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Abstract

Polyphenols are naturally occurring compounds that are found within numerous plant sources. They have a wide variety of structures and functions and have potential clinical uses in multiple disease states. Emerging studies involving polyphenols have demonstrated their antioxidative properties, as well as reduced risks of cardiovascular diseases and certain types of cancer. Due to these discoveries, there has been a marked increase in research related to the chemical properties of polyphenols and their potential uses in prevention of common acquired and inherited disease states. This article focuses on the effects that some polyphenolic compounds exert on immune function in regard to the induction and clinical manifestations of the allergic response and how supplementation with polyphenol-enriched apple extracts may alter the approach to treating atopic dermatitis and food allergies. Currently, due to the lack of large clinical trials detailing efficacy and safety data for these compounds when used to alter immune system responses to allergens, there are no strong recommendations for their use as prevention or acute treatment strategies for allergies.

Introduction

Researchers have been searching for natural products that are able to influence immune responses in regard to allergic disorders. Dietary polyphenols have been identified in multiple preclinical and a limited number of human trials as having the potential to alter the body's sensitivity to allergens and treat the allergic symptoms.[1,2] These compounds have been extensively researched in the past for many other conditions due to their anti-inflammatory and antioxidant properties, but the true connection to allergic disorders is still unclear. Polyphenols have shown benefits in studies focusing on animal models by having activity at the sensitization stage and during re-exposure to an allergen.

Most available therapies focus on treating allergy symptoms and not on the prevention or moderation of the allergic reaction. Current clinical recommendations for the treatment of symptoms associated with allergies include oral and topical antihistamines, corticosteroids, anticholinergics and mast cell stabilizers, which all focus on reducing the severity of the immune response and are relatively effective at doing so.[3,4] However, these medications should not be used long-term or in excessive doses due to an increased risk in associated adverse effects. For instance, long-term use of topical corticosteroids can cause side effects ranging from local skin atrophy to the development of Cushing's syndrome.[5] Also, although uncommon, overuse of antihistamines can result in adverse events as serious as QT prolongation and cardiac arrhythmias due to the drugs' inverse agonist activity at the Histamine 1 receptor (H1).[6] It is clear that there is a need for a therapeutic option that can effectively treat symptoms, as well as decrease the overall frequency of outbreaks by changing sensitivity to an allergen.

Allergic Immune Response

The exact mechanism of an immune response, while varied and specific for a particular allergen, generally revolves around the synthesis and resulting activity of inflammatory mediators, such as cytokines and interleukins that are produced by activated T helper (T_H) cells of the adaptive immune system.[7] These cells communicate with each other and with other cells of the immune system through the timed release of chemical mediators. These mediators' further activation of immune processes focuses on the isolation, destruction and removal of a "non-self" substance in order to avoid potentially adverse insults and to regulate normal internal homeostasis. T_H cells involved in this process are broken down and classified into two subcategories based upon cytokine production, through which subsequent immune cell types are activated and the specific protective outcome induced. T_H1 cells stimulate a nonspecific cellular immune response through the secretion of interferon gamma (IFN-γ) that activates innate immune system mediators including monocytes, tissue macrophages and natural killer (NK) cells. IFN-γ can also stimulate cytotoxic T-lymphocytes (T_C cells), as well as activate inducible nitric oxide synthase (iNOS) to produce nitric oxide (NO) free radicals in order to directly target bacteria and protozoa. T_H2 cells focus on stimulating the production of adaptive immune cells, B lymphocytes, basophils and eosinophils, in addition to up-regulating antigen-specific antibodies, which regulate humoral immunity.[7,8] Other cell types that are activated by this response include Immunoglobulin E (IgE), which stimulates mast cells to release histamine, serotonin and leukotrienes in order to cause bronchoconstriction. Optimal immune function relies on a dynamic balance between the two processes to effectively eradicate any foreign threat that is detected. Exaggerated allergic responses become problematic when there is an imbalance between T_H1 and T_H2 immunity, causing an overproduction of T_H2 pathway products.

An allergic disorder develops when the immune system detects a harmless allergen, considers it a threat and mounts local and systemic responses through T_H2 cell activity.[1] The immune response to the initial allergen exposure not only works to rid the body of the foreign contaminate through innate immune function, but will additionally sensitize the adaptive immune system to recognize the particular allergen more readily upon re-exposure.[9] This is accomplished through the production of antigen-specific IgE by plasma cells matured from activated B lymphocytes in response to the cytokines produced by T_H2 cells, most notably inter-

leukin 4 (IL-4).[9,10] Binding of these antigen-specific IgE molecules to the reintroduced allergen will cause symptoms of acute phase, as well as late phase immune reactions, due to the degranulation of mast cells. Inflammatory mediators released from these mast cells (histamine, interleukins and prostaglandins) can enhance vascular leakage while chemoattractants recruit basophils and eosinophils, as well as leukocytes in later stages, to the area of allergic reaction. Other cytokines cause upregulation of adhesion molecules for these leukocytes on vascular endothelial surfaces, which is critical for the progression to late phase reactions and chronic inflammation in future allergic reactions.[1,2,9,10]

In regard to specific types of allergic responses, food allergies can begin to develop during infancy after ingestion of an allergy-provoking food, but throughout life environmental factors can trigger respiratory allergies or skin allergies such as atopic dermatitis. Allergic reactions can also occur in part due to a genetic predisposition, called atopic syndrome (atopy).[11] This increased reactivity is characterized by the preferential production of IgE in response to allergens whose clinical manifestations may include atopic dermatitis, allergic contact urticaria, dyshidrotic eczema, allergic rhinitis, asthma, conjunctivitis, gastrointestinal allergies or any combination of the above.[11] An important diagnostic criteria of atopic syndrome is the production of allergen-specific IgE. Gene polymorphisms critical for the development of atopic syndrome are involved in the regulation of the T_H1/T_H2 ratio. Upon exposure to a specific allergen in a patient with atopy, the ratio skews toward a predominantly T_H2 cell response and the corresponding cytokine production. An overactivation of T_H2 lymphocytes against these presented antigens will cause a type I IgE-mediated allergy and hypersensitivity. More recently, alterations in genes for mast cell chymase (found only in dermal mast cells), and the α and β chains for the IgE receptor (representing a "gain of function" allele) have also been implicated in the preferential production of T_H2 cells and their respective cytokines.[11]

Polyphenol Chemistry

Polyphenols are naturally occurring and biologically active chemicals that are found in a variety of fruits (apples and grapes), plants (vegetables and legumes) and drinks (wine, cider, beer and tea) that are part of the human diet. They are considered nonnutrients because they are not required for normal body functions such as growth and development.[12] Polyphenolic compounds are byproducts of major metabolic pathways in plants and are extremely diverse in their chemical presentation. Currently, over 8,000 polyphenols have been identified, contributing significantly to the varied structures and bioactivity in plants and humans.[13] The highest concentrations of polyphenols are found in the parts of the plant source that are highly exposed to light, especially the leaves. Lower concentrations of polyphenols are found in portions of the plant that are underground, such as the tubers and roots.

Polyphenols have been considered deleterious to health due to their ability to bind to and precipitate proteins and other macromolecules, altering protein and macronutrient digestion and absorption from the gastrointestinal tract, as well as altering gut physiology (pH, colonic flora, biliary excretion, transit time, etc.).[14] Results of more recent studies have indicated that these interactions may also interfere with the bioavailability of polyphenols although the exact interaction remains undetermined. Renewal of interest in polyphenols, especially flavonoids, has been due to their proven antioxidant effects as free radical scavengers, Vitamin C and E regenerators and inhibitors of low density lipoprotein (LDL) oxidation. These properties have prompted research about other potential health benefits that these compounds may provide, including their potential use in altering immune response to allergic processes.[13] One of the most well-renowned types of polyphenols, the flavonoids, have displayed some medicinal applications in disease states including hypertension, allergies and hypercholesterolemia, and also as anti-inflammatory agents, anti-ulceratives, antibiotics and antidiarrheals.[13]

The overall structure of polyphenols is defined by the presence of one or more hydroxyl groups attached to aromatic rings.[1,12] Additional chemical and structural classifications of polyphenols divide this broad class of molecules into at least 10 subclasses depending on numerous factors including structural complexity, the presence of conjugated sugar groups, as well as other heteroatom linkages such as carboxylic acids, amines and phenols that alter the basic chemical structure.[13] The most basic classifications of polyphenols can be made into the following four groups: flavonoids, phenolic acids, stilbenes and lignans. Flavonoids and phenolic acids are the most abundant classes of polyphenols found in the human diet and can be further categorized based upon the location of hydroxyl groups. Flavonoids, with subclasses of flavones, isoflavones, flavanones, flavanols, flavonols and flavan-3-ols, are naturally abundant and are the basic building blocks of more complex polyphenols such as tannins which are highly hydrolyzed compounds capable of forming insoluble deposits with proteins.[13]

Polyphenols and Atopic Dermatitis

The possible anti-allergic effects of polyphenols have sparked studies looking at the potential benefits that supplementation could bring to patients suffering from skin allergies such as atopic dermatitis. Within the Atopy Outpatient Clinic of Kojima Hospital located in Tokyo, Japan, researchers examined the impact of apple extract supplementation on patients with atopic dermatitis.[15] Apple condensed tannins (ACT) were extracted from unripe apples and formulated into an oral dosage. Condensed tannins, also referred to as proanthocyanidin, are built from the flavan-3-ol class of polyphenols and have comparatively high molecular weights.[12] Previous studies in animal models had predicted that tannins are able to inhibit histamine release from mast cells and basophils, but this pilot study aimed to determine if ACTs are effective in human subjects as well.[15] Twenty-four patients between the ages of 8 and 18 years suffering from atopic dermatitis were selected for participation in the study, and then randomly divided into treatment or standard treatment control groups. Groups were determined to be comparable in regard to gender, age, peripheral eosinophil levels, and se-

rum IgE levels. Initially, both groups of patients began a standardized treatment using bufexamac ointment, half doses of alclometasone dipropionate ointment and hydroxyzine hydrochloride tablets (strengths and doses of medications not specified), which would be continued throughout the study period. Two weeks into the study, the treatment group added the ACT supplement to the regimen, dosed at 10 mg/kg divided into two daily doses. At the end of the ten-week study, the severity of the atopic dermatitis was assessed using a scoring system. The severity of each of the following was rated on a scale of zero to two: inflammation, cracking and hardening of the skin. Each location on the body, defined as trunk, arms, legs and face, counted as a separate score. Itching and sleep disturbances were also evaluated using a scale of zero to three. Total scores greater than 21 points were classified as severe. Starting and ending levels of serum IgE, peripheral eosinophils, glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) were also obtained from each patient. IgE and eosinophil counts were used to measure the change in the immune response with treatment; whereas, GOT and GPT values acted as nonspecific indicators of inflammation and tissue damage that are often elevated in dermatitis cases.

Patients receiving the ACT treatment showed a decrease in dermatitis scores overall (amount of decrease not specified), especially in the categories of itching and sleep disturbance.[15] Also in the treatment group, a statistically significant decrease was seen in peripheral eosinophil levels (525 versus 760/μL at baseline; $p<0.01$), but there was no significant difference in these levels within the control group (673 versus 784/μL at baseline). Neither group showed a significant difference in IgE, GOT and GPT levels. The study concluded that ACT supplementation may be effective at decreasing atopic dermatitis when used in combination with standard treatment with no significant side effects. This study was only performed to gather baseline data on the use of apple extract supplements in the treatment of atopic dermatitis. In summary, results were positive regarding the improvement in allergic symptoms, but additional studies using a larger patient population are needed to assess symptom management and the possibility of an ACT effect on the sensitization stage of allergic disorders.

Polyphenols and Food Allergies

The research regarding the anti-allergic effects of polyphenol research has extended beyond skin allergies to examine the potential impact on food allergies. Researchers in Switzerland studied the use of apple extracts for the reduction of food allergy symptoms in mice.[16] The apple extracts chosen for the trial had been enriched with polyphenols, mainly flavonols. To begin, all mice were sensitized to the allergen ovalbumin (OVA), the main protein found in egg, using weekly doses of 20 mg. As an adjuvant, 10 μg of Cholera toxin (CT) was also given to the mice to ensure sensitivity to the allergen would develop during the seven weeks under study. Previous studies have found CT to stimulate long-term immunological memory, particularly in the gut mucosa.[17] At the same time, mice were divided into four groups.[16] One group received the apple extract (1% weight-in-weight) in their food pellets during the sensitization process, and another group started the apple extract in the final week of the sensitization process which was used to detect secondary prevention. The study used two controls; the positive control group was not treated with the apple extract, and the negative control group was only sensitized to CT and not OVA. At the end of the seven weeks, the mice were given a challenge to the newly sensitized allergen using 100 mg OVA. Allergic reactions in the mice were observed for 30 minutes and scores were recorded based on the severity and frequency of symptoms including scratching, bristled fur, diarrhea, labored respiration and anaphylaxis. Blood, lymph node and intestine samples were then obtained from the animal subjects.

Results of the study were generally positive in concern to the benefits of polyphenol-enriched apple extracts. As expected, the negative control group did not experience any symptoms upon challenge to the antigen. Mice who received the apple extract during the final week of sensitization to test the secondary prevention hypothesis had significantly lower observation scores for symptoms. However, the mice ingesting the apple extract throughout the entire sensitization period did not experience fewer symptoms compared to the positive control group, which may show that polyphenols cannot prevent the development of an allergic response. Serum IgE levels were not found to vary in any of the mice regardless of apple extract treatment, but lower levels of cytokines were released from lymph nodes in the treated population of mice. A protease from intestinal mast cells, known to be involved in allergic responses to food allergens, was found in lower concentrations only in the secondary treatment group, which suggests an inhibition of the effector cell. Researchers tested the hypothesis that polyphenols may bind to proteins and lead to a diminished immune response. In vitro experiments showed that macro-complexes formed between the apple extract and OVA, resulting in decreased antibody reactivity. Contrary to expectation, in mice receiving the apple extract in their food pellets throughout the entire sensitization process, the apple extract provided no benefit as a primary prevention mechanism.

Conclusion

Although common in dietary sources, polyphenols are often used as a supplement and are available as an extract that has been formulated into an oral dosage. A variety of natural polyphenol products are available over the counter, and pharmacists must be knowledgeable about the current options and safety information for proper patient counseling. Supplements on the store shelf may be labeled as tablets or capsules containing polyphenols in general or may specify a particular category of polyphenols such as flavonoids. Polyphenol-containing compounds are marketed mainly for their antioxidant properties. It is expected that extracts from fruits or plants act as the main ingredients in these products. Some of the most common polyphenol products purchased by patients include green tea, grape, berry or apple extracts.

Because of the limited number of human trials that have been conducted, proper dosing of polyphenol supplements is still unknown. Bioavailability of oral preparations of these

compounds is relatively low and dependent on the size of the chemical structure, which varies greatly between the subclasses.[12] Dosing becomes a balance of finding a high enough dose to cause the intended effect, such as decreasing allergic symptoms, but not causing adverse reactions due to excessive intake. For instance, high concentrations of polyphenols have been found to cause decreased viability of liver cells, interruption of cell signaling cascades and auto-oxidation processes within cells.[12]

Additional research is still necessary to fully determine bioavailability, optimal dosing, and overall safety of polyphenolic compounds in human subjects. The ability of polyphenol supplementation to alter the body's sensitivity to allergens and to treat allergic symptoms is still under investigation. Although it seems certain these compounds exhibit chemical mechanisms that may justify their therapeutic use in allergic responses, adequate scientific trials in large patient populations are not yet available. As pharmacists, it is important to educate patients on the risks associated with taking excessive doses of polyphenol supplements. However, difficulties in designing dosing regimen strategies may arise due to limited research data on the levels necessary to achieve a clinically significant effect and also due to the large variety of polyphenolic compounds available for use. Despite the promising potential for the use of polyphenol-containing products in the moderation of allergic immune responses, polyphenol supplements should not be recommended as an effective option for allergy purposes until further research is conducted.

References

1. Singh A, Holvoet S, Mercenier A. Dietary polyphenols in the prevention and treatment of allergic diseases. *Clin Exp Allergy.* 2011;41:1346-59.
2. Magrone T, Jirillo E. Influence of polyphenols on allergic immune reactions: mechanisms of action. *P Nutr Soc.* 2012;71:316-21.
3. Cauwenberge PV, Bachert C, Passalacqua G, Bousquet J, Canonica GW, et al. Consensus statement on the treatment of allergic rhinitis. *Allergy.* 2000;55:116-34.
4. Sur DK, Scandale S. Treatment of allergic rhinitis. *Am Fam Physician.* 2010;81(12):1440-46.
5. Coureau B, Bussières J-F, Tremblay S. Cushing's syndrome induced by misuse of moderate- to high-potency topical corticosteroids. *Ann Pharmacother.* Dec 2008;42:1903-07.
6. Leurs R, Church MK, Taglialatela M. H1-antihistamines: inverse agonism, anti-inflammatory actions and cardiac events. *Clin Exp All.* 2002;32:489-98.
7. Kidd P. TH1/TH2 balance: the hypothesis, its limitations, and implications for health and disease. *Altern Med Rev.* 2003;8(3):223-46.
8. Miles E, Zoubouli P, Calder C. Effects of polyphenols on human TH1 and TH2 cytokine production. *Clinical Nutrition.* 2005;24:780-84.
9. Pearlman DS. Pathophysiology of the inflammatory response. *J Allergy Clin Immunol.* 1999;104(4):132-37.
10. White M. Mediators of inflammation and the inflammatory process. *J Allergy Clin Immunol.* 1999;103:378-81.
11. Bos JD, Van Leent EJM, Sillevis Smitt JH. The millennium criteria for the diagnosis of atopic dermatitis. *Exp Dermatol.* 1998;7:132-38.
12. Martin KR, Appel CL. Polyphenols as dietary supplements: a double-edged sword. *Nutr Diet Suppl.* 15 Dec 2010;2:1-10.
13. Bravo L. Polyphenols: chemistry, dietary sources, metabolism, and nutritional significance. *Nutrition Reviews.* 1998:56(11);317-33.
14. Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. *Am J Clin Nutr.* 2004;79:727-47.
15. Kojima T, Akiyama H, Sasai M, Taniuchi S, Goda Y, Toyoda M, Kobayashi Y. Anti-allergic effect of apple polyphenol on patients with atopic dermatitis: a pilot study. *Allergol Int.* 2000;49:69–73.
16. Zuercher AW, Holvoet S, Weiss M, Mercenier A. Polyphenol-enriched apple extract attenuates food allergy in mice. *Clin Exp Allergy.* 2010;40:942-50.
17. Vajdy M, Lycke NY. Cholera toxin adjuvant promotes long-term immunological memory in the gut mucosa to unrelated immunogens after oral immunization. *Immunol.* 1992;75:488-92.