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Review Article

IMMUNOMODULATORS FROM PLANT ORIGIN: A REVIEW

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Immunomodulatory agents of plant origin increase the immune responsiveness of the body against pathogens. Recently phytopharmaceutical research received much attention to develop safe and effective lead compound/fraction with potential immunomodulatory activity. Use of phytoconstituents has been a supportive practice for our immune system against infectious disease since centuries as these drug substances enhance the immune response against infections. There are plenty of plants which possess immunomodulatory and immunostimulatory activities. Many Plant drugs are rejuvenators, nutritional supplements and possess strong antioxidant activities and acts as potent immunomodulators by exerting antagonistic action on oxidative stressors, giving rise to the formation of different free radicals. The immunomodulatory activities of various plants have been determined in this article through literature review. This review will focus on latest developments regarding immunomodulatory activities of plants.

Keywords: Immunomodulatory agent, phytoconstituents, immunomodulatory activities, plant source.

INTRODUCTION

An immunomodulator is a substance which suppresses or modulates the component of immune system including innate or adaptive immunity of the immune response[1]. Immunomodulator are capable of interacting with the immune system to up regulate or down regulate specific aspects of host response. They play their role in maintaining the immune system by increasing T cell immunity, stimulating the natural killer cells and interferon production as well as inducing specific cytokine production by activating targeting cells[2].

One of the most important sources of immunostimulator which are being explored extensively currently comes from plant derived substances[3]. A large population of India uses plants for its healing, preventive, curative and much therapeutic property together with immunostimulatory property[4].

Certain medicinal plants promote positive health and maintain organic resistance against infection by re-establishing body equilibrium. Many polysaccharides isolated from higher plants are considered to be biological response modifier and enhance various immune responses, like complement activation, proliferation of lymphocytes and stimulation of macrophages. Plant flavonoids also used as immunostimulator, which is important

for growth, development and immunity[5]. Various synthetic agents are used as immunostimulative agent such as levamisole, thalidomide, but there are various side effects of these agents such as nephrotoxicity, hepatotoxicity, bone marrow depression, gastrointestinal disturbance and so on. Because of the side effects associated with synthetic agents and as plants are safer, much more effective and cheaper, conventional immunomodulator plants can be explored[6].Immunomodulatory agents of plant origin increase the immune responsiveness of the body against pathogens by activating primarily the non-specific immune system i. e. stimulation of the function and efficiency of the granulocytes, macrophages and complement etc. However these drugs should be subjected to systematic studies to substantiate the therapeutic claims with regard to their clinical utility.

Classification of Immunomodulators

Clinically, immunomodulators can be classified into the following three categories:

1. Immunoadjuvants

Immunoadjuvants are used to enhance the efficacy of vaccines and therefore could be considered specific immune stimulants. Immunoadjuvants hold the promise of being the true modulators of the immune response. It has been proposed that they be exploited as selectors between cellular and humoral helper T1 (Th1) and helper T2 cells (Th2), immunoprotective, immunodestructive, and reagenic [immunoglobulin E (IgE)] versus IgG type immune respon- sesdposing a real challenge to vaccine designers.

2. Immunostimulants

Immunostimulants are inherently non-specific as they are envisaged as enhancements to a 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 the individual with impairment of immune response, they are expected to act as immunotherapeutic agents.

Immunosuppressants

Immunosuppressants are a structurally and functionally heterogeneous group of drugs, which are often concomitantly administered in combination regimens to treat various types of

organ transplant rejection and autoimmune disease.

Mechanism of Action of the Plant Immuno modulators[7]

Many Plant drugs are rejuvenators, nutritional supplements and possess strong antioxidant activities and acts as potent immunomodulators by exerting antagonistic action on oxidative stressors, giving rise to the formation of different free radicals. They are used mainly to combat the effects of ageing, atherosclerosis, cancer, diabetes, rheumatoid arthritis, autoimmune disease and Parkinson's disease. The Rasayana herbs seem to operate through immunostimulant, immunoadjuvant, and immunosuppressant activities or by affecting the effector arm of the immune response.

Mechanisms of immunomodulation activity occur mainly via phagocytosis stimulation, macrophages activation, immunostimulatory effect on peritoneal macrophages, lymphoid cells stimulation, cellular immune function enhancement and nonspecific cellular immune system effect, antigen-specific immunoglobulin production increase, increased nonspecific immunity mediators and natural killer cell numbers, reducing chemotherapy-induced leukopenia, and increasing circulating total white cell counts and interleukin-2 levels. Modulation of the immune responses through the stimulatory or suppressive activity of a phyto- extract may help maintain a disease-free state in normal or unhealthy people. Agents that activate host defense mechanisms in the presence of an impaired immune response can provide supportive therapy to conventional chemotherapy.A high degree of cell proliferation renders bone marrow a sensitive target, especially to various cytotoxic drugs. In fact, bone marrow is the organ most affected during any immunosuppression therapy with this class of drugs. Loss of stem cells and the inability of the bone marrow to regenerate new blood cells results in thrombocytopenia and leucopenia.Lymphocyte stimulation tests were performed on eight cycloartane-type saponins isolated from *Astragalus melanophrurius*[8]to determine the role of saponins in the immunomodulating effect of the plant. Higher concentrations of tested compounds have exhibited inhibitory effects.

Cycloartane and oleanane-type triterpenes from these species have unmistakably induced

interleukin-2 activity.[9]Immunomodulatory activities of terpenoid compounds such as glycyrrhizinic acid, ursolic acid, oleanolic acid, and nomilin have been reported.[10]A novel triterpenoid has been isolated from the root bark of Ailanthus excelsaRoxb. (Tree of Heaven), AECHL-1, and has potential as an anti-cancer agent.[11]Many studies have reported the identification of immunomodulatory compounds with pharmacological activity and a limited toxicity. In this context, ethnopharmacology represents the most important way possible to uncover interesting and therapeutically helpful molecules. The phytochemical analysis of Rasayana plants has revealed a large number of compounds including tannic acid, flavonoids, tocopherol, curcumin, ascorbate, carotenoids, polyphenols, etc., which have been shown to have potent immunomodulatory properties. The herbal mixture preparations of Indian traditional medicine may stimulate immunomodulation due to their content of plants with immunomodulatory properties that probably act synergistically. This hypothesis along with the lack of toxicity can be important to understand their use in the past as well as currently[12].

Different types of screening methods both *in vivo* and *in vitro* have been employed to determine their pharmacological activity. Some medicinal plants may stimulate the immune system, (e.g., *Panax ginseng, Ocimum sanctum, Tinosporacordifolia,* and *Terminaliaarjuna*), and some may suppress the immune response (*Alternantheratenella*). Also, various secondary metabolites (e.g., alkaloids, glycosides, saponins, flavonoids, coumarins, and sterols) exhibit a wide range of immunomodulating activity.

Examples of Plant Immunomodulators

Several medicinal plants used in the Indian traditional system known as Rasayana (devoted to enhancement of the body's resistance) have attracted the attention of scientists world-wide. Several medicinal plants exhibit immunomodulatory activity are discussed below.

1. Abutilon indicum

Ethanolic and aqueous extract of leaves of *Abutilon indicum* was studied for immunomodulatory activity orally at the dosage levels of 200 mg/kg/day and 400 mg/kg/day body weight in mice. The assessment of immunomodulatory activity on specific and non-specific immunity were studied by

heamagglutination antibody (HA) titer, delayed type hypersensitivity (DTH), neutrophil adhesion test and carbon clearance test. In order to induced immunosuppresion in mice by using cyclophosphamide (100 mg/kg/day, p.o.) and levamisole (50 mg/kg/day, p.o.) used as immunostimulating agents. The study demonstrated that *Abutilon indicum* triggers both specific and non-specific responses to a greater extent[13].

2. *Emblica officinalis* and *Evolvulus alsinoides*

Fruits of Emblica officinalis (family: Euphorbiaceae) and whole plant of *Evolvulus alsinoides* (family: Convolvulaceae) has been extensively used in Indian Ayurvedic medicine for varieties of medical disorders. The immunomodulatory properties of *Emblica officinalis* and *Evolvulus alsinoides* were evaluated in adjuvant induced arthritic rat model. The crude aqueous extracts of both the herbs were administered intraperitonially following a repeated treatment profile. There was a significant reduction in swelling and redness of inflamed areas in treated animals than in untreated controls. The anti-inflammatory response of both extracts was determined by lymphocyte proliferation activity and histopathological severity of synovial hyperplasia. Both extracts showed a marked reduction in inflammation and edema. At cellular level immunosuppression occurred during the early phase of the disease. There was mild synovial hyperplasia and infiltration of few mononuclear cells in treated animals. The induction of nitric oxide synthase was significantly decreased in treated animals as compared to controls. These observations suggested that both the herbal extracts caused immunosuppression. Both are as potent as dexamethasone, a traditionally used immunosuppressant for arthritis[14].

3. Caesalpinia bonducella

Ethanolic seed extract of *Caesalpinia bonducella* Fleming (Family: Caesalpiniaceae) was evaluated for immunomodulatory potential by oral route at a dose of 200-500 mg/kg kg body weight. Results evoked a significant increase in percent neutrophil adhesion to nylon fibers as well as a dose dependent increase in antibody titre values, and potentiated the delayed-type hypersensitivity reaction induced by sheep red blood cells. Also it prevented myelosuppression in cyclophosphamide drug treated rats and good response towards

phagocytosis in carbon clearance assay. The results indicated that *Caesalpinia bonducella* possesses potential immunomodulatory activity and has therapeutic potential for the prevention of autoimmune diseases[15].

4. Carica papaya

Leaf aqueous extract of *Carica papaya Linn*. (CP) was studied on the growth of various tumor cell lines and on the anti-tumor effect of human lymphocytes. The observations showed significant growth inhibitory activity of the CP extract on tumor cell lines. In peripheral blood mononuclear cells, the production of IL-2 and IL-4 was reduced following the addition of CP extract, whereas that of IL-12p40, IL-12p70, IFN-gamma and TNF-alpha was enhanced without growth inhibition. In addition, cytotoxicity of activated PBMC against K562 was enhanced by the addition of CP extract. Moreover, microarray analyses showed that the expression of 23 immunomodulatory genes, classified by gene ontology analysis, was enhanced by the addition of CP extract Result indicated that *Carica papaya* leaf extract can mediate a Th1 type shift in human immune system and CP leaf extract may potentially provide the means for the treatment and prevention of selected human diseases such as cancer, various allergic disorders, and may also serve as immunoadjuvant for vaccine therapy[16].

5. Cinnamomum tamala

Hexane fraction of the leaves of *Cinnamomum tamala Linn*. (CT) (Family: Lauraceae was assessed for evaluated immunomodulating property orally in rats using delayed type of hypersensitivity (DTH), antibody production against sheep red blood cells (SRBCs), mitotic index in bone marrow cells and concanavalin A (Con A) mediated proliferation of lymphocytes. Results indicate change in body weight (BW), spleen weight, thymus weight, bone marrow cellularity and hematological changes and also significantly inhibited the DTH response antibody production, suppressed mitotic index in bone marrow cells along with the suppression of lymphocyte proliferation indicating that the fraction possesses immunosuppressive property at doses, higher than 800 mg kg (-1) BW in rats[17].

6. Chlorophytum borivilianum

Ethanolic extract of the roots of *Chlorophytum borivilianum* belonging to family Liliaceae was evaluated for immunomodulatory activity. Models

used were Non-Specific Immunity Determined by Survival Rate against Fungal Infection, In Vivo Phagocytosis Using Carbon Clearance Method, SRBC-Induced Delayed-Type Hypersensitivity Reaction (DTH Response) and Activity Against Drug-Induced Immunosuppression. Effective dose was 200 mg/kg dose when compared with 100mg/kg of sapogenin as an standard. Immunostimulant activity of ethanolic extract was more pronounced as compared to sapogenins. The results, thus justifies the traditional use of *C. borivilianum* as a rasayana drug[18].

7. Heracleum nepalense D. Don

Methanolic extract of *H. nepalense* roots were assessed for immunostimulatory activity, using different in vitro and in vivo experimental models. The immunostimulatory potential of the test compound was investigated by in vitro, phagocytic index and lymphocyte viability tests, using interferon α-2b, a known immunostimulant drug, as the standard. Other tests such as carbon clearance, antibody titer and delayed type hypersensitivity were studied in mice, using levimasole as the standard. The dried root extract (1000 µg/ml) and isolated quercetin glycoside (50 µg/ml) significantly increased the in vitro phagocytic index and lymphocyte viability in all assays. There was a significant increase in antibody titer, carbon clearance and delayed type hypersensitivity in mice. *H. nepalense* exhibited a dose-dependent immunostimulant effect, which could be attributed to the flavonoid content or due to the combination with other component(s) [19].

8. Ficus benghalensis

Successive Methanolic extract (SME) of aerial roots of *Ficus benghalensis* (Family Moraceae) was studied for immunomodulatory activity. Various extracts of the aerial roots of *Ficus benghalensis*were evaluated for potential immunomodulatory activity, using the in vitro polymorphonuclear leucocyte (human neutrophils) function test, using rats as the animal model, using sheep red blood cells (SRBC) as the antigen and Distilled water served as a control in all the tests. In vitro all the extracts were evaluated at concentrations of 0.5, 1.0 and 2.0 mg/ml. For invivo studies dose of 50, 100 and 200 mg/kg were used. It was concluded that the presence of steroids and flavonoids in the petroleum ether, benzene and chloroform extracts. The acetone, methanol and

water extracts were found to contain flavonoids, phenolics, steroids, glycosides, carbohydrates and proteins which are the responsible chemical constituents for activity. The SME of *Ficus benghalensis* was found to have a significant immunostimulant activity on both the specific and non-specific immune mechanisms[20].

9. Cissampelos pareira

The alkaloidal fraction (AFCP) of roots of *Cissampelos pareira Linn.* (Family: Menispermaceae) was screened for immunomodulatory activity in mice. Results indicated that AFCP found to have significant immunosuppressive activity at lower doses (25 and 50 mg/kg) while no activity was observed at higher doses (75 and 100 mg/kg). Humoral antibody titre was significantly ($p<0.01$) lowered by AFCP at the doses of 25 and 50 mg/kg. Delayed type hypersensitivity response was also significantly ($p<0.01$) suppressed by the AFCP at the dose of 75 mg/kg[21].

10. Cinnamomum zeylanicum

Cinnamomum zeylanicum bark (Lauraceae) commonly known as cinnamon suspension in distilled water with 0.5% sodium carboxy methyl cellulose was used to study the immunomodulatory activity using different experimental models such as carbon clearance test, cyclophosphamide induced neutropenia, neutrophil adhesion test, effect on serum immunoglobulins, mice lethality test and indirect haemagglutination test. *Cinnamomum zeylanicum* bark contains about 0.5 -10% of volatile oil, 1-2 % of tannins (Phlobatannins), mucilage, calcium oxalate, starch and sweet substance in the form of mannitol. Presence of Tannins might be responsible for the proposed activity. Immunomodulatory activity was investigated in 10 mg/kg/po and 100 mg/kg/po dose concentration. Levamisole (2.5 mg/kg p.o) was used as standard drug. It was concluded that cinnamon in high doses stimulated both cellular and humoral immunity and at low dose, increased only the non-specific serum immunoglobulin levels[22].

11. Morus alba Linn.

Methanolic extract of *Morus alba* leaves was evaluated for their effect on immune system by using different experimental models such as carbon clearance test, cyclophosphamide induced neutropenia, neutrophil adhesion test, effect on serum immunoglobulins, mice lethality test and

indirect haemagglutination test. Methanolic extract of *Morus alba* was administered orally at low dose and high dose of 100 mg/kg and 1 g/kg respectively and *Ocimum sanctum* (100 mg/kg, po) was used as standard drug. *Morus alba* increases both humoral immunity and cell mediated immunity. The belief as per traditional medicine that mulberry leaves possess immunomodulatory activity was confirmed[23].

12. Aesculus indica

Aqueous extract of *Aesculus indica* was evaluated for immunomodulatory activity in rats. The assessment of immunomodulatory activity was carried out by testing the humoral (antibody titre) and cellular (foot pad swelling) immune responses to the antigenic challenge by sheep RBCs and by neutrophil adhesion test. On oral administration of 50 and 100 mg/kg of the extract, a significant increase in neutrophil adhesion and delayed type hypersensitivity response whereas the humoral response to sheep RBCs was unaffected. The study concluded that *Aesculus indica* showed a significant stimulation of the cell mediated immunity and no effects on the humoral immunity due to the presence of proteins, flavonoids, alkaloids, steroids and phenolic substances[24].

13. Cleome gynandra

Ethanolic extracts of aerial parts of *Cleome gynandra Linn.* (Family: Capperdiceae) was assesed for immunomodulatory activity at the doses of 50, 100 and 200 mg/kg, p.o. using carbon clearance method for non-specific immunity, haemagglutination antibody titre method for humoral immunity and footpad swelling method for cell mediated immunity on wistar albino rats. Results suggested that the ethanolic extract of *Cleome gynandra Linn* exhibited significant immune suppression effect in dose dependent manner when compare with control group[25].

14. Curcuma longa

Water extract of dried rhizome of *Curcuma longa* was evaluated for immunomodulatory activity in mice by assessing immunological parameters such as concentration of immunoglobulins and complements (IgG, IgM, IgA, C3, C4) at a dose of 5 and 10mg/kg body weight.Results showed a significant raise in the levels of concentration of immunoglobulins and complements (IgG, IgM, IgA, C3, C4) in the treated mice compare to the control

group. Results indicating that Water extract of the dried rhizome of *Curcuma longa* as potent immunomodulatory agent that can modulate the activation of T cells, B cells, macrophages, neutrophils, natural killer cells, and dendritic cells[26].

15. Dodonaea viscose

Ethanolic extract of *Dodonaeav iscosa L.F.* was assessed for immunomodulatory activity using carbon clearance test, delayed type of hypersensitivity (DTH), T-cell population test, and sheep erythrocyte agglutination test (SEAT) in mice treated at a doses of 200 and 400 mg/kg. Results indicated that *D.viscosa* exhibited significantly increased phagocytic index against control group, indicating stimulation of the reticuloendothelial system and significantly decrease in mean difference, in the foot paw thickness in DTH indicates its anti-inflammatory activity. And also showed significant increase in antibody titer against control in normal immune status animals while In T-cell population test, showed significant increase in T-cell rosette formation against control. These results confirmed the immunomodulatory activity of *D. viscosa* extract, which is a known immunomodulator in indigenous medicine[27].

16. Echinacea purpurea

Ethanolic extract of *Echinacea purpurea* was studied for immunomodulatory activity by measuring LPS-stimulated cytokine expression from human PBMCs. Results indicated modulating effect by simultaneously targeting the CB2 receptor indicating immunomodulatory action[28].

17. Eclepta alba

Methanol extracts of whole plant of *Eclepta alba* was assessed for immunomodulatory activity o at five dose levels ranging from 100 to 500 mg/kg body wt. using carbon clearance, antibody titer and cyclophosphamide immunosuppresion parameters. Results showed that *E. alba*, significantly increased the phagocytic index and antibody titer and the F ratios of the phagocytic index and WBC count indicating potent immunomodulatory action[29].

18. Ficus benghalensis

Various extracts of the aerial roots of *Ficus benghalensis* (Family Moraceae) were evaluated for potential immunomodulatory activity, using the in vitro polymorphonuclear leucocyte (human neutrophils) function test. The methanol extract was evaluated for immunomodulatory activity in in vivo studies, using rats as the animal model. The

extracts were tested for ersensitivity and hemagglutination reactions, using sheep red blood cells (SRBC) as the antigen. Distilled water served as a control in all the tests. The successive methanol and water extracts exhibited a significant increase in the percentage phagocytosis versus the control. In the in vivo studies, the successive methanol extract was found to exhibit a dose related increase in the hypersensitivity reaction, to the SRBC antigen, at concentrations of 100 and 200 mg/kg. It also resulted in a significant increase in the antibody titer value, to SRBC, at doses of 100 and 200 mg/kg in animal studies. The successive methanol extract was found to stimulate cell mediated and antibody mediated immune responses in rats. It also enhanced the phagocytic function of the human neutrophils, in vitro[30].

CONCLUSION

The immune system is complex organ high specialized cells and even circulatory separate from blood vessels. Organ and the tissues of the immune system dot the body in a protective network of barrier to infection. Innate and adaptive immunity depends on the activity of white blood cells. Innate immunity largely depends upon granulocytes and macrophages, while adaptive immune response depends upon lymphocytes, which provide long term immunity. Immunomodulation is the ruling of immune responses by stimulating them to prevent transmittable diseases or by suppressing them in the undesired circumstances. Many proteins, amino acids, and natural compounds have shown a significant ability to regulate immune responses, including interferon-γ (IFN-γ), steroids, DMG. Plants have been used since ancient times for the treatment of various diseases and disorders. The few herbal plants have been discussed which are previously explored by the various researchers for their immunomodulatory activity. Several medicinal plants exhibit not only immunomodulatory activity but also a wide range of antioxidant, antiasthmatic, antiarrhythmic, antiinflammatory, hepatoprotective, hypocholesterolemic, antifungal, cardiotonic, diuretic, and other medicinal activities. Immunodeficiencies occur when one or more of the components the immune system are inactive. It included autoimmunity, hypersensitivity and HIV etc. New immunomodulatory plants are important for the discovery of drug with fewer side effects,

less costly, more potent and effective treatment developed for immune and their related diseases. Herbal medications are free from side effects and toxicity unlike the allopathic medicines. This type of study with immunomedicinal herbs will contribute to the benefit of the populations needing herbal treatment to treat immune diseases without being used of synthetic drugs and prevent or reduces the side effect of synthetic drugs.

REFERENCE

1. Amartya KG, Partha G , Upal KM , Shibnath G. Adaptogenic effects of total extracts and steroidal saponins of *Solanum xanthocarpum* and *Solanum nigrum.* Journal of Pharmacy Research. 2009; 2(8):1249-1254.

2. Soumya G, Mainak M, Plaban B. Evaluation of hypoglycemic potential of *Solanum xanthocarpum* (solanaceae) fruits in normal and streptozotocin induced Diabetic rats. European Bulletin of Drug Research.2005; 13: 230-245.

3. Govindan S, Viswanathan S, Vijayasekaran V, Alagappa R. A pilot study on the clinical efficacy of *Solanum xanthocarpum* and *Solanum trilobatum* in bronchial asthma. Journal of Ethnopharmacology.1999; 6(2):205-210.

4. Govindan S, Viswanathan S, Vijayasekaran V, Alagappa R. Further studies on the clinical efficacy of *Solanum xanthocarpum* and *Solanum trilobatum* in bronchial asthma. Phytotherapy Res.2004; 18(10):805-809.

5. Jain SP, Puri HS Ethnobotanical plant of Jaunsar-Bawar Hills, Uttar Pradesh India, J.Ethnopharmacology.1984;12(2):213-222.

6. Venugopal R, Senthilnathan P, Magesh V, Rajkapoor B, Dhanapal S. Chemotherapeutic Efficacy of *Solanum trilobatum* along with Paclitaxel in Lung cancer Bearing Swiss Albino Mice. Int.J of Cancer Res. 2007; 3(2):119-126.

7. Moula SJ, Ganapathy V, Shyamaladevi CS. Effect of *Solanum trilobatum* on hepatic drug metabolising enzymes during diethylnitrosamine-induced hepatocarcinogenesis promoted by Phenobarbital in rat. Hepatology Res. 2007; 37 (1): 35-49.

8. Okram MS, Tockchom PS. Phytochemistry of *Solanum xanthocarpum:* an amazing traditionar healer. J Sci. Ind. Res. 2010; 69:732-740.

9. Okram MS, Subharani K, Singh NI, Babita DN, Nividita L. Isolation of steroidal glycosides from *Solanum xanthocarpum* and studies on their

antifungal activities. Natural Product Research. 2007; 21 (7): 585 – 590.

10.Kadam PD, Patil AG, Patil DA, Phatak AV. Pharmacognostic studies on fruits of *Solanum xanthocarpum* schrad. And wendl. Journal of Herbal Medicine and Toxicology.2010; 4 (1) 25-29 .

11.Tupkari SS, Aoji A N and Deshmukh V K, Phytochemical study of *Solanum xanthocarpum*. Plantamedica.1972; 22(2): 184-187.

12.Kusano G, Beisler J, Sato Y. Steroidal constituents of *Solanum xanthocarpum.* Phytochemistry. 1973; 12(2): 397-401.

13.Gupta MP, Dutt S, Chemical examination of the seed of *Solanum xanthocarpum* II. Constituents. J.Indian.Chem.Soc. 1938; 15: 95-100.

14.Sato Y, Lantham JR. The isolation of diosgenin from *Solanum xanthocarpum*. Journal of American Chemical Society.1953;75: 60- 67.

15.Saived IZ, Fruits of *Solanum xanthocarpum*, Proc.Indian Acad. Sci. Ser.1938; A4: 255-260.

16.Siddiqui S, Faizi S, Shaheen B. Studies in the chemical constituents of the fresh berries of *Solanum xanthocarpum,* Journal of chemical society Pakistan. 1983; 5(2): 99-122.

17.Nadkarni, KM. *Solanum trilobatum*. In: Indian MateriaMedica, Vol.1, 3rd edition, Popular Prakasam Pvt. Ltd. 1976;1153-1154.

18.Govindan S, Viswanathan S, Vijayasekaran V, Alagappan R. Further studies on the clinical efficacy of *Solanum trilobatum* in bronchial asthma. Phytotherapy Res. 2004; 18: 805-809.

*19.*Marina Z , Mariana P , Thiele FB , Aline A B , Michel MM , Sílvio TS , Robson BF Félix AAS, Margareth LA. Antioxidant Activity and Phytochemical Composition of the *Solanum trilobatum* Leaves. Molecules. 2012; 17: 12560-75.

20.Amarnath K, Monvalli B. Anti-cancer effect of saponins isolated from *Solanum trilobatum* leaf extract and induction of apoptosis in human larynx cancer cell lines. Int J Pharm Pharm Sci,2011;3(4): 356-364

21.Manivannan E, Kothai R, Arul B. Hepatoprotective Activity of *Solanum trilobatum Linn.* Against CCl4 Induced Hepatotoxicity in Rats Int. J. Adv. Pharm., Biol. and Chem .2012;1(1):87-90.

22.Shahjahan M, Vani G, Shyamaladevi CS. Effect of *Solanum trilobatum* on the antioxidant status

during diethyl nitrosamine induced and phenobarbital promoted hepatocarcinogenesis in rats. Chem. Biol. Interac.. 2005. 20: 113-123.

23.Mohanan PV, Rao JM, Kutti MAS, Devi KS. Cytotoxicity of extracts of *Solanumtrilobatum* and anticarcinogenic activity of sobatum. Biomedicine. 1998;8: 106-111.

*24.*Moula SJ, Ganapathy V, Shyamaladevi CS. Effect of *Solanumtrilobatum* on hepatic drug metabolising enzymes during diethylnitrosamine-induced hepatocarcinogenesis promoted by Phenobarbital in rat. Hepatology Res; 2007: 37 (1) 35-49.

25.Asirvatham D and Rangasamydhanabalan. Preliminary Phytochemical Screening and Antibacterial Studies of Leaf Extract of *Solanum trilobatum* Linn. *Ethnobotanical Leaflets 2008; 12: 638-42.*

26. Emmanuel S, Ignacimuthu S, Perumalsamy R, Amalraj T. Ant-iniflammatory activity of *Solanumtrilobatum*. 2006. Fitoterapia. 77: 611-612.

27. Brindha P, Sasikala B, Bhima Rao R, Purusothaman KK. Pharmacognostic studies on *Solanum trilobatum*, Bull Med Ethno Bot Res., 1980, 1: 25-36

28. Sathish K, Charles L, Kokati V. Phytochemical composition antimicrobial and haemolytic activity of *Solanum trilobatum*, Pharmacologyonline 2011; 3: 1336-1341.

29. Bala Krishnan. *Solanum trilobatum* extraction including isolation of compounds solasodine, linoleic acid and palmitic acid. J. Biol. Chem . Soci. 1992; 17:1468-78.

30. Vina BP, Maitreyee RB, Isverbhai SR, Jaymin MP. Anti-urolithiatic and natriuretic activity of steroidal constituents of *Solanum xanthocarpum.* Der PharmaChemica, 2010; 2(1): 173-176.