International Research Journal of Education and Technology
ISSN 2581-7795

Immunomodulators: Miraculous Agents in Therapeutics

Akanksha Chaturvedi[1], Swarnima Negi[2], Dr. Sachdev Yadav[3]

[1,2]M. Pharm Scholar, Department of Pharmacology, Banasthali Vidyapith, Rajasthan, India
[3]Associate Professor, Department of Pharmacology, Banasthali Vidyapith, Rajasthan, India

----------***----------

Abstract – *The immune system is essentially one of the most incredible systems of our body. It is the invisible protective shield of our body that functions at the molecular level to combat hundreds of antigens to which the body is exposed from waking up in the morning and till we go to bed. These antigens may be present as animate or inanimate substances which excite either innate or adaptive immunity within the exposed body. The complex nature of the immune cells is not yet fathomed completely. Where on one hand they are the competent defense mechanism of the body but at the same time, they surge a war within the body of the patients with different autoimmune disorders like Multiple Sclerosis, Myasthenia Gravis, etc without the trace of a definite cause. Modulation is a process through which we can make the changes according to our needs and requirements. Immunomodulation is one such method through which we can have a grip on one of the most powerful systems of the body which is indeed a great achievement in medical sciences as it can surely benefit different health conditions. The review article gives crisp information regarding the immunomodulators that are present naturally or produced synthetically to rectify the altered harmony within the body.*

Key Words: Immunomodulators, Immunoadjuvant, Recombinant cytokines, IL-2, Autoimmune disorders.

1. INTRODUCTION

Immunomodulation encompasses modification of the ongoing immune response, it can be by suppressing the overactive immune response or potentiating the compromised immune response to maintain perfect harmony within the body. It is one such method through which we can have a grip on one of the most powerful systems of the body which is indeed a great achievement in medical sciences as it can surely benefit different health conditions. Immunomodulation becomes an absolute necessity in two cases. The first case is of immunodeficiency, which characterizes all the pathological conditions either acquired or congenital conditions in which the immune response is greatly disturbed like HIV AIDS. Second, being the cases where the generation of the immune response against the specific pathological condition is not even reaching the threshold limit. In such cases, immunomodulators play an important role to give a slight push to the immune system to work in the desired manner.

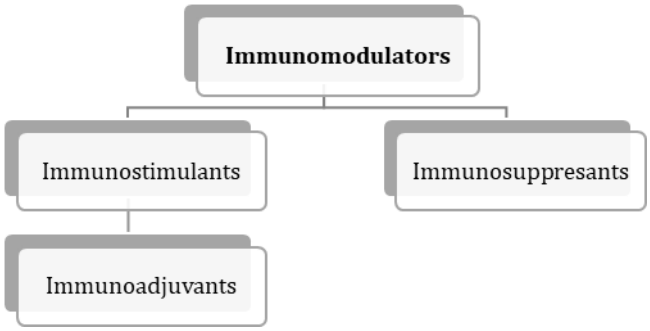

Figure – 1: Immunomodulators broad classification

Requirement of Immunomodulation

Immunomodulation is the process that encompasses both aspects i.e. potentiating the ongoing immune response and suppressing the overactive immune system. Depending upon the pathological condition, the immune system is modulated with the help of different molecules obtained either from natural sources or prepared synthetically. Some of the pathological conditions are mentioned which require the modulation of the immune system to overcome the diseased condition.

Immunomodulation to increase the immune response

Cancer Therapy

Cancer immunotherapy is one of the leading areas of research. there have been certain theories that a strong immune system fights against the tumor. Therefore immunostimulants are generally given to patients

suffering from cancer. Recombinant cytokines (IL-2) are given to enhance the production of antibodies and other immune cells.

Acquired Immunodeficiency Syndrome

Immunodeficiency can be because of various underlying factors such as exposure to any infection via virus or bacteria, chemotherapy (cancer), or malnutrition. The biggest challenge of the medical sciences is to revive the lost immunity within the individual suffering from AIDS. The retrovirus attacks the immune cells only and makes the host completely hollow from inside that person dies because of the opportunistic or secondary infection. Thus, along with the HAAT immunostimulant therapy is also given to those people to boost their immunity, mostly recombinant cytokines are preferred like IL-2 to increase the level of the immune cells.

Immunomodulation to decrease the immune response

Autoimmune Disorders

The autoimmune disorders are characterized by the overactive nature of the immune system in which it fails to detect the body's tissues and starts acting against them. Many autoimmune disorders have come to light over the century which can be distinguished as organ-specific or systemic autoimmune disorders. In former specific organ or part of the organ is targeted by the immune cells specifically T cells for example multiple sclerosis rheumatoid arthritis, myasthenia gravis, etc. Systemic autoimmune disorders are the ones that are not limited to one specific organ but affect more than one organ at a time for example systemic lupus erythematosus. Each one of them has one thing in common that the immune response gets violent and takes the body and the organs as foreign antigen or non-self body part. To stop the overactive behavior of the immune system the immunosuppressant therapy is given to the patients to decrease the immune attack within the body.

Immediate Hypersensitivity Reactions (Type 1)

Allergy or hypersensitivity is one of the common ailments in which the immune response is increased within the body. It is mediated by the degranulation of mast cells to release histamine when IgE antibodies attach to the mast cell surface receptors. It can be due to two basic reasons first being triggered by any extrinsic factor or genetically predisposed abnormality. The histamine released in case of any external stimulation (Allergen) by lead to the stimulation of IgE antibodies has varied effects on the body it precipitates extrinsic asthma, eczema, allergic rhinitis. In the case of a genetically predisposed individual, in this case, histamine release will be very high within the body. Histamine being a vasoactive substance has an adverse effect on two vital organs of the body that are the cardiovascular system and the respiratory system which can lead to severe anaphylactic shock. Therefore to avoid the collapse of vital organs by suppressing the immune response immunosuppressant therapy is recommended in Type I hypersensitivity reactions.

2. IMMUNOSTIMULANTS

The immunostimulants are said to be immunopotentiators or immunotherapeutics. They not only improve the ongoing immune response and the body's natural resistance towards different antigens but also fix the impaired immune system within the body. The main reason to use immunostimulants in different pathological conditions is that it provides non-specific immunotherapy that means it acts on almost all cells of the immune system and potentiates their functioning. It acts on phagocytic cells and enhances their engulfing property, increases the oxidative property of neutrophiles, and enhances the costimulatory factors such as cytokines and interferons which eventually increase the production of different immunoglobulins. It also stimulates the production of different cells such as cytotoxic T cells to overcome the different pathological illnesses. The immunostimulants are the wide category which comprises of specifically subcategorized into two major groups.

International Research Journal of Education and Technology
ISSN 2581-7795

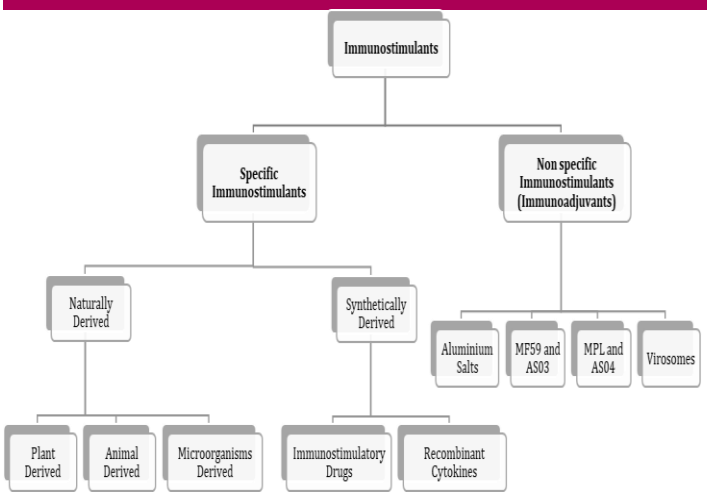

Figure – 2 Immunostimulants classification

2.1 Specific Immunostimulants

They have enough immunogenic properties that they can induce the immunological response all by themselves. They act as the antigen and mediate the immunological response on their own. There is an abundance of such substances in nature as well as to modulate the immune response they are developed synthetically as well.

Naturally derived Immunostimulants

The naturally derived immunostimulants are obtained from different sources such as plants, animals, and microorganisms having their different mechanism of action to potentiate the immune response towards a particular antigen or different antigens.

- **Plants Derived Immunostimulants**

Phytochemicals derived from a wide range of plants have the ability to regulate immunological responses. The secondary metabolites such as alkaloids, flavonoids, terpenoids, steroids show excellent immunostimulant activity when given appropriately. They exhibit a wide range of activity and potentiate the immune response by enhancing the activity of different immune cells. The amalgamation of immunostimulant properties along with antibacterial, antiviral activity, and anti-tumor activity made them irreplaceable, and because of their impeccable response majority of them are already part of the Indian household kitchen for ages. Table 1 is depicting majority of the plants that are being used as immunostimulators along with the mode of action.

Plant Species	Mechanism of action
Eclipta alba (Bhringraj)	Increases the phagocytic potential with increased WBC count.
Crocus sativus (Saffron)	Enhances the secretion of TNF-∝ and boosts the immunity by proliferating T and B cells especially NK cells, cytotoxic T cells, and macrophages.
Ocimum sanctum (Tulsi)	Increases the production of IFN-γ, IL-4, T- helper cells, and Natural Killer cells. It also increases the activity of neutrophils and amplifies the antibody response.
Azadirachta indica (Neem)	Stimulates the production of IFN-γ, IL-1, and TNF-∝
Zingiber officinale (Ginger)	Stimulate the production of neutrophils, lymphocytes, and macrophages. Enhances the phagocytic and lysozyme activities.
Phyllanthus emblica (Amla)	Enhance the activity of Natural Killer cells. It mitigates the abundance of reactive oxygen and nitrogen species within the cell that can trigger the mutation which causes cancer and other neurodegenerative disorders.
Allium sativum	Stimulate the production of overall lymphocytes especially T lymphocytes and NK cells.
Withania somnifera	Stimulates the production of IL-1 and TNF-∝.
Aloe vera	Enhances the cellular lysozyme activity, and especially increases the production of IgM antibodies.
Panax ginseng	Stimulate the production of cytokines and eventually enable antibody production. It enables macrophage migration to the site of infection.
Nyctanthes arbortristis (Jasmine)	Enhance the cellular lysozyme activity and inhibit the production of myeloperoxidase (MPO), reactive nitrogen, and oxygen species.

Table -1 Plant-derived Immunostimulants

- **Animal Derived Immunostimulants**

There is not a wide range of immunostimulants derived from the animal-origin but chitosan and EF203 (fermented product of chicken egg) have shown appreciable immunomodulatory action. Amminopolysaccharide, chitin is obtained from the exoskeleton of the crustaceans (crabs, shrimps, lobsters, etc). The enzymatic deacetylation of chitin leads to the formation of the immunostimulatory product called chitosan. Chitosan has an antimicrobial effect but along with that, it is known for its potent immunostimulatory effect. It acts by stimulating the production of cytokines IL-1β, TNF-α, and ROS (reactive oxygen species) and thus activates the immune response within the body. On the other hand, EF203 (fermented product of chicken egg) potentiates the phagocytic potential of the leukocytes when tested in the animal model, therefore indirectly stimulating the ongoing immune response.

- **Microorganisms Derived Immunostimulants**

The release of cytokines is responsible for bacteria and bacterial compounds' immunostimulatory actions. BCG (bacillus Calmette-Guerin) is an attenuated, live culture of the Mycobacterium Bovis bacillus of Calmette and Guerin strain. It works by inducing a granulomatous reaction at the site of injection, as well as preventing and treating different types of cancer. BCG also boosts both B and T cell-mediated responses, resulting in phagocytosis and infection resistance.

Synthetically Derived

- **Immunostimulatory Drugs**

The drugs in this category were not conventionally used to elevate the immune response, but they are repurposed and after deep analysis. It was found out that some of the drugs used for diverse pathological conditions can enhance the immune response in different ways. They are only prescribed to a patient with severe immune deficiency disorders or the ones undergoing cancer chemotherapy. They are not given as immunity boosters for regular use because they may have severe adverse reactions when taken in long run.

Drug	Mechanism of action
Thalidomide	Enhance production of IL-2, IFN-γ and increase the susceptibility of NK cells against tumor cells.
Levamisole	B and T cells, monocytes, and macrophages to become activated.
Bestatin	Stimulate both humoral and cell-mediated immune response as it binds to the surface of the antigen-presenting cells.
Isoprinosine	Elevate the levels of cytokines IL-1, IL-2, and IFN- γ and boosts the proliferation rate of leukocytes on exposure to an antigen.

Table-2 Synthetically derived immunostimulatory drugs

- **Recombinant Cytokines**

These are the analogs of endogenously produced costimulatory factors such as cytokines and interferons, which help to increase the activity of the immune system by enhancing the production of different immune cells, which is dependent upon the co-stimulation by these factors. These recombinant cytokines are produced in the laboratory either by molecular cloning technique or by amplifying the particular DNA sequence via PCR and then integrated with the cloning vector. Laboratory-produced cytokines are more efficient in generating the immune response by increasing the proliferation of B and T lymphocytes. Interleukin-2 which goes by the name Aldesleukin and Proleukin is one such recombinant version of human interleukin-2 cytokine.

2.2 Non-Specific Immunostimulants (Immunoadjuvants)

The literal meaning of the word adjuvant is to help which is derived from the Latin word adjuvare. The adjuvants are substances that do not possess any immunological activity of their own but have a prominent effect on the vaccine's potency and efficacy. They aid the action of vaccines through different mechanisms and are also known to prolong the immunological memory of the immune cells against the antigen exposed. Producing an immune response either humoral or cellular is the multistep process, various immunoadjuvants have been classified which act on different steps and amplify the immune response by increasing the efficacy of the vaccine along which they are injected. The adjuvants act via different mechanisms within the body such as differentiation

and maturation of immune cells, uptake of antigens, making the APCs sensitive to a specific antigen, and inducing the production of cytokines. Almost all vaccines irrespective of their nature (attenuated live viral or bacterial vaccine or inactivated vaccine) mediate their actions with the help of Toll-Like Receptors (TLR). The down-cell signaling of these receptors helps to achieve the desired immunity within the individual. Therefore some immunoadjuvants tend to act via TL receptors and enhance the immunological process. Some adjuvants approved for human use and are extensively used along with the vaccines are described in Table 4. Several adjuvants are still under trial and show satisfactory results on the animal model but are toxic when used on humans for example mountainsides, inulin, AS01, AS02, Polyphosphazene, etc. Table 3 is highlighting some majorly clinically used adjuvants with the mechanism of action.

Adjuvant	Mechanism of action	Vaccines
Aluminum salts (Alum)	Depot effect It can retain the antigens in the specific sites within the body and release them slowly so that the immune response is prolonged. Increase phagocytosis and uptake of antigen. It acts on antigens and does not allow them to get solubilized in the cellular matrix rather it converts them into a particulate form so that it is recognized by the Antigen Presenting Cells easily. Differentiation and maturation of immune cells. It specifically facilitates the maturation of monocytes, macrophages into dendritic cells and indirectly activated the production of costimulatory cytokines (IL-4 and 5).	Hepatitis A Virus (HAV), Human Papilloma Virus (HPV), Haemophilus Influenzae Type B (HIB), Pertussis, Tetanus, Diphtheria, Inactivated Polio.
Monoposphoryl Lipid A (MPL) and AS04 It is MPL absorbed into alum salts.	Interact with TL receptor and increase the innate immunity by enhancing the production of different immune cells. Increasing the susceptibility of macrophages, monocytes, and dendritic cells for the antigen.	Human Papilloma Virus (HPV), Hepatitis B Virus (HBV)
Virosomes It is a liposome that is covered by the viral glycoprotein the antigen of interest mostly viral antigen is packed or crosslinked within the interior surface of the virosome.	Uptake of antigen Increase the antigen availability to dendritic cells and other antigen-presenting cells, which increases the immune response against the specific antigen.	Influenza Vaccine, Hepatitis A Virus (HAV)

Table – 3 Clinically approved immunoadjuvants used in varied vaccines

3. IMMUNOSUPPRESSANTS

These are structurally and functionally diverse medications that are frequently used in combination regimens to treat several autoimmune disorders such as lupus, Crohn's disease, multiple sclerosis, etc, and organ transplant. These drugs are often known as anti-rejection drugs because of their wide usage in organ transplants. This class of medications acts by suppressing the humoral and cellular immune responses. Different drugs are acting with diverse mechanisms to minimize the overactive immune system. Immunosuppressants used clinically are described vividly in Table 4.

International Research Journal of Education and Technology
ISSN 2581-7795

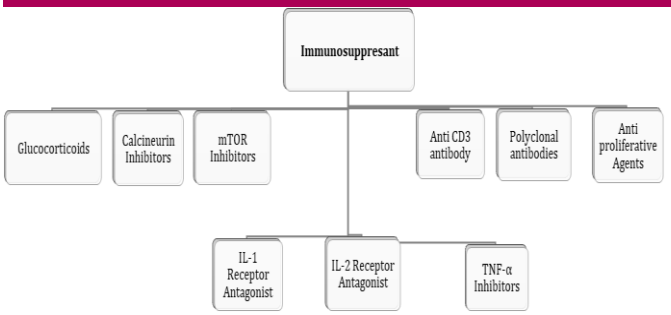

Figure 3 – Immunosuppressant Classification

IL-2 Receptor Antagonist	IL-2 gives an essential stimulus for T cell proliferation and differentiation. Thus antagonist dampens the immunity by not letting it bind to the receptor.	Daclizumab, Basiliximab
TNFα Inhibitors	$TNFR_1$, $TNFR_2$ receptors are present on the surface of neutrophils, fibroblasts, endothelial cells, it blocks the activity of TNF-α to realize cytokines and certain enzymes thus dampening the immune response.	Etanercept, Infliximab, Adalimumab

Class of drug	Mechanism of action	Drugs
Glucocorticoids	They suppress immunity by acting at the gene level as they block the gene expression for cytokines and their receptors IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, and TNF-γ. This eventually decreases the production of T cells and B cells	Prednisolone, Dexamethasone, Hydrocortisone, Betamethasone, etc.
Calcineurin Inhibitors (T cell Inhibitors)	Cyclosporine binds to a protein cyclophilin inhibits the activity of already activated calcineurin. Where Tacrolimus binds to FK-binding protein and inhibits calcineurin which is the main protein to initiate the formation of IL-2 and its receptors by dephosphorylating nuclear factor of activated T-cells (NFAT) that leads to T cell proliferation.	Cyclosporine (Ciclosporin), Tacrolimus
mTOR Inhibitors	It also binds to FKBP which inhibits mTOR (mammalian target of rapamycin) which plays a key role in the proliferation of T cells in later stages.	Sirolimus, Everolimus
IL-1 receptor Antagonist	IL-1 stimulates the T helper cells to release more cytokines to increase the production of T-cells. Thus receptor antagonists resist IL-1 from binding to the site.	Anakinra

Table 4 – Immunosuppressant used clinically

Immunomodulators found in our daily diet

Various immunomodulators are present in abundance in the usual diet which has a direct impact on our immune system. In the definite amount if taken daily in our diet it will not only enrich the immune system but also makes it less vulnerable to seasonal infections. A balanced diet must contain proteins, carbohydrates, vitamins, and minerals. The proper proportion of all these is essential for the body's growth and the development of the immune system.

Food ingredient	Action within the body	Food items
Vitamins : Vitamin A (Retinol) Anti-infective vitamin	It acts as the gatekeeper and nourishes the first line of defense in the body i.e. skin (epithelial barrier). It has a role in the stimulation of natural killer cells and the phagocytic potential of the cells.	Carrots, cod liver oil, cheese, eggs, spinach, sweet potato, etc.
Vitamin B Complex	It has a vital role in the development of the immune system (spleen, thymus) in early development and from time to time therapy of the B complex nourishes the system. It also stimulates the production of plasma cells.	Dairy, chicken, cheese, eggs, etc.
Vitamin C (Ascorbic acid)	It has potent antioxidant action which protects the body from free	Citrus fruits, strawberries, Indian

	radical attack and also enhances the phagocytic action of the leukocytes.	gooseberry, etc.
Vitamin D	It acts as an immunosuppressant.	Egg yolk, oily fish i.e. salmon, sardines
Vitamin E (Tocopherol)	It has a direct action on enhancing the efficiency of the NK cell. It shows a great response along with the ascorbic acid.	Cereal, nuts, plant oils, etc
Amino acids :	Glutamine : Activate immune system and potentiate the action of macrophages, leukocytes, lymphocytes. It stimulated the production of costimulatory cytokines and immunoglobulins. Arginine : It is the precursor for the production of nitric oxide, which is the potent chemical present in the phagosome to kill the invading foreign antigen.	Chicken, fish, dairy, lentils, beans. Soya beans, chicken, lentils, chickpeas.

Table – 5 Immunomodulators present in the diet

CONCLUSION

Immunomodulators appear as the ray of hope since there has not been much advancement in the medical sciences to fully cure autoimmune diseases or any disease targeting the immune system. The immune system is sensitive and can be triggered by our daily diet, environment, stress, etc. Thus by little modulation, a massive impact can be made in the field of research and devising new interventions for the disorders in which the immune system is not harmonized with other vital systems of the body.

REFERENCES

1. Gea-Banacloche JC. Immunomodulation. In Principles of molecular medicine 2006 (pp. 893-904). Humana Press.
   Shahbazi S, Bolhassani A. Immunostimulants: Types and functions. Journal of Medical Microbiology and Infectious Diseases. 2016 Jul 10;4(3):45-51.
2. Beenhouwer DO. Molecular basis of diseases of immunity. In Molecular Pathology 2018 Jan 1 (pp. 329-345). Academic Press.
3. Ingle AM, Verma AK, Tiwari R, Karthik K, Chakraborty S, Deb R, Rajagunalan S, Rathore R, Dhama K. Immunomodulators in day-to-day life: a review. Pakistan journal of biological sciences: PJBS. 2013 Sep 1;16(17):826-43.
4. Bairwa MK, Jakhar JK, Satyanarayana Y, Reddy AD. Animal and plant originated immunostimulants used in aquaculture. Journal of Natural Product and Plant Resources. 2012;2(3):397-400.
5. Agrawal, S. S., Khadase, S. C., & Talele, G. S. (2010). Studies on Immunomodulatory Activity of Capparis zeylanica Leaf Extracts. *International Journal of Pharmaceutical Sciences and Nanotechnology*, *3*(1), 887–892.
6. Ahmad, B., Shah, M., & Choi, S. (2019). Oceans as a Source of Immunotherapy. *Marine Drugs*, *17*(5), 282.
7. Almeida, C. R., Bottazzi, B., de Nardo, D., & Lawlor, K. E. (2020). Editorial: Immunomodulation of Innate Immune Cells. *Frontiers in Immunology*.
8. Andorko, J. I., & Jewell, C. M. (2017). Designing biomaterials with immunomodulatory properties for tissue engineering and regenerative medicine. *Bioengineering & Translational Medicine*, *2*(2), 139–155.
9. Banstola, A., Jeong, J. H., & Yook, S. (2020). Immunoadjuvants for cancer immunotherapy: A review of recent developments. Acta Biomaterialia, 114, 16–30.
10. Barman, D., & Nen, P. (2013). Immunostimulants for Aquaculture Health Management. Journal of Marine Science Research & Development, 03(03).
11. Chi, H., Li, C., Zhao, F. S., Zhang, L., Ng, T. B., Jin, G., & Sha, O. (2017). Anti-tumor Activity of Toll-Like Receptor 7 Agonists. Frontiers in Pharmacology.