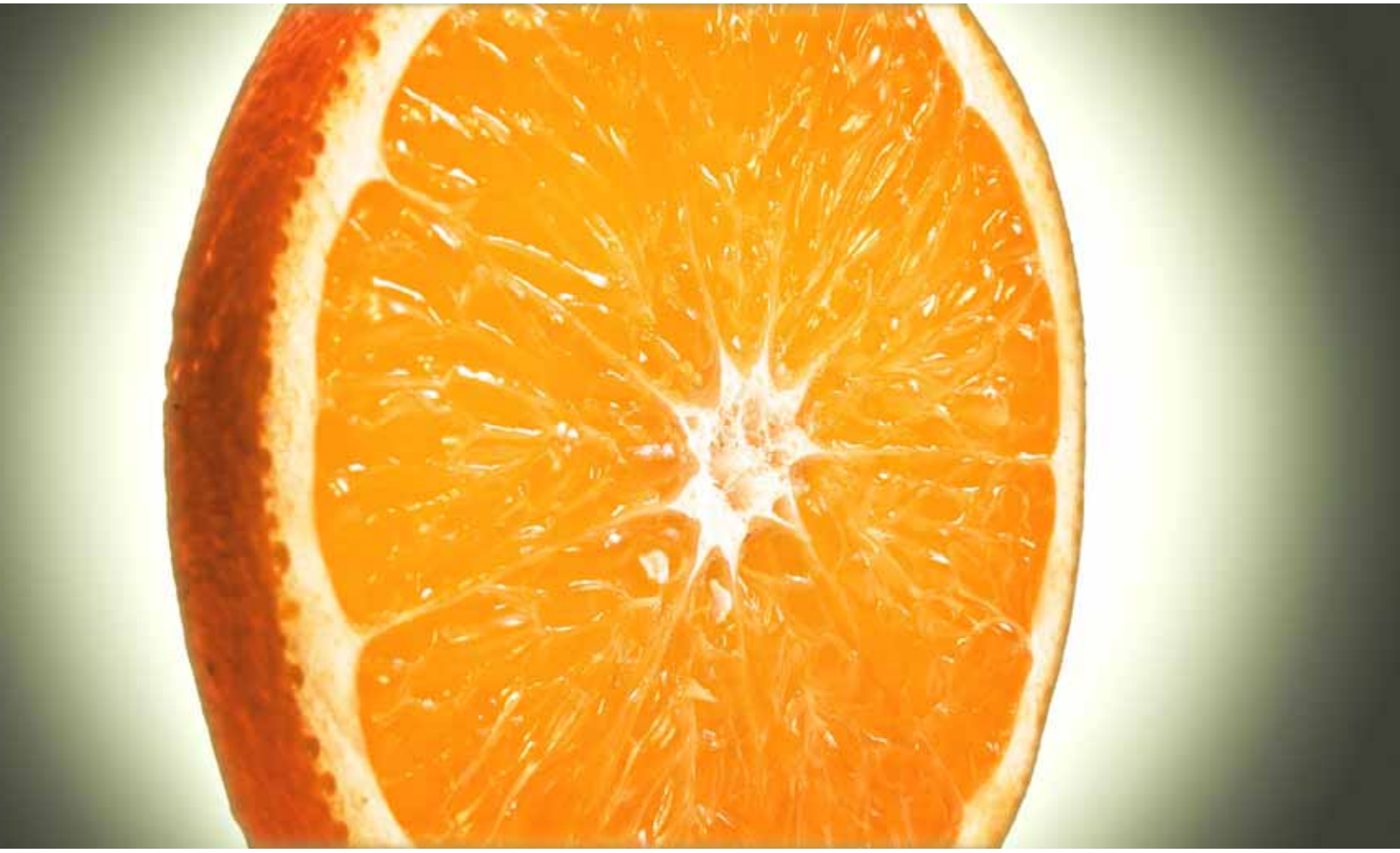
PHYTONUTRIENTS & NUTRITIONAL INTERVENTIONS

for

NATURAL IMMUNE SUPPORT



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INTRODUCTION

Atishoo…! Fall is almost here, and so are seasonal allergies, for some. Allergens appear almost everywhere at any given time of the year, in the form of dust mites, mold spores, pet dander, pollen, insect bites, common household chemicals, medications, or food components.

According to previous survey estimates, allergies affect as many as 40 to 50 million people in the US. Pollen allergy affects nearly 10 percent of the people in the US, (not including people with allergen-induced asthma). Allergic dermatitis is the most common skin condition in children younger than 11 years of age. Hives and swollen throat tissues together affect approximately 15 percent of the US population every year. Chronic sinusitis, most often caused by allergies, affects nearly 35 million people in the US. Eight percent of children younger than 6 years old and 1 to 2 percent of adults experience food allergies or intolerances[1] Incidences of the common cold, flu and respiratory problems, often increase at the onset of the fall season.

[1] Allergies Health Guide http://www.umm.edu/allergies/stats.htm

THE IMMUNE SYSTEM, ALLERGIES AND INFECTIONS

The immune system functions to protect the body against intruding microbes and environmental agents. Immune activity though is a double edged sword and “allergy"[2] and "hypersensitivity" are immune responses with damaging effects on the body. The “hygiene hypothesis” attributes the increase in allergic responses in children in developed countries, to reduced exposure to common infective agents in the early childhood environment. Autoimmune diseases such as rheumatoid arthritis or multiple sclerosis are expressions of hypersensitivity mediated by the immune response.

The immune systems of humans consist of a dynamic network of proteins, cells, organs, and tissues. Immune triggers are “antigens”, usually proteins or polysaccharides that form the cell walls of microbes, environmental toxins, or foreign particles. Inflammation is one of the first responses of the immune system to infection (Kawai, T et al.; 2006) characterized by redness and swelling, which are caused by increased blood flow into a tissue. Inflammation, produced by eicosanoids (prostaglandins, leukotrienes) and cytokines (interleukins, chemokines, interferons), which are released by injured or infected cells, is one of the first responses of the immune system to infection. Cytokines and other chemicals steer immune cells to the site of infection and induce tissue healing and phagocytosis or removal of invading particles.

Typically, allergy is a type I hypersensitivity reaction mediated by the interaction of mast cells (and eosinophils) coated with allergen-specific Immunoglobulin-E (IgE) and a cross-linking allergen. The physiological response is inflammation, commonly perceptible as urticaria (hives), rhinitis, vomiting and diarrhea, depending on the route of allergen entry. In extreme reactions anaphylactic shock can result that may lead to death. Chronic allergic responses most commonly present themselves as asthma and eczema.

Mast cells play a pivotal role in the allergic response. Ubiquitously found around blood vessels, in the connective tissue, in the lining of the gut, and importantly in the lining of the upper and lower respiratory tract, these granulated mononuclear cells contain a number of pharmacologically active substances.

[2] Viennese pediatrician Baron Clemens von Pirquet coined the term "allergy" (from the Greek "allos" meaning changed or altered state, and "ergon" meaning reaction or reactivity) in 1906.

The allergen (antigen) enters into the human body through one or more of several conduits including the respiratory tract, skin and gastrointestinal tract. On exposure to the antigen, antibodies (immunoglobulins IgE or IgG) are formed and attach to their respective receptors on the surface of the mast cells. This process is called sensitization. During the second exposure to antigen, the antigen reacts with these cytotrophic antibodies at the cell surface, each sensitized antigen then combines with two IgE molecules bringing them together. This event leads to a series of biochemical reactions resulting in the secretory expulsion of the granules. This process is called "mast cell degranulation", and the granules contain vasoactive amines and chemotactic mediators. One category of the active substances are pre-synthesized, including histamine (2-(4-imidazoloyl) ethylamine), serotonin (5-hydroxytryptamine), heparin (acid proteoglycan) and eosinophil chemotactic factor of anaphylaxis (ECF-A). The second category consists of substances synthesized and released during the allergic response. They include slow reacting substances that induce anaphylaxis (SRS-A) made of leukotrienes and platelet activating factor (PAF).[3]

Seasonal and perennial allergies, as well as chronic allergic response in asthma are therefore related to inflammatory mediators. It is for this reason that current therapeutic approaches to asthma, for instance, seek to inhibit the formation of inflammatory mediators such as leukotrienes.

NATURAL APPROACHES TO MAINTAINING A HEALTHY IMMUNE RESPONSE

A healthy immune response is necessary to combat allergies and infections. The key to reducing the symptoms of fall allergies and infections therefore lies in providing dietary interventions and lifestyle measures that potentially strengthen immune functions, reduce respiratory congestion, provide antioxidant action, and moderate nutritional imbalance. Traditional medicinal herbs, and phytonutrients from fruits and vegetables in the diet, have been shown to be beneficial in imparting these functions (Spelman, K et al, 2006; Brush, J et al. 2006). The shivering in the initial stages of flu is caused by compounds called pyrogens which act like free radicals and propagate extensively. Antioxidants not only help to alleviate these symptoms, but may also retard the replication of the flu virus. Some of the beneficial natural materials and nutritional interventions are described here.

[3] http://www.sabinsa.com/asthma_book.htm#01

Piper longum (long pepper) has a long history of culinary use. As a medicinal herb, it has been used in the Ayurvedic tradition in various formulations as an appetite stimulant, anticolic, antitussive and immunostimulant. The fruits contain 1% volatile oil, resin, alkaloids, piperine and piperlongumine and a terpenoid substance. The roots contain the alkaloids piperine, piperlongumine or piplartine. *Piper Longum* extract effectively reduced passive cutaneous anaphylaxis in rats and protected guinea pigs against antigen-induced bronchospasm.

In an *in vitro* study, a 30% protection of mast cells was observed. The individual alkaloids were also shown to block histamine release in animal models.

Piper longum is clinically proven to be useful in the management of bronchial asthma in children. In a classic study, 240 children with asthma were subjected to long term treatment with the fruit. Of these, 58.3% showed decreased severity of attacks. In another investigation, 20 children were studied for one year with the same treatment. Of these, 11 had no recurrence of attacks. All patients had strongly positive skin test which became negative in six and decreased significantly in 12 after five weeks of treatment. Clinically effective doses of *Piper longum* are well tolerated (Dahanukar, S. et al.; 1984).

Adathoda vasica has been traditionally included in preparations for the relief of cough, asthma and bronchitis. The plant has been recommended by Ayurvedic physicians for the management of various types of respiratory disorders (Dorsch, W et al.; 1991a). The leaves of the plant contain an essential oil and the quinazoline alkaloids vasicine, vasicinone and deoxyvasicine. Antitussive activity has been demonstrated in animal models (Dhuley, JN; 1999).

Tylophora indica (asthmatica). This herb has been used traditionally in the management of bronchial asthma and respiratory problems, and may act by a direct stimulation of the adrenal cortex. It is therefore probable that the immunosuppressive and anti-inflammatory effects are due to increased secretion of corticosteroids by the direct effect of *Tylophora asthmatica* components on the adrenal cortex (Udupa, AL et al.; 1991).

Several studies confirmed the value of *Tylophora asthmatica* in the treatment of bronchial asthma and allergic rhinitis. Through an unique combination of anti-inflammatory action and immunosuppressive effects, Tylophora asthmatica extracts mitigate inflammatory as well as allergenic symptoms (Dhananjayan, R et al.; 1975).

Conventional anti-asthmatic compounds such as sodium cromolyn and sodium cromoglycate, were developed from analogs of the naturally occurring furanochromone khellin (visammin), found in the Asian plant *Ammi visnaga*. Other furanochromones such as visnagin, khellol and khellinol have also been identified in the extracts of *Ammi visnaga*. Controlled clinical studies have verified the anti-allergic action of sodium cromolyn, which is currently used in the treatment of allergic rhinitis, asthma and allergic gastrointestinal reactions (Brenstein, I et al.; 1978).

Andrographis paniculata has been used in Nordic countries to provide relief from and to reduce the duration of symptoms of the common cold and flu. This plant is traditionally used in the management of infections through strengthened immune functions. The pharmacological effects of the plant are attributed to the presence of the primary active principles, andrographolide and its derivatives deoxyandrographolide, with beneficial effects on liver and serum enzymes, anti-inflammatory activity, antipyretic effects and pituitary adrenal cortical activity. Clinical studies revealed the efficacy of Andrographis paniculata extract in reducing cold and flu symptoms (Jaber, R et al.; 2002; Roxas, M et al; 2007).

Coleus forskohlii is the only known plant source of the adenylate cyclase and cAMP activator, forskolin. *In vitro* studies demonstrated the property of forskolin to inhibit the release of mediators including antigen induced histamine release, in the human hypersensitivity reaction (Marone, G et al.; 1986). An in vitro study employing human peripheral blood basophils demonstrated that forskolin, functioning as a phosphodiesterase inhibitor, significantly suppressed the release of the cytokines interleukin (IL-4 and IL-13) which are secreted by the basophils after cross-linking of cell surface immunoglobulins. This finding validates the capability of forskolin to regulate the release of cytokines (ShichiJo, M. et al.; 1997). Clinical studies have validated the beneficial role of forskolin (colforsin) in the management of asthma (Bauer, K et al.; 1993).

Ocimum sanctum or Tulsi (holy basil) belongs to the class of adaptogens that help to enhance adaptability to changing weather conditions. The leaves have been used in traditional Eastern systems of medicine for centuries in formulations for the management of respiratory problems and to support healthy metabolic functions (Gupta, SK et al. 2002).

Glycyrrhiza glabra, licorice, helps to soothe the respiratory system. *Glycyrrhiza glabra* contains biologically active constituents including glycyrrhizin, and glycyrrhetin, with anti-inflammatory activity. Recent studies in Germany suggest the potential utility of glycyrrhizin as an antiviral agent in respiratory infections as well (Cinatl J et al.; 2003).

Picrorhiza kurroa Royle ex Benth, a perennial herb from the Natural Order *Scrophulariaceae*, has been used in the traditional Indian systems of medicine since ancient times to treat hepatic diseases and bronchial problems. Several biologically active principles, particularly glycosides have been identified in extracts obtained from *Picrorhiza kurroa*. Of these, a mixture of the iridoid glycosides picroside I and kutkoside has been found to be an efficient liver protectant. “Androsin”, a phenolic glycoside isolated from *Picrorhiza kurroa,* has been attributed with anti-asthmatic properties and efficacy against allergies (Dorsch WH et al., 1991b; Mahajani SS et al., 1977).

The plant has also shown anti-allergic, mast cell membrane stabilizing activity similar to that of disodium cromoglycate (Puri, A et al.; 1992). Its anti-inflammatory action (Langer, JG; 1981) may also help to reduce edema. The beneficial effects of *Picrorhiza kurroa* have also been evaluated in open trials in patients with bronchial asthma, both objectively and subjectively.

An interesting observation was made by researchers who performed a year long clinical study in patients with asthma, in that patients having specific food allergy developed tolerance to these items during the period of treatment with a preparation containing *P. kurroa*. Frequency and severity of asthmatic attacks reduced significantly as the treatment progressed. Patients with mild and moderate asthma responded with clinical relief, reduction in the need to use bronchodilators and showed better performance of pulmonary function tests (Yegnanarayanan, R., et al., 1982).

Zingiberaceae extracts including ginger (*Zingiber officinale*), and Galangal (*Alpinia galanga*, *Kaempferia galanga*), (Tewtrakul, S et al.; 2007), as well as curcuminoids from turmeric (*Curcuma longa*), and their derivatives, offer comprehensive benefits including antioxidant, anti-inflammatory, antimicrobial action immune support, and help to reduce the release of mediators such as histamine (Suzuki, M et al; 2005).

Curcuma longa, (turmeric) and its yellow principles called curcuminoids are well recognized phenolic antioxidants and anti-inflammatory agents, which also have antibacterial and antiviral properties. Curcuminoids provide two-pronged antioxidant activity: prevention of free radical formation and intervention to neutralize existing free radicals. Curcumin C^3 Complex®* and the colorless metabolite C3 Reduct™*, are potentially useful in reducing allergy symptoms by several biochemical pathways. They down-regulate cytokines, inhibit cyclooxygenase which is the enzyme responsible for the formation of inflammatory prostaglandins from arachidonic acid, and block histamine receptors. Their healthful role in attenuating airway hyperresponsiveness is linked to anti-inflammatory action, the molecular basis of which is suppression of the nuclear factor-kappaB activation pathway for inflammatory mediators.

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Extracts of boswellic acids from the gum resin of *Boswellia serrata* (Indian frankincense) are clinically proven to benefit patients with asthma (Gupta, S et al.; 1998). Animal model studies also reveal the antiallergic effects of *Boswellia* extract. Boswellic acids have been shown to inhibit the enzyme 5-lipoxygense that catalyzes the formation of leukotrienes from arachidonic acid. In addition to this mechanism, boswellic acids also decrease the activity of Human Leukocyte Elastase (HLE).

This dual action is unique to boswellic acids (Safayhi, H et al., 1997) Because leukotriene formation and HLE release are increased simultaneously by neutrophil stimulation in a number of inflammation and hypersensitivity-based human diseases, it is generally believed that the reported blockade of two proinflammatory enzymes by boswellic acids, their beneficial effects on complement proteins and mast cell stabilizing activity could be the rationale for the anti-allergic/anti-asthmatic activity of Boswellia extracts (Ammon, HPT, et al., 1991, 1993; Majeed, M. et al.; 1996).

Bioflavonoids particularly quercetin and other polyphenolic compounds have also shown promise in the management of allergies and infections through multiple modes of action (Kumazawa, Y., et al.; 2006).

DIETARY INTERVENTIONS, IMMUNE SUPPORT AND THE INFLUENZA VIRUS

Based on epidemiological studies there is a high positive correlation between levels of the antioxidant trace mineral nutrient, selenium, in the body, glutathione levels and the overall state of good health. Selenium modulates the immune system by increasing natural killer cell activity and is believed to have a stimulatory effect on antibody production. It is probable that selenium improves cellular immunity. People living in parts of China, New Zealand and Europe have historically had diets low in selenium. The "Spanish flu" epidemic of 1918 originated in China, and new, more virulent strains of flu have recently surfaced in Asia, and may be attributed to mutant viruses abetted by deficient selenium status in the host.

Selenium nutritional status is reported to be the “driving force” for influenza virus mutations. Studies show that a non-virulent virus, in a selenium-deficient host, mutates to become ‘super virulent’-a "killer" virus (Nelson, HK et al.; 2001). Further, it has been observed that mutations occur in the flu viruses when a comparison is made of the viruses harvested from mice on normal and with selenium deficient diets (Beck, MA et al.; 1995, 2001).

Therefore a healthy selenium nutritional status in populations may be beneficial in containing epidemics, in several ways - through enhanced immunity to infection, through inhibiting the spread of virulence, as well as through a healthier response to the ravages of infection or severe inflammation. SeleniumSelect®* (L(+) Selenomethionine), MethySelene®*(Se-methyl –L-Selenocysteine), and SelenoForce™* (selenium enriched garlic) are bioavailable sources of organic selenium compounds for selenium supplementation.

In addition, interventions that help to support healthy digestive functions are also beneficial. The fruits of *Terminalia chebula, Terminalia belerica*, and *Emblica officinalis* combined in equal proportions are known as Triphala. This formula and its individual ingredients are highly valued in Ayurveda, being compared to a "good manager of the house" in aiding digestion, nutrient absorption, and metabolism. Triphala can be particularly useful in alleviating indigestion, which is more likely to occur during seasonal changes. Supplemental digestive enzymes (such as the branded DigeZyme®*) help to rectify impaired digestion and improve gastrointestinal functions, functioning as adjuncts in maintaining healthy immune functions.

Probiotics offer digestive health support and help to maintain a healthy balance of beneficial microflora in the gastrointestinal tract while preventing the growth of putrefactive organisms. The use of probiotic therapy to prevent allergic disease has been demonstrated in two studies using a probiotic *Lactobacillus rhamnosus* GG in neonates. A long-term reduction in allergy has been shown in the test group, with lactobacillus reducing the incidence of atopic eczema. Management of allergy through probiotics has also been demonstrated in infants, using lactobacilli to control atopic eczema and cow's milk allergy (Furrie, E; 2005). A room temperature stable probiotic culture classified as *Bacillus coagulans* and formerly known as Lactobacillus *sporogenes* (commercially available as Lactospore®*[4]) was shown to be useful in managing allergic skin conditions in infants.

[4] www.lactospore.com

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CONCLUSIONS

Phytonutrients, mineral nutrients, probiotics and digestive aids offer comprehensive support in strengthening immune functions. The selections presented in this article only represent a small fraction of the large number of potentially useful dietary interventions with clinically validated efficacy. Contact Sabinsa Corporation for further information on these and other healthful ingredients for the Fall season.

REFERENCES

1. Ammon, H.P. T et al. (1991) Inhibition of leukotrienes B4 formation in rat peritoneal neutrophils by an ethanolic extract of the gum resin exudate of *Boswellia serrata*. *Planta Med*. 57 (3), 203 -7.
2. Ammon, H.P.T. et al. (1993). Mechanism of anti-inflammatory actions of curcumin and boswellic acids, *J. Ethnopharmacology*, 38, 113-119.
3. Bauer, K. et al., (1993). Pharmacodynamic effects of inhaled dry powder formulations of fenoterol and colforsin in asthma. *Clin. Pharmacol. Ther*., 53:76-83.
4. Beck MA, et al.(1995). Rapid genomic evolution of a non-virulent coxsackievirus B3 in selenium-deficient mice results in selection of identical virulent isolates. *Nat Med* ;1(5):433-6.
5. Beck, M.A. et al. (2001) Selenium deficiency increases the pathology of an influenza virus infection. *FASEB J* 15(8): 1481-1483.
6. Brenstein I. et al., (1978). Therapy with sodium cromolyn. Ann. Int. Med., 89:228-233.
7. Brush, J; et al. (2006).The effect of *Echinacea purpurea, Astragalus membranaceus* and *Glycyrrhiza glabra* on CD69 expression and immune cell activation in humans. *Phytotherapy Research* 20: 687–695.
8. Cinatl J, et al. (2003) Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated corona virus. .Lancet. 361(9374):2045-6.
9. Dahanukar, S. et al., (1984). Efficacy of Piper longum in childhood asthma. *Indian Drugs*, pp. 384-388.
10. Dhananjayan, R., et al., (1975). Studies on the pharmacological effects of extracts and total alkaloids of *Tylophora indica*, *Indian J. Pharmacol.*, 7 : 13.
11. Dhuley JN. (1999) Antitussive effect of Adhatoda vasica extract on mechanical or chemical stimulation-induced coughing in animals. *J Ethnopharmacol*.67 (3):361-5.
12. Dorsch W, Wagner H. (1991a) New antiasthmatic drugs from traditional medicine? *Int Arch Allergy Appl Immunol*. 94(1-4):262-5.
13. Dorsch, W.H. et al., (1991b). Anti-asthmatic effect of Picrorhiza kurroa: Androsin Prevents allergen and PAF induced bronchial obstruction in guinea pigs. *Int. Arch. Allergy Appl. Immunol*., 95 : 128-133.
14. Furrie, E. (2005) Probiotics and allergy. *Proc Nutr Soc*.64(4):465-9
15. Gupta S, et al. (1998) Effects of *Boswellia serrata* gum resin in patients with bronchial asthma: results of a double-blind, placebo-controlled, 6-week clinical study. *Eur J Med Res.* 1998 Nov 17;3(11):511-4.
16. Gupta SK, et al. (2002) Validation of traditional claim of Tulsi, *Ocimum sanctum* Linn. as a medicinal plant. *Indian J Exp Biol.* 40(7):765-73.
17. Jaber R. (2002) Respiratory and allergic diseases: from upper respiratory tract infections to asthma. *Prim Care.* 29(2):231-61.
18. Kawai T, Akira S (2006). Innate immune recognition of viral infection. *Nat Immunol* 7 (2): 131-7.
19. Kumazawa Y et al. (2006) Immunomodulating effects of flavonoids on acute and chronic inflammatory responses caused by tumor necrosis factor alpha., *Curr Pharm Des*. 12(32):4271-9.
20. Langer, J.G. et al., (1981). Clinical trials on *Picrorhiza kurroa*. *Indian J. Pharmacol.*, 13: 98-103.
21. Mahajani, S.S., and Kulkarni, R.D., (1977). Effect of DSCG and P. kurroa root powder on sensitivity of guinea pigs to histamine and sympathomimetic amines. *Aspects of Allergy Appl. Immunnol.*, 11: 137-144.
22. Majeed, M. et al. (1996) Boswellin® : The Anti-inflammatory Phytonutrient. Nutriscience Publishers, Inc., pp. 26.
23. Marone, G. et al. (1986) Forskolin inhibits release of histamine from human basophils and mast cells. *Agents and Actions*, 18(1/2): 96-99.
24. Nelson HK, et al. (2001) Host nutritional selenium status as a driving force for influenza virus mutations. *FASEB J*; 15:1481-3.
25. Puri, A. et al., (1992). Immunostimulant activity of picroliv, the iridoid glycoside fraction of Picrorhiza kurroa, and its protective action against Leishmania donovani infection in hamsters. *Planta Medica*, 58: 528-532.
26. Roxas M, Jurenka J. (2007) Colds and influenza: a review of diagnosis and conventional, botanical, and nutritional considerations. *Altern Med Rev.* 12(1):25-48. Review.
27. Safayhi H. et al (1997) Inhibition by boswellic acids of human leukocyte elastase. J. Pharmacol. Exp. Ther. 281(1):460-3.
28. ShichiJo, M. et al., (1997). Cyclic AMP-elevating agents inhibit mite-antigen-induced IL-4 and IL-13 release from basophil-enriched leukocyte preparation. *Int. Arch. Allergy Immunol.*, 114(4):348-53.
29. Spelman, K; et al. (2006). Modulation of cytokine expression by traditional medicines: a review of herbal immunomodulators. *Alternative Medicine Reviews* 11(2): 128–150.
30. Suzuki, M. et al. (2005) Elucidation of anti-allergic activities of curcumin-related compounds with a special reference to their anti-oxidative activities. *Biol Pharm Bull.* 28(8):1438-43.

31. Tewtrakul S, Subhadhirasakul (2007) S. Anti-allergic activity of some selected plants in the Zingiberaceae family. *J Ethnopharmacol.* 109(3):535-8.
32. Udupa, A.L. et al.., (1991). The possible site of anti-asthmatic action of *Tylophora asthmatica* on pituitary-adrenal axis in albino rats. *Planta Medica*, 57:409-413.
33. Yegnanarayanan, R., et al., (1982). Study of *Picrorhiza kurroa* (PK 300) in cases of bronchial asthma. *Bombay Hosp. J*., 24(2): 15-18.