Immunomodulation: Herbal perspective and investigations - A review

Kasula Masthanaiah*, Karthikeyan E
Department of Pharmacy, Vels Institute of Science, Technology & Advanced Studies, Pallavaram, Chennai-600117, Tamil Nadu, India

Article History:
Received on: 21 Sep 2020
Revised on: 18 Oct 2020
Accepted on: 21 Oct 2020

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 \textit{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.

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 \cite{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-base ment 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 (Dihydro orotate 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 immunomodulatory 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, antiaging 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. Phytomedicine gained its importance...
Table 1: List of plant investigated for immunomodulatory activity.

| S No | Plant name | Method | Reference |
|------|------------|--------|-----------|
| 1    | Allium sativum, Zingiber officinale, Azadirachta indica, Berberis lycium Aloe vera (Linn) | Determination of antibody titer method | (Nidaullah et al., 2010) |
| 2    | Aloe vera (Linn) | Pyrogallol induced immunosuppression in rats | (Nidaullah et al., 2010) |
| 3    | Angelica sinensis (Oliv.) Diels | Determination of antibody titer method | (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 | Haemagglutination titer 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
| 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   | *Gentianaalivieri*         | Hemagglutination antibody titre method, *in vivo* carbon clearance or  | (Nidaullah et al., 2010)       |
|      |                            | phagocytosis in rats                                                  |                                |
| 21   | *Glycine max*              | Amyloid beta (A-beta) induced inflammatory mediators models           | (Valles et al., 2010)          |
| 22   | *Glycyrrhiza glabra*       | Carbon clearance method                                                | (Mishra et al., 2012)          |
| 23   | *Helichrysum italicum*     | In vitro HIV-1 replication in T cells, Carrageenan-induced pleurisy in| (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*    | Contusion spinal cord injury in rats (SCI).                            | (Hu et al., 2013)              |
| 27   | *Lithospermum erythrorhzyon* | TPA induced ear edema in rats. Invitro macrophages RAW 264.7 cells    | (Andújar et al., 2010)         |
|      | *Hort*                     | stimulated with lipopolysaccharide.                                    |                                |
| 28   | *Lycoris radiate*          | lipopolysaccharide-induced invitro iNOS and COX-2 upregulation in RAW264.7 | (Zhang et al., 2011)           |
|      |                            | cells                                                                  |                                |
| 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*           | Visceral leishmaniasis in BALB/c mouse model.                          | (Bhalla et al., 2017)          |
|      | *Linn*, Cocos nucifera Linn | Mast cell-based in vitro and in vivo models                            | (Bae et al., 2011)             |
| 33   | *Picea crassifolia*        | In vitro model of Rabbit platelets and murine macrophage RAW264.7 cells | (Nidaullah et al., 2010)       |
| 34   | *Piper longum Linn*        |                                                                        |                                |

*Continued on next page*
| 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* Radigraveolens | Hemagglutination inhibition (HI) antibody titer method | (Liu et al., 2010) |
| 38   | *Scutellariaaltissima* L. | Activation of pro-inflammatory proteins in HMGB1 activated HUVECs in mice. | (Ye et al., 2014) |
| 39   | *Scutellariaabaicalensis* Georgi | Lipopolysaccharide (LPS) mediated vascular inflammatory response model | (Lee et al., 2015) |
| 40   | *Scutellariaabaicalensis* Georgi | Human and mouse eosinophil apoptosis model | (Oh et al., 2012) |
| 41   | *Scutellariaeaicalensis* Georgi | Anti-inflammatory activity on lipopolysaccharide induced macrophages in mice via Nrf2/ARE activation | (Ye et al., 2014) |
| 42   | *Semecarpus Anacardium*, *Dalbergiaodorifera*, *Toxicodendronverniciulum* Sinomeniumacutum (Thunb.) Rehd.etWils | Nitric oxide suppression via gene suppression | (Zhang et al., 2011) |
| 43   | *Sophora alopecuroides* L. | In vitro models of PMA plus A23187-stimulated HMC-1 Cells. | (Oh et al., 2012) |
| 44   | *Sophora flavescens* Ait | In vitro LPS-induced RAW 264.7 cells | (Shuai et al., 2010) |
| 45   | *Sophora subprosrate* | LPS-induced acute lung injury in mice | (Zhang et al., 2011) |
| 46   | *Stephania tetrandra* | Dexamethasone-induced immunosuppression in mice. | (Shuai et al., 2010) |
| 47   | *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   | *Uncariahynchophylla* (Miq.) Jack | In vitro LPS-induced pro-inflammatory responses | (Aranha et al., 2012) |
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.

ACKNOWLEDGEMENT

Sincere thanks to Dr G. Avinash Kumar, Associate Professor, Rao’s College of Pharmacy, Nellore, for his support in the compilation of the article. 

Funding Support

The authors declare that they have no funding support for this study.

Conflict of Interest

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

REFERENCES

Agrawal, S. S., et al. 2010. Studies on Immunomodulatory Activity of Capparis zeylanica Leaf Extracts. International Journal of Pharmaceutical Sciences and Nanotechnology, 3(1):887–892.

Andújar, I., et al. 2010. Shikonin reduces oedema induced by phorbol ester by interfering with IκBα degradation thus inhibiting translocation of NF-κB to the nucleus. British Journal of Pharmacology, 160(2):376–388.

Anjum, V., et al. 2017. Antithrombocytopenic and immunomodulatory potential of metabolically characterized aqueous extract of Carica papaya leaves. Pharmaceutical Biology, 55(1):2043–2056.

Aranha, I., et al. 2012. Immunostimulatory properties of the major protein from the stem of the Ayurvedic medicinal herb, guduchi (Tinospora cordifolia). Journal of Ethnopharmacology, 139(2):366–372.

Asad, M., et al. 2012. Immunomodulatory activity of cod liver oil. Iranian Journal of Pharmacology and Therapeutics, 11(2):20–25.

Bae, Y., et al. 2011. Chrysín suppresses mast cell-mediated allergic inflammation: Involvement of calcium, caspase-1 and nuclear factor-κB. Toxicology and Applied Pharmacology, 254(1):56–64.

Bhalla, G., et al. 2017. Antileishmanial and immunomodulatory potential of Ocimum sanctum Linn. and Cocos nucifera Linn. in murine visceral leishmaniasis. Journal of Parasitic Diseases, 41(1):76–85.

Bharani, S. E. R., et al. 2010. Immunomodulatory activity of methanolic extract of Morus alba Linn. (mulberry) leaves. Pakistan Journal of Pharmaceutical Sciences, 23(1):63–68.

Choudhary, G. P. 2012. Immunomodulatory activity of alcoholic extract of Terminalia bellerica Linn. in mice. Scholars Research Library, 4(2):414–417.

Hu, J. Z., et al. 2013. Tetramethylpyrazine accelerates the function recovery of the traumatic spinal cord in a rat model by attenuating inflammation. Journal of the Neurological Sciences, 324(1-2):94–99.

Kremer, J. M., et al. 1994. Methotrexate for rheumatoid arthritis. Suggested guidelines for monitoring liver toxicity. Arthritis and Rheumatism, 37(3):316–328.

Lee, W., et al. 2015. Anti-inflammatory effects of Baicalin, Baicalein and Wogonin In Vitro and In Vivo. Inflammation, 38(1):110–125.

Liu, F. X., et al. 2010. Analysis of immunological enhancement of immunosuppressed chickens by Chinese herbal extracts. Journal of Ethnopharmacology, 127(2):251–256.

Mishra, N., et al. 2012. Immunomodulation by Hibiscus rosa-sinensis: Effect on the Humoral and Cellular Immune Response of Mus Musculus. Pakistan Journal of Biological Sciences, 15(6):277–283.

Nidaullah, H., et al. 2010. Aqueous extract from different medicinal plants as anticoccidial, growth promotive and immunostimulant in broilers. Journal of agricultural and biological science, 5:53–59.

Oh, Y., et al. 2012. Anti inflammatory effect of sinomenine by inhibition of pro inflammatory mediators in PMA plus A23187 stimulated HMC-1 cells. European review for medical and pharmacological sciences, 16(6):1184–1191.

Patil, P. R., et al. 2013. Immunomodulatory effects of fruits of Barringtonia racemosa Linn. International Journal of Basic & Clinical Pharmacology, 2(2):216–219.
Patil, V. V., et al. 2010. Studies on immunomodulatory activity of ficus carica. *International Journal of Pharmacy and Pharmaceutical Sciences*, 2:97–99.

Richard, A. G., et al. 2003. *Immunology, Fifth Edition*. W. H. Freeman. Pages: 1-5.

Shuai, X. H., et al. 2010. Immunomodulatory effect of a Sophora subprosrate polysaccharide in mice. *International Journal of Biological Macromolecules*, 46(1):79–84.

Vaibhav, D., et al. 2010. Pharmacological study of tinospora cordifolia as an immunomodulator. *International Journal of Current Pharmaceutical Research*, 2(4):52–54.

Valles, S. L., et al. 2010. Estradiol or genistein prevent Alzheimer's disease-associated inflammation correlating with an increase PPARγ expression in cultured astrocytes. *Brain Research*, 1312:138–144.

Xu, Y. K., et al. 2012. Gelsemum alkaloids, immunosuppressive agents from Gelsemium elegans. *Fitoterapia*, 83(6):1120–1124.

Ye, M., et al. 2014. Oroxylin A exerts anti inflammatory activity on lipopolysaccharide induced mouse macrophage via Nrf2/ARE activation. *Biochemistry and Cell Biology*, 92(5):337–348.

Zhang, B., et al. 2011. Antiinflammatory effects of matrine in LPS-induced acute lung injury in mice. *European Journal of Pharmaceutical Sciences*, 44(5):573–579.