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Systematic review of plant steroids as potential anti-inflammatory agents: Current status and future perspectives

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Abstract

Plant steroids are unique class of chemical compounds that are found throughout the animal and plant kingdom. Glucocorticoids are steroidal agents used to treat inflammatory disorders; on long term treatment it produces severe side effects. In order to overcome these undesirable consequences, investigations have to be made to identify novel bioactive phytochemicals with therapeutic potential with no or significantly reduced side effects. The objective of this review is to discuss medicinal plants having antiinflammatory activity and which contains chemical constituent such as solasodine, diosgenin, boswellic acid, glycyrrihizin, guggulsterones, withnolides or sarsasapogenin with structural similarity with glucocorticoids. These plant steroids classified in different classes based on their chemical structure, pharmacological activities and source from which they have been isolated. This review documents information on anti-inflammatory activity of plant containing steroids like chemical constituents such as *Trigonella foenum* graecum L. [Family: Fabaceae], *Solanum xanthocarpum* L. [Family: Solanaceae], *Boswellia serrata* Roxb. [Family: Burseraceae], *Glycyrrhiza glabra* L. [Family:Fabaceae], *Commiphora mukul* [family:Burseraceae], *Withania sominifera* [Family Solanaceae] by modern clinical and preclinical studies. There is an immense scope in investigation of the anti-inflammatory activity of plant steroids structurally close to glucocorticoids in various inflammatory conditions. Further investigations are needed to explore the more potent lead compounds with lesser side effects.

Keywords: Boswellic acid, Diosgenin, Glycyrrihizin, Guggulsterones, Sarsasapogenin, Solasodine, Withnolides.

Introduction

Inflammation, a process unpleasantly familiar to everyone, occurs in response to allergen, wounds, infection and auto-immune conditions.[1] Inflammation is characterized by heat, edema, pain, redness and alteration of function of affected tissue. Mounting of an inflammatory response is essential for survival. Uncontrolled and excessive inflammation results in a vast array of diseases that includes the highly prevalent conditions of allergic asthma, rheumatoid arthritis, inflammatory bowel diseases, Crohn's disease, allergic conjunctivitis, upper airway diseases such as allergic rhinitis and chronic sinusitis. There are two major groups of medications used in controlling inflammation: steroidal and non-steroidal antiinflammatory agents. Glucocorticoids [steroidal anti-inflammatory agents] are widely used for the suppression of inflammation in chronic inflammatory diseases, which are associated with increased expression of inflammatory genes by binding to glucocorticoid receptor on multiple signaling pathways.[2,3] However, they have adverse effects such as immunosuppression, hypertension, osteoporosis, and metabolic disturbances.[4] All these harmful properties contraindicate prolonged glucocorticoid therapy. Recently, some light has been thrown on steroid like compounds present in number of medicinal plants. The medicinal plants contain chemical constituents which chemically resembles in structure with steroids and modern clinical studies have supported their role as antiinflammatory agents.[5] This review discusses anti-inflammatory activity of some plants whose active principles may have applications for the treatment of inflammatory diseases and this compounds may become a lead compound of a class of antiinflammatory agents without systemic side effect and might thus hold great potential for therapeutic use.

Plant Steroids

The plant is a biosynthetic laboratory for multitude of compounds like alkaloids, glycosides, saponins, steroids, resins, tannins, flavanoids, sesquiterpene lactones which exert physiological and therapeutic effect. The compounds present in plant that are responsible for medicinal property are usually secondary metabolites which are having definite chemical structure.[6] Among all these compounds, steroids have the fundamental structure of four carbon rings called the steroid nucleus [Figure 1]. The addition of

different chemical groups at different positions on backbone leads to the formation of many different types of steroidal compounds including sex hormones progesterone and testosterone, the anti-inflammatory steroids like corticosteroids, cardiac steroids digoxin and digitoxin, animal steroid like cholesterol, steroidal glycosides.[7,8] Plant steroids synthesized by cyclisation of 2,3-epoxysqualene into cycloartenol are further metabolized owing to the enzymatic conversion to produce biologically active steroids.[5] We have reviewed distribution of the various classes of plant steroids in different plants and their pharmacological activities. Plant steroids classified in different classes based on their chemical structure, pharmacological activities and source from which they have been isolated [Table 1]. Plant steroids possess many interesting medicinal, pharmaceutical and agrochemical activities like anti-tumor, immunosuppressive, hepatoprotective, antibacterial, plant growth hormone regulator, sex hormone, antihelminthic, cytotoxic and cardiotonic activity.

Table: 1 Classification of plant steroids

Plant steroids	Chemistry	Pharmacological action	Example	References
Brassinosteroids	Cholestane with two vicinal diols and various substituents in position C-24.	Growth-promoting phytohormone	Brassinolide Catasterone	[9,7]
Bufadienolides	Polyhydroxy C-24 steroid with six membered pyrone ring at C-17.	Cardiotonic, increase the force of contraction of heart	Helleborin, Scillaridine, Physodine, Ouabain	[10]
Cardenolides	C-24 steroids but possess a five-membered lactone ring located at C-17	Cardiotonic, arrow poision, anti-bacterial	Digoxin, Digitoxin, Digitoxigenin	[11,12]
Cucurbitacins	Oxygenated C-30 triterpenoids with a methyl group at C-4	Antitumour, antimicrobial, hepatoprotective, antiinflammatory	Cucurbitacin D, cucurbitacin C Arvenin 1,	[13-16]
Ecdysteroids	C-27 steroids with a 7-en-6-one chromophore, and methyl group at C-24	protect plants against insects (molting hormones)	Ecdysone Oogonial	[17,18]
Sapogenins/ Steroid saponins	Oxygenated C-27 steroids with an hydroxyl group in C-3	Antifungal, hepatitis, sex hormone, antitusive	Spirostanol (diosgenin, sarsepogenin,glycyrrhetinic acid)	[19,20]
Steroidal alkaloids	steroidal skeleton with nitrogen atom integrated into a ring or as a substituent.	Antiinflammatory agent, sex hormone	Solasodine, Solasonine, Solamargine, Solanidine, guggulsterone	[21,22]
Withasteroids/ Withanolides	C-28 steroids with a δ-lactone, the side-chain linked to the steroid nucleus at 17α or 17ß.	Diarrhoea, rheumatic fever, anti-tumor, immunosuppressive, hepatoprotective,	Withaferin A, Iochromolide,Withanolide	[23-26]

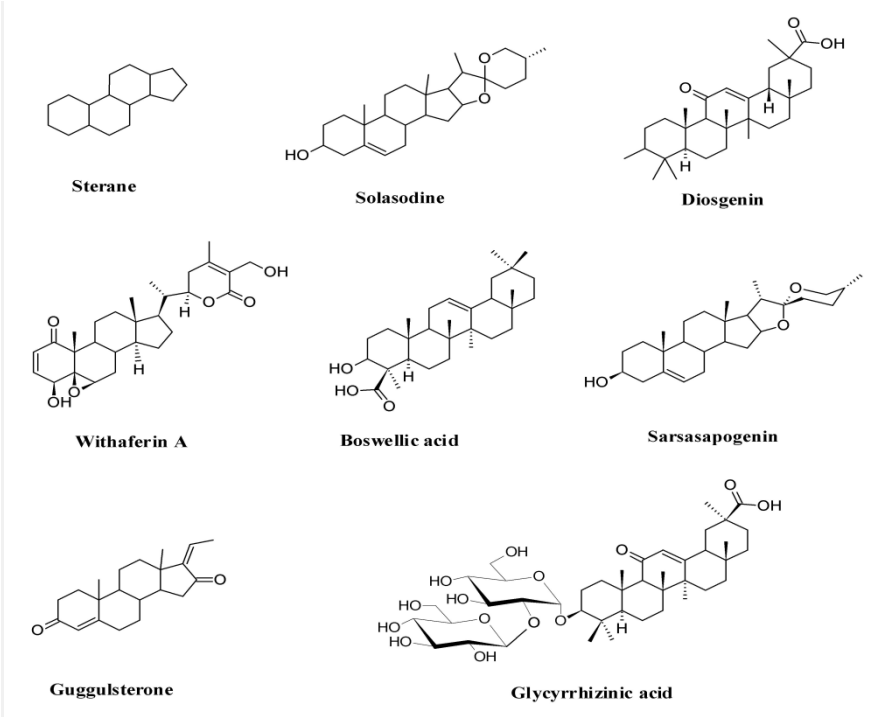

Figure 1: Representative steroidal structures of chemical constituents present in plants showing antiinflammatory activity.

Plants with steroidal constituents and antiinflammatory activity

Number of medicinal plants is known to exist in plant floras which are responsible for antiinflammatory activity. Recently some light has been thrown on steroid like compounds present in number of medicinal plants. Plants containing chemical constituents having steroidal structure like *Trigonella foenum graecum, Solanum xanthocarpum, Boswellia serrata, Glycyrrhiza glabra, Commiphora mukul, Withania somnifera, Smilax officinalis* proved to be anti-inflammatory agents by modern clinical and pre-clinical studies. Therefore, it is necessary to explore these plants to identify lead molecule for anti-inflammatory activity in various inflammatory diseases.

Trigonella foenum graecum

Fenugreek [*Trigonella foenum graecum]* contains diosgenin, a steroidal saponin [Figure 1]. Fenugreek has been reported to suppress inflammation and is has been investigated as a potential treatment for rheumatoid arthritis, especially the acute phase.[27,28] It also been reported that leaf extract of fenugreek possesses a potent anti-inflammatory activity that could inhibit the rat paw inflammation induced by formalin.[29] The chemokines, produces recruitment of lymphocytes leading to tissue damage that are expressed during the inflammatory process are inhibited by steroidal glycoside from *Trigonella foenum graecum*.[30]

Solanum xanthocarpum

Solanum xanthocarpum, belonging to family Solanaceae contains steroidal glycoalkaloids like Solasodine [Figure 1]. It is widely used by practitioners of the Siddha system of medicine in southern India to treat respiratory diseases.[31] *Solanum xanthocarpum* could relieve bronchospasm in asthmatic patients to a significant extent. This confirms the traditional claim for the usefulness of *Solanum xanthocarpum* in bronchial asthma.[32] Solanum species is a convenient source of 16-dehydropregnenolone acetate, which is a starting material for oral contraceptive and anti-inflammatory steroidal drugs. The Steroidal alkaloid fraction of *Solanum xanthocarpum* have been reported to protect sensitized mast cells from degranulation on antigen shock thus confirming the immuno-suppressive and membrane stabilizing effect like sodium chromoglycate.[33] Saponin isolated from *Solanum xanthocarpum* was found to produce protection to sensitized guinea pigs against histamine as well as antigen micro-aerosols. The protective effect of saponin was found to be associated with anti-allergic activity.[34]

Glycyrrhiza glabra

Glycyrrhetinic acid is isolated from *Glycyrrhiza glabra* which is a pentacyclic triterpenoid derivative of the beta-amyrin type [Figure 1]. Glycyrrhetinic acid reported to show a promising anti-inflammatory action, inhibit the release of histamine, serotonin, and bradykinin and lowers vascular permeability.[35,36] It is also reported to inhibit formalin-induced edema formation, granuloma weight and exudate amount.[37] It has been reported that glycyrrhetinic acid produce protection against lung inflammatory diseases by producing anti-inflammatory chemokines, IL-8 and eotaxin 1 from lung fibroblasts, by which neutrophils and eosinophils are strongly attracted during inflammation.[38] Glycyrrhetinic acid act similar to cortisone and useful for all sorts of inflammation. It has an anti-inflammatory or allergic action by the suppression of PAF production.[39] Glycyrrhetinic acid has a reputation as an excellent expectorant in the case of lung congestion and pharmacological studies indicate that it has sodium-retention, antidiuretic and anti-inflammatory actions.[40]

Boswellia serrata

Boswellia serrata contains boswellic acid as a one of chemical constituent. Boswellic acid is a triterpenoid having steroid like structure [Figure 1]. It has been reported that boswellic acid have effects on both the humoral and cell mediated immunity.[41] *Boswellia serrata* has been demonstrated to be a potent antiinflammatory drug in *in-vivo* animal models as well as in clinical studies.[42,43] Boswellic acid is specific, non-redox inhibitor of 5-lipoxygenase and hence inhibit leukotriene biosynthesis in dose dependent manner.[44] It also reported to decreases the pro-inflammatory 5-lipoxygenase products including 5-hydroxyeicosatetraenoic acid and leukotriene B4 levels, which being the active chemotactic factors causing increased vascular permeability. Hence, lesser number of the white blood cell recruited to the site of inflammation, thus dampening the inflammatory response, which leads to faster healing by treatment of boswellic acid.[45] Boswellic acid decreases polymorphonuclear leukocyte infiltration and migration, decreases primary antibody synthesis and causes almost total inhibition of classical complement pathway.[46-48] *In vitro* study of effect of boswellic acid on complement system shown marked inhibition on both classical and alternate pathway of complement system.[49]

Commiphora mukul

Commiphora mukul commonly known as, Guggul contains special group of steroidal compounds called guggulsterones [Figure 1], which ranges from E to Z. They are known as active principle of the plant and accounts for the use of that plant in arthritis.[50-52] *Commiphora mukul* possesses antiinflammatory property and its steroidal fraction considered to be active principle for this activity and the steroidal fraction is twice active as raw extract. HPLC analysis showed that steroidal fraction mainly contains guggulsterone Z which is responsible for antiinflammatory activity.[53]

Smilax officinalis

Smilax officinalis is medicinal plant that is known to contain steroid like compound saponin glycosides known as sarsasepogenin [Figure 1]. It possesses antiinflammatory activity comparable to conventional drugs like dexamethasone and indomethacin.[54] It also has been used as an anti-inflammatory agent in curing arthritis and rheumatism and experimental studies on crude extract of *smilax officinalis* is used as antirheumatic in Saudi traditional medicine.[55,56] It also useful in scaling skin condition such as psoriasis, which is an inflammatory skin disorder.[57]

Withania sominifera

Withania sominifera commonly known as Ashwagandha contain pharmacologically active compounds Withanolide [Figure 1], which is basically steroid lactone and various types have been isolated from plant.[58,59] In the Indian System of Medicine, W*ithania somnifera* finds application for numerous ailments including inflammation.[60] The plant also reported to have antistress, antioxidant, immunomodulatory, hemopoietic, and rejuvenating properties.[61,62] Antiinflammatory activity was seen in methanolic fractions of *Withania* aerial parts, comparable to hydrocortisone; probably the activity was attributed to presence of biologically active steroids in the plant, of which withaferin A is known to be a major component.[63,64]

Future research directions

Numerous reports have suggested that medicinal plants and their components mediate their effects by modulating several of therapeutic targets. However, herbal medicine requires rediscovery in the light of our current knowledge of allopathic medicine. The focus of this review is to elucidate the possible antiinflammatory activity of plant steroids on the basis of their chemical structure. Our understanding of the pathophysiology of inflammation has changed over the past decade. Although the precise basis for the development of inflammation in patients with inflammatory disorders is not fully defined, recent developments in experimental models have helped us to understand some basic mechanisms involved in inflammation. Inflammatory response is associated with many acute and chronic inflammatory diseases, including asthma, rheumatoid arthritis,

rhinitis, conjunctivitis, and multiple sclerosis. Glucocorticoids have been widely and successfully used in the treatment of inflammatory diseases. They exert their effects by different mechanism like interference of most inflammatory pathways and suppression of inflammation in a wide variety of diseases. Indeed they are often the most effective therapy available and their use is limited only by systemic side effects.[65] Inhaled glucocorticoids are highly lipophilic. They rapidly enter and bind to cytosolic receptors, this glucocorticoid-receptor complexes then move quickly into the nucleus and induce gene transcription results in therapeutic effect of glucocorticoids.[66] Unfortunately, the desired antiinflammatory and immunosuppressant effects are often accompanied by severe and partially reversible and non-reversible side effects such as suppression of the hypothalamic-pituitary-adrenal axis, diabetes mellitus, peptic ulcer, Cushing's syndrome, osteoporosis, skin atrophy, psychosis, glaucoma, and many others.[67] The use of glucocorticoids is limited by these side effects, and there is a major need for the development of compounds with the anti-inflammatory potency of standard glucocorticoids but with reduced side effects. The current review aimed at identification of molecule having more desired anti-inflammatory activity comparable to glucocorticoids. Plant steroids possess ideal structural chemistry for the antiinflammatory activity; therefore our attempt is to elucidate weather active constituents of these plants can be used in inflammatory conditions as glucocorticoids with minimal systemic side effects.

Conclusions

This review provide preclinical validation for the use of the active constituents of plants such as solasodine, diosgenin, boswellic acid, glycyrrihizin, guggulsterones, withnolides or sarsasapogenin in the management of inflammatory disorders such as asthma, rheumatoid arthritis, rhinitis, conjunctivitis, and multiple sclerosis. An extensive comparative study of plant steroids with synthetic glucocorticoids on the glucocorticoid receptor mediated side effects may offer insights or realistic possibilities to ascertain whether the plant steroids can really contribute to human well-being as effective antiinflammatory drugs. In view of their safety and efficacy, these herbs can be useful adjuvants to conventional therapeutic approaches to the management of inflammatory disorders.

Conflicts of interests

The author has no conflicts of interest to declare.

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