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A REVIEW ON IMMUNOMODULATOR PLANTS

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INTRODUCTION

Traditional medicinal plants have been used for a long time to treat various diseases. They have immunomodulatory properties, which means they can stimulate both specific and non-specific immunity. India is known for its traditional healthcare system, including Ayurveda, Siddha, and Unani. Ayurveda is believed to have originated over 6 thousand years ago and uses herbal medications for immune response modulation. Immune modulation can be used to substitute for a variety of disease conditions, including immunodeficiency, and herbal immunostimulants are gaining importance. Immunity is the body's natural ability to identify and resist various infectious diseases and disorders and comprises specific and non-specific components. As infants grow, their immune systems continue to develop.[1-5]

IMMUNITY

In Ayurveda, immunity is described as Vyadhikshamatva, which refers to the body's ability to resist and fight off diseases. According to Acharya Chakrapani, immunity is the result of a healthy balance of bodily doshas (energies) and the proper functioning of bodily tissues, organs, and systems. This balance is essential for maintaining overall health and protecting the body against infections and diseases.[6-10]

IMMUNE SYSTEM

The immune system has multiple layers of defense mechanisms to protect the body against invading pathogens and maintain a healthy balance within the body. The first line of defense is the skin, which acts as a physical barrier against pathogens. The second line of defense is

physiological, which includes factors such as temperature and pH that create unfavorable conditions for foreign organisms.[11-13]

The immune system is categorized into two types: innate (non-specific) and adaptive (specific) immunity. The innate immune system provides a nonspecific response to pathogens through a series of host defenses, including barrier function, cytokines, phagocytes, natural killer cells (NK) cells, and gamma delta (gd) T cells. The adaptive immune system is also known as acquired immunity, which differs from innate immunity in that it is specific, has an element of memory, and is unique to vertebrates. Adaptive immunity is responsible for providing a targeted response to specific pathogens and has the ability to recognize and remember past infections, allowing for a more rapid response in future infections.[14-15]

CLSSIFICATION OF IMMUNOMODULATORS

Immunomodulators are substances or drugs that modify the immune system's response to foreign substances or infections. They can be broadly classified into different categories based on their mechanism of action and clinical application. Some common classifications of immunomodulators:

1. **Cytokines:** These are small proteins secreted by immune cells that act as signaling molecules to regulate the immune response. Cytokines such as interferons, interleukins, and tumor necrosis factor are used as immunomodulators to treat various diseases such as cancer, viral infections, and autoimmune disorders.
2. **Monoclonal antibodies:** These are laboratory-produced antibodies that target specific proteins or cells in the immune system. Monoclonal antibodies such as rituximab, infliximab, and adalimumab are used to treat autoimmune disorders and cancer.
3. **Immunosuppressants:** These are drugs that suppress the immune system's activity and are used to prevent organ rejection after transplantation or to treat autoimmune disorders. Examples of immunosuppressants include cyclosporine, azathioprine, and mycophenolate mofetil.
4. **Immunostimulants:** These are substances that stimulate the immune system's activity and are used to trea une response. TLR agonists such as imiquimod and resiquimod are used to treat viral infections and cancer.
5. **Complement inhibitors:** These are drugs that inhibit the complement system, a part of the immune system that helps to clear pathogens and damaged cells. Complement

inhibitors such as eculizumab are used to treat diseases such as paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome.[16-21]

Herbal Plants as Immunomodulator

1. Withania somnifera

The administration of an extract from the root of the Withania somnifera plant stimulated immunological activity in mice. Treatment with five doses of the extract increased the total white blood cell count, bone marrow cellularity, and alpha-esterase positive cell number. When administered with an antigen, the extract enhanced circulating antibody levels and the number of plaque forming cells in the spleen. However, the extract inhibited delayed type hypersensitivity reaction in mice. Additionally, the extract enhanced the phagocytic activity of peritoneal macrophages. These results support the traditional use of W. somnifera as an immunomodulator.[22-25]

2. Morus alba Linn. (Mulberry)

The methanolic extract of Morus alba was administered orally at low and high doses of 100 mg/kg and 1 g/kg, respectively. Ocimum sanctum was used as the standard drug. The extract was found to significantly increase the phagocytic index in carbon clearance assay and provide significant protection against cyclophosphamide-induced neutropenia. It also increased the adhesion of neutrophils in the neutrophil adhesion test. These results suggest that Morus alba can enhance both humoral immunity and cell-mediated immunity.[26-29]

3. Sophora subprosrate

The extract of Sophora subprostrate was found to enhance the production of nitric oxide (NO) and cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha) in macrophages, suggesting an activation of innate immunity. The extract was also found to enhance the proliferation of splenocytes and increase the production of cytokines such as interferon-gamma (IFN-gamma), interleukin-2 (IL-2), and IL-4 in lymphocytes, suggesting an activation of adaptive immunity.[30-31]

4. Picrorhiza Scrophulariiflora

One glycoside, scrocaffeside A, from the methanol extract of Picrorhiza scrophulariiflora has been found to exhibit immunomodulatory properties. Scrocaffeside A has been shown to enhance the proliferation of splenocytes and their response to polyclonal T cell mitogen concanavalin A (Con A) and lipopolysaccharide (LPS). Additionally, it has been found to

increase the activity of peritoneal macrophages and natural killer cells in a dose-dependent manner. The populations of mature T cell subsets have also been found to increase in a dose-dependent manner. The production of cytokines and the CD4/CD8 population of splenocytes were also elevated with scrocaffeside A treatment. Levels of interleukin (IL)-2, IL-4, IL-12, and (IFN)-gamma expressed by cultured splenocytes were significantly increased with scrocaffeside A exposure. These findings suggest that scrocaffeside A may have immunoenhancement effects on the immune system and could potentially be developed as a new immunostimulating agent in the future.[32-36]

5. Plantago asiatica L.

In this study, the researchers aimed to investigate the effects of an extract of the seeds of Plantago asiatica L. (ES-PL) on the maturation of dendritic cells (DCs). DCs are an important component of the primary immune system and play a significant role in regulating immune responses. The researchers were interested in exploring whether ES-PL had immunomodulatory properties that could potentially benefit immunologically weak patients suffering from chronic illnesses. By investigating the effects of ES-PL on DC maturation, the researchers hoped to gain insights into the plant's potential mechanisms of action and its potential as a therapeutic agent for immune-related conditions.[37-39]

6. Panax ginseng

This study aimed to investigate the potential mechanisms underlying the beneficial effects of ginseng, a medicinal plant believed to have various health benefits. Specifically, the researchers hypothesized that ginseng's anti-inflammatory effects may contribute to its physiological actions. They found that a 70% ethanol-water extract of ginseng inhibited the transcription and secretion of CXCL-10, a chemokine involved in inflammation, following TNF-alpha stimulation. The extract contained nine ginsenosides, including Rb1, Rb2, Rc, Rd, Re, Rf, Rg1, Rg3, and Rh1, which were identified using HPLC. Seven of these ginsenosides were found to significantly inhibit TNF-alpha-induced CXCL-10 expression in U937 cells. However, the suppressive effect of individual ginsenosides was weaker than that of the crude extract or a mixture of ginsenosides. The study also found that the CXCL-10 suppression could be correlated with the inactivation of ERK1/2 pathways by ginseng. Overall, these findings suggest that ginseng's anti-inflammatory effects may be a key mechanism underlying its diverse physiological actions, and that the combination of multiple ginsenosides may be responsible for the plant's therapeutic effects.[40]

7. Caesalpinia bonducella

Oral administration of Caesalpinia bonducella seed extract (doses of 200-500 mg/kg) showed potential as an immunomodulator. It increased the adhesion of neutrophils to nylon fibers, raised antibody levels in a dose-dependent manner, and enhanced the delayed-type hypersensitivity reaction to sheep red blood cells. The extract also prevented myelosuppression in rats treated with cyclophosphamide and improved phagocytosis in a carbon clearance assay.[41-45]

8. Garlic (Allium sativum)

Garlic (Allium sativum) is a medicinal spice that has immunomodulatory effects. This study aimed to isolate immunomodulatory proteins from raw garlic and evaluate their effects on lymphocytes, mast cells, and basophils in relation to mitogenicity and hypersensitivity. Q-Sepharose chromatography of a 30 kD ultrafiltrate of raw garlic extract resulted in the separation of three protein components (QR-1, QR-2, and QR-3) with molecular weights of approximately 13 kD in a ratio of 7:28:1. All three proteins showed mitogenic activity towards human peripheral blood lymphocytes, murine splenocytes, and thymocytes.[46]

9. Cynodon dactylon

Cynodon dactylon is a type of grass used in traditional medicine. The fresh juice of this grass was prepared and standardized for solid content. Its total phenol content was estimated using the Folin-Ciocalteau method. In vitro experiments were conducted to evaluate the juice's effect on doxorubicin-induced DNA damage. The juice's immunomodulatory activity was also tested on balb/c mice, using the humoral antibody response. This was measured by haemagglutination antibody titer and spleen cell assay.[47]

10. Terminalia arjuna

Terminalia arjuna bark powder was studied for its effects on inflammation and pain. When administered orally at a dose of 400 mg/kg, it significantly reduced formalin-induced paw edema at 24 hours but not carrageenan-induced paw edema. It also increased the anti-SRBC antibody titre in the secondary phase of immune response. In addition, the same dose reduced the duration of licks and bites in both phases of formalin-induced pain response and increased tail flick latency at a higher dose of 800 mg/kg, orally. However, these effects were antagonized by pretreatment with naloxone (1 mg/kg, intraperitoneally). These findings suggest that Terminalia arjuna has anti-inflammatory potential against some phlogistic

agents, immunomodulatory activity, and antinociceptive action mediated through central opioid receptors.[48-50]

11. Schisandra arisanensi

An acetone extract of Schisandra arisanensis, a medicinal plant from Taiwan, yielded 11 new oxygenated lignans. Four of these lignans, named arisantetralones A-D (1-4), have the aryltetralone skeleton, while the other seven, named arisanschinins F-L (5-11), are polyoxygenated C(18)-dibenzocyclooctadiene lignans. The structures were determined through spectroscopic analyses, particularly 2D-NMR techniques. The structure of compound 1 was confirmed by X-ray crystallographic analysis. The immunomodulatory activity of these lignans was testesd and evaluated.[51-52]

12. Rhus toxicodendron (Rhus tox)

The study evaluated the effects of various dilutions of Rhus toxicodendron (Rhus tox) in the in vivo and in vitro experimental models of immune response. Rhus tox in the form of mother tincture, 6cH, 30cH, 200cH, and 1000cH dilutions were tested on cellular and humoral immune responses induced by sheep red blood cells (SRBCs) in C57/BL6 mice. The effects of Rhus tox dilutions were also evaluated in vitro on the functions of human polymorphonuclear (PMN) cells, such as phagocytosis and intracellular killing of Candida albicans, chemotaxis, and reduction of nitroblue tetrazolium (NBT) dye.[53-55]

13. Pteridium aquilinum (bracken fern)

The study evaluated the immunomodulatory effects of bracken fern extract in mice over a period of 14 to 30 days. The results showed a significant reduction in splenic white pulp area and a decrease in delayed-type hypersensitivity analysis and IFNgamma production by NK cells during T(H)1 priming. The innate response in the hosts, assessed by NK cell cytotoxic functionality, was also reduced. These findings suggest that bracken fern has immunosuppressive effects, which could increase the risk of cancer formation in exposed hosts.[56]

14. Actinidia eriantha Benth

As evidenced by their ability to increase the spleen index, enhance the phagocytosis of macrophages, and promote the production of cytokines such as IFN-gamma, TNF-alpha, and IL-2. The purified polysaccharides also showed a dose-dependent cytotoxic effect on cancer

cells in vitro. These findings suggest that the polysaccharides from Actinidia eriantha roots have potential as immunomodulatory and antitumor agents.[57]

15. Boerhaavia diffusa

Boerhaavia diffusa (Punarnavine) has been found to have an immunomodulatory effect in Balb/c mice. It increases the total WBC count, bone marrow cellularity, and the number of alpha-esterase positive cells. When administered along with the antigen, sheep red blood cells (SRBC), Punarnavine enhances the circulating antibody titer and the number of plaque-forming cells (PFC) in the spleen. It also enhances the proliferation of splenocytes, thymocytes, and bone marrow cells, both in the presence and absence of specific mitogens in vitro and in vivo. Additionally, Punarnavine significantly reduces the LPS-induced elevated levels of proinflammatory cytokines such as TNF-alpha, IL-1beta, and IL-6 in mice. These findings suggest that Punarnavine has immunomodulatory activity.[58]

16. Dioscorea japonica

The study investigated the effects of dioscorin, a major storage protein isolated from two different yam species, Tainong No. 1 and Japanese yam, on the immune activities of mice. The results showed that both TN1-dioscorins and Dj-dioscorins induced the expression of pro-inflammatory cytokines and stimulated phagocytosis of RAW 264.7. The injection of TN1-dioscorins stimulated phagocytosis of bone marrow, spleen, and thymic cells, while the injection of Dj-dioscorins increased the proliferative responses of T and B cells to mitogens in bone marrow, spleen, and thymus. Furthermore, Dj-dioscorins enhanced the proliferation of CD4(+), CD8(+), and Tim3(+) (Th1) cells in spleen and CD19(+) cells in both spleen and thymus. Overall, the study suggests that Dj-dioscorins have immunomodulatory effects on lymphoid cells.[59-60]

17. Andographis paniculata

HN-02, an extract containing a mixture of andrographolides, has been shown to have immunomodulatory activity. In a delayed-type hypersensitivity (DTH) mouse model, it potentiated the DTH reaction and reversed the CYP potentiation of the DTH reaction. It also elevated the depressed hemagglutination antibody (HA) titer and increased the number of plaque-forming cells (PFCs) in the spleen cells of mice that had been treated with CYP and challenged with sheep red blood cells (SRBC). Additionally, it stimulated phagocytosis in mice and increased total WBC count and relative weight of spleen and thymus during 30 days of treatment.[61]

18. Curcuma longa

Curcumin, a polyphenol derived from turmeric, has been shown to have anti-inflammatory and anti-pathogenic properties. A study was conducted to evaluate its effectiveness against schistosomiasis mansoni in mice. The results showed that curcumin treatment led to a significant reduction in parasite burden and liver pathology. It was also found to modulate cellular and humoral immune responses, indicating its immunomodulatory effects.[62-63]

19. Tinospora cordifolia

Tinospora cordifolia, also known as Guduchi, is a medicinal plant used in Ayurvedic medicine for its immunomodulatory and anti-inflammatory properties. Several studies have shown that Tinospora cordifolia extracts and its active components have a positive impact on the immune system.

One study found that treatment with Tinospora cordifolia extract increased the production of cytokines, including IL-2, IL-4, and IL-10, and enhanced the proliferation of lymphocytes in mice. Another study demonstrated that the extract stimulated the production of nitric oxide and tumor necrosis factor-alpha (TNF-α) in macrophages.

In addition, Tinospora cordifolia extract has been shown to enhance the activity of natural killer (NK) cells, which play a critical role in immune surveillance against cancer cells and viral infections. Other studies have demonstrated the extract's ability to enhance the phagocytic activity of macrophages and neutrophils, which are key players in the innate immune response.

Overall, the immunomodulatory effects of Tinospora cordifolia extract have been attributed to its ability to modulate the production of cytokines, enhance the activity of immune cells, and improve the phagocytic activity of macrophages and neutrophils.[64-65]

20. Azadirachta indica

Azadirachta indica, commonly known as neem, has been traditionally used in Ayurvedic medicine for various therapeutic purposes, including as an immunomodulator. Immunomodulation refers to the ability of a substance to regulate or enhance the immune system's response.

Studies have shown that Azadirachta indica possesses immunomodulatory properties that can help to enhance the immune system's ability to fight infections and diseases. The active

compounds in neem, such as polysaccharides, flavonoids, and alkaloids, have been found to modulate various immune system components, including cytokines, lymphocytes, and macrophages.

One study found that neem leaf extract can increase the production of cytokines, which are signaling molecules that play a crucial role in immune system regulation. Other studies have shown that neem extracts can enhance the activity of natural killer cells and promote the phagocytic activity of macrophages, which are immune cells that engulf and digest pathogens.

Neem also possesses antioxidant properties, which can help to protect the immune system from oxidative stress and damage. In addition, neem has been found to have anti-inflammatory properties, which can help to reduce inflammation and promote the healing of tissues.

Overall, the immunomodulatory properties of Azadirachta indica make it a promising candidate for the development of new therapeutic agents for various immune-related disorders. However, more research is needed to fully understand its mechanisms of action and potential clinical applications.[66-68]

21. Aloe barbadensis miller

Aloe barbadensis Miller, commonly known as Aloe vera, has been traditionally used for its medicinal properties, including as an immunomodulator. An immunomodulator is a substance that can either enhance or suppress the immune system's response to various stimuli, depending on the body's needs.

There is some scientific evidence supporting the use of Aloe vera as an immunomodulator. Several studies have shown that Aloe vera contains various bioactive compounds that can stimulate the immune system. For example, polysaccharides found in Aloe vera have been shown to stimulate the production of immune cells such as macrophages, lymphocytes, and natural killer cells, which are important in fighting infections and diseases.

Additionally, Aloe vera has been found to have anti-inflammatory and antioxidant properties, which can help to reduce inflammation and oxidative stress in the body, both of which can negatively impact the immune system.

However, more research is needed to fully understand the effects of Aloe vera on the immune system and to determine the optimal dosage and administration methods for therapeutic use. It is important to consult with a healthcare professional before using Aloe vera as an immunomodulator, especially if you have any underlying health conditions or are taking any medications.[69-71]

22. Ocimum sanctum

Ocimum sanctum, also known as holy basil or tulsi, has been traditionally used in Ayurveda for its medicinal properties. It is believed to have immunomodulatory effects, meaning it can help regulate the immune system.

Studies have shown that holy basil contains several bioactive compounds, such as eugenol, rosmarinic acid, and ursolic acid, which may contribute to its immunomodulatory properties. These compounds have been found to have anti-inflammatory and antioxidant effects, which can help regulate the immune response.

Research has shown that holy basil can stimulate the production of immune cells, such as T-helper cells and natural killer cells, which can help fight infections and diseases. Holy basil has also been found to increase the production of cytokines, which are signaling molecules that play a crucial role in the immune response.

Moreover, holy basil has been found to have a protective effect against radiation-induced immune suppression and can improve the survival of animals exposed to radiation. This suggests that holy basil may have potential as an immunomodulatory agent for individuals undergoing radiation therapy.

In conclusion, while more research is needed to fully understand the immunomodulatory effects of holy basil, current evidence suggests that it may have potential in regulating the immune system and improving immune function. However, it is important to consult with a healthcare provider before using holy basil or any other herbal supplement for its potential health benefits.[73-74]

23. Hydrastis Canadensis

Hydrastis canadensis, commonly known as goldenseal, has been traditionally used in herbal medicine as an immunomodulator. Immunomodulators are substances that can enhance or regulate the immune system's function, helping to fight infections and prevent diseases.

Goldenseal contains several active compounds, including berberine, hydrastine, canadine, and beta-hydrastine, which have been shown to have antimicrobial, anti-inflammatory, and immune-stimulating properties. Berberine, in particular, has been extensively studied for its immunomodulatory effects.

Research has shown that goldenseal extracts can stimulate the production of immune cells, such as macrophages and natural killer cells, which play a critical role in the body's defense against infections. Additionally, goldenseal extracts have been found to increase the levels of immunoglobulins, which are antibodies that help to neutralize harmful pathogens.

While goldenseal has been traditionally used as an immunomodulator, more research is needed to fully understand its mechanisms of action and potential therapeutic benefits. As with any herbal supplement, it's important to talk to a healthcare provider before using goldenseal, especially if you have any underlying medical conditions or are taking medications.[75-78]

CONCLUSION

The use of various plant extracts and herbal fed additives in specific dose during the scheduled vaccination regimen may be helpful in obtaining higher protective antibody against different infections including production and development of more effective cell mediate immune response for protection against various bacterial, viral and other diseases. Herbal formulation may be therefore recommended for use as positive immunomodulator. There are several botanical products with potential therapeutic applications because of their high efficacy, low cost and low toxicity.

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