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The Potential of Natural Products as Effective Treatments for Allergic Inflammation: Implications for Allergic Rhinitis

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Abstract: The impact of natural products on human health has been enormous, and the study of natural products continues to influence research in the fields of chemistry, biology, and ecology. Historically, the majority of our medicines originate from natural products and their synthetic derivatives, many of which have taught us valuable lessons about biology. While advances in synthetic and combinatorial chemistry have given rise to notable successes in the development of new drugs, the perceived value of natural products in the treatment of allergic disease has yet to be fully explored. The immune system is a highly complex, intricately regulated group of cells whose integrated function is essential to health. Cells of the immune system may interact in a cell-cell manner and may also respond to intercellular messages including hormones, cytokines, and effector molecules produced by various cells. These effector molecules include histamine, kinins, leukotrienes, prostaglandins, and serotonin. The immune system can be modified by diet, pharmacologic agents, environmental pollutants, and naturally occurring food chemicals, such as vitamins and flavonoids. Allergic inflammation is mediated by several types of immune cells all of which can be effected by these naturally occurring bioactive compounds but this review will focus on mast cells and their mediators since these cells are the focal point of allergic reactions such as allergic rhinitis. The molecular mechanisms and scientific validity of some herbal remedies currently used clinically in the treatment of allergic rhinitis will be explored.

Keywords: Allergy, rhinitis, inflammation, sesquiterpenes, polyphenols, quercetin, proanthocyanidins, isolipquiritigenin, gnetuhainin, synephrine, ephedrine.

MAIN TEXT

Allergic rhinitis is inflammation of the nasal mucous membranes due to an immunoglobulin E (IgE) mediated response to allergens such as dust mites or pollen. Symptoms generally include nasal itching, sneezing, runny nose and nasal congestion. Although not life threatening, allergic rhinitis is very common. It affects approximately 17% of the population in North America and in the last 30 years, there has been a dramatic increase in the incidence of allergic rhinitis [1]. People with allergic rhinitis are more likely to develop asthma, bronchitis, sinusitis, eustachian tube inflammation, otitis media, and other complications [1-4]. Allergic rhinitis can either be seasonal or perennial, based on the recurrence of symptoms at different times of the year. Pollens and mold spores are the principal allergens responsible for seasonal allergic rhinitis. It is worth noting that only plants that depend upon the wind for cross pollination such as grasses, trees and weeds cause allergens of sufficient quantities to sensitize individuals and cause allergic rhinitis [5]. Plants that depend on insect pollination such as goldenrod, dandelions and most plants with obvious flowers do not cause allergic rhinitis symptoms. This has important implications for natural products and therapeutic compounds that are generated from plants.

The best treatment for allergic rhinitis is obviously to avoid the triggering allergens but since this is often very difficult to achieve for most patients, particularly those expo-

sed to outdoor allergens on a regular basis, drug treatment is required to control symptoms. There are many clinically prescribed and over-the-counter medications currently on the market. However, some of these medications have undesirable side-effects such as drowsiness and they have variable effectiveness in most patients. Therefore, almost half of patients with allergies try a natural product to relieve symptoms of their allergic rhinitis [6]. Some recent articles have reviewed the use of complementary and alternative therapies for allergic rhinitis, particularly their potential clinical efficacy and the lack of sufficiently controlled clinical studies [4-7]. Therefore, this review will examine, when possible, the cellular targets and molecular mechanisms of the bioactive compounds isolated from these herbal remedies and their potential effects on the inflammatory processes that underlie allergic rhinitis.

Allergic rhinitis is principally mediated by the activation of mast cells. Mast cells are tissue cells that store and release pro-inflammatory mediators such as histamine upon activation of their high affinity IgE (FcεRI) receptors Fig. (1). Allergic rhinitis begins when small antigen molecules, part of a large allergen such as pollen, cross the epithelial barrier in the nasal mucosa (or any epithelial barrier including the gut or the skin) and activates the production of allergen-specific IgE. IgE subsequently bind to the FcεRI receptor on the surface of mast cells, effectively arming them for the next exposure to the allergen. When an individual is not exposed to the allergen, mast cells are thought to be largely quiescent and continue to produce and store histamine, leukotrienes (LTs) and some cytokines in their large intracellular granules. However, upon exposure to an allergen (to

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Fig. (1). Mast cell sensitization is initiated by exposure to an allergen. In this case, a pollen grain allergen crosses the epithelial barrier and activates the production of IgE antibodies from B cells. The IgE bind surface high affinity receptors (FcεRI) on the surface of mast cells and arm them for subsequent exposure.

which the mast cells have been sensitized), the FcεRI receptors are crosslinked by the multivalent antigen and this activates mast cell degranulation releasing a vast variety and quantity of mediators (such as histamine) within minutes, resulting in the rapid and severe allergic symptoms associated with most atopic diseases Fig. (2). As such, inhibiting mast cell activation and peripherally blocking the effects of mast cell mediators is the target of most commercially available medications. Yet, even these medications have limitations and side-effects. While medications such as leukotriene (LT) receptor antagonists and anti-histamines are effective at blocking the downstream effects of LTs and histamine, there are few commercial medications that adequately inhibit the “production center” of these potent pro-inflammatory mediators – the mast cell itself. Some natural products have been promoted as effective treatments for allergic rhinitis and inhibitors of mast cell activation and this review will examine some of these bioactive compounds and their various potential in treating allergic rhinitis.

Most compounds used to treat allergic rhinitis can be classified into five major categories: (1) antihistamines, (2) decongestants, (3) mast cell stabilizers, (4) LT inhibitors and (5) immune modulators.

ANTIHISTAMINES

Commercially available antihistamines have proven effective treatment against many of the symptoms associated with allergic rhinitis including itching, sneezing and runny nose. Antihistamines are the foundation of symptomatic therapy for allergic rhinitis and are most useful in controlling the symptoms of sneezing, rhinorrhea and pruritus. Antihistamines are less effective against the nasal obstruction and eye symptoms that occur in some patients. Pharmaceutically manufactured antihistamines currently on the market are of

varied chemical structures that have the property of antagonizing some of the actions of histamine – primarily by binding the histamine receptors and blocking binding of histamine. Since activation of histamine receptors (H1, H2, H3 and H4) causes smooth muscle contraction, increased vascular permeability, increased production of mucus and activation of sensory nerves, blocking their activation is extremely effective at alleviating allergic rhinitis. However, antihistamines are not very effective for more severe allergies or for nasal congestion [5]. Moreover, some of the early generation antihistamines are not histamine receptor specific and can simultaneously bind muscarinic, cholinergic, and adrenergic receptors and cause sedative, antiemetic or local anesthetic effects [8]. Many of the first-generation anti-histamines also result in anticholinergic effects, which account for side effects such as blurred vision or dry mouth. Therefore, a natural product that blocks histamine receptors but does not have these side effects has been the focus of many research and development platforms.

Some naturally occurring bioactive compounds have some antihistamine effects although the data is scattered and incomplete (Table 1). Grape seed extract (*Vitis vinifera*) is sometimes professed to be a natural antihistamine and contains antioxidants such as catechins and proanthocyanidins. There are no published studies on the effects of grape seed extract or grape seed-derived bioactive compounds on the effects of histamine receptors and their signaling pathways. However, one can extrapolate some information from data published on bioactive compounds extracted from other sources but similar in structure to grape seed bioactives such as isoliquiritigenin. Isoliquiritigenin, one of the major constituents of *Glycyrrhiza uralensis* (licorice), is a natural pigment with a simple chalcone structure 4,2',4'-trihydroxychalcone. Isoliquiritigenin shows selective H₂ histamine receptor antagonistic effects and reduces several

Fig. (2). Mast cell activation occurs when allergens crosslink FcεRI. When an allergen crosses the epithelial barrier and contacts a sensitized mast cell, it crosslinks surface FcεRI receptors and initiates a signal cascade resulting in the release of mast cell mediators such as histamine, LTs and pro-inflammatory cytokines. These mediators act on other cell types to facilitate the development of allergic symptoms associated with allergic rhinitis, asthma and urticaria.

Table 1. Natural Products that May Function as Antihistamines

Compound/Formulation	Structure	Source	Target	Reference(s)
isoliquiritigenin		<i>Glycyrrhiza uralensis</i>	H ₂ histamine receptors on U937 and HL-60 hematopoietic cell lines	[8]
gnetuhainin I		<i>Gnetum hainanense</i>	histamine receptor anagonist activity?	[10, 11]

H₂R-mediated physiological responses in U937 and HL-60 hematopoietic cell lines [8]. H₂R are expressed on several cell types including smooth muscle cells and gastric epithelial cells and therefore antagonists to the H₂R have been very effective in therapy of allergy and ulcers [9]. Therefore, it is possible that isoliquiritigenin could be an effective therapy for histamine-mediated allergic inflammatory conditions such as allergic rhinitis.

The isorhapontigenin tetramer, gnetuhainin R (1) and a recently characterized dimeric stilbene, gnetuhainin S (2) are isolated from the lianas of *Gnetum hainanense*, a tropical evergreen woody vine. Based on structure analysis by 2D NMR and X-ray crystallography and some enzyme assays it has been shown to have a structure consistent with histamine receptor antagonist activity [9, 10]. However, it is unclear whether this ability to block histamine receptors has func-

tional consequences such as inhibition of histamine-mediated smooth muscle contraction, for example.

There is very little clinical data available that supports the use of grape seed extract or its constituents as antihistamines, however. In a randomized, double-blind, placebo-controlled study of grape seed extract by Bernstein *et al.* in 2002, it was found that there was no significant difference in quality of life, symptom scores or requirements for rescue antihistamines between patients with seasonal rhinitis receiving grape seed extract and those on placebo [11]. The lack of an effect could be due to the relatively low concentration of beneficial bioactive compounds in the whole extract and a study with a purified compound such as isoliquiritigenin may yield more favorable outcomes.

DECONGESTANTS

A few natural products have been used as decongestants (Table 2) although their use has been somewhat controversial. Recently, federal law in the US has moved pseudoephedrine products behind the pharmacy counter and, as such, many off-the-shelf products have substituted the arguably less effective phenylephrine. This has opened the need for safer but effective decongestive products. Some natural products have been promoted as natural decongestants and therefore useful in the treatment of allergic rhinitis. Many of these products contained the herb ephedra (*Ephedra sinica*) that is a natural source of ephedrine and pseudoephedrine. Ephedrine can effectively block passive cutaneous anaphylaxis in a rat model by inhibition of mast cell degranulation [12] and is an effective treatment of itch, sneezing and discharge associated with allergic rhinitis [13].

However, in 2004, ephedra was banned due to some serious safety concerns. Some of the natural products that had previously used ephedra switched their formulations and started using bitter orange (*Citrus aurantium*) which contains 1% to 6% synephrine, an adrenergic agonist related to ephedrine. Most products that contain bitter orange provide between 10-40 mg synephrine per dose [14]. Although bitter orange may have some decongestant-like properties, it has not been specifically studied in placebo-controlled double-blind clinical studies for allergic rhinitis and therefore its efficacy and safety for this type of treatment is still unknown. In one study using acoustic rhinometry to measure nasal cavity cross-sectional area, it was shown that synephrine may have some beneficial effects in terms of opening the nasal airways [15] but without modifying the underlying mucosal inflammation. However, there are some cautionary notes with respect to using bitter orange or bitter orange-containing products for the treatment of allergic disease. Principally, bitter orange may increase the levels of some drugs in a similar mechanism to grapefruit juice. Bitter orange increases the levels of dextromethorphan (*Robitusin*®), felodipine (*Plendil*®) and midazolam (*Versed*®) potentially causing some complications [16, 17].

MAST CELL STABILIZERS

Mast cells are resident in the submucosa and are central to the pathogenesis of the early allergic response in allergic rhinitis Figs. (1) and (2). Examination of nasal scrapings and tissue from patients with allergic rhinitis shows mast cell degranulation in the nasal mucosa and the release of mast

cell-specific mediators, including histamine, leukotriene C4 (LTC4), prostaglandin D2 (PD2) this and various pro-inflammatory cytokines. In addition, this early response is characterized by the release of neuropeptides such as substance P (SP) and vasoactive intestinal peptide (VIP) which can activate mast cell degranulation and mediator release [18]. With continuation of allergic inflammation, an accumulation of CD4+ T lymphocytes, eosinophils, neutrophils and basophils occurs, accompanied by further disruption of the respiratory epithelium. Mast cells are also thought to be important in the late phase response, principally through their recruitment and activation of lymphocytes. As such, inhibition of mast cell activation in the initial stages of an allergic response is highly desirable.

There are several natural products that have been shown to inhibit mast cell activation with variable degrees of potency (Table 3). For example, pycnogenol® (*Pinus pinaster*), also known as pine bark extract, is sometimes used to treat allergic rhinitis. Pycnogenol is a standardized extract composed of a mixture of flavonoids, mainly procyanidins and phenolic acids. Studies indicate that pycnogenol components of this extract are highly bioavailable and therefore would have the greatest activity if taken as oral therapy. Uniquely pycnogenol displays greater biologic effects as a mixture than its purified components do individually indicating that the components interact synergistically. Pycnogenol has been reported to have cardiovascular benefits, such as a vasorelaxant activity, angiotensin-converting enzyme (ACE) inhibiting activity, and the ability to enhance the microcirculation by increasing capillary permeability. Pycnogenol has been used by some patients to treat symptoms associated with other diseases such as melasma, erectile dysfunction, attention deficit hyperactivity disorder, arthritis and diabetes. In terms of its anti-allergic effect, pycnogenol inhibits compound 48/80 or calcium ionophore A23187 activated degranulation of rat peritoneal mast cells (RPMC) [19] possibly via its ability to scavenge free radicals [20]. In a randomized, double-blinded, placebo-controlled, crossover study in patients with varying asthma severity some beneficial effects of pycnogenol on asthma treatment were observed [21]. In this study, twenty two patients with asthma were placed on either 1 mg/lb/day pycnogenol or placebo for 4 weeks and then crossed over to the alternative regimen for another 4 weeks. Pycnogenol treatment significantly reduced serum leukotrienes in patients compared to placebo and most patients reported an alleviation of their asthma symptoms.

Grapes (*Vitis genus*) and grape extracts have also been professed by some patients as having anti-allergic benefits. In passive cutaneous anaphylactic models in mice, a methanol extract of grapes has been shown to inhibit both histamine release and reduce serum IgE in response to compound 48/80 challenge. This effect may be principally mediated by inhibition of mast cell activation since this methanol extract inhibited both RPMC and human leukemic mast cell (HMC-1) release of cytokines and reduced the associated intracellular calcium flux [22]. However, the grape extract also reduced activation of NF- κ B as measured by a luciferase reporter assay in HMC-1 cells. As such, it is difficult to determine if these effects are mast cell specific or a global de-activation of NF- κ B mediated gene transcription.

Table 2. Natural Products that May Function as Decongestants

Compound/Formulation	Structure	Source	Target	Reference(s)
ephedrine pseudoephedrine		<i>Ephedra sinica</i>	Adrenergic agonist Blocks passive cutaneous anaphylaxis. Blocks mouse mast cell degranulation. Inhibits nasal itch, sneezing and discharge.	[13, 14]
synephrineI		<i>Citrus aurantium</i>	Adrenergic agonist May open airways as measured by acoustic rhinometry	[16]

Table 3. Natural Products that May Function as Mast Cell Stabilizers

Compound/Formulation	Structure	Source	Target/Functions	Reference(s)
pycnenol		<i>Pinus pinaster</i>	Vasorelaxant activity, angiotensin-converting enzyme (ACE) inhibiting activity, and increases capillary permeability. Inhibits ionophore-induced rat peritoneal mast cell degranulation.	[20-22]
procyanidins		<i>Vitis sp.</i> apples, pine bark, cinnamon, cocoa, bilberry, black currant, green tea	Inhibits IgE-mediated RBL-2H3 degranulation by interfering with actin polymerization. Inhibits cytokine production, protein tyrosine phosphorylation and ROS generation by BMBC.	[24]
Flavones ex: apigenin luteolin tangeritin chrysin baicalein		<i>Vitis sp.</i> cereals herbs	Inhibit HMC-1 proliferation. Increase histamine and leukotriene content in HMC-1 granules.	[25,26]

(Table 3) Contd....

Compound/Formulation	Structure	Source	Target/Functions	Reference(s)
kaempferol		<i>Vitis sp</i> tea, apples, broccoli, <i>Delphinium</i> Witch-hazel, grapefruit, brussel sprouts	Inhibits HMC-1 proliferation. Increase histamine and leukotriene content in HMC-1 granules.	[26]
quercetin		<i>Vitis genus</i> <i>Kalanchoe</i> <i>pinnata</i> fruits, vegetables, wine and other herbs	Inhibits human cord blood progenitor-derived mast cell (CBMC) degranulation and mediator release. May inhibit anaphylaxis in a mouse model.	[28-31, 35, 37-41]
gallic acid		<i>Vitis genus</i> <i>Kalanchoe</i> <i>pinnata</i> fruits, vegetables, wine and other herbs	Inhibits proliferation of a mast cell line (MC/9) and rat mast cell degranulation.	[32-34]
curcumin		Zingiberaceae	Inhibits IgE-mediated signaling by blocking phosphorylation of Syk kinase. Inhibits protease activated receptor (PAR) mediated activation of mast cells.	[43,44]

It is also difficult to determine which bioactive compounds in grapes actually mediate the mast cell inhibitory effects. For example, a study by Kondo *et al.* demonstrated that polymeric grape seed procyanidins, but not the monomeric catechins and oligomeric procyanidins impair rat mast cell (RBL-2H3) degranulation [23]. Polymeric grape seed procyanidins interfered with actin polymerization and cytoskeletal rearrangement thereby preventing exocytosis.

Grapes and grape extracts are currently used as food supplements as a means of preventing and treating disease. There is some evidence that moderate intake of wine reduces the predisposing factors of coronary heart disease and compounds found in grapes have been suggested to prevent atherosclerosis, certain cancers and inflammatory disease. One possible mechanism of these effects is free radical scavenging and interference with the division cycle of rapidly and abnormally proliferating cells. Grapes contain flavonoids such as quercetin, small phenolic acids such as gallic acid, stilbenes such as resveratrol and cyanidins such as malvidin-3-*o*-glucoside. Studies using rodent cell lines have shown that some of these compounds are able to inhibit

mast cell activation. Flavonoids such as flavone and kaempferol inhibit human leukemic mast cell (HMC-1) proliferation by over 80 percent but increase histamine and tryptase content in mast cell granules [24, 25]. Flavones are capable of binding and modifying cytochrome P450 (CYP450) which is a very large and diverse superfamily of hemoproteins found in most living organisms and are involved in energy metabolism [26]. Therefore, flavones tend to have a diversity of functions in the immune system and it is difficult to predict the effects of these compounds in a specific disease.

Quercetin inhibits the release of histamine, leukotrienes (LTs), prostaglandin D₂ (PGD₂), and granulocyte macrophage-colony stimulating factor (GM-CSF) from human cultured mast cells by inhibiting calcium influx and protein kinase C and Syk kinase phosphorylation [27, 28]. As a result of this mast cell inhibitory activity, quercetin has been marketed as a natural treatment for allergic rhinitis. Quercetin is a flavonoid found in fruits, vegetables, wine and some herbs. *In vivo* models demonstrate the anti-inflammatory effect of quercetin and quercetin-containing extracts.

For example, oral treatment of a mouse anaphylactic model with an aqueous extract of *Kalanchoe pinnata* effectively inhibited pro-anaphylactic inducing immune responses [29]. Since this extract contains quercetin compounds, it is believed that part of this activity is dependent on this flavonoid. Similarly, in a mouse and human model of niacin-induced flush, quercetin effectively eliminated the flush associated with plasma production of PGD_2 [30]. Another component of grapes and wine is gallic acid which inhibits the proliferation of a mouse mastocytoma cell line (MC/9) [31] by inducing the expressing of pro-apoptotic *Bax* expression [32]. Gallic acid also inhibits mast cell degranulation possibly by blocking tyrosine phosphorylation [33].

It appears that quercetin's anti-inflammatory activity *in vivo* is mediated by its ability to inhibit LT, prostaglandin and histamine production by mast cells. Quercetin, along with other flavonoid compounds such as fisetin, kaempferol, myricetin, quercetin, and rutin inhibited IgE or phorbol-12-myristate 13-acetate and calcium ionophore A23187-mediated histamine release from RBL-2H3 cells [34]. These five flavonoids also effectively inhibited production of IL-6 and tumor necrosis factor (TNF) through inhibition of NF- κ B activation. However, RBL-2H3 have been shown to be an imprecise model for these type of natural product studies because their phenotype is so variable and subject to changes due to culture conditions [35]. Yet, similar studies in HMC-1 showed that quercetin decreased the gene expression and production of TNF, IL-1 β , IL-6, and IL-8 in phorbol-12-myristate 13-acetate and calcium ionophore A23187-stimulated cells [25, 36]. These compounds may also change the phenotype of HMC-1 cells by modifying their expression of tryptase and histidine decarboxylase, the enzyme necessary to produce histamine [37-39]. Although there are a number of papers published on quercetin effects on mast cells, they share a few common features: (1) invariably the mast cells tested are cell lines that either do not express Fc ϵ RI receptors or do not resemble *in vivo*-derived human mast cells, (2) the concentrations required to inhibit mast cell responses are relatively high compared with some clinically effective drugs such as corticosteroids, (3) there is little data comparing quercetin effects on mucosal mast cells since these are the type that interface the mucosal surfaces in the nose and gut and would likely be the primary target of a flavonoid-derived therapy, and (4) the stimuli used to activate these mast cells is often not physiologic and involves such artificial chemicals like compound 48/80, phorbol-12-myristate or calcium ionophore. It is also not known if quercetin is absorbed from the gut in high enough amounts to have a beneficial effect [40].

Curcumin is the principal curcuminoid of the popular Indian curry spice turmeric, which is a member of the ginger family (Zingiberaceae). The other two curcuminoids are desmethoxycurcumin and bis-desmethoxycurcumin. These three curcuminoids are polyphenols and are responsible for the yellow color of turmeric. Curcumin itself has been shown to inhibit IgE-mediated mast cell activation possibly via inhibition of membrane proximal signaling events such as phosphorylation of Syk kinase [41]. Yet, curcumin can also inhibit non-Fc ϵ RI-mediated mast cell activation. For example, curcumin blocks cytokine production from mast cells

that are activated via protease-activated receptors (PAR), which do not require Syk phosphorylation for signaling [42]. As such, curcumin may be another natural product that non-specifically disrupts a variety of signaling pathways. Many *in vitro* studies have been hampered by the poor solubility of curcumin and difficulty of administering in liquid culture. However, recent studies have shown that complexing curcumin with cyclodextrin can overcome these solubility issues and this method of administering curcumin has proven effective *in vivo* [43]. To date, curcumin has not been tested for the treatment of allergic rhinitis. Although curcumin and tumeric have been used in the treatment of a wide variety of diseases including anterior uveitis, colorectal cancer, rheumatoid arthritis and skin cancer, there is reliable evidence that it is only effective in the treatment of dyspepsia [44]. In fact, there is some evidence that long term use of curcumin may be detrimental since tumeric can cause gallbladder contractions [45] and inhibit platelet aggregation resulting in excessive bleeding [46].

Spirulina, a type of blue-green algae, has also been promoted for the treatment of allergies. It contains protein, B vitamins and various minerals. In some *in vivo* animal models, spirulina can inhibit mast cell-mediated allergic reactions. In two particular studies, spirulina dose-dependently inhibited the systemic allergic reaction induced by compound 48/80 in rats and reduced serum histamine levels [47, 48]. Yet, there are some safety concerns with respect to using spirulina to treat allergic rhinitis. Blue-green algae is sometimes naturally contaminated with "microcystins" that can cause liver damage. There are no regulatory standards that require supplement manufacturers to monitor for microcystin contamination [49]. Due to these potential safety concerns, most physicians advise their patients to avoid blue-green algae supplements.

Flos Magnoliae, also known as Magnolia, is a commonly used Chinese medicinal herb that has been used traditionally for symptomatic relief of allergic rhinitis, sinusitis and headache. Extracts and dried formulations from Magnolia can inhibit compound 48/80-induced rat peritoneal mast cell degranulation [50] suggesting that these effects are mediated by direct inhibition of mast cells. However, compound 48/80 is a non-specific agonist of G protein signaling pathways that are only partially related to IgE/Fc ϵ RI activation and therefore it remains to be determined whether Magnolia can also inhibit allergen induced mast cell activation.

Since the majority of the above studies have been conducted using rodent mast cells or immature human mast cells that do not express Fc ϵ RI, it is difficult to extrapolate these results to human allergic disease. Yet, there is evidence that Fc ϵ RI-mediated, and therefore allergen-induced, mast cell responses are sensitive to some of these bioactive compounds. Procyanidins from other sources such as apple extracts inhibit Fc ϵ RI-mediated mast cell activation. Procyanidin C1, for example, from apple extracts dose dependently decreased Fc ϵ RI-dependent degranulation, cytokine production, protein tyrosine phosphorylation and generation of intracellular reactive oxygen species (ROS) by mouse bone marrow derived mast cells (BMMC) [51].

LEUKOTRIENE INHIBITORS

During an asthmatic response, LTs modulate several events including production of hematopoietic progenitor cells, survival and recruitment of eosinophils to inflamed tissue, activity of cytokines and chemokines, quantity of exhaled nitric oxide, smooth-muscle contraction, and proliferation of fibroblasts. As a result, LT receptor antagonists (LRA) such as Singulair® have been used to effectively treat patients with asthma. Butterbur, has been reported to act as LT or LT receptor inhibitor (Table 4). Butterbur (*Petasites hybridus*) is becoming an increasingly popular herbal treatment for allergic rhinitis patients [52]. The plants commonly referred to as butterbur are found in the daisy family *Asteraceae* in the genus *Petasites*. They are robust plants with thick, creeping underground rhizomes and large Rhubarb-like leaves during the growing season and another common name for many species of this genus is sweet coltsfoot. Much of the safety and efficacy information available for butterbur comes from Japan since the Japanese butterbur is a popular vegetable and domestic plant in that country. In a study by Shimoda *et al.*, butterbur aqueous extract from aerial parts of the plant were evaluated for its ability to modify a rat model of passive cutaneous anaphylaxis and on its *in vitro* effects on RBL-2H3 activation [53]. The authors found that butterbur extract inhibited IgE-sensitized RBL-2H3 cell degranulation, LTC₄/D₄/E₄ synthesis, and TNF production. Degranulation assay-guided fractionation and testing revealed that two eremophilane-type sesquiterpenes, six polyphenolic compounds, and two triterpene glycosides had mast cell inhibitory activity. Of these compounds, fukinolic acid, a principal polyphenol constituent, showed potent inhibitory activity (IC₅₀ value = 2.1 µg/mL). These results suggest that butterbur may have global anti-allergic activity because it inhibits mast cell mediator release. However, an extremely high dose of this extract (1 mg/mL) also inhibited smooth muscle constriction induced by histamine (10 µM) and LT D₄ (10 nM) in a guinea pig trachea strip suggesting that the extract may also act directly on histamine and LTs or their receptors.

The active component in butterbur is petasin, a sesquiterpene that functions as an inhibitor of cysteinyl LT biosynthesis, eosinophil cationic protein (ECP) release and cytoplasmic phospholipase A2 (cPLA2) cPLA2 activity [54]. LT synthesis relies on cPLA2 activity and translocation of 5-lipoxygenase to the nucleus and therefore, blockade of cPLA2 is very effective at blocking LT production. Neopetasin, an analogue of petasin, does not inhibit ECP release or suppresses cPLA2 activity [55] so this activity appears to be

specific to this ester of the sesquiterpene. The mechanisms of petasin-mediated inhibition of LT synthesis are similar in eosinophils and neutrophils suggesting that this compound is not cell specific but could be applicable in a series of LT-mediated inflammatory conditions such as eosinophil-mediated allergic rhinitis and neutrophil-mediated asthma [54]. Yet, the positive effects of butterbur on allergic inflammation may not only be due to its ability to inhibit LT production. For example, petasin and butterbur lactones can block voltage gated calcium channels in vascular muscle cells [56] thereby relaxing smooth muscles and opening constricted airways.

Thomet *et al.* conducted a small clinical study on the efficacy of *Petasites hybridus* tablets in the treatment of allergic rhinitis symptoms [57]. Patients suffering from allergic rhinitis received two tablets of butterbur three times per day for 1 week. The tablets contained 8 mg petasins per tablet. After 5 days of treatment, the patients receiving the butterbur showed significant improvement in their daytime and nighttime nasal symptoms. Nasal resistance, which was measured by rhinomanometry, gradually decreased as a consequence of butterbur treatment and reached normal levels (healthy controls) after 5 days of treatment. Concentration of inflammatory mediators in nasal fluids and serum were measured 90 min after drug administration every day in the morning. After 5 days of treatment, a significant reduction of histamine and LT concentration in samples from patients taking butterbur was observed. Moreover, quality-of-life scores significantly improved in the butterbur treatment group. Butterbur did not appear to alter the distribution of lymphocyte subpopulations in the blood or the capacity of blood leukocytes to generate cytokines and lipid mediators.

Yet, it appears that efficacy of butterbur is dependent on the severity of underlying inflammation. In a similar study by Gray *et al.*, thirty-five patients (14 men and 21 women) with intermittent allergic rhinitis received butterbur, 50 mg twice daily, or placebo for 2 weeks [58]. Domiciliary measurements were taken in the morning and evening for peak nasal inspiratory flow, nasal and eye symptoms, and rhinoconjunctivitis-specific quality-of-life score. Butterbur treatment had no significant effect on peak nasal inspiratory flow, total nasal symptom score, eye symptom score, or quality of life compared with placebo use. Therefore, this study showed that there was no significant clinical efficacy of butterbur use versus placebo use on objective and subjective outcomes in intermittent allergic rhinitis. The efficacy of butterbur in persistent allergic rhinitis has yet to be determined. In a small clinical study of twenty patients

Table 4. Natural Products that May Function as Leukotriene Inhibitors

Compound/Formulation	Structure	Source	Target/Functions	Reference(s)
petasin		<i>Petasites hybridus</i>	Inhibits LT biosynthesis. Inhibits release of eosinophil cationic protein. Inhibits activation of cPLA2. Effectively used to treat allergic rhinitis.	[54-60]

with grass-pollen-sensitized allergic rhinitis, butterbur was effective at reducing adenosine monophosphate-induced nasal responsiveness during the grass pollen season [59].

There are some cautionary notes for the use of butterbur to treat allergic rhinitis, however. Butterbur naturally contains unsaturated pyrrolizidine alkaloids which are hepatotoxic [60], carcinogenic, mutagenic, renal toxic, and can cause veno-occlusive disease [61]. Furthermore, butterbur is related to the ragweed family of plants and may display cross-allergenicity with the *Asteraceae/Compositae* family.

IMMUNOMODULATORY COMPOUNDS

Since allergic inflammatory responses like allergic rhinitis are primarily mediated by immune responses, immunomodulatory drugs can often ameliorate symptoms. Many natural bioactive compounds modify the immune system and have been used to successfully treat allergic rhinitis. Echinacea (*Echinacea* spp.), for example, has been suggested to be a potent immunostimulatory herb and has been used to treat the common cold. Commercially available Echinacea products have been found to stimulate macrophages from a variety of species. For example, dried Echinacea root stimulates murine macrophage cell line (RAW264.7) to produce cytokines [62] but these immunostimulatory effects are likely via the activation of innate pattern recognition receptors like toll-like receptors (TLR) that recognize the bacterial lipoproteins and lipopolysaccharide contaminants in these preparations [63]. Melanin, one of the biologically active components of Echinacea, activates NF- κ B in monocytes through a TLR-2-dependent process and can induce production of IL-6, IFN- γ and IgA in Peyer's patch cells [64] which has profound implications for mucosal immunity and may be relevant in the mucous membranes of allergic rhinitis patients. However, the majority of these studies have been conducted using transformed cells and there is insufficient evidence to show that these effects are immune cell specific. However, there is equal evidence that Echinacea may inhibit immune responses, particularly beneficial innate immune responses to pathogens. The water soluble extract of Echinacea can inhibit LPS activated macrophages [65, 66] and some of the compounds in Echinacea have either stimulatory or inhibitory effects on T cells [67]. There is no reliable evidence that Echinacea is effective as a treatment for allergic inflammation and, in fact, its immunostimulatory properties may worsen symptoms. Certainly, Echinacea can exacerbate symptoms of severe thrombotic thrombocytopenic purpura possibly by irritating the already damaged endothelial cells lining the blood vessels and possibly increased release of Willebrand factor [68]. Some reports associate autoimmune disorders with the use of Echinacea supplements and increase risk of hematotoxicity and exacerbations of allergies and asthma, sometimes resulting in anaphylactic reactions [69, 70]. Echinacea is also a member of the *ragweed* family of plants and may induce cross-allergenic reactions.

Thymus extract from bovine thymus gland is sometimes promoted as a treatment for allergic rhinitis due to its theoretical immunostimulatory properties. It has been argued that hormones and growth factors present in the extract augment immune responses and therefore are beneficial

during bacterial infections [71], vaccinations [72] and even in the treatment of breast cancer [73]. Critics of this type of therapy point out that it is unlikely that these hormones and factors survive the digestive tract and therefore are unlikely to be absorbed into the blood stream to be even marginally effective. There is also the problem of cross-species heterogeneity of hormone receptors and the unlikelihood that a bovine hormone could bind and activate a human hormone receptor. Historically, glandular or organotherapy, which refers to the use of animal tissues or cell preparations to improve physiologic functioning and support the natural healing process, first gained popularity in the early to mid 1900s. The idea of homeopathic glandular therapy was first introduced almost 200 years ago. Thymus extracts for nutritional supplements are usually derived from young calves (bovine) and are found in capsules and tablets as a dietary supplement. Marketed calf thymus extracts include the semi-purified calf thymus extract (TFX) produced by the Polish Pharmaceutical Industry (POLFA) [74], thymomodulin, and thymostimulin. Many of these products are not available in the United States or Canada. Some preliminary evidence shows that thymomodulin taken orally for 4 months might reduce the frequency of symptoms in patients with perennial allergic rhinitis [75]. It has been argued that digestive juices in the stomach and intestines will destroy oral thymus extract resulting in a lack of absorption and therefore limited efficacy [76]. Another potential concern is that any bovine glandular extract has the potential to contain the virus that causes "mad cow disease." Since these thymus extracts contain growth factors and hormones with the potential to cross-react with different species, there is some concern that these extracts could seriously modulate the endocrine system in human patients. Preliminary evidence in animal models suggests that bovine thymus extract may modify the size of the thyroid gland and modify its hormone production and enzyme activity [77]. However, in general, side effects have not been demonstrated in clinical trials.

Tinospora cordifolia is a commonly used ayurvedic or traditional Indian medicine that has some immunostimulatory effects (Table 5). A small clinical study showed that taking a specific extract (Tinofend, Verdue Sciences) at 300 mg three times daily decreased allergic rhinitis symptoms such as sneezing, nasal itching, and nasal discharge [78]. *Tinospora* is often used as a whole plant extract that contains several bioactive compounds including the bitter diterpenoids columbin, chasmanthin and palmarin. The leaves of *Tinospora cordifolia* also contain minerals such as calcium, phosphorus and alkaloids such as tinosporide, tinospic acid, tinosporol and protoberberine. Other constituents identified include lignans, diterpenes, furan lactones, phenyl propane glycosides, and arabinogalactan. Several of these constituents have immunomodulating effects. For example, clerodane furano diterpene glycoside, cordioside, syringin, cordifolioside A and B, and cordiol inhibit C3-convertase and therefore inhibit the complement cascade [79]. In this study, it was also shown that cordioside can modify serum immunoglobulin (IgG) levels and activate macrophages. The mechanism of macrophage activation is unclear but may occur by direct cordioside interactions with Fc γ receptors which bind IgG and are themselves involved in regulation of the adaptive and innate immune system.

Table 5. Natural Products that May Function as Immune Modulators

Compound/Formulation	Structure	Source	Target/Functions	Reference(s)
melanin		<i>Echinacea spp.</i>	Activates NF- κ B in monocytes. Induces production of IL-6, IFN- γ and IgA in Peyer's Patch cells. Inhibits LPS activated macrophages. Inhibits T cell activation.	[65-68]
bovine thymus extract	<i>Various proteins (hormones and growth factors) and lipid molecules (fatty acids)</i>	<i>Bos spp.</i>	May inhibit symptoms associated with allergic rhinitis.	[76]
tinosporide cordioside		<i>Tinospora cordifolia</i>	Inhibits complement fixation. Activates macrophages. Modifies IgG levels in serum. Activates NK, T and B cells. Activates production of IL1, IL6, IL-12, IL-18, IFN- γ , TNF and MCP-1	[80,81]

Tinospora cordifolia also contains an immunostimulatory alpha-glucan polysaccharide which *in vitro* activates natural killer (NK) cells, T cells, and B cells and activates production of IL-1 β , IL-6, IL-12, IL-18, IFN- γ , TNF and monocyte chemoattractant protein (MCP)-1 [80]. Whole plant extracts assessed in a randomized double blind placebo controlled trial of 75 patients with allergic rhinitis show that *Tinospora* extract can reduce eosinophil and neutrophil numbers in the nasal mucosa and possibly goblet cell activation [78]. Therefore, *Tinospora* is a promising treatment for allergic rhinitis but more evidence is needed to confirm effectiveness and long-term safety. The specific effects of *tinospora* on mast cell activation or mast cell mediators is not known.

COMPOUNDS WITH UNDETERMINED MECHANISM OR QUESTIONABLE EFFECTIVENESS

There are several natural compounds and extracts that are currently used to treat allergic rhinitis whose effects are incompletely understood. Similarly, there are natural compounds that have been shown to not be effective or even deleterious in the treatment of atopic diseases. There is currently insufficient available evidence to recommend either for or against eucalyptus oil as a decongestant-expectorant. Studies show that eucalyptus oil may be effective for treating upper respiratory tract infections. Eucalyptus can inhibit the growth of bacteria associated with respiratory tract infections [81] and can influence the ciliary beat frequency of human nasal epithelial cells [82]. The major constituent of eucalyptus oil, 1,8-cineole (also called eucalyptol), can relax guinea pig tracheal smooth muscle [83], suggesting that this compound could be used to inhibit airway constrict-

tion associated with atopic inflammation. It is interesting that 1,8-cineole can inhibit cytokine release and arachidonic acid metabolism by human blood monocytes *in vitro* [84-86] therefore acting as an immunosuppressant of innate immune responses. However, patients should avoid the use of these products if they are allergic to eucalyptus oil or pollen [87]. Also, patients with a history of seizure, diabetes, asthma, heart disease, abnormal heart rhythms, intestinal disorders, liver disease, kidney disease, lung disease, or the blood condition known as acute intermittent porphyria should avoid treatments containing eucalyptus. There is also some evidence that eucalyptus can be an irritant that can cause vocal cord dysfunction independent of an allergic response [88].

Anecdotal clinical observations and some case studies have suggested that methylsulfonylmethane (MSM) may help ameliorate the symptoms associated with seasonal allergic rhinitis. MSM is a constituent of natural products used to treat arthritis and therefore has been shown to inhibit cyclooxygenase-2 (COX-2) one of the most important enzymes necessary for the production of pro-inflammatory prostaglandins [89]. Since mast cells similarly produce vast quantities of prostaglandins during an allergic reaction, it is possible that MSM may ameliorate allergic rhinitis via inhibition of this mast cell-dependent pathway. According to one preliminary clinical study of 50 subjects with seasonal allergic rhinitis, MSM taken orally (2600 mg) once a day for 30 days reduced symptoms as evaluated by a self questionnaire [90]. No changes were observed in plasma IgE or histamine levels in these patients. However, larger, randomized, double-blind, and placebo-controlled trials are needed

to confirm these findings. Long-term effects of supplementation with MSM have not been examined.

Eicosapentaenoic acid (EPA) is a long-chain n-3 polyunsaturated fatty acid that is found in the tissues of marine mammals and oily fish. EPA has sometimes been suggested as a treatment for allergic rhinitis but most of the evidence to date suggests that EPA would augment not ameliorate allergic reactions. For example, mast cells cultured in media containing EPA show enhanced release of histamine and pro-inflammatory mediators in response to FcεRI activation [91]. Since EPA is able to insert itself into the plasma membrane and displace cholesterol, it is able to change the liquid ordered state of the lipid bilayer. Therefore, it is possible that EPA changes plasma membrane fluidity and lipid raft formation thereby increasing the probability of FcεRI aggregation. Yet, EPA competes with arachidonic acid for inclusion in cyclooxygenase and lipoxygenase pathways [92] and this evidence has sometimes been used to support the use of EPA for the treatment of inflammatory disease such as psoriasis [93]. The protective effects of breastfeeding on the development of bronchial asthma have been attributed to the fatty acid (and EPA) content of breastmilk [94] and omega-3 long-chain polyunsaturated fatty acid supplementation of mothers in their third trimester can reduce some of the immune responses associated with allergic inflammation [95]. Thus, if EPA is having a beneficial role in allergic diseases, it is unlikely to occur via modulation of mast cell responses and the exact role of EPA in allergic rhinitis is difficult to gauge until further mechanistic studies have been done.

CONCLUSIONS

Natural compounds and formulations that have been used to treat the symptoms associated with allergic rhinitis have had variable success. While some have shown promising effectiveness in clinical trials, others have not been rigorously tested in carefully controlled trials and therefore their safety and efficacy is in doubt. Nevertheless some data suggests that some compounds may target some of the specific pathways, mediated by histamine, LTs, pro-inflammatory cytokines or mast cells themselves, all of which are key players in the etiology of allergy rhinitis. Since seasonal and perennial allergies affect millions of people there is a vast market for any products that could potentially alleviate symptoms associated with atopic inflammation. There are many "natural" or herb-based products currently available but very few of these have enough efficacy research to recommend them. Butterbur is perhaps the most extensively studied in the context of allergic rhinitis but the extracts that have been studied are not available in North America. As well, there is insufficient clinical information available about the long-term effects of butterbur particularly on its possible carcinogenic effects and damage of the liver. Therefore, as with any largely untested set of pharmaceuticals, concerns are raised not because they may not be efficacious, but because they may be potentially detrimental long-term. In patients with an already underlying inflammatory response, some of these products could potentially exacerbate immunostimulatory mechanisms and increase the severity of disease. Furthermore, many of these natural compounds are obtained from plants that are members of the ragweed

family. Since many patients with allergic rhinitis are allergic to ragweed proteins, cross allergenicity becomes an issue. At the very least, proper processing and purity of the medicinal bioactive compounds from these types of plants becomes imperative to remove the allergenic proteins. Yet, the use of these bioactive compounds should not be completely discounted since there is molecular evidence to suggest that some of these bioactive compounds may be acting as antihistamines and leukotriene inhibitors. Further studies on the molecular, cellular and clinical effects of these bioactive compounds is required before their effectiveness as wide-scale medicinal treatments can be gauged.

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ABBREVIATIONS

IgE	=	Immunoglobulin E
LTs	=	Leukotrienes
ACE	=	Angiotensin-converting enzyme
RPMC	=	Rat peritoneal mast cells
HMC-1	=	Human leukemic mast cell
cPLA2	=	Cytoplasmic phospholipase A2
PGD ₂	=	Prostaglandin D ₂
GM-CSF	=	Granulocyte macrophage-colony stimulating factor
TNF	=	Tumor necrosis factor
PAR	=	Protease-activated receptors
ROS	=	Reactive oxygen species
BMMC	=	Bone marrow derived mast cells
LRA	=	LT receptor antagonists
ECP	=	Eosinophil cation protein
TLR	=	Toll-like receptors
TFX	=	Thymus extract
MSM	=	Methylsulfonylmethane
COX-2	=	Cyclooxygenase-2
EPA	=	Eicosapentaenoic acid

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