



International Journal of Research in Pharmacology & Pharmacotherapeutics (IJRPP)

IJRPP | Vol.14 | Issue 1 | Jan - Mar -2025

www.ijrpp.com

DOI : <https://doi.org/10.61096/ijrpp.v14.iss1.2025.84-88>

ISSN: 2278-2648

Review

The Role Of Immunostimulants In Improving The Immunity In Autoimmune Diseases

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	Abstract
Published on: 08 Feb 2025	<p>The proper functioning of human immune system is essential for organism survival against infectious, toxic and oncogenic agents. Immunomodulators are natural or synthetic materials that regulate the immune system and induce innate and adaptive defense mechanisms. These substances are classified into two types, immunostimulants and immunosuppressants. Immunostimulants can enhance body's resistance against various infections through increasing the basal levels of immune response. These agents could increase the oxidative activity of neutrophils, augment engulfment activity of phagocytic cells and stimulate cytotoxic cells as necessary defense mechanisms. The immunostimulants are classified on the basis of origin and mode of action such as bacterial products, complex carbohydrates, vaccines, cytokines, immunoenhancing drugs, nutritional factors, animal extracts, and plant extracts. The link between immune system with diet, exercise, sleep, stress, microbial exposure, alcohol, water, hygiene are found to influence the immune response to a greater extent. Immunostimulants and some immunity enhancing nutrients improve the functioning of the immune system.</p>
Published by: DrSriram Publications	
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	Keywords: Immunomodulators, Immunostimulants, Adjuvant, Mechanism, Immune system

INTRODUCTION

Two main compounds are able to enhance immune responses including adjuvants and immunostimulants. An adjuvant is a substance combined with an antigen for increasing its immune response, but an immunostimulant can induce the immune response without injection with an antigen. There are several types of stimulants with different mechanisms and functions such as bacterial products, complex carbohydrates (e.g.,

glucans, schizophyllan, scleroglucan, lentinan, statolon, bestatin, acemannan), vaccines, immunoenhancing drugs (e.g., Levamisole, Isoprinosine, Fluoro-quindone, Avridine, Polyribonucleotides), nutritional factors (e.g., vitamins, carotenoids, lipids, trace elements, selenium), animal extracts (e.g., chitosan from shrimp), cytokines (e.g., macrophage activating factor, interferon, interleukin-2, tumor necrosis factor), and plant extracts (e.g., Lectins, mitogens such as phytohemagglutinin, concanavalin A). Two main approaches were determined to evaluate the efficiency of an immunostimulant such as in vivo protection against pathogens, and in vitro assay of cellular and humoral immune mechanisms. In vitro tests should be performed before in vivo experiments to clarify the basic mechanisms responsible for the protection. In vitro immunostimulant evaluation is usually based on some parameters such as serum lysozyme, complement, total leucocyte count, monocyte/lymphocyte/granulocyte count, antibody titers, phagocytosis, respiratory burst and leucocyte proliferation. Immunomodulation can be either specific or non-specific. Specific immunomodulation is limited to a single antigen such as vaccination, whereas non-specific immunomodulation leads to a further change in immune response both in innate and adaptive immunity causing altered host reactivity to many various antigens¹.

Due to the absence of specific vaccines to many diseases, other methods of prophylaxis are tried which includes use of immunostimulants, bioremediators and probiotics. Fish depends on non-specific defence mechanisms more heavily for health maintenance, so immunostimulants play a significant role in the management of fish health and disease control. Immunostimulant is a chemical, drug, stressor or action that elevates the non-specific defence mechanisms by increasing phagocytosis, leucocytic activity, macrophage and neutrophil migration or specific immune response².

In addition, they also reduce the immune suppressive effects of stress. Different compounds like select proteins, lipids, carbohydrate based cell wall extracts and synthetic compounds have been used as immunostimulants in farm reared fish and shellfish. The immunostimulants used in aquaculture include glucans, lipopolysaccharides, chitin, chitosan, peptidoglycans, muramyl dipeptides, polypeptides, levamisole, Vitamin C, Vitamin E etc³.

Pharmacology

Concept of Immunostimulants

Immunostimulants known as immunostimulators are biologically active substances; are the products derived from natural sources or synthetically made with different chemical properties and mechanisms of action. These are attractive substances that activate the immune system of humans and animals for prevention of diseases and improvement of the body's natural resistance to various viral and bacterial infections. In general, immunostimulants induce synthesis of specific antibodies and cytokines for treatment of infectious diseases. Two major groups of immunostimulants contain a) specific immunostimulants acting as antigen for stimulation of immune responses (e.g., vaccines), and b) non-specific immunostimulants without antigenic properties enhancing immune responses to other antigens (e.g., adjuvants and non-specific immunostimulators). Moreover, immunostimulants were classified based on their origin and mode of action⁴⁻⁵.

Types of Immunostimulants

Immunostimulants are divided into seven groups such as bacterial products, complex carbohydrates, vaccines (antigens and adjuvants), cytokines, immunoenhancing drugs, plant extracts, and animal extracts. The immunostimulatory drugs (Endogenous immunostimulants or Synthetic immunostimulants) have been developed to induce humoral or cellular immune responses or both of them against bacterial or viral infections, immunodeficiency diseases, and cancer.

They were classified as follows:

a) Levamisole (Ergamisol):

Levamisole is a synthetic drug inducing B and T lymphocytes, monocytes, and macrophages. It was used in adjuvant therapy with 5-fluorouracil after surgical resection in patients with Duke's stage C colon cancer. Its disadvantages are allergy, nausea, flu, and muscle pain. Levamisole has been successfully used in combination with polymers for treatment of dermatologic disorders. For example, it was combined with cimetidine for treating recalcitrant warts, and with prednisolone for treating aphthous ulcers of the mouth⁶⁻⁷.

b) Thalidomide: Thalidomide or Immunoprin is an immunomodulatory drug. Thalidomide could decrease circulating TNF- α in patients with erythema nodosum leprosum. In contrast, it increased TNF- α in HIV seropositive patients. Furthermore, its therapeutic effects were determined in severe rheumatoid arthritis and angiogenesis.

c) Isoprinosine: Isoprinosine is a combination of inosine, acetamidobenzoic acid, and dimethylamino isopropanol. Isoprinosine could enhance the levels of cytokines including IL-1, IL-2, and IFN- γ . It increased the proliferation of lymphocytes against mitogenic or antigenic stimuli. Moreover, Isoprinosine augmented active T-cells and induced T-cell surface markers on prothymocytes. It was used to treat Herpes simplex infections, Epstein-Barr, and Measles viruses. Its disadvantages are minor CNS depressant, transient nausea, and increased level of uric acid in serum and urine⁸.

d) Immunocynin:

Immunocynin is a stable form of haemocynin, a copper-containing protein, found in molluscs and arthropods. It was used to treat urinary bladder cancer with poor side effects such as rare-mild fever.

e) Bestatin:

Bestatin, a dipeptide [(2S, 3R)-3-amino-2-hydroxy-4-phenylbutanoyl]-L-leucine, is an immunostimulant with low toxicity which binds to the cell surface of lymphocytes and macrophages and enhances both humoral and cellular immune responses. It is a leucine aminopeptidase and aminopeptidase-B inhibitor. Bestatin possesses antitumor activity and also increase the antitumor activity of bleomycin and adriamycin. Bestatin efficiently prevented the metastasis of P388 leukemia when the antibiotic was constantly injected after tumor inoculation. The dipeptide was immunorestorator in the elderly and cancer patients and HIV-infected subjects. It stimulated

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Bacterial products

The immunostimulatory effects of bacteria and bacterial products are due to the release of cytokines. Live bacillus Calmette-Guerin (BCG) is an attenuated, live culture of the bacillus of Calmette and Guerin strain of *Mycobacterium bovis*. Its mechanism of action includes: a) induction of a granulomatous reaction at the site of administration, and b) prevention and treatment of carcinoma types. Furthermore, BCG enhances both B and T cell-mediated responses leading to phagocytosis and resistance to infection. Its disadvantages are hypersensitivity, fever, shock, and immune complex disease⁹⁻¹⁰.

Recombinant cytokines

Several interferons and interleukins are suggested to stimulate effective immune responses. Interferons could be obtained from trout leucocytes after stimulation with mitogens. It was able to cause an in vitro resistance against pancreatic necrosis virus in trout cells. In mammalian, low doses of interferon could induce stable positive results without side effects. On the other hand, vaccination of animals with the recombinant IL2 against different infections increased the protective effects. However, IL-2 was a very toxic compound in high doses causing side effects such as fever and diarrhea. The purified cytokines showed unsatisfactory results in clinical trials, because the immune responses were produced by a mixture of cytokines generated by the immune cells, but not against a single cytokine. Thus, the enhancers of nonspecific cytokine synthesis may improve immune responses and solve this problem. Thus, recombinant cytokines are produced recently in different expression systems (e.g., plants) and used in clinical trials such as interferons, TNF- α and IL-2.

Immunostimulants used in vaccines

Vaccines contain a wide range of immunostimulants. For example, an adjuvant heat-labile enterotoxin from *Escherichia coli* (LT), administered as an immunostimulant (LT-IS) patch on the skin may further enhance immune responses to influenza vaccine in the elderly. Also, the immune activation mediated by LT-IS improved the potency of generating Alzheimer's disease (AD)-specific vaccination responses as an adjuvant in the clinical trial. Co-administration of a potent adjuvant in IS patches containing heat-labile enterotoxin from *E. coli* placed on the skin at the site of DNA vaccination significantly increased anti-influenza antibody immune response. Adjuvants enhance and modulate immune responses to antigens. This is important when the purified antigens do not elicit the effective innate or adaptive immune systems. Adjuvants are different in the types and levels of immune responses. Expected advantages of adjuvants contain stronger immune priming, effective immune responses in low-response populations (e.g., the elderly or immuno-compromised patients), the use of smaller amounts of the antigen, and safety profile.

New adjuvants have already applied to more efficient influenza vaccines, as well as vaccines targeting hepatitis B (HBV) and human papillomavirus (HPV). On the other hand, CpG oligonucleotides and imiquimod drugs (an antiviral agent) could activate dendritic cells, induce in situ maturation and migration of DCs, and

augmented both humoral and cellular immune responses. The unmethylated CpG motif in bacterial DNA was identified as a B-cell stimulating adjuvant, and synthetic oligodeoxynucleotides (ODNs) containing the CpG motifs were shown to induce potent therapeutic activities in different infections and tumor animal models. Imiquimod was typically used for patients with anogenital warts as well as basal-cell carcinoma. The studies indicated that CpG ODNs and imiquimod (resiquimod) drugs act as synthetic ligands for TLR9 and TLR7, respectively, and both stimulate efficiently DC maturation¹¹⁻¹³.

Plant derived immunostimulants

Natural plant product promote various activities such as anti-stress, growth promotion, appetite stimulation, immunostimulation, aphrodisiac and antimicrobial properties, due to the active substances such as alkaloids, flavanoids pigments, phenolics, terpenoids, steroids, and essential oils. Medicinal plants have been known as immunostimulants, growth promoters, immune enhancers, where they act as antibacterial and antiviral agents to the host immune system. Unfortunately, the mechanisms were not understood¹⁴⁻¹⁶.

Some medicinal plants were described as following:

- a) *Ocimum sanctum* (Tulsi): Leaves of *O. Sanctum* containing water-soluble phenolic compounds and various other constituents may act as an immunostimulant. Leaves extract of *O. sanctum* affected both specific and nonspecific immune responses. It stimulated both antibody response and neutrophil activity.
- b) *Phyllanthus emblica* (Amla): *P. emblica* has antioxidant, anti-fungal, anti-microbial.

Immunomodulators are natural or synthetic materials that regulate the immune system and induce innate and adaptive defense mechanisms. These substances are classified into two types, immunostimulants and immunosuppressants. Immunostimulants can enhance body's resistance against various infections through increasing the basal levels of immune response. These agents could increase the oxidative activity of neutrophils, augment engulfment activity of phagocytic cells, and stimulate cytotoxic cells as necessary defense mechanisms. Many disorders could be treated using some immunostimulants such as autoimmune diseases, viral infections, and cancer. The researchers classified the immunostimulants using their origin and mode of action such as bacterial products, complex carbohydrates, vaccines (antigens and adjuvants), cytokines, immunoenhancing drugs, nutritional factors, animal extracts, and plant extracts¹⁷⁻²⁰.

CONCLUSION

Currently many viruses causing dangerous infections in human beings, in these situations, the immunostimulants or vaccines are helpful to prevent the infections or reduces the severity of disease. Hence the immune stimulants are significantly important in future.

ACKNOWLEDGEMENT

MRM College of Pharmacy, Chintapallyguda, Hyderabad, provided facilities to complete this work.

REFERENCES

1. Carter D, Reed SG. Role of adjuvants in modeling the immune response. *Curr Opin HIV AIDS*. 2010; 5 (5): 409-13.
2. Galeotti M. Some aspects of the application of immunostimulants and a critical review of methods for their evaluation. *J Appl Ichthyol*. 1998; 14 (3-4): 189-99.
3. Dhama K, Saminathan M, Jacob SS, Singh M, Karthik K, Amarpal, Tiwari R, Sunkara LT, Malik YS, Singh RK. Effect of immunomodulation and immunomodulatory agents on health with some bioactive principles, modes of action and potent biomedical applications. *Int J Pharmacol*. 2015; 11 (4): 253-90.
4. Labh SN, Shakya SR. Application of immunostimulants as an alternative to vaccines for health management in aquaculture. *Int J Fish Aquat St*. 2014; 2 (1): 153-6.
5. Petrunov B, Nenkov P, Shekerdjiisky R. The role of immunostimulants in immunotherapy and immunoprophylaxis. *Biotechnol & Biotechnol Eq*. 2007; 21(4): 454-63.
6. Patil US, Jaydeokar AV, Bandawane DD. Immunomodulators: A pharmacological review. *Int J Pharm Pharm Sci*. 2012; 4 (1): 30-6.
7. Biswajit D, Suvakanta D, Chandra CR, Jashabir C. An overview of levamisole hydrochloride with immunostimulant activity. *Am J Pharm Health Res*. 2014; 2 (4): 1-9.
8. Tsuruo T, Naganuma K, Iida H, Yamori T, Tsukagoshi S, Sakurai Y. Inhibition of lymph node metastasis of P388 leukemia by bestatin in mice. *J Antibiot (Tokyo)*. 1981; 34 (9): 1206-9.
9. Mathe G. Bestatin, an aminopeptidase inhibitor with a multipharmacological function. *Biomed Pharmacoter*. 1991; 45: 49-54.

10. Sirko A, Vanek T, Gora-Sochacka A, Redkiewicz P. Recombinant cytokines from plants. *Int J Mol Sci*. 2011; 12 (6): 3536-52.
11. Sahoo PK, Mukherjee SC. Effect of dietary β -1, 3 glucan on immune responses and disease resistance of healthy and aflatoxin B1-induced immunocompromised rohu (*Labeo rohita* Hamilton). *Fish Shellfish Immunol*. 2001; 11 (8): 683-95.
12. Madrigal-Bujaidar E, Morales-González JA, SánchezGutiérrez M, Izquierdo-Vega JA, Reyes-Arellano A, ÁlvarezGonzález I, Pérez-Pasten R, Madrigal-Santillán E. Prevention of aflatoxin B1-induced DNA breaks by β -D-glucan. *Toxins (Basel)*. 2015; 7 (6): 2145-58.
13. Vetvicka V. Glucan-immunostimulant, adjuvant, potential drug. *World J Clin Oncol*. 2011; 2 (2): 115-9.
14. Davtyan H, Ghochikyan A, Hovakimyan A, Petrushina I, Yu J, Flyer D, Madsen PJ, Pedersen LO, Cribbs DH, Agadjanyan MG. Immunostimulant patches containing *Escherichia coli* LT enhance immune responses to DNA and recombinant proteinbased Alzheimer's disease vaccines. *J Neuroimmunology*. 2014; 268 (1-2): 50-7.
15. Mkrtychyan M, Ghochikyan A, Movsesyan N, Karapetyan A, Begoyan G, Yu J, Glenn GM, Ross TM, Agadjanyan MG, Cribbs DH. Immunostimulant adjuvant patch enhances humoral and cellular immune responses to DNA immunization. *DNA Cell Biol*. 2008; 27 (1): 19-24.
16. Garçon N, Leroux-Roels G, Cheng WF. Understanding modern vaccines: Perspectives in Vaccinology. Elsevier BV. 2011; 1: 89-113. 23. Pasquale AD, Preiss S, Da Silva FT, Garçon N. Vaccine adjuvants: from 1920 to 2015 and Beyond. *Vaccines (Basel)*. 2015; 3 (2): 320-43.
17. Parant M, Audibert F, Parant F, Chedid L, Soler E, Polonsky J, Lederer E. Non-specific immunostimulant activities of synthetic Trehalose-6, 6'-Diester. *Infect Immun*. 1978; 20 (1): 12-9.
18. Oswald IP, Dozois CM, Petit JF, Lemaire G. Interleukin-12 synthesis is a required step in Trehalose Dimycolate-induced activation of mouse peritoneal macrophages. *Infect Immun*. 1997; 65 (4): 1364-9.
19. Song SK, Beck BR, Kim D, Park J, Kim J, Kim HD, Ringø E. Probiotics as immunostimulants in aquaculture: A review. *Fish Shellfish Immunol*. 2014; 40 (1): 40-8.
20. Frech SA, Kenney RT, Spyr CA, Lazar H, Viret JF, Herzog C, Glück R, Glenn GM. Improved immune responses to influenza vaccination in the elderly using an immunostimulant patch. *Vaccine*. 2005; 23 (7): 946-50.