

Safety Considerations for Natural Products Commonly Used By Patients with Allergic Disease

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39 **Abstract**

40 Natural products are a category of complementary and alternative medicine that include
41 medicinal plants, vitamins and dietary supplements. These products are often utilized by
42 patients with allergies in conjunction with, or as an alternative to, their conventional
43 medical therapies. Despite the wide use of these modalities, many clinicians often have
44 limited knowledge and training in their use. It is important for health care providers to
45 know the safety and risks of these products that their patients may use. This *Clinical*
46 *Commentary* reviews the side effects and adverse reactions of several natural products
47 commonly used by patients with allergies and gives an overview of the FDA
48 requirements for manufacturing, advertising and distribution.

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Introduction

Natural products are a category of complementary and alternative medicines (CAM) that fall under a broader classification that the National Center for Complementary and Integrative Health defines as “Nutritional Approaches”; they include herbs, vitamins, and supplements¹. The products have become commonplace in the American health and wellness culture and can be found on the shelves of pharmacies, supermarkets, and farmers markets alike. Americans spend 12.8 billion dollars annually on these products, with a mean annual out-of-pocket expenditure of \$368². As per the 2012 National Health Interview Survey, natural products are used by 33% of adults³. More recent data from the National Health and Nutrition Examination Survey reported that 57.6% of US adults aged 20 and over have used a dietary supplement in the past 30 days².

According to allergists surveyed, almost 90% of allergy patients using CAM are motivated by a desire to use, what they deem to be, more natural interventions.⁴ Patients preference for these interventions is often attributed to distrust in the relationships between pharmaceutical companies and physicians⁵. Although ‘natural’ is often conflated with ‘safe’, adverse reactions can occur with these products⁶ with an estimated 23,000 yearly emergency room visits attributed to adverse reactions, including allergies ⁷. However, this represents only 1.8% of all ED visits for adverse drug events, so relative to prescription medications, this number is quite low⁸. A 2013 survey by the AAAAI revealed that almost 60% of allergists have seen adverse reactions to CAM ⁴. It is important for clinicians to understand both the safety and risks of natural compounds, as well as governmental oversight of these products.

In 1994 the Dietary Supplement and Health Education Act (DSHEA) defined the term “dietary supplement” and set guidelines for manufacturers⁹. Dietary supplements include: vitamins, minerals, herbs, other botanicals, amino acids and “dietary substances” that are part of food items (e.g., enzymes and probiotics). They are not considered to be drugs or food, and thus are not beholden to many of the same rules and regulations(*Table 2*)⁹. According to the DSHEA, unlike drugs, these products can be marketed without evidence of safety or efficacy (the exception being supplements containing novel dietary ingredients that are not normally present in the food supply). The manufacturer is not required to report adverse events to the FDA, and the burden of proof is on the FDA to demonstrate that the product is unsafe before legal actions can take place.⁹ These over-the-counter products can often be illegally adulterated; recently, the FDA detected sildenafil in certain erectile dysfunction products, anabolic steroids in muscle growth supplements, and sibutramine in weight loss supplements.¹⁰

The DSHEA also set guidelines that prohibit making claims to prevent, treat or cure specific illnesses. However, manufacturers are permitted to make broader health claims as long as the label includes: “This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.”⁹ Improved regulation of quality and assurance of accurate ingredient content would better protect the consumer. Without oversight, the consumer is at the mercy of the manufacturer.

To remedy this, many manufacturers use external, private certification services to assay and confirm quality and quantity of active ingredients. The certifiers are nationally recognized, and include the United States Pharmacopeia (USP), which certifies

pharmaceuticals, and the National Sanitation Foundation (NSF)¹¹. Manufacturers pay a fee for each individual product certified and are then allowed to display the certification seal on the product label¹¹. While these companies provide a much needed and valuable service these fees can also be prohibitive to smaller manufacturers.

CAM is loosely defined as those healthcare interventions that exist outside of the mainstream of conventional medical practice. Integrative medicine is distinct from CAM by grounding itself in the purposeful coordination of these modalities by the conventional medical care team¹ (*Table 1*). Eighty-one percent of allergists report having encountered patients opting to use CAM interventions in lieu of conventional approaches⁴. In spite of the prevalent use of CAM, non-disclosure rates reach 77%¹².

Navigating natural products presents many challenges for the practicing allergist, but it is prudent that they familiarize themselves with these interventions in order to best care for their patients who prefer such approaches. Unfortunately, research on natural products is often limited making it a challenge for practitioners who appropriately insist upon a strict evidence-based approach to guide their patients using them. This review is intended to give an overview of some of the recognized, both clinical and potential adverse reactions from natural products often utilized by allergic patients.

Specific Herbs/Herbs Supplements (Table 3)

STINGING NETTLE

Stinging nettle is an herbaceous, perennial, flowering plant with hair-like projections along its leaves¹³. Its Latin name *Urtica dioica* shares similar etymology to urticaria, due to its ability to induce hives upon skin contact with these projections. Interestingly, these projections contain histamine, serotonin, and acetylcholine, all of which are associated with allergic disease¹⁴. Traditionally, stinging nettle has been used as an anti-hypertensive, to treat muscle and joint pain¹⁵ and as a galactagogue¹⁶. Recent research also suggests a role in glycemic control¹⁷.

The use of stinging nettle in allergic rhinitis has been studied using both freeze-dried leaf¹⁸ and root extract preparations¹³. The anti-allergy effect is believed to be secondary to quercetin (see below).¹⁹ *In vitro* work demonstrated antagonist and negative agonist activity against H1 receptors, and the inhibition of mast cell tryptase. Anti-inflammatory effects on COX-1 and COX-2 have also been demonstrated²⁰.

Two randomized controlled studies examined the potential benefit of stinging nettle on allergic rhinitis. Two of 31 patients receiving nettle experienced worsening of allergic symptoms, and several patients developed mild gastric discomfort.¹⁸ Bakhshaei, et al. reported, that of the 35 patients in the intervention arm “no serious, deleterious adverse effects” were observed.¹³ Stinging nettle has been studied in the management of glycemic control¹⁷, therefore caution should be exercised when using it in conjunction with medications that may lower blood sugar, although no hypoglycemia has been reported. Not surprising, given its historical use as a galactagogue, there have been several cases reported of gynecomastia, hypoestrogenism and

galactorrhea²¹⁻²². While murine models have demonstrated interference with the cytochrome P450 pathway²³ the clinical relevance of this remains unclear.

Finally, topical use of stinging nettle should be avoided, given the risk of urticaria, with a single case in the literature of severe tongue angioedema after ingesting uncooked nettle²⁴.

QUERCETIN

Quercetin is a member of the flavonoid family, a group of plant-derived compounds recognized for their anti-oxidative properties. It occurs naturally in a multitude of fruits and vegetables including, onions asparagus, broccoli and berries²⁵. It is also found in herbs such as St. Johns Wort²⁶ and elderberry²⁷. As mentioned above, it is found in stinging nettle and hypothesized to be the active constituent in its potential benefit in treating allergic rhinitis.

In vitro studies and animal models suggest that quercetin impacts atopic disease through a number of mechanisms including suppression of mast cell activation, histamine release and suppression of eosinophilic inflammation as well as helping to prevent a Th2 skew^{25,28}.

Clinical studies using oral quercetin in allergic disease are scant, but two studies—one involving children²⁹ and the other with adults³⁰—used a product that also included *Perilla frutescens* extract and vitamin D3. In the pediatric study, no serious adverse

events were reported, but 50% of patients in the treatment arm did experience adverse reactions, versus 36% in the control arm. Unfortunately, the authors did not detail these adverse reactions.

In a small study of 17 patients examining its benefit in prostatitis one subject reported mild paresthesia and another reported headache, both of which resolved upon cessation of treatment³¹. Subjects using quercetin (n=44) following myocardial infarction³² and those with chronic obstructive pulmonary disease (n=6)³³ reported no adverse reactions. In vitro studies demonstrated inhibition of CYP3A4 and CYP2C19 in human liver microsomes³⁴ and CYPs 1A1 and 3A4 in human intestinal Caco-2 cells³⁵ but the clinical relevance of these findings is unknown.

DAO - Diamine Oxidase

Histamine intolerance is a popular, yet theoretical, physiologic response to both excessive endogenous and exogenous histamine sources³⁶. Symptoms are non-specific, including facial flushing, dizziness, nausea, diarrhea and brain fog³⁷ and are largely attributed to foods with high histamine content or medications that may inhibit the activity of diamine oxidase³⁸. Diamine oxidase is the enzyme responsible for degradation of extracellular histamine within the body and theorized to be deficient in patients with histamine intolerance³⁶. While the diagnosis of histamine intolerance is controversial, it is often made by alternative medicine practitioners, and a supplement form of diamine oxidase is commonly prescribed to help manage symptoms. DAO supplements are most commonly prepared using porcine kidney concentrate³⁹ but

vegetal sources such as Indian Pea (*Lathyrus sativus*)⁴⁰ are also commercially available.

When studied in subjects with migraine and DAO deficiency, no adverse effects were 'registered' in patients treated with the enzyme supplement⁴¹. Two small interventional studies using a DAO supplement—one in patients with 22 symptoms associated with histamine intolerance (n=35),⁴² and another in patients with chronic spontaneous urticaria(n=20)⁴³— did not report adverse reactions.

ECHINACEA

Echinacea (coneflower) is a perennial flowering plant part of the Asteraceae family. It is indigenous to the Rocky Mountains and was traditionally used by Native Americans⁴⁴. Commercial preparations of echinacea tend to be quite heterogenous in their preparation, parts of the plant used, and even in the exact species used⁴⁵. Three separate species of Echinacea, *E. angustifolia*, *E. purpurea*, and *E. pallida* can be found commercially⁶.

Echinacea is not generally used in the management of atopic disease, but it remains one of the most commonly purchased botanical supplements. It is often used in the management of upper respiratory infections⁴⁵ which are difficult to distinguish from allergic rhinitis. In fact, 38% of allergists report that their patients use Echinacea.⁴

Due to its cross reactivity to its fellow member of the Asteraceae family Echinacea can pose a theoretical risk to the allergic patient—especially those with preexisting

sensitizations to other members such as ragweed. There have been prior reports in the literature of anaphylaxis to echinacea^{6,46} but given the prevalence of echinacea use, this risk is likely low. Echinacea is generally well tolerated in both adults and children⁴⁷

LICORICE ROOT

Licorice root (*Glycyrrhiza glabra*) is a botanical with a history of ancient use by herbalists and traditional Chinese medicine practitioners that was adopted as a conventional medical therapy nearly 75 years ago⁴⁸. Historically, licorice root extracts were used as anti-inflammatories in the treatment of respiratory infections and gastric ulcers that predates the Egyptian and Babylonian empires⁴⁹. In the late 1940's, it was noted that approximately 20 percent of patients treated with licorice root developed mineralocorticoid side effects, including hypertension and edema⁴⁸. Careful evaluation of these patients revealed a desoxycorticosterone acetate (DOCA)-like activity⁴⁸—one that mimicked the activity of the recently described adrenocortical hormones. This steroidal activity was verified when patients with Addison's disease were successfully treated using licorice root extract in the early 1950's⁴⁸. Within a decade, more potent, synthetic corticosteroids replaced licorice root as a treatment of adrenal insufficiency and as an anti-inflammatory.

The mechanism of action of several compounds contained in licorice root extract was elucidated in the 1980's. Two primary active components of licorice root extract, glycyrrhizic acid and glycyrrhetinic acid (GA), have been shown to inhibit the activity of 11- β -hydroxysteroid dehydrogenase (11 β HSD), an enzyme that catalyzes the conversion of the active steroids cortisol (hydrocortisone) and corticosterone to the

inactive compounds cortisone and 11-dehydrocorticosterone⁵⁰. Inhibition of 11 β HSD leads to an accumulation of active corticosteroids, by inhibiting steroid metabolism. This mechanism is implicated in the potential benefit of licorice in treating asthma⁵¹

In terms of adverse effects, licorice root can occasionally cause a state of excess mineralocorticoid activity (or pseudohyperaldosteronism) that can lead to increases in blood pressure, edema, and occasionally hypokalemia. This is typically much rarer than effects seen with systemic corticosteroids, however monitoring of blood pressure and potassium levels are recommended.

BUTTERBUR

Butterbur (*Petasites hybridus*) has a long history of use for migraine prophylaxis, however there is also a small body of evidence supporting its use in allergic and respiratory diseases^{52,53}. The leaf and root are commonly used in preparations of the butterbur extract, which is typically standardized based upon petasin and isopetasin concentrations. Extracts inhibit the formation of cyclooxygenase, leukotrienes and histamine⁵⁴.

The butterbur plant in its natural state contains pyrrolizidine alkaloids (PA's) which have been causally linked to liver cancer, so no raw, unprocessed preparations should ever be used⁵⁴. Care should be taken to ensure that the butterbur extract used is free of all detectable PA's. In addition, there is a potential for cross reactivity in patients with ragweed sensitivity, but no documented cases have been published.⁵⁵.

FISH OIL

Essential fatty acids have been the subject of study for decades. Their supplement use was popularized in the late 1970s when Danish researchers determined that members of the Inuit population in Greenland had a significantly delayed death rate from acute myocardial infarction, relative to matched individuals in Denmark⁵⁶. The researchers concluded that high levels of omega-3 fatty acids in the fish-based diet of the Inuit were responsible for this difference.

Since that time, hundreds of *in vitro* and *in vivo* studies have examined the effect of high or low dietary omega-3 ingestion on dozens of conditions, including asthma. *In vitro* stimulation of neutrophils from asthmatic patients supplemented with fish oil showed reduced arachidonic acid release by over one-third and inhibited 5-lipoxygenase products by nearly 50% has been demonstrated⁵⁷.

There are few adverse effects noted with fish oil. The absence of parvalbumin in molecularly distilled and pharmaceutical-grade preparations make fish oil even safe for those with finned fish-allergic individuals⁵⁸. Many people experience mild nausea following ingestion of fish oil, which is readily mitigated by storing the fish oil in the freezer and taking the capsules frozen. There were some reports of an increased frequency of cardiac arrhythmias in individuals taking high-dose fish oil as part of a study⁵⁹⁶⁰, but this has not been uniformly seen⁶⁰. Caution should be exercised when using fish oil along with anticoagulation therapy, as bleeding time may be increased.

CURCUMIN (TURMERIC)

Curcumin (*Curcuma longa*) is a polyphenol that has been shown to have anti-inflammatory properties with broad use in autoimmune, intestinal, and neoplastic disorders⁶¹. Its use has been supported in various atopic conditions including allergic rhinitis and asthma^{62,63}. Extracts of the root are commonly used in supplements and as a dietary herb.

Adverse reactions to curcumin have been reported in the literature, though appear to be rare⁶¹. Hypersensitivity reactions, including anaphylactoid reactions, have been described but true anaphylaxis is a rare occurrence.^{64,65} Moreover, a handful of case reports of contact allergic dermatitis have appeared in the literature as well as at least two cases of contact urticaria^{66,67,68,69}. While infrequent, skin hypersensitivity reactions are a possible side effect of topical preparations.

Metal toxicity is a theoretical concern with curcumin use due to associated cobalt-binding properties⁷⁰ and speaks to quality sourcing. Case reports of hepatotoxicity related to curcumin exist, usually in conjunction with other treatments such as chemotherapy⁷¹. Reports of hepatotoxicity with curcumin were hypothesized due to the presence of heavy metals, chromate, illegal dyes, non-steroidal anti-inflammatory agents, and pyrrole alkaloids but not proven in a 90-day prospective study of a curcumin compound containing 380mg of daily curcuminoids⁷².

Curcumin has been touted for its antiplatelet properties which may be beneficial in specific settings⁷³. However, understanding the impact of these physiologic properties is important. Tetrahydrocurcumin (THC), the active metabolite of curcumin has been shown to attenuate platelet generation offering cardioprotective benefits therefore there is theoretical concern of bleeding risk, however no impacts on surgical bleeding risk have been reported⁷⁴.

GINGER

Ginger (*Zingiber officinale*), is a traditional spice that has been long touted for its anti-inflammatory and anti-viral properties⁷⁵. It has favorable effects as an anti-emetic with application in digestive disorders as well as potential benefit in allergic rhinitis, asthma and other respiratory conditions.

The side effect profile is limited. Reactions to ginger can vary from hypersensitivity to physiologic effects. As a common spice in the occupational setting, contact dermatitis reports are known to exist in the literature but lacking in standardization and qualification^{76,77}. IgE-mediated hypersensitivity reactions to ginger are not commonly reported in the medical literature though have been described⁷⁸. Though considered in the same family as curcumin, no cross-reactivity of allergenicity has been reported. Moreover, the overall safety profile of ginger is favorable across many studies related to systemic disease though reflux symptoms have been reported⁷⁹. Finally, toxicity related to heavy metals or toxic compounds remains a concern of herbal supplements in

the medical community⁸¹, and even though not substantiated, speaks to the importance of sourcing, ultimately favoring use of the natural product where possible.

Bleeding risk and hypoglycemia have been postulated but there is no medical literature to predict or estimate this risk. A small randomized double-blind, placebo-controlled study of eight healthy males revealed no effect of up to 2g of dried ginger powder on bleeding time or platelet function⁸². With respect to hypoglycemia this may be beneficial as a potential therapeutic in diabetic patients, though hypoglycemic effects have been demonstrated in normoglycemic murine models and would require further study in the general population for further application ⁸³.

PROBIOTICS

Probiotics is a broad term, used to categorize microorganisms used as supplements to support the microbiome. Given the plethora of different probiotic strains and formulations of probiotics on the market it is challenging to speak to each individually but it is important to understand potential exposures to hidden allergens including lactose and cow's milk and soy. Similar to the understanding of excipients of lactose in medications, there is plausible risk of hypersensitivity in suspected individuals and children⁸⁴. A small study examined probiotics labeled with and without lactose and discovered that in addition to cow's milk protein, hen's egg protein was also identified, potentially putting those with a history of anaphylaxis to these foods at risk⁸⁵. In a large double-blind, placebo-controlled randomized study of pregnant women with eczema receiving different strains of probiotics, only a single patient on treatment demonstrated

an exacerbation of eczema suggesting that hypersensitivity responses in an otherwise susceptible population is uncommon ⁸⁶. Although rare, checking labels to ensure they do not contain cow's milk, soy or other allergen products is good practice. While probiotics can be found in dairy-rich foods such as yogurt or kefir, this is not to say that all probiotics supplements contain dairy. Thus it is important to recognize that lactobacillus as a common active bacteria in dairy preparations is not the same and should not be mistaken for lactose. In addition the bacillus component in a particular strain did not correlate with specific toxins related to the bacteria during in vitro analysis⁸⁷. Sourcing of probiotics and regulation of probiotics to specify exact colony forming units (CFUs) remains a challenge and potential limitation of their use⁸⁸

The most common side effects of probiotics in patients with atopic disease are gastrointestinal complaints, including abdominal pain, diarrhea and flatulence, though not necessarily more than placebo and rarely resulting in discontinuation of therapy ^{89,86}. Furthermore, in post-partum women with eczema taking probiotics and nursing, gastrointestinal symptoms of the infants were noted in over 40%, but not significant across probiotics and compared to placebo⁸⁶. However, in a cohort of 52 patients receiving probiotics consisting of Lactobacillus and Bifidobacterium in chronic urticaria, no adverse effects were reported though 14 patients withdrew for unrelated reasons ⁹⁰. Given the broad use of probiotics in multiple disease states, systematic reviews do not show significant adverse reactions and there has been no meaningful discontinuation of probiotics due to side effects or reactions ⁹² Special populations in which to exercise caution of common strains of probiotics are those who are immunocompromised,

critically ill, with chronic gastrointestinal issues, and extremes of age due to risk of bacteremia, impaired gut health and rare but serious infectious complications⁹³.

VITAMIN D

Vitamin D is readily available both in prescription and over-the-counter forms for various conditions, yet toxicity remains a serious, albeit rare, concern in modern clinical practice. Vitamin D has been suggested as an adjunct therapy in the management of asthma, especially in the case of steroid resistance in severe asthma⁹⁴. Dosing of Vitamin D varies, and often obtained through diet including fortified sources. The Institute of Medicine recommends that for most individuals up to the age of 70, no more than 600 IU of daily Vitamin D are needed⁹⁵. Maximum doses allowed have not been universally established but in the setting of Vitamin D deficiency, doses as high as 50,000 IU weekly are often indicated for short periods. However, long-term higher dosing of Vitamin D may place an individual increased risk for toxicity and is not recommended. Ranges of excess Vitamin D have been reported more than 150 ng/mL, however, one study of adults found that levels as high as 80 ng/mL and 120ng/mL were observed in 1% and 0.1% respectively, yet clinical signs of toxicity were still exceedingly rare⁹⁶.

Hypervitaminosis D may result in hypercalcemia and nephrocalcinosis in which patients present with signs of fatigue, abdominal pain, and nausea. Of consequence, renal failure and cardiac arrhythmias can ensue as a result of these metabolic effects. Broader analysis of risks for toxicity focus on incorrect dosing regimens but also

incorrect manufacturing resulting in increased exposure and effects⁹⁷ The pediatric setting may be particularly vulnerable to such errors thus requiring closer monitoring⁹⁸. Nevertheless, Vitamin D replacement appears to be safe and beneficial when indicated⁹⁹. In addition, drug-drug interaction of Vitamin D is occasionally a concern, particularly with extremely high doses that may impact drugs that rely upon calcium homeostasis.

CONCLUSION

The use of natural products is common among allergy patients, and it is important that the practicing allergist educate themselves on these modalities as a means of both nurturing the therapeutic relationship and being able to advocate for the safety and success of their patients (*Table 4*).

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Table 1: Glossary of Terms

Alternative Medicine: Medical treatment modalities with emerging levels of evidence used to treat illness in place of standard medical care.

Complementary Medicine: Medical treatment modalities with emerging levels of evidence but often derived from traditional, ethnic or indigenous healing practices used in conjunction with standard medical care.

CAM (Complementary and Alternative Medicine): A generic term used to group both Alternative and Complementary therapies, typically used in place of standard medical care.

Integrative Medicine: The judicious use of complementary modalities and standard medical care in a collaborative and coordinated manner ideally overseen by a practitioner with knowledge of both.

Natural Products: A category of treatments used in integrative medicine and CAM that can include dietary supplements, herbs, vitamins, minerals, amino acids or live microbials (ie probiotics).

Dietary Supplement: Compounds added to, or supplementing, standard nutritional intake beyond food.

696

697 **Medicinal Herb:** Any plant or botanical used for the treatment or prevention of medical
698 illness. Different parts of the plant (ie flower, leaf, root) may be used for different
699 purposes.

700

701 **Vitamin** Organic substances required for normal cell development and function, but
702 typically unable to be synthesized by humans. Commonly found in foods, but also
703 available as dietary supplements.

704

705 **DSHEA Dietary Supplement and Health and Education Act of 1994**, is US federal
706 legislation that defined dietary supplements and enacted regulation of these products by
707 the FDA (though using a different set of regulations than those covering foods and drug
708 products).

709

710 **Table 2: Defining drug versus supplement**

Drug	Supplement
<p data-bbox="203 342 747 373"><u><i>Federal Food, Drug and Cosmetic Act</i></u></p> <p data-bbox="203 415 763 814">“intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease”; “articles (other than food) intended to affect the structure or any function of the body of man or other animals.”</p>	<p data-bbox="823 342 1269 447"><u><i>Dietary Supplement Health and Education Act</i></u></p> <p data-bbox="823 489 1421 961">A product intended to supplement the diet that contains one of the following ingredients: vitamins and minerals; herbs and other botanicals; amino acids; dietary substances that are part of the food supply, such as enzymes and live microbials</p>

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713 **Table 3: Overview of supplements**

Supplement	Reported uses	Proposed mechanism of action	Reported Adverse Effects
Stinging nettle (<i>urticaria dioica</i>)	AR, asthma, diabetes	Mast cell stabilizer; decreased IFN-g, IL-6 and TNF-alpha	<i>Systemic:</i> Mild GI discomfort, Hypoglycemia, gynecomastia. <i>Topical:</i> Urticaria and angioedema
Quercetin	AR, asthma, inflammatory conditions, cancer prevention, anti-viral,	Mast cell stabilizer, COX-2 and NFKB inhibition, antioxidant	Nausea, vomiting, paresthesia,
DAO (diamine oxidase)	MCAS	Enzyme responsible for extracellular histamine degradation	No reported adverse effects
Echinacea (<i>E. angustifolia</i> , <i>E. purpurea</i> , and <i>E. pallida</i>)	Prevention of URIs	Inhibition of several inflammatory cytokines including TNF-alpha, and IL-6	Allergic reactions due to cross reaction to members of members of the Asteraceae family
Licorice root	Steroid-sparing agent; asthma; GERD; inflammatory conditions	Inhibits 11-B-HSD enzyme preventing endogenous CS degradation	Similar to CS. Pseudohyperaldosteronism; elevations in BP; edema; hypokalemia
Butterbur	Allergic rhinitis; migraines; sinus headache	Inhibits leukotriene and prostaglandin synthesis; decreases mast cell priming	Potential hepatotoxicity with some preparations containing pyrrolizidine alkaloids
Fish Oil	Asthma; CAD (1° and 2°); hyperlipidemia; inflammatory and rheumatologic conditions	Competes with omega-6 fats; inhibit synthesis of arachidonic acid, leukotrienes, and certain cytokines	Nausea; diarrhea; potential cardiac arrhythmias
Curcumin	AR, asthma, Inflammatory, rheumatologic, and neoplastic conditions	Polyphenol, anti-inflammatory and antioxidant; COX-1/COX-2 inhibition	<i>Systemic:</i> rare (anaphylactoid, metal toxicity 2/2 sourcing) <i>Topical:</i> discoloration, dermatitis/urticaria (rare)
Ginger	AR, URIs, GI related disorders	Antimicrobial, Anti-inflammatory, Anti-emetic	Overall, rare, such as hypersensitivity or physiologic (reflux, bleeding, hypoglycemia)

Probiotics	AD, AR, asthma and food allergies.	Immunomodulatory, Microbiome restoration	Abdominal pain, flatulence, diarrhea Caution in critically ill, GI patients, elderly/newborn infants Rare hypersensitivity reactions (if includes known allergens, ie cow's milk, soy)
Vitamin D	Broad applications, including pulmonary disease, severe and steroid-dependent asthma, AD and AR	Anti-inflammatory, Immunomodulatory	Vitamin D toxicity (often asymptomatic with increased levels): abdominal pain, fatigue and rarely, renal failure, cardiac arrhythmia

AD, Atopic Dermatitis; AR, Allergic rhinitis; CS, corticosteroids; GERD, Gastroesophageal Reflux Disease; GI, gastrointestinal; IFN-g, Interferon gamma; MCAS, Mast Cell Activation Syndrome; URI, Upper Respiratory infections.

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718 **Table 4: Additional Resources to select quality supplements**

<p>Natural Medicine Database</p> <p>(https://naturalmedicines.therapeuticresearch.com/)</p>	<p>Highly annotated resource for examining available published evidence and indications for botanicals and supplements. It includes adverse reactions and recognized drug interactions</p>
<p>ConsumerLab (https://www.consumerlab.com/)</p>	<p>Performs independent testing of quality and purity of many retail products, and can be a useful guide to recommending specific brands or products. Product comparisons help consumers and healthcare professionals identify the best quality health and nutrition products.</p>
<p>AboutHerbs (https://www.aboutherbs.com)</p>	<p>Large compendium of herbs and supplements with primary focus on oncology. Sections built separately for clinicians and for patients.</p>