Review on traditional plants with phytochemical having immunomodulatory activities.

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Abstract

Immunomodulatory agents initiate the activation of non-specific immune responses and work without antigenic specificity. They directly activate different cell populations of the immune system and modify the production of cytokines and initiate the production of various effect or molecules that take part in the modulation and enhancement of the immune response. Since ancient times, plants have been an exemplary source of medicine. Some of the medicinal plants valued in Ayurvedic Rasayana for their therapeutic potential have been scientifically investigated with promising results. A number of plant-based principles have been isolated with potential immunomodulatory activity that can explain and justify their use in traditional medicine in the past and can form the basis for further research in the future as well. The present work constitutes a review of the medicinal plants whose immunomodulator activity has been proven. We performed PUBMED, EMBASE, Google scholar searches for research papers of medicinal plants having immunomodulator activity. This review shall hopefully encourage researchers to undertake further work on medicinal plants with potential immunomodulatory activity.

Keywords: Immunomodulators, Medicinal Plants, Immune system, Phytochemical, Pharmacology

Introduction

Disturbances of the immune system lead to the development and complications of chronic diseases. Numerous studies have proved that the restoration of immune system function is a prerequisite for the successful therapy of various illnesses [1,2]. Herbs with immunomodulatory properties are a moderately recent concept in Phytomedicine. In addition to the enhancement of the humeral and cell-mediated immunity, the concept of immunomodulator initiates the activation of the "non-specific" immune responses which include the activation of the complement system, granulocytes, macrophages and natural killer cells. Hence activation of these essential immune cells initiates the production of various effect or molecules (e.g. cytokines) that take part in the modulation and enhancement of the immune responses [3,4].

Immunomodulators may be synthetic drugs or of herbal origin. Due to the severe side effects related to synthetic drugs, immune-modulation using herbal drugs can provide an alternative to conventional chemotherapy for a variety of diseases, especially when the host defense mechanism has to be activated under the conditions of an impaired immune response [5]. Herbal drugs are easily affordable and less potent than synthetic prescription Immunomodulators and are also less likely to cause side effects. Natural adjuvant, synthetic agents, antibody reagents are used as immunosuppressive and immune stimulating agents. But there are major limitation to the general use of these agents such as increased risk of infection and generalized effect throughout the immune system [6]. Traditional Indian system of medicines like Siddha and Ayurveda

has suggested means to increase the body's natural resistance to disease. A number of Indian medicinal plants and various 'rasayanas' have been claimed to possess immunomodulatory activity [6, 7].

Medicinal plants can inhibit or stimulate immune response which could be useful in the treatment of various human diseases. In particular, medicinal plants capable of inhibiting the cellular and humeral responses could have useful applications in the treatment of immunological disorders [8]. A number of medicinal plants as Rasayanas have been claimed to possess immunomodulatory activity, e.g., *Withania somnifera*, *Tinospora cordifolia* and *Mangifera indica* [9,10]. Medicinal plants used by traditional physicians or reported as having immunomodulator activity include *Acacia concocinna*, *Camellia sinensis*, *Lawsonia inermis* Linn, *Piper longum* Linn, *Gelidium amansii*, *Petroselinum crispum*, *Plantago major* and *Allium sativum* [11].

Many plant-derived compounds, like sterols, polysaccharides, alkaloids, flavonoids, lectins and glycoprotein, are used for immune-modulation [12]. Among polysaccharides, acidic arabinogalactan and ramnogalacturonan have been shown to manifest immune-stimulatory effect in vitro and in vivo [13]. Numerous studies look into the immune-modulatory activities of saponin [14-17]. The proven effect of triterpenoids glycosides on the immune system of mammals contributed to the development of a wide range of dietary supplements for the prevention of the immune system disturbances, i.e., human immunity system enhancement [18], and for the prevention and treatment of allergies [19, 20].

Herbal medicine is an integral part of the development of modern civilization. In herbal medicine single plants and complex formulations are prescribed to treat diseases. With all these aspects keeping in mind, the present review focuses on an overview of a number of medicinal plants and their immunomodulatory activity.

Plants as Immunomodulators

Allopathic drugs are available for counteracting the oxidative stress and hence improve immunity, but the side effects and prohibitive cost of these allopathic drugs makes it necessary to search for an alternative. The Ayurvedic system of medicines not only provides that alternative, but also scores over the side effects and cost factor of allopathic medicine [21, 22]. Immunomodulators are becoming very popular in the worldwide natural health industry as people start to realize the importance of a healthy immune system in the maintenance of health and the prevention of diseases. 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.

The immunomodulatory characteristics of plant-based therapeutics have gathered attention of researchers. Innovative technologies and the excessive research on immunomodulatory natural products, plants, their extracts, and their active moieties with immunomodulatory potential, may provide us with valuable entities to develop as novel immunomodulatory agents to supplement the present chemotherapies. Immunomodulatory therapy could provide an alternative to conventional chemotherapy for a variety of diseased conditions, especially when host's defense mechanisms have to be activated under the conditions of impaired immune responsiveness or when a selective immunosuppression has to be induced in a situation, like inflammatory diseases, auto-immune disorders ad organ/bone marrow transplantation. A number of Indian medicinal plants and various 'Rasayana' have been claimed to possess immunomodulatory activity [Table 1].

Table 1: List of common plant-derived immune-modulators

S.No.	Botanical name and family	Parts used	Active constituent	Ref.
1.	*Abutilon indicum* linn. (Malvaceae)	Whole plant	Flavonoids, triterpenoids	[23]
2.	*Acacia catechu* Willd. (Leguminosae)	Leaf	Flavonoids, quercetin	[24]
3.	*Achiella wilhelmsii* C. Koch (Compositae)	Leaves	Flavonoids, alkaloids, polyacetylenes, coumarins, triterpenes	[25]
4.	*Actinidia macrosperma* C. F. Liang (Actinidiaceae)	Fruits	Alkaloids, saponins	[26]
5.	*Agelas mauritianus* (Porifera)	Sponge	Glycolipid (a-galactosylceramide)	[27]
6.	*Allium hirtifolium* Boiss. (Alliaceae)	Herb	Thiosulfinates, flavonoids	[28]
7.	*Aloe vera* Tourn.ex Linn. (Liliaceae)	Gel from leaves	Anthraquinone glycosides	[29, 30]
8.	*Alternanthera tenella* Colla (Amaranthaceae)	Herb	Flavonoids, triterpenes	[31]
9.	*Andrographis paniculata* Nees (Acanthaceae)	Leaves	Diterpenes	[32]
10.	*Aphanothece halophytica* (Chroococcales)	Cyanobacterium	Exopolysaccharide	[33]
11.	*Apium graveolens* Linn. (Apiaceae)	Leaves, seeds	Flavonoids, coumarins	[34]
12.	*Artemisia annua* Linn. (Compositea)	Herb	Artemisinin	[35]
13.	*Asparagus racemosus* Wild. (Liliaceae)	Roots	Saponins, sitosterols	[36]
14.	*Bauhinia variegata* Linn. (Caesalpiniaceae)	Roots, bark, buds	Flavonoids, beta-sitosterol, lupeol	[37]
15.	*Bidens pilosa* L. (Asteraceae)	Flowers, leaves	Polyacetylenes	[38]
16.	*Boerhaavia diffusa* (Nyctaginaceae)	Herb	Alkaloid	[39]
17.	*Botryllus schlosseri*	Tunicates	Cytokines	[40]

	(Botryllidae)			
18.	*Bugula neritina* L. (Bugulidae)	Marine invertebrates	Macrocyclic lactones	[41]
19.	*Byrsonima crassa* Nied. (Malpighiaceae)	Leaves	Flavonoids, tannins, terpenes	[42]
20.	*Calendula officinalis* L. (Asteraceae)	Flowers	Polysaccharides, proteins, fatty acids, carotenoids, flavonoids, triterpenoids	[43]
21.	*Camellia sinensis* L. (Theaceae)	Leaves	(-)Epigallocatechin gallate, quercetin, gallicacid	[44]
22.	*Cannabis sativa* (Cannabaceae)	Leaves	Cannabinoids	[45]
23.	*Carpobrotus edulis* L. (Aizoaceae)	Flowers, fruit	Alkaloids	[46]
24.	*Centella asiatica* Linn. (Umbelliferae)	Herb	Triterpenoid saponins	[47]
25.	*Chlorophytum borivilianum* Sant. F (Liliaceae)	Roots	Sapogenins	[48]
26.	*Cissampelos pareira* Linn. (Menispermiaceae)	Roots	Hayatine alkaloids	[49]
27.	*Cistanche deserticola* (Orobanchaceae)	Herb	Polysaccharide	[50]
28.	*Citrus auraptene* (Rutaceae)	Fruits	Auraptene, flavonoids	[51]
29.	*Cleome gynandra* Linn. (Capperdiceae)	Leaf, seeds, roots	Hexacosanol, kaempferol	[52]
30.	*Cliona celata* (Clionaidae)	Sponge	Clionamide, dehydrodopamine	[53]
31.	*Cordyceps militaris* L. (Clavicipitaceae)	Fungus	Cordycepin, cordyceps acid	[54]
32.	*Couroupita guianensis* Aubl. (Lecythidaceae)	Fruits, flowers	Steroids, flavonoids, phenolics	[55]
33.	*Crinum latifolium* Andr. (Amaryllidaceae)	Herb	Alkaloids	[56]
34.	*Dracocephalum kotschyi* (Lamiaceae)	Herb	Essential oil	[57]
35.	*Echinacea angustifolia* (Asteraceae)	Flowers	Polysaccharide	[58]

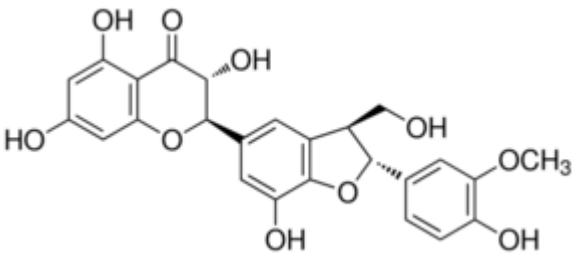
36.	*Eclipta alba* L. (Compositae)	Leaves	Triterpenoid glucoside	[59]
37.	*Euphorbia hirta* linn. (Euphorbiaceae)	Herb	Quercitol, myricitrin, gallic acid	[60]
38.	*Evolvulus alsinoides* Linn. (Convolvulaceae)	Herb	Alkaloids	[61]
39.	*Ganoderma lucidum* (Fr.) P. Karst. (Polyporaceae)	Whole plant	Flavonoids, triterpenes	[62]
40.	*Genus Ardisia* (Myrsinaceae)	Shrub, branches, leaves	Peptides, saponins, Isocoumarins, quinones and alkyl phenols	[63]
41.	*Genus aristolochia* (Aristolochiaceae)	Leaves	Aristolochic acid	[64]
42.	*Genus aspergillus* (Trichocomaceae)	Fungus	Polyene, triazole	[65]
43.	*Gymnema sylvestre* R.Br. (Asclepiadaceae)	Leaves	Sapogenins	[66]
44.	*Haussknechtia elymatica* (Apioideae)	Herb	Phenolics	[67]
45.	*Heracleum persicum* Desf. (Apiaceae)	Shurb	Flavonoids, furanocoumarins	[68]
46.	*Hibiscus rosa sinensis* Linn. (Malvaceae)	Flowers	Cyclopropanoids	[52]
47.	*Hyptis suaveolens* (L.) Poit. (Lamaceae)	Leaf, flowers	Lupeol, beta-sitosterol	[69]
48.	*Inonotus obliquus* Pers. (Hymenochaetaceae)	Mushroom	Polysaccharide	[70]
49.	*Lagenaria siceraria* Mol. (Cucurbitaceae)	Leaves, fruit	Cucurbitacin, beta-glycosidase	[71]
50.	*Larrea divaricata* DC. (Zygophyllaceae)	Herb	Lignans	[72]
51.	*Lycium barbarum* Linn. (Solanaceae)	Fruits	Polysaccharide-protein complexes	[73]
52.	*Matricaria chamomilla* (Rhabdoviridae)	Flowers	Protein	[74]
53.	*Mollugo verticillata* L. (Molluginaceae)	Herb	Quercetin, triterpenoid glycosides	[75]

54.	*Moringa oleifera* L. (Moringaceae)	Leaves	Vitamin A, B, C, carotenoids, saponins	[76]
55.	*Morus alba* Linn. (Moraceae)	Fruits, leaves, Bark	Flavonoids, anthocyanins	[77]
56.	*Murraya koenigii* (L) Spreng. (Rutaceae)	Leaves	Coumarin, carbazole alkaloids, glucoside	[78]
57.	*Nyctanthes arbortristis* L. (Oleaceae)	Leaf, seeds	Iridoid glucosides	[79]
58.	*Ocimum sanctum* Linn. (Labiateae)	Entire plant	Essential oils such as eugenol, cavacrol, derivatives of ursolic acid, apigenin	[80]
59.	*Panax ginseng* Wall. (Araliaceae)	Fruits, root	Saponins such as ginsenosides, panaxdiol, panaxtriole and oleanolic acid	[81]
60.	*Pestalotiopsis leucothes* (Amphisphaeriaceae)	Fungus	Terpenes	[82]
61.	*Picrorhiza scrophularii* flora Benth. (Scrophulariaceae)	Roots	Iridoid glycosides, amphicoside	[83]
62.	*Piper longum* L. (Piperaceae)	Fruits	Alkaloids	[84]
63.	*Randia dumetorum* Lamk. (Rubiaceae)	Fruits	Saponins, triterpenes	[85]
64.	*Rhodiola imbricate* Gray. (Crassulaceae)	Rhizomes	Phenolics	[86]
65.	*Salicornia herbacea* (Chenopodiaceae)	Herb	Polysaccharides	[87]
66.	*Silybum marianum* L. (Asteraceae)	Flowers	Flavonoid	[88]
67.	*Terminalia arjuna* Roxb. (Combretaceae)	Leaves, bark	Flavonoids, oligomeric proanthocyanidins, tannins	[89]
68.	*Thuja occidentalis* L. (Arborvitae)	Leaves	Polysaccharides	[90]
69.	*Tinospora cordifolia* Miers. (Menispermiaceae)	Entire herb	Alkaloidal constituents such as	[91]

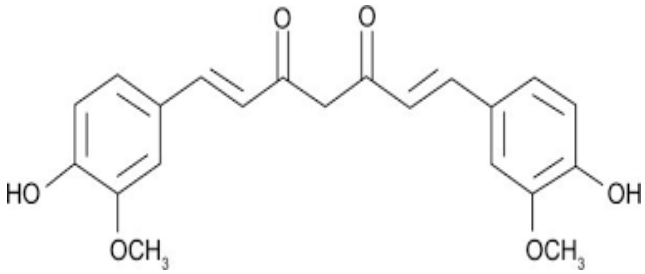
			berberine, tinosporic acid	
70.	*Urena lobata* Linn. (Malvaceae)	Roots, flowers	Flavanoids	[92]
71.	*Viscum album* L. (Loranthaceae)	Leaves and young twigs, berries	Viscotoxins, polyphenols, polysaccharides	[93]

Additionally, the potential use as immunomodulatory agents, modes of action and plant origin of numerous important plant-based lead compounds has also been comprehensively discussed. Important approach for immunomodulator is to boost an individual's immune defence systems by giving either physiologic or supraphysiological dosages of exogenous cytokines or therapeutic substances to treat the associated chronic malignancies and viral infections [94]. Immunomodulatory entities with additional safety and effectiveness are still in need. Due to the occurrence of chemical drugs-related adverse effects, natural Immunomodulators are the potential agents to replace them in therapeutic regimens. Though, the path from traditional medicines to western pharmaceutical practices is not always easy. The inconsistency of responses of phytomedical practices can be clarified in terms of the typically strong reliance of plant secondary metabolite profiles on environmental signals that can disturb reproducibility of results with extracts. This can be decreased if the principles of standardization of extracts and enriched fractions are thoroughly applied.

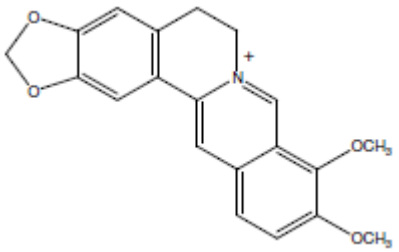
Plant-derived compounds showing promising potential as immunomodulatory agents. Based on the evidence, it is important to investigate the chemical structures from traditional Phytomedicine to evaluate their usefulness as immunomodulatory agents for immune disorders. Below, we provide examples of Phyto-compounds whose specific chemical structures and immunomodulator activities have been elucidated [Figure 1]. Beside these compounds, other phytochemical including essential oils, steroids, terpenoids, phenolic, pigments, flavonoids, and alkaloids, etc. have exhibited worth mentioning immunomodulatory effect [95-99].



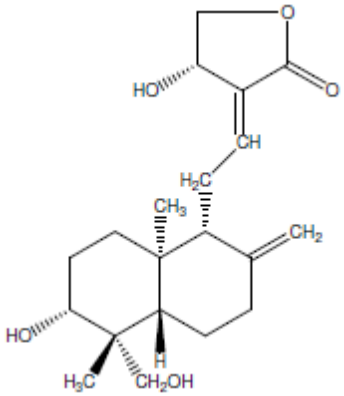
Silymarin



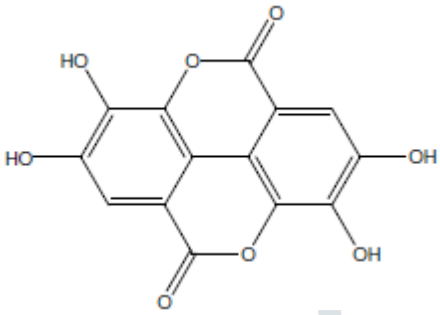
Curcumin



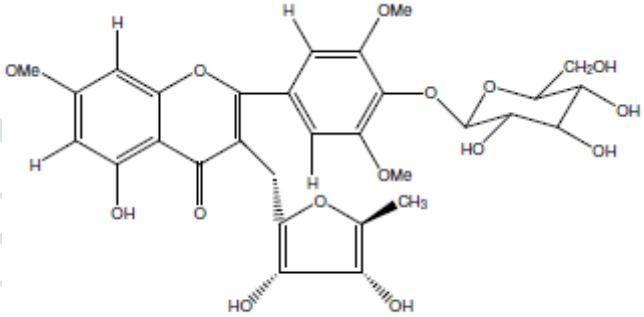
Berberine



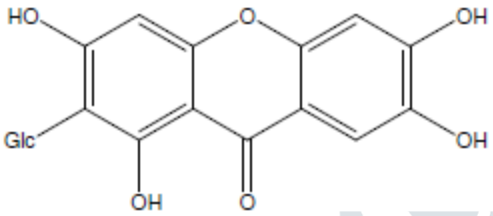
Andrographolide



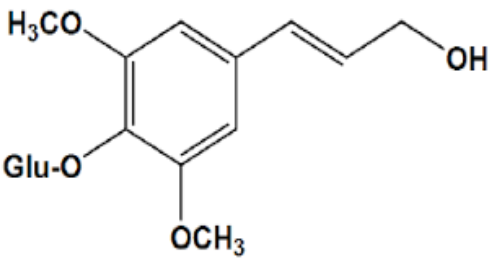
Ellagic acid



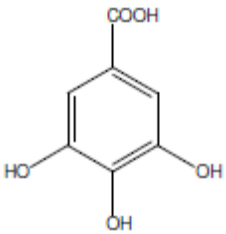
Flavone glucoside



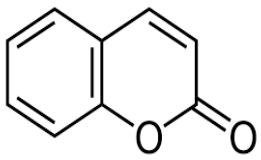
Mangiferin



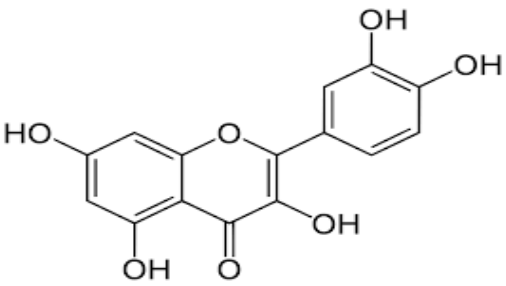
Syringin



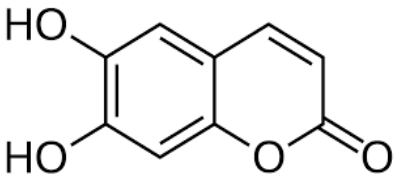
Gallic acid



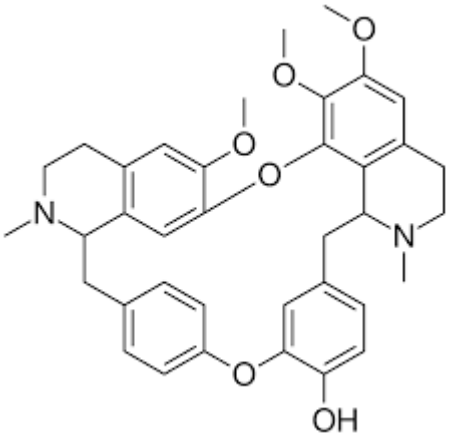
Coumarin



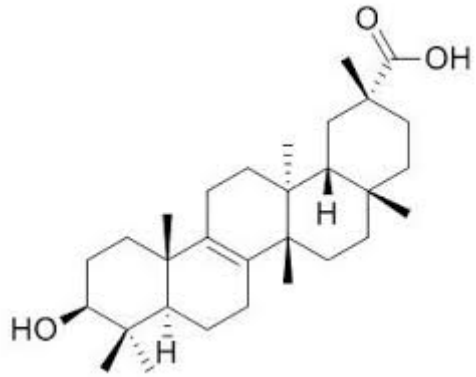
Quercitin



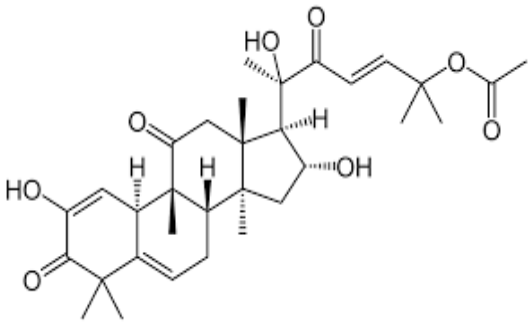
Esculetin



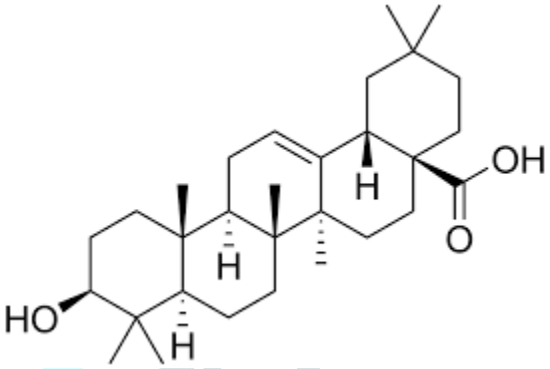
Berbamine



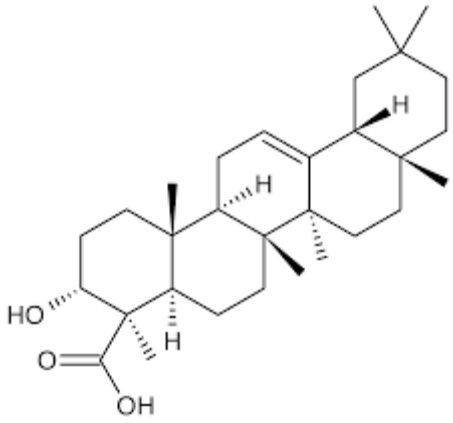
Bryonolic acid



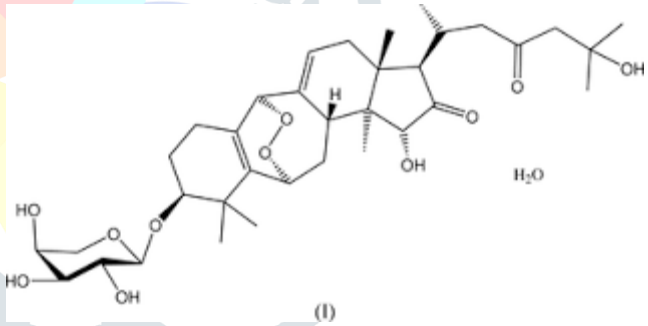
Cucurbitacin



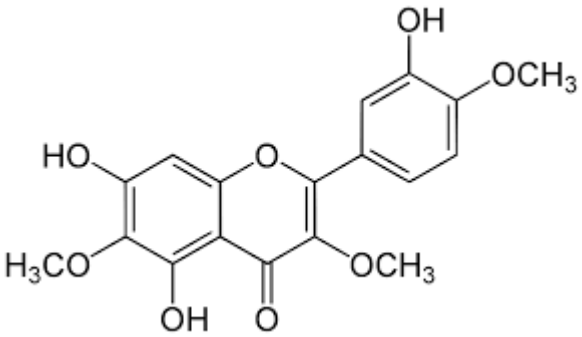
Oleanic acid



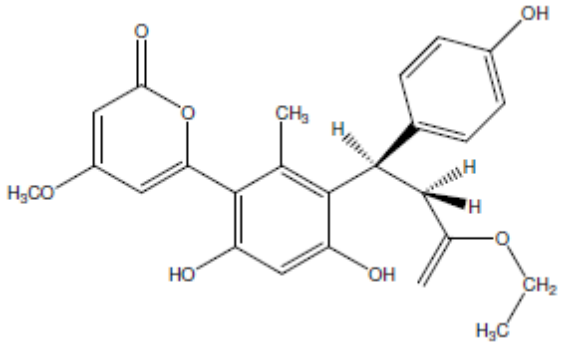
Boswellic acid



Podocarpaside



Centauriedin



Aloe compound

Figure 1: Structure of immunomodulatory phytoconstituents from plants

Future potential

Various herbal medicines have been found to modulate various components of innate and acquired immune system. In fact, based on proper understanding of various immunomodulatory activities of herbal plants, plants derived the secondary metabolites in natural products can be the lead molecules for the future development of Immunomodulators for therapeutic use. Some medicinal plants may stimulate the immune system, (e.g., *Panax ginseng*, *Ocimum sanctum*, *Tinospora cordifolia*, and *Terminalia arjuna*), and some may suppress the immune response (*Alternanthera tenella*). Also, various secondary metabolites (e.g., alkaloids, glycosides, saponins, flavonoids, coumarins, and sterols) exhibit a wide range of immunomodulating activity [100]. Researcher are on the search for some plant biochemicals in the form of the single compound which is like lead molecule concerned with particular target linked with disease. To transform this lead molecule with least toxicity and maximum selectivity and potency with respect to its target, its further design and development through chemical modification to make it therapeutically fit is nowadays gaining much interest. The contribution of combinatorial chemistry in search for a novel pharmacophore using varied chemical modifications and optimizations of the herbal lead molecule is appreciating. Curcumin or Haldi in Indian parlance has been chemically modified and optimized to have drug candidate with efficient efficacy and therapeutic action using combinatorial chemistry approach [101]. The underlying mechanisms involved in the immunomodulatory effects of the medicinal plants are not in depth studied due to limitations in terms of design, conduct, and interpretation. Extensive experimental and preclinical studies on the immunomodulator potential of medicinal plants needs to be address to provide sufficient data to prove that their traditional uses are inherently effective and safe and will allow clinical trials to be pursued for their further development as therapeutic agents to treat immune-related disorders. Immunogenic chemotherapy has recently emerged as an interesting approach, based on the ability of a Cytotoxic compound to induce immunogenic tumour cell death, which are characterized by the changes of danger-associated molecular pattern, including heat shock protein, calreticulin, glucose-related protein and high-mobility group protein box 1 [102]. Network pharmacology in combination with “omics” techniques such as genomics, proteomics and transcriptomics, metabolomics, and metabonomics have recently become possible to examine simultaneous molecular effects of chemical compounds present in plant extracts.

Conclusion

The relevant literature shows that many plants or plant products have been used as an alternative source for the treatment of different diseases. Several of these herbs have been used to exert immunomodulatory effect in the treatment of various diseases. Major highlights of this review are on the description about immunomodulator from plant origin with phytochemical compounds and this study represents perspective of the medicinal plants effective as immunomodulatory agents from natural resources. 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. This review will help the researchers to recommend lead compounds from natural resources for drug development and establishing their efficacy from traditional resources.

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