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Immunodmodulation: Herbal perspective and investigations - A review

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Abstract

Immunomodulation had been in application in medical systems and the traditional Indian systems like Ayurveda. It has various applications in medicine for altering the defence of the body that is immunity. A lot of conditions that require immunomodulation are supported by drugs for immune suppression and immune stimulation. They are often called as immune suppressants and immune stimulants. There are other class of drugs, immune adjuvants. Synthetic drugs are notorious for causing side effects and the herbal alternatives had been investigated for the activity. So the herbs stand as the alternatives for the synthetic drugs in better treating the disease that concern the immune system. The inconsistency of the *in-vivo* response of the immunity, with the phytochemicals, is also a limiting step for their effective usage as immunomodulatory agents when it comes to practical application. Overall, herbs had been supplying the chemical constituents that can be used directly or in the purified form as immunomodulatory agents. This review is the segregation of the various methods available to perform the screening of the drugs and extracts for immunomodulatory activity. This paper also enlists various herbs used for immunomodulation and had been proven for the same recently from 2010 to date.

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INTRODUCTION

Immunity is a significant and flexible defence mechanism in the body that protects from pathogens and microorganisms. It prevents disease-causing organisms from attacking and depleting the body's normal functions. The body's immunity has an ability to synthesize a wide range of molecules that can recognize and eliminate any foreign organisms (Richard *et al.*, 2003). Immunomodulation is not a new term that is evolved recently in medicine. It had been in practice from late 1800 till today. The use of vaccines was the general method to modulate immunity in human beings. The term immunomodulation reminds few scientists names like Louis Pasteur, Jonas Salk, Edward Jenner and Emil von Behring. Vaccines involve the process of invoking the body's natural immune system. Artificially generated antigens or weakened or attenuated disease causing microorganisms are used to target and provoke the synthesis of antibodies against a specific antigen. This provocation induces the needed defence mechanism in the body and is a huge milestone in immunomodulation. Immunomodulation is defined as alteration (increase/decrease) of the immune response of the body to antigens. Any enhancement or stimulation in the immunity is called as immune-stimulation, and lowering of the immune response of the sensitivity is termed as immune-suppression. The core concept of the immunomodulation lies in

alteration of immunity by any agent that causes disease or toxicity but at a varied dose and time.

Need for Immunomodulation

Immune suppression is usually applied in the following cases.

1. To suppress the transplant rejection after organ or tissue transplantation (Heart, Kidney, Liver, Skin etc.).
2. To limit the GVHD (Graft v/s Host Disease) after bone marrow transplantation.
3. To suppress elevated immunity in autoimmune disorders like Myasthenia gravis, SLE, RA and Psoriasis.
4. To suppress selectively the Rh of the hemolytic disease of the newborn babies.

Immune-stimulation is needed when the immune system of the host is inactive or impaired. This is a therapeutically needed in the conditions with infections, disease and prophylactically need in the period post-surgery to prevent opportunistic infections.

MATERIALS AND METHODS

Screening of immunomodulatory activity

There are various methods by which a herbal extract or a drug can be screened for the immunomodulatory activity. In general, there are two classes of screening methods. They are *in vivo* and *in vitro* evaluation. Usually, *in vivo* evaluation employs Rats or any other higher animals for screening. There are different methods to estimate the activity in animals by measuring various body tissues analysis. The analyses were made by inducing the hypersensitivity or allergens into the animal body, followed by the drug administration and examined for the activity. The following are the induction methods and estimation types of immunomodulation.

Transplantation

Induction of the allogenic transplant rejection and GVHD (Graft v/s Host Disease) determination.

Thyroidal induction

Experimental induction of autoimmune thyroiditis and hypersensitivity in the thyroid.

Arthritis estimation

Induction of adjuvant arthritis, induction of reversed passive arthritis, progressive arthritis induced by proteoglycans and arthritis induced by collagen type II.

Skin and nerves related

Cutaneous passive anaphylaxis method, MRL/IPR strain mice to test SLE and experimentally induced myasthenia gravis.

Hypersensitivities

Systemic induction of anaphylaxis, immediate hypersensitivity of Arthus type, induction of delayed hypersensitivity and Schultz-Dale reactions.

Other Systems

Induction of glomerulonephritis by anti basement membrane antibody, induction of autoimmune myocarditis by porcine cardiac myosin and myocarditis induced by coxsackievirus.

As there is raising concern for the testing and treatment of animals in the laboratories, the use of animals is slowly replaced by simulation software and *in vitro* procedures. The following parameters are evaluated when doing *in vitro* evaluation. They are,

1. In *vitro* Plaque Forming Colonies (PFC test).
2. Estimation of the histamine inhibition release that occurs in mast cells.
3. Estimation of the enzyme DOD (Dihydroorotate dehydrogenase).
4. Estimation of the proliferation of lymphocytes that is induced by Mitogen.
5. Determination of the chemiluminescence in the macrophages.
6. Estimation of Inhibition of the proliferation of T cells.

Herbal investigations

There are synthetic drugs that have potent immuno modulatory activity but are not devoid of side effects. Few of them include Alopecia, Lung toxicity, Lymphoma, Nephrotoxicity, Hepatic fibrosis, Seizures, Hirsutism, etc. (Kremer *et al.*, 1994). Immunomodulation has been adopted in the traditional systems of medicine like Ayurveda, in which the concept of rasayana has most prominence. Various plants have been studied as rasayana drugs in Ayurveda and other Indian systems of medicines. Immunomodulatory activity of various plants had been used for their immunoadjuvant activity, antirheumatic activity, antiageing property, anticancer and adaptogenic activity. This folklore and scientific activity in this field had a holistic and innovative approach for the discovery of powerful lead molecules and affordable drugs. The medicinal plants and herbs are known to be safer and better alternatives.

Table 1: List of plant investigated for immunomodulatory activity.

S No	Plant name	Method	Reference
1	*Allium sativum, Zingiber officinale, Azadirachta indica, Berberis lycium*	Determination of antibody titer method	(Nidaullah *et al.*, 2010)
2	*Aloe vera (Linn)*	Pyrogallol induced immuno-suppression in rats	(Nidaullah *et al.*, 2010)
3	*Angelica sinensis (Oliv.) Diels*	lipopolysaccharide (LPS) stimulated RAW264.7 cells macrophages model	(Nidaullah *et al.*, 2010)
4	*Apocynum cannabinum L. (Canadian hemp), Picrorhiza kurroa Royle ex Benth.*	Inhibit NADPH oxidase in anti-inflammatory activity.	(Patil *et al.*, 2013)
5	*Barringtonia racemosa*	Haemagglutinationtiter method.	(Patil *et al.*, 2013)
6	*Camellia sinensis L.*	TNF-α-induced pulmonary inflammation via ROS-dependent ICAM-1 inhibition in rats	(Lee *et al.*, 2015)
7	*Capparis zeylanica*	Haemoagglutination antibody titre method	(Agrawal *et al.*, 2010)
8	*Carica papaya*	Carbon clearance method	(Anjum *et al.*, 2017)
9	*Chelidonium majus L.*	Writhing response induced by Acetic acid in rats.	(Nidaullah *et al.*, 2010)
10	*Citrus nobilis Lour, Citrus aurantium L.*	Mouse macrophage RAW 264.7 induced by lipopolysaccharide cells models	(Zhang *et al.*, 2011)
11	*Cod liver oil (CLO)*	1. Mice lethality test 2. Carbon clearance assay, neutrophil adhesion test 3. Cyclophosphamide induced neutropenia 4. Indirect haemagglutination method	(Asad *et al.*, 2012)
12	*Coptischinensis Franch*	Gene expression of Th1/Th2 Cytokine in Primary splenocyte in mice	(Lee *et al.*, 2015)
13	*Cuminum cyminum, Mentha longifolia, Foeniculum vulgare*	Carbon clearance Technique, hemagglutination titer method.	(Zhang *et al.*, 2011)
14	*Curcuma longa*	Phagocytosis and nitric oxide release. Release of Myeloperoxidase.	(Patil *et al.*, 2010)
15	*Dysosma veitchii Hemsl. et Wils*	Decreased expression of genes of pro inflammatory cytokines, NF-κB, and iNOS.	(Lee *et al.*, 2015)
16	*Fallopia japonica, grape, nuts*	Decrease iNOS gene expression	(Xu *et al.*, 2012)

Continued on next page

Table 1 continued

S No	Plant name	Method	Reference
17	*Ficus carica*	Antibody titer by haemagglutination reaction method	(Patil *et al.*, 2010)
18	*Gallic acid*	Cyclophosphamide and Cisplatin induced method	(Valles *et al.*, 2010)
19	*Gelsemium elegans*	Inhibition of T lymphocyte proliferation invitro	(Xu *et al.*, 2012)
20	*Gentianaolivieri*	Hemoglutination antibody titre method, *in vivo* carbon clearance or phagocytosis in rats	(Nidaullah *et al.*, 2010)
21	*Glycine max*	Amyloid beta (A-beta) induced inflammatory mediators models	(Valles *et al.*, 2010)
22	*Glycyrhiza glabra*	Carbon clearance method	(Mishra *et al.*, 2012)
23	*Helichrysum italicum*	In vitro HIV-1 replication in T cells, Carrageenan-induced pleurisy in rats	(Andújar *et al.*, 2010)
24	*Hibiscus rosasinensis*	Carbon clearance method	(Mishra *et al.*, 2012)
25	*Leonurus japonicas Houtt*	LPS-induced mouse mastitis model	(Hu *et al.*, 2013)
26	*Ligusticum chuanxiong Hort*	Contusion spinal cord injury in rats (SCI).	(Hu *et al.*, 2013)
27	*Lithospermum erythrorhyzon Sieb. etZucc.*	TPA induced ear edema in rats. Invitro macrophages RAW 264.7 cells stimulated with lipopolysaccharide.	(Andújar *et al.*, 2010)
28	*Lycoris radiate*	lipopolysaccharide-induced invitro iNOS and COX-2 up-regulation in RAW264.7 cells	(Zhang *et al.*, 2011)
29	*Moringa oleifera Lam*	Cyclophosphamide-induced method	(Mishra *et al.*, 2012)
30	*Moris alba*	Cyclophosphamide-induced Carbon clearance method	(Bharani *et al.*, 2010)
31	*Nigella sativa L.*	Invitro isolated human RA fibroblast like synoviocytes (FLS Rat adjuvant-induced arthritis model of RA.	(Bae *et al.*, 2011)
32	*Ocimum sanctum Linn, Cocos nucifera Linn*	Visceral leishmaniasis in BALB/c mouse model.	(Bhalla *et al.*, 2017)
33	*Piceacrassifolia*	Mast cell-based in vitro and in vivo models	(Bae *et al.*, 2011)
34	*Piper longum Linn*	In vitro model of Rabbit platelets and murine macrophage RAW264.7 cells	(Nidaullah *et al.*, 2010)

Continued on next page

Table 1 continued

S No	Plant name	Method	Reference
35	*Polygonum amplexicaule D. Don var. sinense Forb.*	Cells Proliferation and differentiation of osteoblastic MC3T3-E1 cell in vitro.	(Liu *et al.*, 2010)
36	*Pueraria lobata (wild) Ohwi*	Cerebral ischemia/reperfusion-induced by Puerarin in rats.	(Liu *et al.*, 2010)
37	*Radix astragali, Radix codonopis, Herbaepimedii, Radix glycyrrizae*	Hemagglutination inhibition (HI) antibody titer method	(Liu *et al.*, 2010)
38	*Rutagraveolens*	Activation of pro-inflammatory proteins in HMGB1 activated HUVECs in mice.	(Ye *et al.*, 2014)
39	*Scutellariaaltissima L.*	lipopolysaccharide (LPS) mediated vascular inflammatory response model	(Lee *et al.*, 2015)
40	*Scutellariabaicalensis Georgi*	Human and mouse eosinophil apoptosis model	(Oh *et al.*, 2012)
41	*Scutellariaebaicalensis Georgi*	Anti-inflammatory activity on lipopolysaccharide induced macrophages in mice via Nrf2/ARE activation	(Ye *et al.*, 2014)
42	*Semecarpus Anacardium, Dalbergiaodorifera, Toxicodendronvernicifluum*	Nitric oxide suppression via gene supression	(Zhang *et al.*, 2011)
43	*Sinomeniumacutum (Thunb.) Rehd.etWils*	In vitro models of PMA plus A23187-stimulated HMC-1 Cells.	(Oh *et al.*, 2012)
44	*Sophora alopecuroides L.*	In vitro LPS-induced RAW 264.7 cells	(Shuai *et al.*, 2010)
45	*Sophora flavescens Ait*	LPS-induced acute lung injury in mice	(Zhang *et al.*, 2011)
46	*Sophora subprosrate*	Dexamethasone-induced immunosuppression in mice.	(Shuai *et al.*, 2010)
47	*Stephania tetrandra*	IL-1β induced inflammation in Primary rat mesangial cells (PRMCs) similar to glomerulonephritis.	(Vaibhav *et al.*, 2010)
48	*Terminalia bellerica*	Delayed type hypersensitivity reaction induced by sheep red blood cells (SRBC)	(Choudhary, 2012)
49	*Tinospora cordifolia*	SDS-PAGE, Periodic acid Schiff staining in vitro	(Aranha *et al.*, 2012)
50	*Tinospora cordifolia*	Cyclophosphamide induced method	(Vaibhav *et al.*, 2010)
51	*Uncariarhynchophylla (Miq.) Jack*	In vitro LPS-induced pro-inflammatory responses	(Aranha *et al.*, 2012)

Phytomedicine gained its importance recently in this arena and this article is one of the attempts to review the immunomodulatory plants that have been investigated for activity after 2010.

CONCLUSIONS

Medicinal plants and natural drugs are used as potent sources of immunomodulation and contributors for the derivation of the leads responsible for the development of immunomodulatory agents. The drug discovery and isolation of those leads from the herbal origin are more specific in the chemotherapy. Apart from the advantages of the herbal medicines in view of their safety and potency, the limitations for the use of herbs concerning their variations in the quantity of chemical constituents had to be addressed. The inconsistency of the *in vivo* response with the phytochemicals is also a limiting step for their effective usage as immunomodulatory agents. Overall, herbs had been supplying the chemical constituents that can be used directly or in the purified form as immunomodulatory agents.

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Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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