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Medicinal significance, pharmacological activities, and analytical aspects of solasodine: A concise report of current scientific literature

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ABSTRACT

Alkaloids are well known phytoconstituents for their diverse pharmacological properties. Alkaloids are found in all plant parts like roots, stems, leaves, flowers, fruits and seeds. Solasodine occurs as an aglycone part of glycoalkloids, which is a nitrogen analogue to sapogenins. Solanaceae family comprises of a number of plants with variety of natural products of medicinal significance mainly steroidal lactones, glycosides, alkaloids and flavanoids. It is a steroidal alkaloid based on a C27 cholestane skeleton. Literature survey reveals that solasodine has diuretic, anticancer, antifungal, cardiotonic, antispermatogenetic, antiandrogenic, immunomodulatory, antipyretic and various effects on central nervous system. Isolation and quantitative determination was achieved by several analytical techniques. Present review highlights the pharmacological activity of solasodine, with its analytical and tissue culture techniques, which may be helpful to the researchers to develop new molecules for the treatment of various disorders in the future.

1. Introduction

Genus *Solanum* (Solanaceae) is rich in steroidal glycoalkloids, an important group of plant secondary metabolites. These compounds are used as starting material for the synthesis of steroidal drugs. In majority of solanaceous plants, solasodine occurs as aglycone part of glycoalkloids, which is a nitrogen analogue of sapogenins. Solasodine (C27 cholestane skeleton) (Figure 1) can be readily converted to 16-dehydropregnenolone, a key intermediate in the synthesis of steroidal drugs such as progesterone and cortisone[1]. Solasodine is obtained by chemical or microbial hydrolysis of solamargine. It is a potential moiety to be used as a substitute for diosgenin in the semi-synthetic production of steroidal hormones in pharmaceuticals. Therefore, steroidal glycoalkaloid from Solanaceae plants have become increasingly important as the starting material for the production of steroidal hormones[2]. Various species of *Solanum* like *Solanum khasianum* (*S. khasianum*), *Solanum lyratum* (*S. lyratum*), *Solanum xanthocarpum* (*S. xanthocarpum*), *Solanum nigrum* (*S. nigrum*), *Solanum gracile* (*S. gracile*), *Solanum tuberosum* (*S. tuberosum*), *Solanum laciniatum* (*S. laciniatum*) are being extensively used for the treatment of various ailments like asthma, liver diseases and inflammation in the traditional system of medicine. Glycoalkaloids are nitrogen containing secondary metabolites found in plants belonging to Solanaceae and Liliaceae family. More then 100 different types of glycoalkaloids have been isolated from more than 350 *Solanum* species[3].

Plant such as *S. tuberosum* contains glycoalkaloids as the main phytoconstituents along with chaconine and solanine. Glycoalkaloids concentration depends upon species as well as part of plant such as leaf, root, flower and stem. The amount of glycoalkaloids increases due to injury and exposure to light[4]. Glycoalkaloids play key role in defense mechanism of plants against invading microbes. Glycoalkaloids have antimicrobial, insecticidal and fungicidal properties which account for their activity

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against several insects, pests and herbivores. Small quantities of glycoalkaloids are known to improve flavour, but at levels above 200 mg/kg these compounds may impart the bitter taste[5]. Glycoalkaloids exhibited toxicity in living organism at higher concentrations mainly because of their anticholinesterase activity and disruption of cell membranes coupled with some other effects including teratogenicity, embryotoxicity and genotoxicity. Glycoalkaloids toxicity not only depends upon its amount but also on the type of glycoalkaloids[5,6]. Symptoms of glycoalkaloid poisoning includes abdominal pain, vomiting and diarrhea[4]. In contrast, some glycoalkaloids can also have positive effects on plant growth and human diet. They may provide plant protection from damage by insects and fungi, and are reported to elicit anti-inflammatory and anticancer effects in humans[6].

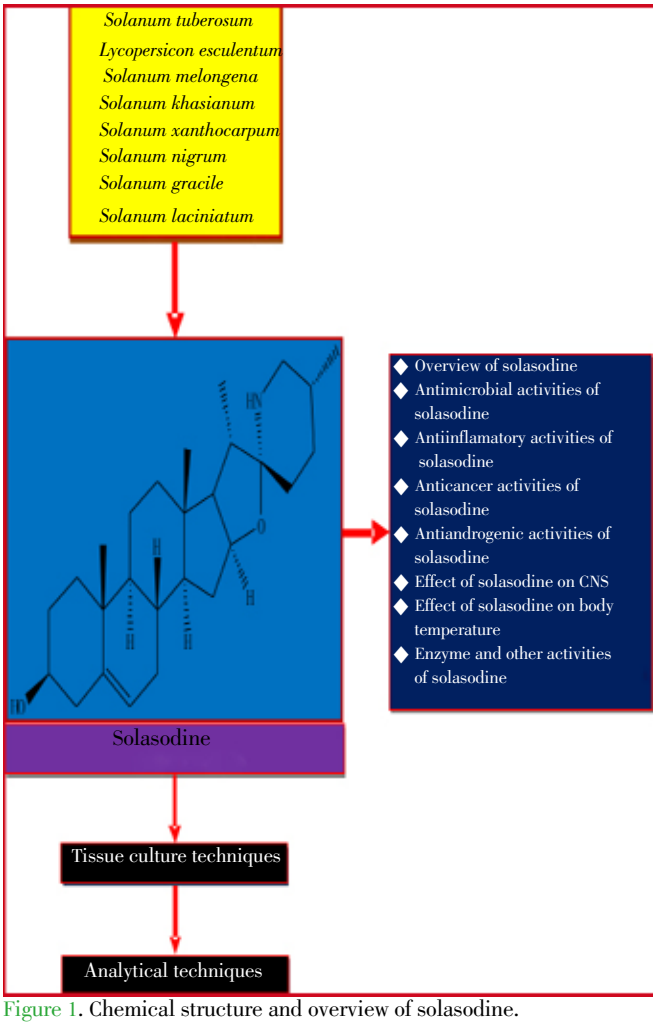

Figure 1. Chemical structure and overview of solasodine.

The steroidal glycoalkaloids are the family of secondary metabolites produced by Solanaceous plants, including potato, tomato and eggplant[7]. Steroidal glycoalkaloids are nitrogen containing compounds which have the C27 skeleton of cholestane and are the product of steroidal biosynthesis pathway[5]. Synthesis of steroidal alkaloids involves glycosylation of the alkamine steroidal skeleton (aglycone) at C-3b to form steroidal glycoalkaloids[8]. Steroidal glycoalkaloids have antimicrobial, insecticidal and fungicidal properties which provide resistance against several insect pests and herbivores[9]. Solasodine is an important phytochemical of Solanaceae plant including *S. lyratum* Thunberg, which is commonly used in the traditional Chinese medicines in China, Taiwan and Korea. It has been used to regulate immune function and treat allergic responses for generations[10]. Further, it is also used to treat cancer of liver, lung, esophagus and blood, as well as tumours and warts[11-14].

A number of analytical methods like high performance thin-layer chromatography, high-performance liquid chromatography, capillary electrophoresis, gas chromatography have been developed and used for the determination of solasodine from plant materials[15]. Solanaceae family comprises a number of plants widely known for the presence of variety of natural products of medicinal significance mainly steroidal lactones, glycosides, alkaloids and flavanoids. *S. nigrum* L. a member of the Solanaceae, has a wide range of medicinal application[16]. Literature survey reveals that solasodine has wide range of pharmacological activity such as diuretic, anticancer, antifungal, hepatoprotective, cardiotonic, antispermatogenetic, antiandrogenic, immunomodulatory, antishock, antipyretic and central nervous system related activity[17]. Because of pharmaceutical importance, its isolation and quantitative determination was achieved by several researchers using an array of analytical techniques like spectroscopy, thin layer chromatography, immunostaining usingmonoclonal antibodies, gas chromatography and high performance liquid chromatography and most recently, using non aqueous capillary electrophoresis[1].

2. Pharmacological activities of solasodine

2.1. Antimicrobial activities of solasodine

Antifungal activity of Solasodine was investigated using Saccharomyces cerevisiae GL7 and *Prototheca wickerhamii* (*P. wickerhamii*). Solasodine directly or indirectly interfered with the synthesis and function of genetic substance in *S. cerevisiae* and *P. wickerhamii*[18]. In another study, solasodine was tested as growth inhibitors of *Trypanosoma cruzi* in LIT medium using ketoconazole as a positive control[19]. Evaluation of solasodine on larvae of the red flour beetle, *Tribolium castaneum*, was investigated. Larval growth was inhibited on diets containing solasodin as one component and found that solasodine is inactive[20]. Effect of aqueous suspensions of glycoalkaloids including solasodine on herpes simplex virus Type I in tissue culture was also investigated and found to be inhibited by prior incubation with solasodine[21].

2.2. Anti-inflammatory and antinociceptive activities of solasodine

Solasodine isolated from *Solanum trilobatum* has been examined for anti-inflammatory activity in acute and chronic inflammatory animal models. Solasodine exerted statistically significant and dose-dependent anti-inflammatory activity in carrageenan-induced rat paw oedema. Topical application of solasodine significantly inhibited the ear inflammation induced by multiple applications of tetradecanoyl-phorbol 13-acetate[22]. Solasodine, isolated from the roots of *Solanum trilobatum* Linn., was tested for antinociceptive activity using several experimental murine models, viz. the writhing, formalin, and hot plate tests. Solasodine exhibited a significant and dose-dependent decrease in the nociception induced by an intraperitoneal injection of acetic acid. Furthermore, the alkaloid produced a significant increase in the reaction time in the hot plate test[23]. LPS-stimulated macrophage as a model of inflammation was used to investigate the anti-inflammatory effects of tomatidine and solasodine whereby it was found that tomatidine exhibited a more potent anti-inflammatory effect than solasodine in the tested concentration[24]. The anti-inflammatory effect of solasodine was evaluated in another study and was found to elicit significant anti-inflammatory activity[25].

2.3. Anticancer activities of solasodine

Natural molecules structurally close to diosgenin including solasodine have been tested for their biological activities on human 1547 osteosarcoma cells[26]. In an another study, solasodine has been utilized to determine the role of carbohydrate moiety in the mechanism of apoptosis. The C3 side chain of solasodine contains 4′Rha-Glc-Rha2′, 4′Rha-Glc and H, respectively[27]. In another study, solasodine showed significant cytotoxic effects against human PLC/PRF/5 cells *in vitro*[28].

2.4. Antiandrogenic activities of solasodine

Oral administration of solasodine isolated from the berries of the *S. xanthocarpum* to dogs significantly decreased the epithelial cell height of cauda epididymides. The cells became atrophic and the lumen was devoid of spermatozoa. Castration followed by the adminstration of solasodine further reduced the epithelial cell height in comparison to castrated controls. Total protein, sialic acid, glycogen and acid phosphatase activities were significantly reduced in solasodine treated cauda epididymides. These results suggests the anti-androgenic potency of solasodine[29]. Effect of solasodine derived from solasonine in eggplants was evaluated for their effects on liver weight increase in non-pregnant and pregnant mice and on fecundity in pregnant mice fed for 14 d. In non-pregnant mice, observed ratios of liver weights to body weights were found to be significantly greater in solasodine treated group than the control[30]. Solasodine obtained from the *S. xanthocarpum* berries was administered to Rhesus monkeys for 150 d to evaluate its effect on testicular cell population dynamics. Solasodine brings about an interference with spermiogenesis at the stage XII of late spermatids. No significant change was found in the population of spermatogonia/primary and secondary spermatocytes. The production of immature and mature Leydig cells was decreased. The testicular protein, sialic acid and glycogen contents were depleted following solasodine treatments to rhesus monkeys[31]. Chronic administration of solasodine caused testicular lesions resulting in a severe impairment of spermatogenic elements. The epididymides were devoid of spermatozoa. Total protein, sialic acid and glycogen contents of the testis and epididymis were reduced significantly whereas the testicular cholesterol was elevated. Solasodine administration in dogs definitely rendered the male infertile as evidenced by the absence of sperms in the cauda epididymis and ductus deferens[32].

2.5. Effect of solasodine on CNS

Effect of solasodine to promote neurogenesis *in vitro* and *in vivo* in mouse embryonic teratocarcinoma P19 cells was investigated. *In vivo*, a 2-week infusion of solasodine into the left ventricle of the rat brain followed by a 3-week washout resulted in a significant increase in bromodeoxyuridine uptake by cells of the ependymal layer, subventricular zone, and cortex that co-localized with doublecortin immunostaining, demonstrating the proliferative and differentiating properties of solasodine on neuronal progenitors[33]. An anticonvulsant and CNS depressant effect of solasodine isolated from *S. sisymbriifolium* using several experimental models was investigated. The results showed that intraperitoneal injection of solasodine significantly delayed latency of hind limb tonic extensor (HLTE) phase in the PCT-induced convulsions. In the MES model, solasodine significantly reduced duration of HLTE in a dose-dependent manner. Prior treatment of solasodine significantly potentiated thiopental-provoked sleep in a dose-dependent manner[34].

2.6. Effect of solasodine on body temperature

Effect of solasodine from *S. laciniatum* Ait., was studied on normal and pyretic body temperature of rats and mice. In rats, single dosage depressed the normal temperature for 24 h. With larger dosages or longer treatment the effect could not be intensified and tolerance was also not observed. In mice, the temperature decrease and effect was reproducible by repeated treatment[35].

2.7. Enzyme and other activities of solasodine

UDP-glucose-dependent glucosylation of solasodine and diosgenin by a soluble, partially purified enzyme fraction from eggplant leaves is affected in a markedly

different way by some phospholipids. The glucosylation of solasodine is unaffected or slightly stimulated. Significant inhibition of diosgenin glucoside synthesis and stimulation of solasodine glucosylation was found only with PC molecular species containing fatty acids with chain length of 12-18 carbon atoms[36]. A series of 31 side-chain-modified analogues of steroidal alkaloids solasodine was studied as inhibitors of (S)-adenosyl-L-methionine:delta 24(25)-sterol methyl transferase (SMT) enzyme activity from Saccharomyces cerevisiae[37]. Solasodine, a steroid present in the mucilaginous exotesta of the seed in *S. viarum* Dunal is a major source of steroidal raw material. Evidence for the site of solasodine synthesis was sought through reciprocal grafts involving steroid-bearing *S. viarum* (both diploid and autotetraploid) and steroid-free, edible *S. melongena* L. (brinjal). The results indicate that the synthesis of solasodine is scion-specific[38]. The increase in relative liver weight induced by solanidine and solasodine is a reversible adaptive response. These findings and the apparent effects of structure on biological activity should serve as a guide for the removal of the most toxic compounds from plant foods[39]. Impregnated CD2 transgenic mice, which contain multiple copies of a lambda gt10lacZ construct integrated into the genome of each cell, were given a predetermined estimated maximum tolerated dose of several steroidal alkaloids including solasodine[40]. Embryos of two species of fish Japanese rice fish, medaka (Oryzius latipes) and the rainbow trout (Oncorhynchus mykiss) were also evaluated for their suitability as model systems for steroidal alkaloid toxicity including solasodine[41]. Effect of several potato glycoalkaloids and aglycones in the frog embryo teratogenesis assay--Xenopus (FETAX) with and without metabolic activation by Aroclor 1254-induced rat liver microsomes was investigated. The aglycones solasodine was found to be less toxic than the glycosides[42]. Isolation of the glycosyltransferases that catalyze the transfer of sugar molecules to steroidal compounds will help to clarify the mechanisms that produce diverse saponins and control their activities in plants. Gene expression analysis revealed that the accumulation of SaGT4A transcripts showed a unique response to wounding stress indicating the involvement of SaGT4A in plant defense system[43].

3. Tissue culture techniques

Single chain fragment-variable (scFv) enhanced solasodine glycoside accumulation in *S. khasianum* hairy root cultures transformed by the ScFv solamargine (As)-scFv gene. The expressed anti-solamargine scFv protein could be useful for determination of total solasodine glycoside content in plant samples by ELISA[44]. In another study using genetic transformation of Agrobacterium rhizogenes and liquid culture, induction and culture conditions for *S. nigrum* L. var. pauciflorum Liou hairy roots and its solasodine production and consumption changes of N resource and calcium in the medium during liquid culture were investigated. The hairy roots could produce medicinal secondary metabolites solasodine and the amount of solasodine in the hairy root cultures[45]. The role of plant growth regulators and various concentrations of NaCl during *in vitro* production of solasodine were studied. Solasodine content was maximum in regenerative callus when grown on medium added with 150 mM NaCl; followed by *in vitro* raised leaf of microshoot[46]. Leaf and hypocotyl explants of 15 d old aseptically grown seedlings of *S. laciniatum* were cultured on MS medium supplemented with NAA and kinetin for callus initiation. The solasodine content in callus culture was maximum after 30 d of incubation. Organogenesis promoted solasodine accumulation in the cultures. Regenerated shoots yielded higher solasodine content than undifferentiated as well as organogenic callus[47].

Hairy root cultures of *Physalis minima* L. were developed using *Agrobacterium rhizogenes*, strain ATCC 15834 mediated transformation and grown in half strength of Murashige and Skoog medium containing sucrose. Media supplementation with naphthalenacetic acid and benzyladenine increased solasodine glycoside which was 20 times higher than that in the native root[48]. Hairy root clones of *S. aviculare* which were transgenic for hmgr typically grew faster than those which did not contain extra copies of this gene and also accumulated up to 4.2 times more solasodine when grown under dark, but not light conditions[49]. The effect of a fungal elicitor obtained from *Alternaria* sp. on growth and solasodine production by free and alginate-entrapped cells of *S. eleagnifolium* Cav. was studied. The solasodine production increased in suspension cultures and in entrapped cells. In both cases, about 50%-60% of intracellular solasodine was released into the medium[50]. Procedures were developed for 'self-immobilisation' of *S. aviculare* cells to eliminate the need for artificial immobilisation supports. Most of the product was stored in the aggregates to reach a maximum concentration of 0.3% dry weight; this is between 1.5 and 10 times the levels reported for suspended cells under similar conditions. A substantial amount of solasodine was produced after growth ceased. A simple air-driven bioreactor was tested for culture of the aggregates; solasodine yields were comparable to those measured in shake flasks[51].

4. Analytical methods to identify and isolate solasodine

The mass fragmentations of solasodine were studied using the Orbitrap Fourier transform (FT) mass spectrometer[52]. The development of sequential injection analysis with lab-at-valve semi-automated system on-line liquid-liquid extraction is demonstrated for spectrophotometric determination of solasodine in various *Solanum* species fruits. The method performances, including reproducibility, linearity, sensitivity and accuracy were also evaluated[53]. Quantitative estimation of solasodine was carried out using a novel HPTLC method, which is validated for its recovery and precession. The proposed HPTLC method showed a

good linear relationship in the concentration ranges[46]. A prechromatographic derivatization of solasodine was done by forming an ion-pair complex of the heterocyclic nitrogen using the acidic dye methyl orange and acetate buffer of pH 4.7. Detection could be made in the visible range at 530 nm in this method. The method has good reproducibility and was found to be suitable for estimation of solasodine[54]. Concomitant extraction and hydrolysis of *Solanum* steroidal glycoalkaloids in a two-phase system containing an aqueous mineral acid and an organic water immiscible solvent, and having a boiling point under 100 °C is described. Application of the process to fruits, leaves, and tissue cultures of *Solanum khasianum* using a two-phase aqueous hydrochloric acid-toluene system, proved to be very suitable for continuous production of pure solasodine which is a valuable raw steroid for the preparation of steroidal drugs[55].

Nonaqueous capillary electrophoresis coupled to UV detection is described for the separation and determination of steroidal alkaloids. After optimization of electrophoretic parameters, including the electrolyte nature and the organic solvent composition, a reliable separation of solasodine and solanidine was achieved in a methanol-acetonitrile (20:80, v/v) mixture containing 25 mM ammonium acetate and 1 M acetic acid[56]. GC-MS analysis of hydrolysates of purified extracts of the test *Solanum* species revealed that solasodine was a principal or sole aglycone of the alkaloid glycosides in each of the test species except *S. tuberosum*[57]. Glycoalkaloids were extracted from plant material of *S. Sodomaeum* L. High-performance liquid chromatographic studies indicated that several glycoalkaloids were present. Mass spectral analyses showed that all the glycoalkaloids contained solasodine[58]. A potentiometric nonaqueous titration procedure was developed for the quantitative determination of solasodine in fruits of the *Solanum* species[59]. In another study solasodine has been isolated from *S. platanifolium*[60]. The fresh bulbs of *Lilium brownii* var. colchesteri were found to contain five steroidal saponins including solasodine along with several phenolic constituents[61]. High-pressure liquid chromatography was used to separate the steroidal alkaloids including solasodine. The method was used to prepare crystalline solanidine from a crude mixture of aglycones obtained from *S. chacoense*, and to separate radioactive solanidine from extracts of potato plants fed with (4-C) cholesterol[62]. A combined derivatization method for gas chromatographic-mass spectrometric (GC-MS) analysis of steroidal glycoalkaloid including solasodine was developed using both trimethylsilylation and pentafluoropropionylation[63].

5. Conclusion

Herbal medicines are used for the treatment of various disorders and gaining popularity both in developing and developed countries due to its fewer side effects. Many traditional medicines are derived from medicinal plants, minerals and organic matter. According to the World Health Organization (WHO) more than 21 000 plants are used for medicinal purposes in the world[64-66]. Due to presence of diverse phytoconstituents, many medicinal plants have excellent pharmacological actions and could lead to the development of new classes of possibly safer agents for the treatment of disease. Plants have been used as a source of drugs, and many of the currently available drugs have been derived directly or indirectly from them[67].

Several medicinal plants have been used as dietary supplements and in the treatment of numerous diseases without proper knowledge of their mode of action. Only a few herbs and bioactive chemical moiety have attracted the interest of scientists and have been put forward for investigations. Therefore, there is a need of more well-documented clinical trials and more laboratory work to justify their pharmacological actions and toxicity for safe and effective treatment[68,69]. Solasodine may have all these actions and could be used for the treatment of various complications in the near future. The present review comprises updated information regarding pharmacological activity and analytical techniques of solasodine. Moreover tissue culture techniques on solasodine have been also discussed. The overall information provided in the present review article may prove as an important source of information to the researchers in the research area of natural product.

Conflict of interest

The authors declare they have no conflict of interests.

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