

Notes to Editor

Immunity and the role of selected plants as immunomodulators: A Review

Abstract: The immune system is an incredible constellation of cells, tissues, organs and molecules that provides protection against a wide spectrum of pathogens and particles keeping us healthy within the challenging microbial environment.

Immune system is capable of neutralizing most of the pathogenic attacks without leaving any trace of disease or abnormality in normal functionality of the body. However, some pathogens are strong enough to cause infectious diseases. In the battle against pathogens the immune system adopts two distinct pathways namely, innate immunity and adaptive immunity. Nonspecific innate immunity elicits the same generic response regardless of the pathogen and it mediated by key phagocytic cells. Adaptive immunity elicits pathogen specific immune responses carrying immunological memory.

In therapeutic approaches the immune system is fine-tuned with the aid of external agents called immunomodulators. Immunomodulation refers to any alterations in the immune system involving induction, expression, amplification or inhibition of any part or phase in the immune response in order to achieve a better immune response. In clinical perspective immunomodulators appear in three categories including Immuno adjuvants, immune stimulants, and immune suppressants. A diverse array of synthetic and natural agents is applied in therapies. Plants are a rich source of bioactive substance exerting their effects on almost all the systems of the body while playing as immunomodulators. Thus the present review is focused on the immunomodulating activity of various plants in experimental perspective

Keywords: Immune system, Immunomodulators, phytochemicals

Host defense mechanisms against infections

Within the environment a wide spectrum of organisms carries the potential to infect us and, if they do so, can cause us harm in many different ways. As hosts for these aggressors animals are equipped with sophisticated host defense mechanisms referred to as immunity in order to neutralize these potential threats. Bacteria, Viruses, Fungi and Parasites may act as potential pathogens. In terms of infection capability primary pathogens can infect host at its presence or activity and opportunistic pathogens usually occur with the host and tend attack only when the host defense become weak (Ryan & Ray; 2004). In order to stay safe from challenging microbes animals are armed with a sophisticated defense system known as the immune system. Architecture of immune system is

summarized in figure 1. Within the territory of microbes in astronomical numbers vertebrates are protected by two systems of immunity as innate and adaptive (Owen, et al., 2013).

Innate immunity

Innate immunity constructs the first line of the defenses against infection that is ready for immediate activation prior to attack by a pathogen. The innate immune system is armed with physical (skin and mucous membranes), chemical (pH and microcidal molecules), and biological barriers (Commensal microbes colonizing the skin and gastrointestinal tract) in order to eliminate the threats at the origin (Thao, et al., 2008; Playfair & Chain, 2013).

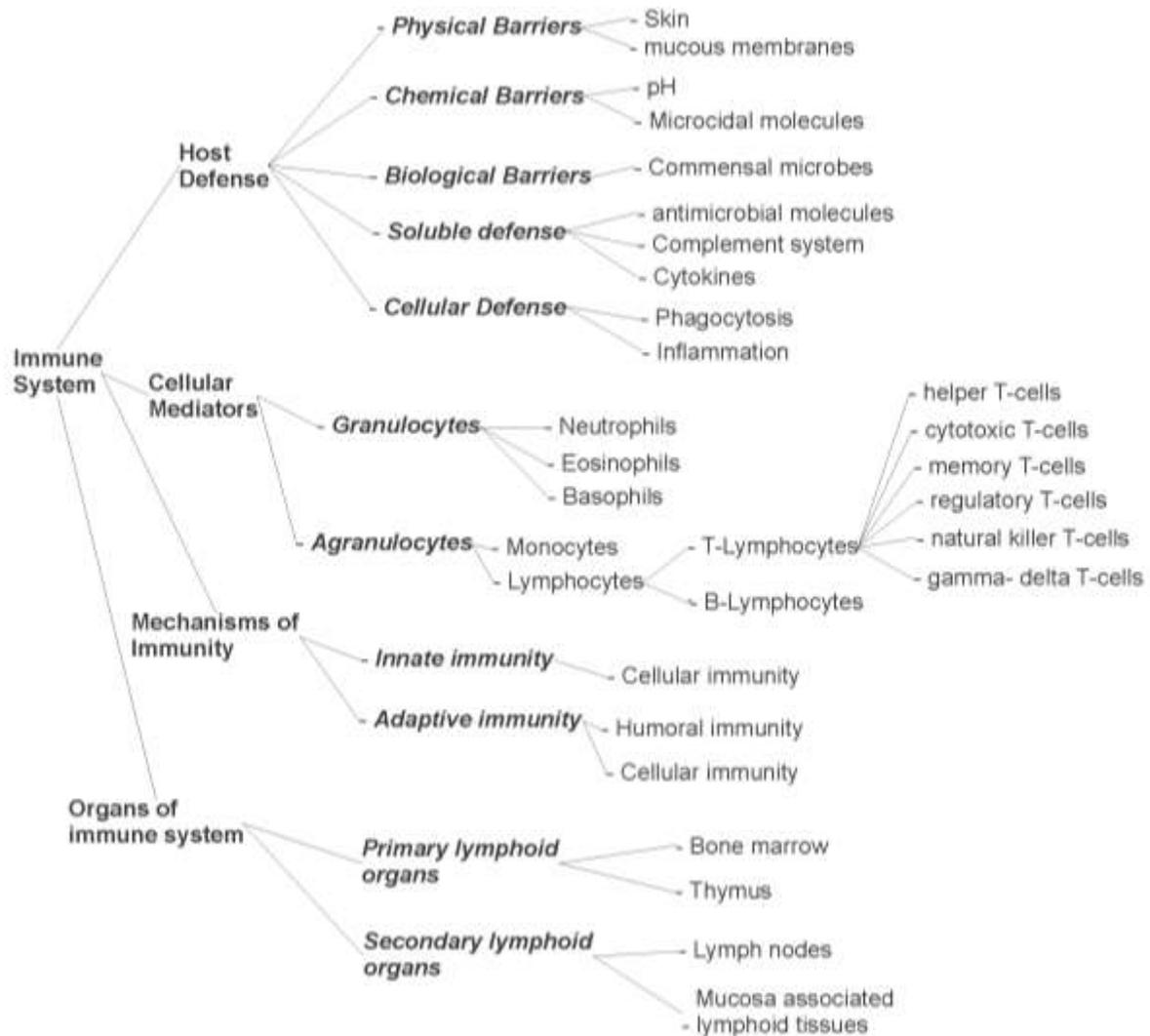


Figure 1: Overview of Immune system

Innate immune function

If infectious agents are skilled to cross the first line of defense or the mechanical, chemical, and biological barriers the second line of defense the innate immune system retains in an activated or nearly activated state to battle the infection. Innate immune system undergoes identification of pathogens, activation of phagocytic cells, localized protective response known as inflammation in order to eliminate the pathogens rapidly. Phagocytosis, Oxygen independent and dependent killing and inflammation are the key mechanisms in innate immunity. In contrast to the adaptive immune response the innate immune response is rapid and nonspecific (Thao, et al., 2008)

Adaptive immunity

In contrast to the innate immune system the adaptive immune system or third line of defense is characterized by diversity, antigen specificity and immunological memory. The innate immune system is required to trigger the adaptive immune response against a particular antigen. In turn the adaptive immune can recognize targets within a wide spectrum. Adaptive immune system carries two distinct branches humoral immunity and cell mediated immunity.

Humoral immunity

Antibodies, the key elements in humoral immunity are the major fraction of serum proteins and often called immunoglobulin. Plasma cells (differentiated B

lymphocytes) produce antigen specific antibodies upon activation. Antibodies can specifically bind to antigens on microbial cells or molecules such as toxins leading to opsonization (Playfair & Chain, 2013). Immunoglobulin family is occupied by five distinct classes including IgM, IgG, IgD, IgA and IgE (Raven, et al., 2014).

Cell mediated immunity

T (Thymus cells) lymphocytes and B (Bursa derived cells) lymphocytes act as the key cellular mediators of adaptive immunity (Alberts, et al., 2002). The way T and B lymphocyte recognizes its antigen is critically different. B cells recognize their cognate antigen in its native form. They can identify free (soluble) antigens in the blood or lymph using their surface receptor. In contrast, T cells recognize their cognate antigen via T cell receptor in a processed form such as a protein fragment presented by an antigen presenting cell on its MHC molecule. B cells mainly engaged in humoral branch while T cells handle cellular branch of adaptive response (Kenneth, et al., 2012).

Cellular mediators of immunity

White blood cells

White blood cells or leukocytes act as the key cellular mediator of the immune system. Based on the presence of granules in the cytoplasm leukocytes are characterized as granulocytes and agranulocytes (LAFleur, 2008).

Granulocytes/ (Polymorphonuclear leukocytes)

Granulocytes are characterized by polymorphic nuclei and differentially staining granules in cytoplasm under light microscopy. The granules are membrane bound containers of enzymes that facilitate lysis of foreign invaders. Neutrophils, eosinophils and basophils are the major constituents of the family (Witko, et al., 2000).

Neutrophils

Neutrophils are the major occupant of WBC family in mammals and play an essential role in the innate immune response. They are short lived and highly mobile (Witko, et al., 2000; Nathan & Carl, 2006). Neutrophils are the first responders to the foreign challenges and reach the affected site within minutes and act as the hallmark of acute inflammation (Cohen, et al., 2002).

Neutrophils carry a variety of specific cell surface receptors for chemokines, cytokines, leptins and proteins, and Fc receptors for opsonin. Chemokine receptors capable of detecting chemical gradients of chemotactic molecules such as IL-8, C5a, fMLP, and Leukotriene B4 usually produced by resident cells in tissues in response to infection and lead neutrophils to the site of infection. The migration of neutrophils is facilitated by surface adhesion molecules that can be expressed upon stimulation by cytokines. Opsonin receptors enable the cells to destroy opsonized or antibody coated pathogenic targets (Cassatella, 2010).

In addition to phagocytosis neutrophils also attack microbes by releasing soluble anti-microbial including granule proteins, and generating neutrophil extracellular traps (NETs) comprised of chromatin and serine proteases that trap and kill microbes extracellularly (Hickey & Kubes, 2009; Clark, et al., 2007).

Eosinophils

Same as neutrophils, eosinophils are mobile phagocytic cells having the ability to migrate from the blood into the tissue spaces. Although the phagocytic role of eosinophils is significantly less important in contrast with neutrophils they play an important role in the killing of multicellular parasites (Owen, et al., 2013). The granules in mature eosinophils contain several proteins including major basic protein, eosinophil cationic protein, eosinophil derived neurotoxin and eosinophil peroxidase (Male, et al., 2007). Major basic protein, eosinophil peroxidase, and eosinophil cationic protein exert cytotoxic effects on tissues (Rothenberg & Hogan, 2006). Eosinophil cationic protein and eosinophil-derived neurotoxin are ribonucleases with potent antiviral activity. The toxic pores created by eosinophil cationic protein on target cell membranes allow other cytotoxic molecules to enter the cell (Morgan & Costello, 2005). Reactive oxygen species nitrogen intermediates developed by eosinophil peroxidase promote oxidative stress in the target causing cell death by apoptosis and necrosis (Rothenberg & Hogan, 2006). Upon activation eosinophils release these granules in order to kill pathogens that are too large to be phagocytosed. Eosinophils are therefore thought to play a specialized role in immunity to parasitic worms using this mechanism (Male et al., 2007).

Basophils

Basophils are non-phagocytic granulocytes that function by releasing pharmacologically active substances from their cytoplasmic granules. These substances play a major role in certain allergic responses (Owen et al., 2013).

Agranulocytes/ Mononuclear leukocytes

Agranulocytes are characterized by single lobed nuclei and apparent absence of cytoplasmic granules. Lymphocytes, monocytes and macrophages (differentiated monocytes) are the major occupants of the agranulocyte family (Gartner & Hiatt, 2007).

Monocytes

Monocytes are the largest cell type of WBC and play an important role in innate immune response. Monocytes in circulation migrate into tissues and undergo differentiation into resident macrophages and dendritic cells in order to maintain the level of these cells within the tissues under normal states. Migration and differentiation occur at higher rates in response to signals of inflammation in order to elicit the immune attack (Swirski, et al., 2009).

Macrophages

Macrophages are phagocytic cells derived from monocytes and act a key mediator in both innate and adaptive immune responses. Macrophages also contribute the removal of aged cells, dead cells and cellular debris through phagocytosis (Owen et al., 2013).

Macrophage-like cells serve different functions in different tissues and are named based on their location and collectively construct the mononuclear phagocytic system. Alveolar macrophages in the lung, Histiocytes in connective tissues, Kupffer cells in the liver, Mesangial cells in the kidney, Microglial cells in the brain and Osteoclasts in bones are some players of the mononuclear phagocytic system (Owen, et al., 2013).

In the presence of antigens different stimuli result activation of macrophages and the activity may be augmented by other inflammatory mediators such as inflammatory cytokines, components of bacterial cell walls. In contrast with resting macrophages activation results up regulation of phagocytic activity, secretion of inflammatory mediators, expression of MHC class II molecules and secretion of various cytotoxic

proteins capable of eliminating a broad range of targets such as pathogens, virus-infected cells, tumor cells, and intracellular bacteria. Enhanced expression of MHC proteins enables the macrophages to function as effective APCs (Playfair & Chain, 2013).

In addition Macrophages can metabolize the amino acid arginine to form either a killer molecule (Nitric Oxide) or a repair molecule (Ornithine). The killer phenotype known as M1 Macrophages are activated by LPS and IFN- γ , and secreted in high levels of IL-12 and low levels of IL-10. The repair phenotype M2 mediate repair activities such as wound healing and tissue repair and they produce high levels of IL-10, TGF- β and low levels of IL-12 (Mills, 2012; Owen et al., 2013).

Dendritic cells

Dendritic cells are characterized by long membrane extensions that resemble the dendrites of nerve cells and get their origin from both myeloid and lymphoid lineages.

Hematopoietic stem cells give rise to four different types of dendritic cells including Langerhans cells, interstitial dendritic cells, myeloid cells and lymphoid dendritic cells via different pathways. All the four types express MHC Class II molecules and co stimulatory molecules of B7 family enabling them to function as more powerful APCs for T helper cells resulting activation (Owen, et al., 2013).

Dendritic cells express pattern recognition receptors such as the toll-like receptors for pathogenic antigen recognition. In the encounter with an antigen immature DCs internalize the antigen via phagocytosis the DC becomes activated and attain maturity. Mature DCs migrate into lymph nodes and the processed antigen on MHC molecules is presented to T helper cells. Activation of DCs also drive up regulation of cell surface receptor molecule CD40 and co receptor molecules of B7 family including B7-1 (CD80) and B7-2 (CD86) that deliver activation signals to the T cell (Kenneth, et al., 2012; Owen, et al., 2013).

Conventional dendritic cells (Myeloid dendritic cells) express TLR-2 and TLR-4 surface receptors and occur in several subsets. They are professional APCs whose major function is priming T cells and secrete IL-12 (Sallusto & Lanzavecchia, 2002). In contrast plasmacytoid dendritic cells express TLR-7 and TLR-9 receptors. These are not much effective at priming T cells and mainly take care of viral infections and

secrete Class I interferons (Vanbervliet, et al., 2003; Liu, 2005).

Follicular dendritic cells are special type of cells that do not arise in bone marrow and found in lymph follicles B cell zone in lymph nodes. These cells are not phagocytic and do not express MHC class II molecules. Although they are not functioning as APCs follicular dendritic cells express high levels of membrane receptors for antibody which facilitate binding with antigen- antibody or antigen-complement complexes. The resultant combination remains intact and more accessible for B cells. It is also important for the development of B cell follicles (Kenneth, et al., 2012; Owen, et al., 2013)

Lymphocytes

Lymphocytes are the class of WBC that acts as the key players of adaptive immune response. B Lymphocytes, T lymphocytes and NK cells are the major occupants of the lymphoid lineage.

B Lymphocytes

The principal functions of B cells are to make antibodies against antigens contributing humoral branch of immunity, to perform the role of APCs and to develop into memory B cells after activation by antigen interaction (Mauri, et al., 2012). Each B cell is characterized by a surface membrane-bound immunoglobulin known as BCR. BCR allows the distinction of B cells from other lymphocytes and act as the main protein involved in B cell activation. In order to produce antibodies B cells should be fully activated. Activation may occur T cell independently or T cell dependently.

When a native B cell encounters an antigen B cell gets activated in T cell dependent or Independent manner. Activation induces rapid proliferation of the cell and the resultant progeny undergoes differentiation into memory B cells and Plasma cells (Mauri, et al., 2012). Plasma cells produce antibodies specific to the original antigen that resulted B cell activation. Antibodies produced by the plasma cell may be in secreted or membrane bound form and result subsequent elimination of antigen via opsonization. In contrast with native B cells Memory B cells have a longer life span and express the same membrane bound specific antibody same as the parent B cell of the progeny. Immunological memory is maintained by the memory B cells (Owen, et al., 2013).

T Lymphocytes

Cellular arm of adaptive immune response is handled by T lymphocytes that are characterized by surface protein T cell receptor. Progenitor T cells originated at the sites of hematopoiesis migrate to thymus and attain maturity. Within the thymus the developing T cells or thymocytes undergo rearrangements of the germ-line TCR genes, expression of various membrane markers, proliferation and differentiation giving rise to functionally distinct subpopulations of mature T cells (Owen, et al., 2013).

In contrast with B cells TCR cannot recognize antigens alone and it is capable of identifying only the antigens that are presented on MHC molecules of B cells or other APCs. TCR of majority of T cells is composed of two glycoprotein chains known as α and β . There are several sub populations of T cells.

T helper cells

Helper T cells are characterized by the glycoprotein CD4 on the surface and also referred to as CD4+ T cells. The major function of helper t cells is to assist activation of other cell types such as B cells, Cytotoxic T cells and macrophages (Alberts, et al., 2002).

Cytotoxic T cells

The cells are also known as CD8+ T cells due to the presence of CD8 glycoprotein on the surface. Cytotoxic T cells mainly engage in elimination of virally infected cells, tumor cells and foreign tissue grafts (Male, et al., 2007).

Memory T cells

Memory T cells are a subset of long lasting antigen specific T cells that originate in the exposure to a particular antigen for the first time and maintain immunological memory. Memory T cells may be CD8+ or CD4+ and typically they express the protein CD45RO on their cell surface (Akbar, et al., 1998).

Regulatory T cells

Regulatory T cells are involved in the maintenance of peripheral immunological tolerance. As the major role these cells suppress the functionality of self-reactive T cells (T cells having TCRs that recognize self-components other than self MHC and potentially

attack normal cells leading to auto immunity) that survived from the deletion mediated by negative selection in thymus (Kenneth, et al., 2012; Male, et al., 2007).

Natural Killer T Cells

The subset of NK T cells exists in thymus and peripheral lymphoid organs. In contrast with conventional T cells NKT cells are capable of recognizing glycoprotein antigens presented on MHC molecules. Activated NKT cells secrete cytokines such as IL-4, IL-10 and IFN- γ (Kenneth, et al., 2012) and share the function of NK cells (Jerud, et al., 2006).

Gamma-delta T Cells

This subset of T cells express a distinctive TCR composed of a γ chain and a delta chain. $\gamma\delta$ T cells are much less abundant and occur at highest abundance in the gut mucosa, within a population of lymphocytes known as intraepithelial lymphocytes (Holtmeier & Kabelitz, 2005). Studies suggest that $\gamma\delta$ T cells act as potent eliminator of tumor cells via direct or indirect on other cells (Kenneth, et al., 2012).

Natural killer cells

Natural killer cells which are a type of cytotoxic lymphocyte and act as a key mediator in innate immune response and it also impart in adaptive immune response (Owen, et al., 2013). They share the same killing mechanism with NK T cells. NK cells carry surface receptors for MHC class I molecules expressed on almost all the cells and this recognition creates negative signals that inhibit killing mechanism of NK cell leading to self-recognition. Metabolic stress in infected cells with pathogens such as virus and bacteria results altered expression of MHC class I molecules on surface and altered self MHC molecules are incapable of making inhibitory signals. Thus such cells are attacked by NK cells (Viver, et al., 2011). In contrast uninfected cells promote the expression of MHC class I molecules in response to cytokines such as IFN- α and IFN- β in order to resist NK cell mediated killing (Kenneth, et al., 2012). In addition NK cells express a Fc receptor CD16 for IgG. With the aid of this receptor NK cells can attach and destroy target cells coated with antibodies exhibiting antibody-dependent cell mediated cytotoxicity (Owen, et al., 2013). In addition to receptor signaling NK cells get activated in response to cytokines including IL-12, IL-15, IL-18, IL-2, and CCL5 and NK cells also secrete

IFN- γ and TNF- α that coordinate the immune responses.

NK cells keep cytoplasmic granules containing cytotoxic proteins known as granzymes including perforin and proteases. Upon attachment to a target NK cell release these proteins to initiate killing. Perforin make pores on target cell membrane creating an aqueous channel for cytotoxic molecules or other destructive molecules to enter the cell and kill the target via either apoptosis or osmotic cell lysis. Osmotic lysis of virally infected cell may only release the virions within destroying cell whereas apoptosis eliminate the target with internal virions. NK cells also release an antimicrobial substance namely α -defensins that can kill bacterial cells by disrupting cell walls (Iannello, et al., 2008).

Organs of the immune system

Origin, growth, development and deployment of immune cells including lymphocytes occur within specialized anatomic microenvironments known as lymphoid organs. These structurally and functionally diverse lymphoid organs and tissues are interconnected by the blood vessels and lymphatic vessels to facilitate circulation of lymphocytes.

Primary lymphoid organs

The organs where lymphocytes arise and mature are referred to as primary or regenerative lymphoid organs.

Bone marrow

Bone marrow supports self-renewal and differentiation of hematopoietic stem cells either mature cells or precursors of cells that migrate out of the bone marrow to continue their maturation in thymus. It gives rise to B cells, natural killer cells, granulocytes and immature thymocytes, in addition to red blood cells and platelets. The proliferation and maturation of precursor cells in the bone marrow occur under the influence of cytokines, many of which are colony stimulating factors (Kenneth, et al., 2012)

Thymus

Final stages of T cell development, selection and maturation occur in the thymus. T cell precursors (still capable of producing multiple hematopoietic cells) travel from bone marrow to the thymus through blood stream. In the thymic environment immature T cells generate unique antigen receptors (TCR) and are then

selected based on their reactivity to self MHC-peptide complexes expressed on the surface of thymic stromal cells. Thymocytes having too high affinity to self MHC are subjected to negative selection (death) and cells having intermediate affinity are subjected to positive selection resulting in their survival, maturation, and migration to the thymic medulla (Owen, et al., 2013). The developmental strategies occur in two distinct regions, outer cortex and inner medulla. The cortex contains mostly immature thymocytes, some of which mature and migrate to the medulla. T cells leave the medulla to enter the peripheral blood circulation, through which they are transported to the secondary lymphoid organs. A huge majority of thymocytes entering the thymus is negatively selected and a few leaves the thymus as mature T cells (Kenneth, et al., 2012).

Secondary lymphoid organs

The organs where mature lymphocytes respond to foreign antigens are referred to as secondary or peripheral lymphoid organs.

Lymph nodes

Lymph nodes are small nodular aggregates of lymphoid tissue located along lymphatic channels throughout the body. They are the most specialized secondary lymphoid organs dedicated for immune response and the first organized lymphoid structure to encounter antigens entering the tissue spaces. Lymph nodes are composed of networks of stromal cells packed with lymphocytes, macrophages, and dendritic cells and connects with both lymphatic and blood vessels. Antigen presentation to the native T cells by APCs occurs in lymph nodes. In addition it act as the site where B cells are activated and differentiate into high-affinity antibody-secreting plasma cells. In the cases of adaptive immune response against infection, lymphocytes migrate to lymph nodes in elevated counts and proliferate into antigen specific T and B cells. This intense activity results swelling and pain of lymph nodes particularly during those first few days after infection (Kenneth, et al., 2012).

Spleen

In contrast to lymph nodes dealing with responses to antigens in the lymph, spleen acts as the major site of immune responses to blood borne antigens. Spleen does not connect with lymphatic vessels and connects with blood stream via splenic artery and vein. The events that initiate the adaptive immune response

against antigens resemble the same in both lymph nodes and spleen (Playfair & Chain, 2013).

Mucosa-associated lymphoid tissue

Internal surfaces such as digestive, respiratory, and urogenital tracks are lined by mucous membranes. The mucous membranes are more vulnerable for the entry of pathogens. Thus protection of mucous membranes is provided by lymphoid tissues associated with them. These lymphoid tissues are collectively known as mucosa-associated lymphoid tissue (MALT). Depending on the location MALTs are given specific names. Lymphoid tissue associated with intestinal epithelium is referred to as gut-associated lymphoid tissue (GALT) and epithelium of respiratory track is referred to as bronchus-associated lymphoid tissue (BAL) or nasal-associated lymphoid tissue (NALT) (Playfair & Chain, 2013).

Immunomodulation

Immunomodulation is the therapeutic approach that adjusts the activity of a patient's immune response, either up or down, until a desired level of immunity is reached (Hall & Virella, 2007). The major interests of immune modulation are the specific components of the immune response such as T and B lymphocyte clones, which can hopefully be selectively fine-tuned in their function to promote the better health of the patient. Bioactive agents engaged in this process are commonly referred to as immunomodulators. The landscape of immunomodulation deals with three clinical scenarios including immunopotentiality, immunosuppression and induction of immunological tolerance and the responsible therapeutic agents are referred to as immune stimulants, immune suppressants and tolerogens respectively (Bhardwaj & Waldmann, 2009; Hall & Virella, 2007).

Immunopotentiality

Immunopotentiality is the therapy of enhancing the immune response. The attempt is to boost the overall neutrophil, B lymphocyte, and/ or T lymphocyte functionality of the patient. Physiologically this can be accomplished either by actively stimulating the patient's own immune system to higher performance levels through immunization techniques or by passively introducing protective immune system components such as gamma globulin from outside sources into the patient's body (Hall & Virella, 2007). In immunotherapy immunopotentiality is achieved

via cytokine therapy, adoptive immunotherapy and vaccination (Bhardwaj & Waldmann, 2009).

Immunosuppression

Immunosuppressive therapies deal with the retardation of functionality of immune system resulting a lowered immune response. Suppressive measures are utilized when specific T and B lymphocytes of the patient's immune system have become activated against the patient's own body organs, such as in autoimmune diseases or in order to avoid rejection of organ or tissue transplantation (Hall & Virella, 2007).

Induction of immunological tolerance

Immunologic tolerance or hypo responsiveness is the capability of the immune system to avoid immune attacks on own tissues. Induction of tolerance in immune system has the advantage of targeting the undesirable immune response rather than inducing a generalized immunosuppression and commit the immune system not attack own cells and tissues by mistake and to accept foreign transplantations (Romagnani, 2006).

Plant based immunomodulators

For thousands of years plants have been playing an integral part of different healthcare systems all over the world. The term alternative medicine refers to a wide variety of healthcare practices, products and therapies engage in maintenance of normal health status against diseases in the place of conventional medicine. Alternative medicine used together with conventional medical treatment in a belief, not proven by using scientific methods is referred to as complementary medicine (Ernst, 1995; Joyce, 1994). Integrative medicine is the combination of the

practices and methods of alternative medicine with conventional medicine for therapies on a scientific basis (May, 2011). The healing power of plants is mediated by a wide variety of plant derived secondary metabolites such as proteins, flavonoids, alkaloids, steroids and phenolic substances (Perianayagam, et al., 2004).

Recognition of the value of alternative therapies has raised the involvement of herbalists and pharmacologists to explore medicinal plants from traditional herbal pharmacopeias. Already most of the drugs applied in conventional chemotherapy are initially of plant origin (Astal, et al., 2005; Adeboulou & Salau, 2005). The impact of medicinal plants on immune system has been extensively tested in vivo and in vitro and many plant species are found to be potent immune boosters in both cellular and humoral aspects.

Experimental investigations on immunomodulatory properties of herbal plants

Most plants are rich sources of potentially curative agents for many health issues including infections and already employed in traditional healing systems all over the world. As the infectious diseases exerts a considerable impact on global health risks investigations on novel immunomodulators particularly of plant origin are gaining an increased attention of scientific community. Numerous studies have been performed on plant based immunomodulators and many plants have been proven as potent bioactive agents on immune system. A summary on available experimental knowledge on immunomodulatory herbal plants is shown in table 1.1.

Table 1.1: Summary on experimental findings on immunomodulatory herbal plants.

Plant	Immunomodulatory properties
<i>Azadirachta indica</i>	<ol style="list-style-type: none"> i. Up regulates <ul style="list-style-type: none"> - Production of IL-1, IFN-γ, TNF-α. - Proliferation of spleen cells to Con A and tetanus toxoid. - Phagocytic potential and expression of MHC class II molecules - PMN leukocyte activation and cell mediated immunity. - Production of interferons. - Antibody response and DTH response against ovalbumin. ii. Attenuation of stress and xenobiotic induced cell mediated and humoral immune suppression. iii. Inhibits intracellular multiplication of Chlamydia and cytopathic effects of herpes. iv. Reduced erythema desquamation and infiltration of psoriatic lesions in a clinical study. v. Reduced mortality induced by Tacaribe viral encephalitis. (Gulati, et., 2002)
<i>Tinosporacordifolia</i>	<ol style="list-style-type: none"> i. Up regulates <ul style="list-style-type: none"> - Expression of class II MHC expression and antigen presenting capability of macrophages. - Production of IL-1, TNF-α - Ig G production and macrophage activation - Peritoneal macrophage number and their phagocytic activity in cholestatic animals. - Lag in tumor development. - granulocyte macrophage colony forming units in mice serum - Kupffer cell function in chronic liver disease in rats. - Protection against gastric mucosal damage. ii. Shows anticancer activity against D11 and Ehrlich ascites carcinoma cells. iii. Enhances humoral immune response to Sheep red blood cells and response to Con A was suppressed. iv. Increases granulocyte macrophage colony forming units in mice serum. v. Mitogenic to splenocytes and lymph node cells. vi. Inhibits cyclophosphamide induced immunosuppression. vii. Induces resistance to infection and reduces mortality in mice in response to E. coli. viii. Inhibits ochratoxin a induced suppression of IL-1 and TNF-α and macrophage chemotaxis. (Gulati, et., 2002)

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- Allium sativum*
- i. Up regulate
 - Enhances capillary skin perfusion.
 - Humoral immune response.
 - Oxidative burst of macrophages and blastogenesis of T lymphocytes.
 - Protection from UV induced suppression of contact hypersensitivity.
 - IL-2 production
 - ii. Inhibit the growth of cancer cell lines and tumors.
 - iii. Modulates the activity of chemical carcinogens.
 - iv. Protects heart, liver and pancreas against isoproterenol induced cytotoxicity.

(Gulati, et., 2002)

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- Rhodiola imbricate*
(Immunostimulant)
- i. An aqueous extract of rhizome increased
 - Production of IL-6 and TNF- α in human PBMCs as well as RAW 264.7 cell line.
 - Production of nitric oxide synergistically in combination with lipopolysaccharide in RAW 264.7.
 - Phosphorylated-I κ B expression and activated nuclear translocation of NF- κ B in human PBMCs. Thus, it is most likely activated proinflammatory mediators via phosphorylated inhibitory κ B and transcription factor NF- κ B.

(Alamgir & Uddin, 2010)

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- Acorus calamus*
(Immunosuppressant)
- i. In *In vivo* study rhizom extract,
 - Inhibited proliferation of mitogen (phytohaemagglutinin) and antigen (purified protein derivative) stimulated human peripheral blood mononuclear cells (PBMCs).
 - Inhibited growth of several cell lines of mouse and human origin.
 - Inhibited production of NO, IL-2 and TNF- α .
 - Intra cytoplasmic IFN- γ and expression of cell surface markers, CD16 and HLA-DR, on human PBMC, were not affected but CD25 expression was down regulated.

(Alamgir & Uddin, 2010)

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- Boerhaavia diffusa*
(Immunosuppressant)
- i. Ethanolic extract of the plant
 - Significantly inhibited the cell proliferation.
 - Extracts of roots inhibited human NK cell cytotoxicity *in vitro*, production of nitric oxide in mouse macrophage cells,
 - IL-2 and TNF- α , in human PBMCs.
 - Exerted no effect on intracytoplasmic IFN- γ and cell surface markers such as CD16, CD25, and HLA-DR.

(Alamgir & Uddin, 2010)

<i>Nyctanthes</i> <i>Arbortristis</i> (Immuno-restorative/ anti-immunosuppressive)	i. Aqueous leaf extract <ul style="list-style-type: none">- Found as a potent immune restorative or anti- immunosuppressive agent in response to malathion exposed immunosuppression.- Up regulated suppressed immunological parameters (humoral and cell mediated immunity, numerical values of immunocytes and functions of phagocytes) towards normalcy.
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(Alamgir & Uddin, 2010)

<i>Aloe vera</i>	i. Up reregulate <ul style="list-style-type: none">- Leukocyte infiltration was seen in injured areas and wound recovery.- Leukocyte and lymphocyte stimulation and phagocytic activity.- Expression of IL-1, IL-6 and TNF-α.- Lymphocyte proliferation in the spleen and bone marrow.- Macrophage activity. ii. Inhibit activity of microbes such as <i>Staphylococcus</i> sp. and <i>Candida</i> sp. iii. Prevents UV-induced suppression of DTH. iv. Inhibits inflammation. v. Serves as oxygen radical scavenger showing anticancer activity. vi. Causes regression of tumors.
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(Tan & Vanitha, 2004; Gulati, et., 2002)

<i>Zingiber officinale</i>	i. Essential oils of rhizome retard growth rate of a variety of bacteria and fungi, including <i>Staphylococcus</i> sp. and <i>Candida</i> sp. ii. Ethanolic extracts inhibit growth of gram-negative and gram-positive bacteria. iii. Promote secretion of IL-1 and IL-6 dose and time dependently.
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(Tan & Vanitha, 2004)

<i>Hippophae rhamnoides</i>	i. leaf extract up regulates IL-2 and IFN- γ production. ii. Flavones fraction from fruits stimulated production of IL-6 and TNF- α , NF- κ B and p-I- κ B in peripheral blood mononuclear cells with suppressed expression of CD 25. iii. Leaf extract inhibited chromium induced free radical production, apoptosis and DNA fragmentation. iv. Leaf extract inhibited chromium induced immunosuppression and related oxidative stress..
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(Singh, et al., 2005)

Discussion

Modulation of immune response with plant based drugs is a popular concept in most traditional health care systems such as Ayurveda. Within the scope of scientific findings, it has revealed that a lot of plant species possesses various immune pharmacological properties including immune stimulant, immune suppressant, and immune adjuvant properties. Potential

immune stimulants can be successfully integrated in therapies as immune boosters in order to treat impaired immune functionality. Selective immunosuppression becomes preferable in the treatments for autoimmune diseases

As suggested by the studies plant species carry potentially bioactive compounds that can enhance both innate and adaptive immune functions. Cytokines

are a diverse group of products of immune cells that play a vital role as signaling molecules in cellular communication. According to the analysis a lot of plants are capable of up regulating inflammatory cytokines including IL-1 β , IL-4, IL-6, IL-10, IL-12, IFN- γ and TNF- α . In addition to innate immunity cytokines also play a vital role in adaptive immune response.

With recent technological advancements a plenty of synthetic drugs including immunomodulators are flooding into the market. Although these synthetic agents seem to be fast acting and convenient, they are often carrying undesirable side effects, overdose complications and potential health risks in the long run. In contrast, herbal medicines are reputed enough as safer therapeutic agents than the existing synthetic stuff. Thus research activities on herbal medicines have become dominant especially in recent years. There is a plenty of epidemiological studies and experimental evidences to establish the relationship between herbal medicines and immune system and this article illustrates a few studies on immunomodulators. Such studies illustrating immunologically active herbs will contribute the populations to adopt safe, effective

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and more accessible therapies for immunity related healthcare needs. On the other hand, it will be an incentive for herbal drug manufacturers to develop more effective herbal drugs.

Conclusion

The use of plant derivatives for therapeutic purposes may be as old as the human civilization. This is further evidenced by traditional healthcare systems that date back to ancient times. Although these plant based medicines are employed in therapies, most of them have not been scientifically validated for their bioactivity at mechanistic level. Thus the major highlight of this review is immunological effects of common herbal medicines and their mechanisms of action in relation to current scientific findings. In this perspective we believe that the content might be useful for scientific community for drug design and to establish effective herbal therapies.

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