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A comprehensive review of medicinal plants possessing immunosuppressive properties

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Abstract
A number of medicinal plants are in use for their immunosuppressive effects in immune mediated diseases. Plants such as *Salvia miltiorrhiza* and *Tripterygium*, *Wilfordii hook* F have been shown to reduce inflammatory cytokines & mediators suggesting their value in treatment of acute graft rejection and autoimmunity. *Curcuma longa* down regulates expression of cytokines and chemokines, *Camellia sinensis* (green tea) and *Withania somnifera* have been shown to possess significant immunosuppressive properties. Synthetic immunosuppressive drugs available for use have been reported to have serious/intolerable side effects. There has been growing interest to isolate & investigate novel and safe immunosuppression from medicinal plants. This review describes some medicinal plants possessing immunosuppressive properties.

Keywords: immunosuppression, herbal plants, curcuma longa, flavonoids, medicinal plants

Introduction

Normal immune system is important to maintain healthy life and to protect our body from any microorganism invading against disease. Abnormal functioning of immune system leads to autoimmune disease e.g. Type I diabetes mellitus, systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis and parkinsonism etc. [1]. These problems can be treated by using appropriate drugs that affect immune system. Now a days immunosuppressants are commonly used to prevent rejection of graft in cases of organ transplantation [2, 3] and for treatment of wide variety of autoimmune diseases [1] including AIDS, cancer, inflammatory conditions, cardiovascular disorders & other disorders. Monoclonal antibodies are under clinical evaluation for various rare or refractory diseases. Use of synthetic immunosuppressants (glucocorticoids, cyclophosphamide, azathioprine, methotrexate, chlorambucil cyclosporine, tacrolimus, vincristine, cytarabine, calcineurin inhibitors etc.) are associated with serious side effects like nephrotoxicity, increased risk of lymphoma, organotoxicity, increased risk of infections, hyperglycemia, hypertension, hyperkalemia etc [4]. To avoid such serious side effects recently plants and their products are being explored to provide alternative to conventional chemotherapy. Some well-known immunosuppressants used in the therapy are also obtained from natural source like cyclosporine A from a fungus *Beauveria nivea* [5], *Sirolimus from Streptomyces* hygroscopicus and mycophenolic acid from *Penicillium glaucum* [6].

Plans such as *Salvia miltiorrhiza* and *Tripterygium wilfordii* hook has been shown to reduce inflammatory cytokines and mediators indicating their value in the treatment of acute graft rejection and autoimmunity [7]. *Tanacetum parthenium* inhibits the release of pro inflammatory mediators from macrophages and lymphocytes, *Curcuma longa* down regulates the expression of cytokines and chemokines as well as transcription factor NF-kappa β [7]. There has been growing interest to investigate novel immunosuppressive compounds form herbal products. This review describes some medicinal plants possessing immunosuppressive properties.

1. *Allium cepa* Linn. (Liliaceae)
English Name: Onion
Hindi Name: Piyaz
Effect of onion extract (freshly crushed homogenized bulbs) 400 mg/kg, p.o. was studied on experimentally induced immune response in rabbit. Onion extract significantly inhibited antibody titre, inhibition was 76.3 % in case of typhoid 'H' antigen and 78.3% in case of sheep erythrocytes. Study suggested immunosuppressive activity of onion particularly, involving humoral immunity. [8]

2. *Allium sativa* Linn. (Liliaceae)
English Name: Garlic
Hindi Name: Lahasun
Garlic has shown to reduce the pro inflammatory cytokines IL-1, TNF-α, IL-8 and stimulate IL-10 secretion [9]. IL-10 in an antagonist of pro inflammatory cytokines [10].

3. *Andrographis paniculata* (Burm f.) Acanthaceae)
English Name: The Ereat
Hindi Name: Kalmegh
Andrographolide (30,100 and 300 mp/kg p.o.) isolated from the plant showed marked anti-inflammatory activity against carrageenan, kaolin & nystatin induced paw edema in rats. Freund's adjuvant induced arthritis also improved, it also reduced peritoneal inflammation induced acetic acid [11].

4. *Aphanamixis polystachya,* Parker Syn *Amoora rohituka,* (Meliaceae);
Hindi Name: Harinhara
Immunosuppressive effects of A. polysta eliya bark were studied in guinea pig and results were compared with prednisolone. Animal treated with A. polystachya bark powder solution (50 mg/kg i.p.) for 16 days and prednisolone (40 mg/kg i.p. × 8 days) showed reduction in absolute

lymphocyte count and an increase in spleen weight. [12]. Efficacy of bark in prevention of experimental allergic orchitis in guinea pig has also been demonstrated [13]. Aqueous solution of bark extract (125 µg) revealed immunosuppressive activity as assessed by depression of blastogenic response induced by Phytohaemagluttinin [14]

5. *Astragalus membranaceus*
English Name: Mongolian
Hindi Name: Katira
Plant used as a tonic in Chinese folk medicine, has shown to decrease secretion of 1L-6 which in involved in inflammatory disorders [15].

6. *Berberis Species* (Berberidaceae)
Berbamine an ingredient extracted from Berberis vulgaris has inhibitory effects on delayed type hypersensitivity reaction [16] and also prolonged allograft survival in skin transplanted mice. Recently, study on production of cytokines from CD_4 T cells treated with berbamine has shown selective inhibitory effect on $STAT_4$ expression and production of interferon-γ in cells indicating immunosuppressive effects [17].

7. *Camellia sinensis* (Theaceae)
English Name: Tea;
Hindi Name: Chaay
Polyphenolic compounds from green tea possess anti-inflammatory and immunosuppressive properties. Green tea reduced autoimmune symptoms in rat adjuvant arthritis, a model for human rheumatoid arthritis [18] and also in murine model for human sjogren's syndrome [18]. Epigallocatechin-3-gallate extracted from green tea has been shown to inhibit human monocyte derived dendritic cells (MODCs) and T cell mediated immune response [19].
Aktas *et al.* reported that Epigallocatechin-3-gallate suppressed brain inflammation and neuronal damage in experimental autoimmune encephalomyelitis induced by a proteolipid protein [20].

8. *Cedrus deodara (Roxb. ex. D don)* Pinaceae
English Name: Deodar;
Hindi Name: Devdar, toona
Volatile oil of wood (50 and 100 mg/kg p.o.) significantly inhibited neutrophil adhesion. It also significantly inhibited type III hypersensitivity reaction ie Arthus reaction induced by methylated bovine serum albumin and type IV ie delayed type hypersensitivity reaction induced by sheep erythrocytes & oxazolone, indicating inhibitory effect on humoral & cell mediated immune response [2]

9. *Cassia occidentalis* Linn. (Caesalpiniaceae)
English Name: coffee-sennafoetid cassia;
Hindi Name: badi kasondi, chakunda
Aqueous extract of plant (100 mg/kg for 14 days) protected mice from cyclophosphamide (50mg/kg) induced suppression of humoral immunity. Extract enhanced plaque forming cell response in cyclophosphamide treated animals, reversed reduced bone narrow cell count in cyclophosphamide treated animals to normal levels. [22]

10. *Commiphora wightii* (Arm) Burseraceae)
English Name: Gum gugal;
Hindi Name: Gugal
Administration of gugal 30,100 and 300 mg/kg p.o. for 10 days) immediately after antigen stimulus, showed dose dependant immunosuppressant effect in rabbit [23].

11. *Curcuma longa* (Zingiberaceae)
English Name: Turmeric;
Hindi Name: Haldi
Turmeric has been shown to inhibit activation of human dendrific cells (DC) in response to inflammatory cytokines. Treatment of dendrific cells with turmeric also inhibited the ability of DCs to stimulate mixed lymphocyte reaction [24]. Curcumin has been shown to be active on lymphocytes and affect antigen presentation, humoral and cell mediated immunity and cytokine production [25]. Curcumin can inactivate transcription factor NF- kappa-β and down regulate secretion of a variety of proinfkmmatory cytokines and chemokines [26]. Xie *et al* reported beneficial effect of curcumin in experimental autoimmune encephalomyelitis due to inhibition of Th17 cells differentiation and development. Clinical trials showed therapeutic potential of curcumin in inflammatory bowel disease, pancreatitis, arthritis and chronic anterior uveitis [26].

12. *Decalepis hamiltonii* Wight (Asclepiadaceae)
English Name: Swallow-Root,
Hindi Name: Sariba
Aqueous and 50% ethanolic extract of root exhibited immunosuppressive effect by decreasing hypersensitivity reaction and antibody titre in rats. Inhibition of phagocytosis of reticuloendothelial system and polymorphonuclear cells was observed. [27]

13. *Dysoxylum binectariferum* Hook F (Meliaceae)
English Name: Indian white cedar;
Hindi Name: Bili devdari
A piperdinyl benzophyranone isolated from stem bark (2.5 mg/kg p.o.) inhibited Arthus reaction in rat. The compound inhibited immune complex mediated inflammation. In adjuvant induced arthritis, compound exhibited a biphasic activity similar to that of disease modifying antirheumatic agents [28].

14. *Glycyrrhiza glabra,* (fabaceae)
English Name: Liquorice;
Hindi Name: Mulathi
Diammonium glycyrrhizanale (DG) extracted from liquorice has been shown to prevent murine T cell mediated fulminant hepatitis [29]. DG inhibited recruitment of lymphocytes into liver and protected hepatocytes from apoptosis through an IL-6 dependant pathway [29]. In a pilot randomised open label study, beneficial effect of milk protein and glycyrrhiza glabra extract in patients with psoriasis was demonstrated [30]. Inhibition of calcineurine activity and T cell proliferation by glycyrol from glycyrrhiza uralensis has also been reported. [31]

15. *Haussknechtia elymatica*
H. elymatica plant extract has been shown to decrease production of IL-2. [32]

16. *Linum usitatissimum* Linn. (Linaceae)
English Name: Linseed, flax plant;
Hindi Name: Alsi
Morita *et al.* –[33]. Reported potent immunosuppressive properties of seeds of *Linum usitatissimum which was*

comparable with that of cyclosporine A.

17. *Periploca sepium: Asclepiadaceae*
English Name: Gymnema;
Hindi Name: Term Gurmar
Periplocoside extracted from the plant suppresses IL-17 production and inhibits differentiation of Th17 cells. It also inhibits NKT- derived inflammatory cytokine production. [34]

18. *Polygala tenuifolia*
Commonly known as milkworts or snakeroots
Hong T. *et al*. [35] reported protective effect of polygaloroot in experimental colitis in mice. Protective effect was suggested to be due to reduced secretion of interfereon-γ.

19. *Salvia miltiorrhiza* (Labiatae)
English Name; Sage Weed;
Hindi Name: Kamrkash
This plant has been shown to inhibit IL-12 production in activated macrophages and interferon- γ production in lymph node cells.[36] It is useful in the treatment of immunological disease dominated by TH-1 derived cytokine responses [36]. A clinical study showed usefulness of S.miltiorrhiza extract in the treatment of patient with severe acute pancreatitis [37]. Major active component of this plant is Tanshione II A. It reduces inflammatory cytokines like IL-2, IL-4, IFN- γ and TNF- α. Transhion II A protects mice against concanavalin induced immune mediated liver injury [38].

20. *Stachys obtusicrena* Labiatae (Lamiaceae)
Amirghofram *et al*. [39] reported immunosuppressive properties of plant S. obtusicrave by reducing secretion of IL-2.

21. *Tanacetum parthenium* (Asteraceae)
English Name: Wild Chamomile;
Common Name: Fever few
It has been used as a folk remedy for rheumatoid arthritis. Crude extract and its purified Parthenolide can modulate adhesion molecule expression in human cynovial fibroblast [39]. Plant has been shown to inhibit pro inflammatory enzymes e.g. 5-lipoxygenase, phosphodiesterase 3 and 4. It also inhibits release of prostaglandin E_2 and TNF-α from macrophages & IFN-γ and IL-4 from human mononuclear cells [40].

22. *Tinospora cordifolia* (wild), Menispermaceae
English Name: Timospora;
Hindi Name: Giloy.
Immunosuppressive properties of this plant has been reported by various workers [41].

23. *Tripterygium wilfordii* Hook f. (Celastraceae)
T. wilfordii (Thunder god vine) has been extensively used to treat autoimmune disease such as systemic lupus erythematosus and rheumatoid arthritis. This plant inhibits mitogen stimulated lymphoproliferation and production of proinflammatory cytokines by monocyte & lymphocyte [42]. Clinical efficacy of this plant versus sulfasalazine for treatment of rheumatoid arthritis was demonstrated [43]. Triptolide isolated from the plant has been shown to possess anti-inflammatory and immunosuppressive effects by inhibitory effect on T cells. Beneficial effects of Triptolide has been reported in collagen induced arthritis and experimental autoimmune encephalomyelitis [44].
Immunosuppressive activity of the plant has also been shown in organ transplantation e.g. rat kidney transplant model [45]. Demethyl zeylasteral isolated from this plant in combination with prednisone showed potential usefulness in treatment of acute graft rejection and autoimmunity [45].

24. *Withania sommifera* L. Dunal (Solanaceae)
English Name: Winter Cherry;
Hindi Name: Asganth, Pumir
Aggrawal *et al*. [46] reported immunosuppressive and anti-ageing properties of this plant.

25. *Zizyphus lotus* L (Desg.)
English Name: Marula
This plant has been shown to decrease IL-2 secretion and affect human T cell proliferation [47].

Other immunosuppressive plants
Flavonoids extracted from the leaves of *Santalum album, Butea frondosa and Emblica officinale* have been shown to possess anti-inflammatory and immunosuppressive activity [48]. Flavonoids from these plants, in high doses demonstrated a significant decrease in human peripheral blood mononuclear cells (PBMC), proliferation, nitric oxide (NO) production and CD_{14} surface marker. Gupta and Chaphalkar (2015) [49] isolated immunosuppressive flavonoids from *Terminalia arjuna, Prosopis spicigera and Mimusops elengi* immunosuppressive terpenoids from the extracts of Emblica officinale, Ficus racimosa and Strychnos nux vomica have been isolated by these workers [50].

Conclusion
Various herbal products have been used in the treatment of disease related to immune system, there are many evidences that a variety of active ingredients from plants could act as immunosuppressive agents. Many pharmacological studies have been conducted to confirm efficacy of these agent plants such as *Bupleurum flacatum* [50], Artemisia vestita [51], *Agyrolobium rosum* [52], *Clerodendron trichotomum* [53] *(Verbenaceae), Dracocephalum kotschyi* [54], *Stachys obtusicrena* [38]. However, their active principles have not yet been identified.

References

1. Steinman L. Immune therapy for autoimmune diseases. Science. 2004; 305:212-216.
2. Hong JC, Kahan BD. Immunosuppressive agents in organ transplantation: past, present and future. Semin Nephrol. 2000; 20:108-125.
3. Pescovitz MD, Bumgardner GL, Gaston RS, *et al*. Addition of daclizumab to mycophenolate mofetil, cyclosporine, and steroids in renal transplantation: pharmacokinetics, safety, and efficacy. Clinical Transplantation. 2003; 17:511-517.
4. Flechner SM, Kobashigawa J, Klintmalm G.Calcineurin inhibitor-sparing regimens in solid organ transplantation: focus on improving renal function and nephrotoxicity. Clin Transplant. 2008; 22:1-15.
5. Brunton, Laurence L, Chabner Bruce, Knollmann, Björn C. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. Ed, New York: McGraw-Hill, 2011.

6. Katzung BG, Masters SB, Trevor AJ. *Eds*. *eds*. Basic & Clinical Pharmacology, 13e New York, NY: McGraw-Hill; 2014.
7. Zahra A. Herbal Medicines for immunosuppression. Iran J Allergy Asthma Immunol. 2012; 11(2):111-119.
8. Vyas DS, Acharya RP, Dadhich AP, Godhwani JL, Purohit VS. Effect of Allium cepa (onion) on immune response in rabbit. Indian J Physiol Pharmacol. 1983; 27(3):259-60.
9. Colić M, Vucević D, Kilibarda V, Radicević N, Savić M. Modulatory effects of garlic extracts on proliferation of T-lymphocytes in vitro stimulated with concanavalin A. Phytomedicine. 2002; 9(2):117-24.
10. Hodge G, Hodge S, Han P. Allium sativum (garlic) suppresses leukocyte inflammatory cytokine production in vitro: potential therapeutic use in the treatment of inflammatory bowel disease. Cytometry. 2002; 48(4):209-15.
11. Madav S, Tandon SK, Lal J, Tripathi HC. Antinflammatory activity of and rographolide. Fitoterapia. 1996; 67:452-458.
12. Gupta A, Gupta RM, Gupta IM, Udupa KN, Singh LM. Immunosuppressive effects of Amura rohitaka and prednisolone on normal guinea pig Indian J Exp. Biol. 1977; 15:105-107.
13. Gupta A, Gupta RM, Gupta IM, Udupa KN, Singh LM. Immunosupressive effects of Amura rohitaka and prednisolone on experimental allergic orchitis in guinea pig. Indian J. Exp. Biol. 1978; 16:758-761.
14. Singh LM, Chatterjee S. effect of Amoora rohitaka on in vitro blastogenesis of lumphocytes; J. Res Indian Med. Yoga and Homoeop. 1979; 14:44-48.
15. Qin Q, Niu J, Wang Z, Xu W, Qiao Z and Gu Y. Astragalus membranaceus Extract Activates Immune Response in Macrophages via Heparanase. Molecules. 2012; 17:7232-7240.
16. Luo CN, Lin X, Li WK, Pu F, Wang LW, Xie SS, Xiao PG. Effect of berbamine on T-cell mediated immunity and the prevention of rejection on skin transplants in mice. J Ethnopharmacol. 1998; 59(3):211-15.
17. Ren Y, Lu L, Guo TB, Qiu J, Yang Y, Liu A, Zhang JZ. Novel immunomodulatory properties of berbamine through selective down-regulation of STAT4 and action of IFN-gamma in experimental autoimmune encephalomyelitis. J Immunol. 200815; 181(2):1491-8.
18. Kawaguchi K, Matsumoto T, Kumazawa Y. Effects of antioxidant polyphenols on TNF-alpha-related diseases. Curr Top Med Chem. 2011; 11(14):1767-79.
19. Yoneyama S, Kawai K, Nelson H, Tsuno, Okaji Y, Asakage M, *et al*. Epigallocatechin gallate affects human dendritic cell differentiation and maturation. J Allergy Clin Immunol. 2008; 121:209-14.
20. Aktas O, Prozorovski T, Smorodchenko A, Savaskan N E, Lauster R, Kloetzel PM, *et al.* Green Tea Epigallocatechin-3-Gallate Mediates T Cellular NF- κB Inhibition and Exerts Neuroprotection in Autoimmune Encephalomyelitis. J Immunol. 2004; 173:5794-5800.
21. Shinde UA, Phadke AS, Nair AM, Mungantiwar A A, Dikshit VJ, Saraf M. Preliminary studies on the immunomodulatory activity of Cedrus deodara wood oil. Fitoterapia. 1999; 70:333-339.
22. Bin-Hafeez B, Ahmad I, Haque R, Raisuddin S. Protective effect of Cassia occidentalis L. on cyclophosphamide induced suppression of humoral immunity in mice J Ethnopharmacol. 2001; 75:13-18.
23. Shukla B, Khanna NK, Dadhich AP, Jagdev N, Bairwa AK. A comparative study of gugal and yograj gugal on immune response in rabbit. Indian Drugs. 1986; 23:335-37.
24. Krasovsky J, Chang DH, Deng G, Yeung S, Lee M, Leung PC, *et al*. Inhibition of human dendritic cell activation by hydroethanolic but not lipophilic extracts of turmeric (Curcuma longa). Planta Med. 2009; 75(4):312-5.
25. Xie L, Li XK, Funeshima-Fuji N, Kimura H, Matsumoto Y, Isaka Y. Amelioration of experimental autoimmune encephalomyelitis by curcumin treatment through inhibition of IL-17 production. Int. Immunopharmacol. 2009; 9(5):575-81.
26. Jurenka JS· Anti-inflammatory properties of curcumin, a major constituent of Curcuma longa: a review of preclinical and clinical research. Altern Med Rev. 2009; 14(2):141-53.
27. Mengi SA, Babhulgaonkar SC, Chintamanneni MK. Immunomodulatory activity of Decalepis hamiltonii Proc. XXXIII annual conference Indian Pharmacol society Dec. 28-30 2000. Indian J Pharmacol. 2000; 33:58.
28. Naik RG, Kattige SL, Bhatt SV, Alreja B, Desouza NJ, Rupp RH. An antiinflammatory cum immunomodulatory piperidinylbenzopyranone from *Dysoxylum binectariferum* : isolation, structure and total synthesis, Tetrahedron. 1988; 44:2081-86.
29. Cassano N, Mantegazza R, Battaglini S, Apruzzi D, Loconsole F, Vena GA. Adjuvant role of a new emollient cream in patients with palmar and/or plantar psoriasis: a pilot randomized open-label study. G, Ital Dermatol Venerol. 2010; 145(6):789-92.
30. Barfod L, Kemp K, Hansen M, Kharazmi A. Chalcones from Chinese liquorice inhibit proliferation of T cells and production of cytokines. Int Immunopharmacol. 2002; 2(4):545-55.
31. Li J, Tu Y, Tong L, Zhang W, Zheng J, Wei Q. Immunosuppressive activity on the murine immune responses of glycerol from Glycyrrhiza uralensis via inhibition of calcineurin activity. Pharmaceutical Biology. 2010; 48(10):1177-1184.
32. Amirghofran Z, Azadmehr A, Javidnia K. Haussknechtia elymatica: a plant with immunomodulatory effects Iranian Journal of Immunology. 2007; 4:26-31.
33. Morita H, Shishido A, Matsumoto T, Takeya K, iItokawa H, Hirano T *et al*. A new immunosuppressive cyclic nonapeptide, cyclolinopeptide b from *linum usitatissimum.* Bioorganic Med Chem letter. 1997; 7(10):1269-1272.
34. Zhang J, Ni J, Chen Z H, Li X, Zhang R J, Tang W. Periplocoside A prevents experimental autoimmune encephalomyelitis by suppressing IL-17 production and inhibits differentiation of Th17 cells. Acta Pharmacol Sin. 2009; 30(8):1144-1152.

35. Tie Hong, Guang-Bi Jin, Gen Yoshino, Myota Miura, Yoko Maeda, Shigefumi Cho, Jong-Chol Cyong. Protective effects of Polygalae root in experimental TNBS-induced colitis in mice. Journal of Ethnopharmacol. 2002; 79(3):341-346.
36. Wan JMF, Sit WH, Lee CL, Fu KHM, Chan DKO. Protection of lethal toxicity of endotoxin by *Salvia miltiorrhiza* BUNGE is via reduction in tumor necrosis factor alpha release and liver injury. Intern. Immunopharmacol. 2006; 6(5):750-58.
37. Peng GL, Zhang XY. Effects of *Salvia miltiorrhiza* on serum levels of inflammatory cytokines in patients with severe acute pancreatitis. Zhong Xi Yi Jie He Xue Bao. 2007; 5(1):28-31.
38. Qin XY, Li T, Yan L, Liu QS, Tian Y. Tanshinone IIA protects against immune-mediated liver injury through activation of t-cell subsets and regulation of cytokines. Immunopharmacology and Immunotoxicology. 2010; 32(1):51-55.
39. Z Amirghofran, M Bahmani, A Azadmehr, K Javidnia, Immunomodulatory and apoptotic effects of Stachys obtusicrena on proliferative lymphocytes, Med. Sci Monit. 2007;13(6):145-15.
40. Mathema VB, Koh YS, Thakuri BC, Sillanpää M. Parthenolide, a sesquiterpene lactone, expresses multiple anti-cancer and anti-inflammatory activities. Inflammation. 2012; 35(2):560-5.
41. Rege NN, Nazareth HM, Bapat RD, Dahanukar SA. Modulation of immunosuppression in obstructive jaundice by Tinospora cordifolia. Indian J Med Res. 1989; 90:478-83.
42. Wong KF, Chan JK Chan KL, Tam P, Yang D, Fan ST *et al*. Immunochemical characterization of the functional constituents of *tripterygium wilfordii* contributing to its anti-inflammatory property. Clin Exp. Pharmacol Physiocol 2008; 35(1):55-59.
43. Marks WH. Tripterygium wilfordii Hook F. versus Sulfasalazine in the treatment of rheumatoid arthritis: a well-designed clinical trial of a botanical demonstrating effectiveness. Fitoterapia. 2011; 82(1):85-7.
44. Setty AR, Sigal LH. Herbal medications commonly used in the practice of rheumatology: mechanisms of action, efficacy, and side effects. Semin Arthritis Rheum. 2005; 34(6):773-84.
45. Wilasrusmee C, Siddiqui J, Bruch D, Wilasrusmee S, Kittur S, Kittur DS. In vitro immunomodulatory effects of herbal products. Am Surg. 2002; 68(10):860-4.
46. Agarwal R, Diwanay S, Patki P, Patwardhan B. Studies on immunomodulatory activity of Withania somnifera (Ashwagandha) extracts in experimental immune inflammation. J Ethnopharmacol. 1999; 67(1):27-35.
47. Benammar C, Hichami A, Yessoufou A, Simonin AM, Belarbi M, Allali H, Khan NA. Zizyphus lotus L. (Desf.) modulates antioxidant activity and human T-cell proliferation. BMC Complement Altern Med. 2010; 10:54-67.
48. Gupta A, Chaphalkar SR. Anti-inflammatory and immunosuppressive activities of flavonoids from medicinal plants. J Herbmed Pharmacol. 2016; 5(3):120-124.
49. Gupta A, Chaphalkar SR, Immunosuppressive activity of flavonoids isolated from Terminalia arjuna, Prosopis spicigera and Mimusops elengi. Int J Res pharmacy Sci 2015; 5(4):14-17.
50. Gupta A, Chaphalkar SR. Immunosuppressive activity of crude terpenoids from extracts of Emblica officinalis, Ficus racemosa and Strychnos nux-vomica. Micro Medicine. 2016; 4 (1):1-7.
51. Wang J, Sun Y, Li Y, Xu Q. Aqueous extract from aerial parts of Artemisia vestita, a Traditional Tibetan medicine, reduces contact sensitivity in mice by down regenerating the activation adhesion and metallo-proteinase Production of T lymphocytes. Int. immunopharmacol. 2005; 5:407-15.
52. Chauhan PS, Gupta KK, Bani S. The immunosuppressive effects of *Agyrolobium roseum* and pinitol in experimental animals, Int. immunopharmacol 2010; 11(2):286-291.
53. Park MA, Kim HJ. Anti-inflammatory constituents isolated from Clerodendron trichotomum Tunberg Leaves (CTL) inhibits pro-inflammatory gene expression in LPS-stimulated RAW 264.7 macrophages by suppressing NF-kappa B activation. Arch Pharm Res. 2007; 30(6):755-60.
54. Sani TA, Mohammadpour E, Mohammadi A, Memariani T, Yazdi MV, Rezaee R, *et al*. Cytotoxic and apoptogenic properties of dracocephalum kotschyi aerial part different fractions on calu-6 and mehr-80 lung cancer cell lines. Farmacia. 2017; 65(2):189-99.