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Potential source of immunomodulators from medicinal plant products: Review

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Abstract
According to the World Health Organization, more than 80 % of the world's population totally relies on traditional forms of medicine, largely plant based to meet the primary health care needs of the people. In India, collection of medicinal plants from different regions, i.e. Western Ghats, Himalayan region etc. and processing these plant products like leaf, stem, and root and separates its primary as well as secondary metabolites and contributes a major part in Immunopharmacology especially for immunomodulatory activities. These immunomodulatory activities are so important for human beings pertaining to safe from various types of diseases. Currently, researchers more focused on medicinal plant products and considered as modulators of the complex immune system. Various studies were conducted and explored the metabolites chemicals in the form of saponins, flavonoids, terpenoids, glycoside, etc. These metabolites are mainly responsible to cause alterations or changes in the immunomodulatory properties. In this article, we collect some information about immunomodulatory activity of medicinal plant products. The major aim is too focused on plant based immunomodulators and capable for determining and modifying the immune response. Now a day, these immunomodulators may be required to speed up the process, development and maturation of specific and non-specific immunity in young susceptible animals, and also maintain immune surveillance.

Keywords: medicinal plants, immunomodulator, specific, non-specific

Introduction

Immunomodulators are basically the chemical substances which modifies the functioning of our immune system either by stimulating (antibody formation) or inhibiting the activity of immune system. In clinical practice, immunomodulators are classified into immunoadjuvants, immunosuppressants and immunostimulants [1, 4]. The immunomodulators activate or stimulate the immune system, which provides some resistance against a wide variety of various infectious diseases including autoimmunity, cancer, allergically disorders, etc. [5, 8]. In contrast, immunoadjuvant also belongs to the class of immunomodulatory agents which have more capability to enhance the efficacy of the vaccines [9, 11]. In recent years, immunomodulatory properties of plants have drawn keen interest in among the researchers. Phytochemicals such as flavonoids, polysaccharides, lactones, alkaloids, terpenoids and glycosides are presented in several plants [12] which are responsible for their immunomodulatory properties. The natural immunomodulatory (derived from plants) agents are used worldwide to treat a wide number of infectious diseases. Some of these natural medicines are found to be working not only by eliminating the infection but also by stimulating the overall natural and adaptive immunity of the host. In addition to the treatment of infectious diseases, plant derived immunomodulators are also used in the treatment of a number of non- infectious disease like asthma, arthritis, allergy etc. [5, 8]. According to the data of 2015-2016 approximately 300 different plants are reported and around 122 chemicals are derived from various plants which have therapeutic properties and are used in commercial drugs. Most familiar example is seen in case of salicylic acid obtained from the bark of willow tree act an as active metabolite of aspirin. The bark of this willow trees have been used since ancient times as pain killers and antipyretic substance. Drugs like digoxin, quinine, opium are also plant derived which is being used by doctors widely to treat patients [5, 6]. Drugs like Azathioprine, cyclophosphamide, cyclosporine A, pencillamine etc which are used as immunosuppressors have a major disadvantage of related to their cytotoxicity and their associated side effects [6, 8]. In contrast, evaluation of plant based immunomodulators, as the alternative adjuvants for providing a maximum and lasting protective immune response with existing vaccines, is justified because of their being safer in comparison to synthetic variants. One such plant derived QS21 from *Quillaja saponaria*, which possess significant immunomodulatory activity and is being chemically tested [13]. In view of credibility of plant-based adjuvants with numerous supporting and related bioactivities, it seems worthwhile that the directional approach may help grant potential protection to immune system in combination with vaccines. Strategy for the development of immune adjuvants of plant origin may thus open a new era of vaccination therapy. The ability of plant-based vaccine adjuvant to deliver sufficient antigen to induce protective immune responses is now well established for a wide range of antigens. A plant-based vaccine adjuvant may offer a range of advantages over traditional vaccine production and delivery systems. Plant based adjuvants are emerging as suitable candidates and increasing efforts are being made to discover potential suitable adjuvants. Several features seem to be involved in adjuvant selection such as the antigen, the animal species to be vaccinated, the route of administration etc. Presently, a majority of researches, are being focused on the derivation of immunomodulators from plants. Plant based immunomodulatory agents are considered as safer alternatives and as compared to the synthetic immunomodulator they possess less side effects in the body and are less toxic [9, 11].

Examples of plant based immunomodulators are currently under investigation

Immunostimulation and immunosuppression both needs to be tackled to regulate the normal immunological functioning. Hence, search for these agents exerting more immunobiologically activities and becoming the major interest of people all over the world. In general, natural adjuvants or synthetic type of agents are now used and applied as immunosuppressive and immunostimulative agents [5, 8]. But there is major limitation to the general use of these agents such as an increased risk of infection and generalized effect throughout the immune system. New immunomodulators are therefore needed to provide a wider range of immunomodulator function for specific areas with a minimum of undesirable side effects. The discovery of low molecular weight immunomodulator compounds would be, yet another advance in this area.

Over past years several plants derived compounds are identified for immunomodulatory properties. Plant derived immunomodulators are now used over various synthetically produced immune modulators due to its less toxicity and less side effects. The discovery and isolation of more specific type of immunomodulatory agents from plant based origin and possesses some potential to counteract the side effects including high cost of synthetic compounds. There is a major variety of plants from which immuno modulators are derived from different regions of the respective plants. Some examples of such plants are mentioned below:

- *Withania somnifera* (Ashwagandha or Indian ginseng), small evergreen shrub that grows up to 5 feet (1.52 m) tall and used over for so many years in Ayurvedic medicines for multiple factors. The entire herb is more beneficial and showing several advantages, especially leaves i.e. anti-inflammatory, antibacterial properties; fruits and seeds are diuretic; roots are considered having majored immunomodulatory properties. Administration of the dry powdered form of the roots have shown to increase the WBC count, and also showed several medicinal properties, i.e. immunomodulation, antibacterial, sexual behaviour and cardiovascular protection [14, 15].
- Curcumin, used worldwide in various ways due to its multiple health benefits. In India, curcumin is consumed via the consumption of turmeric which is an essential component in Indian curries, in Japan it is served in tea, in Korea it is served in drinks etc. Curcumin, polyphenol which has been shown to benefit inflammatory conditions, metabolic syndrome, pain and have been observed to help in the management of inflammatory and degenerative eye conditions, it has also shown certain benefits to kidney ailments. Most of these benefits of curcumin is due to its antioxidant and anti-inflammatory effects. Curcumin is available in several forms like capsules, tablets, ointments, energy drinks. The use of curcuminoids have been approved by FDA (food and drug administration) as “safe for consumption”.Curcumin lessened inflammatory responses by inhibiting NO production, cyclooxygenase-2 (COX-2), nuclear factor-kappa B (NK-kB), inducible nitric oxide synthase (iNOS) and lipoxygenase in NK cells and IFN-γ, or TNF-α activated macrophages [16, 17].
- Capsaicin, hydrophobic alkaloid immunomodulator which is majorly derived from chilli peppers. It has been used for a long time as traditional medicine in different regions to use it for joint and muscle pain. The research on capsaicin resulted in the discovery of transient receptor potential channel vanilloid subfamily member 1 (TRPV1), which is the direct target of capsaicin. TRPV1 is a positively charged indiscriminate channel mainly located in nociceptive neurons with high preference for Ca2+. It is activated by physical and chemical stimuli, like certain inflammatory mediators, capsaicin, low pH and heat [18].
- *Stellera chamaejasme,* grassland poisonous plant and majorly distributed over northern and southern part of China. The roots of this plant are mainly applied and are used as a traditional medicine for the treatment of cough, stubborn skin ulcers. Phytochemical analysis have led to the isolation of diterpenoids, bioflavonoids and lignans. Recent studies of this plant has revealed that it has an anti-tumour, anti-microbial properties, inhibiting the growth of leukaemia cells and immunomodulatory properties. Eudesmin, isolated by silica gel chromatography exhibits immunomodulatory activity [19].
- *Andrographis paniculata,* an erect annual herb which is bitter in all parts of the plant body. The herb is used in China, India and other Asian regions as traditional medicines. The recent studies have revealed that it contains compounds with a potent antioxidant, anti-ulcer, anti-inflammatory and immunostimulating properties. The immunomodulatory properties of this herb promotes positive health and maintain a good resistance of body to fight against various infections. Besides enhancing the immunity the herb also strengthens the liver and maintains a good heart health. The herb contains diterpenoids, flavonoids, polyphenols as major bioactive components. Immunomodulatory effect of andrographolide and 14 -deoxy-11, 12-didehydroandrographolide show immunostimulatory activity by increasing the production of interleukin and lymphocytes [20].
- *Lithospernum erythrorhizon,* herb widely distributed over Australia and nearby regions. The roots of this plant has antiviral, anti-HIV (HIV type 1) properties. Naphthoquinone compounds extracted from the roots and showed immunostimulatory properties and also claimed its anti-microbial, anti-inflammatory, wound healing, and anti-tumor properties. Shikonin is a compound which has also showed immunomodulatory effects [21].
- *Phyllanthus emblica,* fruits contain Gallic acid, quercetin, kaemferol, emblicanin, flavonoids, glucosides, vitamin C, tannins which make it a very powerful immunostimulant and antioxidant in nature. Quercetin extracted from this plant using ethanol, which is a flavonoid constituent [22, 23].
- *Petiveria alliacia,* herb distributed widely over the South American regions. Roots of these plants have anti-inflammative, anti-nociceptive, hypoglyciment, diuretic, sedative, and abortifacient properties. Dibenzyl trisulphide, lipophilic compound extracted from the roots of the plant have been observed as one of the potent immunomodulatory component which has anti-proliferative and cytotoxic properties [24]
- *Panax ginseng,* perennial plant, cultivated mainly in northern parts of Asia. Ginsenosidese, extracted from

the roots of this plant and considered as one of the major immunomodulatory component. In contrast, Asian ginseng is mainly used for diabetes, and male erectile dysfunction whereas American ginseng also used for diabetes and also applied for reducing the risk of the common cold and flu [25].

- *Adhatoda vasica* (family *Acanthaceae*)**,** leaves and flowers are used medicinally and showed numerous health benefits and considers as immunomodulatory e.g. Juice of leaves given along with honey, for treating cough and asthma. It contains drug vasacine, which is brancho-dialator. The most Ayurvedic cough mixtures contain juice extracted from the leaves of this plant. Leaves are used as green manure, and for packing purposes [26, 27].
- *Bambusa arundinacea* (family *Poaceae*), used in diarrhea, dyspepsia, flatulence and worm problems, fever, inflammations, ulcers, wounds, vomiting. Also it shows antihelminthic, stimulant, astringent, tonic antiperiodic, aphrodisiac activities [28].
- *Ficus infectoria* (family *Moraceae*), used in many parts of the world for the treatment of a number of diseases, e.g. as an antibacterial, antifungal and hyperglycemic properties in diabetic conditions. Traditionally, bark decoction's used for washing ulcers and also used as a gargle in salivation and menstrual disorders including leucorrhoea [29].
- *Terminalia arjuna* (family *Combretaceae*), bark is considered as cardiac stimulant and proved to be beneficial for asthmatic patients e.g. fresh leaves juice used beneficially especially in case of earache and also showed immunomodulatory properties [30].
- *Mimusops elengi* (family *Sapotaceae*), bark, flowers and fruits are acrid, astringent, cooling and anthelmintic. Bark is useful in urethrorrhoea, diarrhea and dysentery, flowers are used for preparing a location for wound and ulcers, powder of dried flowers is considered a brain tonic and is used as a snuff to relieve cephalogia [31].
- *Mangifera indica* (family *Anacardiaceae*), showed various medicinal properties i.e. anti-inflammatory, analgesic, hypoglycemic effect etc. Normally, dried mango flowers used especially for the treatment of diarrhea, chronic dysentery and some problems of the bladder. These dried flowers particularly used in the treatment of diarrhea, chronic dysentery etc [32]
- *Azadirachta indica* (neem; family *Meliaceae*), well known medicinal plant and showed medicinal properties i.e. immunostimulatory/immunosuppressive, anti-inflammatory, anti-oxidant etc. [33]. In contrast, *Acacia catechu* (khair, family *Fabaceae*) exhibit various immunopharmacological effects like hepatoprotective, antioxidant etc. [34] Another medicinal plant i.e. *Salmalia malabarica* (Saavar, family *Bombacaceae*), medicinal plants showed medicinal uses and considered as immunomodulator e.g. gum is useful for pulmonary tuberculosis (TB), flu, dysentery, etc. In addition, the flowers of this plant are used for eye complaints [35].

Conclusion

As per the literature, these medicinal plant products showed some potential to explore various immunopharmacological activities i.e. antioxidant, hepatoprotective etc. In other words, these medicinal plants reported various chemical constituents in the form of primary and secondary metabolites and ultimately used for various purposes, i.e. prophylactic and therapeutic. In this article, we mentioned various medicinal plant products along with medicinal properties as well. Recently, a lot of studies were conducted on medicinal plants (*in vitro* and *in vivo*) and it is used by various pharmaceutical companies especially for drug manufacturing related to human health care. Although, mechanism of action along with its efficacy of medicinal plant products is still needed to validate scientifically. Therefore, it is important to search other type of alternatives with respect to medicinal plants which is highly effective in the treatment of these infections (intracellular or extracellular).

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