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IMMUNOMODULATORY CONSTITUENTS FROM PLANT ORIGINS: A REVIEW OF ISOLATED BIOMOLECULES

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ABSTRACT: Plant products such as leaves, barks, seeds etc., hold pharmacologically active moieties for drug discovery and development of semisynthetic drugs from natural products. However, as therapeutically effective these plant derived molecules may be, most herbal medicines lack in the scientific information regarding their constituents and impurities. In recent times, due to the development of chromatographic techniques, their medicinal uses are substantiated with relevant to the constituents present. Standardization of plant extract before formulation of herbal medicines and export is much needed. In the present article an attempt was made to enlist the immunomodulatory constituents from plant origin.

INTRODUCTION: According to an estimate of the World Health Organization (WHO), about 80% of the world population still uses herbs and other traditional medicines for their primary health care needs ¹. Herbal formulations have reached widespread acceptability as therapeutic agents for diabetics, arthritics, liver diseases, cough remedies, memory enhancers and adaptogens ².

As per WHO definition, there are three kinds of herbal medicines: raw plant material, processed plant material and medicinal herbal products. Processed plant materials are most often, crudely processed for enhanced shelf life and biological activity.

They often involve solubilization of plant materials in hydro-alcoholic solutions or pulverization of dried plant materials by mortar and pestle. Medicinal herbal products are formulated, finished labeled products that contain active ingredients extracted from parts of plant or other plant materials and they contain, although not required, the name and strength of the active principle(s) along with indication and dosage. However, by virtue of it being a plant derived or of “natural” origin, they are not required to be quality compliant by regulatory authorities.

In spite of natural products being non-regulated, herbals are traditionally considered harmless and increasingly being consumed by people without prescription. The use of herbal medicines, thus, has increased remarkably in line with the global trend of people returning to natural therapies ³. Herbal medicine products are also sold as dietary supplements that people take to improve their health and are sold as tablets, capsules, powders, teas, extracts and fresh or dried plants.

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Plant-based Immunomodulators:

A growing field: In recent years, the immunomodulating properties of plants are being studied extensively with ever-increasing interest due to the benefits by immune system modulation for disease prevention and cure. Several plant remedies, practiced throughout the world, are well-known for their anti-infective effects not only by directly affecting the pathogen, but also by stimulating natural and adaptive defence mechanisms of the host. In addition to treating infectious diseases, the immunomodulatory responses of these medicinal plants are used for treatment of arthritis, allergy, asthma, general debility, geriatric problems, analgesic, anti-convulsive, sedative etc. Therefore, plant-remedies are becoming versatile means with improved knowledge and application of immunotherapy.

An immunomodulator is defined as a biological or non-biological substance that directly influences a specific immune function or modifies one or more components of immunoregulatory network to achieve an indirect effect on a specific immune function. The basic function of immune system is to detect and destroy the non-self organism or foreign particle and thus act as a defence mechanism. The system works throughout the body through a complex regulation of cellular and humoral factors. Currently, the field of immunomodulation attracted tremendous attention from the scientific community, in view of the growing awareness regarding the need to modulate the immune system to achieve the desirable effects of preventing an infection rather than treating it at an advanced state.

A number of clinical conditions, like cancer⁴, surgery⁵ or administration of synthetic chemotherapeutic drugs are known to affect the different components of the immune system, thereby making the host susceptible to infections. Also, stress, be it physical or psychological, causes immunosuppression⁶. Such are the situations, which call for immunostimulant drugs to boost the immune defences against the host. The result has been the development of the concept of "pro-host therapy"⁷ and administering drugs, like glucans⁸⁻¹⁰, muramyl dipeptide, interleukin-1 and colony stimulating factors, to enhance the non-specific host resistance against infections.

However, the major drawbacks of these substances are their prohibitive cost and development of local reactions like granuloma formation.

As opposed to the need for immunostimulants, there also are cases of immune-hypersensitivity reactions, such as asthma, autoimmunity, graft rejection, arthritis, allergy and inflammatory disorders, in which an immune-suppressor is, indicated. Drugs such as azathioprine cyclophosphamide, prostaglandins, cyclosporine A, Thicarbomate, Levamisol Niridazole and Pencillamine are used as immunosuppressor but, main disadvantage of these drugs are their cytotoxicity and associated side effects.

Isolated Immunomodulatory constituents of plant origin:

Against this background of growing importance of immunomodulators, the use of herbal drugs, to restore and rejuvenate positive health and to maintain organic equilibrium has been in trend since ancient times. In this paper, an effort has been made to consolidate the investigations and findings carried out on various constituents as an immunomodulators of plant origin.

1. ***Andrographis paniculata*:** *Andrographis paniculata* is an erect annual herb extremely bitter in taste in all parts of the plant body. The aerial part of *A. paniculata* is commonly used in Chinese medicine. The herb contains diterpenoids, flavonoids and polyphenols as the major bioactive components. Andrographolide and 14-deoxy-11, 12-didehydroandrographolide the major constituent of the extract, is implicated in its pharmacological activity. Immunostimulatory activity of andrographolide and 14-deoxy-11, 12-didehydroandrographolide is evidenced by increased proliferation of lymphocytes and production of interleukin¹¹.

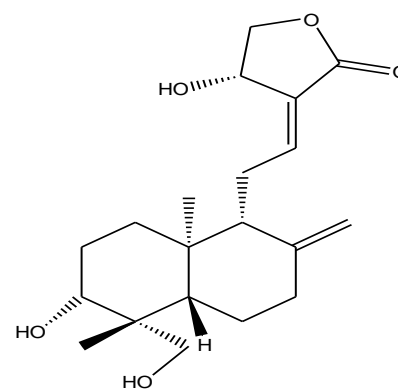


FIGURE 1: ANDROGRAPHOLIDE

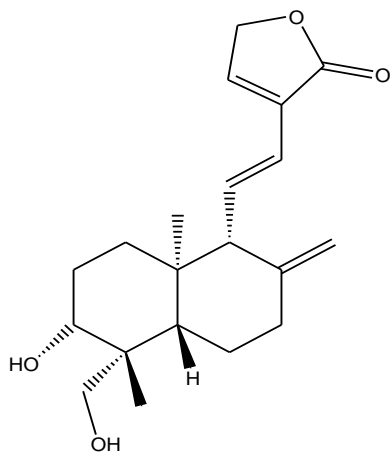


FIGURE 2: 14- DEOXY-11, 12-DIDEHYDROANDROGRAPHOLIDE

2. ***Tinosporacordifolia*:** *Tinosporacordifolia* is important drug of Indian systems of medicine and used in medicines since times immemorial. The drug has been subjected to extensive phytochemical, pharmacological and clinical investigation and many interesting findings in the areas of immunomodulation, anticancer activity, liver disorders and hyperglycemic are reported¹².

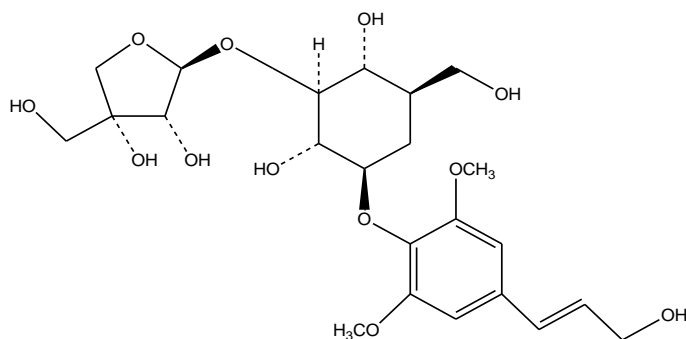


FIGURE 3: CORDIFOLIOSIDE A

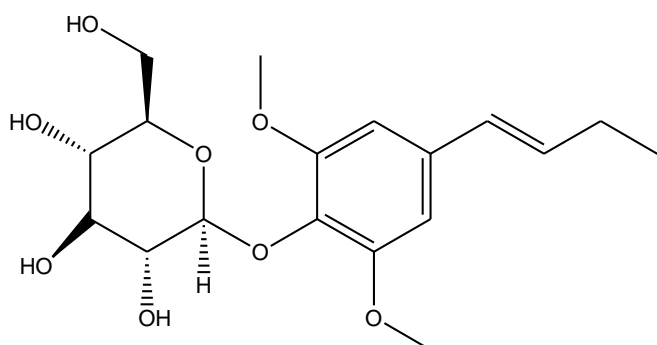


FIGURE 4: SYRINGIN

3. ***Lithospermum erythrorhizon*:** *Lithospermum* is a herbs or small shrubs, they are widely distributed except in Australasia. The dried root of *Lithospermum erythrorhizon* is a Chinese herbal medicine with various antiviral and

biological activities, including inhibition of human immunodeficiency virus (HIV) type 1 (HIV-1). Naphthoquinone compounds present in root extracts of a traditional Chinese medicinal herb, *Lithospermum erythrorhizon* plant have been reported to confer many medicinal properties such as antibacterial, wound healing, anti-inflammatory, antithrombotic, and antitumor effects. Shikonin has been showed Immunomodulatory effects of phyto-compound characterized by in vivo transgenic human GM-CSF promoter activity in skin tissues¹³.

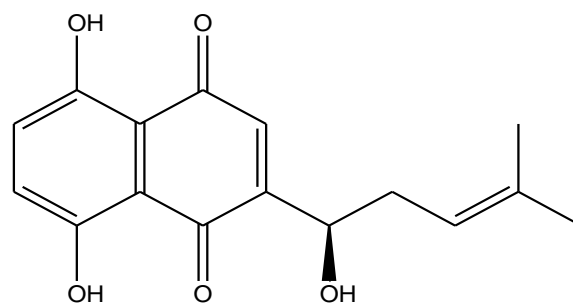


FIGURE 5: SHIKONIN

4. ***Agave sisalana*:** Flavones and homo isoflavonoids were isolated from the methanolic extract of the leaves of *Agave sisalana*. Their structures are elucidated on the basis of spectroscopic analysis. The isolated compounds were also evaluated for immunopharmacological activity¹⁴.

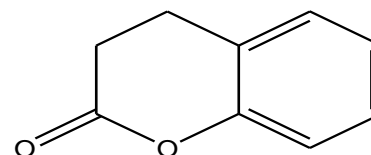


FIGURE 6: ±3,9-DIHYDROCOUMARIN

5. ***Opuntia polyacanth*:** *Opuntia polyacantha* has been used extensively for its nutritional properties however, less is known regarding medicinal properties of *Opuntia* tissues. *Opuntia* polysaccharides consisted primarily of galactose, galacturonic acid, xylose, arabinose, and rhamnose. Analysis of the effects of *Opuntia* polysaccharides on human and murine macrophages demonstrated that all four fractions had potent immunomodulatory activity. *O. polyacantha* and support the concept of using *Opuntia* polysaccharides as an immunotherapeutic adjuvant¹⁵.

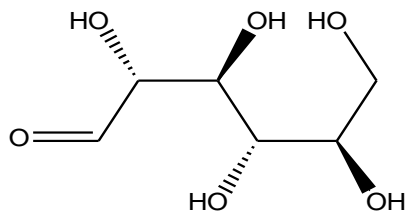


FIGURE 7: GALACTOSE

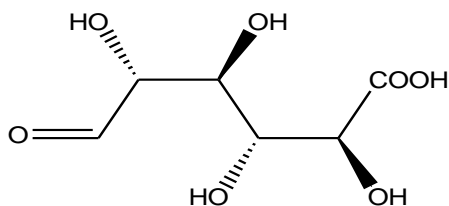


FIGURE 8: GALACTOURCINIC ACID

6. ***Petiveria alliacea***: In folk medicine, *Petiveria alliacea* is used to treat a wide variety of disorders. Root in decoction, powder or leaves infusion are used as antispasmodic, antirheumatic, anti-inflammatory, antinociceptive, hypoglycemic and abortifacient. Also, there are reports describing the plant with sudorific, anti-venereal, diuretic, sedative, antihelminthic, emmenagogue, anesthetic and depurative properties. Isolation and identification of three glutamyl dipeptides from roots of this plant have also been reported. Dibenzyl trisulphide, a lipophilic compound found in the plant and identified as one of the potent immunomodulatory compounds, exhibiting anti-proliferative and cytotoxic activity pertaining to the cytoskeleton is implicated¹⁶.

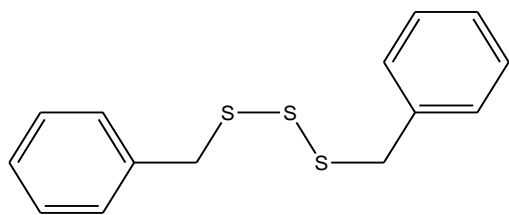


FIGURE 9: DIBENZYLTRISULPHIDE

7. ***Nothapodytesfoetida***: Natural products from entophytes have a broad spectrum of biological activity and can be grouped into several categories such as alkaloids, steroids, terpenoids, isocumarins, quinones, phenyl propanoids, lignans, aliphatic metabolites, lactones etc. A novel Camptothecin producing endophytic fungus, *Entrophospora inferquensis* isolated

from an important Indian medicinal plant *Nothapodytesfoetida*. *E. inferquensis* synthesizes camptothecin having potential immunomodulatory activity¹⁷.

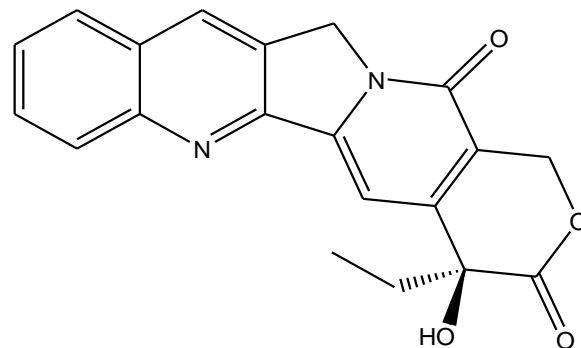
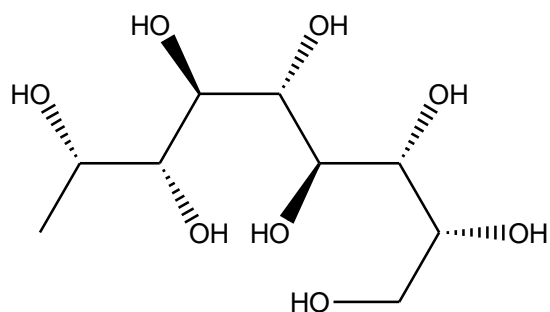


FIGURE 10: CAMPTOTHECIN

8. ***Syzygium guineense***: Plant polysaccharides have attracted attention due to their therapeutic potential as anti-tumour, wound healing, antiulcer, or anti-atherosclerotic agents. Most of these actions are thought to involve components of the innate immune system such as the complement system, and the release of reactive oxygen species (ROS), nitric oxide (NO), and cytokines by macrophages, dendritic cells, and granulocytes. Diverse plant polysaccharides are shown to interact specifically with pattern recognition receptors on innate leukocytes such as lectin-like receptors, toll-like receptors, and scavenger receptors on leukocytes. Authors are claimed that isolation, chemical composition, and immunological activities of pectic polysaccharides from the leaves of *S. guineense*¹⁸.

FIGURE 11: ARABINO GALACTON TYPE-II POLYSACCHARIDE (sg50A₁)

9. ***Phyllanthus emblica***: *Emblica officinalis* adores a hallowed position in Ayurveda- an Indian indigenous system of medicine. According to believe in ancient Indian mythology, it is the first tree to be created in the universe.

The fruits of *Emblica officinalis* are widely used in the Ayurveda and believed to increase defense against diseases. It has its beneficial role in cancer, diabetes, liver treatment, heart trouble, ulcer, anemia and various other diseases. Similarly, it has application as antioxidant, immunomodulatory, antipyretic, analgesic, cytoprotective, antitussive and gastro-protective.

Quercetin is isolated and characterized from ethanolic extract of *Phyllanthus emblica* Linn. and this is a flavonoidal constituent¹⁹.

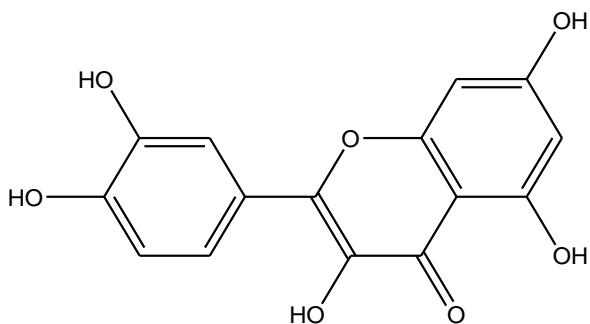


FIGURE 12: QUERCETIN

10. ***Curcuma longa***: Various species of the perennial plant *Curcuma longa* are found as common ingredients in many health supplements in Asia. *Curcuma longa* is a spice commonly used in Indian and Chinese cuisine and traditional medicine. The immunomodulatory activities of turmerones (α and aromatic) isolated from CL are also examined using human peripheral blood mononuclear cells²⁰.

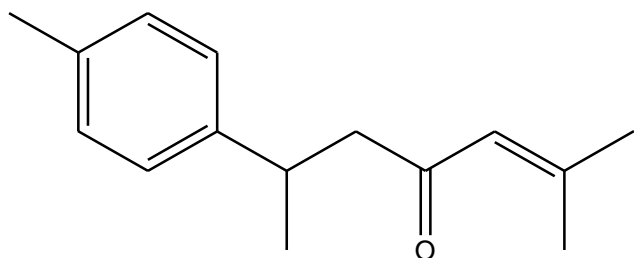


FIGURE 12: AROMATIC α -TURMERONE

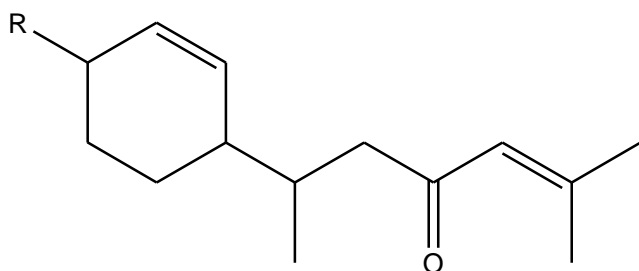


FIGURE 13: α -TURMERONE R= ME, β -turmerone R= CH₂

11. ***Boerhaavia diffusa***: Punarnavine is an alkaloid present in the plant *Boerhaavia diffusa*. It is also considered as the active principle in the plant extract. Antimetastatic potential of Punarnavine which can also activate cell mediated immune responses in B16F-10 metastatic melanoma-bearing mice. *B. diffusa* has attracted lot of attention due to its prevalent uses in Ayurvedic system of medicine. It is widely used in jaundice, hepatitis, edema, oligurea, anemia, inflammations, and eye disease. Pharmacologists and clinicians have investigated "Punarnava" for all these activities and the findings support the existing clinical uses²¹.

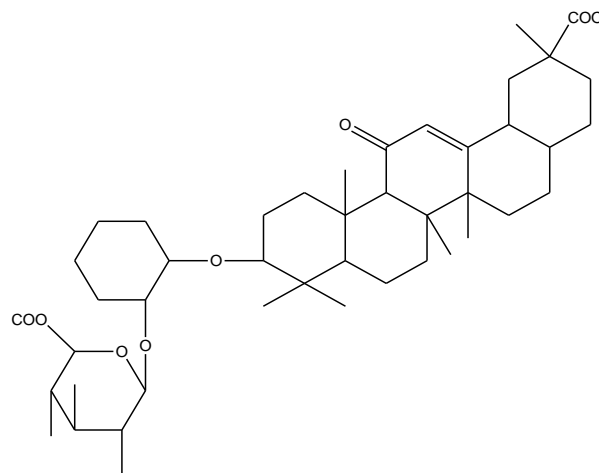


FIGURE 14: PUNARNAVINE

12. ***Bergenia crassifolia***: Bergenin is a C-glucoside of 4-O-methyl gallic acid found in the form of colourless crystalline compound. It is isolated from plant such as *Bergenia crassifolia*. Isolation and characterization of bergenin is confirmed through different spectroscopic methods. Bergenin exhibits antihepatotoxic, antiulcerogenic, anti-HIV, antifungal, immunomodulatory and wound healing properties²².

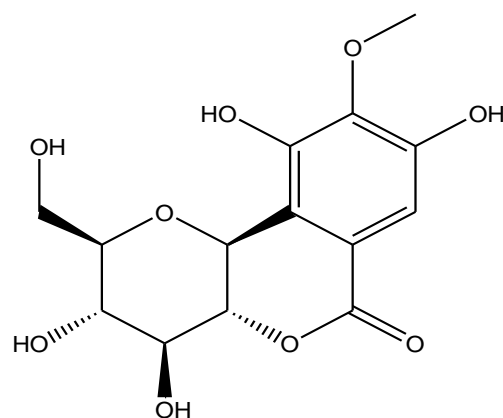


FIGURE 15: BERGENIN

13. ***Panax ginseng***: The biological and pharmacological efficacy of Korean ginseng is revealed by modern isolation techniques. The constituents of ginseng root have been investigated and several classes of compounds have been isolated such as triterpene, saponins, essential oil-containing polyacetylenes and sesquiterpenes, polysaccharides, peptidoglycans, nitrogen-containing compounds and various ubiquitous compounds such as fatty acids, carbohydrates, and phenolic compounds.

Ginsenosides appear to be responsible for most of the activities of ginseng including anticarcinogenic, immunomodulatory & anti-inflammatory²³.

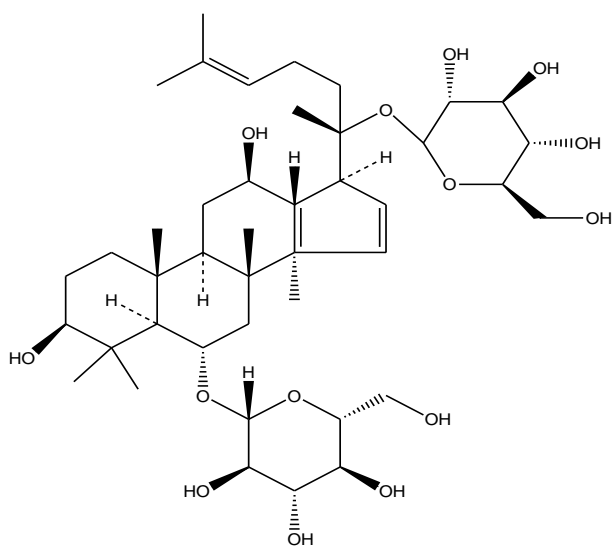


FIGURE 16: GINSENOSE

14. ***Withania somnifera***: *Withania somnifera*, is a commonly used herb in Ayurvedic medicine. Various benefits such as immunomodulation,

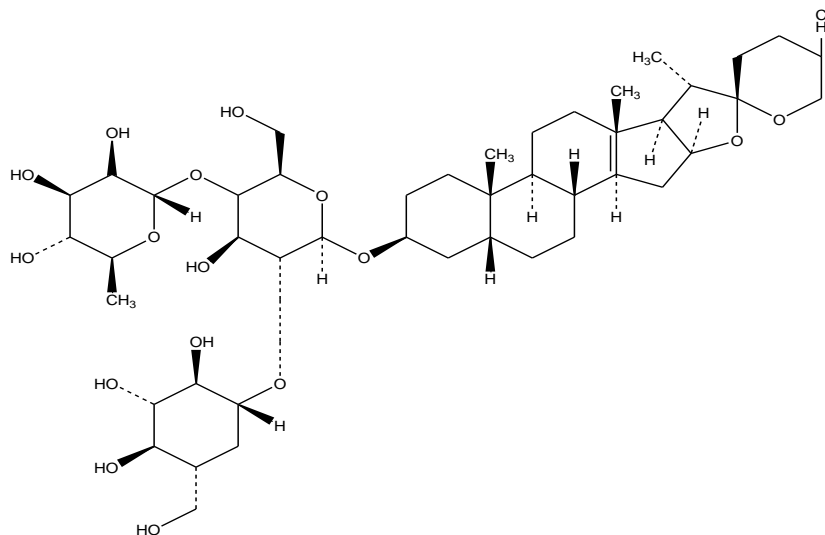
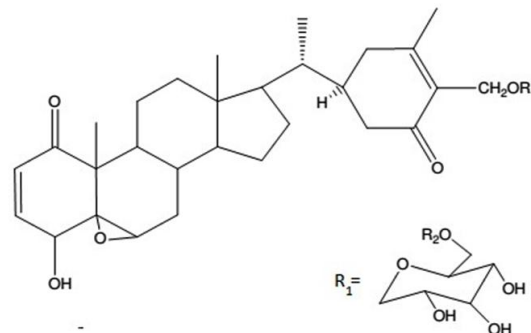


FIGURE 18: SHATAVARIN IV

hypolipidemic, antibacterial, cardiovascular protection, sexual behaviour, tolerance and dependence have also been studied. These results are very encouraging and indicate this herb should be studied more extensively to confirm these results and reveal other potential therapeutic effects²⁴.



Sitoindoside IX: $R_1 = D\text{-glucoside}$; $R_2 = H$
Sitoindoside X: $R_1 = D\text{-glucoside}$; $R_2 = \text{Palmitoyl}$

FIGURE 17: SITOINDOSIDE IX AND SITOINDOSIDE X

15. ***Asparagus racemosus***: Shatavari means the one who possesses a hundred husbands. It is considered both a general and female reproductive tonic. Shatavari is the main Ayurvedic rejuvenating tonic for the female, as is *Withania* for the male. Shatavari is however, used for sexual debility and infertility in both sexes. It is also used for menopausal symptoms and to increase lactation. It is a sweet and bitter herb which is said to be particularly balancing to Pitta Dosha (problem in bile secretion). Recent research has shown it to be an immunomodulator with antioxidant, healing and adaptogenic properties²⁵.

16. ***Aconitum taipaicum***: Aconite has long been used in the traditional medicine of Asia. In Ayurveda the herb is used to increase pitta (fire, bile) dosha and to enhance penetration. To investigate the chemical constituents of the roots of *Aconitum taipaicum*, silica gel column chromatography is used for the isolation and purification of compounds. A new norditerpenoid alkaloid is isolated and identified²⁶.

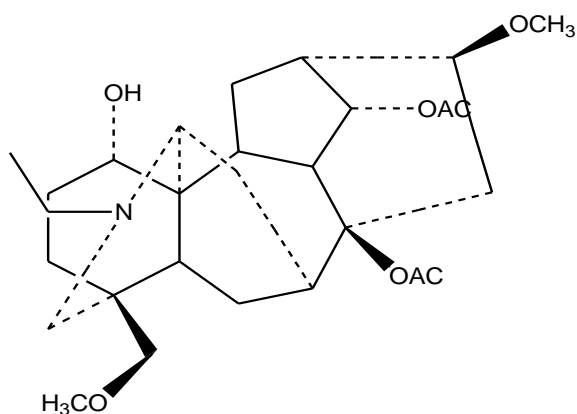


FIGURE 19: NORDITERPENOID

17. ***Delphinium grandiflorum***: All parts of the plant contain various diterpenoid alkaloids, typified by methyllycaconitine, and hence are very poisonous. Extracts of the plant have been used in herbal medicine in trace amounts. Lycoctonine is isolated and purified by various chromatographic methods and their structures were identified by spectral analysis²⁷.

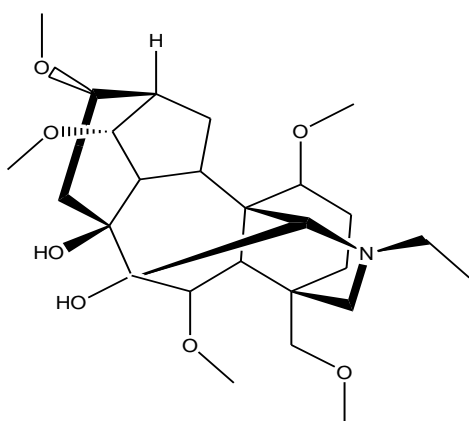


FIGURE 20: LYCOCTONINE

18. ***Angelica pubescens***: The dried root is commonly known in Chinese as Radix *Angelicae sinensis* or Chinese Angelica and is widely used in traditional Chinese medicine to treat *gynecological distrubi*, fatigue. Fresh roots of *Angelica pubescens* are extracted with

ethanol, the nodakenetin chemical constituent in the extract are isolated by column chromatography as macroporous absorption resin, and ODS etc. Their structures were confirmed by spectral analysis²⁸.

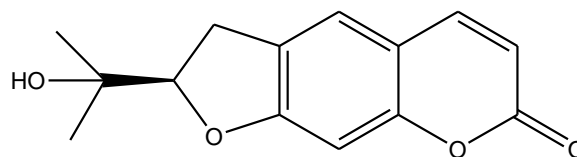


FIGURE 21: NODAKENETIN

19. ***Plumbagozeylanica***: The plumbagin constituent of the ethyl acetate-soluble portion in the 95% ethanol extract are isolated and purified by means of chromatography. Compounds are identified by their physical characteristics and spectral features. The plumbagin constituent revealed as potent immunomodulatory²⁹.

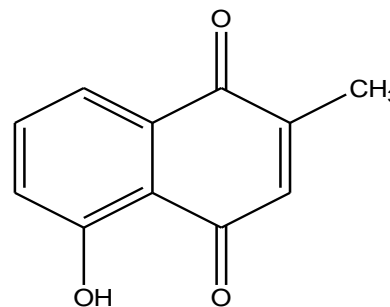


FIGURE 22: PLUMBAGIN

20. ***Stellera chamaejasme***: *Stellera chamaejasme*, belongs to the family of Thymelaeaceae, is a perennial grassland poisonous plant widely distributed in north and southwest China. The root of *S. chamaejasme* is a well-recognized traditional Chinese medicine for treatment of hydrothorax, ascites, carbuncles, sores, scrofula, cough, chronic tracheitis and skin diseases. Recently, studies also shows that *S. chamaejasme* had antitumor, antiviral, free radical scavenging, inhibition of leukemia cell growth and immunomodulatory activities.

Eudesmin chemical constituent is isolated by used various column chromatographies on silica gel and Reverse Phase C-18 column are employed for isolation and purification. Structures of compounds were elucidated by spectral analysis. Eudesmin exhibited immunomodulatory activity³⁰.

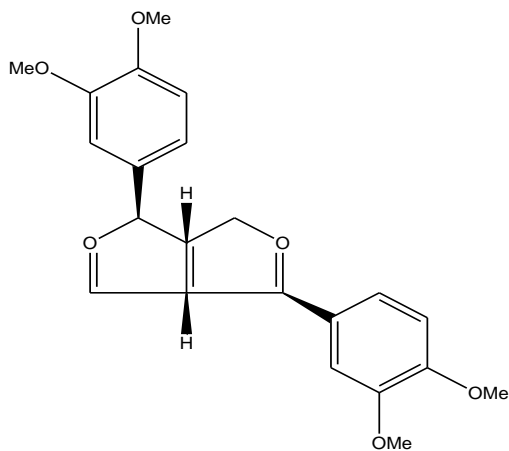


FIGURE 23: EUDESMIN

21. *Drosera peltata*: Droserone compound is separated by means of pH gradient extraction and chromatography on silica gel and the structures were determined by spectral analysis and physicochemical evidence³¹.

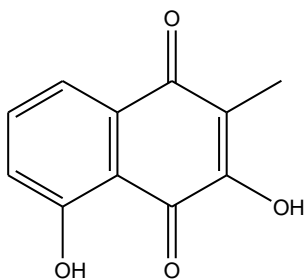


FIGURE 24: DROSERONE

22. *Hydrangeae dulcis* Folium: Investigated the immunomodulatory effects of antiallergic constituents from *Hydrangeae dulcis* Folium. Thunberginol A and hydrangenol significantly suppressed T lymphocyte proliferation induced by Concanavalin-A. Thunberginol A also suppressed B lymphocyte proliferation induced by lipopolysaccharide, but other constituents induced significant increases. These inhibitory effects of thunberginol-A on splenocyte proliferation seemed to contribute to the suppressive effect on type IV allergy³².

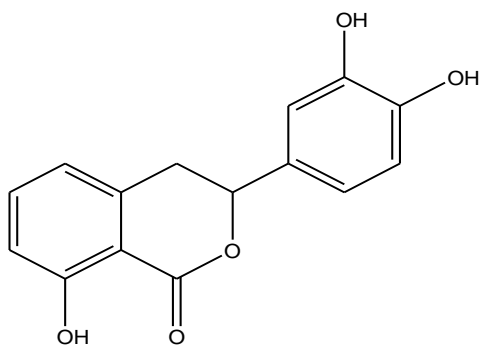


FIGURE 25: THUNBERGINOL A

23. *Dolichos lablab*: It is traditionally grown as a pulse crop for human consumption in south and Southeast Asia and eastern Africa. Flowers and immature pods are also used as a vegetable. From the glycoside mixture with adjuvant activity obtained from the hyacinth bean, the seeds of *Dolichos lablab*. The structures of Lablabosides A, B and C were determined on the basis of chemical and physicochemical evidence³³.

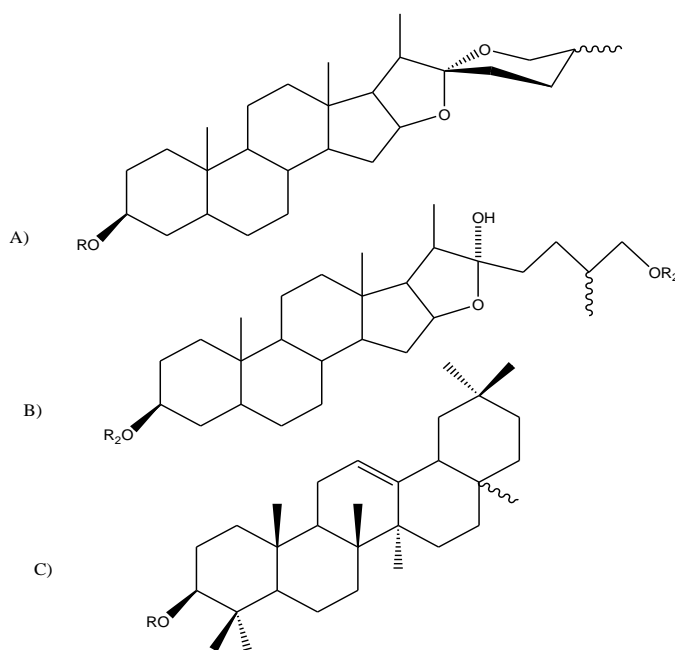


FIGURE 26: LABLABOSIDES A, B, AND C

24. *Phlomis young husbandii*: The active principles of plant *Phlomis young husbandii* are isolated and purified by various chromatographic techniques and physicochemical and spectral data were used to identify the structures of obtained compounds. Barlerin has been reported immunomodulatory³⁴.

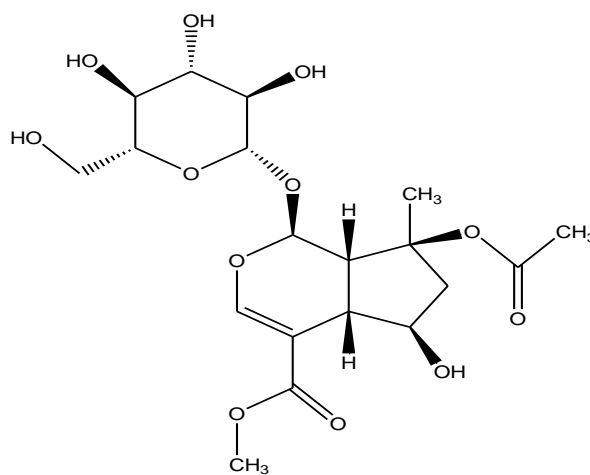


FIGURE 27: BARLERIN

25. **Rhizoma imperatae:** 5-Methoxy flavone is isolated and purified by silica gel column chromatography, Sephadex LH-20 and reversed-phase column chromatography. The structures were identified by the various spectroscopic data of ESI-MS, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$. The compounds were evaluated for anti-complementary & immunosuppressant³⁵.

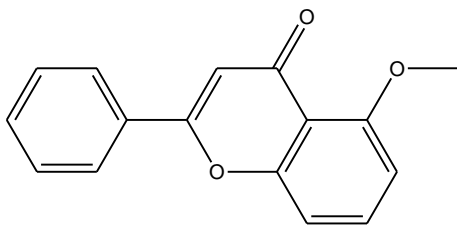


FIGURE 28: 5¹METHOXYFLAVONE

26. **Buddlejal biflora:** Ursolic acid constituent are isolated by column chromatography and their structures are elucidated by spectroscopic analyses³⁶.

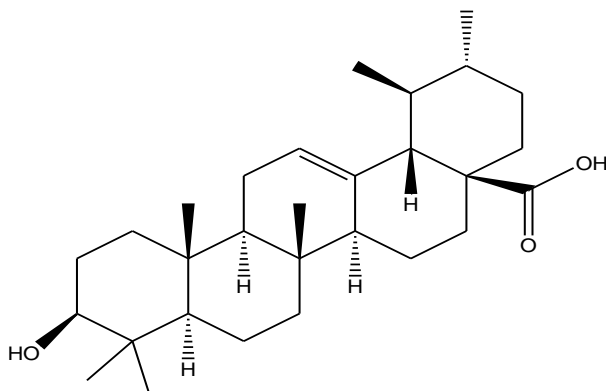


FIGURE 29: URSOLIC ACID

27. **Prunus mume:** Isorhamnetin compound is separated by silica gel. Their structures are identified and elucidated by spectral analysis and chemical methods. Isorhamnetin has been revealed as an Immunosuppressant³⁷.

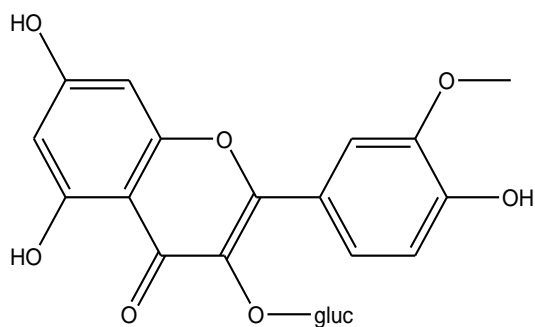


FIGURE 30: ISORHAMNETIN

28. **Prunella vulgaris:** Chemical constituents of *P. vulgaris* are isolated by using various kinds of chromatography. Their structures are identified on the basis of spectral analysis³⁸.

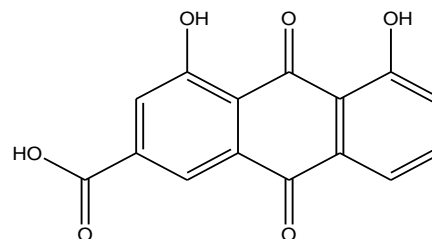


FIGURE 31: RHEIN

29. **Phlomis umbrosa:** The chemical constituent from the rhizome of *Phlomis umbrosa* chemical is isolated from the plant by using repeated silica gel and preparative HPLC chromatography³⁹.

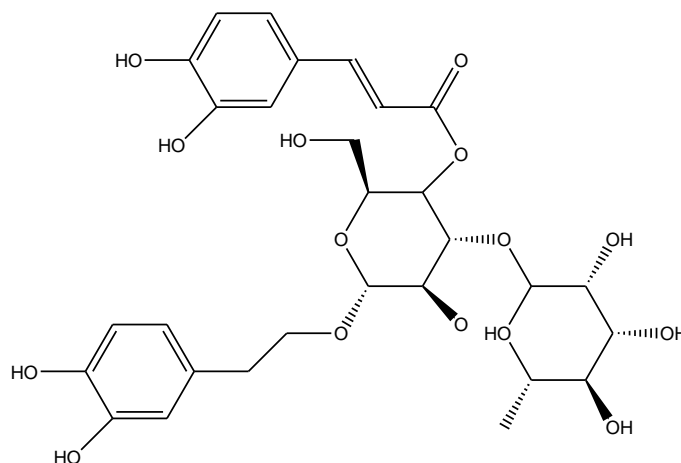


FIGURE 32: VERBASCOSIDE

30. **Polygonum aviculane:** Rosmarinic acid chemical constituent is significant as immunosuppressant isolated by silica gel column chromatography and preparative silica thin layer chromatography, and their structures are elucidated on the basis of physico-chemical evidences and spectroscopic analysis (IR, MS, ^1H and $^{13}\text{C-NMR}$)⁴⁰.

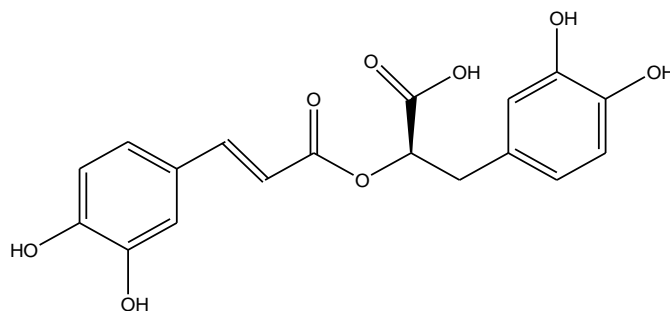


FIGURE 33: ROSMARINIC ACID

CONCLUSION: There are a growing number of natural agents and herbal products which are used for the enhancing of the body's response to disease. In recent times, a large number of drugs extracted from the plants are coming in to the market by isolation, purification and systematic clinical trials. Our review of immunomodulatory biomolecules serves the list of isolated and well-characterized moieties derived from plant origins. Readers are encouraged to consult the references provided for each molecule for more in-depth information for isolation techniques, pharmacology and structure-activity relationship (SAR) related studies.

Under the current scenario, it may be mentioned that immunomodulation using medicinal plants can provide an alternative to conventional chemotherapy for a variety of diseases, especially when host defence mechanism has to be activated under the conditions of impaired immune response or when a selective immunosuppression is desired in situations like autoimmune disorders. There is great potential for the discovery and isolation of more specific immunomodulatory molecules from plant origins to counteract the steep cost of synthetic molecules and their deleterious side effects.

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