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CLINICAL APPRAISAL OF IMMUNOMODULATORS IN AYURVEDA IN THE LIGHT OF RECENT PHARMACOLOGICAL ADVANCES

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ABSTRACT

The biological system and processes undergoing inside the system are aimed at restoring an equilibrium. According to view point of Ayurveda, the restoration of biological equilibrium of three humors (*Vata*, *Pitta* & *Kapha*) and *Dhatus* (constitutional body tissues) is very important for immunomodulation. From a therapeutic point of view, immunomodulation refers to a process and a course of action in which an immune response is altered to a desired level. '*Oja*' (the ultrafiltrate of healthy digestion and all constitutional tissues of the body) has been considered as basis of immunity in Ayurvedic system of medicine. Traditionally the *Rasayana* drugs are reputed to promote physical & mental Health and are used for the management of wide range of disorders. Usually, in most of the cases *Rasayana* works via the process of immunomodulation and several clinical & experimental studies on different *Rasayana* validate the same. Natural

immunomodulators of herbal, mineral and animal origin from Ayurveda can be used as principal regimen or as viable adjunct to established modalities, thus offering a novel approach for the treatment of several infective, chronic inflammatory and auto-immune disorders in the forthcoming future. Immunomodulation is recognized as an important alternate to conventional chemotherapy in many diseases. Immunology is probably one of the most rapidly developing areas of medical biotechnology research. Natural immunomodulators from Ayurveda provide great option regarding prevention and management of a wide range of disorders. In this review, effort has been made to discuss about some common herbal, mineral and animal origin drugs from Ayurveda claimed for their immunomodulatory effect.

KEYWORDS: Oja, Vyadhikshamatva, Immunomodulation, Immunomodulatory effect, Rasayana, Dhatus.

INTRODUCTION

The immune system is one of our most complex biological systems in the body. The immune system dysfunction is responsible for various infective, chronic inflammatory and autoimmune diseases. Therefore, immunomodulation needed to control over such type of diseases especially by natural drugs which offers no side effects.

The factors responsible for the *Bala* or *Vyadhikshamatva* (immunity) include normal equilibrium state of *Dosha* (humors), *Dhatu* (constitutional body tisuues), *Agni* (digestive power) and patent *Srotus* (body channels) etc. or factors which Support the equilibrium state of all physiological parameters. The immune response or immunity inside the biological system comprises of two units, one which prevents from manifestation of diseases (innate/nonspecific immune response) and other fight against or attenuate the manifested disease (adoptive/specific immune response). The innate immune response is more or less similar to the concept of *Sahaja Bala* and the adoptive immune response is more or less

Macrophages are extremely versatile cells involved in a number of complex processes in immune responses. When activated they acquire microbicidal effector functions and secrete cytokines, resulting in recruitment of immune cells and subsequent elimination of the pathogen by phagocytosis or release of reactive oxygen and nitrogen species. NO is important intracellular as well as intercellular regulatory molecule of multiple biological functions, including macrophage mediated cytotoxicity.^[2-5]

Immunomodulators exert their effect by modulating the defence mechanism and have capability to either augment or suppress an immune response. In addition to an altered immune response, modulation of haematopoiesis, including increased RBC and WBC counts, increased PCV and enhanced macrophage activation have also been reported.^[6]

Currently, it is estimated that almost 50% of the synthetic medicines are derived from, or patterned after phytochemicals.^[7] Various physiological products, microbial products, synthetic chemicals, cow therapy (*Panchagavya*) and herbal products have immunomodulatory effect.^[8] Traditionally used natural medicines may well provide the basis for the development of a modern and highly successful phyto-pharmaceutical that meets the international criteria required for quality, safety and efficacy for an evidence based therapy.

Rasayana mentioned as a class of important drugs in the Ayurvedic system of medicine is reputed to promote physical as well as mental health, improve defence mechanism and enhance longevity. *Rasayana* help to impede the aging process by delaying the degenerative processes inside the biological system. In this way, *Rasayana* aid in the immunomodulation & general wellbeing, improve the functioning of fundamental organs and keep the signs of early aging at bay. Till date many of the *Rasayana* drugs claimed for their immunomodulatory effects via modulation of cytokine secretion, histamine release, immunoglobulin secretion, class switching, cellular co-receptor expression, lymphocyte expression, phagocytosis and so on. Therefore, *Rasayanas* are used to improve the general health or for the management of wide range of disorders by modulating the immune system.^[9]

Ayurveda has also suggested some non-pharmacological *Rasayana* (rejuvenative measures) that directly or indirectly promote physical as well as mental health, reduces the stress, enhance longevity and therefore, may help in the prevention as well as management of wide range of disorders, probably via the process of immunomodulation.^[50,51]

RANGE OF IMMUNOMODULATORS IN AYURVEDA

The immunomodulators mentioned in Ayurveda can be grouped into following three categories depending upon their source of origin.

- 1. Herbal (plant origin)
- 2. Mineral
- 3. Animal origin

Here, in this review we would discuss some common drugs from above three sources, claimed for their immunomodulatory effect.

Haridra (Curcuma longa Linn.)

Transcription of HIV-1 (type 1 human immunodeficiency virus), provirus is governed by the viral long terminal repeat (LTR). Drugs can block HIV-1 replication by inhibiting the activity of its LTR. Li et al. examined the effect of 'curcumin' (a phytochemical from *Haridra*) on HIV-1 LTR-directed gene expression and virus replication.^[10] Curcumin was found to be a potent and selective inhibitor of HIV-1 LTR-directed gene expression, at concentrations that have minor effects on cells. At the studied concentrations, curcumin inhibited p24 antigen production in cells either acutely or chronically infected with HIV-1 through transcriptional repression of the LTR. Sui et al. examined the effect of curcumin and curcumin boron complexes on the HIV-1 and HIV-2 proteases and validate their immunomodulatory effect.^[11]

Mazumder et al. examined the effect of curcumin analogs with altered potencies against HIV-1 integrase.^[12] They reported the inhibitory activity of curcumin against HIV-1 integrase. They also synthesized and tested analogs of curcumin to explore the structure-activity relationships and mechanism of action of this family of compounds in more detail. They found that two curcumin analogs, dicaffeoylmethane and rosmarinic acid, both inhibited the activities of integrase.

The transcription of HIV-1 provirus is regulated by both cellular and viral factors. Various pieces of evidence suggest that Tat protein secreted by HIV-1 infected cells may have additional activity in the pathogenesis of AIDS because, it is also be taken up by non-infected cells. Barthelemy et al. showed that curcumin used at 10–100 nM inhibited Tat transactivation of HIV1-LTR lacZ by 70–80% in HeLa cells.^[13]

Guduchi (Tinospora cordifolia Willd)

P.K. Raveendran Nair et al have reported the effect of *Guduchi* extract on the lymphocytic activation. Lymphocytic activation reported with the extract at the dose of 100 μ g/ml (activation of β -cells is 39%, T-cells is 105% and NK cells is 331%). Activity of natural killer (NK) cells was markedly increased proving its tremendous role, as the NK cells are important effectors of innate immune system.^[14] It stimulates reticuloendothelial system, bone marrow cellularity, proliferation of stem cells and enhances the activity of haemopoietic growth factor & IL-3. It also enhances the activity of GSH and absorption of Vitamin C.^[15]

The aqueous extract of this plant reported to increase leukocyte count in mice.^[16] It is being used as an adjuvant for immunomodulation in HIV patients. It inhibited ochratoxin-A induced suppression of chemotactic activity and production of IL-1 and TNF- α in mice macrophages. Polyclonal B cell mitogen (G1-4A) found in its stem extract, also enhanced immune response in mice. By the activation of macrophages, it stimulate the granulocyte-macrophage colony stimulating factor (GM-CSF), leading to leukocytosis and improved neutrophil activity. It is also modulate the functioning of classical complement pathway by inhibiting C3-convertase.^[17] Immunomodulatory proteins in its stem reported to increase the number of macrophages and their phagocytic activity.^[18]

Tulsi (Ocimum sanctum Linn.)

Traditionally *Tulsi* has been used as anti-infective and immunomodulatory agent since many centuries. In an experimental study, Alcoholic and aqueous extracts of *Ocimum sanctum* were administered orally at doses of 50, 100 and 200 mg/kg/day for 14 days to healthy albino swiss mice. The assessment of immunomodulatory activity was carried by testing the humoral (haemagglutination antibody titre models) and cellular immunity (delayed type hypersensitivity reaction models). On oral administration, the aqueous and alcoholic extracts had stimulatory effect on delayed type hypersensitivity (DTH) and significantly (p<0.01) improved humoral immunity. The study resulted in stimulatory effect on the humoral and delayed type hypersensitivity but the alcoholic extract was more potent in producing immune stimulation than aqueous extract.^[19]

R. Caroline Jeba et. al evaluated the immunomodulatory effect of *Tulsi* by using rat as experimental material. Aqueous extract of *Ocimum sanctum* were administered orally at doses of 100, 200 mg/kg/day for 45 days in wistar albino rats. Immunomodulatory effect and biochemical & haematological changes were tested by standard methods. Aqueous extract resulted in increased antibody production in dose dependent manner. It enhanced the production of RBC, WBC & haemoglobin and not affected the biochemical parameters.^[20]

Ashwagandha (Withania somnifera Linn.)

M. Suresh Gupta et. al in a study [on Albino wistar rats of the either sex (weighing 180-200 gm each)] found that, *churna* (powder) of *Ashwagandha*, showed significant increase in neutrophil adhesion (p < 0.05) at the dose of 300mg/ kg/day in rats when compared with untreated control indicating possible immunostimulant effect. The DTH (delayed type hypersensitive) response, which is a direct correlate of cell-mediated immunity (CMI), was

significantly increased at the doses of 200 and 300mg/ kg/day of the *Ashwagandha churna*.^[21] In another study it is found that *Ashwagandha* significantly increased the total leukocytes count in normal Balb/c mice and in mice with leukopenia, induced by sub-lethal dose of gamma irradiation.^[22]

It possess both immunostimulatory and immunosuppressive properties. It prevents myelosuppression, induced by cyclophosphamide, azathioprin and prednisolone. It is reported to enhance the mobilization and activation of macrophages (i.e. phagocytosis), resulted in increased activity of lysosomal enzymes and anti-stress effect in mice and rats. In this way it is considered as a potent immunomodulator along with anti-tumour and cytoprotective agent.^[23, 24] *Ashwagandha* significantly inhibited the ochratoxin-A induced suppression of the chemotactic activity and production of IL-1 & TNF- α by macrophages.^[25]

Kumari (Aloe vera Tourn. ex Linn.)

Aloe vera extract at the dose of 100 mg/kg was found to suppress delayed type hypersensitivity reaction induced by SRBCs (Sheep red blood cells) in mice. It reveals the effect of drug on T-lymphocytes and other cell types required for expression of humoral response to SRBCs, as evidenced by marked increase in haem-agglutination titres in mice. From the above study it can be concluded that *Aloe vera* extract produces stimulatory effect on the humoral and cell mediated immune response in the experimental animals (healthy mice, 25-30 gm of either sex) and suggested its therapeutic usefulness in disorders of immunological origin.^[26]

Pippali (Piper longum Linn.)

Immunomodulatory action of *Pippali* (long pepper) fruits (via modulation of both specific and non-specific immune response) has been reported by using macrophage migration index (MMI), haem-agglutination titre (HA) and phagocytic index (PI) in mice. The effect was more prominent at lower dose (225 mg/kg) and was marginally reduced when the dose was increased. In another study, it was found to offer protection against externally induced stress. *Pippali Rasayana*, a famous Ayurvedic preparation, reported to activate macrophages significantly in mice, infected with Giardia lamblia as shown by an increased MMI and phagocytic activity.^[27]

Alcoholic extract from the fruits of *Piper longum* and 'piperine' (a phytochemical from *Piper longum*) was studied for their immunomodulatory and antitumor activity. Alcoholic extract of

the fruits was 100% toxic at the concentration of 500 µg/ml to Dalton's lymphoma ascites (DLA) cells and 250 µg/ml to Ehrlich ascites carcinoma (EAC) cells. Piperine was found to be cytotoxic towards DLA and EAC cells at the concentration of 250 µg/ml. Administration of alcoholic extract of *Piper longum* (10 mg/dose/animal) as well as piperine (1.14 mg/dose/animal) could inhibit the solid tumor development in mice induced with DLA cells and increase the life span of mice, bearing Ehrlich ascites carcinoma tumor to 37.3 and 58.8%, respectively. Administration of *Piper longum* extract and piperine increased the total WBC count to 142.8 and 138.9%, respectively, in Balb/c mice. The number of plaque forming cells also increased significantly by the administration of the extract (100.3%) and piperine (71.4%) on 5th day after immunization. Bone marrow cellularity and α -esterase positive cells were also increased by the administration of extract and piperine.^[28]

Amalaki (Emblica officinalis Gaertn.)

Immunomodulation is an effective protective approach against emerging infectious diseases, certain cancers and many auto-immune disorders. Ayurvedic immunostimulants enhance the overall immunity of the host, offers nonspecific immune response against microbial pathogens and increase humoral & cellular immune responses, by either enhancing cytokine secretion or by directly stimulating B-lymphocytes or T-lymphocytes.^[29] In Ayurveda, *Amalaki* is considered one of the important *Rasayan* having anti-oxidant and immunomodulatory effect and several scientific researches validated the same.^[30,31]

Amalaki enhanced natural killer (NK) cell activity and antibody-dependent cellular cytotoxicity in BALB/c mice bearing Dalton's lymphoma ascites tumor and also increases the life span of tumor bearing animals. However, the increase in survival was completely abrogated when the NK (natural killer) cells and their activity were depleted, either by cyclophosphamide or by anti-asialo-GM1 antibody treatment, validating that the observed effects were because of its immunomodulatory action.^[32]

Amalaki enhanced immunity by augmenting both cell mediated and humoral response. It enhances IL-2 and gamma-IFN production and inhibits apoptosis. It also enhances NK cell activity and Antibody Dependent Cellular Cytotoxicity (ADCC). It is established as a potent immunomodulator in repeated respiratory infections in human beings.^[33]

Yashtimadhu (Glycyrrhiza glabra Linn.)

It provides resistance against herpes simplex virus-1 infection and Candida albicans by IFN and Th2 cytokines secretion. Glycyrrhizic acid and its aglycone reported to modulate the function of NF-kB and IL-10 production which explains reduction of inflammation in liver.^[34] It is also evaluated for its anti-viral activity against HIV, validating its immunomodulatory effect.^[35]

Ardrak (Zingiber officinale Rosc.)

In a study *Ardrak* (ginger) evaluated for its immunomodulatory action and resulted in suppressed lymphocyte proliferation by decrease in IL-2 and IL-10 production. Another study reported that, an aqueous ginger extract significantly increased the production of IL-1 β , IL-6 and TNF- α in activated peritoneal mouse macrophages.^[36] A study in which mice fed 50% ethanolic ginger extract (25 mg/kg) for seven days showed higher haem-agglutinating antibody titre and plaque forming cell counts, consistent with improved humoral immunity.^[37]

Swarnamakshika Bhasma

Swarnamakshika is the most abundant Copper bearing mineral. It mainly contains Copper, Iron and Sulphur. Chemically the *Swarnamakshika* is Copper pyrite/Chalco pyrite (CuFeS₂). Its *Bhasma* contains Fe₂O₃, FeS₂, CuS and SiO₂.^[38]

In an experimental study (on laboratory breed swiss albino mice of either sex, weighing $25\pm2g$), *Swarnamakshika Bhasma* used in 5 separate doses of 1, 0.5, 0.25, 0.125, 0.06 mg and the result assessed by using Nitro blue tetrazolium test (NBT), Phagocytosis & Candidacidal assay and Neutrophil & Chemotaxis test. The doses of 1.0 and 0.5 mg showed significant (p<0.0077) increase in the % of NBT stimulated cells when compared to negative control group. Positive control group showed significant (p<0.001) phagocytic activity at the dose of 0.6 mg when compared to other different doses. Positive control group showed significant (p<0.001) increase in the dead candidal cells when compared to 1.0 mg. It also resulted in significant difference in (p<0.001) neutrophil and chemotactic activity at the dose of 1 and 0.5 mg when compared to negative control. *Swarnamakshika Bhasma* at the dose of 1 mg showed statistically significant results. Modified from.^[39]

Swarna Bhasma/ Swarna preparation (gold Bhasma/ gold preparation)

Traditionally, Acharya Kashyap mentioned about the immunomodulatory effect of *Swarna*. He cited that if a child continuously fed *Swarna* powder (*Bhasma*) then he/she will not be attacked by any disease. Traditionally, *Swarna Prashan* has been used in infants in Ayurvedic system of medicine as a preventive measure from wide range of disorders, acting probably via the process of immunomodulation. Mainly after delivery, raw gold is rubbed on a stone with the help of little amount of water and is administered along with honey and ghee. In some places, *Swarna Bhasma* is administered to newborn babies along with drugs like *Vacha Churna* (powder of *Acorus calamus* Linn.), *Brahmi* (*Bacopa monnieri* Linn.), etc.^[40]

In an experimental study, Bajaj et al (2001) evaluated the efficacy of *Swarna Bhasma* on nonspecific immunity in mice. Male mice were administered with the incremental doses of *Swarna Bhasma* orally for 10 days. It was observed that, it significantly (p<0.001) increased counts of peritoneal macrophages and also stimulated the phagocytic index of macrophages, validating its immunomodulatory effect.^[41]

Mukta Bhasma

Mukta Bhasma is a unique calcium containing preparation, prepared by trituration and calcination of pearl. Chemically, it contains mainly CaCo₃.^[42]

Mukta Bhasma used in 5 dosage (1, 0.5, 0.25, 0.125, 0.06 mg) in an experimental study which resulted in significant (p<0.001) increase in the % of NBT stimulated cells. *Mukta Bhasma* has shown significant (p<0.001) increase in neutrophil count and chemotactic activity at the dose of 0.06 and 0.125 mg when compared to 0.5 and 1.0 mg. Increase in the NBT assay, Phagocytosis and Chemotaxis represents good Immunomodulatory effect of *Mukta Bhasma* at the dose of 0.06mg. The above study suggested its cytotoxic activity at higher doses and immunomodulatory effect at lower doses. Modified from.^[43]

Gomutra (cow urine)

Urine as well as other four products, milk, ghee, curd and dung obtained from cow possess medicinal properties, and are used alone or in combination with some other drugs for the management of wide range of disorders including Cancer, AIDS and Diabetes mellitus.^[44,45]

Ambwani S et.al reported that cow urine enhances, both cellular and humoral immune responses. The study was done to evaluate the blastogenic activity of lymphocytes and effect of in-vivo cow urine treatment.^[46]

D D Gosavi et.al evaluated the immunomodulatory effect of *Gomutra Ark* in rats (Adult Wistar albino rats weighing 200-250 gm of either sex). The study is assessed by using haemagglutination reaction. The result was found statistically significant (P < 0.05) validating the immunomodulatory effect of *Gomutra*.^[47]

DISCUSSION

Immunomodulation is the process of modifying an immune response in a positive or negative manner by administration of a drug or compound. The potential uses of immunomodulators in clinical practice include the reconstitution or restoration of immune deficiency (e.g. in AIDS) and the suppression of normal or excessive immune function (e.g. in graft rejection or autoimmune disease).^[48]

The principles and practice of *Rasayana* in Ayurveda is based on the principle of immunomodulation. *Rasayanas* as described in Ayurveda nourish the body, boost immunity and help to keep the body and mind in the best of its health. It is a multi-angled approach, taking care of body, mind and spirit thus affecting total wellbeing of an individual. It seems that the *Rasayana* act at three levels of the bio-system to promote nutrition, at the level of *Agni* by promoting digestion and metabolism, at the level of *Srotus* by promoting microcirculation & tissue perfusion and at the level of *Rasa* itself by acting as direct nutrient. Thus the *Rasayana* remedies act essentially on nutrition dynamics and rejuvenate both the body and psyche. In this way *Rasayanas* modulate immunity by its pharmacological & neutraceutical action and therefore, help in the management of wide range of disorders. Modified from.^[49]

As many modern drugs are often patterned after phytochemicals, therefore, by studying the effect of each compound on immune cells as well as on microbes can provide useful insights to the development of potentially useful new pharmacological agents in the field of immunomodulation. Recently, there has been progress on the ethno-medicinal plants as immunomodulatory agents because of the fact that plant extracts have been widely investigated during last few decades, in different parts of the world for their possible immunomodulatory effect.

The recent researches reveals that the *Rasayana* drugs can modulate the immune system by different mechanism. *Guduchi* leads to immunomodaltion by activating the lymphocytes, *Haridra* inhibits the HIV-1 replication, *Tulsi* act by modulating the humoral immunity,

Ashwagandha act by modulating cellular immunity, *Kumari & Gomutra* stimulate both cellular as well as humoral immunity, *Pippali* works via modulation of both specific and non-specific immune response, *Amalaki* stimulates B or T- lymphocyte & enhanced the natural killer cells activity, *Swarnamakshika Bhasma* acts by modulating the functioning of neutrophils and process of phagocytosis and *Swarna Bhasma* acts via the modulation of functioning of phagocytosis & phagocytic activity.

CONCLUSION

The stress, unhealthy nutrition and continuous exposure to several toxins in the present era lead to compromised immune system. Therefore, immunomodulation should be of central importance in medical field to combat several infective, chronic, autoimmune & inflammatory diseases. Natural immunomodulators belonging to herbal, mineral and animal sources from Ayurveda provide a safer & cost effective way of treatment for such type of disorders. Some of the important *Rasayan* drugs with evidence based immunomodulatory effect are *Haridra, Guduchi, Amalaki, Tulsi, Pippali, Swarna Bhasma, Swarnamakshika Bhasma, Gomutra* etc. These drugs have potential to change the entire structure of the present day immunomodulatory therapy in future.

REFERENCES

- Byadgi P.S. Concept of immunity in Ayurveda. Journal of Applied Pharmaceutical Science, 2011; 01(05): 21-24.
- 2. Moncada, S.; Palmer, R.M.J.; Higgs, E.A. Nitric oxide: Physiology, pathophysiology, and pharmacology. Pharmacol. Rev., 1991; 43: 109-142.
- 3. Nathan, C.F.; Hibbs, J. Role of nitric oxide synthesis in macrophage antimicrobial activity. Curr. Opin. Immunol., 1991; 3: 65-70.
- 4. Liew, F.Y.; Wei, X.Q.; Proudfoot, L. Cytokines and nitric oxide as effector molecules against parasitic infections. Phil. Trans. Royal Soc. Lond. B, 1997; 352: 1311-1315.
- 5. Bogdan, C.; Röllinghoff, M.; Diefenbach, A. Reactive oxygen and reactive nitrogen intermediates in innate and specific immunity. Curr. Opin. Immunol., 2000; 12: 64-76.
- Cox, W. I. examining the immunologic and haematopoietic properties of an immunostimulant. Veterinary Medicine, 1988; 6: 424–428.
- Chetan Savant, Narasimhachar Joshi, Suyodhana Reddy, Basheerahmed Abdulaziz Mannasaheb, Hanumanthachar Joshi. Immunomodulatory Medicinal Plants of India: A Review. International Journal of Pharmacology & Toxicology, 2014; 4(2): 109-115.

- 8. Verma, A.K. Cowpathy and human health. Indian Cow: Scient. Econ. J., 2005; 2: 39-45.
- 9. Kumar PV, Kuttan R, Kuttan G. Effect of "Rasayanas" a herbal drug preparation on cellmediated immune responses in tumor bearing mice. Indian J Exp. Biol., 1999; 37: 23.
- 10. Li CJ, Zhang LJ, Dezube BJ, Crumpacker CS, Pardee AB. Three inhibitors of type 1 human immunodeficiency virus long terminal repeat-directed gene expression and virus replication. Proc Natl Acad Sci USA, 1993; 90: 1839–1842.
- Sui Z, Salto R, Li J, Craik C, Ortiz deMontellano PR. Inhibition of the HIV-1 and HIV-2 proteases by curcumin and curcumin boron complexes. Bioorg Med Chem, 1993; 1: 415– 422.
- Mazumder A, Neamati N, Sunder S, et al. Curcumin analogs with altered potencies against HIV-1 integrase as probes for biochemical mechanisms of drug action. J Med Chem, 1997; 40: 3057–3063.
- Barthelemy S, Vergnes L, Moynier M, Guyot D, Labidalle S, Bahraoui E. Curcumin and curcumin derivatives inhibit Tat-mediated transactivation of type 1 human immunodeficiency virus long terminal repeat. Res Virol, 1998; 149: 43–52.
- PK Raveendran; N S Rodrigueza; R Ramachandrana; A Alamoa; S J Melnicka; E Escalona; P I Garcia; S F Wnukb; C Ramachandrana. Int. Immunopharmacol., 2004; 4: 1645–1659.
- 15. Prince, P.S., M. Padmanabhan and V.P. Menon. Restoration of antioxidant defence by ethanolic Tinospora cordifolia root extract in alloxan-induced diabetic liver and kidney. Phytother. Res., 2004; 18: 785-787.
- 16. Ganguly, S. and A. Prasad. Role of plant extracts and cow urine distillate as immunomodulators: A review. J. Med. Plant Res., 2011; 5: 649-651.
- 17. Archana, S.J., R. Paul and A. Tiwari. Indian medicinal plants: A rich source of natural immuno-modulator. Int. J. Pharmacol., 2-11; 7: 198-205.
- 18. Rege, N.N., U.M. Thatte and S.A. Dahanukar. Adaptogenic properties of six rasayana herbs used in Ayurvedic medicine. Phytother. Res., 1999; 13: 275-291.
- 19. J. Vaghasiya et al. Comparative Evaluation of Alcoholic and Aqueous Extracts of Ocimum Sanctum for Immunomodulatory Activity. International Journal on Pharmaceutical and Biological Research, 2010; 1(1): 25-29.
- 20. R. Caroline Jeba et. al. Immunomodulatory activity of aqueous extract of Ocimum sanctum in rat. International Journal on Pharmaceutical and Biomedical Research (IJPBR), 2011; 2(1): 33-38.

- M. Suresh Gupta, H.N. Shivaprasad, M.D. Kharya, and A.C. Rana. Immunomodulatory Activity of the Ayurvedic Formulation "Ashwagandha Churna". Pharmaceutical Biology, 2006; 44 (4): 263–265.
- Kuttan G. Use of Withania somnifera Dunal as adjuvant during radiation therapy. Ind. J. Exp. Biol., 1996; 34: 854-856.
- 23. Mishra, L.C., B.B. Singh and S. Dagenais. Scientific basis for the therapeutic use of Withania somnifera (ashwagandha): A review. Altern. Med. Rev., 2000; 5: 334-346.
- 24. Kushwaha, S., S. Roy, R. Maity, A. Mallick and V.K. Soni et al. Chemotypical variations in Withania somnifera lead to differentially modulated immune response in BALB/c mice. Vaccine, 2012; 30: 1083-1093.
- Dhuley J N. Effect of some Indian herbs on macrophage function in ochratoxin- A treated Mice. J. Ethanopharmacol., 1997; 58: 15-20.
- 26. Atul N Chandua, Santhosh kumar. C, Chiranjib Bhattacharjee, Subal debnath, K. kamala kannan. Studies on Immunomodulatory Activity of Aloe vera (Linn). International Journal of Applied Biology and Pharmaceutical Technology, 2011; 2(1): 19-22.
- 27. Chauhan Khushbu, Solanki Roshni, Patel Anar Macwan Carol, Patel Mayuree. Phytochemical and therapeutic potential of piper longum linn a review. IJRAP, 2011; 2(1): 157-161.
- 28. E.S Sunila, G Kuttan. Immunomodulatory and antitumor activity of Piper longum Linn. and piperine. Journal of Ethnopharmacology, 2004; 90 (2–3): 339–346.
- Spelman K, Burns J, Nichols D, Winters N, Ottersberg S, Tenborg M. Modulation of cytokine expression by traditional medicines: a review of herbal immunomodulators. Altern Med Rev, 2006; 11: 128–150.
- Khan KH. Roles of Emblica officinalis in medicine A review. Bot Res Int, 2009; 2: 218–228.
- 31. Krishnaveni M, Mirunalini S. Therapeutic potential of Phyllanthus emblica (amla): the Ayurvedic wonder. J Basic Clin Physiol Pharmacol, 2010; 21: 93–105.
- 32. Suresh K, Vasudevan DM. Augmentation of murine natural killer cell and antibody dependent cellular cytotoxicity activities by Phyllanthus emblica, a new immunomodulator. J Ethnopharmacol, 1994; 44: 55–60.
- 33. Ganju, L., D. Karan, S. Chanda, K.K. Srivastava, R.C. Sawhney and W. Selvamurthy. Immunomodulatory effects of agents of plant origin. Biomed. Pharmacother., 2003; 57: 296-300.

- Yoshikawa, M., Y. Matsui, H. Kawamoto, N. Umemoto and K. Oku et al. Effects of glycyrrhizin on immune-mediated cytotoxicity. J. Gastroenterol. Hepatol., 1997; 12: 243-248.
- 35. Akamatsu, H., J. Komura, Y. Asada and Y. Niwa. Mechanism of anti-inflammatory action of glycyrrhizin: Effect on neutrophil functions including reactive oxygen species generation. Planta Med., 1991; 57: 119-121.
- 36. Santosh Kumar Singh, Jay Ram Patel and Deepak Bachle. A Review on Zingiber Officinale: A Natural Gift. Int J Pharm Bio Sci, 2014; 5(3): 508 525.
- 37. Puri, A, Sahai, R, Singh, KL, Saxena, RP, Tandon, JS, Saxena, KC. Immunostimulant activity of dry fruits and plant materials used in indian traditional medical system for mothers after child birth and invalids. Journal of Ethnopharmacology, 2000; 71: 89-92.
- Singh S, Tripathi JS, Rai NP. A Review of Pharmacodynamic Properties of 'Nishadi Vati' A Herbomineral Ayurvedic Formulation. IJPRS, 2014; 3(2): 849-868.
- Dr. Veena B Kupati, Dr.P.G.Jadar. Immunomodulatory Effects of Ayurvedic Drugs: A Review. Indian Journal of Applied Research, 2014; 4(11): 28-30.
- 40. Dr. Mahapatra Arun Kumar, Dr. Nisha Kumari Ojha, Prof. Abhimanyu Kumar. Rationality of Swarna Prashan in Pediatric Practice. International journal of Ayurvedic & Herbal Medicine, 2013; 3(3): 1191-1200.
- 41. Bajaj S, Ahmad I, Raisuddin S, Vohora SB. Augmentation of non-specific immunity in mice by gold preparations used in traditional systems of medicine. Indian J Med Res., 2001; 113: 192-6.
- 42. Nitin Dubey, Nidhi Dubey, RS Mehta, AK Saluja, DK Jain. Antiulcer Activity of a Traditional Pearl Preparation: Mukta Bhasma. Research J. Pharm. and Tech., 2009; 2(2): 287-290.
- 43. Dr. Veena B Kupati, Dr.P.G.Jadar. Immunomodulatory Effects of Ayurvedic Drugs: A Review. Indian Journal of Applied Research, 2014; 4(11): 28-30.
- 44. Dhama K, Chauhan RS, Singhal L. Anti-Cancer Activity of Cow Urine: Current Status and Future Directions. Int Jr of Cow Sci, 2005; 1(2): 1-25.
- Jarald EE, Edwin S, Tiwari V, Garg R, Toppo E. Antidiabetic Activity of Cow Urine and a Herbal Preparation Prepared Using Cow Urine. Pharmaceutical Biology, 2008; 46 (10-11): 789-92.
- 46. Ambwani S, Ambwani T, singhal L, chauhan RS. Immunomodulatory effects of cow urine on dimethoate induced immunotoxicity in avian lymphocytes. International journal of cow science; 2(1): 45-46.

- 47. D D Gosavi, D Sachdev, K Salwe. Immunomodulatory and Antioxidant Effect of Gomutra Ark in Rats. J MGIMS, 2011; 16(ii): 37-41.
- 48. Agrawal Surendra S, Khadase Saurabh C., Gokul S., Studies on Immunomodulatory Activity of Capparis zeylanica Leaf Extracts, International Journal of Pharmaceutical Sciences and Nanotechnology, 2010; 3: 887-892.
- 49. Satyapal singh, J.S. Tripathi, N.P. Rai. An overview of Ayurvedic & contemporary approaches to Psychodermatology. The Journal of Phytopharmacology, 2014; 3(4): 286-299.
- 50. Agnivesha, Charaka, Dridhabal. Charak Samhita. reprint, Varanasi; Chaukambha Bharti Academy, 2001.
- 51. Sushruta, sushruta samhita. 14th ed., Varanasi; Chaukambha Sanskrita Sansthan, 2003.