Immune system and antioxidants, especially those derived from Indian medicinal plants

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During the functioning of the immune system, such as in phagocytosis, reactive oxygen and nitrogen species are generated. If they are left unchecked they can affect the components of the immune system by inducing oxidative damage. This is more so in the elderly or during inflammation where there is excess generation of these reactive species than can be taken care of by the defenses in the form of antioxidants. Dietary supplementation with antioxidants may greatly help in such conditions. There are some indications of possible benefits of antioxidant supplementation. Natural compounds from medicinal plants having antioxidant and immunomodulatory activities have potential as therapeutic agents in this regard. Indian medicinal plants with these activities have been identified and their antioxidant and immunomodulatory effects reviewed. The possible future prospects in this regard are also outlined.

During the last 30 years immunology has witnessed an explosion of knowledge and experimental skills that has expanded our view of the immune system and means of searching for its structures and functions in an impressive way. The basic function of the immune system is to protect against foreign pathogens and infectious agents. This is achieved either through innate or natural immunological mechanisms which essentially serve as a short term first line of defense or through elaborate adaptive mechanisms which are highly specific, complex and are marked by diversity and memory. In both types of immunity, cells and molecules play important roles. While in natural or innate responses the cellular players are monocytes, macrophages, polymorphonuclear phagocytes and natural killer cells, in the adaptive immunity the pivotal role is played by two classes of lymphocytes, viz., T (thymus derived) and B (Bursa - or bone marrow derived) cells and these are assisted by accessory cells such as antigen presenting cells. Further, the cellular dichotomy in adaptive immune responses is also reflected in functional division of labour as the T cells serve as effectors of cell-mediated immune responses such as delayed type hypersensitivity and killing of virus infected cells and also as helpers for the production of highly specific proteins, called antibodies, by the B lymphocytes. These antibodies possess binding sites complementary to the antigen and are responsible for their removal from the system. The molecular constituents of the natural immune system are the complement proteins some of which help in opsonisation of foreign bacteria, lysozyme, defensin peptides, certain cytokines, etc.

While the natural immune mechanisms have been considered by and large non-specific with respect to the antigen, interesting new data have revealed pattern recognition by certain receptors such as toll receptors, mannose receptors etc. The adaptive immunity, on the other hand, relies heavily on the selection of antigen specific clones (clonal selection) and their expansion through activation, proliferation and differentiation. An overwhelming majority of T-cells recognize only peptide antigens in association with one’s own major histocompatibility (MHC) complex antigens on the antigen presenting cells, with the help of clonally distributed T-cell receptors (TCR). A few T cells may recognize non-peptide antigens in association with other cell surface molecules. T cells differentiate in inflammatory or cytotoxic sub-types. B cells, on the other hand, recognize any type of antigen (protein, lipid, carbohydrate etc.) with the help of clonally distributed B cell receptors which consist of surface bound antibody molecules in association with signal-transduction facilitating molecules and differentiate into antibody producing plasma cells. The repertoire of antigen specific receptors and antibodies is very diverse (>10^12 possible molecules of antibodies and even more for TCR) and they are assembled by processes of recombination and gene rearrangements.
(VDJ recombination) from multiple copies of different gene segments, junctional diversity, combinatorial diversity and somatic hypermutation (in case of BCR and antibodies)\(^1\)\(^2\).

Another set of molecules whose role has come to light in recent years is cytokines. These are elaborated by different types of cells, may act in autocrine, paracrine or endocrine manner, stimulate or regulate the growth and functions of nearby cells through specific receptors and are highly potent as they are effective in picomolar quantities. They are truly the language of communication between cells of the immune system. Some of them produce inflammation and some are chemotactic (chemokines) and these may facilitate innate immune reactions. Interleukins constitute one of the classes of cytokines.

In adaptive immunity, the activation of the antigen specific T or B cells by the specific antigen involves two signals. The first signal is the binding of the MHC associated epitope to its specific receptor on T cells or the direct binding of the epitope to B cells. The second is the binding of co-stimulatory molecules on the antigen presenting cells/helper T cells/antigen itself to their corresponding ligands on the T or B cells which have recognized the antigen. In absence of this second (co-stimulatory) signal the immunocompetent cell is rendered functionally inactive or anergic\(^2\). Some of the cytokines play an important role in the expansion of antigen activated T cells and B cells.

It is obvious that immune system has potential to go astray and harm the host himself. This can be in the form of allergy or autoimmunity. Yet another form—its basic rejection function e.g. transplant rejection, is a major hurdle in the effort to replace malfunctioning tissues or organs. All these situations demand regulation or modulation of immune responses. Likewise, one may need to boost or stimulate the immune system so as to facilitate effective vaccination against infective agents or to combat the deleterious aftermath of immunosuppressive radiotherapy. It is in the quest of suitable immunomodulators that natural products derived from medicinal plants provide a vast resource to draw upon.

Free radical generation in the immune system

During normal biochemical reactions in our body there is a generation of reactive oxygen and nitrogen species (ROS and RNS). This gets enhanced during patho-physiological conditions creating ‘oxidative stress’. During this phenomenon cellular constituents get altered resulting in various diseased states. This may be effectively neutralized, by enhancing the cellular defenses, in the form of antioxidants\(^6\)\(^1\)\(^1\). Reactive species are also generated during ‘phagocytosis’, a manifestation of innate immunity. The migration of leukocytes at an inflammatory site results in phagocytosis with the release of enzymes and cytokines from both macrophages and neutrophils. Phagocytosis stimulates various independent processes, especially “respiratory burst”, which results from activation of NADPH oxidase, an enzyme normally inactive in resting cells. The generation of ROS begins with the rapid uptake of oxygen and activation of NADPH oxidase and the production of the superoxide free radical (O\(_2^\cdot\)).

\[
2 \text{O}_2 + \text{NADPH oxidase} \rightarrow 2 \text{O}_2^\cdot + \text{NADP}^+ + \text{H}^+
\]

Superoxide is then rapidly converted to hydrogen peroxide (H\(_2\)O\(_2\)) by superoxide dismutase (SOD)

\[
2 \text{O}_2^\cdot + 2\text{H}^+ \rightarrow \text{H}_2\text{O}_2 + \text{O}_2
\]

These ROS can act by either of the two oxygen-dependent mechanisms resulting in the destruction of the microorganism or other foreign matter. The reactive species can also be generated by the myeloperoxidase-halide-H\(_2\)O\(_2\) system. The neutrophil cytoplasmic granules contain the enzyme myeloperoxidase (MPO). In presence of chloride ion, which is ubiquitous, hydrogen peroxide is converted to hypochlorous acid (HOCI), a potent oxidant and antimicrobial agent\(^2\)\(^2\).

\[
\text{Cl}^- + \text{H}_2\text{O}_2 + \text{H}^+ \rightarrow \text{MPO} \rightarrow \text{HOCI} + \text{H}_2\text{O}
\]

The MPO-independent mechanism, though not as important as the previous one, is still essential. ROS are generated from superoxide and H\(_2\)O\(_2\) produced via ‘respiratory burst’ by Fenton (A) and/or Haber-Weiss (B) reactions\(^2\)\(^3\).

(A) \[
\text{H}_2\text{O}_2 + \text{Fe}^{2+} \rightarrow \text{OH}^- + \text{OH}^- + \text{Fe}^{3+}
\]

(B) \[
\text{O}_2^\cdot + \text{H}_2\text{O}_2 \rightarrow \text{OH}^- + \text{OH}^- + \text{O}_2
\]

Reactive nitrogen species are also important. The free radical nitric oxide (NO), first described as endothelium-derived relaxation factor (EDRF), is produced from arginine by nitric oxide synthase (NOS)

\[
\text{L-Arg} + \text{O}_2 + \text{NADPH} \rightarrow \text{NO}^* + \text{citrulline}
\]

An inducible nitric oxide synthase (iNOS) is capable of continuously producing large amounts of NO. In activated immune cells, it acts as a ‘killer molecule’\(^2\)\(^4\).
Although the direct toxicity of NO is modest, it gets greatly increased when it reacts with superoxide to form peroxynitrite, a very strong oxidant.

$$\text{NO}^+ + \text{O}_2^{-} \rightarrow \text{ONOO}^-$$

Peroxynitrite can react with aromatic amino acid residues to form nitrotyrosine, which can lead to enzyme inactivation. It can also kill E. coli cells directly. However, nitric oxide is an important cytoxic effector molecule in defense against tumor cells, various protozoa, fungi, helminthes, and mycobacteria.

**Modulation by antioxidants**

Cellular components of immune system are rich in polyunsaturated fatty acids and these are very much susceptible to oxidative attack resulting in highly damaging lipid peroxidation. The peroxidation products formed are also highly cytoxic. This phenomenon may result in increased prostaglandin levels that are strong immunomodulators. More ROS and radical-derived products are also generated during the action of lipoxygenase and cyclooxygenase. The increased endogenous ROS present during ageing and various disease states affect integral membrane function, including the cell-mediated immune reaction involving phagocyte membrane NADPH oxidase that depends on the triggering of protein kinase C to produce superoxide. Depressed immunocompetence associated with ageing, various diseases, and poor nutrition may result from an excess generation of ROS due to the down-regulation of these two enzymes. Various antioxidants may prevent and/or correct immune dysfunction. These include the intracellular superoxide dismutase, catalase, glutathione peroxidase and glutathione besides the dietary or oral supplements in the form of vitamin C, vitamin E, beta-carotene, zinc and selenium.

Catalase inactivates H$_2$O$_2$ formed by SOD by converting it to water and oxygen. Glutathione peroxidase in the presence of glutathione, converts H$_2$O$_2$ to water. Zinc is an essential trace element, being a cofactor for about 200 human enzymes, including cytoplasmic antioxidant Cu-Zn SOD. Selenium is also an essential trace element and a cofactor for glutathione peroxidase. Vitamin E is an efficient lipid soluble antioxidant that functions as a 'chain breaker' during lipid peroxidation in cell membranes and various lipid particles including LDL. Vitamin C (ascorbic acid) is a water-soluble free radical scavenger and it also regenerates vitamin E in cell membranes in combination with glutathione or compounds capable of donating reducing equivalents and maintains LDL particle integrity. This vitamin is important in neutrophil functions. Beta-carotene, lycopene, lutein and other carotenoids function as important antioxidants and they quench singlet oxygen and peroxyl radicals. These compounds modulate host defense systems. Supplementation with other antioxidants, especially from natural sources, like medicinal plants will also greatly help in boosting the immune system.

Chronic inflammatory disorders such as rheumatoid arthritis, asthma, psoriasis and inflammatory bowel disease result in the production of several cytokines. These can recruit activated inflammatory and immune cells to the involved site and thereby may amplify and perpetuate the inflammatory process. The transcription factor NF-kB governs the expression of several genes some of which encode cytokines, chemokines, cell adhesion molecules, growth factors, and some acute phase proteins in health and in some diseases. The agents that activate this factor include ionizing radiation, H$_2$O$_2$, OH and ozone. Antioxidant prevention of NF-kB activation may be beneficial in suppressing toxic/septic shock, acute inflammatory responses, graft-vs-host reactions, and radiation damage. Hence immunomodulation can go hand in hand with antioxidant activity.

**Effect of immunomodulatory agents**

Immunomodulatory agents can enhance or inhibit the immunological responsiveness of an organism by interfering with its regulatory mechanisms. These may be antigen independent and may directly induce production of mediators and effector molecules by the immunocompetent cells. This type of antigen independent immunity is thus distinct from the one achieved by conventional immunization or by passive immunization using antibodies. The primary target of the immunomodulatory compounds is believed to be the macrophages, which play a key role in the generation of an immune response. It is known that the activated macrophages display not only increased phagocytosis and intra-cellular killing of pathogens by producing effector molecules like free radicals and nitric oxide, but also produce cytokines like tumor necrosis factor (TNF)-, and interleukin (IL)-1, IL-6, IL-12 etc. These cytokines may, in turn, activate T cells or NK cells.

The immunomodulatory agents may selectively activate either cell mediated or humoral immunity by
stimulating either T_{H1} or T_{H2} type of cell response, respectively. It is now realized that enhancement of T_{H1} type of T cell response may be of therapeutic significance for a variety of intracellular pathogens, like protozoan parasites or mycobacteria; whereas T_{H2} type of response may be beneficial against extracellular pathogens. Recent progress in our understanding of the immune system has also opened many possibilities for the selective immunosuppression. Selective immunosuppression by agents inhibiting signal transduction pathways for T cell activation, considered as a therapeutic strategy against graft rejection or autoimmune diseases, has already been demonstrated. Oxidative stress may influence the immune system either by hyperexcitation to cause autoimmune disorders or suppress it, resulting in higher susceptibility to infections. Excited mental states such as various forms of stress are now known to enhance the generation of excess free radicals in the biological systems and these free radicals lead to several disorders. Ayurvedic rasayana drugs may play a major role in handling these problems. However, their full potential still remains to be explored.

**Immunomodulation by natural products**

The modulation of immune response by using medicinal plant products as a possible therapeutic measure has become a subject of active scientific investigations. The basic concept has, however, existed in the ancient Vedic scripture, the Ayurveda, and has been practiced in Indian traditional medicine for many centuries. This ancient system of medicine that evolved in India thousands of years ago, probably represented the first record of scientific medicine in the history of the world. The story goes that the sages converged on the snow-clad slopes of the Himalayas to discuss ways to alleviate human misery. They, then approached the gods who taught them this elaborate science in a highly simplified way. The two main approaches to illness in Ayurveda are preventive and curative. The main reason for the sages' request to the gods was to avoid diseases and remain fit for a long time. Hence the major approach to therapy in Ayurveda is one which emphasizes prevention. The second approach is the curative one, i.e. that which attempts to alleviate diseases after they have occurred.

According to the Ayurvedic theory, a harmonious balance between three humors of the body viz. 'Vayu', 'Pitta' and 'Kaf' is needed for positive health; imbalance of these may cause disease(s). A significant part of Ayurvedic therapeutics is preventive in nature. It aims to promote positive health. An entire section of the Materia Medica of Ayurveda termed 'Rasayanas' is devoted to enhancement of body's resistance. The prescribed procedures include not only drugs but also daily routine including exercise, diet and nutrition besides mental attitude and discipline. One of the therapeutic strategies in Ayurvedic medicine is to increase body's natural resistance to the disease causing agent rather than directly neutralizing the agent itself. In practice, this is achieved by using extracts of various plant materials called rasayanas. The claims of the Rasayana therapy are far reaching: In terms of Charaka, by using Rasayana therapy, one obtains longevity, regains youth, gets sharp memory and intellect, freedom from diseases, lustrous complexion and the 'strength of a horse'. In order to understand the concept of Rasayana and draw parallels in contemporary science, we have to become familiar with some of the basic principles of Ayurveda, which is termed as 'science of life'. Credited with divine origins, this science rests on the dosh-dhatu-mala tripod. There are three doshas, namely vayu, pitta and kaf, each with specific characteristics and functions. There are seven dhamas or tissues. Formed by assimilation of dietary items, the tissues influence the characteristics and behaviour of the doshas. The dhatus are arranged in hierarchical fashion-rasadhatu being the primordial tissue. The rasadhatu has been likened to the plasma, although its exact interpretation remains elusive. The tissues receive nutrients from the rasadhatu, picking up the components they need. It is obvious then, that the quality of the rasadhatu is very important and also follows that it would influence the working of subsequent tissues. Drugs that improve the quality of this rasadhatu and thereby of the entire body are the Rasayanas. This term Rasayana has been split up into 'Rasa' and 'Ayana' meaning the path the Rasa takes. Several plants are described to have Rasayana properties. On ingesting the appropriate formulation of the Rasayana in the appropriate season by the appropriate person, the beneficial effects of Rasayana are seen.

Immunomodulation, especially using Rasayana drugs, could provide an alternative to conventional chemotherapy under the conditions of impaired immune responsiveness or following organ transplantation. This concept of using rasayanas for health, also gains a little more credibility, when we realize that herbal antioxidants concurrently exhibit significant
immunomodulatory activities, like in Shilajit and Chyawanprash Awaleha. Further, Indian medicinal plants are a rich source of substances that are claimed to induce paraimmunity, the non-specific immunomodulation of essentially granulocytes, macrophages, natural killer cells and complement functions. Similar immunomodulatory properties have also been reported in the natural products from various plants from other countries. Agarwal reported in the natural products from various plants reviewed Indian medicinal plants that have immunomodulation of essentially granulocytes, macrophages, antioxidant activities.

Medicinal plants with immunomodulatory and antioxidant activities

The following plants (with common/ayurvedic names in brackets) are known to have potent immunomodulatory and/or antioxidant activities: Aconitum heterophyllum (Ativisha), Allium sativum (Lahsuna), Allium cepa (Onion), Aloe vera (Ghrtitkumari), Andrographis paniculata (Kalmegh), Asparagus racemosus (Shatavari), Azadirachta indica (Nimba or Neem), Berberis aristata, Boswellia serrata, Corchorus olitorius, Curcuma longa (Haridra), Emblica officinalis (Amlaki), Glycyrrhiza glabra (Yashimadhu), Gmelina arborea (Gambhari), Hemidesmus indicus (Sharira), Holarrhena antidysenterica (Kutaja), Mangifera indica (Amra), Nyctanthes arbor-tristis, Oldenlandia corymbosa, Picrorhiza kurroa (Kattukarohini), Piper betel (Tamalpatra, Peepal), Piper longum (Pippali), Randia dumatorum (Madanphala), Sphaeranthus indicus (Mundi), Terminalia chebula, Tinospora cordifolia (Guduchi), Tylophora indica (Anant mool), Viscum album, Withania somnifera (Ashwagandha) and Zingiber aromaticum.

Details of data available on medicinal, immunomodulatory and antioxidant properties of some selected plants are listed below, in alphabetical order. Please also refer to Table 1 for an abridged version of the same.

Aloe vera (Ghrtitkumari)

This plant is extensively used in skin care preparations and other health products. Shamman et al. have studied the effects of Aloe vera gel extract supplementation on hepatocarcinogenesis induced by diethylnitrosamine and 2-acetylaminofluorene in male Sprague-Dawley rats. The severity of the carcinogenesis process was determined by measuring the increase in gamma-glutamyl transpeptidase and the placental form of glutathione S-transferase, histochemi-}

ally in situ and in plasma and liver fractions. Supplementation with Aloe vera gel extract in the diseased rats suppressed this increase significantly.

In traditional South-East Asian medicine the therapeutic value of the parenchymatous leaf-gel of Aloe vera for inflammation-based diseases was reported. Extracts from the leaf-gel contains glutathione peroxidase activity. The low molecular weight constituents of this extract inhibit the release of reactive oxygen species (ROS) by phorbol myristic acetate (PMA)-stimulated human polymorphonuclear leukocytes (PMN). These compounds also inhibit the ROS-dependent extracellular effects of PMN such as lysis of red blood cells. However, the capacity of the PMN to phagocytose and kill microorganisms is not affected. The inhibitory effect of these compounds has been shown to be the indirect result of the diminished availability of intracellular free Ca
d(42).

Allium sativum (Lahsuna, garlic) and Allium cepa (onion)

Garlic is another herb with proclaimed Rasayana effect in Ayurveda. Garlic and onion (Allium cepa) are among the oldest of all cultivated plants. Both have been used as medicinal agents for thousands of years and shown to have applications as antimicrobial, antithrombotic, antitumor, hypolipidaemic, antiarthritic and hypoglycemic agents. These effects have been linked to their influence on eicosanoid metabolism that influences immune functions in various ways. Nicotine, a major component of tobacco, is partly responsible for the development of atherosclerosis. The antioxidant effects of oils isolated from onion and garlic on nicotine-induced lipid peroxidation in rat tissues were studied. Lipid peroxidation was significantly increased in the tissues of nicotine-treated rats. Both the garlic oil and onion oil supplementation to nicotine-treated rats increased resistance to lipid peroxidation. With garlic oil or onion oil supplementation, nicotine-treated rats showed increased activities of antioxidant enzymes and increased concentrations of glutathione.

Through a series of investigations, garlic was also found to exert a diverse range of health promoting effects. It was found to enhance human immune functions, by stimulating peripheral blood mononuclear cells in vitro. Pre-treatment with garlic led to a protective effect on heart, liver and pancreas against isoproterenol induced damage. Garlic extract and S-allyl cysteine isolated from garlic were noted to protect
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<td>Aconitum heterophyllum</td>
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<td>Stimulate macrophages &amp; phagocytic activity</td>
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<td>Aconitum heterophyllum</td>
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<td>Inhibit ROS generation by stimulated PMN</td>
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<td>Allium sativum</td>
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<td>Allium sativum (allicin)</td>
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<td>Decreases lipid peroxidation</td>
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<tr>
<td>Glycyrrhiza glabra (livanoids)</td>
<td>For inflammatory diseases</td>
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<td>May have antioxidant effects</td>
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<tr>
<td>Glycyrrhiza glabra (glabridin)</td>
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<td>Glycyrrhiza glabra (shoot &amp; root polysaccharide fraction)</td>
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<td>Glycyrrhiza glabra (glabridin)</td>
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<td>Glycyrrhiza glabra (7 polyphenols)</td>
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<td>Holarrhena antidysenterica</td>
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<td>Immunomodulatory activity</td>
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<td>Inhibit SOD, catalase &amp; Gper</td>
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<td>Increases GSH-dependent enzymes Antioxidant effects</td>
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<tr>
<td>Inhibits lipid peroxidation</td>
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<tr>
<td>Inhibits LDL oxidation</td>
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<tr>
<td>Inhibits LDL oxidation &amp; Destruction of β-carotene</td>
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<tr>
<th>Plant/compound</th>
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<tr>
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<td>Immunomodulatory compounds</td>
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<td>Reduce effect of stressors</td>
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<td>Anti-hyperglycaemic effect</td>
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<td><em>Terminalia chebula</em></td>
<td>Reduce effect of stressors</td>
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<tr>
<td><em>Terminalia chebula</em></td>
<td>Anti-bacterial</td>
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<td><em>Terminalia beleira</em></td>
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<td><em>Tinospora cordifolia</em></td>
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<tr>
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<td><em>Tinospora cordifolia</em></td>
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<td>Chemotactic activity &amp; production of TNF-α inhibited</td>
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<td><em>Tinospora cordifolia</em></td>
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<td><em>Tinospora cordifolia</em></td>
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<td>Polyclonal B cell activators</td>
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<td><em>Tinospora cordifolia</em> (root)</td>
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<td>Anti-complementary activity</td>
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<td><em>Tinospora cordifolia</em> (root)</td>
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<td>Inhibits lipid peroxidation</td>
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<td><em>Zizyphus indica</em></td>
<td>Anti-hyperglycaemic effect</td>
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<td><em>Viscum album</em></td>
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<td><em>Withania somnifera</em></td>
<td>Anti-bacterial</td>
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<tr>
<td><em>Withania somnifera</em></td>
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<tr>
<td><em>Withania somnifera</em></td>
<td>Reduce effect of stressors</td>
<td>Synthesize prostaglandins</td>
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<td><em>Withania somnifera</em></td>
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<td>Chemotactic activity &amp; production of TNF-α inhibited</td>
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<tr>
<td><em>Withania somnifera</em></td>
<td>Anti-inflammatory</td>
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<td>Protects glutathione &amp; enzymes</td>
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<tr>
<td><em>Withania somnifera</em> (salicinosides withaferin A)</td>
<td>Anti-stress, anti-inflammatory</td>
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<td><em>Zingiber officinale</em></td>
<td>Anti-inflammatory, anti—cancer</td>
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<tr>
<td><em>Zinger officinale</em></td>
<td>Anti-stress, anti-inflammatory</td>
<td>—</td>
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pulmonary endothelial cells *in vitro* against hydrogen peroxide induced oxidative damage. Enhanced cell viability and an inhibition of lactate dehydrogenase and lipid peroxidation were also reported. Diallyl sulhide, a sulfur-containing volatile compound in garlic, exerts anticarcinogenic activity in various rodent tumor models. Allicin from garlic has been found to induce programmed cell death and therefore, arrest of proliferation in cancer cells. Such compounds can thus also exercise immunosuppressive effects.

**Andrographis paniculata** (Kalmegh)

This plant is credited with anti-snake venom activities. Prolonged survival was observed when extracts were administered to mice before or after treatment with different elapid or crotalid venoms. Ethanolic extract and purified diterpene andrographolides induced significant stimulation of antibody and delayed type hypersensitivity (DTH) response to sheep red blood cells in mice. The plant preparations also stimulated nonspecific immune responses in the animals as measured in terms of macrophage migration inhibition (MMI), phagocytosis of 14C-leucine labelled *Escherichia coli* and proliferation of splenic lymphocytes. The stimulation of both antigen specific and nonspecific immune responses was, however, of lower order with andrographolide than with the extract, suggesting thereby that substance(s) other than andrographolide present in the extract may also be contributing towards immunostimulation. In rats treated with *Andrographis paniculata* nees the activity of Ca2+-ATPase and Na+-K+ ATPase increased remarkably, and lipid peroxidation decreased significantly.

**Asparagus racemosus** (Shatavari)

The aqueous extract of whole plant of *Asparagus racemosus* administered orally to experimental animals, protected against exposure to a variety of biological, physical and chemical stresses. Studies on the mechanisms of action revealed that it produced immunostimulation. Treatment with *A. racemosus* significantly inhibited suppression of chemotactic activity and production of IL-1 and TNF-α by murine macrophages induced by 17 weeks of treatment with ochratoxin A (OTA). Thatte and Dahanuakar have studied the protective effects of aqueous extracts of *A. racemosus* and three other plants against the myelo-suppressive effects of single and double doses of cyclophosphamide in mice. Kamat et al. have examined the antioxidant effects of crude extract as well as purified polysaccharide fraction of *A. racemosus* against membrane damage induced in rat mitochondria and liver by free radicals generated during γ-irradiation. They found that these materials had potent antioxidant properties.

**Azadirachta indica** (Neem)

Neem has been reported to exert several therapeutic effects. Aqueous extract of Neem bark acted as immunomodulator, as assessed by alternative and classical C pathway activities, migration inhibition factor and chemiluminescence assay for phagocytic activity. There is a wide spectrum of infectious and non-infectious diseases against which preparations from *A. indica* are reported to be efficacious. Hence, it was suspected that the general immunopotentiating ability could be one of the mechanisms by which it ameliorates these disease conditions.

Using the haemolytic plaque assay technique, an aqueous extract of *A. indica* bark was shown to enhance the immune response of BALB/C mice to sheep red blood cells *in vivo*. Neem extracts/oil also have been found to have anti-fertility effect and were proposed to stimulate local immunity in the uterine wall.

In another study, the effects of feeding powdered dry leaves of Neem were investigated on humoral and cell mediated immune responses, in a flock of broilers which had survived an outbreak of infectious bursal disease (IBD). The treatment significantly enhanced the antibody titre against new castle disease virus antigen and also potentiated the inflammatory reactions to 1-chloro-2,4-dinitrobenzene in the skin contact sensitivity test. The water-soluble constituents of the alcoholic extract of Neem leaves exerted significant antiinflammatory activity in cotton pellet granuloma assay in rats. The extract also inhibited synthesis of DNA and RNA as well as reduced the level of lipid peroxide(s).

In yet another study, the animals were treated intraperitoneally with the neem oil. Peritoneal macrophages exhibited enhanced phagocytic activity and expression of MHC class-II antigens. Neem oil treatment also induced the production of gamma interferon. Spleen cells showed a significantly higher proliferative response to Con A and tetanus toxoid *in vitro* compared to that of the controls. Pretreatment with neem oil, however, did not augment...
the anti-TT antibody response. These data suggested that neem oil acts as a non-specific immunostimulant for cell-mediated immune (CMI) mechanisms. This was further supported by the observations that in vitro treatment of mouse splenocytes with neem leaf extract stimulated production of IL-2, IFN-γ and TNF-α reflecting activation of T_H1 type of T cell response. An antioxidant principle was isolated from Neem seed using high pressure liquid chromatography with a hydrophobic reverse-phase column. It was found to be a potent inhibitor of plant lipoxygenases. However, such data on mammalian systems are not yet available.

*Curcuma longa* (Turmeric)

Turmeric has several components with immunomodulatory and antioxidant properties. Selvam et al. have isolated turmeric anti-oxidant protein (TAP) from the aqueous extract of turmeric. The protein showed a concentration-dependent inhibitory effect on lipid peroxidation. Ca^{2+}-ATPase of rat brain homogenate was protected to nearly 50% of the initial activity from the lipid peroxidant induced inactivation by this protein. This protection of Ca^{2+}-ATPase activity was found to be associated with the prevention of loss of −SH groups.

Turmeric contains several small molecular weight components with antioxidant, medicinal and immunomodulatory activities. Natural curcuminoids, isolated from turmeric, were compared for their cytotoxic, tumour reducing and antioxidant activities. These compounds were also checked for their potential use as anti-promoters. The curcuminoids inhibited lipid peroxidation besides the production of superoxides and hydroxyl radical.

Curcumin, an antioxidant present in turmeric, has been shown to inhibit chemical carcinogenesis in animal models and has been shown to be an anti-inflammatory agent. It modulates glutathione (GSH)-linked detoxification mechanisms in rats. Singhal et al. have examined the effects of curcumin on GSH-linked enzymes in K562 human erythroleukemia cells. These results suggest that glutathione S-transferases (GST) play a major role in detoxification of lipid peroxidation products in K562 cells, and that these enzymes are modulated by curcumin. It is reported to inhibit chemically induced carcinogenesis in the skin, forestomach, and colon when it is administered during initiation and/or postinitiation stages.

The inhibition of apoptosis by curcumin in rat thymocytes was accompanied by partial suppression of AP-1 activity. Complete suppression of AP-1 activity was observed in Con A-treated, proliferating thymocytes. The capacity of curcumin to inhibit both cell growth and death strongly implies that these two biological processes share a common pathway at some point and that curcumin affects a common step, presumably involving modulation of the AP-1 transcription factor.

*Emblica officinalis* (Amlaki)

Fruits of Amlaki have been used in Ayurveda as a potent Rasayana and also for treatment of diseases of diverse etiology. It is an acknowledged rich source of Vitamin C. The role of vitamin C as a potent antioxidant has been well documented. Unlike other citrus fruits, Amlaki fruits have ascorbic acid conjugated to gallic acid and reducing sugars, forming a tannoid complex. Such complex of vitamin C is known to be more stable. It has been suggested that, due to an internal mechanism, tannoid complex liberates the nascent ascorbic acid into the body. The antioxidant activity of tannoid active principles of *E. officinalis* consisting of emblicanin A (37%), emblicanin B (33%), punigluconin (12%) and pedunculagin (14%), was investigated on the basis of their effects on rat brain frontal cortical and striatal concentrations of the oxidative free radical scavenging enzymes, superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX), and lipid peroxidation, in terms of thiobarbituric acid-reactive products. The active tannoids of *E. officinalis* (EOT), induced an increase in both frontal cortical and striatal SOD, CAT and GPX activity, with concomitant decrease in lipid peroxidation in these brain areas when administered once daily for 7 days. Acute single administration of EOT had insignificant effects. The results indicate that the antioxidant activity of *E. officinalis* may reside in the tannoids which have vitamin C-like properties, rather than vitamin C itself.

The extract obtained from *E. officinalis* fruits also inhibited lipid peroxidation. The extract is traditionally used to treat inflammatory diseases. Alcoholic extract of *E. officinalis*, was found to show potent bactericidal activity.

*Glycyrrhiza glabra* (Yashtimadhu)

Glabridin, an isoflavon isolated from *Glycyrrhiza glabra* (licorice) root, and its derivatives have been reported to inhibit the oxidation of LDL induced by copper ions or mediated by macrophages. The antioxidant effect of glabridin on LDL oxidation appears
to reside mainly in the 2' hydroxyl moiety of the isoflavon. The effect of the consumption of glabridin, on the susceptibility of LDL to oxidation was also studied in atherosclerotic apolipoprotein E deficient mice. The in vivo and in vitro inhibitory activities may be related to the absorption or binding of glabridin to the LDL particle and subsequent protection of LDL from oxidation and by protecting LDL associated carotenoids.

The study by Vaya et al. also analyzed the antioxidative properties of natural compounds from the root of licorice toward LDL oxidation. Seven constituents, with antioxidant capacity were isolated from G. glabra. The isolated compounds were identified as the isoflavans hispaglabridin A, hispaglabridin B, glabridin, and 4'-O-methylglabridin, the two chalcones, isoprenylechalcone derivative and isoliquiritigenin, and the isoflavone, formononetin. Among these compounds, glabridin constituted the major amount in the crude extract (11.6%, w/w) as detected by HPLC analysis. The antioxidative capacities of the isolated compounds (1-7) were tested against beta-carotene destruction and LDL oxidation. These results suggest that the first 6 constituents were very potent antioxidants with glabridin being the most abundant and potent antioxidant. As LDL oxidation is a key event in the formation of the early atherosclerotic lesion, the use of these natural antioxidants may prove beneficial to attenuate atherosclerosis.

Nose et al. have investigated the effects of crude polysaccharide fractions obtained from the shoot and hairy root of Glycyrrhiza sp. grown under aseptic conditions on murine peritoneal macrophage function. All crude polysaccharide fractions induced nitric oxide production by murine peritoneal macrophages in vitro.

From the air-dried roots of G. glabra L. (Leguminosae) five new flavonoid compounds named glucoliquirit apioside (a flavonone bisdesmoside), prenylicoflavone A (a bisprenylflavone), shiinflavone (a prenylated pyranoflavonone), shinpterocarpin and 1-methoxyphasellin (both pyranoptercarpsins), were isolated together with 8 known saponins, 7 known flavonoid glycosides, and 11 flavonoids. The structures of the new potent antioxidant compounds have been elucidated on the basis of their chemical and physicochemical properties.

Hemidesmus indicus (Shariba)

Hemidesmus indicus is known for its use in the treatment for snakebites. An organic acid, isolated and purified from the root extract possessed viper venom inhibitory activity. The compound (designated H-RVIF) was isolated by solvent extraction, silica gel column chromatography and thin layer chromatography, and was homogeneous in nature. The adjuvant effect of 2-hydroxy-4-methoxy benzoic acid from H. indicus in the generation of anti venom antiserum was explored by Alam et al. The antiserum raised in presence of the compound showed the higher neutralization capacity (lethal and hemorrhage) when compared with the antiserum raised with venom alone. The pure compound potentiated the neutralization of the lethal action of venom by commercial equine polyvalent snake venom antiserum in experimental models. The same authors have also shown that it possessed potent anti-inflammatory, antipyretic and antioxidant properties. The compound effectively neutralized inflammation induced by Viper russelli venom in male albino mice. It also neutralized free radical formation as estimated by TBARS and enhanced the activity of antioxidant enzyme superoxide dismutase. The anti-snake venom activity of this compound may at least be partly mediated through the above physiological process.

Nyctanthes arbor-tristis (Harsingar)

Nyctanthes arbor-tristis L. (Oleaceae), a plant widely used in the traditional medicinal systems of India, has been reported to possess hepatoprotective, antileishmanial, antiviral and antifungal activities. Strong stimulation of antigen specific and non-specific immunity, as evidenced by increases in humoral and delayed type hypersensitivity (DTH) response to sheep red blood cells (SRBC) and increased macrophage migration inhibition (MMI), has been demonstrated in mice fed 50% ethanolic extract of seeds, flowers and leaves of this plant. Maximum activity was found in the seeds in which the active principle(s) appear to be mainly associated with lipids. The immunostimulant substance(s) found in N. arbor-tristis are likely to play an important role in its antiamoebic, antileishmanial, antiviral and certain other activities.

The effect of the water soluble fraction of the ethanol extract of N. arbor-tristis on TNF-α level in the plasma of arthritic and soluble protein A (SpA)-treated BALB/C mice has been studied. Oral administration of this fraction in arthritic mice showed a consistent depletion of TNF-α from the host plasma. A similar depletion of TNF-α in the plasma of SpA-
treated mice has been observed. The extract also reduced plasma interferon-gamma level but the plasma IgM and IgG levels were not affected.

*Piper longum* (Pippali)

Pippali rasayana (PR), an Ayurvedic herbal medicine, prepared from *Piper longum* (Pippali) and *Butea monosperma* (Palash), and prescribed for the treatment of chronic dysentery and worm infestations was tested for anti-jaundice and immune-stimulatory activity in mice, infected with *Giardia lamblia* trophozoites. It produced up to 98% recovery from the infection. The rasayana had no killing effect on the parasite in vitro. It significantly increased macrophage migration inhibition and phagocytic activity, thus indicating activation of T cells. Enhancement of host resistance as a consequence could be one of the possible mechanisms contributing towards the recovery of animals from the giardial infection after the treatment with this rasayana.

*Tinospora cordifolia* (Guduchi)

*Tinospora cordifolia* is a plant widely used in Ayurveda and is known as Amrita/Gulvel/Gulancha/Guduchi. *T. cordifolia* is claimed to be useful, in Ayurvedic literature, for treatment of jaundice, skin diseases, diabetes, anaemia, emaciation and infections. 'Guduchi satwa', a starchy water extract prepared from it is recommended for its bitter principle and is used as a tonic vitalizer, anti-diabetic, diuretic, anti-phlogistic and anti-allergic agent. On oral feeding, aqueous extracts of *T. cordifolia* exhibited anti-bacterial, anti-phlogistic, analgesic and anti-pyretic activities. It was reported to mediate augmentation of neutrophils and activation of macrophages in abdominal sepsis infection and in cyclophosphamide mediated leukaemia/neutropenia. Other related studies also show the medicinal properties of *T. cordifolia*.

Dahanukar and co-workers have examined various beneficial properties of *T. cordifolia* and Rege et al. have reported that *T. cordifolia* provides protection against experimental infections in mice. Pre-treatment with *T. cordifolia* reduced mortality in mice injected with *E. coli* intraperitoneally, abdominal sepsis and candida infection. They have also shown that the plant extract specifically stimulates macrophages and enhanced their phagocytic activity and intracellular killing activity. Immunosuppression associated with deranged hepatic function and sepsis results in poor surgical outcome in obstructive jaundice. *T. cordifolia* was reported to improve surgical outcome by strengthening host defenses. The protection offered by *T. cordifolia* against stress induced gastric mucosal damage was lost if macrophage activity was blocked. Recent data from this group suggest that *T. cordifolia* may induce adaptation.

An in vitro assay technique was used to determine the phagocytic and microbicidal activity of a monocyte-macrophage cell line using *Candida* species as test organisms. The degree of activation of macrophages induced by metronidazole and *T. cordifolia* was compared with that induced by a standard immunomodulator muramyl-dipeptide. All the three test agents increased the phagocytic and killing capacity of macrophages in a dose dependent manner up to a certain dose, beyond which either of these activities plateaued or decreased.

The effect of dry stem crude extracts of *T. cordifolia* and another locally available species *T. malabarica* on lymphocytes of mice and humans was examined by Sainis and coworkers. Taking mitogenic activity as a bioassay purification of the active principles was attempted. The data obtained show that dry stem crude extracts of *T. cordifolia* and *T. malabarica* contain polyclonal B cell activator(s) that are polysaccharides in nature. Thus in addition to macrophages and PMN, B lymphocytes can also serve as targets for action of *Tinospora* extract. Partial structural characterization of these polysaccharides has been carried out. The mitogenic activity was very much more pronounced against mouse B cells compared to human B cells. Further, after treatment of mice with the purified component G1-4A, both humoral response to SRBC, and T cell response to protein antigen and mitogen in vitro were enhanced. Studies on the binding of this immunomodulator showed that in addition to a subpopulation of B cells a vast majority of murine macrophages had binding sites for it.

Two active principles of *T. cordifolia* were found to possess anticomplementary and immunomodulatory activities. Syringin and cordiol inhibited the in vitro haemolysis of antibody-coated sheep erythrocytes by guinea pig serum. The reduced haemolysis was attributed to the inhibition of the C3-convertase of the classical complement pathway. The compounds also gave rise to significant increases in IgG antibodies in serum and cell-mediated immunity.

Antioxidant properties of various components from *T. cordifolia* have been reported. Oral administration of an aqueous *T. cordifolia* root extract for 6 weeks resulted in a decrease in the levels of plasma lipid
peroxidation, ceruloplasmin and alpha-tocopherol in alloxan diabetic rats\textsuperscript{39}. The root extract also caused an increase in the levels of glutathione and vitamin C in alloxan diabetes. Transina a herbal preparation containing \textit{T. cordifolia} induced a dose-related decrease in streptozotocin (STZ) induced hyperglycemia and attenuation of STZ induced decrease in islet SOD activity\textsuperscript{100}. This indicates that the anti-hyperglycemic effect of transina may be due to free radical scavenging activity. The hyperglycemic activity of STZ may be the consequence of decrease in islet SOD activity leading to the accumulation of free radicals in islet beta-cells.

Extract of \textit{T. cordifolia} has been shown to inhibit the lipid peroxidation and formation of superoxide, and hydroxyl radicals \textit{in vitro}\textsuperscript{101}. Administration of the extract partially reduced the elevated lipid peroxides in serum. \textit{Tinospora} extract may be useful in reducing the chemotoxicity induced by free radical forming chemicals like cyclophosphamide. Several glycosides with potential antioxidant activity were also isolated, as polyacetates, from the \textit{n-BuOH} fraction of the \textit{T. cordifolia} stems. The structures of three new nortriterpene, furan glycosides cordifoliside A, B and C have been established by \textit{1D} and \textit{2D} NMR spectroscopy\textsuperscript{102}. Other related compounds, with potential beneficial effects, were also isolated\textsuperscript{103,104}. Further studies need to be carried out for providing evidence for the antioxidant effect of these compounds.

\textbf{Withania somnifera (Ashwagandha)}

\textit{Withania somnifera} effectively inhibits inflammatory process. It can also bring about a specific reduction in a-2 macroglobulin synthesis, unlike the conventionally used NSAIDS and has significant antioxidant activity. It gave significant protection against depletion of glutathione peroxidase and glutathione induced by exposure to UV-300 nm. The granuloma formation inhibiting activity of various fractions of an extract of the aerial parts of \textit{W. somnifera} was established using subcutaneous cotton-pellet implantation in rats\textsuperscript{105}. Antiinflammatory activity was attributed to the high content of biologically active steroids in the plant, of which withaferin A (a steroidal lactone) is known to be a major component. This compound also has radiosensitizing effect in cancer cells\textsuperscript{106}.

The aqueous suspension of the root extract \textit{W. somnifera} was evaluated for its effect on lipid peroxidation in lipopolysaccharide-treated animals\textsuperscript{107}. Simultaneous oral administration of ashwagandha (100 mg/kg) prevented the rise in lipid peroxidation in rabbits and mice. The antiinflammatory property of root powder has been shown by Begum \textit{et al.}\textsuperscript{108} in a rat model of arthritis.

Antioxidant activity of active principles of \textit{W. somnifera}, consisting of equimolar concentrations of siddhuradiosides VII-X and withaferin A, was investigated for their effects on rat brain frontal cortical and striatal concentrations of superoxide dismutase, catalase and glutathione peroxidase\textsuperscript{108}. Active glycowithanolides, administered once daily for 21 days, induced a dose-related increase in SOD, CAT and GPX activity in frontal cortex and striatum, which was statistically significant on days 14 and 21. At the lower dose of WSG on GPX, the effect was evident only on day 21 (ref. 109). Antioxidant effect of active principles of \textit{W. somnifera} may explain, at least in part, the reported antistress, immunomodulatory, cognition-facilitating, anti-inflammatory and anti-ageing effects produced by them in experimental animals, and in clinical situations\textsuperscript{110}.

\textbf{Zingiber officinale}

Plants of ginger family (Zingiberaceae) have been frequently and widely used as spices and also, in traditional oriental medicine\textsuperscript{31}. Yakuchinone A [1-(4'-hydroxy-3'-methoxyphenyl)-7-phenyl-3-heptanone] and yakuchinone B [1-(4'-hydroxy-3'-methoxyphenyl)-7-phenylhept-1-en-3-one] present in \textit{Alpinia oxyphylla} Miquel (Zingiberaceae) have inhibitory effects on phorbol ester-induced inflammation and skin carcinogenesis in mice, and oxidative stress \textit{in vitro}. These diarylheptanoids suppress phorbol ester-induced activation of ornithine decarboxylase and production of tumor necrosis factor-alpha or interleukin-1 alpha and their mRNA expression. They also nullified the phorbol ester-stimulated induction of activator protein-1 (AP-1) in cultured human promyelocytic leukemia (HL-60) cells. In addition, both yakuchinone A and B induced apoptotic death in HL-60 cells. Ginger (\textit{Zingiber officinale} Roscoe, Zingiberaceae) contains such pungent ingredients as [6]-gingerol and [6]-paradol, which also have anti-tumor promotional and antiproliferative effects\textsuperscript{29}.

\textbf{Nitric oxide and immunomodulation}

Recent studies have shown that in addition to reactive oxygen intermediates, macrophages may also produce reactive nitrogen intermediates (RNI), especially nitric oxide (NO), as effector molecules. NO is a labile and highly reactive gas and acts as cytotoxic/
cytostatic effector molecule against tumor cells and various intracellular and extracellular pathogens. One of the possible therapeutic strategies against tumours and infections, could be to upregulate or restore production of NO in tumor-bearing or parasitized hosts. Studies by Upadhyay indicate that modulation of NO production using plant derived immunomodulators could provide a cost effective and less toxic alternative to chemotherapy against tumor and infections or such molecules can be used in conjunction with anti-tumor or antibiotic drugs for a synergistic action.

Conclusions and future prospects

Considering the entire array of components involved in the immune system, it presents as a complex, but precisely interwoven network of biochemical mechanisms. It is vulnerable to oxidative stress from reactive oxygen and nitrogen species, which have the potential to damage various biological molecules produced during the functioning of the immune system. During certain diseased states as well as during ageing there is a need for boosting the antioxidant availability and thereby potentiating the immune mechanisms. In this context immunomodulators having antioxidant abilities, especially derived from Indian medicinal plants have considerable potential. In this review we have identified certain extracts/compounds from several medicinal plants which display both immunomodulating and antioxidant effects.

These immunomodulating compounds can also act as adjuvants, or inhibit the immune response. The low molecular weight immunosuppressants can inhibit cell proliferation or may bring about selective inhibition of events in signal transduction pathways. The immunostimulants may have potential applications following radiotherapy and in ageing.

There is a lot more to be done to understand the mechanisms behind these effects as well as to employ them as possible therapeutic agents. A systematic approach is needed for identifying active constituents from different medicinal plants and their multifarious effects, both toxic and beneficial, using modern techniques. A multidisciplinary approach will be more rewarding in this direction. Since Rasayana drugs are capable of influencing the biological systems in a multidimensional manner, it is equally worthwhile to examine them for other effects, such as anti-stress, adaptogenic and anti-ageing activities. The task is quite demanding since each plant in the Rasayana category contains a plethora of constituents with similar, synergistic or antagonistic properties.

Acknowledgement

Thanks are due to Ms. Jai C. Tilak for help in the preparation of manuscript.

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