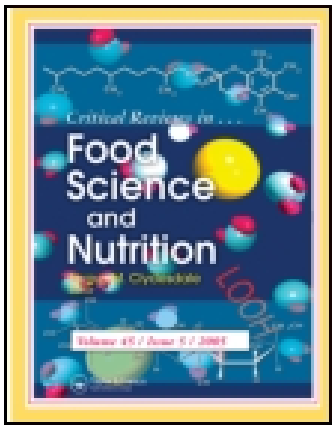

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Immunity: Plants as Effective Mediators

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Immunity: Plants as Effective Mediators

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In the domain of nutrition, exploring the diet–health linkages is major area of research. The outcomes of such interventions led to widespread acceptance of functional and nutraceutical foods; however, augmenting immunity is a major concern of dietary regimens. Indeed, the immune system is incredible arrangement of specific organs and cells that enabled humans to carry out defense against undesired responses. Its proper functionality is essential to maintain the body homeostasis. Array of plants and their components hold immunomodulating properties. Their possible inclusion in diets could explore new therapeutic avenues to enhanced immunity against diseases. The review intended to highlight the importance of garlic (Allium sativum)*, green tea* (Camellia sinensis)*, ginger* (Zingiber officinale)*, purple coneflower* (Echinacea)*, black cumin* (Nigella sativa)*, licorice* (Glycyrrhiza glabra)*, Astragalus and St. John's wort* (Hypericum perforatum) *as natural immune boosters. These plants are bestowed with functional ingredients that may provide protection against various menaces. Modes of their actions include boosting and functioning of immune system, activation and suppression of immune specialized cells, interfering in several pathways that eventually led to improvement in immune responses and defense system. In addition, some of these plants carry free radical scavenging and anti-inflammatory activities that are helpful against cancer insurgence. Nevertheless, interaction between drugs and herbs/botanicals should be well investigated before recommended for their safe use, and such information must be disseminated to the allied stakeholders.*

Keywords Immunomodulation, medicinal plants, nutraceuticals, phytochemicals

INTRODUCTION

The tenet "Let food be thy medicine and medicine be thy food," exposed by Hippocrates nearly 2500 years ago, gained renewed interests that resulted in coinage of terms like pharma, nutraceuticals, and functional foods. These terms are not only gaining popularity among researchers, but consumers are also interested toward natural diet based regimens. These natural products act as immune boosters thus improving the quality of life (Ares et al., 2009; Sultan et al., 2009). Augmenting immunity is a major concern of diet-based therapies to cure various disorders, and researchers are thriving for immune boosters (Bourgeon et al., 2007; Butt et al., 2009).

The immune system is an incredibly intricate network of specialized cells that prevents infections and diseases by engulfing, modulating, and moderating malignant and foreign cells. Human's immune system is composed of organs like spleen and thymus, whereas additionally lymph nodes and bone marrow also contribute in immune system by producing and storing specific immune cells (Chaouat et al., 2007). Immune cells are of two major types, i.e., B cells and T cells. B cells are responsible for producing antibodies (immunoglobulins) that are proteins designed to recognize and mark a specific antigens, whereas T cells are charged moieties with destroying antigens tagged with an antibody (Chanana et al., 2007; Zhang et al., 2007).

T cells play critical role in controlling the adaptive immune functions, and their responses could be used to develop protective vaccines and may induce tolerance to antigens causing inappropriate immune responses, e.g., autoimmune diseases (Cooper and Alder, 2006; Li et al., 2007). In addition, phagocytes such as granulocytes, macrophages and natural killer cells (NK cells) release pyrogens and interferons that act as immunoregulatory moieties (Currier and Miller, 2002; Fauci et al., 2005). Chemical mediators like cytokines (monokines and lymphokines) are also effective in regulating immune responses.

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Some other mediators like tumor necrosis factor-alpha (TNF-α), interleukins (IL), chemokines, and interferon bodies (IFN) also contribute in proper functioning of immune system (Timár et al., 2007).

Interest in medicinal plants has burgeoned owing to increased efficiency of new phytodrugs and the growing awareness among consumers regarding natural product consumption. A larger number of plants and their isolated constituents have shown health benefits, including antioxidant, anti-inflammatory, anticancer, antimicrobial, and immunomodulatory effects (Butt et al., 2009; Sultan et al., 2009; Butt and Sultan, 2011). Plants produce thousand of bioactive compounds, and their complexity must be well investigated (Schwager et al., 2008). Several plants and their metabolites have health-promoting properties, i.e., vitamins, antioxidants, dietary fibers, phytosterols, flavonoids, omega-3-fatty acids, etc. (Butt et al., 2008; Wang et al., 2009). Human diet containing these phytochemicals possess antimutagenic and immunomodulatory potential and have shown anti-inflammatory, antistress, and anticancer properties. It is important for clinicians to document use of herbal medicines as part of the patient's drug profile (Ramaa et al., 2006; Roller et al., 2007).

Summarizing nutraceutical potential of all herbs is out of scope for this paper, thus emphasis paid on some of promising plants like garlic (*Allium sativum*), green tea (*Camellia sinensis*), ginger (*Zingiber officinale*), purple coneflower *(Echinacea),* black cumin (*Nigella sativa*)*,* licorice (*Glycyrrhiza glabra*), *Astragalus* and St. John's wort (*Hypericum perforatum*) as natural immune boosters.

Garlic

Garlic (*Allium sativum L.*) was originated from Central Asia over 6000 years ago and holds potential to be employed as medicinal agent (Butt et al., 2009). The health benefits of garlic appear to be true today as diet-based therapy and its use as a dietary supplement is recommended in many countries (Raman et al., 2008). Most of its biological effects are attributed to organosulfur compounds including, diallyl sulfide (DAS), diallyl disulfide (DADS), δ-glutamyl-S-allyl-L-cysteines, S-allylmercaptocysteine (SAMC), S-allyl-L-cysteine sulfoxides, and nonstarch polysaccharides (Clement and Venkatesh, 2010; Liang et al., 2011). Various garlic preparations such as aged garlic extract (AGE) and aqueous extract, garlic oil are being sold in the market with distinct health claims (Chandrashekar et al., 2011).

Immunomodulatory properties of garlic and its bioactive profile include immune stimulation, reduce platelet aggregation, and chemoprevention of cancer (Gamboa-Léon et al., 2007; Wojcikowski et al., 2007). Garlic and AGE can scavenge free radicals and act as successful antioxidant. In addition, they also have the potency to enhance and regulate the activities of the antioxidant enzymes, such as glu-tathione peroxidase, glutathione S-transferase (GST), catalase, acid soluble sulfhydryl (-SH) cytochrome b5 and cytochrome P450, and superoxide dismutase (Borek, 2001; Kris-Etherton et al., 2002; Zhou et al., 2007; Nagaraj et al., 2012)

The role of garlic in immuonutrition is multifarious both as immunostimulant and immunosuppressant. The consumption of garlic results in improvement in hematological attributes, e.g., total white blood cell (WBC) count as well as homeostasis characteristics (Wilson and Demmig-Adams, 2007). Consumption of garlic may increase the production and release of nitric oxide (NO) that is further responsible for enhanced release of IFN-alpha in humans, beneficial against viral, or proliferative diseases (Bhattacharyya et al., 2007). The overall improvement in immune system could be attributed to the activation of specific responses and detoxification mechanisms (Chandrashekar and Venkatesh, 2009; Zamani et al., 2009). Proliferation of lymphocytes; macrophage phagocytosis; infiltration of macrophages and lymphocytes; and stimulating release of IL-2, TNF-alpha, and IFN-γ are some possible routes of garlic for its immunomodulatory properties. In addition, it can enhances NK cell and lymphokine-activated killer cell activities that represent effective stimulation of the immune responses (Iciek et al., 2009; Kim and Kwon, 2009).

Inhibiting growth of cancerous cells is perhaps the most remarkable beneficial action of garlic. It has been reported from the last decade that garlic and garlic preparations may posses anticancer activities against skin, colon, prostate, mammary carcinoma, lungs, gastric cancer, etc. (Wu et al., 2009; Altonsy and Andrews, 2011; Wang et al., 2012). The development of successful strategy employing dietary chemopreventive agent reside in their mode of actions. Certainly, it does not appear that a single mechanism could account for the observed protection based on the variety of carcinogens (Galeone et al., 2006; Chen et al., 2012). Organosulfur compounds of garlic inhibit carcinogen activation/formation, boost phase-II detoxifying processes, cause cell cycle arrest mostly in G2/M phase, stimulate the mitochondrial apoptotic pathway, increase acetylation of histones, and suppression of tumor proliferation (Iciek et al., 2009; Bat-Chen et al., 2010; Altonsy and Andrews, 2011; Wu et al., 2011) Earlier, Galeone et al. (2006) provided evidence using multivariate odd ratios that garlic is inversely associated with the risk of several common cancers. Some of its preparations like aged garlic extract and fresh garlic juice hold potential to inhibit cell proliferation and induce apoptosis (Sengupta et al., 2004). Recently, it has been suggested that the DAS, diallyl trisulfide (DADS) and DATS can initiate a cascade of molecular events characteristic of apoptosis of cancerous cells (Chandra-Kuntal and Singh, 2010; Altonsy and Andrews, 2011). The mechanism through which garlic and its functional ingredients imparts anticancer effects needs further elaborations.

Studies suggest that garlic may be useful in preventing the suppression of immune response, associated in increased risk of malignancy. In the nutshell, it can be assumed that garlic is one of the most potential candidates as immune booster, improves the antioxidants status of the body, and protects body from free radicals, inflammation, and cancer insurgence.

Green Tea

Green tea (*Camellia sinensis*) is one of the most popular beverages consumed worldwide, and its consumption is increasing day by day. The changing trends of consumers are mainly attributed to its perceived antioxidant, anti-inflammatory, and anticarcinogenic properties (Almajano et al., 2011). Catechin (epicatechin, epigallocatechin, epicatechin gallate, and epigallocatechin gallate) are its active ingredients (Baliga and Katiyar, 2006). Among these, epigallocatechin-3-gallate (EGCG) is identified as the principal antioxidant moiety contributing approximately 30% of the total antioxidant capacity (Colic and Pavelic, 2000; Stewart et al., 2005).

Recently, Butt and Sultan (2009) provided molecular and cellular insights of green tea for their antioxidant and anti-inflammatory potential. EGCG has marked effect in modulating production of immunoregulatory cytokines in stimulated dendrite cells and hence acts as suppressor of T cell activation (Rogers et al., 2005). It can also prevent angiogenesis as observed in angiogenic assay in vivo and inhibits the growth of the highly angiogenic Kaposi's sarcoma tumor cells in rodent experimental modeling (Noonan et al., 2007; Kawai et al., 2011). Green tea and EGCG effectively mitigate cellular damage by lowering the inflammatory reaction and reduce lipid peroxidation and formation of NO radicals (Norwood et al., 2006; Tipoe et al., 2007; Bais et al., 2010).

The anticancer perspectives of green tea catechins have been highlighted in the last few decades. It can significantly reduce the risk of cancers as revealed in experimental animal studies, human cell lines, and human clinical studies (Thakur et al., 2012). Overall, it can be used as adjunct in the treatment of bladder, breast, and colon cancer (Sartippour et al., 2002; Singh et al., 2011; Yang et al., 2011). Green tea is also effective in leukemia, liver, biliary tract, and lung cancer (Fujimoto et al., 2002; Choudhury et al., 2011; Wang et al., 2011). Current applications of green tea polyphenols can provide protection against ultra violet-induced skin cancers (Mantena et al., 2005). Some other scientific data reported its beneficial effects in esophageal and prostate cancer too (Gupta et al., 2003). The studies suggested that multiple mechanisms are involved in its chemoprevention properties including induction of apoptosis, cell cycle arrest downregulation of telomerase, inhibition of vascular endothelial growth factor, and suppression of aromatase activity (Sartippour et al., 2002; Butt and Sultan, 2009; Yang et al., 2011). Green tea assumed to induce apoptosis and promote cell growth by altering expression of cell cycle regulatory proteins, altering Bax/Bcl2 function, activating killer caspases, and suppressing nuclear factor kappa B function (Aktas et al., 2004; Khan et al., 2006). Green tea catechins especially EGCG has been shown to block each stage of carcinogenesis by modulating the signal transduction pathways during proliferation, inflammation, apoptosis, and metastasis (Kang et al., 2007; Butt and Sultan, 2009; Al-Hazzani and Alshatwi, 2011; Singh et al., 2011). Some studies do suggest that green consumption effectively improve the overall antioxidant capacities of the body in human subjects (Ellinger et al, 2011). However, some scientific intervention, cohort studies, and meta-analysis suggested that green tea intake is not completely useful for all populations, e.g., smokers and exsmokers are at risk of lung cancer if they keep consuming green tea. The synergistic and antagonistic effect of green tea catechins with other drugs/natural products needs further attention as some studies suggested that EGCG can help curcumin against cancer insurgence (Manikandan et al., 2011; Xu et al., 2011). The Japanese Public Health Center-based prospective study (JPHC) highlighted the association between green tea consumption and decreased risk of cancer insurgence (Iwasaki and Tsugane, 2011).

Green tea and EGCG are now of clinical importance for the treatment of lifestyle-related disorders and cancer insurgence (Sueoka et al., 2001). Watson et al., 2005 also recommended that green tea and catechins especially EGCG could be useful for enteric immune disorders and T cell driven immunopathologies. The instant discussion is a message for adopting "designer approach" to get maximum health benefit from green tea catechins.

Ginger

Recent research has rejuvenated the centuries old traditional herbs to cure various ailments by using the modern tools like diet-based therapy or regimen. Ginger (*Zingiber officinale*) is one of the classic examples used for not only culinary preparations but also holds unique therapeutic significance (Baliga et al., 2011; Butt and Sultan, 2011). The bioactive molecules present in ginger include α-zingiberene, α-farnesene, β-bisabolene, α-curcumene, [6]-gingerol and [6]-shogaol, paradol, zingerones, and allied derivatives (Zhan et al., 2008). Owing to the rich phytochemistry, it has been used in Chinese, Ayurvedic medicines (Hung et al., 2009; Jeong et al., 2009).

Ginger and its bioactive molecules are effective in controlling the extent of colorectal, gastric, ovarian, liver, and skin cancers. The molecular targets involved in chemoprevention include inhibition of NF-κB activation, suppresses cIAP1 expression and cell proliferation, arrests cell cycle in G2/M phases, upregulates cytochrome c, Apaf-1, activates PI3K/Akt/I kappaB kinases IKK. It also induces apoptosis, chromatin condensation, and increases caspase-3/7 activation and the number of tumor-infiltrating lymphocytes (Kim et al., 2009; Oyagbemi et al., 2010; Ju et al., 2012).

Ginger is consumed in many cultures as immune boosters (Kannappan et al., 2011), and its anti-inflammatory potential has been highlighted in number of scientific investigations. The mechanisms for its anti-inflammatory properties include inhibition of arachidonic acid-induced platelet aggregation and formation of thromboxane B, upregulation of histone H3 acetylation, and suppressed histone deacetylase (HDAC)1 expression (Shim et al., 2011), inhibition of IL-1, TNF-α and IL-8, downregulation of inflammatory inducible NO synthase (iNOS) and cyclooxygenase 2 (COX-2) gene expression through

inactivation of Nuclear Factor Kappa B (NF-κB) (Rani et al., 2011). The other molecular mechanisms, include extracellular signal-regulated kinases 1 and 2 (ERK1/2), p38 mitogen-activated protein kinase (MAPK), c-Jun N-terminal kinase (JNK), and the inactivation of Nuclear factor-jB (NF-jB) (Zhou et al., 2006; Jung et al., 2009). Likewise, 6-gingerol, 10-gingerol, 8-shogaol, and 10-shogaol can decrease iNOS and TNF-a expression through suppression of I-jBa phosphorylation, Nuclear factor-jB (NF-jB), gene activation of proinflammatory enzymes, COX-2, nuclear activation, and protein kinase C (PKC)-a translocation (Lee et al., 2009; Kim et al., 2010; Li et al., 2011; van Breemen et al., 2012).

Immune system also helps the body by protecting it from hazardous effects of chemicals. The ginger and its bioactive molecules are effective in providing protection against hepatotoxicity induced through bromobenzene, ethanol, and acetaminophen via modulation of enzymes (Mallikarjuna et al., 2008; Atta et al., 2010). 8-gingerol (50, 100 mg/kg) suppressed humoral and cellular immune responses through direct inhibition of sensitized T and B lymphocytes (Ueda et al., 2010; Lu et al., 2011; Nievergelt et al., 2011; Shim et al., 2011). Intraperitoneal injections of ginger extract decreased the eosinophils to the lungs along with diminished levels of IL-4, IL-5, and eotaxin levels (Ahui et al., 2008). Further evidences can also be presented in this regard as [6]-gingerol (25–50 mg/kg) inhibited acetic acid-induced writhing response and formalin-induced licking time. However, higher doses of [6]-gingerol (50–100 mg/kg) are required to inhibit paw edema induced by carrageenin (Young et al., 2005).

The anti-inflammatory potential of ginger is helpful for the management of disorders like respiratory infections (Podlogar and Verspohl, 2012), arthritis (Funk et al., 2009), allergic diseases (Chen et al., 2009), and gout (Sabina et al., 2010). In the nutshell, it can be observed that ginger and its components hold anti-inflammatory activities. They are effective in reducing the extent of chemical toxicity and are of significance importance in treating the inflammatory disorders. Cohort studies and controlled trails should be conducted to warrant its pharmacological applications.

Purple Coneflower (Echinacea)

Echinacea is one of the most important plants having various herbal preparations that purport to improve immune functioning (Brush et al., 2006). The diversity of phytochemicals in *Echinacea* sp. includes betain, sesquiterpenes, caryophylene, polyacetylene, rosmarinic acid, glycosides, echinacoside, chicoric acid, alkyl amides, and arabinogalactan-proteins (Hwang et al., 2004; Huntley et al., 2005).

Alkyl amides present in *Echinacea* sp. have reported immunomodulatory actions as they suppressed the ability of activated Jurkat T cells (key mediators of antiviral immunity) to produce IL-2 independently (Sasagawa et al., 2006; Woelkart et al., 2006). Arabinogalactan-protein and various other bioactive constituents of this plant were clearly identified as stimulators of both the classical and alternative pathway of complement activation and modulation involving inhibition or stimulation of immunity. These modules would also be interesting targets for drug development to ease the mucosal immune suppression and lessen the duration of upper respiratory tract infections (Alban et al., 2002; Bonifati and Kishore, 2007; Hall et al., 2007).

Echinacea preparations activate cellular immunity and stimulate phagocytosis of neutrophils both in vitro and in vivo. Stimulatory effect and immune-modulating action by *Echinacea* juice increase cellular immune parameters, e.g., the percentage of phagocyting cells, NBT-positive granulocytes and lysozyme level reported by Truchlinski et al. (2006). It effectively stimulates immunocompetence, and the plant extract behaves as hematinic agent, i.e., one can improve the quality of blood by increasing hemoglobin levels and the number of erythrocytes. Consequently, these effects result in improvements of oxygen transport that are further useful in improving the exercise physiology and performance (O'Neill et al., 2002).

Echinacea stimulates the immune system against bacterial and viral infections, and its extracts are widely used in prophylaxis and various other therapies (Bany et al., 2003; Gan et al., 2003). In contrary, South and Exon (2001) were on opinion that it holds immunosuppressive activity instead of immunostimulatory activity. However, it is able to stimulate innate immune responses including macrophages and natural killer cells regulated responses. Research carried out by Cundell et al. (2003) suggested that *Echinacea* affects both at mononuclear cell levels and circulating IL-2 levels. The recent advances has advocated the idea that combinatorial therapy, involving specific tumor cell immunization, followed by daily phytotherapy by *E. purpurea*, could lead to life span prolongation greater than immunization alone (Currier and Miller, 2002).

In brief, mode of action of *Echinacea* in enhancing immunity moves around activating and modulating cell-mediated immune responses and, indeed, as hematinic agents. In this context, the use of *E. purpurea* in diet-based therapies has the potential to enhance both humoral immune responses as well as innate immune responses.

Black Cumin (Nigella sativa)

Seeds of black cumin (*Nigella sativa*) have been used in herbal medicine for the treatment and prevention of a number of diseases, supplement to maintain good health and nutrition (Salem and Hossain, 2000; Sultan et al., 2009; Jafri et al., 2010; Abusnina et al., 2011). In the literature, numbers of evidences unveiled its anti-inflammatory and immunomodulatory effects (Tekeoglu et al., 2006; Salem et al., 2011). *N. sativa* displays its regulatory effects via inflammatory cells (Ozugurlu et al., 2005) by directly influences immune system and improves helper T cell (T4) to suppressor T cell (T8) ratio. It also improves natural killer cell activity. Moreover, due to the presence of antioxidant components, it protects central nervous compartments like brain and medulla spinalis tissues against autoimmune encephalomyelitis (Butt and Sultan, 2010).

The oral administration of black cumin essential oil, a phytochemicals rich fraction, holds significant analgesic effect as reflected from acetic acid-induced writhing, formalin, and light tail flick tests. Moreover, it can inhibit carrageenan-induced paw edema and croton oil-induced edema (Hajhashemi et al., 2004; Ghannadi et al., 2005). The therapeutic potential of black cumin essential oil for curing rheumatism is also validated (Mahmood et al., 2003). Later, Tekeoglu et al. (2006) confirmed that thymoquinone (active ingredient of essential oil) suppressed adjuvant-induced arthritis in rodent experimental modeling. Thymoquinone holds ability to inhibit the leukotrienes (LTs) formation by modulating 5-lipoxygenase and LTC4 synthase activity (Dijsselbloem et al., 2004; Mansour and Tornhamre, 2004; El Gazzar et al., 2006).

N. sativa especially its bioactive component thymoquinone holds anticancer perspectives (Banerjee et al., 2010; Sayed-Ahmed et al., 2010; Arafa et al., 2011). It was reported in one case study that they inhibited carcinogenesis in the postinitiation stage, and inhibition was associated with suppression of cell proliferation in colonic mucosa (Salim and Fukushima, 2003; Gali-Muhtasib et al., 2004). These fractions are effective in reducing the extent of oxidative stress and mammary carcinoma (Norwood et al., 2006; Velho-Pereira et al., 2011; Woo et al., 2011). Likewise, *N. sativa* and thymoquinone reduce the carcinogenic effects of 7, 12 di-methylbenz(a)anthracene and benzo(a)pyrene (B(a)P), respectively (Rooney and Ryan, 2005; Badary et al., 2007).

Another active ingredient of black cumin is α-hederin that possesses antitumor activity. It is effective against cultured SiHa cells, B16 melanoma cells, Lewis lung carcinoma, hepatocellular carcinoma (HepG2), and murine leukemia P388 cells (Swamy and Huat, 2003; Ng et al., 2011). The mode of action of this active ingredient includes production of reactive oxygen species (ROS) that inhibit DNA, RNA, and protein synthesis (Kumara and Huat, 2001).

Health benefits associated with *N. sativa* supplementation might be due to its antioxidant potential that improves natural defense system of the body. Further studies are urgently required to explore bystander effects of *N. sativa*, and its active ingredients and their possible use as therapeutic agents. The nutritional quality of black cumin can find its prospects of adding up in diet-based strategies to improve the human health (Sultan et al., 2009; Butt and Sultan, 2010).

Astragalus

In Chinese, Astragalus is known as Huang-qi and is written in 2000-year-old Shen Nong Ben Cao Jing and is still considered one of the superior tonics in traditional Chinese medicine (Yip and Kwan, 2006; Xu et al., 2007; Walsh et al., 2011). Astragalus membranaceus extract (AME) has therapeutic potential in regulating human immune functions and antitumor activities and may be applied in clinical practice for immunomodulation and cancer therapy (Wang et al., 2002). The immune boosting potential of Astragalus includes stimulation of immune cells against stimulus-response action (Brush et al., 2006). Furthermore, AME could promote the proliferation of human peripheral blood mononuclear cell (PBMC), elevates the tumor cell-killing activity of cytotoxic T-lymphocyte, strengthens the tumor cell phagocytosis and cytokines (TNF-alpha and IL-6) production from peripheral blood adherent monocytes and IgG production from same types of cells (Wang et al., 2002).

Wu et al. (2006) are of the view that auxiliary use of Astragalus injection (AI) is beneficial to the restoration of cellular immunity after serious abdominal trauma (SAT). AI also improves the immune function of congestive heart failure (CHF) patients. Mechanism behind its action involves increased CD4 level and CD4/CD8 ratio while it lowers the levels of IL-2R, IgG, and IgA (Liu et al., 2003). AI supplemented with chemotherapy could inhibit the development of cancer insurgence. It also decreases the adverse consequences of chemotherapy through elevation of immune function that, in turn, improves the quality of life in cancerous patients (Duan and Wang, 2002; Guo et al., 2004).

The aforementioned effects are attributed to the phytochemical profile of Astragalus like Astragalus polysaccharide (APS) and lectins (Yan et al., 2005). APS significantly induces NO production and iNOS transcription through the activation of nuclear factor-kappaB/Rel (Lee and Jeon, 2005). APS promotes lymphocyte proliferation and both humoral and cellular immune responses that would be expected to be new-type of immunopotentiator drugs (Kong et al., 2004). APS and astragalosides (AS) have strong promoting effects on macrophages that result in enhanced secretion of IL-l beta, IL-6, and TNF -alpha (Xu et al., 2007). Recently, Liu et al. (2011) suggested that APS might induce the differentiation of splenic dendritic cells (DCs) to CD11c(high)CD45RB(low) DCs followed by shifting of Th2 to Th1 with enhancement of T lymphocyte immune function. The differentiation of DCs was not associated with the inhibition of IL-10 production in CD11c(low)CD45RB(high) DCs. In addition, APS can induce increased TLR4 expression that can result in upregulation of innate immunity during mucosal bacterial infection (Yin et al., 2010). The same component effectively improves the quality of life in subjects with advanced nonsmall cell lung cancer (Guo et al., 2011).

In herbal medicines, it is common to use herbs in combination in the form of decoction. Such herbal remedies containing Astragalus are also important in improving phagocytic activity of peritoneal macrophage (Ning et al., 2005). The efforts should be directed toward exploration of herbal combinations that could be useful in enhancing the functionality of immune systems. These improvements will not only be helpful in chemotherapies but also immune related disorders.

Licorice (Glycyrrhiza glabra)

Herbal medication in the United States is a popular form of therapy and Licorice, the root extract of *Glycyrrhiza glabra*

is used as a medicine for various diseases (Abebe, 2003). It holds anti-inflammatory as well as antiallergic activities that are mainly attributed to its bioactive constituents, like glycyrrhizin, aglycone, beta-glycyrrhetinic acid (Kroes et al., 1997). In this context, Yang et al. (1990) characterized 10 flavonoids that are licochalcone A, isoschaftoside, schaftoside, liquiritin, isoviolanthin, violanthin, ononin, isoliquiritin, 4′,7-dihydroxyflavone, and licoflavone A. Medicinal importance of flavonoids present in *Glycyrrhiza* is not known yet, but some of them are reported to play vital roles in proper functionality of immune system.

Glycyrrhizin has anti-inflammatory and anti-allergic properties (Shibata, 2000), and of its mode of action is actually revolve around production of IL-10 and IL-12 in large amount. Glycyrrhizin holds dose-dependent priming effect on lipopolysaccharide (LPS)-induced IL-12 p40 and IL-12 p70 (heterodimer of p40 and p35) protein production by peritoneal macrophages (PM). IL-12, being monocyte/macrophage-derived cytokine it plays a prominent role in the development of T helper type 1 (Th1) cell-mediated immune responses (Dai et al., 2001).

Likewise, the reduction in cellular immunocompetence in the gamma-irradiated mice can be recovered with the treatment of glycyrrhizae and glycyrrhizic acid (active fractions of licorice). These fractions are found to be effective in enhancing the leukocyte count and the blastogenic responses of splenocytes to mitogens (Dorhoi et al., 2006). Glycyrrhizin is well known to have various immunemodulating and biological response-modifier activities. In one case study, SNMC (stronger neominophagen C), active component is glycyrrhizin improved the liver function (Abe et al., 2003).

Some scientific evidences support its use as immunostimulating agent that is involved in proper metabolisms and functioning of various important mediators in adaptive or acquired immunity. The claims mentioned in the earlier section suggested that *Glycyrrhiza glabra* could act as immunostimulating agent (Brush et al., 2006). However, the mechanisms underlying the anti-inflammatory activities of glycyrrhizin are still poorly understood.

St. John's Wort (Hypericum perforatum)

St. John's wort (*Hypericum perforatum*) is effective in wounds and injuries healing and holds anti-inflammatory and antioxidative activities and indeed acts as antidepressant agent. The characteristic metabolites of St John's wort are the photodynamic active plant pigment hypericin and the phloroglucin-derivative hyperforin. In addition, it contains many polyphenolic compounds, e.g., flavonoids and phenolic acids (Genovese et al., 2006).

Owing to the presence of these functional ingredients, it has high antioxidant potential that can reduced the peroxidative and chlorinating activity of human leukocyte MPO in concentration-dependent manner. The inhibition of MPO activity is further responsible for its anti-inflammatory potential (Pabuccuoglu et al., 2003). Moreover, Hypericum extract and its bioactive component, hyperforin, inhibit proliferation of T lymphocytes that is helpful in mediating inflammatory skin disorders (Wan et al., 2003). In another study, compounds like hyperguinone and hyperforin have strong potential in reducing oxygen production by polymorphonuclear cells (PMNs) after stimulation with N-formyl-methionyl-leucyl-phenylalanine (Heilmann et al., 2003).

Its potential as antidepressant agent has been highlighted in several studies. Proper functionality of immune system results in faster recovery from state of depression as immunological changes occur in depressed persons including increase in total number of white blood cells and in the numbers and percentages of neutrophils and lymphocytes. Enumeration of lymphocyte subsets also revealed that depression was associated with decreases in the number and percentage of lymphocytes and NK cells (Zorrilla et al., 2001). Immunomodulation is of clinical and practical consideration not only as targets for the treatment of depression but also to reduce the risk of development and progression of infectious diseases. Hypericum extract possesses antidepressant activity and is popular herbal supplement used to treat mild to moderate depression. It possesses serotonergic properties such as inhibition of serotonin (5-hydroxytryptamine; 5-HT) reuptake. Serotonergic pharmacotherapy is associated with amelioration of depression as well as increases in natural killer cell activity (Helgason et al., 2000). Postmarketing surveillance conducted by Rudolf and Zeller (2004) that included 4337 depressive patients suffered from mild to moderate depression shows that a single-dose therapy with highly dosed St. John's wort extract reduces severity of depression and significantly improving the quality of life.

St. John's wort no doubt possesses various health benefits, but questions arose about its efficiency. It interferes with certain drugs such as xenobiotics and reduces their efficiency. St. John's wort activates a nuclear receptor called pregnane X receptor (PXR). PXR is a ligand-activated transcription factor that induces a number of xenobiotic-metabolizing enzymes and transporters including cytochrome P4503A4 (CYP3A4) in humans. Because CYP3A4 alone metabolizes about 60% of all clinically relevant drugs, induction of CYP3A4 may result in the rapid elimination of these drugs and a consequent reduction in drug efficacy (Choudhuri and Valerio, 2005). Thus, care should be taken for its use and its responsibility of clinician to document use of herbs of botanicals to cure various maladies.

CONCLUSIONS

Use of herbals/botanicals has been gaining wide popularity in recent years in the United States as well as in other parts of the world, but the mechanism of action of most of these herbals/botanicals has not been subjected to thorough scientific investigations. Plants and botanicals hold therapeutic potential in clinical therapy to prevent or cure certain health risks with additional benefit of reduction in prevention cost. Indeed, findings suggested that these plants and their bioactive metabolites

are effective in balancing and proper functionality of immune system through various modules of immune modification like stimulation and suppression. Thus, current scenario demands form scientific research to explore the mode of actions of the selected botanicals/herbs. Nutritionists, physicians, and other health professionals can use such information effectively for the treatment of various ailments in the vulnerable segments. Overall, certain plants and botanicals can be utilized as an additional tool for disease prevention and risk management.

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