by allergen, aggregation of FcεRI triggers a complex intracellular signaling process [32]. Activated mast cells release a diverse array of biologically active mediators: preformed granule-associated mediators, lipid-derived mediators, and *de novo* synthesized cytokines, chemokines, growth factors and other biologically active molecules (Table 2) [33]. The release of mast cell-derived mediators contributes to acute signs and symptoms associated with EAR that may range from mild rhinitis to anaphylactic shock. These mediators induce vasodilation, contraction of the bronchial smooth muscle (producing airflow obstruction and wheezing) and increased mucus secretion (exacerbating airflow obstruction in the lower airways) [26].

3.1.1. Lipid mediator blockers

Montelukast is a current FDA approved drug used in asthma treatment and serves a prototypical drug for Lipid Mediator Blocking class of drugs. Its mechanism of actions works through the blocking of the CysLT receptor for leukotriene D₄ which reduces bronchoconstriction and inflammation. Zileuton, a related drug in the same class, is a 5-lipoxygenase inhibitor which blocks the synthesis of cysLTs and leukotriene B₄. These drugs while not natural products serve as a models in the search for nutraceuticals whom may share same or related mechanism of action and therefore may prove useful in asthma management. Antagonists of the prostaglandin D₂ receptors DP1 and CRTH2 reduce inflammation in a murine model of asthma, possibly by inhibiting prostaglandin synthesis [49, 50]. Antagonist of the leukotriene B₄ receptor BLT1 (R05101576) prevents airway inflammation and AHR in animal models and non-human primates [51]. Quercetin and luteolin, flavonoids found in fruits, vegetables and wine, inhibit the release of leukotrienes and PGD₂ from human cultured mast cells [52]. Table 4 summarizes phytochemicals that act on pathways related to the synthesis of lipid mediators in allergic inflammation.

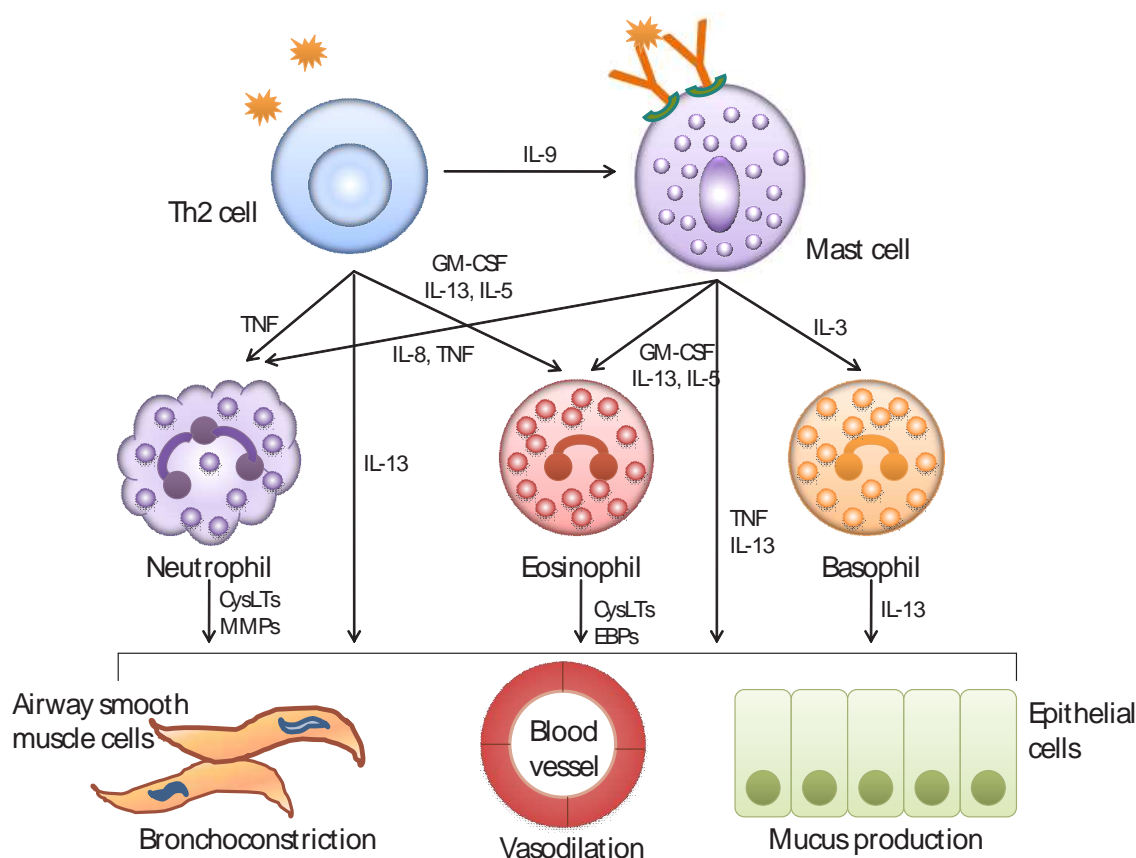
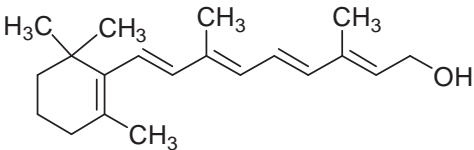
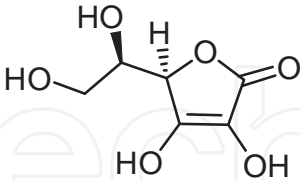
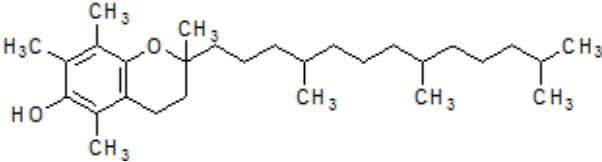


Figure 3. The LAR typically develops 2-6 hr following allergen challenge, often peaks after 6-9 hr, and has a more severe and prolonged phase. In general, allergen activated mast cells release various *de novo* synthesized cytokines, chemokines and growth factors, which are released more slowly than granule-associated mediators [34]. Thus, LAR is sustained by *de novo* synthesized mast cell-derived mediators which recruit inflammatory cells to the airways several hours after allergen challenge. These recruited cells include effector cells, such as eosinophils, basophils, neutrophils, macrophages, T cells, and DCs [34, 35]. These inflammatory cells are activated when they reach the airway and produce a vast array of inflammatory mediators that act on specific receptors and exacerbate airway inflammation and airway remodeling. Eosinophils are the central effector cells in the LAR [36], and are present not only in the airway wall [37] but are also found in large numbers in the sputum and bronchoalveolar lavage fluid (BALF) [38]. Eosinophils are a rich source of granule basic proteins (EBP), such as major basic proteins (MBP), eosinophil cationic protein (ECP), eosinophil peroxidase (EPO), and eosinophil-derived neurotoxin (EDN), and can also generate lipid-mediators (prostaglandins and cysteinyl leukotrienes), cytokines (such as TNF, TGF- β , IL-4 and IL-13) and chemokines [39]. These eosinophil-derived products promote some of the pathophysiological hallmarks of asthma such as AHR [40]. The activation of peripheral blood neutrophils during allergen challenge results in their intravascular migration, adhesion to the endothelium, and migration to the site of inflammation and can be responsible for significant damage. Nocturnal asthma is associated with high levels of neutrophils, which correlate with the severity of the disease [41]. Furthermore, in a small number of patients who died of sudden-onset asthma, the predominant cell type in the sputum is the neutrophils, not eosinophils [42]. Neutrophils also predominate more frequently in the sputum of patients with acute exacerbations of asthma, mostly associated with respiratory tract infection [43]. T cells are not only important during the induction phase, but play also a very important role during ongoing inflammation. Th2 cells and their cytokines are crucial for promoting acute hypersensitivity responses, and for maintaining the state of chronic and relapsing eosinophil-predominant inflammation that is characteristic of chronic allergic inflammation. Elevated levels of CD4⁺ T cells are observed in the bronchial mucosa of biopsy samples, BALF and sputum from patients with asthma [44]. In a majority of studies, T cells found in asthmatic patients express cytokines or transcription factors characteristic of Th2 cells, especially IL-4, IL-5, IL-9 and IL-13 [45].

Class of Product	Examples	Biological Effects
Preformed Mediators	Histamine, heparin	Increase vascular permeability, smooth muscle contraction
Enzymes	Tryptase, chymase, cathepsin G, carboxypeptidase	Remodel tissue matrix
Cytokines	IL-4, IL-13	Stimulate Th2 cell response
	IL-3, IL-5, GM-CSF	Promote eosinophil production and activation
Chemokines	Tumor necrosis factor (TNF)	Promotes inflammation and cytokine release by immune cells
	CCL2, CCL3, CCL4, CXCL1, CXCL2, CXCL3, CXCL10	Attract monocytes, macrophages and neutrophils
Lipid Mediators	Prostaglandin D ₂ , E2 Leukotriene B4, C4	Cause smooth muscle contraction, increase vascular permeability, stimulate mucus secretion
	Platelet-activating factor	Attracts leukocytes, amplifies production of lipid mediators, activates neutrophils, eosinophils and platelets

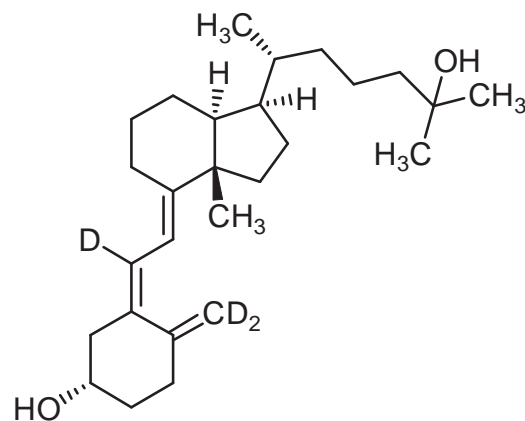
Table 2. Mast cell-derived proinflammatory mediators

Antioxidants	
<div><div>Vitamin A</div><div></div></div>	<p>Vitamin A (retinoid) occurs in many foods, including carrots, broccoli, sweet potato, butter, spinach, pumpkin, and liver, cod liver oil. The form found in colorful fruits and vegetables is called provitamin A carotenoid.</p>
<div><div>Vitamin C</div><div></div></div>	<p>Vitamin C (ascorbic acid) is an essential nutrient for humans as it protects the body against oxidative stress and is a necessary in collagen synthesis. Fruits (kakadu plum, camu camu, rose hip, indian gooseberry, blackcurrant, orange, tangerine, and guava) and vegetables (green and red chilli pepper, red pepper, broccoli, Brussels sprout, spinach, and cabbage) are good sources of Vitamin C.</p>
<div><div>Vitamin E</div><div></div></div>	<p>Vitamin E is a fat-soluble vitamin that exists in eight different forms. It consists of a group of substances belonging to two closely related families, the tocopherols and tocotrienols, with each existing in a number of isomeric forms (α, β, γ, and δ). α-tocopherol is the most active form of Vitamin E in humans and is considered the major</p>

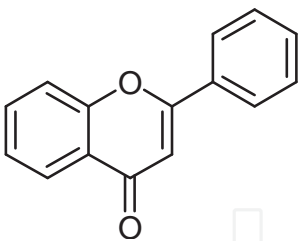
Antioxidants

membrane-bound antioxidant employed by cells. Its main antioxidant function is protection against lipid peroxidation. There is an interaction between Vitamin E and other nutrients, particularly selenium and vitamin C in the antioxidant role. Vitamin E is found in fruits (tomato, mango, and papaya), green leafy vegetables (lettuce, spinach, turnip, and beet), nuts and nut oils (almonds and hazelnuts), vegetable oils (wheat germ oil, sunflower oil, and safflower oil), meat, and poultry.

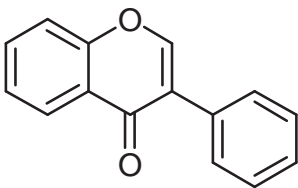
Vitamin D



Flavonoids



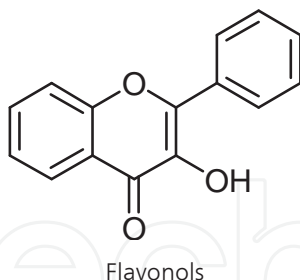
Flavones



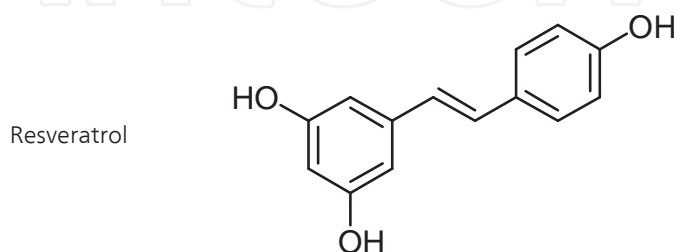
Isoflavones

Flavonoids constitute the most important single group of polyphenols of low molecular weight polyphenolic secondary plant metabolites, with more than 8,000 compounds described. They are found in fruits, vegetables, nuts, seeds, stems, flowers, roots, tea, wine, and coffee and are common substances in our daily diet. Their structure is a heterocyclic hydrocarbon, chromane, and substitution of its ring C in position 2 or 3 with a phenyl group (B-ring) results in flavans or isoflavans. An oxo-group in position 4 leads to flavanones and isoflavanones. The presence of a double bond between C2 and C3 provides flavones and isoflavones. An additional double bond in between C1 and C2 makes these compounds colourful anthocyanidins. Based on their structure, flavonoids are categorized into eight groups:

Antioxidants



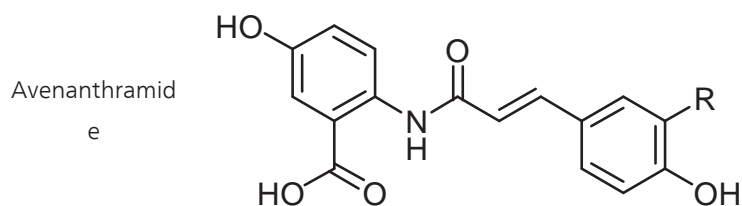
flavans, flavanones, isoflavanones, flavones, isoflavones, anthocyanidins, chalcones, and flavonolignans (Table 11].



Resveratrol is a stilbenoid, a type of natural phenol, and a phytoalexin produced naturally by several plants when under attack by pathogens such as bacteria or fungi. Resveratrol is found in the skin of red grapes and in other fruits. It is sold as a nutritional supplement derived primarily from Japanese knotweed.

Selenium

Selenium is derived from both vegetable and animal products, particularly seafood, liver, and cereals. As a member of the sulfur family of elements, it shares several chemical properties with sulfur, including valence states and the ability to form covalent bonds with carbon. It is unique among antioxidants in that it exerts its biological effects through direct incorporation into proteins (selenoproteins) as the amino acid selenocysteine. Some selenoproteins that have been characterized as important antioxidant enzymes include GPX-1, GPX-4, thioredoxin reductase-1 and thioredoxin reductase-2, and selenoprotein P. The selenium-dependent enzyme, GPX recycles glutathione, reducing lipid peroxidation by catalyzing the reduction of peroxides, including hydrogen peroxide.



Oats contain unique, low-molecular-weight, soluble phenolic compounds called avenanthramides (Avns), which are not present in other cereal grains. These compounds are antipathogens (phytoalexins), which are produced by the plant in response to exposure to pathogens

Antioxidants	
	such as fungi. Avns are conjugates of a phenylpropanoid with anthranilic acid or 5-hydroxy anthranilic acid. More than 20 different forms of Avns are present when extracted from oats, and the three major forms are A, B, and C.

Table 3. Some of the dietary nutraceuticals indicated in asthma prevention.

Phytochemicals	
Flavonoids	Target/Function
4,3',5'-trihydroxystilbene	Inhibits Cyclooxygenase 1
4,3'-dihydroxy-5'methoxystilbene	inhibits Cyclooxygenase 1
4-hydroxy-3'5'-dimethoxystilbene	Inhibits Cyclooxygenase 1
Acacetin	Inhibits Cyclooxygenase 1
Andanthoflavone	Inhibits 12-Lipoxygenase, 15-Lipoxygenase
Apigenin	Inhibits Cyclooxygenase 2, 12-Lipoxygenase, 15-Lipoxygenase
Artotin E	Inhibits Cyclooxygenase 1, 5-Lipoxygenase, 12-Lipoxygenase, 15-Lipoxygenase
Baicalein	Inhibits Cyclooxygenase 1, Cyclooxygenase 2, 5-Lipoxygenase, 12-Lipoxygenase, 15-Lipoxygenase
Bicalin	Inhibits Cyclooxygenase 1, Cyclooxygenase 2
Buddledin A	Inhibits Cyclooxygenase 1
Chrysin	Inhibits Cyclooxygenase 1, 5-Lipoxygenase
Chrysol	Inhibits 5-Lipoxygenase
Cirsiliol	Inhibits 5-Lipoxygenase, 12-Lipoxygenase
Daidzein	Inhibits Cyclooxygenase 2
Epicatechin	Inhibits 5-Lipoxygenase
Epigallocatechin	Inhibits 5-Lipoxygenase
Fisetin	Inhibits Phospholipase A2, 5-Lipoxygenase, 12-Lipoxygenase, 15-Lipoxygenase
Flavone	Inhibits 5-Lipoxygenase
Gambogenic acid	Inhibits Cyclooxygenase 2
Genistein	Inhibits Cyclooxygenase 2

Ginkgetin	Inhibits 5-Lipoxygenase
Glycitein	Inhibits Cyclooxygenase 2
Isoliquiritigenin	Inhibits Cyclooxygenase 1, Cyclooxygenase 2
Kampferol	Inhibits Phospholipase A2
Kaempferol	Inhibits 5-Lipoxygenase
Kenusanone A	Inhibits 5-Lipoxygenase
Kisetin	Inhibits Phospholipase A2
Kurardin	Inhibits Cyclooxygenase 1, 5-Lipoxygenase
Kurarinone	Inhibits Cyclooxygenase 1, 5-Lipoxygenase
Kuwanon C	Inhibits 5-Lipoxygenase, 12-Lipoxygenase
Luteolin	Inhibits 5-Lipoxygenase, 15-Lipoxygenase
Morelloflavone	Inhibits Phospholipase A2
Morusin	Inhibits Cyclooxygenase 1, 12-Lipoxygenase
Mosuin	Inhibits 15-Lipoxygenase
Myricetin	Inhibits 5-Lipoxygenase
Narigenin	Inhibits Phospholipase A2, 5-Lipoxygenase
Oroxidin	Inhibits 5-Lipoxygenase
Pedalitin	Inhibits 5-Lipoxygenase
Quercetin	Inhibits Cyclooxygenase 1, Cyclooxygenase 2, 5-Lipoxygenase, 12-Lipoxygenase
Resveratrol	Inhibits Cyclooxygenase 1, Cyclooxygenase 2, 5-Lipoxygenase
Rhamnetin	Inhibits 5-Lipoxygenase
Sanggenon B	Inhibits Cyclooxygenase 1, 5-Lipoxygenase
Sanggenon D	Inhibits 5-Lipoxygenase
Scutellarein	Inhibits Phospholipase A2
Silibinin	Inhibits 5-Lipoxygenase
Sophoflavanone A	Inhibits Cyclooxygenase 1
Sophoflavanone G	Inhibits Cyclooxygenase 1, 5-Lipoxygenase, 12-Lipoxygenase
Tectorigenin	Inhibits Cyclooxygenase 2
Wogonin	Inhibits Cyclooxygenase 2
Polyphenols	
Anisic acid	Inhibits Phospholipase A2
Caffeic acid	Inhibits 5-Lipoxygenase
Catechin	Inhibits Cyclooxygenase 1, 5-Lipoxygenase

Curcumin	Inhibits Phospholipase A2, Cyclooxygenase 1, Cyclooxygenase 2, 5-Lipoxygenase
Diphyllin acetapioside	Inhibits 5-Lipoxygenase
EGCG	Inhibits Cyclooxygenase 2
Eugenol	Inhibits 5-Lipoxygenase
Gingerol	Inhibits 5-Lipoxygenase
Ginkgetin	Inhibits Phospholipase A2, 5-Lipoxygenase
Hydroxytyrosol	Inhibits 5-Lipoxygenase
Hyperforin	Inhibits 5-Lipoxygenase
Medicarpin	Inhibits 5-Lipoxygenase
Ohenethyl ferulate	Inhibits Cyclooxygenase 2
Onosmins A and B	Inhibits 5-Lipoxygenase
Panaxynol	Inhibits 5-Lipoxygenase
Phenethyl ferulate	Inhibits 5-Lipoxygenase
Quercetagetin-7-O-beta-O-glucoside	Inhibits 5-Lipoxygenase
Rosmarinic acid	Inhibits 5-Lipoxygenase
Rosmarinic acid methylester	Inhibits 5-Lipoxygenase
Rosmarol	Inhibits Cyclooxygenase 20
n-3 PUFA	Inhibits Cyclooxygenase 2 and 5-Lipoxygenase

Table 4. Phytochemical inhibitors of lipid mediators

3.1.2. *Cytokines blockers*

Cytokines exhibit pleiotropy and have overlapping functions in the pathogenesis of asthma, making them a major target for new asthma therapies. Allergic inflammation is driven by an imbalance between Th1 and Th2 cytokines, favoring the Th2 arm of the immune response and inhibition of Th2 cytokines IL-4, IL-5 and IL-13 prevents asthma progression in animal models. Anti-IL-4 administration in mice prevents development of acute and chronic allergic inflammation [53], therefore, natural products that specifically target cytokines or their receptors have the potential to be effective asthma treatments.

Our current pharmacological approach include the use humanized monoclonal antibodies against specific cytokine or receptor targets. This class of drugs, known as the biologics, has been approved for use in treatment of cancer, autoimmune and inflammatory diseases. Omalizumab is a drug currently approved for the management of asthma and is antibody targeting IgE. While not specifically a cytokine blocker it functions through the same mechanism of action. These drugs while very effective carry the risk of unforeseen side effects and under current production treatment costs remain very high ranging upwards from \$15,000 to 60,000 per annum. Others examples including humanized IL-4-specific antibodies that block

IL-4 receptor α that are under clinical trial [54]. Neutralizing antibodies against IL-5 (Mepolizumab and Reslizumab) and IL-5 receptor α (MEDI-563) remarkably inhibits IL-5 related pathways resulting in reduction of asthma exacerbations [55]. Tralokinumab, an anti-IL-13 monoclonal antibody, prevents the development of asthmatic phenotype, both in murine model as well asthmatic patients [56]. Suplatast tosilate inhibits IL-4 and IL-5 production from T cells and reduces AHR in asthmatic patients.

Some of the phytochemicals and potential treatments indicated against cytokines function are listed in Table 5. These products if proved to be effective, could be cost effective alternatives and being natural products have the potential to have less side effects.

Phytochemicals	Target/Function and Effective Concentration(s)	References
Anti-oxidants		
Vitamin A	Inhibits release of Th2 cytokines IL-4, IL-5 and IL-13 <i>in vitro</i> as well as <i>in vivo</i> . Suppresses production of IP-10, IL-6, TNF, GM-CSF and IFN- γ .	
Vitamin C	Effect on Th1/Th2 balance controversial.	
Vitamin E	Inhibits IL-1 β , IL-6 and TNF response of human monocytes in asthmatic patients. Suppresses IL-4 levels in lungs of experimental allergic mice.	
Flavonoids		
Apigenin	Reduces airway inflammation by down-regulating Th2 cytokines IL-4 and IL-13. Suppresses the expression of Th2 cytokines (IL-4, IL-13 and IL-5) in human basophils. Inhibits production of TNF, IL-6 and GM-CSF in HMC-1 cells.	[57, 58]
Baicalein	Decreases inflammatory cytokines such as TNF and IL-6 in allergic inflammation. Inhibits production of IL-6 in activated human mast cells, and GM-CSF from human cultured mast cells.	[52, 59]
Bicalin	Reduces TNF and IL-6 levels in plasma and BALF in cigarette smoke-induced COPD rat model.	[60]
Chrysin	Downregulates IL-4 and IL-13 expression and production in allergen-sensitized mice. Inhibits TNF, IL-1 β , IL-4 and IL-6 expression in RBL-2H3 and HMC-1 cells.	[61]
Chrysol	Inhibits IL-4 production in antigen-stimulated RBL-2H3 cells.	[62]
Daidzein	Mast cell stabilizer; inhibits Th2 cytokines production.	
Fisetin	Inhibits IL-13 production in RBL-2H3 cells, and TNF, IL-6, IL-4 and IL-1 β production in HMC-1 cells. Suppresses the expression of Th2 cytokines (IL-4, IL-13 and IL-5) in human basophils. Attenuates LPS-induced TNF, IL-6 and IL-10 release in leukocytes of patients with COPD.	[57, 63-65]
Genistein	Inhibits TNF production in PBMCs from asthmatic patients.	
Ginkgetin	Inhibits TNF expression in activated macrophages.	

Phytochemicals	Target/Function and Effective Concentration(s)	References
Anti-oxidants		
Isoliquiritigenin	Inhibits the release of TNF and IL-6 in activated inflammatory cells.	
Kaempferol	Impairs Th2 cytokines production (IL-5 and IL-13) in OVA-sensitized mice. Suppresses the release of IL-4 and TNF in RBL-2H3 cells and macrophages. Inhibits IgE-mediated TNF and IL-6 release in hCBMCs.	
Kurardin	Suppresses expression of TNF and IL-1 β in LPS-stimulated macrophages (40 μ M).	[66]
Kurarinone	Suppresses expression of TNF and IL-1 β in LPS-stimulated macrophages (40 μ M).	[66]
Luteolin	Reduces the levels of TNF and IL-1 β in LPS-stimulated macrophages (8 & 16 μ M). Inhibits induction of TNF, IL-6 and GM-CSF in HMC-1 cells (10 & 50 μ M). Inhibits Th2 cytokines (IL-4, IL-5 and IL-13) expression in murine asthma model (50 & 100 mg/kg body wt.). Inhibits myelin basic protein-induced IL-6, TGF- β 1, and TNF release in hCBMCs (10 & 100 μ M). Decreases TNF (IC ₅₀ 7.9 \pm 4.6 μ M) and IL-1 β (IC ₅₀ 5.1 \pm 0.4 μ M) in PBMCs. Reduces IL-4 and IL-5 levels in BALF of murine asthma model (0.1 mg/kg body wt.). Inhibits antigen-IgE-mediated TNF (IC ₅₀ 5.8 μ M) and IL-4 (IC ₅₀ 3.7 μ M) production in RBL-2H3 cells.	[57, 67-73]
Morin	Inhibits IgE-mediated TNF and IL-6 release in hCBMCs (10 & 100 μ M). Inhibits TNF secretion in LPS-activated macrophages.	[74, 75]
Myricetin	Inhibits TNF (30 μ M) and IL-6 (30 μ M) production in HMC-1 cells. Inhibits IgE-mediated TNF (10 & 100 μ M) and IL-6 (1, 10 & 100 μ M) release from hCBMCs.	[75, 76]
Naringenin	Suppresses Th2 cytokines production from CD4 T cells (0.8 mg/kg body wt.). Reduces IL-4 (25, 50 & 100 mg/kg body wt.) and IL-13 (50 & 100 mg/kg body wt.) levels in BALF of murine asthma model. Suppresses LPS-induced IL-1 β (10, 25 & 50 μ g/mL), IL-6 (5, 10, 25 & 50 μ g/mL), and TNF (25 & 50 μ g/mL) production in macrophages and human whole-blood samples.	[77-79]
Pedalitin	Inhibits TNF and IL-12 production in LPS-activated macrophages (40 μ M).	[80]
Quercetin	Inhibits IgE-mediated TNF (10 & 100 μ M) and IL-6 (1, 10 & 100 μ M) release from hCBMCs.	[75]
Resveratrol	Inhibits increase in Th2 cytokines (IL-4 and IL-5) in plasma and BALF in asthmatic mouse model (30 mg/kg body wt.). Inhibits TNF induced GM-CSF and VEGF release in HASM cells. Inhibits PMA- and A23187-induced TNF and IL-6 release in HMC-1 cells. Decreases production of IL-1 β in lung tissue of mice with LPS-induced acute lung injury (1	[68, 81-86]

Phytochemicals		
Anti-oxidants	Target/Function and Effective Concentration(s)	References
	mg/kg body wt.). Attenuates C5a-induced TNF, IL-1 β and IL-6 production in mouse model (10 mg/kg body wt.).	
Scutellarein	Inhibits TNF and IL-12 production in LPS-activated macrophages (40 μ M).	[80]
Silibinin	Polarizes Th1/Th2 balance towards Th1 by increasing IFN- γ (200 & 400 mg/kg body wt.) and decreasing IL-4 levels (200 & 400 mg/kg body wt.) in asthmatic mouse model.	[87]
Polyphenols		
Caffeic acid	Inhibits increase in TNF and Th2 cytokines (IL-4 and IL-5) in BALF in asthmatic mouse model (10 mg/kg body wt. IP). Inhibits IL-10 expression in allergic patients' DCs (10 μ M). Suppresses TNF and IL-6 levels in asthmatic patients (13% solution).	[88-90]
Curcumin	Attenuates the expression of IL-4 and IL-5 in BALF in asthmatic mouse model (20 mg/kg body wt.). Inhibits release of IL-10, TNF and IL-1 β in HDM-activated eosinophils and bronchial epithelial cells (10 μ M). Inhibits IL-5, GM-CSF and IL-4 production in lymphocytes from bronchial asthmatics (10 μ M). Inhibits TNF secretion in activated HMC-1 cells (10 & 100 μ M/L). Inhibits tryptase-induced IL-6 release in eosinophils (25 μ M).	[91-95]
EGCG	Reduces TNF in BALF in asthmatic guinea pigs (25 mg/kg body wt. SC). Inhibits TNF and IL-6 production in HMC-1 cells (100 μ M). Attenuates production of TNF in lungs of mice with LPS-induced acute lung injury (10 mg/kg body wt. IP).	[96-99]
Eugenol	Inhibits IL-1 β , TNF and IL-6 release in macrophages.	[100, 101]
Gallic acid	Inhibits TNF and IL-6 in HMC-1 cells (10 μ M).	[102]
Gingerol	Inhibits IL-1 β and IL-12 release in peritoneal macrophages 100 ng/mL)	[103]
Hydroxytyrosol	Inhibits LPS-induced TNF production in THP-1 cells (25, 50 & 100 μ M). Reduces TNF levels in LPS-treated mice.	[104, 105]
Rosmarinic acid	Reduces IL-4, IL-5 and IL-13 expression in lung of HDM-sensitized asthmatic mouse model (1.5 mg/day PO). Attenuates IL-1 β , IL-6, and TNF increase in spleen and nasal mucosa of asthmatic mouse model (4 mg/kg body wt.). Inhibits IL-4 and IFN- γ release from CD4 ⁺ T cells (1 & 5 μ M). Inhibits diesel exhaust particles-induced IL-1 β expression in mice lung (4.6 μ g/kg body wt.).	[106-110]
Terpenes		
Celastrol	Reduced mRNA expression of IL-5, IL-5, IL-13, TNF, and IFN- γ in BAL cells and lung tissue of asthmatic mouse model.	

Phytochemicals Anti-oxidants	Target/Function and Effective Concentration(s)	References
Costunolide	Inhibits production of TNF, IL-1 β and IL-6 by LPS-stimulated macrophages (0.1, 0.5 & 1 μ M).	[111, 112]
Helenalin	Inhibits TNF and IL-6 secretion by ASMCs (1 μ M).	[113]
n-3 PUFA	EPA and DHA Lower BALF concentration of pro-inflammatory cytokines IL-1 α , IL-2, IL-5, IL-9, IL-13, G-CSF and RANTES. EPA (120 μ M) suppress TNF and IL-1 β expression and production in LPS-stimulated alveolar macrophages from asthmatic patients	Ref?

Table 5. Phytochemical inhibitors of proinflammatory cytokines

3.1.3. Chemokines and chemokine receptors blockers

Chemokines (CC) and their receptors (CCR) play a crucial role in the recruitment of inflammatory cells into the airways and development of asthma. CC-chemokine receptor 3 CCR3, CCR4, and CRTH2 antagonists are being targets currently being evaluated for the treatment of asthma. A study found that treatment of asthmatic mice with an anti-CCR3 monoclonal antibody inhibits allergen-induced eosinophilia and CD34⁺ progenitor cell infiltration into the lung, which is accompanied by reduced AHR [114, 115]. RS-1748, a CCR4 antagonist, inhibits OVA-induced airway inflammation in guinea pigs [116]. The number of CCR4-expressing Th2 cells is increased in the airways of asthmatic patients which can be blocked by a selective CCR4 antagonist [117], and therefore could be an effective therapy for asthma. Ramatroban and closely related TM30089 are antagonists for CRTH2, a chemokine receptor expressed on Th2 cells. They have been shown to attenuate allergen-induced EAR and LAR in animal models of asthma [118, 119]. Some of the phytochemicals indicated against chemokines function are listed in Table 6.

Phytochemicals Flavonoids	Target/Function and Effective Concentration(s)	References
Apigenin	Suppresses the production of MDC and IP-10 in THP-1 cells (10^{-6} and 10^{-5} M). Inhibits release of LPS-induced MCP-1 in J774.2 macrophages (10 & 30 μ M). Inhibits production of IL-8 in HMC-1 cells.	[58, 120, 121]
Baicalein	Inhibits IL-8 and MCP-1 release in activated human mast cells. Inhibits eotaxin production in human dermal fibroblasts (10 μ g/mL).	[59, 122]
Baicalin	Reduces IL-8 levels in plasma and BALF in cigarette smoke-induced COPD rat model. Inhibits eotaxin production in human dermal fibroblasts (10 μ g/mL).	[60, 122]

Phytochemicals Flavonoids	Target/Function and Effective Concentration(s)	References
Chrysin	Inhibits TNF-induced IL-8 expression in HEK 293 cells (20, 40 & 80 μ M).	[123]
Chrysol	Inhibits MCP-1 production in antigen-stimulated RBL-2H3.	[62]
Fisetin	Inhibits TNF-induced IL-8 expression in HEK 293 (20, 40 & 80 μ M). Inhibits IL-8 production in HMC-1 cells.	[65, 123]
Genistein	Blocks HDM-induced IL-8 release in human lung epithelial cells (50 μ M). Inhibits IL-8 release in TNF-stimulated human keratinocytes (60 μ M). Inhibits chemokine-stimulated eosinophil adherence (10^{-7} , 10^{-6} and 10^{-5} M).	[124-126]
Isoliquiritigenin	Inhibits eotaxin-1 secretion in human fetal lung fibroblasts (IC_{50} 0.92 \pm 0.05 μ g/mL).	[127]
Kaempferol	Suppresses LPS-induced production of MDC, IP-10 and IL-8 in THP-1. Inhibits MCP-1 production in antigen-stimulated RBL-2H3 and J774.2 macrophages (10 & 30 μ M). Inhibits TNF-induced IL-8 expression in HEK 293 (20, 40 & 80 μ M).	[62, 123, 128, 129]
Kurardin	Suppresses expression of MCP-1 in LPS-stimulated macrophages (40 μ M).	[66]
Kurarinone	Inhibits MCP-1-induced chemotaxis of THP-1 cells (IC_{50} 19.2 μ g/mL). Suppresses expression of MCP-1 in LPS-stimulated macrophages (40 μ M).	[130]
Luteolin	Inhibits TNF-induced expression of MCP-1 (10, 20 & 30 μ M) and CXCL-1 (20 & 30 μ M) expression in keratinocytes. Inhibits induction of IL-8 in activated HMC-1 cells (50 μ M) and hCBMCs.	[70, 131, 132]
Morin	Inhibits IL-8 production in antigen-stimulated hCBMCs (100 μ M).	[75]
Myricetin	Inhibits IL-8 production in antigen-stimulated hCBMCs (100 μ M).	[75]
Naringenin	Decreases secretion of PMA-induced IL-8 in HL-60 cells (20 μ M). Suppresses LPS-induced IL-8 production by macrophages and human whole-blood samples (25 & 50 μ g/mL). Inhibits expression of RANTES and eotaxin-1 in BALF and lungs in asthmatic mouse model (50 & 100 mg/kg body wt.).	[78, 79, 133]
Quercetin	Decreases production of IL-8 (3 & 30 μ M) and MCP-1 (10^{-4} , 10^{-5} and 10^{-6} M) in activated HMC-1 and IL-8 in human bronchial epithelial cells (0.1, 10 & 25 μ M).	[134-136]
Resveratrol	Decreases production of MIP-1 α in lung tissue of mice with LPS-induced acute lung injury (10 mg/kg body wt.). Reduces TNF-induced IL-8 release in HASMCs in COPD. Inhibits IFN γ -induced production of IP-10 and MIG in macrophages and HMC-1 cells.	[68, 82, 83, 85, 86, 137]

Phytochemicals	Target/Function and Effective Concentration(s)	References
Flavonoids		
	Inhibits IL-8 production in THP-1 cells (0.1, 1, 10 & 100 µg/mL). Attenuates C5a-induced MIP-1α production in mouse model (1 mg/kg body wt.).	
Tectorigenin	Inhibits MCP-1 expression in endothelial cells.	[138]
Wogonin	Suppresses mite antigen-induced TARC expression in human keratinocytes (250 ng/mL).	[139]
Polyphenols		
Caffeic acid	Decreases IL-8 release in chitinase-activated human airway epithelial cells (1 µM). Inhibits production of eotaxin in human lung fibroblast cells (1, 10 & 100 µM). Inhibits IP-10 expression in allergic patients' DCs (10 µM). Decreases expression of CXCR4 receptor on CD4 T cells (20 µg/mL). Suppresses IL-8 levels in asthmatic patients (13% soln.).	[89, 90, 140-143]
Curcumin	Inhibits tryptase-induced IL-8 release in eosinophils (25 µM).	
EGCG	Inhibits IL-8 release in TNF-stimulated human keratinocytes (0.5, 1, 5 & 10 µM). Reduces airway inflammation in asthmatic mouse model by binding to chemokines CXCL9, CXCL10 and CXCL11 (10 & 100 µM). Decreases MCP-1 and CCR2 expression on THP-1 cells (100 µM). Attenuates production of MIP-2 in lungs of mice with LPS-induced acute lung injury. Reduces expression of MCP-1 and IL-8 in HMC-1 cells (100 µM). Inhibits neutrophil migration by suppression of CINC-1 production (15, 50 & 150 µg/mL). Downregulates cigarette smoke-induced IL-8 release from bronchial epithelial cells.	[97, 99, 125, 144-147]
Gallic acid	Inhibits production of IL-8 and TARC (5 & 10 µg/mL) in neutrophils and keratinocytes respectively. Inhibits eotaxin and RANTES in pleural lavage fluid of allergen-challenged mouse model (100 mg/kg body wt.). Inhibits IL-8 release in HMC-1 cells (10 µM).	[148-150]
Rosmarinic acid	Inhibits LPS-induced production of MCP-1 and MIP-1α in bone-marrow derived DCs (100 µM). Reduces diesel exhaust particles-induced MIP-1α, MCP-1 and KC expression in mice lung (4.6 µg/kg body wt.). Inhibits expression of eotaxin in lungs of mite antigen-sensitized mice (1.5 mg/kg body wt. PO). Inhibits expression of CCL11 and CCR3 genes induced by TNF in human dermal fibroblast cells.	[102, 107, 110, 151]
Helenalin	Inhibits eotaxin and RANTES secretion in ASMCs (1 µM).	[113]

Table 6. Phytochemical inhibitors of chemokines

3.1.4. Miscellaneous: IgE, histamine, enzymes

The activation of mast cells involves the cross-linking of IgE bound to the $F_{\epsilon}RI$ surface receptor. Activation is measured in the laboratory by the release of the Beta-hexosaminidase enzyme (β -hex) from cytosolic granules into the interstitial fluid. The following compounds (Table 7) have been found to be inhibitors of β -Hex release in vitro and have to potential to be inhibitor of IgE-antigen activation.

Phytochemicals	IC ₅₀	References
Anti-oxidants		
Vitamin A/carotenoid	?	[152]
Flavonoids		
Apigenin	4.5 μ M	[153]
Baicalein	17 μ M	[153]
Chrysin	?	[62]
Daidzein	?	[83]
Fisetin	3 μ M	[73]
Genistein	28.5 μ g/mL	[83]
Ginkgetin	6.52 μ M	[154]
Glycitein	28.5 μ g/ml	[83]
Isoliquiritigenin	24 μ M	[155]
Kaempferol	7.5 μ M	[62]
Luteolin	3 μ M	[73]
Morin	51 μ M	[153]
Myricetin	6.7 μ M	[153]
Naringenin	29 μ M	[156]
Quercetin	3 μ M	[73]
Resveratrol	14 μ M	[157]
Sophoflavanone G	20 μ M	[158]
Tectorigenin	0.193 mM	[159]
Polyphenols		
Caffeic acid	?	[160]
Curcumin	5.3 μ M	[161]
EGCG	?	[162]
Ginkgetin	?	

Phytochemicals	IC ₅₀	References
Medicarpin	>100 µM	[155]
Rosmarinic acid	?	[160]
Terpenes		
Celastrol	?	[163]
Costunolide	34 µM	[164]

Table 7. Phytochemical inhibitors of beta-hexosaminidase enzyme

3.2. Inhibitors of intracellular signaling pathways

The previous section focused on compounds that affected the function of extracellular, cell surface/receptor and cell to cell interactions. The following group of compounds affect the intercellular functions of the cells particular the components of cell signalling pathways.

3.2.1. Protein kinase inhibitor

Protein kinases have a key role in the expression and activation of inflammatory mediators implicated in airway inflammation. Enhanced activation of p38 mitogen-activated protein kinase (MAPK), c-Jun N-terminal kinase (JNK), spleen tyrosine kinase (Syk), and phosphoinositol 3-kinase (PI3K) signaling pathways have all been proposed to have a role in the pathogenesis of asthma.

p38 MAPK is involved in the airway inflammation and remodeling. A selective synthetic p38 MAPK inhibitor SB2439063 reduces synthesis of Th2 cytokines [54] and thus has a potential application in asthma treatment. Inhaled p38 MAPK antisense oligonucleotide attenuates asthma in OVA-sensitized and –challenged mice [165]. The natural product limonene inhibits eosinophil migration in p38 MAPK dependent manner and was investigation in an *in vitro* bronchial asthma model [166].

JNK activity is increased in corticosteroid-resistant asthma and SP600125, a JNK inhibitor, reduces cytokines expression and inflammatory cells accumulation in BALF of asthmatic animal models. Celastrol, a natural compound, modulates the expression of JNK in asthma [167]. It supresses allergen-induced mouse asthma by decreasing expression of MAP kinases, ERK and JNK [168].

Syk is a protein kinase involved in signal transduction in many inflammatory cells, and its aberrant regulation is associated with asthma, thus is considered an interesting target for asthma therapies. BAY 61-3606, a synthetic Syk inhibitor, inhibits inflammatory mediator release from mast cells, basophils, eosinophils, and monocytes, and reduces allergic asthma in rats [169]. Eupatilin, a biological extract, inhibits Syk and blocks downstream signaling pathways in mast cell from guinea pig lung tissues, leading to inhibition of mediator release [170]. Thus, Syk inhibitors may have use clinically as a treatment for asthma.

The PI3K pathway plays a major role in the pathogenesis of asthma by promoting eosinophil and neutrophil recruitment and degranulation [171]. *Sorbus commixta* water extract, an anti-inflammatory medicinal plant, remarkably blocks PI3K activity in antigen-activated macrophages, suggesting the usefulness of PI3K inhibitors in asthma [172].

3.2.2. *Transcription factor inhibitors*

The increased expression of various inflammatory proteins seen in asthma is the result of enhanced gene transcription, since many of the genes are not expressed in normal cells but are selectively induced during inflammation. Changes in gene transcription are under the control of transcription factors which therefore play a key role in the pathogenesis of asthma.

Transcription factors such as nuclear factor- κ B (NF- κ B), GATA-3, signal transducers and activators of transcription protein (STAT)s, nuclear factor of activated T cells (NFAT), and peroxisome proliferator-activated receptors (PPAR) have been implicated in asthma and therefore represent therapeutic targets.

NF- κ B is induced by many factors involved in asthmatic inflammation and is implicated in glucocorticoid-resistant asthma. Inhibition of I κ B (inhibitor of NF- κ B) by small molecule inhibitors suppresses inflammatory responses in mast cell [173], OVA-induced rat model of airway inflammation [174], and macrophages from BALF of asthmatic patients. A number of herbal preparations (i.e. andrographolide and naringenin) have been demonstrated to inhibit airway inflammation and AHR by inhibiting NF- κ B activity in OVA-induced murine asthma [78, 175]. Many inhibitors of NF- κ B have been identified belonging to the Flavonoids, Polyphenols and Terpenoids classes of compounds as well as n-3 PUFA (see Table 8).

Flavonoid	Polyphenols	Terpenoids	PUFA
Apigenin	CAPE	Parthenolide	n-3 PUFA
Capsaicin	Curcumin	Costunolide	
Fisetin	Epigallocatechin-3-gallate	Helenalin	
Kurardin	Gallic acid	Celastrol	
Kurarinone	Gingerol	Celaphanol A	
Luteolin	Rosmarinic acid	Kamebanin	
Myrecitin		Kamebacetal A	
Naringenin		Excisanin A	
Quercetin		Orbiculin	
Resveratrol			

Table 8. Naturally occurring NF- κ B inhibitors

GATA-3 is a critical transcription factor that is specifically expressed by Th2 cells and is involved in their differentiation [176]. GATA-3 has been indicated in the development of airway eosinophilia and expression is increased in atopic asthma [177] and therefore is an obvious target for inhibition. Direct inhibition by using a specific antisense oligonucleotide or

interference RNA promises a novel approach for asthma treatment [178]. Polyphenols, such as apigenin and quercetin, ameliorate asthma symptoms, and suppress the translocation of GATA-3 in the cytosol of lung tissue of OVA-sensitized and -challenged mice [179].

NFAT transcription factor is mostly involved in the production of Th2 cytokines through its interaction with GATA-3 and activator protein-1 (AP-1) [180]. Immunosuppressive drugs cyclosporin A and FK506 block NFAT activation [181]. The use of peptides known as inhibitors of NFAT-calcineurin association (INCA) represents an alternative asthma treatment strategy [182].

PPARs are transcription factors belonging to the nuclear receptor superfamily activated by PUFA derivatives, oxidized fatty acids and phospholipids. PPAR γ activation might exhibit anti-inflammatory properties in different inflammatory processes. In a murine model of asthma, treatment with PPAR γ ligand ciglitazone significantly reduces AHR and lung inflammation [183]. PPAR α and PPAR γ ligands also decreases allergen-induced AHR, lung inflammation as well as serum IgE levels in different asthma models [184]. Popular anti-asthmatic Traditional Chinese Medicine San-ao Decoction (SAD), comprising *Herba Ephedrae*, *Radix et Rhizoma Glycyrrhizae* and *Seneb Armeniacae Amarum*, has a significant effect on PPAR γ activation [185].

3.3. Inhibitors of oxidative stress

Oxidative stress plays a critical role in the development of asthmatic conditions. Oxidative stress and its by-products drive a Th2-dependent immune response. A number of antioxidants have been explored for their anti-inflammatory and anti-asthmatic properties, and a number of natural products have emerged as promising candidates. Resveratrol, a component of red wine, possesses anti-inflammatory and antioxidant properties. It inhibits inflammatory cytokines release in patients with chronic obstructive pulmonary diseases (COPD) [186] and may be beneficial in asthma. Several other biological compounds such as *Sanguisorba officinalis* [187], aqueous extract from the root of *Platycodi Radix* [188], stem and bark of *Ulmus davidiana* [189], and *Alpinia katsumadai* seed extracts [190] attenuate oxidative stress and asthmatic activity in OVA-induced murine asthma. The flavonoids and polyphenols are the main groups of compounds that display anti-oxidative properties as listed in table 9.

Phytochemicals	Function and effective concentration(s)	References
Flavonoids		
Apigenin	Suppresses LPS-induced NO production in RAW264.7 macrophages	[191]
Baicalein	Inhibits LPS-induced NO production and iNOS expression in RAW264.7 macrophages	[192]
Chrysin	Inhibits NO production (IC ₅₀ 7.50±1.84 μ M) in LPS-activated RAW264.7 macrophages	[74]
Fisetin	Inhibits TNF-induced ROS production in HEK cells	[123]

Phytochemicals	Function and effective concentration(s)	References
Kaempferol	Inhibits NO production (IC ₅₀ 9.83±1.55 µM) in LPS-activated RAW264.7 macrophages	[74]
Kuraridin	Inhibits ROS, NO production (20 & 40 µM) and iNOS gene expression (40 µM) in LPS-activated RAW264.7 macrophages.	[66]
Kurarinone	Inhibits ROS, NO production (40 µM) and iNOS gene expression (40 µM) in LPS-activated RAW264.7 macrophages.	[66]
Luteolin	Inhibits NO production (4, 8 & 16 µM) in LPS-activated RAW264.7 macrophages.	[67]
Morin	Inhibits NO production (IC ₅₀ 44.86±1.05 µM) in LPS-activated RAW264.7 macrophages	[74]
Naringenin	Inhibits lung iNOS expression in allergen-induced mouse asthma model	[78]
Quercetin	Inhibits NO production (IC ₅₀ 36.9±1.24 µM) in LPS-activated RAW264.7 macrophages	[74]
Resveratrol	Inhibits NO production in mice with acute lung injury (1 mg/kg body wt.).	[85]
Polyphenols		
Caffeic acid	Reduces ROS levels in BALF of OVA-sensitized and -challenged mice (10 mg/kg body wt. IP).	[88]
Curcumin	Reduces iNOS expression in lung tissue of OVA-sensitized asthmatic mice.	[91]
EGCG	Reduces NOS activity in lungs of OVA-sensitized asthmatic guinea pigs.	[96]
Hydroxytyrosol	Inhibits NO ₂ production as well as iNOS expression in THP-1 cells (50 & 100 µM)	[104]
Rosmarinic acid	Inhibits formation of ROS and RNS in activates macrophages	[193]
Helenalin	Inhibits iNOS expression in LPS-stimulated macrophages (10 µM)	[137]
n-3 PUFA	Decreases exhaled NO from asthma patients challenged with mite allergen	[194]

Table 9. Phytochemical inhibitors of oxidative stress

4. Experimental models of asthma

Understanding respiratory sensitization mechanisms is the first step to designing therapeutic agents that may relieve patients of their asthma symptoms. A number of *in vitro* and *in vivo* experimental models are able to reproduce one or more features of allergic response and have

been studied for a few decades. Animal models of asthma are the best characterized in terms of the inflammatory and remodeling processes. The use of gene knockout and transgenic animals and the therapeutic administration of antibodies or pharmacological antagonists/inhibitors have helped to identify a range of pre-clinical targets for subsequent evaluation in humans. Small animal models of asthma, using mice, rats and guinea pigs, are most commonly used. Most of these models are based on active sensitization to an allergen such as OVA via the airways. *In vitro* model systems using inflammatory cells and airway-related cell types are widely used in studies on immuno-biological mechanisms of asthma. A more detailed description of the most commonly used models of asthma can be found in Table 10.

In Vivo Model	Route(s) of Administration	Primary Effects
OVA-induced allergic asthma	Intranasal or aerosol challenge, intrathoracic inoculation, intradermal challenge	Increased serum IgE levels, histological changes in airways including cellular infiltration, mediator release, AHR, and remodeling.
LPS lung inflammation model	Intranasal	Leukocytes (mainly neutrophils) recruitment to lung within 4 hr of LPS treatment.
House dust mite exposure	Intraperitoneal sensitization followed by inhalational challenge	Increased serum IgE levels, histological changes in airways including cellular infiltration, mediator release, AHR, and remodeling.
Infection by Aspergillus fumigatus	Intraperitoneal sensitization followed by inhalational challenge	Increased serum IgE levels, histological changes in airways including cellular infiltration, mediator release, AHR, and remodeling.
Ragweed allergen exposure	Intraperitoneal sensitization followed by inhalational challenge	Airway inflammation and AHR.
Infection with Ascaris suum	Subcutaneous and intratracheal sensitization, aerosol challenge	Bronchoconstriction, AHR and cellular infiltration.
In Vitro Cell Model	Cell Type	Primary Response(s)
Mast cells:		
Human mast cells	CD34 ⁺ -derived primary mast cells, cord blood mast cells, skin mast cells, lung mast cells, LAD2, LUVA , HMC-1, RBL-2H3	Release of proinflammatory mediators such as histamine, tryptase, chymase, cytokines, chemokines, leukotrienes, and prostaglandins.
Rodent mast cells	Bone marrow-derived mast cells, peritoneal mast cells	Release of proinflammatory mediators such as histamine, tryptase, chymase, cytokines, chemokines, leukotrienes, and prostaglandins.
Eosinophils	Primary cells, EoL-1, AML14.3D10	Release of proinflammatory mediators such as ECP, EPO, EDN, MBP, cytokines, and chemokines.

In Vivo Model	Route(s) of Administration	Primary Effects
Bronchial epithelial cells	Primary cells, NHBE, BEAS-2B	Release of proinflammatory mediators such as cytokines and chemokines. Morphological changes.
Alveolar epithelial cells	Primary cells, A549	Release of proinflammatory mediators such as cytokines and chemokines. Morphological changes.
Monocytes/ Macrophages	Primary cells, Mono-Mac-6, THP-1, RAW 264.7	Release of proinflammatory mediators such as cytokines, chemokines, leukotrienes, prostaglandins, ROS, and RNS.
Dendritic cells	Primary cells, U-937, CD34-DC, Mo-DC, KG-1, MUTZ-3	Release of proinflammatory mediators such as cytokines and chemokines.

Table 10. *In vivo* and *in vitro* models for asthma studies

5. Evidence for the association between diet and asthma

5.1. Antioxidants

The airways are continuously exposed to oxidants, either generated endogenously by various metabolic reactions (e.g. from mitochondrial respiration or released from phagocytes) or derived from exogenous sources (e.g. air pollutants and cigarette smoke). Allergen-activated inflammatory cells from asthmatic patients produce more ROS than from healthy individuals. In addition, several inflammatory mediators including histamine, lipid mediators, cytokines, chemokines, ECP, and EPO are potential stimuli for ROS production in the airways, leading to asthma exacerbation.

Deficiency of endogenous antioxidant defenses has been reported in asthma [195]. Since a diet rich in vitamin A or carotenoids, vitamin C vitamin E, and flavonoids, has been associated with a decreased prevalence of asthma, understanding the relationship between dietary antioxidants and asthma-associated inflammatory responses has been a recent focus.

5.1.1. Vitamin A and carotenoids

A systemic review and meta-analysis by Allen *et al.* has shown that dietary vitamin A intake is significantly lower in asthmatic patients than in healthy subjects [196]. Asthmatic children have a lower serum vitamin A concentration than healthy controls [197]. Supplementation of the diet with lycopene, a carotene found in tomatoes and carrots, has a protective effect against asthma development in a murine model [198].

All-trans retinoic acid (ARTA), a derivative of vitamin A, inhibits airway inflammation in asthmatic rats. ARTA inhibits total cell counts and the proportion of inflammatory cells in BALF, suppresses the expression of NF- κ B and intercellular adhering molecule-1 (ICAM-1), and increases the expression of κ B [199]. Retinoid acid also downregulates the expression of Th1 and Th2 chemokines in monocytes, including macrophage-derived chemokine and IP-10,

which are all important in the inflammatory process [200]. Airway smooth muscle cell migration, which contributes to the airway remodeling in chronic asthma is also inhibited by ARTA [201]. However, excessive intake of vitamin A exacerbates pulmonary hyperresponsiveness in murine asthma model, suggesting that excessive vitamin A may increase the risk and severity of asthma [202].

Mechanistically, vitamin A may regulate bronchial hyperreactivity by altering the function and abundance of the muscarinic M(2) receptors in bronchial tissue [203]. Moreover, carotenoids may regulate activation of a variety of transcription factors. Treatment of cells exposed to oxidative stress with β -carotene suppresses oxidative stress-induced activation of NF- κ B and production of IL-6, TNF, and inflammatory cytokines. Carotenoids may influence the process of apoptosis in healthy cells. While the pro-apoptotic protein Bax is downregulated after induction of external stimuli, β -carotene is able to increase expression of the anti-apoptotic protein Bcl-2 in normal cells. In addition, β -carotene exhibits a pro-apoptotic effect in colon and leukemic cancer cells, and this effect occurs by a redox-dependent mechanism linked with NF- κ B activity. These dual roles of vitamin A, including carotenoids, on apoptosis provide the capability of carotenoids as an effective anti-inflammatory agent in various diseases.

5.1.2. Vitamin C

Many observational studies have reported associations between reduced dietary/blood vitamin C levels and reduced lung functions. Asthmatic children undergoing an exacerbation have significant lower serum levels of vitamin C [204]. There is a positive correlation between serum vitamin C levels and asthma development in children (OR=0.72 per mg/dl, 95% CI=0.55, 0.95) [10]. Furthermore, asthma patients have significantly lower vitamin C level in both the cellular and fluid-phase fraction in induced sputum [205]. Higher maternal intake of citrus fruits rich in vitamin C during pregnancy is significantly associated with a reduced risk of allergic inflammation in the offspring [206]. Administration of vitamin C in OVA-challenged mice decreases AHR, influx of inflammatory cells in BALF and attenuates lung inflammation [207]. Similarly, high dose vitamin C supplementation significantly reduces eosinophilic infiltration in BALF and increases the Th1/Th2 cytokine secretion ratio; thus, skewing the Th1/Th2 balance toward non-allergic Th1 immune response in asthmatic mice [208].

A randomized, placebo controlled, double-blinded crossover trial has shown that vitamin C supplementation (1500 mg/day) attenuates asthma symptoms. Moreover, exhaled nitric oxide, urinary leukotriene C₄, D₄, E₄ and 9 α , 1 β -prostaglandin F₂ after exercise are downregulated [209]. On the contrary, there are also studies showing no significant effect of vitamin C supplementation on asthma symptoms. For example, in a randomized, placebo-controlled, double-blind parallel group trial three hundred asthma patients provided with 1 g/day vitamin C or placebo for 6 weeks do not show any improvements of asthma symptoms [210], therefore, there is insufficient evidence from randomised-controlled trials to support the use of vitamin C for asthma treatment [211].

As its mechanism of action, vitamin C may regulate factors that can influence gene expression, apoptosis, and other cellular functions indicated in inflammation. In fact, vitamin C protects

against cell death triggered by various stimuli, and major proportion of this protection is associated with its antioxidant ability [212]. Vitamin C inhibits the AP-1 activation by regulating MAPK-ERK pathway [213]. Treatment of cells exposed to UV-B irradiation with vitamin C results in a 50% decrease in JNK phosphorylation, which activates AP-1, therewith inhibiting the JNK/AP-1 signaling pathways [214]. At present, however, evidence from randomized controlled trials is insufficient to recommend a specific role for vitamin C in the treatment of asthma due to variable study design and generally poor reporting system.

5.1.3. Vitamin E

The body of evidence from multiple studies suggests that a positive association between asthma outcomes and vitamin E intake or serum vitamin E levels. Asthmatic children have significantly lower serum levels of vitamin E than non-asthmatic children [204, 215]. A longitudinal birth cohort study has explored association between maternal plasma vitamin E, fetus and fetal lungs growth, and childhood asthma. The findings have shown that maternal vitamin E status has a positive effect on the growth of fetus and fetal lungs during early pregnancy and better asthma outcomes during childhood [216]. Moreover, high maternal vitamin E intake during pregnancy also reduces the risk of infantile wheeze [206]. Vitamin E intake is higher in control subjects than in asthma patients [217]. However there is no relationship found between serum vitamin E level and asthma [4, 218]. On the other hand, administration of vitamin E for 6 weeks does not have an effect on asthma features and serum immunoglobulin levels in adults [219].

Role of Vitamin E has been investigated in animal models of allergic asthma. Administration of Vitamin E to allergen-challenged mice reduces mitochondrial dysfunction, Th2 cytokines production, allergen-specific IgE, and expression of lipid mediators in lung leading to alleviation of asthmatic features [220]. Expression of IL-5 mRNA and protein in lung, and plasma IgE level are reduced after OVA sensitization and challenge compared to wild type mice in vitamin E transfer protein knockout mice [221]. Moreover, dietary supplementation with vitamin E affords variable degree of protection against ozone-induced enhanced airway response in allergen-sensitized guinea pigs [222]. However, oral α -tocopherol has no protective effect on lung response in rat model of allergic asthma. There is no improvement in OVA-induced AHR, the inflammatory cell infiltrate and histological changes [223]. The observed opposite effects of vitamin E could be associated with the study design in an animal model of asthma. The effect of vitamin E deserves further evaluation.

Vitamin E may induce immunological effects via modulation of the functional activity of T cells and enhancing the phagocytic activity of peripheral granulocytes [224]. A derivative γ -tocopherol appears to be a more potent anti-inflammatory agent than α -tocopherol. It decreases systemic oxidative stress, cytokine release from monocytes in asthmatic patients, and inhibits monocyte response to LPS and LPS-induced degradation of I κ B and JNK activation [225]. There is a contradictory study demonstrating that γ -tocopherol elevates inflammation and ablates the anti-inflammatory benefit of the α -tocopherol by regulation of endothelial cell signals during leukocyte recruitment in experimental asthma [226]. Dietary tocopherols are taken up from the intestine and transported via the lymph to the blood and then to the liver.

In the liver, α -tocopherol is transferred to plasma lipoproteins, resulting in retention of γ -tocopherol in tissues at 10% that of α -tocopherol. On interpreting these two contradictory results, one should consider their serum levels with caution since low plasma level of γ -tocopherol (1.2–7.0 μM) may act as prooxidant, while higher level of γ -tocopherol (19.5 μM at 8 days) exerts antioxidative and anti-inflammatory effects.

5.1.4. Vitamin D

Over the past several years, the role of vitamin D in immunomodulation has been studied and shown to have a significant impact on innate and adaptive immunity to infections, including the pathophysiology of allergic asthma. It has been proposed that the increase in allergy and asthma is a consequence of widespread vitamin D insufficiency which appears to be frequent in industrialized countries, reflecting the insufficient intake of diet-sourced vitamin D.

The serum vitamin D level is associated with asthma in children as well as adults. A randomized, placebo controlled clinical study with 1024 children suffering from mild-to-moderate persistent asthma has shown that Vitamin D deficiency is associated with a higher rate of severe asthma [227]. There is a significant positive correlation between forced vital capacity percent predicted and serum vitamin D level children with asthma. Moreover, 91.6% of these asthmatic children are not sufficient in serum vitamin D level [228]. Low level of vitamin D in serum are also associated with increased hyperresponsiveness and reduced glucocorticoid response in adults with asthma [229]. These studies have indicated that the low serum vitamin D level is related to reduced lung function and higher risk of asthma. Reduced the risk of asthma exacerbation triggered by acute respiratory tract infection is observed in a vitamin D supplementation [230]. Higher consumption of vitamin D during pregnancy may reduce the risk of childhood wheeze and asthma.

One possible mechanism of vitamin D's protective effect against asthma can be that it inhibits the maturation process of dendritic cells by suppressing the expression of costimulatory molecules HLA-DR, CD86, CD80, the maturation marker CD83, and IL-12 which are important for the recruitment of Th1 cells [231]. Vitamin D also upregulates the expression of IL-10 receptor in dendritic cells, which is an anti-inflammatory cytokine. In addition, it can promote the production of FoxP3 positive and IL-10 positive regulatory T cells, and induce the release of IL-10, TGF- β and CTLA-4 [232]. Furthermore, it may reverse steroid-resistance in asthmatic patients through induction of IL-10 secreting T-regulatory cells [233], and vitamin D has been shown to regulate expression of many genes in ASM cells, including genes previously implicated in asthma predisposition and pathogenesis [234].

5.2. Flavonoids

Flavonoids interfere with oxidation of lipids and other molecules and this strong antioxidative property makes them protective against airway diseases linked to oxidative stress. In fact, several epidemiologic studies suggest the beneficial effects of flavonoids on asthma. A population-based case-control study has shown that apple consumption and red wine intake are inversely associated with asthma prevalence or severity, perhaps due to a protective effect

of flavonoids [18]. Moreover, a 30-year longitudinal epidemiological study has reported that the incidence of asthma is lower in populations with higher intake of flavonoids [235].

Flavonoid Subclass	Dietary Flavonoids	Some Common Food Sources
Anthocyanidins	Cyanidin, Delphinidin, Malvidin, Pelargonidin, Peonidin, Petunidin	Red, blue, and purple berries; red and purple grapes; red wine
Flavanols	Monomers (Catechins): Catechin, Epicatechin, Epigallocatechin Epicatechin gallate, Epigallocatechin gallate Dimers and Polymers: Theaflavins, Thearubigins, Proanthocyanidins	Catechins: Teas (particularly green and white), chocolate, grapes, berries, apples Theaflavins, Thearubigins: Teas (particularly black and oolong) Proanthocyanidins: Chocolate, apples, berries, red grapes, red wine
Flavanones	Hesperetin, Naringenin, Eriodictyol	Citrus fruits and juices, e.g., oranges, grapefruits, lemons
Flavonols	Quercetin, Kaempferol, Myricetin, Isorhamnetin	Widely distributed: yellow onions, scallions, kale, broccoli, apples, berries, teas
Flavones	Apigenin, Luteolin	Parsley, thyme, celery, hot peppers
Isoflavones	Daidzein, Genistein, Glycitein	Soybeans, soy foods, legumes

Table 11. Common dietary flavanoids.

Beyond antioxidative effects, flavonoids inhibit the release of histamine and other preformed granule associated mediators by inhibiting the activation of basophils and mast cells [66]. Flavonoids inhibit synthesis of IL-4, IL-13, and CD40 ligand but initiate generation of new phospholipid-derived mediators. One of the well-characterized flavonoids, quercetin, inhibits eosinophilic secretion of Charcot-Leyden crystal protein and ECP in a concentration-dependent manner. Very recently, Li *et al.* demonstrated that apigenin exhibits an anti-inflammatory activity in a murine asthma model and can switch the immune response to allergens toward the Th1 profile. These findings suggest that flavonoids are anti-allergenic and anti-inflammatory agents effective in treating/preventing asthma.

Vascular changes are one of the major components of asthmatic pathogenesis. These changes include an increase in vascular permeability, vascular dilation/engorgement, and vasculogenesis/angiogenesis. Flavonoids and their related compounds have been shown to modulate expression of HIF-1, VEGF, matrix metalloproteinases (MMPs), and epidermal growth factor receptor but also inhibit NF-κB, PI3K/Akt, and ERK1/2 signaling pathways [236]. These observations suggest that flavonoids as well as their related compounds inhibit certain steps of angiogenesis including cell migration, microcapillary tube formation, and MMP expression.

Many flavonoids have been tested for their anti-asthma effect. Quercetin decreases the eosinophil recruitment, reduces IL-5 and IL-4 levels, and inhibits NF-κB activation in BALF in OVA-induced mouse model [237]. It also regulates Th1/Th2 balance by enhancing IFN-γ and decreasing IL-4 levels in mouse asthma model [179]. Naringenin alleviates airway inflamma-

tion and reactivity by decreasing serum total IgE level and IL-4, IL-13 level in BALF and inhibiting NF- κ B activity [78]. Licorice is a Traditional Chinese Medicine, which contain many flavonoids. Flavonoids extracted from licorice attenuates LPS-induced acute pulmonary inflammation by inhibiting inflammatory cells infiltration and inflammatory mediator release [238]. Neutrophils, macrophages and lymphocytes accumulation in BALF, lung TNF and IL-1 β mRNA expression and lung myeloperoxidase activity are reduced; whereas BALF superoxide dismutase activity is increased [238]. Flavonoids from red algae decrease eosinophil infiltration, levels of TNF, IL-4 and IL-5 in BALF, airway luminal narrowing, AHR and level of allergen-specific IgE in the serum [239]. A complex mixture of bioflavonoids derived from purple passion fruit peel extract supplemented to asthma patients in a randomized, placebo-controlled, double-blinded trial alleviates asthma clinical symptoms, including FVC and FEV1 [240].

5.3. Resveratrol

Resveratrol scavenges intracellular ROS by inducing and stabilizing antioxidant enzymes such as catalase, SOD, and glutathione peroxidase hemoxigenase. In addition to its reducing properties, resveratrol has been shown to attenuate inflammation via inhibition of prostaglandin production [241] and to decrease the phosphorylation of ERK1/2, COX-2 activity, and activity of various transcription factors including NF- κ B, STAT3, HIF-1 α , and β -catenin [236]. Resveratrol also inhibits protein kinases (e.g. src, PI3K, JNK, and Akt) and the production of inflammatory mediators (e.g. IFN- γ , TNF, COX-2, iNOS, CRP and various interleukins). Recent studies have reported that resveratrol activates sirtuin1 (SIRT1) which is modulates apoptosis and has been shown to increase longevity in some experimental systems [242]. SIRT1 modulates poly (ADP-ribose) polymerase-1 (PARP-1) activity upon DNA damage. Activation of SIRT1 by resveratrol leads to a decrease in PARP-1 activity and promotes cell survival, which can attenuate the inflammatory reaction. We investigated the effects of resveratrol on human mast cell activation in comparison to the anti-allergic drug tranilast. The results show that resveratrol inhibits mast cell degranulation, cytokine, chemokine and leukotriene release, and is more efficacious than tranilast [316].

Resveratrol is able to modulate innate immune response by inhibiting expression of costimulatory molecules (CD80 and CD86) and major histocompatibility complex classes I and II in bone marrow-derived dendritic cells and inhibit angiogenesis pathway that is mediated through expression of MMPs, VEGF, cathepsin D, ICAM-1, and E-selectin [236]. These findings suggest that resveratrol can be a very attractive compound for preventing/treating asthma since this compound displays multiple therapeutic effects, showing antioxidative, anti-inflammatory, immune modulating, and vascular protective property.

Resveratrol has been shown to inhibit the airway inflammation and hyperresponsiveness in OVA-induced mouse asthma by reducing eosinophil/neutrophils infiltration, the levels of IL-4 and IL-5 in plasma and BALF [81]. It can modulate Th1/Th2 balance, polarization of naive CD4⁺ T cells to the Th2 phenotype, and the expression of Th2 regulatory transcription factor, GATA-3 [81]. It also inhibits cytokine release in vitro by alveolar macrophages from patients with COPD, including IL-8 and GM-CSF [186].

5.4. Selenium

Selenium is an important molecule in both innate and adaptive immune responses. It stabilizes activated platelets by inhibiting platelet aggregation and secretion of adenine nucleotide, thus possibly blocking the release of arachidonic acid from platelet membrane [243]. In asthma, platelets participate by acting as inflammatory cells, by releasing mediators, spasmogens and/or by interacting with other inflammatory cell types [168]. Selenium affects the expression of endothelial cell adhesion molecules, E-selectin, P-selectin, ICAM-1, VCAM-1, and ELAM-1, which are crucial in the inflammatory process for recruitment of inflammatory cells into the target tissue [244].

Some studies have reported that asthma patients have lower selenium level in platelets and serum compared to healthy controls [245, 246]. While others studies have found no relationship between serum selenium level and asthma in Japanese and Europe populations [247, 248]. Selenium supplementation studies in mouse OVA-induced asthma models have shown that selenium has some protective effects on asthma-associated inflammation. Mice with decreased and increased levels of selenium intake show lower cytokine levels, airway inflammatory cell infiltration, serum anti-OVA IgE, airway hyperreactivity, and phosphorylated STAT-6 levels in the lung compared to medium selenium intake [249]. Selenium supplementation does not show any clinical benefit in adult asthma patients [250].

Despite the data showing positive effects of selenium on some of the pathologies associated with asthma, there are still some conflicting findings of selenium supplementation in animal and human studies. Thus the issue regarding selenium is not conclusive.

5.5. Avenanthramides

Avenanthramides (Avns) are extracted from oats and those synthetically prepared exhibit potent antioxidant properties *in vitro* and *in vivo*. The antioxidant activity of Avns is 10–30 times greater than that of oats' other phenolic antioxidants such as vanillin and caffeic acid. Avn-C, one of the three major Avns of oats, often comprises about one-third of the total concentration of Avns in oat grain (although the relative proportion of Avns is highly variable), it has the highest antioxidant activity *in vitro*. By far, these Avns constitute the major phenolic antioxidants present in the oat kernel. The antioxidant activity of Avn-enriched extract of oats has been investigated in laboratory animals. Supplementing the diet of rats at 100 mg/kg diet (providing about 20 mg Avns/kg body weight) has been reported to increase superoxide dismutase (SOD) activity in skeletal muscle, liver, and kidneys, and to enhance glutathione peroxidase activity in heart and skeletal muscles [251]. Supplementation at 200 mg/kg diet, which provides about 40 mg Avns/kg body weight in rats, attenuated the exercise-induced production of ROS [251].

In addition to demonstrating antioxidant activity, Avn compounds may also interact with cellular components, through their interactions with the molecular and signaling pathways that govern cellular responses during inflammation. Using the human aortic endothelial cell (HAEC) culture system, the potentially beneficial health effects of oat Avns was found to be mediated via modulation of the cellular and molecular processes that are known to play an

important role in the inflammation of arteries and the development of atherosclerosis [251]. They have been shown to inhibit vascular endothelial cell expression of adhesion molecules, including ICAM-1, VCAM-1, and E-selectin. Suppression of these adhesion molecules resulted in inhibition of monocyte adhesion to HAEC monolayers and reduced production of several inflammatory cytokines and chemokines, including IL-6, IL-8, and MCP-1, the inflammatory components involved in fatty streak formation in arteries. The production of proinflammatory cytokines, chemokines, and adhesion molecules by endothelial cells has been shown to be regulated by redox-sensitive signal transduction involving nuclear transcription factor NF- κ B. The above-observed effects of Avns on HAEC and other cells are reported to be mediated through inhibition of NF- κ B. More recently, dihydroavenanthramide (DHA_v), a synthetic analog of Avn, has been shown to protect pancreatic β -cells from damage via inhibition of NF- κ B. In a series of experiments, Guo *et al.* determined that suppression of the expression of NF- κ B activity by Avns is mediated via inhibition of the phosphorylation of IKK and $\text{I}\kappa\text{B}$, and by suppression of proteasome activity in endothelial cells [252]. A study by Sur *et al.* demonstrated anti-inflammatory activity of Avns in skin, inhibiting the degradation of $\text{I}\kappa\text{B}-\alpha$ in human keratinocytes which correlates with decreased activation of NF- κ B and subsequent reduction in IL-8 release [253]. Topical application mitigates skin inflammation in murine model of contact hypersensitivity and neurogenic inflammation and reduces pruritogen-induced scratching in murine itch model [253]. Taken together these observations suggest that Avns are potent anti-inflammatory agents with a potential application in asthma treatment.

5.6. Herbal preparations

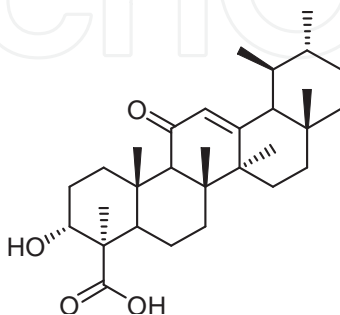
Herbs have been used to treat airway diseases including asthma for thousands years in many nations, especially in Asian and African countries. In recent decades, some Chinese, Japanese, Indian, and African herbs have been tested for their anti-asthmatic effects.

5.6.1. *Boswellia serrata*

Boswellia serrata, Indian frankincense, is commonly found in many regions of the world, such as South Asia, Northern Africa, and Middle East. Traditional medicine using extract made from sap, has long been used to treat inflammatory diseases [204]. These extracts contain resin, amino acids, phenols, terpenes, polysaccharides [205] and β -boswellic acid the major active anti-inflammatory component [206].

Extract of *Boswellia Serrata* or β -boswellic acid has been reported to inhibit hypersensitivity reactions by regulating both the humoral and cellular immune systems. They decrease primary antibody synthesis, inhibit polymorphonuclear leukocyte proliferation and infiltration, enhance the phagocytotic function of macrophages, and suppress the classical and alternate complement pathways [254, 255] and suppress the inflammation process, one of the critical pathological features in asthma. It has been shown that β -boswellic acid inhibits the production of proinflammatory cytokines, including TNF, IL-1, IL-2, IL-6, IL-12 and IFN- γ by suppressing the activation of NF- κ B [256]. It also inhibits histamine release from mast cells challenged with G protein stimulator c48/80 in a dose-dependent manner [257]. β -boswellic acid can down-regulate the synthesis of prostaglandins by inhibiting COX-1 in intact human platelets [258].

The synthesis of 5-hydroxyeicosatetraenoic acid (5-HETE) and leukotriene B₄ from rat peritoneal polymorphonuclear leukocytes, which contribute to bronchoconstriction, and increased vascular permeability, are reduced by *Boswellia Serrata* extract as a result of 5-LO inhibition [259]. These results suggest that *Boswellia Serrata* might be effective in controlling the inflammation process and contraction of airway smooth muscle in asthmatic condition by inhibiting enzymes required for production of proinflammatory mediators and bronchoconstrictor.



Boswellia serrata

Preliminary clinical investigation has shown *Boswellia Serrata*'s potential therapeutic effect on asthma. In a double-blind, placebo-controlled clinical study [260], 40 patients took 300 mg of extract daily for six weeks, while a control group received a lactose placebo for the same period of time. Lung and immune functions were recorded, including dyspnoea, rhonchi, frequency of attacks, FEV₁, FVC, peak expiratory flow rate (PEFR), eosinophil count and erythrocyte sedimentation rate. In the treatment group 70% of patients and 27% in the control group showed improvement in terms of recorded physical symptoms and signs. These results suggest that *Boswellia Serrata* extract has potential benefit for asthma patients, although the age for control and treatment group was not perfectly matched. However, there is not enough evidence to draw a conclusion on the potential use of *Boswellia Serrata* for treating asthma in human.

5.6.2. Bromelain

Bromelain is an extract from the pineapple stem, *Ananas comosus*, containing a mixture of cysteine proteases, peroxidase, acid phosphatase, protease inhibitors, and calcium, with cysteine proteases being the main functional components [214].

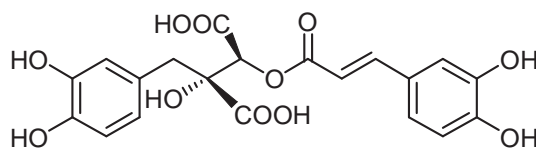
Bromelain modulates immune responses both *in vitro* and *in vivo*. *In vitro*, it downregulates mRNA expression of IL-2, IL-4, and IFN- γ in T cells induced by phorbol myristate acetate (PMA), with the mechanism thought to be the inhibition of p21ras and subsequent ERK-2 [261, 262]. In a study using peripheral blood mononuclear cells (PBMC), Bromelain decreases the expression of migration/activation related cell surface markers on leukocyte by proteolysis, including CD14, CD16, CD21, CD25, CD44, CD45RA, CD62L [263]. In addition, it can dose-dependently reduce CD25 expression in anti-CD3 antibody-stimulated CD4⁺ T cells, which is upregulated when T cells are activated in inflammation, autoimmunity and allergy [264].

These results indicate that Bromelain may regulate inflammatory process by interfering the migration and activation of immune cells, primarily T cells. *In vivo*, Bromelain may inhibit IgG production and decrease IL-2 gene transcription in spleen, and significantly reduce blood CD4⁺ T cell count [262]. In addition, it downregulates IFN- γ mRNA expression in spleen [265]. These results indicate that Bromelain has regulatory effects on the adaptive immunity, principally by targeting T cell responses.

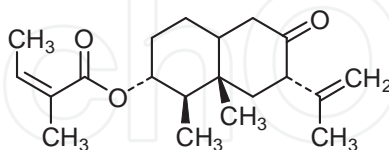
Bromelain administration via intraperitoneal injection alleviates some of the features of airway inflammation in the OVA-induced murine asthma model. It reduces the total numbers of leukocytes, eosinophils, CD4⁺ and CD8⁺ T cells in BALF, and decreases IL-13 concentration, which is a critical mediator for AHR in asthma [266]. In separate study, oral supplementation has been shown to suppress airway methacholine sensitivity, decrease IL-13 level, and eosinophils, CD19⁺ B cells and CD8⁺ T cells counts in BAL [267]. These results suggest that Bromelain modulates airway reactivity by altering the presence of leukocytes in airway, which is consistent with the *in vitro* results mentioned above. However, there is no clinical report available on the use of Bromelain against asthma so far.

5.6.3. Butterbur (*Petasites hybridus*)

Butterbur is a member of the perennial sunflower family found in Europe and northern Asia. The ancient Greeks used butterbur roots to treat airway diseases and alleviate bronchial spasms [268].



Fukinolic acid



Petasin

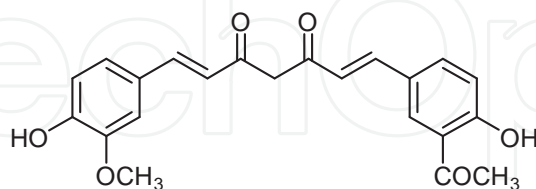
Extract from the flower bud, leaves and root have been shown to inhibit β -hexosaminidase release, leukotriene C4/D4/E4 synthesis, and TNF production from IgE-sensitized RBL-2H3 cell [223]. A group of Japanese researchers reported that Japanese butterbur contains multiple active compounds including two eremophilane-type sesquiterpenes, six polyphenolic compounds, and two triterpene glycosides [223], and based on its inhibitory activity on mast cell degranulation, fukinolic acid is believed to be the most active component [269]. Another active component petasin, can reduce leukotriene and ECP production from eosinophils activated

by platelet-activating factor (PAF) or C5a via suppression of cytosolic phospholipase A2 (cPLA2) activity, decreasing intracellular calcium concentration and inhibiting 5-LO translocation from the cytosol to nuclear membrane [270]. Pepsin inhibits leukotriene production from macrophages [271] and suppresses bronchial constriction induced by histamine, carbachol, KCl and leukotriene D₄ in isolated guinea pig trachea [272]. In the OVA murine model, butterbur extract given intranasally together with antigen challenge has been shown to inhibit airway inflammation induced by OVA and hyperresponsiveness to aerosolized methacholine, reduce eosinophil count and decrease Th2 cytokine production including IL-4, IL-5 and RANTES in BALF [227]. These results suggest that Butterbur may have inhibitory effects on proinflammatory mediator release from a broad range of immune cells.

In 2003, a prescription-based Butterbur extract was approved in Switzerland for the treatment of seasonal allergic rhinitis and in response some researchers have tested Butterbur extract for the treatment of asthma. Ziolo *et al* conducted an open clinical study on its effects on bronchial reactivity in asthma patients. Provided orally in a single dose for three time periods patients show significant improvement on FEV1, especially subjects those in longer treatment group [273]. In another randomized, double-blind, placebo-controlled clinical study, results have shown that the signs of asthma are significantly suppressed by Butterbur treatment including FEV1, exhaled NO, serum ECP and peripheral blood eosinophil count, suggesting Butterbur reduces some of the inflammatory markers associated with allergic respiratory inflammation [274]. However, some long term adverse side effects have been reported including abdominal pain, flatulence, and sneezing in pediatric patients and hair loss, cough, dyspnea, and severe depression for adult patients [230]. More studies with larger sample size are needed for the evaluation of Butterbur's clinical use on asthma.

5.6.4. Curcumin

Curcumin is a yellow polyphenol compound, extracted from the rhizomes of *Curcuma longa* [231]. In ancient time, curcumin containing turmeric plants were widely used to treat swelling and wounds in Southern Asia [275].



Curcumin

Many pharmacological effects of curcumin have been reported, including antioxidative, anti-inflammatory and antimicrobial activities [276]. In terms of its antioxidative effects, curcumin is thought to be more potent than vitamin E [277] with the mechanism including downregulation of NO production, scavenging free radicals, and inducing heme oxygenase-1 to repair the oxidative damage caused by free radicals [278-280]. Curcumin can inhibit the production of proinflammatory cytokines such as IL-1 β and IL-8, suppress inducible iNOS and NO

production, and modulate steroid activity. Its effect on steroid activity may be the result of inhibition of NF- κ B through blocking IKK activity [281-284].

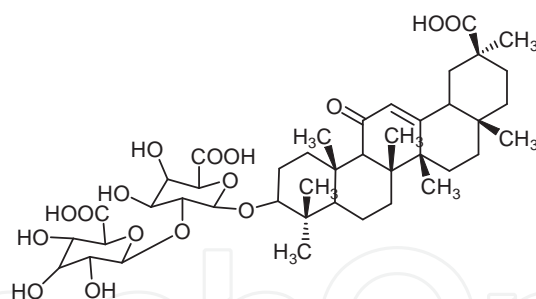
During allergic inflammation, curcumin may modulate both early and late phase responses by altering Th2 responses. In a murine latex-induced allergy model, characterized by an increased serum total IgE and latex specific IgG₁, elevated peripheral blood eosinophils count, and enhanced lung tissue IL-4, IL-5 and IL-13, intragastric curcumin administration reduces lung inflammation. Protein expression of costimulatory molecules CD80, CD86, and OX40-Ligand, and RNA expression of MMP-9, ornithine aminotransferase (OAT), and thymic stromal lymphopoietin (TSLP) in antigen-presenting cells are all decreased. These results suggest that curcumin may disrupt antigen presentation, so that has potential therapeutic value on allergen triggered airway inflammation [285].

Curcumin has been shown to have anti-asthmatic effects in both *in vivo* and *in vitro* studies. In OVA-induced asthma model in guinea pigs, curcumin treatment during OVA sensitization or following antigen challenge shows significant protective effects through attenuation of bronchial constriction and hyperreactivity [286]. This indicates curcumin has both preventive and therapeutic effects on asthma. In another study in an OVA-induced murine asthma model, curcumin's anti-asthmatic function is attributed to the suppression of iNOS and subsequent NO production, inhibition of inflammatory cytokine synthesis and downregulation of eosinophil recruitment to airway [91]. *In vitro*, curcumin supplementation inhibits IgE/antigen activation of mast cells through the principal activation pathway mediated by Fc ϵ RI directly inhibiting Syk kinase phosphorylation, which is critical for the propagation of signaling cascade. Subsequently, the phosphorylation of MAP kinases including p38, ERK 1/2 and JNK are suppressed, which are crucial for gene transcription and production of proinflammatory cytokines [287]. In addition, curcumin inhibits HDM-induced lymphocyte proliferation and production of IL-2, IL-4, IL-5, and GM-CSF by lymphocytes from asthma patients [246]. These results indicate that curcumin may attenuate asthma symptom by inhibiting production of cytokines related to eosinophil function and IgE synthesis, and suppressing IgE-mediated reactions and hyperreactivity.

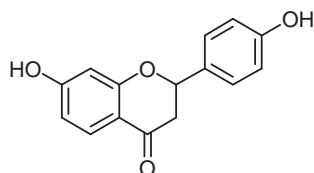
5.6.5. Licorice root (*Glycyrrhiza glabra*)

Licorice root has been widely used around the world to treat cough since ancient time [247]. It contains the active compounds including glycyrrhizin, glycyrrhetic acid, flavonoids, isoflavonoids, and chalcones [248]. Glycyrrhizin and glycyrrhetic acid are considered to be the main active components [249] and are potent inhibitors of cortisol metabolism, due to their steroid like structures inhibiting the key steroid metabolic enzymes, delta 4-5-reductase, 11 beta-hydroxysteroid dehydrogenase and 20-hydroxysteroid dehydrogenase [250, 251]. Therefore, the benefits and side effects of steroid are both expected to be enhanced in the presence of glycyrrhetic acid and glycyrrhizin.

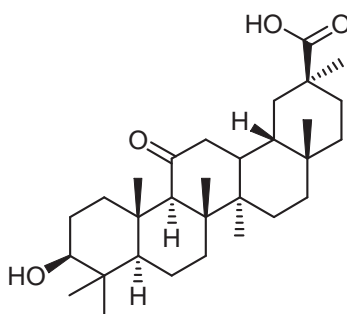
Glycyrrhizin



Liquiritige



Glycyrrhetic acid



The anti-inflammatory effect of glycyrrhizin during virus infection has been well documented [288-290] and may alleviate allergic inflammation as well. In a contact skin hypersensitivity mouse model, glycyrrhizin and its metabolite 18 β -glycyrrhetic acid-3-O- β -D-glucuronide show protective effects in terms of reduced passive cutaneous anaphylaxis and inflammation, with glycyrrhizin being more potent than 18 β -glycyrrhetic acid-3-O- β -D-glucuronide [291]. In an OVA-induced murine asthma model, glycyrrhizin provided orally alleviates airway constriction and hyperreactivity, pulmonary inflammation. In BAL, IFN γ level is increased, while IL-4, IL-5 levels and eosinophil count are decreased. It also reduces OVA-specific IgE levels and upregulates total IgG_{2a} in serum as well [292]. These results indicate that glycyrrhizin interfere the production of IgE by decreasing the IgE-stimulating cytokines.

The effects of glycyrrhetic acid and liquiritigenin (a flavonoid of licorice root) on asthma have been tested both *in vivo* and *in vitro*. *In vitro*, glycyrrhetic acid and liquiritigenin inhibits β -hexosaminidase release from RBL-2H3 cells induced by IgE/DNP, and from rat peritoneal mast cells challenged with c48/80. *In vivo*, they can suppress c48/80 induced passive cutaneous anaphylactic reaction in mice. In OVA-induced murine asthma model, glycyrrhetic acid but

not liquiritigenin reduces the level of IgE in serum [293]. Flavonoids extracted from licorice root quench LPS-induced pulmonary inflammation by inhibiting the recruitment of neutrophils, macrophages and lymphocytes in BALF, and suppressing the mRNA expression of TNF and IL-1 β in LPS-challenged lung tissue in mice [238]. The reported side effects of licorice root includes headache, hypertension, hypokalemia, premature birth, muscle weakness, and increase body weight, which were attributed to its function on inhibiting the steroid metabolism [294].

5.6.6. *Modified Mai-Men-Dong-Tang*

Mai-Men-Dong-Tang is an old Chinese herb formula commonly used for treating lung diseases, which contains Ophiopogon, Ginseng, Pinellia, Licorice, Jujube, and Oryza [260]. It is reported to increase the cough threshold to inhaled capsaicin in asthmatic patients. Also, the eosinophil count in peripheral blood, sputum eosinophil ratio, and serum eosinophil cationic protein level are significantly decreased, especially in patients with severe airway inflammation [261], which suggests that Mai-Men-Dong-Tang may alleviate asthma-related cough by inhibiting eosinophil function.

Modified Mai-Men-Dong-Tang (mMMDT) contains five herbs, Ophiopogon, American ginseng, Pinellia, Licorice root, and Lantern tridax [262]. The efficacy and safety of this formula to persistent, mild to moderate asthma has been evaluated in a double-blind, randomized clinical study of 100 patients with mild to moderate asthma. After 4 months, improvements in FEV1 and symptom scores has been reported in mMMDT treatment groups with decreased serum IgE and no drug-related adverse effects seen in terms of blood test, and liver, kidney functions [295]. Modified Mai-Men-Dong-Tang is a potential effective herb formula in treatment of childhood asthma for long time use. However, recommendation cannot be made because of small sample size used in the study.

5.6.7. *Ding-Chuan-Tang*

Ding-Chuan-Tang (DCT) is a traditional Chinese herb formula used for the treatment of cough, wheezing, and chest tightness, developed about four hundred years ago during the Ming dynasty. This formula contains nine herbs including *Radix glycyrrhizae*, *Tuber pinellia*, *Ginkgo bilboae*, *Herba ephedrae*, *Flos tussilaginis farfarae*, *Cortex mori albae radices*, *Fructus perilla frutescens*, *Semen pruni armeniacae*, *Radix scutellariae baicalensis* [263]. In OVA-induced pig asthma model, DCT given orally to animals 30 min before antigen challenge inhibits the antigen induced immediate asthmatic responses. If it is given together with sensitization, immediate and late asthmatic responses are all suppressed. In addition, DCT relaxes trachea contracted with carbachol. The effects are attributed to decreased eosinophil infiltration to airway [263].

Randomized double-blind, placebo-controlled study to assess the effect of DCT on airway hyperreactivity in children with mild to moderate persistent asthma has shown that the FEV1 is significantly increased in DCT group (196%, $p=0.034$), but not in placebo control group. Compared to placebo control group, total clinical/medication score shows improvement in the DCT group ($p=0.004$). No side effects have been reported [296]. These results suggest that DCT

might be effective in treating asthma in children. Larger sample size and wider population are required in further investigations.

5.6.8. STA-1 and STA-2

STA is a combination of mMMDT and another Chinese herb formula Liu-Wei-Di-Huang-Wan (LWDHW), which is also used by Chinese as an anti-cough agent. LWDHW contains six herbs including *Rehmannia* root, *Alisma* rhizome, *Dioscorea* rhizome, *Poria*, *Hoelen*, *Moutan* root bark, *Shanzhu yu*. The formula for STA-1 and 2 are the same while the only difference being in the preparation of LWDHW is different [265]. In a mouse asthma model induced by intraperitoneally administrated dermatophagoides pteronyssinus group 5 allergen (Der p 5), oral STA-1 treatment during sensitization suppresses Der p 5-specific IgE production from animals in response to inhaled Der p 5 challenge. In addition, eosinophil and neutrophil airway infiltration, and airway hyperreactivity are all significantly reduced in STA-1 group compared to control animals [266]. The efficacy and side effects of STA-1 and STA-2 on childhood asthma treatment have been evaluated in a randomized, double-blind, placebo-controlled study. The herbs and placebo provided to pediatric patients with mild to moderate asthma reduces symptom scores, serum steroid concentration, total IgE, and allergen-specific IgE levels and improves FEV1 in the STA-1 group. STA-2 does not show protective effects. No severe side effects were reported [297]. These results indicate that STA-1 might be a valuable formula for childhood asthma, especially subjects induced by dust mite antigen. However, there is not enough evidence to draw a concrete conclusion. It is worthwhile to evaluate their potential use as immunotherapy as well.

5.6.9. Anti-Asthma Herbal Medicine Intervention (ASHMI)

ASHMI is a relatively new formula developed by a group of Chinese researchers and physicians, which is an extract from three herbs: *Radix glycyrrhizaen prednisone*, *Radix sophorae flavescentis*, and *Ganoderma* [267]. In OVA-induced asthma, oral ASHMI treatment before and during OVA sensitization and challenge reduces AHR represented by time-integrated change in peak airway pressure. Eosinophil infiltration in BALF, lung inflammation, OVA-specific IgE production, and level of IL-4, IL-5, and IL-13 in lung and splenocyte cultures are significantly lower in ASHMI treated mice, whereas IFN- γ production is increased [267, 268]. A 6-week treatment of ASHMI beginning 24 hr after the first OVA challenge in mice reduces early phase response by decreasing histamine, leukotriene C, and OVA-specific IgE levels, and suppresses late phase responses by decreasing eosinophil count and Th2 cytokines in BALF. In addition, it relieves contraction of murine tracheal rings by increasing the production of PGI₂ [269]. These results suggest that ASHMI inhibits asthmatic inflammation and airway muscle contraction, primarily by inhibiting Th2 cell function and might be suitable for treating antigen-induced asthma in both young and old subjects.

In clinical trial, ASHMI has been shown to improve lung function indicated by increased FEV1 and peak expiratory flow. Clinical symptom scores, use of β_2 -bronchodilators, serum IgE level, serum IL-5, IL-13 concentrations are all reduced, and some effects are even better than prednisone. During the study no adverse effect were recorded [298]. These results indicate the

effectiveness of ASHMI on treating asthma in both young and old adult patients. More adequately powered investigations are needed to evaluate ASHMI's effect on asthma.

5.7. n-3 polyunsaturated fatty acids

PUFA are a group of fatty acids with more than two carbon-carbon double bonds. There are three types of PUFA, n-3, n-6 and n-9, with their names based on the position of first double band from methyl end in their chemical structures. Currently, many studies have focused on n-3 and n-6 PUFA because EPA (20:4 n-3), Dihomo- γ -Linolenic acid (DGLA, 20:3 n-6) and Arachidonic acid (AA, 20:4 n-6) in cell membrane can be metabolized and become eicosanoid precursors, which are important modulatory autocrine molecules. Eicosanoids include prostaglandins, leukotrienes, thromboxanes, resolvins, lipoxins, are signal molecules that exert complex effects on health. They can modulate inflammation, fever, blood pressure, the immune system, etc. Eicosanoids can be made by oxidation of twenty carbon n-3 (EPA) and n-6 (DGLA, AA) PUFA. Eicosanoids from AA are proinflammatory, while those from EPA and DGLA are less so. There is competition between n-3 PUFA and n-6 PUFA in oxidation in terms of cyclooxygenase and lipoxygenase, which are critical enzymes for eicosanoid generation. AA is the predominant n-6 PUFA in body. In general, n-3 and n-6 are hypothesized to be beneficial and detrimental respectively [299, 300]. Fish, fish oil, krill, mussel and seal oil are natural sources of n-3 PUFA.

The major n-3 PUFA are listed in Table 12. In mammals, including humans, n-3 PUFA cannot be synthesized *de novo*. Therefore they must be absorbed through the diet or produced from α -Linolenic acid (ALA), which is an essential fatty acid. Among them, the health beneficial effects of EPA and DHA (22:6 n-3) are well documented in a broad range of health and disease conditions. The consumption of EPA and DHA are associated with lower risk of cancer, hyperlipidemia, and cardiovascular disease, high blood pressure, and neurodegenerative diseases [301-304]. Their regulating function on immune system was also well known and are involved in activation of immune cells like of T cells, B cells, mast cells and basophils [305, 306].

In recent decade, the relationship between n-3 PUFA and inflammatory diseases has been investigated in many studies. In a study conducted in rheumatoid arthritis patients, significant improvement in symptoms have been reported after 3 month fish oil supplementation in terms of tender joint count and duration of morning stiffness [307]. Besides reduction in the production of proinflammatory eicosanoids by competition with n-6 PUFA, n-3 PUFA has been found to be effective in inhibiting the synthesis of proinflammatory cytokines. In *fat-1* transgenic mice, which have a much lower n-6:n-3 PUFA in tissues because they are genetically modified to possess the ability to convert n-6 PUFA to n-3 PUFA, serum proinflammatory cytokines, including TNF, IL-1 β , and IL-6 are lower. [280]. DHA and ALA also reduce the mRNA expression of IL-1 β , IL-6 in a cerulein-induced pancreatitis model. They inhibit the activation of AP-1, suppress DNA fragmentation and decrease mRNA expression of apoptotic genes including p53, Bax and apoptosis-inducing factor in hydrogen peroxide-treated pancreatic acinar cells [308]. A randomized, double-blind human study has confirmed their suppressing effect on production of proinflammatory cytokines [309]. It has been shown that n-3 fatty acids

Common name	Lipid name	Chemical name	Formula/MW	Structure
(HTA)	C16:3 (n-3)	all-cis-7,10,13-hexadecatrienoic acid	C ₁₆ H ₂₆ O ₂ /250.376	
α-Linolenic acid (ALA)	C18:3 (n-3)	all-cis-9,12,15-octadecatrienoic acid	C ₁₈ H ₃₀ O ₂ /278.430	
α-Parinaric acid	C18:4 (n-3)	all-cis-9,11,13,15-octadecatetraenoic acid	C ₁₈ H ₂₈ O ₂ /276.414	
Stearidonic acid (SDA)	C18:4 (n-3)	all-cis-6,9,12,15-octadecatetraenoic acid	C ₁₈ H ₂₈ O ₂ /276.414	
(ETE)	C20:3 (n-3)	all-cis-11,14,17-eicosatrienoic acid	C ₂₀ H ₃₄ O ₂ /306.483	
(ETA)	C20:4 (n-3)	all-cis-8,11,14,17-eicosatetraenoic acid	C ₂₀ H ₃₂ O ₂ /304.467	
(EPA)	C20:5 (n-3)	all-cis-5,8,11,14,17-eicosapentaenoic acid	C ₂₀ H ₃₀ O ₂ /302.451	
(DPA)	C22:5 (n-3)	all-cis-7,10,13,16,19-docosapentaenoic acid	C ₂₂ H ₃₄ O ₂ /330.504	
(DHA)	C22:6 (n-3)	all-cis-4,7,10,13,16,19-docosahexaenoic acid	C ₂₂ H ₃₂ O ₂ /328.488	

Table 12. The common name, lipid name and chemical name of major n-3 PUFA

can alleviate inflammatory process by modulating cell signalling pathways in immune cells, such as T cell receptor pathway and cytokine receptor pathways. [310-312]

There have been a number of clinical studies that have shown n-3 PUFA's potentially protective effects on asthma, especially on childhood patients. There is a positive association between the n-6:n-3 PUFA in diet and risk for asthma [313]. A randomized, double-blind, placebo-controlled 3-year study on effect of n-3 PUFA supplementation on asthma has found that high n-3 PUFA diet intervention significantly reduced the prevalence of cough in atopic children, suggesting that n-3 PUFA may be effective in preventing the development of asthma in early childhood [314]. In a cohort study on the relations between fish/cod oil intake and asthma,

results have shown that adults with low fish intake frequency (less than weekly) have increased risk to have asthma [315]. Another randomized double-blind study with 5-weeks n-3 PUFA supplementation has reported a significant decrease in exhaled NO from asthma patients challenged with mite allergen. Serum eosinophils count and ECP, and the production of CysLTs from isolated leukocyte stimulated with mite antigen are also reduced [194]. Overall, n-3 PUFA might be a promising remedy agents for allergic diseases like asthma but the mechanism remains to be elucidated.

6. Conclusion

The prevalence of asthma is becoming the mortality and morbidity pandemic of the 21st century. The cost of in quality of patient's lives and economic burden of treatment is continuing to grow at pace unmatched in our current health system. It is impossible to enter public classroom now without seeing a young sufferer of this condition and any trip to the emergency department will show how dangerous this disease can be. As the incidence and severity of the disease continues to rise, medical research is continuing to search new treatment strategies. While many treatments currently exists those reserve for the severest of conditions carry their own inherent risk which may match the severity of disease itself. It is for these reasons alone that health care professionals are now examining the traits of our ancestors in time when this epidemic was less severe to determine if their medicines and practices hold the answer for the next treatment strategy. By combining the scientific knowledge at the molecular and clinical level and the resources of past it might hold the answer to breathless pandemic of the 21st century.

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