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A review on immunomodulators

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Abstract
Helping the body to help itself by optimizing the immune system is of central importance. The antibiotics will not be effective beyond 2020 as estimated by WHO. A novel alternative to antibiotics is the immuno modulation. Immunomodulation is the ruling of immune responses by stimulating them to prevent transmittable diseases or by suppressing them in the undesired circumstances. The active components in medical plants have always represented an important source of clinical therapeutics since they offer a chemical diversity often associated with a multi-pharmacological activity. Their use in traditional medicine for their properties and health benefits is well recognized since ancient times. New immunomodulatory plants are important for the discovery of drug with fewer side effects, less costly, more potent and effective treatment developed for immune and their related diseases.

Keywords: Immunomodulation, medicinal plants, immunomodulators, immunostimulant, immunosuppressants

Introduction
Immune system is a remarkably sophisticated defense system within vertebrates, to protect them from invading agents. The basic function of 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 defense or through elaborate adaptive mechanisms which are highly specific, complex, and marked by diversity and memory. In both types of immunity, cells and molecules play important roles (Roshan *et al*., 2013) [15]. Immunomodulation is the alteration of immune response which may increase or decrease the immune responsiveness. The immune response is how our body recognizes and defends itself against bacteria, viruses, and substances that appear foreign and harmful. An immunomodulators is defined as a substance, biological or synthetic, which can stimulate, suppress or modulate any of the components of the immune system including both innate and adaptive arms of the immune response (Agarwal and Singh, 1999) [1]. Modulation of the immune system denotes to any change in the immune response that can involve induction, expression, amplification or inhibition of any part or phase of the immune response. Thus, immunomodulator is a substance used for its effect on the immune system (Quinn, 1990) [14]. Naturally occurring or synthetic compounds that are capable of altering those mechanisms offered further possibilities for modulating immune responses (Singh *et al.*, 2017) [16]. The immune response has two ways of dealing with foreign pathogens. The B-lymphocytes synthesize specific antibodies called immunoglobulins. This is known as humoral immunity. The other system involves T-lymphocytes, which regulate the synthesis of antibodies as well as direct killer cell activity and the inflammatory response of delayed type hypersensitivity. This system is known as cell-mediated immunity (Srikumar *et al*., 2006) [17].

Objectives of Immunomodulation
1) To induce effective and sustained immune response against infections. When your immune system is in this highly prepared state, the invading organisms do not have the time to build up force and strength before the immune system attacks destroys and/or weakens the invader.
2) To speed up the maturation of non-specific and specific immunity during neonatal period and in young animals.
3) To enhance local immunity by airway epithelial cells have been demonstrated to control local innate and adaptive immune responses. epithelial cells produce factors that act on local immune cells including dendritic cells, macrophages, and lymphocytes.
4) To overcome the immunosuppressive effects of stress and environmental pollution. Stress is known to suppress immune function and increase susceptibility to infections and cancer. Acute or short-term stress experienced at the time of immune activation can enhance

innate and adaptive immune responses. Chronic or long-term stress can suppress immunity by decreasing immune cell numbers and function and/or increasing active immunosuppressive mechanisms (e.g. regulatory T cells). Chronic stress can also deregulates immune function by promoting proinflammatory and type-2 cytokine-driven responses. Effects of stress on leukocyte distribution: Compartments that are enriched with immune cells during acute stress show immunoenhancement, while those that are depleted of leukocytes, show immunosuppression. Pollutants can suppress immune processes and thus cause increased development of neoplastic and infections diseases.

5) To maintain immune surveillance (www.nature.com).

Characteristics of an Ideal Immunomodulator

It should be short withdrawal period with low tissue residues. Withdrawal periods were calculated so that no residue could be detected using the available analytical methods. It should be stimulate both specific and non-specific immune response. Nonspecific protective mechanisms repel all microorganisms equally, while the specific immune responses are tailored to particular types of invaders. It should be act as an adjuvant along with vaccine. It should be active through oral route. It should be compatible with other drugs. Drug-drug interactions can decrease how well your medications work, may increase minor or serious unexpected side effects. It should be defined chemical composition and Biological activity. It should be Inexpensive. It should not be toxic. It is difficult to attain single compound chemicals with high selectivity and potency, and low toxicity for targeted molecular/cellular targets and diseases. It should not be Pyrogenic (inducing fever), long side effects in the body (like high blood pressure and increased risk of infection), excreted in milk or egg (Trease and evans, 1983) [19].

Mechanisms of Immunomodulation

Drugs may modulate immune mechanism either by suppressing or by stimulating one or more of the following steps:

1. Antigen recognition & phagocytosis. Antigen recognition by T cells is a sophisticated process mediated by the T cell receptor (TCR). Phagocytes can also recognize molecular structures that are common to many groups of antigen. Such structures are called Pathogen-Associated Molecular Patterns (PAMPs)**.** Once pathogen recognition and attachment occurs, the pathogen is engulfed in a vesicle and brought into the internal compartment of the phagocyte in a process called phagocytosis.
2. Lymphocyte proliferation/differentiation (example: curcumin- suppression of lymphocyte proliferation, development of cell-mediated cytotoxicity, and cytokine production).
3. Synthesis of antibodies (An antibody is a protein that is synthesized by an animal in response to the presence of a foreign substance in our body, called an antigen. They play a great role in the immune system, and are usually found in blood and other bodily fluids. Antibodies are created by white blood cells, or more specifically, B cells.
4. Ag –Ab interaction (antigen-antibody reaction, is a specific chemical interaction between antibodies produced by B cells of the white blood cells and antigens during immune reaction.).
5. Release of mediators due to immune response (The cytokines are peptide mediators released from immune and epithelial cells that activate other immune cells to release mediators, induce chemotaxis, or induce phagocytosis.).
6. Modification of target tissue response (A group of cells that have receptors embedded in the plasma membrane that are complementary in shape to specific molecules.).

Types of Immunomodulators: Based on Action

1. Immunostimulant: These agents are inherently nonspecific in nature as they envisaged enhancing body's resistance against infection. They can act through innate immune response and through adaptive immune response. In healthy individuals the Immunostimulant are expected to serve as prophylactic and promoter agents i.e. as immunopotentiators by enhancing basic level of immune response, and in the individual with impairment of immune response as immunotherapeutic agents. (Nayak and Mengi, 2009) [13]

2. Immunosuppressants: These are a structurally and functionally heterogeneous group of drugs, which are often concomitantly administered in combination regimens to treat various types of organ transplant rejection and autoimmune diseases.

3. Immunoadjuvant: These agents are used for enhancing vaccines efficacy and therefore, could be considered specific immune stimulants example in this regard is of Freud's adjuvant. The immunoadjuvant hold the promise of being the true modulators of immune response. It has proposed to exploit them for selecting between cellular and humoral, Th1 (helper T1 cells) and Th2, (helper T2 cells) immunoprotective and immunodestructive, and allergenic (IgE) versus immunoglobin G (IgG) type of immune responses, which poses to be a real challenge to vaccine designers (Chakraborthy *et al*., 2009) [5].

Types of Immunomodulators: Based on Source

Microbial Products: Immunomodulating substances related to bacteria have been found to either enhance or inhibit the functioning of immune cells. It is, therefore, probable that these substances influence the host's specific immune resistance to infection. In addition, because the host is continually exposed to and colonized by bacteria, it is possible that substances derived from such bacteria may exert a continuing influence on the immune response system by both specific and non-specific mechanisms. The antimicrobials are specific in nature whereas immunomodulators provide broad spectrum capability against bacterial, viral and fungal diseases and thereby provide non-specific emergency-therapeutic approaches in the event of emergence of a strange pathogen or bio warfare agents (Lee *et al*., 2013) [8]. Example:

1. ***Propionibacterium acnes:*** It is heat killed or formaldehyde treated suspension are used for immunotherapy, activate macrophage, clear particulate material from the circulation, enhance humoral & cell mediated immune response, alter liver enzyme levels, tumor regression, generalised stimulation of T & B, lymphocytes, NK cell & macrophage.
2. **Lentinan:** It augment antigen specific cellular immune response, anti tumor action, cytokine production including, Interferon, activate the complement pathway,

increased activity on precursor effector cells, cytotoxic T-lymphocytes, NK cells, macrophage and antibody production (Dhama *et al.* 2015) [7].

Synthetic chemical compounds: synthetic compound refers to a substance that is man-made by synthesis, rather than being produced by natay also refer to a substance or compound formed under human control by any chemical reaction, either by chemical synthesis or by biosynthesis. These target specific drugs appear to have less drug interactions than earlier immunomodulating medicines but have nevertheless potential side effects such as activating latent infections. different kinds of drugs have been developed that selectively either inhibit or intensify the specific populations and subpopulations of immune responsive cells, i.e. lymphocytes, macrophages, neutrophils, natural killer (NK) cells, and cytotoxic T lymphocytes (CTL). Immunomodulators affect the cells producing soluble mediators such as cytokines (Sultana and Saify, 2012) [18]. Side Effects of Chemical Immunomodulator Drugs-There are various side effects associated with the use of these drugs like pulmonary toxicity, myelosuppression, alopecia, increased risk of infection, hepatic fibrosis, lymphoma, nephrotoxicity, neurotoxicity (tumor and headache), hypertension, hyperkalemia, hyperglycemia, hyperlipidemia, hyperuricemia, hyper cholesterolemia, diabetes, renal dysfunction, gum hyperplasia, nephrotoxicity, hypertension, diabetogenic *etc.* (Amato *et al*., 2017) [4]

Cow Therapy: Immunomodulatory properties of cow urine distillate in mice recorded an increase in humoral and cellular immunity of 45% and 59%, respectively. The cow urine also stimulated the production of interleukin 1 and 2 by 16% and 21%, respectively, Cow urine given to the poultry birds in water as an alternative to antibiotics demonstrated excellent immunomodulatory properties in addition to the increase in the egg production and egg quality of the layer birds. In another important study effect of cow urine on the lymphocytes damaged by pesticides was observed. It protecting the DNA from oxidative damage which is responsible for ageing, cancer. Cow urine was found to enhance the humoral and cell mediated immune response in mice, increases B and T lymphocyte blastogenesis, increases IgG and IgA antibody titers in mice (Chauhan, 2017) [6].

Herbal immunomodulators: The medicinal plants and their isolated bioactive components with immunomodulatory potential are gaining importance to discover alternative immunomodulatory agents. The usage of medicinal plants with immunostimulatory effects in patients, reported less toxicity and side effects. Researchers around the world are focusing to explore medicinal plant and plant derived substances which can alter certain immune responses. Thus, these natural substances can replace conventional medicinal therapies for modulation of immune response. Immunomodulatory regimens offer an attractive approach as they often have fewer side effects than existing drugs (Masihi, 2001) [12]. Several herbal preparations are used to enhance the body's immune status. Many plants constituent like saponins, glycosides, polysaccharides, alkaloid, flavonoids, sterols have unique ability to modulate immune system (Kala *et al*., 2015) [9].

Table 1: Commonly used food ingredients

Plants	Active ingredient	Property
Allium sativum	Allicin	Active NK cell and stimulate T lymphocytes. Increase the CD4 and total WBC counts
Zingiber officinale	Terpenes and oleoresin, Gingerols, Shogaol	Antioxidant, Antibacterial properties, Combats travel sickness helpful in cough and cold
Aloe vera	Carboxypeptidase and salicylate. Acemannan	Anti inflammatory effect, improves wound healing. Enchance production of II, I and TNF
Andrographis paniculota	Enthanol extract and diterpene, andrographolides	Stimulate antibody and DT Inhibit induction of NO synthase
Asparagus racemocus	Steroidal sponins	Anticancer activity
Azodirachna indica	Terpenoids	Stimulates production of IL 1, IFN gamma and TNF; Lysis of tumor cells
Curcuma longa	Curcumine	Anti inflammatory effect, Effective against cancer

Mahima *et al*. (2013) [11]

Examples:

Ali *et al*. (2017) [3] examined immunomodulatory activity of methanolic extract of *Drypetes Roxburghii* leaves. Serum immunoglobulin level was raised from normal 61.4±1.47 NTU upto 69.083±1.549 and 101.416±1.367 NTU in *Drypetes roxbhrghii* low dose (DHLD) (100mg/kg) and *Drypetes roxbhrghii* high dose (DRHD) (200mg/kg), respectively. Phagocytic index of animals in control group was found to be 1.8±0.186 and was raised upto 2.98±0.069 and 3.97±0.690 *Drypetes roxbhrghii* low dose (DHLD) (100mg/kg) and *Drypetes roxbhrghii* high dose (DRHD) (200mg/kg), respectively. This study showed that methanolic extract of *Drypetes roxburghii* leaves possessed immunostimulatory activity.

Kumolosasi *et al*. (2018) [10] reported immunostimulant activity of standardized extracts of *Mangifera indica* leaf and *Curcuma domestica* rhizome in mice. For both plant extracts, adaptive immunity groups showed the highest response compared to innate groups. In adaptive immunity, the WBC count of MI and CD treated animals was significantly higher than in the untreated and vehicle treated groups. Moreover, the SI of mice from MI and CD treated groups differed significantly that of the untreated group. MI and CD extracts, in appropriate doses, exerted immunostimulant effects in mice by enhancing both innate and adaptive immune systems via increase in WBC, SI and HA titer.

Aji *et al.* (2019) [2] studied *in vivo* immunomodulatory activity of faloak bark extract (*Sterculia quadrifida* R.Br). The macrophage phagocytic capacity and phagocytosis index were significantly increased, nitric oxide production were altered significantly but OD of lymphocyte proliferation and production of IgG titers were unchanged This study showed that the faloak bark could increase the macrophages phagocytic activity, but no effect on lymphocyte cells and therefore did not influence the adaptive immune response.

Conclusion

An immune response requires the coordinated actions of both innate immunity and the more powerful and flexible acquired immunity. Immunomodulation is a normalizing process which correct weak immune systems and temper immune systems that are overactive. Attention should directed towards developing effective plant products or preparations which act as an ideal immunomodulator.

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