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Review Article

A review on medicinal plants as potential sources of natural immunomodulatory action

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Abstract

The concept of immunomodulation was proposed by Edward Jenner, while working on polio vaccine in 1796. A brawny, fine-functioning immune system is the keystone of excellent health. Immune replies are the consequence of an effectual interaction among innate (natural and non-specific) and acquired (adaptive and specific) components of the immune system. Inequity or failure of the immune systems is connected with a variety of chronic illness counting allergies, autoimmune diseases, cancers and furthers. Diverse innate and adaptive immune cells that are incorporated in this multifaceted networking organization may symbolize talented targets for expanding immunotherapeutics for treating specific immune illness. An assorted array of natural, synthetic, and recombinant compounds is accessible with both advantages and demerits. A range of phytochemicals have been remote, differentiated and customized for expansion and employ as avoidance or cure of human diseases, but the request of customary or novel medicinal plants for employ as immunomodulators in indulgencing immune diseases is still comparatively limited. At present, there is much-growing interest in the use of medicinal plants as modulators of the complex immune system. Numerous therapeutic consequences of plant extracts have been recommended to be because of their extensive assortment of immunomodulatory effects and persuade on the immune system of the human body. In present review paper, various medicinal plants, their resultant crude or fractionated phyto extracts and the precise phytochemicals remote from them are conversed in terms of their immunomodulatory bioactivities. We also review their possible for future expansion as immunomodulatory or inflammation-regulatory therapeutics or agents.

Keywords: Immunomodulation, Immune system, Phytochemicals, Medicinal plant, Plant extracts

Introduction

It is an evident from the human history that medicinal plants have been the treatment regimen to cure a variety of diseases, including diseases origins by bacteria, fungi, insects, and viruses. The consequences revealed by the plants are because of the chemicals there in them and they toil in the similar way as the conventional drugs. Though, there are equally possibilities for these plants to have several prospective injurious and poisonous consequences too. These undesired side consequences can be abridged by processing of the plant's crude result[1]. A moment ago, the elevated thought of plant-based natural products is salaried by researchers because of many unfavorable side effects of contemporary salutary medicines. Also, the synthetic drugs are extra pricey to get in association with herbal products. Huge quantity of chemical entities with a variety of pharmacological activities created from plants is helpful to encourage human fitness. In 2013, 1453 novel chemical entities patented from natural products accepted by US Food and Drug Administration[2]. They have been widely used as health supplements, nutritive products, medications since prehistoric times. Natural product-based drugs promote a significant role of the pharmaceutical industry. Recently, secure drugs with little side consequences and elevated discriminating ligands that work on sole disease target become a assignment of drug development programs[3]. Immunity is the body's capability to recognize and repel/fight against wide range of diseases and also possibly against toxic microorganisms.The immune system maintains homeostasis within the body in a normal condition of host. Assorted endogenous and exogenous agents contribute to the competence and purpose of the immune system that guide to the immunosuppression or immunostimulation[4]. The alteration of host's immune system contributes to the progression of abnormal conditions such as cancer. Therefore, the intonation of host's immune reply to raise the capability of this system in eliminating the aetiological

agents that caused diseases might reduce this trouble[5]. Immunomodulation could be defined as the modification process of immune reactions that function to regulate immune responsiveness to treat illnesses[6]. The request of immunomodulators for either as a treatment or avoidance of a variety of illness that connected with malfunctioning of immune reactions became the main thought[7]. The main purposes of immunomodulators are either to suppress immune responses as a treatment for autoimmune diseases or to enhance them that applied in immunodeficiency and infectious diseases[8]. Additionally, the usage of immunostimulant agents also essentially acts as an adjuvant to chemotherapy for various illnesses[9]. These compounds may get affected by some factors like dose, route of administration, timing of administration and also site of action[10].

Immunity and classification of immunomodulators

Immunity is the mainly significant essential fundamental construction of the body; to be precise it is a complex system with multiple shields. The chief shield/barricade is: The skin; here hotness and pH of body there may be inappropriate for obtainable requirement. albeit, the microbes go into the body, they are provoked by acquired or innate immune systems[11]. Innate immunity is one of the chief immune protections, in answer to foreign and dangerous objects. Innate immunity is an immune protection mechanism that is set with receptors, for immediate reply. Here, there is no need of any genetic recombination or any other process[12]. Acquired immunity known as adaptive immunity. It is mostly observed in blood, in tissue juices, or co-joined to cell surface. Immunoglobulin also known as the antibody receptor is the chief key as antigen-specific receptor in the shape of 'Y'[13].

The biomolecules of artificial or biological source able of suppressing, modulating, and stimulating each feature of immune system with innate and adaptive immune system are recognized as immunorestoratives, immunomodulators, immunoaugmentors, or biological response modifiers. Scientifically, Immunomodulators are usually classified into immunostimulants, immunoadjuvants, and immunosuppressants in clinical practice[14].

- Immunoadjuvants-These are utilized to improve the effectiveness of preparations/shots and thus are deemed as immune stimulants. They are regarded as genuine modulators of the immune system. It is noticed quite often that they are manipulated as selectors among cellular and humoral assistant/helper T1 (TH1) and helper T2cells (TH2), immune-protective, immune-destructive and immunoglobulin E vs. immunoglobulin G (IgE vs. IgG) reactions, an immense task for the vaccines/shot designers[15].
- Immunostimulants-These are foreseen as improvements of a body's opposition towards infection which is integrally not precise. They have ability to function by adaptive or innate immune reaction. As they increase the body's fundamental level of immune these are recognized as immunopotentiators and promoter agents[16].
- Immunosuppressants-These are considered as intrinsically and operationally heterogenous class of drugs, concurrently dispensed in an amalgamation so as to cure several sorts of tissue/organ transplant dismissal and autoimmune disorder[17]. Furthermore, these agents can also be employed in the cure of infection connected hypersensitivity reactions, immunopathology, and autoimmune illness. A quantity of monoclonal antibodies and chemically created compounds are also being employed as immunomodulators. Consequently, immunomodulatory entities with extra security and efficiency are still in require. Because of the incidence of chemical drugs-related unfavorable results, natural immunomodulators are the possible agents to restore them in therapeutic schedules.

Screening methods for immunomodulatory property

In-vitro and animal models are used to test the effectiveness and toxicity of the active constituents, which are separated and extracted from a plant extract that illustrates the bioactivities. Numerous *in vitro* and *in vivo* techniques of pharmacological screening of therapeutic plants having immunomodulatory activity have been reported[18].

In vitro methods

- Inhibition of histamine discharge from mast cells
- Mitogens persuaded lymphocyte proliferation
- Inhibition of T cell proliferation
- Chemiluminescence in macrophages
- Inhibition of dihydroorotate dehydrogenase
- Plaque forming colony

In vivo methods

- Spontaneous autoimmune diseases in animals
- Passive cutaneous anaphylaxis
- Acute systemic anaphylaxis in rats
- Anti-anaphylactic activity (Schultz-Dale reaction)
- Delayed-type hypersensitivity
- Reversed passive Arthus reaction
- Arthus type immediate hypersensitivity
- Adjuvant arthritis in rats
- Proteoglycan-induced progressive polyarthritis in mice
- Experimental autoimmune thyroiditis
- Coxsackievirus B3-induced myocarditis
- Collagen type II-induced arthritis in rats
- Porcine cardiac myosin-induced autoimmune myocarditis in rats
- Experimental allergic encephalomyelitis
- Inhibition of allogeneic transplant rejection
- Acute graft versus host disease in rats
- Influence on SLE-like disorder in MRL/lpr mice
- Prevention of experimentally induced myasthenia gravis in rats
- Glomerulonephritis induced by anti-basement membrane antibody in rats
- Autoimmune uveitis in rats[19].

Plant derived immunomodulators

Currently, mainstream of investigate and expansion motionless centers on biochemical's, biologics or sole complexes as guide compounds that aspire at exacting targets connected with a illness. It is tricky to achieve solo

complex chemicals with elevated selectivity and effectiveness and short toxicity for targeted molecular/cellular targets and illness. Therefore, the design and expansion of drug applicants from several conservative or complementary and substitute medicines is expanding attention. The avoidance and cure of illness using plant-supported medicines has been accounted in human history. In every culture and through all ages dissimilar parts of an enormous quantity of plants were employed as drugs against every type of ailments. Vincristine vinblastine, and their semi-synthetic imitative isolated from the *Catharanthus roseus* paclitaxel from *Taxus brevifolia*, capsaicin from *Capsicum* species, and galantamine from *Galanthus caucasicus* are instances of medicines based on plant complexes. The plant-based complexes that provided as lead structures and/or were chemically altered are morphine (scores of derivatives), dicoumarol (warfarin), camptothecin (topotecan and irinotecan), artemisinin (artemether), and salicylic acid (acetylsalicylic acid) [20]. The immunomodulatory traits of plant-based therapeutics have assembled thought of researchers[21]. Innovative expertise's and the extreme research on immunomodulatory natural products, their extracts, plants, and their lively moieties with immunomodulatory possible, may give us with precious entities to expand as new immunomodulatory agents to addition the current chemotherapies. This reviewfocuses on the various plants have immunomodulatoryactivity. Several herbs have potent immunomodulatory action was mention in Table 1.

Table 1List of medicinal plants having immunomodulatory activity[22-103]

Plant name	Parts used	Chemical constituent	Model used
Allium sativum	Bulbs	Allicin	Hemagglutination
Adhatoda vasica	Leaves	Quinazoline, vasicinone, essential oils	Neutrophil adhesion, DTH
Abrus precatorius	Seeds	Alkaloids, phenolics, tannins, saponins	HA titer, DTH response, PI
Abutilon indicum	Whole plant	Flavonoids, triterpenoids	HA titer, DTH response, neutrophil adhesion test, and carbon clearance test
Argyreia speciosa	Roots	Glycosides	Cellular, humoral immunity, DTH reaction
Asparagus racemosus	Roots	Saponins, sitosterols	SRBC-sensitized animals
Andrographis paniculata	Leaves	Diterpenes	DTH mouse model
Acanthopanax sessiliflorus	Shoots, roots	Biopolymers	Lymphocyte-proliferating effects
Acacia catechu	Leaf	Tannins, flavonoids	Neutrophil adhesion, carbon clearance test
Artemisia annua	Herb	Artemisinin	DTH, lymphocytic proliferation assay
Achillea millefolium	Leaves	Flavonoids, alkaloids, coumarins	DTH, hemagglutination
Aloe vera	Gel from leaves	Anthraquinone glycosides	Hematological, serological studies
Aesculus indica	Leaf	Alkaloids, saponins, tannins	Neutrophil index, neutrophil adhesion
Azadirachta indica	Flowers	Azadirachtin	Antibody titer phagocytic activity, nitro blue tetrazolium dye, DTH reaction
Bauhinia variegata	Root, bark	Flavonoids, β-sitosterol, lupeol	Human neutrophils
Boerhaavia diffusa	Herb	Alkaloids	Circulating antibody titer
Balanitesrox burghii	Leaf	Alkaloids, flavonoids, tannins, saponins	Carbon clearance test, serum immunoglobulin
Tridax procumbens	Aerial parts	Tannins, flavonoids, alkaloids, steroids	DTH model
Urena lobata	Fruits	Flavonoids, glycosides	Phagocytic activity
Withania somnifera	Root	Withanolides	Bone marrow cellularity
Chlorophytum borivilianum	Roots	Polysaccharides	Phagocytosis using carbon clearance method
Cleome gynandra	Leaf, seeds, roots	Hexacosanol, kaempferol	Carbon clearance test, DTH, antibody titer
Calendula officinalis	Flowers	Polysaccharides, proteins, fatty acids	Phagocytosis
Centella asiatica	Herb	Triterpenoid saponins	Cell-mediated, humoral immune

			responses
Clitoria ternatea	Aerial parts	β-sitosterol, kaempferol	DTH, antibody, drug-induced myelosuppression
Citrus aurantifolia	Fruits	Volatile oils	Cell proliferation assay, immunoblotting
Capparis zeylanica	Leaf	Flavonoids	Phagocytosis, delayed hypersensitivity
Curcuma longa	Rhizome	Curcumin	Humoral antibody response to SRBC
Cleome gynandra	Aerial parts	Flavonoids, alkaloids, terpenoids, steroids	Carbon clearance method, cell-mediated immunity, immunostimulatory
Eclipta alba	Leaves	Triterpenoid glycosides	Phagocytic index antibody titer
Euphorbia hirta	Herb	Quercitol, myricitrin, gallic acid	Phagocytic index
Ficus carica	Leaf	Phenolic compound, phytosterol, volatile oils	Cellular immune response, humoral antibody response
Cissampelos pareira	Roots	Alkaloids	Humoral antibody titer
Caesalpinia bonducella	Seeds	Flavonoids, alkaloids, tannins, amino acids	Neutrophil adhesion test, HA
Ficus benghalensis	Root	Alkaloids, steroids, flavonoids, tannins	Hypersensitivity, hemagglutination reactions.
Ganoderma lucidum	Whole plant	Flavonoids, triterpenes, polysaccharides	Proliferation of lymphocytes
Gymnema sylvestre	Leaves	Alkaloids, tannins, flavonoids	Neutrophil locomotion, chemotaxis test
Nyctanthes arbortristis	Leaf	Iridoid glucosides	Humoral immunity, DTH
Murraya koenigii	Leaves	Coumarins, carbazole alkaloids, glucoside	PI, nitric acid assay, humoral antibody, DTH reaction
Mangifera indica	Stem bark	Alkaloids, tannins, flavonoids	Humoral antibody response to SRBC
Moringa oleifera	Leaves	Vitamin A, B, C, carotenoids, saponins	DTH test neutrophil adhesion, HA
Morus alba	Fruits, leaves, bark	Flavonoids, anthocyanins	Humoral immunity, serum immunoglobulin
Habenaria intermedia	Tubers	Alkaloids phenolic compounds	DTH test, carbon clearance test for phagocytic activity
Hyptis suaveolens	Leaf, flowers	Lupeol, β-sitosterol	Humoral immune response, lipid peroxide enzyme
Hibiscus rosa-sinensis	Flowers	Alkaloids, flavonoids, terpenoids, tannins	Carbon clearance method, cell-mediated immunity, immunostimulatory
Lycium barbarum	Fruits	Polysaccharide-protein complexes	HA PI lymphocytic proliferation
Salicornia herbacea	Herb	Polysaccharides	Phagocytic activity on opsonized
Syzygium cumini	Seeds	Alkaloids, flavonoids, glycosides, phytosterols	Carbon clearance method, hemagglutination titer, DTH
Panax ginseng	Fruits, root	Ginsenosides, panaxdiol, panaxtriole, oleanolic acid	Antibody plaque-forming cell response, circulating antibody titer against sheep erythrocytes
Salacia chinensis	Roots	Flavonoids, tannins, alkaloids, carbohydrates	HA titer, DTH response
Silybum marianum	Flowers	Flavonoids	Macrophage migration index
Ocimum sanctum	Entire plant	Essential oils such as eugenol, carvacrol, derivatives of ursolic acid, apigenin	Enhance the production of RBC, WBC, hemoglobin
Picrorhiza kurroa	Leaf	Alkaloids, flavonoids, tannins, saponins	Cell-mediated, humoral components

Piper longum	Fruits	Alkaloids	HA, PI, macrophage migration index
Terminalia arjuna	Leaves, bark	Flavonoids, oligomericproanthocyanidins, tannins	Hemagglutination
Tinospora cordifolia	Entire herb	Alkaloids	DTH, bone marrow cellularity
Trapa bispinosa	Fruits	Flavonoids, proteins, carbohydrates	Neutrophils, hemagglutination titer

DTH: Delayed-type hypersensitivity, RBC: Red blood cell, WBC: White blood cell, SRBC: Sheep red blood cell, HA: Hemagglutination antibody, PI: Phagocytic index

Future Prospects

From ancient times plant derived medicines and folklore medicines have been employed for the drug design and development of therapeutic agents[104]. Herbal and traditional botanical products are good alternatives to conventional chemotherapy[105]. Currently researchers are enthralled towards plant gained therapeutics and the research is based on study for a few plant biochemicals in the type of the sole complex as lead molecule concerned with particular target linked with disease[106]. Several plant obtained complexes have been recognized over the years which possess immunomodulatory traits but the appropriate, efficient, and multidisciplinary approach is requisite for picking out active constituents from different medicinal plants and their different medicinal effects using modern techniques[107]. Two approaches can be followed for developing successful drugs from medicinal plants. First one is the phytochemical approach, which depends on identifying the active principle and developing pure phytochemicals as drugs. Yet this type of drug discovery is costly and also time consuming. The second approach is a phytotherapeutic approach wherein standardized crude drug preparations can be employed as drugs with modern standards of protection and efficiency. As far as the Indian therapeutic plants are concerned, the second approach could be followed.

Conclusion

Immunomodulation employed medicinal plants can give alternative to conservative chemotherapy for a diversity of illness, particularly when host protection mechanism has to be stimulated under the situations of impairedimmune response or when a discriminating immunosuppression is preferred insituations like autoimmune disorders. There is great potential for the detection of further precise immunomodulators which mimic or antagonize the biological effects of cytokines and interleukins, and the refinement of assays for these mediators will create specific and sensitive screens. Naturalremedies should be revisited as important sources of novel ligands capable of targeting specific cellular receptors.

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Conflict of interest

None

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