

Herbal Immunomodulators as Drug Candidates

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ABSTRACT

Ayurveda is the earliest medicinal system developed in India and describes an enormous range of herbal and mineral medicines. Three hundred years ago, herbal therapy was recognized as holistic healing practice to counter physical ailments in Asia. An entire section of the Materia Medica of Ayurveda is devoted to "Rasayana", drugs reputed to enhance body resistance. Herbal preparations constitute a large section of ethnoveterinary medicines and many of them were used to boost the immune status of domestic animals. Moreover, traditional medicine presents a large source of natural immunomodulator that might serve as leads for development of novel drugs. Herbal preparations can increase the efficacy of chemotherapy for control and prevention of infections. Enough strong immunity is needed to prevent or survive from COVID-19 pandemic. Ayurveda provides ways for evolving physiological responses to built immunity. Cure of an illness matter much more but prevention is always better than cure. Various studies have identified a variety of herbal compounds as immunostimulants, with proven stimulatory effects on macrophages, T and B lymphocytes, and the modulation of cytokine secretion and immunoglobulin secretion. Various bioactive principles- polyphenols, glycosides, flavonoids, coumarins, alkaloids, terpenoids, saponins and polysaccharides etc. are responsible for immunomodulatory effects of medicinal plants. Various polyherbal preparations like ImmuplusR have shown immunopotentiality along with vaccines. Herbal preparations aid in production and development of more effective immune response for protection against various diseases.

Keywords: Herbal, immunomodulator, immune response, macrophages, cytokine.

I. INTRODUCTION

Ayurveda is the earliest medicinal system developed in India and describes an enormous

range of herbal and mineral medicines. Three hundred years ago, herbal therapy was recognized as holistic healing practice to counter physical ailments in Asia (Archana et al., 2011). Currently Ayurveda is the most vital tradition practiced in India, Sri Lanka and other countries. Rigveda, Atharvaveda (around 1200 BC), Charak Samhita and Sushrut Samhita gave a detailed description of over 700 herbs. An entire section of the Materia Medica of Ayurveda is devoted to "Rasayana", drugs reputed to enhance body resistance (Thattai and Dahanukar, 1997).

Presently, the power of herbal therapy is being admired globally, and a wide array of studies and their results justifies their successful impact in various treatments. Enough strong immunity is needed to prevent or survive from COVID-19 pandemic. Ayurveda provides ways for evolving physiological responses to built immunity. Cure of an illness matter much more but prevention is always better than cure. Ayurveda offers simple natural ways (daily regimens), herbal combinations, herbo-mineral formulation and exercises such as Yoga for prevention of COVID-19. Multiple actions of herbal preparations are claimed to have a lower risk of drug resistance, in addition to being more environmental friendly, compared to modern medicines. Herbal preparations constitute a large section of ethnoveterinary medicines and many of them are used to boost the immune status of domestic animals. In addition to their immunoregulatory activities, natural products have various beneficial effects, including antipyretic, antioxidant, anti-inflammatory, antiulcer, antidiabetic, cytoprotective and anticancer etc. (Dar et al., 2015).

Advantages of herbal immunomodulators

Herbal extracts may confer potential advantages, including easy accessibility, low cost, the convenience of preparation, no or minimal side effects and usage in human medicine, animal health, and animal production. Rising interest in

medicinal herbs has increased scientific scrutiny of their therapeutic potential and safety. The knowledge and assessments of the biological properties of extracts from plants can serve as a source of future drug candidates in many areas of health. Moreover, traditional medicine presents a large source of natural immunomodulator that might serve as leads for development of novel drugs.

Immunomodulation

Many infectious diseases and disorders arise because of stressful environmental conditions associated with suppression of immune system. Certain types of stress evoke physiological changes that influence susceptibility to infection and malignance. The ability to modify the immune response in animals and humans evolved from a desire to confer greater protection against infectious agents through a more complete understanding of the functioning of the immune system. Naturally occurring or synthetic compounds capable of altering those mechanisms offered further possibilities for modulating immune responses.

Clinically, immunomodulators have three categories:

Immunostimulants are inherently non-specific and enhances body's resistance to infection. They can act through innate as well as adaptive immune responses. In healthy individuals, the immunostimulants are expected to serve as prophylactic and promoter agents, i.e., as immunopotentiators, by enhancing the basic level of immune response. In individual with impaired immune response they are expected to act as immunotherapeutic agents.

Immunosuppressants are the drugs, which suppress both cell mediated and humoral immune response and are often used in combination regimens to treat various types of organ transplantation and autoimmune diseases.

Immunoadjuvants are used to enhance the efficacy of vaccines and so are considered as specific immune stimulants.

Mechanism of action of the immunomodulators

Herbal preparations can increase the efficacy of chemotherapy for control and prevention of infections. Variety of herbal compounds is identified as immunostimulants, with proven stimulatory effects on macrophages, T and B lymphocytes, modulation of NF-kB and secretion

of cytokine and immunoglobulin (Vasanthakumar et al., 2015).

Two arms of immune system- innate and acquired works together. Innate or natural immunity is primitive, non specific and highly reactive. Acquired or learned immunity is antigen specific, depends on antigen exposure and has memory. An adaptive immune response also consists of two subtypes of immune responses, humoral immune response concerned with β -lymphocytes and cell-mediated immune response mediated by T-cells. Besides a vast range of specialized immune cells, certain molecules called cytokines are important mediators of the immune system. These are of two types:

a) Cytokines of non- specific immune system: interleukin-1 (IL-1), IL-6, IL-23, IL-27, TNF- α (tumor necrosis factor- α), INF- α (interferon- α).

b) Cytokines of specific immune system: IL-2, IL-4, IL-5, IL-12, IL-17, TNF- β , IFN- γ .

Cytokines regulate the intensity and duration of the immune response by stimulating or inhibiting the activation, proliferation, and differentiation of various cells and by regulating their secretion of antibodies or other cytokines (Coffman, 2006). Inflammatory cytokines are of two types- The pro-inflammatory cytokines involved in acute inflammation, promote systemic inflammation and include IL-1, IFN- γ , and TNF. By contrast, anti-inflammatory cytokines are responsible for regulating and maintaining homeostasis. Major anti-inflammatory cytokines are IL-4, IL-6, IL-10, and IL-13.

NF-kB (nuclear factor-kappa B) is a protein complex which control transcription of DNA, cytokine production and cell survival. It acts as mediator of immune and inflammatory responses, and involved in regulation of cell proliferation and apoptosis.

The innate immune mechanisms involved in immunomodulation are orchestrated by an array of cells, including Natural killer cells, NKT cells, macrophages, granulocytes (neutrophils, eosinophils and basophils) and dendritic cells. Adaptive immunity is created by networking among B cells, CD4+Tcells including helper T cells (including Th1, Th2, Th17 cells), induced regulatory T cells (iTreg cells) and the natural regulatory T cells differentiated from thymus.

Macrophages are pivotal key in the maintenance of tissue homeostasis and are responsible for detecting, engulfing, and destroying pathogens. During macrophage activation, several compounds are released such as cytokines, reactive oxygen species (ROS), nitric oxide (through NOS), and lipid inflammatory mediators which are implicated in the inflammatory response (Abbas et al., 1991).

Adaptive immunity involves antigen specific reactions. The strong phagocytic action of myeloid cells and cytotoxic T lymphocytes is enhanced by Th1 lymphocytes which produce TNF- α , IFN- γ , and IL-2. The Th2 lymphocytes produces IL-4, IL-5, and IL-10; B lymphocytes mediates production of antibodies. The toxins or microorganisms are neutralized after binding with the antibodies.

The cell types involved in innate and adaptive immune responses are



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Medicinal plants capable of inhibiting the cellular and humoral responses could have useful applications in the treatment of immunological disorders. Various compounds of plants have immunomodulatory activity.

Herbal immunomodulator principles

1. Polyphenol: i) Stilbene - Resveratrol bind to a wide range of inflammation-related cell-

signalling molecules. It has antioxidant, cardioprotective, antimutagenic, antiinflammatory, chemopreventive and antiplatelet effects. Cytotoxic effect in cancer cell is due to suppressed activation of NF- κ B.

ii) Hydroxycinnamic acids: Curcumin from *Curcuma longa* and Gingerol from *Zingiber officinale* are highly pleiotropic molecules with anti-inflammatory, antioxidant and chemopreventive activities.

2. Glycosides:

i) Iridoid glycosides- Picroliv (*Picrorhiza scrophulariiflora*)

ii) Anthraquinone glycosides - *Andrographis paniculata*.

iii) Sesquiterpene glycosides - Dendroside A and dendronobilosides A and B - found to stimulate the proliferation of T and B lymphocytes.

3. Flavonoids: Categorized into seven groups: flavones, flavanones, flavonols, flavanols, isoflavones, flavanols and anthocyanidins. Flavonoids possess anti-inflammatory, anti-hepatotoxic, anti-atherogenic, anti-osteoporotic, anti-allergic and anticancer activities.

i) Quercetin: a flavonol in amla, onions, apples and leafy green vegetables.

ii) Epigallocatechingallate (EGCG) in green tea (*Camelia sinensis*) is a potent antioxidant, anti-inflammatory.

Both inhibits transcriptional factors (NF κ B) and reduces pro-inflammatory mediators.

iii) Apigenin of *Terminalia arjuna*

iv) Isoliquiritin of *Glycyrrhiza*

4. Coumarins

i) Esculetin from *Artemisia capillaries* and *Euphorbia lathyris* have lipoxxygenase-inhibitory, free radical scavenging, suppression of oxidative damage to DNA, cancer chemopreventive and antitumor activities.

5. Alkaloids: Quinine alkaloid from *Cinchona* sp. has antimalarial and Solanum alkaloids have cytotoxic activity. Piperine (*Piper longum*) reduce level of pro inflammatory cytokines IL-1 β , IL-6, and TNF- α , down regulate expression of COX-2 (cyclooxygenase-2), NOS-2 (Nitric oxide synthase-2), and NF- κ B and inhibit phospholipase A2 and TXA2 (Thromboxane-2) synthase activity.

6. Terpenoids: Phenolic compounds and terpenoids are the major phytochemicals present in vegetables, fruits and other dietary or medicinal

foods. Terpenoids exhibits immunomodulatory activity, e.g., eugenol from *Ocimum sanctum*.

a) Monoterpenes:

- i) Limonene, from citrus fruits, cherries and apricots suppress NF- κ B activation.
- ii) Geniposide (*Gardenia jasminoides*) used to treat inflammation, fever, headache and inhibit NF- κ B and iNOS expression.

b) Sesquiterpenoids

- i) Artemisinin is an effective antimalarial drug, especially against multidrug- resistant malaria and also confers antifungal, anti-cancer, anti-angiogenesis and immunosuppressive properties.

c) Diterpenoids

- i) Taxol: potent anti-cancer agent named as Paclitaxel, Docetaxel.
- ii) Diterpene from *Andrographis paniculata*.
- iii) Abietane-type diterpenoids and 2 labdane-type diterpenoids can suppress SARS-CoV replication, suggesting that they could be further evaluated for use as antiviral agents (Wen et al., 2007).

d) Triterpenoids:

- i) Ursolic acid (apples, basil, peppermint, lavender) confer anti-hyperlipidaemic, anti-cancer and hepatoprotective activities.
- ii) Betulinic acid and its derivatives (*Betula* spp, Ber tree -*Ziziphus mauritiana*), have therapeutic potential against pathogen infections (e.g. HIV), conferred anti- SARS-CoV activities.
- iii) Lupeol (common vegetables, fruits and medicinal herbs, *Bauhinia variegata*) effective for specific cancers and inflammatory disorders.

7. Carotenoids: are powerful antioxidants and are reputed to alleviate several chronic diseases, such as cardiovascular disease, osteoporosis and cancer. Some carotenoids such as β -carotene, lutein and lycopene offer protection against some inflammatory responses, possibly via modulation of redox-sensitive signalling pathways such as NF- κ B and ROS signaling.

i) β -Carotene: Provitamin A

- ii) Lutein: a derivative of β -carotene and is widely present in a variety of fruits and vegetables as well as in egg yolks. It protects against oxidative stress and exhibit a neuroprotective effect in retinal inflammation.
- iii) Lycopene: antioxidant, more potent than vitamin E, reduces the risk for various chronic diseases, such as cardiovascular diseases and atherosclerosis.

These carotenoids exhibiting antioxidant activities may warrant future development as immunomodulators.

8. Sapogenins: Ginsenosides (*P. ginseng*) the bioactive components with immunomodulatory action.

9. Organosulphur containing compounds

i) Cysteine sulphoxides (alliin) and allicin from garlic: Suppress the in vitro activities of inflammatory enzymes such as cyclooxygenase and lipoxygenase and inhibit the expression of iNOS in inflammatory white blood cells, exhibit anti-inflammatory effects through inhibition of the NF- κ B activity and modulate inflammatory responses through suppression of TLR activation.

10. Polysaccharides: One of the main classes of various bioactive substances present in various traditional herbal medicines with a spectrum of pharmacological activities, especially on immunomodulatory, anti-tumour effects or cancer chemopreventive effects.

These are categorized into: D- glucans, acetylated glucomannans, sulphated polysaccharides, arabinans, arabinogalactans I, arabinogalactans II, rhamnogalacturonan I (RG-I), RG II and pectins.

Polysaccharides can activate macrophages to secrete pro-inflammatory cytokines (e.g. IL-1, TNF- α and IFN- γ), increase the production of NO, ROS and myeloperoxidase; enhance the activities of cytotoxicity, phagocytosis and cell proliferation. Polysaccharides are involved in maintenance of the Th1/Th2 balance, promotion of differentiation of B cells and the production of IgG and IgM and can be used as adjuvants for DC-based vaccines.

plants in india with immunomodulatory activity

- *Withania somnifera* (Ashwagandha)
- *Tinospora cordifolia* (Giloy)
- *Ocimum* spp (Tulsi)
- *Curcuma longa* (Haldi)
- *Zingiber officinale* (Ginger)
- *Allium sativum* (Garlic, Lasun)
- *Cinamomum* (Dalchini)
- *Aloe vera* (Ghrita kumari)
- *Phyllanthus emblica* (*Emblica officinalis*, Amla)
- *Glycyrrhiza glabra* (Mulethi, Licorice or Sweetwoods)
- *Azadirachta indica* (Neem)
- *Moringa oleifera* (Moringa, Sahajan, Drumstick)
- *Nigella Sativa* (Black cumin)
- *Picrorhiza kurroa* (Kutaki)

- *Andrographis paniculata* (Kirayat)
- *Asparagus racemosus* (Satawar)
- *Panax ginseng* and *P. pseudoginseng* (Ginseng)
- *Terminalia arjuna* (Arjun)
- *Piper longum* (Black pepper, pippali)
- *Camelia sinensis* (Green tea)
- *Bauhinia variegata* (Kachanar)
- *Nyctanthes arbortristis* (Harsinghar)
- *Terminalia chebula* (Harad)
- *Boerhavia diffusa* (Punarnava)
- *Aegel marmelos* (Bael, wood apple)
- *Cynodon dactylon* (Doob grass)
- *Calendula officinalis* (Marigold)

1. *Withania somnifera* (Ashwagandha, Family - Solanaceae)

Ashwagandha is Indian ginseng and an important Rasayana in Ayurveda. It is well known for cytoprotective, immunomodulatory, antibacterial, antioxidant, diuretic, anti-inflammatory, antitussive, anticancerous, sedative/anxiolytic, antitumor, analgesic, anti-stress effects and better anabolic activities. It has excellent immunostimulating potential among herbs, and it is one of the most extensively studied and widely used herbal immunomodulators in a variety of species. The active constituents, commonly called as withanoloids, are withaferin A and withanolide A. Ashwagandha extracts enhance activity of macrophages. It modulates effects of cytotoxic lymphocytes and reduces tumor growth even better than doxorubicin (Jayaprakasam et al., 2003). The cell-mediated immunity increased significantly by administration of *Withania* root extract in poultry and normal and cyclophosphamide induced myelosuppressed mice, mediated by Th1-stimulating cytokines (Malik et al., 2007). Several Indian animal studies proved a stimulatory effect on the immune system, enhanced antibody and red blood cells level, and an increased number of white blood cells to devour germs. It modulates immune response markers, such as TNF- α , IL-6.

Withania forms the principal component of many polyherbal preparations (Immu-21, Amrit, Su-Ruksh, Ashwagandha, and ImmuPlus). ImmuPlus increased the antibody titer in dogs in addition to the stimulation of T and B cells and immunopotential along with vaccines. It causes better immune stimulation with vaccination against viral diseases such as canine parvovirus infection and rabies in pups, (Chauhan et al., 1999) and infectious bursal disease and Newcastle disease

vaccines in poultry (Yang et al., 2011). Another polyherbal preparation, Immu-21, modestly improved the condition of HIV patients by immunomodulatory effect (Singh et al., 2001).

2. *Tinospora cordifolia* (Guduchi, Amrita, Giloy, Family - Menispermaceae)

Tinospora cordifolia is known for boosting the immune system by immunomodulatory and cytoprotective activities through various non-specific immune mechanisms. The effective principles include alkaloids, diterpenoids, flavonoids, tinocordiside, syringin, and lignins. Many of these principles have potent immunostimulatory properties. The alcoholic extract of *Tinospora* possess greater immunomodulatory function through augmentation of antibody production (Aher and Wahi, 2010), whereas the methanolic extract is excellent antimicrobial properties. The treatment of visceral Leishmaniasis in a murine model with TC, along with cisplatin, was effective and reduced the undesirable effects of cisplatin and modulated the immune response (Sachdeva et al., 2014).

Preparations activate macrophages leading to increase in granulocyte-macrophage colony-stimulating factor (GM-CSF), leukocytosis, and improved neutrophil function. Polysaccharide (α -D-glucan) from this plant activates NK cells, the complement system, and Th1-pathway cytokines, coupled with low nitric oxide synthesis (Ramachandran, 2004). *Tinospora* root extract has antibacterial and immunomodulatory effects in treatment of bovine clinical mastitis (Mukherjee et al., 2010). The novel polysaccharide, (1,4)- α -D-glucan, isolated from *T. cordifolia* act as a TLR4 agonist, so has potential as an adjuvant. *T. cordifolia* growing on neem possess better immunomodulatory properties than in the absence of neem (Narkhede et al., 2014).

3. *Ocimum spp* (Tulsi, Family - Labiatae)

Ocimum sanctum is a holy plant in India. The main parts of the plant commonly used are the leaves, flowers, stem, and seeds. The potential of *O. sanctum* in medication is due to bioactive molecules such as saponin, tannins, steroid, flavonoids, eugenol, terpenoids, ursolic acid, rosmarinic acid, cardiac glycerides, carvacrol and caryophyllene (Nahak and Sahu, 2014). Eugenol is most active compound and is effective against allergic and inflammatory disorders and has immunostimulatory property. Immunomodulatory properties are maximum from the steam distilled

extract of *O. sanctum* through humoral immunity. Seed oil has potential anti-inflammatory and immunomodulatory effects via improvement in cell-mediated and humoral immunity parameters (Mediratta et al., 2002). The aqueous extract of *O. sanctum* leaf infused via intramammary route was found to increase neutrophil and lymphocyte count and increased phagocytic index in bovine mammary gland (Mukherjee et al., 2005). Although various species are present in *Ocimum* genus with different phytochemical composition, it is the high eugenol content that is responsible for the multiple pharmacological effects of *Ocimum*. Sweet basil (*O. basilicum*) also possesses immunomodulatory activity. Supplementation of Tulsi could limit the serum cortisol level and augment immunity (Swathi et al., 2012).

4. *Curcuma longa* (Haldi, Family - Zingiberaceae)

Curcuma longa is widely cultivated in India and powder of its rhizome called turmeric, a spice with flavoring and digestive properties. This is, first and foremost, herbal medicine studied extensively by the modern scientific methods in the past few decades, mainly for establishing its biological nature and pharmacological potentials. The key biological component is curcumin- a yellow-orange polyphenol with diverse therapeutic applications, including anticancer, antidiabetic, antiseptic, antimicrobial, antivenom, and antiulcer activities, along with hypotensive and hypocholesterolemic effects and protection against Alzheimer's disease (Reddy et al., 2016). Anti-inflammatory and immunomodulatory activity is by regulating cytokine secretion from immune cells, inhibiting NO production, COX-2, NFkB, inducible nitric oxide synthase (iNOS), lipoxygenase in NK cells and IFN- γ , or TNF- α activated macrophages. The plant can be applied in both acute as well as chronic cases of inflammation. Its potency is comparable to the condition induced by the popular anti-inflammatory drug phenylbutazone (ElHage, 2005). The activated immune cells release pro-inflammatory cytokines that play key role in inflammation. The expression of pro-inflammatory cytokines TNF- α , IL-1, IL-6, and IL-12 were inhibited by curcumin via LPS or PMA-stimulated monocytes, macrophages, dendritic cells, and splenic lymphocytes. It is a good modulator of lymphocyte-mediated immune functions, especially CD4 (+) T cells, and B cells. It can regulate B cell lymphomas by arresting growth and inducing apoptosis (Churchill et al., 2000). Dietary curcumin

found to increase IgG levels in rats (South et al., 1997). Supplementation of rabbit diet with turmeric significantly enhanced serum IgG and IgM values and have antioxidant properties similar to vitamin C that can improve immune functions (Alagawany et al., 2016).

5. *Zingiber officinale* (Ginger, Family - Zingiberaceae)

Ginger is the rhizomic part of *Zingiber officinalis* with a long therapeutic history. Major constituents are carbohydrates, lipids, and oleoresins. Oleoresins include gingerols and other homologs shogaol, zingerone, and volatile oils.

Ginger has an anti-inflammatory activity similar that of non-steroidal anti-inflammatory drugs (NSAIDs) but distinguished from NSAIDs due to its ability to inhibit 5-lipoxygenase. The discovery of the ginger-induced inhibition of both COXs and 5-lipoxygenase heralded the possibility of improved pharmacological potential and reduced adverse effects than NSAIDs (Aggarwal et al., 2004). In mice experimentally-induced with autoimmune encephalomyelitis, the administration of ginger extract modulated IL-12 and TGF- β expression in mice (Jafarzadeh, et al., 2017). As an immunostimulant agent it enhances non-specific immunity.

6. *Allium sativum* (Garlic, Lasun, Family - Liliaceae)

Allium sativum is renowned throughout the world for its unique flavor and therapeutic properties, often called the 'the herbal antibiotic', has anthelmintic, immune modulator, antioxidant, antitumor and antiseptic properties. Garlic comprises mainly sulfur compounds, various enzymes, amino acids, vitamins A, C, and E and minerals including selenium. Antioxidant effect is exerted mainly by flavonoids, cyanidin and quercetin. Aged garlic extract boost the peripheral blood lymphocyte's cytotoxic activity and indicating the immunostimulant function. It also reduced allergic Ig E production, enhanced NK cell activity against tumors, and supported in overcoming stress-induced immunosuppression (Eikai et al., 2001). Dietary garlic supplement could improve the immune system owing to the elevation in the immunoglobulin concentrations (IgG and IgM) of rabbits compared to the control diet (Alagawany et al., 2016). Nutrigenomic studies in broilers suggested that a diet supplemented with garlic powder and *Ocimum sanctum* leaf powder improved the T-cell mediated immunity and

increased expression of TLR2, TLR4, and TLR 7 mRNA levels in the broiler blood and supported the growth parameters and immunity (Sheoran et al., 2017).

7. Cinamomum spp. (Dalchini, Family - Lauraceae)

As a folk medicine, Cinnamon has been traditionally applied to the treatment of inflammatory disorders and gastric diseases. Cinnamon's components possess various biological activities including antimicrobial, antiviral, antioxidant, antitumor, antihypertension, antilipemic, antidiabetes, gastroprotective and immunomodulatory. Among bioactive principles Cinnamaldehyde is a major constituent, others are eugenol, cinnzeylanine and cinnzeylanol. Chao et al., 2005 identified different bioactive components in the leaf extracts of Cinnamon demonstrated the anti-inflammatory effects, which indicated a potential therapeutic action for chronic inflammation. The polyphenol extracts are found to overcome inflammation by modulating pro- and anti-inflammatory cytokine gene expression in mouse macrophages (Cao et al., 2008). Cinnamaldehyde from bark inhibit lymphocyte proliferation and modulate T-cell differentiation. Cinnamon extracts also modulate Cytotoxic-T cells and helped in the suppression of tumor progression (Kwon et al., 2009).

8. Aloe vera (Ghrita kumari, Family - Liliaceae)

Aloe plant is regarded as the universal panacea. Its gel is used as a laxative, antihelminthic, and hemorrhoid remedy and has immunomodulatory functions. Acemannan, the active carbohydrate from *A. vera* gel increased the respiratory burst of macrophages and phagocytic activity. It stimulates synthesis and release of interleukin-1 (IL-1) and tumor necrosis factor from macrophages which in turn initiate an immune attack resulting in necrosis and regression of the cancerous cells (Peng et al., 1991). Aloe ingredients, aloin, and aloe-emodin have an anti-inflammatory effect by reducing prostaglandin E and nitric oxide synthesis in macrophages (Park et al., 2009). Aloin has potential anti-inflammatory effect by inhibition of cytokines, ROS production, decreased the level of LPS-induced iNOS expression, inhibiting the release of interleukin (IL)-1 β , IL-6, tumour necrosis factor- α and NO (Ma et al., 2018). Moreover, aloe-emodin sulfates/glucuronides, rhein sulfates/glucuronides, aloe-emodin, and rhein inhibits pro-inflammatory

cytokines and nitric oxide production, iNOS expression, and MAPKs phosphorylation (Li et al., 2017). Alprogen inhibit calcium influx into mast cells, thereby inhibiting the antigen-antibody-mediated release of histamine and leukotriene from mast cells (Ro et al., 2000).

9. Phyllanthus emblica (Emblica officinalis, Amla, Family - Euphorbiaceae)

The active ingredients in Amla are phyllaemblic compounds, Phyllemblicin, Emblicanin, quercetin, gallic acid, flavonoids, tannins, pectin, Vit A, Vit C, protein, flavonoid and polyphenolic molecules make amla extract as the main constituent of many ayurveda tonics recommend for rejuvenation, and recuperation, etc. (Jain., 1994). The useful applications of *P. emblica* have been identified for conditions such as cancer, diabetes, liver and heart disorders and anemia, among others. Amla is reported to have numerous bio-related activities such as antioxidant, anti-inflammatory, antipyretic immunomodulatory, growth promoter, gastro-protectant, cytoprotectant, hypoglycemic, hypolipidemic, memory enhancer and protective against arsenic-induced liver toxicity (Khan, 2009). Vit. C increases NK cell and Ab dependent cytotoxicity. Anti-inflammatory and analgesic properties of amla are similar to the non-steroidal anti-inflammatory drugs (NSAIDs), i.e. through the inhibition of inflammatory mediators (Jaijoy et al., 2010). Amla use has significantly reduced the inflammation and edema in rats induced with arthritis, indicating that it can be adopted for arthritic therapy (Khan, 2009). Amla have its protective impact on hypercholesterolemia induced cardiac diseases through hypolipidemic effects in experimentations with hypercholesteremic rats. *Phyllanthus emblica* has an important role as a natural immunostimulant, stimulating nonspecific immune mechanisms (Paul and Khanna, 2016). Regular use of this plant enhances the immunity and fights cancers in the body.

10. Glycyrrhiza glabra (Mulethi, Licorice or Sweetwoods, Family-Fabaceae)

The roots of the plant are known as licorice or sweetwoods and have carminative and expectorant activity. It is described in Ayurveda as Rasayana against throat infections. The major components responsible for pharmacological activity are triterpene saponins, flavonoids, and pectins. Compounds in licorice have steroid-like anti-inflammatory activity by inhibition of phospholipase A2 and also interfere with platelet

aggregation (Ohuchi and Tsurufuji, 1982). The extract of plant was reported to increase resistance to *Candida albicans* and herpes simplex virus through its influence on the secretion of Th-2 cytokines (Sekizawa et al., 2001). Isoprenylated phenolics and echinatin conferred the hepatoprotective properties. The anti-inflammatory and hepatoprotective function of licorice increased the production of NF- κ B and IL-10. Isoliquiritigenin and naringenin enhanced regulatory T cells and possess anti-inflammatory properties and efficacy against autoimmune diseases (Guo et al., 2016). Ethanol extracts of licorice enhanced cellular immunity in birds. *G. uralensis* (Chinese licorice) regulates cytokine IL-7, involved in immune cell proliferation and maturation (Ayeka et al., 2016). Various studies have indicated that *G. glabra* is a strong medicine for the treatment of inflammatory disorders and immunosuppressive conditions.

11. *Azadirachta indica* (Neem, Family - Meliaceae)

Neem is also known as sacred gift of nature, Divine tree and Heal all. Every part of Neem viz., leaf, flower, fruit, seed, kernel bark, root, wood, twig, oil and their purified products possess medicinal properties and have been used in traditional remedies. Secondary metabolites are alkaloids, steroids, flavanoids and saponins etc. Neem plant extract stimulates the immune system in various ways viz., enhancing phagocytic activity and antigen presenting ability of macrophages and augmenting cytokines (Thatte and Dhanukar, 1997). Production of IL-1, IFN γ and TNF- α stimulation indicate activation of Th1 type of responses (Mahima et al., 2013). Neem oil administered by injection enhanced phagocytic activity of macrophages MHC II expression, production of IFN- γ and lymphocyte proliferation (Upadhyay et al., 1992) thereby the Cell Mediated Immunity (CMI). Neem leaf extract given orally in mice enhanced the levels of white blood cells, IgG and IgM (Ray et al., 1996). The plant extracts are anti-allergic and limits anaphylactic reactions. Neem enhances Delayed Type of Hypersensitivity (DTH).

Neem leaves powder increased both humoral and cell mediated immune responses in immunosuppressed birds (Sadekar et al., 1998). Neem leaves extracts and infusion has immunoadjuvant (Newcastle's disease) and immunomodulatory effects (Durrani et al., 2008). Neem has antiviral activity against Duck Plague

Virus (DPV) in poultry (Xu et al., 2012). The metabolites of neem strongly and differentially suppressed proliferation of T-cells and inhibited of interleukin-2 (IL-2) (Khan et al., 2013).

12. *Moringa oleifera* (Moringa, Sahajan, Drum-stick, Family- Moringaceae)

Moringa is a folk remedy for various health-related conditions including cancer, catarrh, skin disease, gastric ulcer, nervous condition and diabetes. It strengthens eye, brain, liver, gall and immune system and prevention of myriads of illnesses. Moringa is a source of various bioactive compounds including riboflavin, vitamins A, folic acid, nicotinic acid, ascorbic acid, pyridoxine, iron, beta carotene, calcium and α -tocopherol. Gupta et al., 2010 worked on the immunomodulatory impact of ethanolic extract of *M. oleifera* leaves on normal and immunosuppressed mice model and noticed that *M. oleifera* treated group revealed a significant increase in hematological parameter, phagocytic index and serum enzyme level. Aqueous extract of *M. oleifera* leaves lowered the expression of NF- κ B and enhanced the cytotoxic effect against the pancreatic cancer cells (Berkovich et al., 2013). Three kinds of extracts viz., alcoholic, hot and cold extracts of *M. oleifera* can be used for therapeutic applications. It has high nutritional values and biomedical activities of *M. oleifera* such as immunomodulatory, antidiabetic, anti-ulcer, anthelmintic, anti-inflammatory, antipyretic, analgesic, cardioprotective, anti-hyperlipidemic, anti-hypertensive, hepatoprotective, anti-nephrotoxicity and antimicrobial activity (Sakthivel et al., 2019).

13. *Nigella Sativa* (Black cumin-Ranunculaceae)

The black seed of *N. sativa* has been used as a natural medicine for several diseases for many years. *N. sativa* seed contains: mucilage, thymoquinone, crude fiber, reducing sugars, resins, alkaloids, flavonoids, organic acids, sterols, tannins, saponins, and proteins. It is an alternative source of antibiotics and vaccines in the enhancement of poultry immunity and declining mortality owing to immunomodulatory and therapeutic activities.

N. sativa inhibit many inflammatory mediators, including prostaglandins and leukotrienes, amend splenocyte proliferation, Th1/Th2 cytokine profile, macrophage function and NK anti-tumor activity (Majdalawieh and Fayyad, 2016). It exerts antioxidant, antiproliferative,

antibacterial, and anti-inflammatory effects, which induce positive impacts on the immunity.

14. Picrorhiza kurroa (Kutki, Family - Scrophulariaceae)

It is a renowned herb used by traditional medical practitioners. An iridoid glycoside named Picroliv obtained from the root and rhizome of *P. kurroa* enhance antibody titer, plaque forming cells and DTH response to sheep RBC when orally administered in mice (Puri et al., 1992). It also has anti-allergic and immune boosting potentialities (Baruah et al., 1998). It has proven anti-inflammatory, antioxidant and antineoplastic actions. The methanolic and aqueous extracts have been recognized with antioxidant, and anti-neoplastic potential, thus paving the way for the future clinical application (Rajkumar et al., 2011). A bi-polymeric extract of *P. kurroa* enhanced HA titer, DTH response, phagocytic index and CD4/CD8 response in a dose-dependent manner. Humoral antibody response was improved with oral administration of an ethanolic and aqueous extract of the rhizomes of *Picrorhiza kurroa* (Hussain et al., 2013).

15. Andrographis paniculata (Kirayat, Family - Acanthaceae)

Andrographis paniculata is one of the extensively used traditional plants, worldwide and commonly known as King of Bitters or kalmegh. Various active compounds are labdane diterpenoid, lactones and flavonoids. A significant stimulation of antibody and DTH response to sheep RBCs in mice has been observed in *A. paniculata* ethanolic extract and purified diterpene andrographolides. These preparations also stimulate macrophage migration, phagocytosis and in-vitro proliferation of splenic lymphocytes. Andrographolides are mainly concentrated in leaves and are protective against cellular damages due to hypoxia/reoxygenation (Woo et al., 2008) by upregulation of reduced glutathione (GSH) level and other antioxidant enzyme activities. It was lower with purified andrographolides than with the ethanolic extract indicating the presence of a substance(s) other than andrographolides may be contributing towards immunostimulation. The combination of *Andrographis paniculata* and *Tinospora cordifolia* was found to increase macrophage count, neutrophil adhesion and cellular responses thus showing the immunostimulatory property of these herbs (Yadav et al., 2016).

16. Asparagus racemosus (Satawar, Family - Asparagaceae)

Asparagus racemosus (Shatavari) is a vital component of almost all traditional Ayurvedic preparations. It has multiple actions as nervine tonic, galactagogue, carminative, stomachic, aphrodisiac, diuretic as well as an antiseptic. The unique medicinal potential of *Asparagus* is attributed due to the presence of steroidal saponins (or Shatavarins) as well as sapogenins present in the root, other compounds like quercetin, hyperoxide and rutin are distributed in various parts of the plant (Bopana and Saxena, 2007).

Extract of *A. racemosus* showed only a delay in tumor development instead of a complete prevention against the development of solid tumors (Seena et al., 1993). The protective effect of *A. racemosus* against myelosuppression in mice induced by cyclophosphamide as a single dose has been reported by Thatte and Dahanukar, 1998. They found that the plant is a potent immunostimulant and may be a good candidate for evaluation in patients receiving cytotoxic drugs. In vitro membrane studies described that crude and purified fractions of *Asparagus* significantly inhibited the lipid peroxidation and regulated protein oxidation (Kamat et al., 2000). The reduction in lipid peroxidation imparts a cardioprotective role in in-vivo study using hypercholesteremic rats.

A. racemosus root extract is being recognized as a potent immunostimulant. Decoction of its powdered root caused marked leukocytosis and enhanced phagocytic activity. It is a potent herbal adjuvant as revealed by its alcoholic extract which improves both humoral and cell-mediated immunity.

A. racemosus is suggested to be a potent immunoadjuvant as shown by in-vivo immunization study with diphtheria, tetanus, pertussis vaccines (Sharma et al., 2011). It has been reported to be devoid of antibacterial action, and in this regard, the protection accessible by *A. racemosus* in septic conditions through the regulation of macrophages indicates its inherent immunomodulatory property.

17. Panax ginseng and P. pseudoginseng (Ginseng, Family - Araliaceae)

P. ginseng is widely used as a general health tonic. *P. pseudoginseng* of Indian origin possesses similar activity. *P. ginseng* has antioxidant, anti-inflammatory, and apoptotic, anti-tumor activity and stimulatory activity on

reticuloendothelial system, T- cell proliferation in-vitro, phagocytosis, chemotaxis, augmentation of NK cell activity, production of IL-1, IL-2, TNF- α , GM-CSF, increase in population of CD3, CD4, CD8 cells and immunosuppression in virus-infected mice in various studies. Ginsenosides are the major factor for therapeutic activity of *P. ginseng* which influences the vital hypothalamus-pituitary-adrenal axis as well as immune system. Ginseng has immune modulating potential towards influenza virus. Th2 stimulation can prove it a promising herbal adjuvant towards those antigens requiring an IL4 response for their clearance (Sakure et al., 2008). Saponins from Indian pseudoginseng possesses effective prophylactic and immunostimulating functions by influencing macrophage migration, antibody plaque-forming cells and haemagglutinating antibody titer against sheep red blood cells, enhances the longevity and mental ability especially in young ages (Castleman, 2009). Owing to its anticarcinogenic property, ginseng has been successfully employed in adjuvant breast cancer therapy and proven to augment the physical and psychomotor performance along with the improvement of general health. Supplementation of red ginseng improved the activation of T and NK cells of immune system as well as increased the survival rate (Kim et al, 2016).

18. *Terminalia arjuna* (Arjun, Family - Combretaceae)

T. arjuna (Arjuna, Koha, Kahu, Arjan, and White Marudah) is used as cardiac tonic. Kapoor et al. 2015 studied the cardio-protective impacts of *T. arjuna* on immuno-inflammatory markers in coronary artery disease and found improved immune functions. Tannins, arjunic acid, arjunantin, arjunolic acid and stilbesterol are the major components in *Terminalia arjuna* extract. Bark decoction of Arjun believed to be most effective with sugarcane juice. It has also been used for immunopotentiality in animals wound treatment and fracture.

19. *Bauhinia variegata* (Kachanar, Family - Leguminosae)

In Ayurveda, *Bauhinia variegata* is used as a tonic for treatment of leprosy, blood impurities, liver, wounds, menorrhagia, ulcer, tuberculosis and asthma (Nandkarni and Nandkarni, 2005). Various active principles are steriods, flavonoids, tannins, saponin and alkaloids, vitamin C, quercetin, flavanone, lupeol, β -sitosterol, and kaempferol. An

ayurvedic remedy indicated for increasing WBC, Bark powder used as herbal tonic called kanchanar guggul. Immunomodulatory effect of *B. variegata* was evidenced by the potential of ethanolic extract of its stem bark extract which enhanced both primary and secondary antibody responses. Also, it can improve the natural immune compounds like neutrophil function and phagocytosis (Al-Snafi, 2013).

20. *Nyctanthes arbortristis* (Harsinghar, Family - Oleaceae)

Leaves, flowers, and seeds of harsinghar are extensively used in traditional herbal therapy for conditions like arthritis, scurvy, and malaria. It possesses multiple functions such as antioxidant, antifungal, anti-inflammatory, antinociceptive, antipyretic, antileishmanial, immunomodulatory and hepatoprotective activities. Extracts of the root, leaves, seeds, and flowers possess immune enhancing property which indicated increased humoral and DTH response to sheep RBC and macrophage migration. Iridoid glycosides stimulated humoral immune response and macrophage activity which protected swiss albino mice against *Candida albicans* (Khan et al, 1995). Its phytochemistry revealed several bioactive chemicals that include phytosterols, tannins, flavonoids, phenolics, saponins and glycosides. Iridoid and phenylpropanoid glycosides are responsible for immunomodulatory and antileishmanial activities (Banerjee et al, 2007).

21. *Terminalia chebula* (Harad, Family - Combretaceae)

The dry ripe fruit of *T. chebula* is widely used as adjuvant formulation to Triphala and Menosan or alone in traditional Indian and Asian medicine. A range of pharmacological activities includes antiviral, antibacterial, antidiabetic, renoprotective, radioprotective, anticancer, antioxidant, immunomodulatory and adaptogenic activities. Chemical constituents such as flavonoids, tannins, sterols, fructose, amino acids, resins and fixed oils have been found in *Terminalia* species.

22. *Boerhavia diffusa* (Punarnava, Family - Nynctaginaceae)

Boerhavia diffusa, commonly called Punarnava possesses functionalities such as diuresis, antifibrinolytic, anti-convulsion, anti-inflammatory and hepatoprotection. The biologically active compounds in *B. diffusa* are

sterols and alkaloids, ursolic acid, myricyl alcohol, myristic acid, hypoxanthine-9-L-arabinofuranoside and punarnavine 1 and 2 are the important components. These agents are the major factors for imparting antidiabetic with antioxidant activity to *B. diffusa*. Root extract and alkaloid possess immunomodulatory effect. Ethanolic extracts of *B. diffusa* inhibit NK cell cytotoxicity in human, NO production in mouse macrophage, IL-2 and TNF- α secretion in human. Punarnavine, a glycoside from *B. diffusa*, enhances proliferation of splenocytes, thymocytes, and bone marrow haematopoietic cells (Manu and Kuttan, 2009) and significantly reduce the levels of LPS induced pro-inflammatory cytokines. These all proves the evident role of Punarnavine in immunomodulation.

23. *Aegel marmelos* (Beal, Family - Rutacea)

The fruit of *Aegle marmelos* contain many functional and bioactive compounds such as carotenoids, phenolics, alkaloids, coumarins, flavonoids, terpenoids, vitamins and minerals including vitamin C, vitamin A, thiamine, riboflavin, niacin, calcium, and phosphorus. The chemical profile indicates *Aegle marmelos* as good sources of immunomodulatory agents. The fruit of plant is used for many disorders such as chronic diarrhoea & dysentery and act as a tonic for the heart and brain. It is widely used as indigenous traditional medicine for variety of stress disorders including immunodeficiencies (Das and Das, 1995). Extensive studies show that this plant possesses various significant activities such as antifungal, antioxidant, antibacterial, antiprotozoal, antispermatogenic, anti-inflammatory, anthelmintic, antidiabetic, laxative, febrifuge, and expectorant, chemopreventive, antipyretic, ulcer healing, antigenotoxic, and diuretic (Samanta et al, 2018).

24. *Cynodon dactylon* (Doob grass, family-Poaceae)

Cynodon dactylon contains phenolic phytotoxins viz. ferulic, syringic, paracoumaric, vanillic, para hydroxyl benzoic and orthohydroxy phenyl acetic acid, flavonoids, glycosides, alkaloids, vitamin C, β carotene, fats and palmitic acid etc. Fresh juice of *C. dactylon* doses equivalent to 50, 100 and 200 mg total phenols/kg body weight protected human DNA against doxorubicin-induced DNA damage (Mangathayaru et al, 2009). Fresh juice possesses immunomodulatory activity. Immunomodulatory activity of the protein fraction of *C. dactylon*

showed significant increase in neutrophil test, haemagglutinating antibody titre and delayed type hypersensitivity response (Santhi and Annapoorani, 2010). The polyphenols significantly prevented the immunosuppression caused by pyrogallol in mice (Saradha et al, 2011). *C. dactylon* promises strong utility for effective immunostimulant in swine albino mice (Santhi and Annapoorani, 2010).

25. *Calendula officinalis* (Marigold, Family - Asteraceae)

This is a popular herbal remedy having cosmetic and anti-inflammatory properties. Different active agents are triterpene saponins, alcohols, carotenoids, coumarins, fatty acid esters, flavonoids, essential oils, hydrocarbons and fatty acids. Immunostimulating property of *C. officinalis* is attributed to the presence of its polysaccharide fraction and had been validated by in vitro granulocyte tests. But at higher dosage elevate the blood urea nitrogen and alanine aminotransferase levels, indicating liver overloading (Muley et al, 2009).

II. CONCLUSION

- The use of various plant extracts and their preparation in specific dose concurrently during the scheduled vaccination regimen may be helpful in immunoprotection against different infections through enhanced immunity.
- Environmental stresses like heat stress is common in animals resulting into immune compromised status consequently reduce the growth and production. Production can be enhanced by supplementation of dietary immunomodulatory agents, among which herbal preparations can have a significant place.
- Ashwagandha, Giloy, Dalchini, Aloe vera, Tulsi, Amla, Curcuma, Ginger, Garlic and their formulation may be recommended as promising immunomodulating agents.
- Therefore, more and more research should be focused on existing herbal products to remove therapeutic dilemma as well as to reinforce target-based approach to identify the lead molecule.

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