Review Article

Exploring phytochemicals as novel immunomodulators

Mandeep Kaur, Jayshree Mahanty, Sudhir Kumar, Alok Sharma*

Department of Pharmacognosy, ISF College of Pharmacy, Moga, Punjab, India

Correspondence:
Dr. Alok Sharma, Department of Pharmacognosy, ISF College of Pharmacy, Moga, Punjab, India.
E-mail: alokalok22@gmail.com
How to cite this article: Kaur M, Mahanty J, Kumar S, Sharma A. Exploring phytochemicals as novel immunomodulators. Pharmaspire 2020;12(2):44-49.

Source of Support: Nil,
Conflicts of Interest: None declared

ABSTRACT

Although synthetic and biological immunodrugs acting on single or, multiple targets have been used to treat immunity-related disorders and ailments, therapy is somehow irrational while treating the infection and presently most of immunostimulants and immunosuppressants in clinical use possess adverse side effects. There is a strong urge to use herbal medicines and natural products as multi-component agents in existing immunotherapy with a view to modulate the complex immune system in treating infection. Therapeutic efficacy of plant extracts has been suggested due to their wide array of immunomodulatory effects and influences on the immune system of the human body. Phytochemicals such as alkaloids, flavonoids, polysaccharides, lactones, diterpenoids, and glycosides have been reported to be responsible for the immunomodulating properties of medicinal plants. Thus, the search for natural products of plant origin as new leads for the development of potent and safe immunosuppressant and immunostimulant agents is gaining attention in today's research and need. The present review will give an overview of secondary metabolites (alkaloids, polysaccharides, phenolics, terpenoids, flavonoids, saponins, and sterols) derived from natural origin exhibiting potent effects on cellular and humoral immune functions in preclinical investigations along with their clinical potential.

Keywords: Immunomodulators, phytochemicals, secondary metabolites, immunodrugs, medicinal plants

INTRODUCTION

The immune system safeguards the human body against various infectious diseases and also deals with a previous microbial infection, immunization, and various external stimuli which trigger immunity. Besides, this immune response is capable of discrimination among body's own protein or cells and foreign entities whether a pathogen or antigen.[1] As soon as the foreign pathogen is identified, the collective and coordinated biological reaction of specific immune cells and mediators against unknown strange substances activates the defense mechanism and even produce cidal effect against a foreign substance, thereby producing the immune response. The immune system has been categorized based on the function, namely, innate immune system (non-specific immune system) and adaptive immune system (specific immune system).[2] Biologicals barriers or chemical agents are also sometimes involved in innate immunity; however, the main mediators of the immune system which deliver instant defense include cytokines, acute phase proteins, macrophages, monocytes, complement, and neutrophils.[3] Distinct moieties expressed by pathogens, specifically known as pathogen-associated molecular patterns (PAMPs), are recognized by the host to detect the presence of a pathogen.[4] The present review will describe phytochemicals utilized as immunomodulators exhibiting potent effects on cellular and humoral immune functions in pre-clinical and clinical investigations.

Access this article online	
Website: www.isfcppharmaspire.com	**P-ISSN:** 2321-4732 **E-ISSN:** XXXX-XXXX

MECHANISM OF IMMUNOMODULATORS

Natural immunomodulators act through germline-encoded and evolutionarily conserved host sensors known as pattern recognition receptors (PRRs), which further recognize the PAMPs. Once the PRRs recognize the PAMPs, an array of immune responses is quickly triggered through induction of different type I interferons, chemokines,

and cytokines.[5] Secondary metabolites also play a pivotal role in all phases of non-specific immunity including antigen-presenting cells and macrophages which are further engaged in antibody-dependent cell-mediated cytotoxicity, secretion of cytokines, nitric oxide production, antigen presentation, processing, and phagocytosis.[6] Dendritic cells are responsible for the activation of basic and memory B and T cells. Phytochemicals affect various phases of dendritic cells' differentiation, the effectors of innate immunity including natural killer cells are regulated, which govern specific and natural immune responses by producing tumor necrosis factor-α, interferon-γ, and granulocyte–macrophage colony-stimulating factor.[7]

PHYTOCHEMICALS AS IMMUNOADJUVANTS

Plant-based immune adjuvants 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.[8] It has been proposed that they may 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 responses are posing a real challenge to vaccine designers.[9]

PHYTOCHEMICALS AS IMMUNOSTIMULANTS

Plant-based immunostimulants are inherently non-specific as they are envisaged as enhancements to a body's resistance to microbial infection. They can act through innate as well as adaptive immune responses or by potentiating immune response in healthy individuals.[10] The immunostimulants are expected to serve as prophylactic and promoter agents, thereby enhancing the basic level of host immune response. However, in individuals with impairment of immune response, they are expected to act as immunotherapeutic agents treating disorders caused by pathogens.[11]

PHYTOCHEMICALS AS IMMUNOSUPPRESSANTS

Phyto based immunosuppressant are structurally and functionally heterogeneous group of drugs [Figure 1], often concomitantly administered in combination regimens with conventional immunity boosters to treat various types of organ transplant rejection and autoimmune diseases.[12,13]

NATURAL IMMUNOMODULATORS

At present, majority of research and development still focuses on biochemicals, biologicals, or single compounds as leads that aim at particular targets linked with a disease. Countless single compound and chemical entity isolated from a natural source with marked selectivity, potency, and low toxicity for targeted molecular/cellular targets and diseases have been explored by researchers in the past decade.[14] Hence, the design and development of drug candidates from numerous conventional, complementary, and alternative medicines are gaining interest in the formulation and development of novel immunomodulators.[15] The prevention and treatment of disease using plant-based medicines have been reported in mankind history, saving human lives during the pandemic in the past. In all cultures and through all ages, different parts of a huge number of medicinal plant species were used in therapy while treating various ailments.[16] Vinblastine, vincristine, and their semi-synthetic derivatives isolated from the Madagascar periwinkle (*Catharanthus roseus*), capsaicin from chili peppers (*Capsicum* species), paclitaxel from Pacific yew (*Taxus brevifolia*), and galantamine from the Caucasian snowdrop (*Galanthus caucasicus*) are examples of medicines based plant compounds as natural immunomodulators.The plant-based compounds which were chemically altered are included as warfarin, artemether, topotecan and irinotecan, morphine (scores of derivatives), and acetylsalicylic acid.[17] Immunomodulatory characteristics of plant-based therapeutics have made them potential candidate for research community and innovative technologies and the extensive research on immunomodulatory herbal drugs, plants, their extracts, and active compounds with immunomodulatory potential, may provide the valuable entities to develop as the novel immunomodulatory product.[18] Phytochemicals including alkaloids, glycosides, steroids, terpenoids, phenolics, pigments, flavonoids, and alkaloids possessing immunomodulatory properties and claiming potential secondary metabolites for promising immunomodulatory agents are discussed in the present review [Table 1].

ALKALOIDS AS IMMUNOMODULATORY AGENTS

Alkaloids represent a large group of potent secondary metabolites exhibit marked physiological activity on innate immunity and adaptive immunity, regulating the immune system in humans and animals.[33] Plant-based alkaloids have been consumed as potent therapeutics and improve immune function, demonstrating possible immunomodulatory roles of alkaloids.[19,20]

POLYSACCHARIDES AS IMMUNOMODULATORY AGENTS

Polysaccharides exhibit numerous therapeutic benefits and being investigated for their immune-boosting activity, inducing modulation of macrophage function. Scientific validation of polysaccharides fraction had explored discovery zones of novel therapeutic agents as a beneficial immunomodulatory agent.[21]

FLAVONOIDS AS IMMUNOMODULATORY AGENTS

Water-soluble flavonoids, composed of C6-C3-C6 skeleton possessing chemoprotective property, have attracted the attention of researchers to explore potentially important dietary supplements for enhancing immunity in disorders caused by microbes.[22]

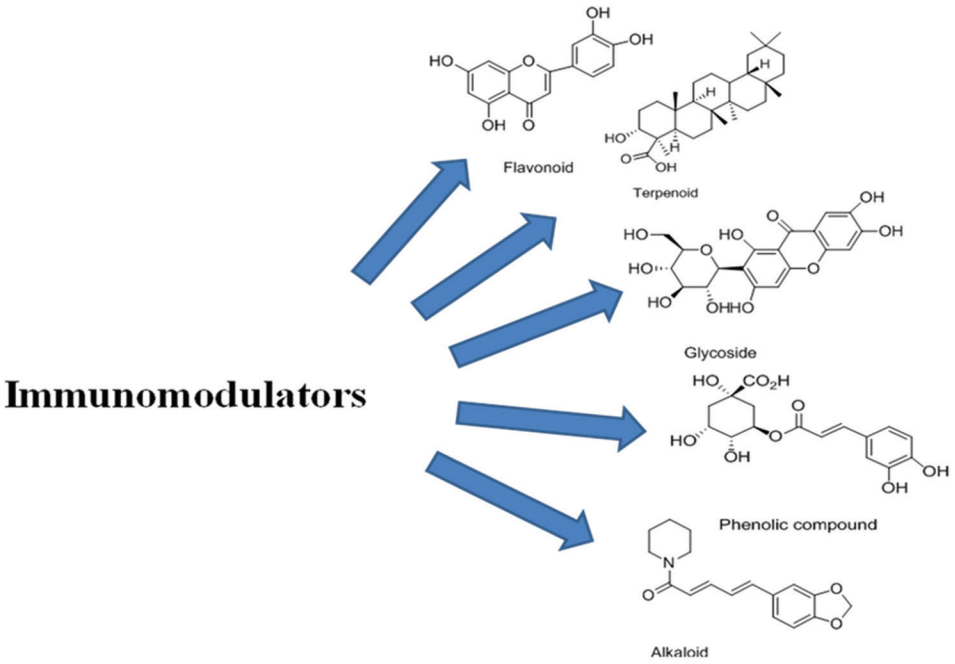

Figure 1: Potential Phytochemicals as immunomodulators

GLYCOSIDES AS IMMUNOMODULATORY AGENTS

These organic compounds from plant and animal sources, on enzymatic or acid hydrolysis, yield one, or more sugar moieties. A wide range of polar compounds consisting of at least one sugar molecule linked to another non-sugar moiety possesses immunomodulatory action. Moreover, another glycosides such as glycosides and anthraquinone glycosides sesquiterpene glycosides are also reported as immunomodulator.[23]

TERPENOIDS AS IMMUNOMODULATORY AGENTS

Optically active terpenoids having a high melting point are reported to possess anti-arthritic activity, and their therapeutic role appears to be mediated by modulating immunological processes. Terpenoids also reported to enhance antibody production and suppress T-cell response; therefore, it can be bioevaluated for immunomodulatory activity.[24]

TANNINS AS IMMUNOMODULATORY AGENTS

Water-soluble complex phenolic substances classified under tannins occur widely in vascular plants and angiosperms, induce marked physiological activities such as stimulation of phagocytic cells, host-mediated tumor activity, and a wide range of anti-infective action.[25]

SAPONINS AS IMMUNOMODULATORY AGENTS

Triterpenoids and steroidal saponins possess an antitumor effect on cancer cells and inhibit tumor growth by cell cycle arrest and apoptosis. Saponins, in combination with conventional tumor treatment strategies, can be evaluated for improved immune response and claim promising therapeutic success rate.[26]

PHENOLIC COMPOUNDS AS IMMUNOMODULATORY AGENTS

Water-soluble secondary metabolites possessing aromatic ring and bearing one or more hydroxyl substituents are considered potentially toxic to the pathogens and can be well explored for bioevaluating immunomodulatory activities.[27,28]

STEROLS AS IMMUNOMODULATORY AGENTS

Sterols and sterolins such as phytosterols and β-sitosterol enhanced *in vitro* proliferative response of T-cells possessing immunomodulatory activities.[29]

CONCLUSION

The relationship between the beneficial effects of phytochemicals and diseases is required to research long-term multidisciplinary studies. People are searching for herbal drugs and want to benefit medicinal values and live healthily. For this reason, the herbal market is growing day by day. The present paper can support to validate the bioactive compounds as for immunomodulator. The research result can be recognized as a global patent, and it may increase the economy of the country after commercialization. A number of phytochemicals have been isolated with the potential immunomodulatory activity that can explain and justify their use in traditional medicine in the past

Table 1: Secondary metabolites of Phytochemicals along with their mechanism and biological activity

Phytochemical	Secondary metabolite	Plant Source	Mechanism of action	Biological activity	References
Alkaloids	Berberine	*Hydrastis canadensis Tinospora cordifolia*	↓ TNF-α, IFN-γ and NO levels	Anti-pyretic	[31]
	Harmine	*Ophiorrhiza nicobarica*	Inhibit lysine specific demethylase-1 during viral transcription	Anti-herpes	[30]
	Punarnavine	*Boerhavia diffusa*	↑ WBC count, antibody formation and suppress pro-inflammatory cytokines	Anti-metastatic, anti-hepatitis	[19]
	Piperine	*Piper longum*	↑Total WBC count, bone marrow cellularity, total antibody production	Anti-asthmatic	[32]
	Tetrandrine	*Stephania tetrandra*	↓ Cytokine production inhibits NFκb mediated release of inflammatory factors	Anti-arthritic	[34]
	Sinomenine	*Sinomenium acutum*	Inhibitions of Ca2+ channel, PK-C activity, activations of NO and prostaglandin-I2 syntheses in endothelium	Graft survival	[35]
	Shankhpushpine	*Evolvulus alsinoides*	Modulates the level of dopamine	Brain tonic	[36]
	Lycorine	*Crinum latifolium*	Inhibit protein synthesis, prevent tumor cells from calprotectin induced apoptosis	Anti-rheumatic, Antitumor	[37]
	Betonicine, stachydrine, trigonelline	*Achillea millefolium*	Inhibits pro-inflammatory cytokines	Useful in multiple sclerosis	[38]
	Mahanimbine	*Murraya koenigii*	↓Systemic inflammation and oxidative stress	Insulin resistance, anti-inflammatory	[39]
Glycosides	Eupalitin3OβDgalactopyranoside	*Boerhaavia diffusa*	Inhibited PHAstimulated proliferation of peripheral blood mononuclear cells IL2 and TNFα	Immune suppression	[40]
	Aucubin	*Plantago major*	↑ Lymphocyte proliferation and secretion of IFNγ	Possess strong immune modulatory activity	[23]
	Mangiferin	*Mangifera indica*	↑The production of igg1 and igg2b	Immuno modulatory action	[41]
	SHE	*(Echinacea angustifolia)*	↑ Cytokine production, nitric oxide release, expression of surface molecules in dose dependent manner, induces activation of macrophage	Anti-cancer, antiasthmatic antiarthritic antidiabetic	
	Arabinogalactan, fructan	*(Echinacea angustifolia)*	↑T-cell function by *stimulate* interferon (IFN-γ) production in anti-CD3-treated murine T-cell cultures	respiratory infections, auto immune uveitis, mastitis	[42]
	CDP	*(Cistanche deserticola)*	↑ Cytotoxicity and apoptosis and resuces oxidative stress	Hepatoprotective, used in vitiligo and achromic naevus	[43]
Flavonoids	Centaurein	*(Bidens pilosa)*	Augmentation of IFNγ promoter activity, anti-oxidation	Anti-cancer	[44]
	Rhoifolin	*(Jatropha curcas)*	↑ Humoral and cell-mediated immune response	Immuno suppressive action in asthma	[45]
	Luteolin	*(Plantago major)*	↑ Lymphocyte proliferation and secretion of IFN	Auto immune thyroiditis,	[46]
	Baicalein	*(Plantago major)*	↑ Lymphocyte proliferation and secretion of IFN	UVB induced inflammation food	[47]
	Quercetin3Orutinoside	*(Urtica dioica)*	Immunomodulation	Allergy, modulates immune responses	[48]
	Fisetin	*(Cotinus coggygria)*	↓of NF-κb	Allergic airway inflammation, atopic dermatitis	[49]
Phenolic compounds	Chlorogenic acid	*(Plantago major)*	↑ Lymphocyte proliferation and secretion of IFN	Antiarthritic activities	[50]
	Curcumin	*Curcuma longa*	↑ Bone marrow cellularity, α esterase positive cells and phagocytic activity Inhibits IL2 expression and NFκb	infections	[27]
	PCoumaric acid	*Plantago major*	↑ Lymphocyte proliferation and secretion of IFN	Rheumatoid arthritis	[28]
Terpenoids	Andrographolide	*Andrographis paniculata*	↑ Expression of IL2 inhibition of NO in endotoxin ↑ macrophages	Anti-hepatitis agent	[51]
	Boswellic acid	*Boswellia serrata*	Significant inhibition of mast cell degranulation	Anti-anaphylactic	[24]
Tannins	Chebulagic acid	*Terminalia chebula*	Free radical scavenging	Anti-Arthritic	[52]
	Punicalagin	*Punica granatum*	Immunosuppressive action	Anti-viral and skin diseases	[25]
Saponins	Asiaticoside	*(Centella asiatica)*	↑ Phagocytic index and total WBC count	Strong immune modulatory activity	[53]
	Glycyrrhizin	*(Glycyrrhiza glabra)*	Inhibits classical complement pathway	Anti-duck hepatitis virus	[26]
Sterols	Withanolide	*(Withania somnifera)*	↑ Murine macrophages, phagocytosis and lysosomal enzyme activity	psoriasis, arthritis and rheumatism	[54]
	β-Sitosterol	*(Withania somnifera)*	↑ Human peripheral lymphocyte proliferation	rheumatoid arthritis	[29]

IFN-γ: Interferon-γ, TNF-α: Tumor necrosis factor-α, NF κB: Nuclear factor κB, NO: Nitric oxide, IL: Interleukin, WBC: White blood cells

and could be helpful in the future as well. The aim of this review was to highlight the results of research done on immunomodulators of classified phytochemicals. Many plants and some phytoconstituents responsible for immunomodulation have been explained. The review also discussed the pharmacodynamics of various plant drugs that focus on revealing the mechanism involved in immunomodulation. This work could encourage researchers to undertake further work on medicinal plants with potential immunomodulatory activity.

REFERENCES

1. Manu KA, Kuttan G. Immunomodulatory activities of punarnavine, an alkaloid from *Boerhaavia diffusa*. Immunopharmacol Immunotoxicol 2009;31:377-87.
2. Patil US, Jaydeokar AV, Bandawane DD. Immunomodulators: A pharmacological review. Int J Pharm Pharm Sci 2012;4:30-6.
3. Vinothapooshan G, Sundar K. Immunomodulatory activity of various extracts of *Adhatoda vasica* Linn. in experimental rats. Afr J Pharm Pharmacol 2011;5:306-10.
4. Gabhe S, Tatke P, Khan T. Evaluation of the immunomodulatory activity of the methanol extract of *Ficus benghalensis* roots in rats. Indian J Pharmacol 2006;38:271-5.
5. More P, Pai K. Immunomodulatory effects of *Tinospora cordifolia* (Guduchi) on macrophage activation. Biol Med 2011;3:134-40.
6. Chandu AN, Kumar CS, Bhattacharjee C. Studies on immunomodulatory activity of *Aloe vera* (Linn). Int J Appl Biol Pharm Technol 2011;2:19-22.
7. Lu Y, Fan J, Zhao Y, Chen S, Zheng X, Yin Y, *et al*. Immunomodulatory activity of aqueous extract of *Actinidia macrosperma*. Asia Pac J Clin Nutr 2007;16:261-5.
8. Barbosa A de P. Anti-inflammatory properties and immunoadjuvant activitiy of *Samanea saman* extract. Emirates J Food Agric 2014;26:818-21.
9. Cherng JM, Chiang W, Chiang L. Immunomodulatory activities of common vegetables and spices of umbelliferae and its related coumarins and flavonoids. Food Chem 2008;106:944-50.
10. Chakraborty SB, Hancz C. Application of phytochemicals as immunostimulant, antipathogenic and antistress agents in finfish culture. Rev Aquac 2011;3:103-19.
11. Ghule BV, Murugananthan G, Nakhat PD, Yeole PG. Immunostimulant effects of *Capparis zeylanica* Linn. leaves. J Ethnopharmacol 2006;108:311-5.
12. Gu C, Yang M, Zhou Z, Khan A, Cao J, Cheng G. Purification and characterization of four benzophenone derivatives from *Mangifera indica* L. leaves and their antioxidant, immunosuppressive and α-glucosidase inhibitory activities. J Funct Foods 2019;52:709-14.
13. Salminen A, Kaarniranta K, Kauppinen A. Phytochemicals inhibit the immunosuppressive functions of myeloid-derived suppressor cells (MDSC): Impact on cancer and age-related chronic inflammatory disorders. Int Immunopharmacol 2018;61:231-40.
14. Jantan I, Ahmad W, Bukhari SN. Plant-derived immunomodulators: An insight on their preclinical evaluation and clinical trials. Front Plant Sci 2015;6:1-18.
15. Seyed MA. A comprehensive review on *Phyllanthus* derived natural products as potential chemotherapeutic and immunomodulators for a wide range of human diseases. Biocatal Agric Biotechnol 2019;17:529-37.
16. Harun NH, Septama AW, Wan Ahmad WA, Suppian R. The potential of *Centella asiatica* (Linn.) urban as an anti-microbial and immunomodulator agent: A review. Nat Prod Sci 2019;25:92-102.
17. Carqueijeiro I, Langley C, Grzech D, Koudounas K, Papon N, O'Connor SE, *et al*. Beyond the semi-synthetic artemisinin: Metabolic engineering of plant-derived anti-cancer drugs. Curr Opin Biotechnol 2020;65:17-24.
18. Nair A, Chattopadhyay D, Saha B. Plant-derived immunomodulators. In: New Look to Phytomedicine: Advancements in Herbal Products as Novel Drug Leads. Amsterdam, Netherlands: Elsevier Inc.; 2018. p. 435-99.
19. Manu KA, Kuttan G. Anti-metastatic potential of punarnavine, an alkaloid from *Boerhaavia diffusa* Linn. Immunobiology 2009;214:245-55.
20. Lee YC, Kim SH. Effects of piperis Longi fructus on regulatory T cells number, IgE, histamine production in asthma model mice and Th1/Th2 cytokine balance *in vitro*. Korea J Herbol 2009;24:79-88.
21. Tzianabos AO. Polysaccharide immunomodulators as therapeutic agents: Structural aspects and biologic function. Clin Microbiol Rev 2000;13:523-33.
22. Abotaleb M, Samuel SM, Varghese E, Varghese S, Kubatka P, Liskova A, *et al*. Flavonoids in cancer and apoptosis. Cancers (Basel) 2019;11:28.
23. Vaidya HB, Ahmed AA, Goyal RK, Cheema SK. Glycogen phosphorylase-a is a common target for anti-diabetic effect of iridoid and secoiridoid glycosides. J Pharm Pharm Sci 2013;16:530-40.
24. Ammon HP. Boswellic acids in chronic inflammatory diseases. Plant Med 2006;72:1100-16.
25. Houston DM, Robins B, Bugert JJ, Denyer SP, Heard CM. *In vitro* permeation and biological activity of punicalagin and zinc (II) across skin and mucous membranes prone to herpes simplex virus infection. Eur J Pharm Sci 2017;96:99-106.
26. Dai JH, Iwatani Y, Ishida T, Terunuma H, Kasai H, Iwakula Y, *et al*. Glycyrrhizin enhances interleukin-12 production in peritoneal macrophages. Immunology 2001;103:235-43.
27. Ballard E, Coote PJ. Enhancement of antibiotic efficacy against multi-drug resistant *Pseudomonas aeruginosa* infections via combination with curcumin and 1-(1-naphthylmethyl)-piperazine. J Antimicrob Agents 2016;2:1-6.
28. Pragasam SJ, Venkatesan V, Rasool M. Immunomodulatory and anti-inflammatory effect of p-coumaric acid, a common dietary polyphenol on experimental inflammation in rats. Inflammation 2013;36:169-76.
29. Raj VB, Kumar KL, Kumar SS. Traditional Indian medicinal plants as a potential anti inflammatory phytomedicine for psoriasis control. J Pharm Phytochem 2015;4:118-22.
30. González D, Carvalho M, Cantillo J, Aixalá M, Farré M. Potential use of ayahuasca in grief therapy. OMEGA J Death Dying 2019;79:260-85.
31. Neag MA, Mocan A, Echeverría J, Pop RM, Bocsan CI, Cri G. Berberine: Botanical occurrence, traditional uses, extraction methods, and relevance in cardiovascular, metabolic, hepatic, and renal disorders. Front Pharmacol 2018;9:557.
32. Kim S, Lee Y. Piperine inhibits eosinophil infiltration and airway hyperresponsiveness by suppressing T cell activity and Th2 cytokine production in the ovalbumin-induced asthma model. J Pharm Pharmacol 2009;61:353-9.
33. Bjurström H, Wang JY, Ericsson I, Bengtsson M, Liu Y, Kumar-Mendu S, *et al*. GABA, a natural immunomodulator of T lymphocytes. J Neuroimmunol 2008;205:44-50.
34. Yuan X, Dou Y, Wu X, Wei Z. Tetrandrine, an agonist of aryl hydrocarbon receptor, reciprocally modulates the activities of STAT3 and STAT5 to suppress Th17 cell differentiation. J Cell Mol Med 2017;21:2172-83.
35. Mark W, Candinas D. The alkaloid sinomenine in rat transplant models: And yet it does move. Transpl Int 2001;14:124.
36. Sethiya NK, Nahata A, Singh PK, Mishra SH. Neuropharmacological evaluation on four traditional herbs used as nervine tonic and commonly available as Shankhpushpi in India. J Ayurveda Integr Med 2019;10:25-31.
37. Park HJ, Gholam-Zadeh M, Suh JH, Choi HS. Lycorine attenuates autophagy in osteoclasts via an axis of mROS/TRPML1/TFEB to reduce LPS-induced bone loss. Oxid Med Cell Longev 2019;2019:8982147.
38. Hussein AA, Al-Ezzy RM, Abdallah MT. Biochemical, enzymatic, and immunological study on antimutagenic *Achillea millefolium* methanolic extract *in vivo*. J Pharm Pharmacol 2019;7:69-74.
39. Jang MH, Piao XL, Kim JM, Kwon SW, Park JH. Inhibition of cholinesterase and amyloid and aggregation by resveratrol oligomers from Vitis amurensis. Phyther Res 2008;22:544-9.
40. Kanjwani DG, Marathe TP, Chiplunkar SV, Sathaye SS. Evaluation of immunomodulatory activity of methanolic extract of *Piper betle*. Scand J Immunol 2008;67:589-93.
41. Selles AJ, Daglia M, Rastrelli L. The potential role of mangiferin in cancer treatment through its immunomodulatory, anti-angiogenic, apoptopic, and

gene regulatory effects. BioFactors 2016;42:475-91.

42. Dobrange E, Peshev D, Loedolff B, Van Den Ende W. Fructans as immunomodulatory and antiviral agents: The case of *Echinacea*. Biomolecules 2019;9:1-12.
43. Nan ZD, Zeng KW, Shi SP, Zhao MB, Jiang Y, Tu PF. Phenylethanoid glycosides with anti-inflammatory activities from the stems of *Cistanche deserticola* cultured in Tarim desert. Fitoterapia 2013;89:167-74.
44. Chang SL, Chiang YM, Chang CL, Yeh HH, Shyur LF, Kuo YH, *et al*. Flavonoids, centaurein and centaureidin, from *Bidens pilosa*, stimulate IFN-γ expression. J Ethnopharmacol 2007;112:232-6.
45. Eldahshan OA, Azab SS. Anti-inflammatory effect of apigenin-7-neohesperidoside (rhoifolin) in carrageenin-induced rat oedema model. J Appl Pharm Sci 2012;2:74-9.
46. Xia N, Chen G, Liu M, Ye X, Pan Y, Ge J, *et al*. Anti-inflammatory effects of luteolin on experimental autoimmune thyroiditis in mice. Exp Ther Med 2016;12:4049-54.
47. Huang KF, Ma KH, Chang YJ, Lo LC, Jhap TY, Su YH, *et al*. Baicalein inhibits matrix metalloproteinase 1 expression via activation of TRPV1-Ca-ERK pathway in ultraviolet B-irradiated human dermal fibroblasts. Exp Dermatol 2019;28:568-75.
48. Olthof MR, Hollman PC, Buijsman MN, Van Amelsvoort JM, Katan MB. Chlorogenic acid, quercetin-3-rutinoside and black tea phenols are extensively metabolized in humans. J Nutr 2003;133:1806-14.
49. Kim GD, Lee SE, Park YS, Shin DH, Park GG, Park CS. Immunosuppressive effects of fisetin against dinitrofluorobenzene-induced atopic dermatitis-like symptoms in NC/Nga mice. Food Chem Toxicol 2014;66:341-9.
50. Chen W, Tang J, Bao J, Hu P, Shi Z, Wu L. International immunopharmacology anti-arthritic effects of chlorogenic acid in interleukin-1 β -induced rabbit chondrocytes and a rabbit osteoarthritis model. Int Immunopharmacol 2011;11:23-8.
51. Sinha RK, Sharma SN, Verma SS, Zha J. Effects of lovastin, fosmidomycin and methyl jasmonate on andrographolide biosynthesis in the *Andrographis paniculata*. Acta Physiol Plant 2018;40:165.
52. Nair V, Singh S, Gupta YK. Anti-arthritic and disease modifying activity of *Terminalia chebula* Retz. in experimental models. J Pharm Pharmacol 2010;62:1801-6.
53. Duggina P, Kalla CM, Varikasuvu SR, Bukke S, Tartte V. Protective effect of *Centella* triterpene saponins against cyclophosphamide-induced immune and hepatic system dysfunction in rats: Its possible mechanisms of action. J Physiol Biochem 2015;71:435-54.
54. Yang B, Zhou Y, Liu Y, Lu Z, Kuang H. Withanolides as potential immunosuppressive agents against. Nat Prod Commun 2017;6:10-3.