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An update of therapeutic potential and bioanalytical aspects of steroidal glycoalkaloid (solanidine)

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ABSTRACT

Alkaloids are one of the main secondary metabolite of original plants and known for their beneficial health aspects. Chemically alkaloids are basic compounds and found in various parts of plants like fruits, flowers, seeds, stems, roots and leaves. Alkaloids also play an important role in the defense mechanism of plants against herbivorous animals and pathogens as they are bitter in test and also have toxicity in the animal and human being. Alkaloids have numerous medicinal, pharmacological, medical and veterinary importances. There are different types of alkaloid which is present in the nature and we can categorize into different classes on the basis of their chemical structure. Steroidal glycoalkaloids are N based compounds having C_{27} basic skeleton and mainly found in Solanaceae family. Potato, tomato and eggplant are some of the best examples of the steroidal glycoalkaloids and so far, more than 100 different types of glycoalkaloids have been isolated from *Solanum* species. Biologically glycoalkaloids have insecticidal, antimicrobial and fungicidal properties and are found to be active against various pests, insects and herbivores animals. Solanidine is a steroidal aglycon of potato glycoalkaloids having $C_{27}H_{43}NO$ chemical structure. Glycoalkaloids are basically used as a precursor moiety for the synthesis of various pharmacologically active hormones and solanidine is one of the best examples of these chemical classes. Unlike many other steroids, solanidine has N containing heterocyclic unit and also has less toxicity than its glycosidal derivatives. Medicinally solanidine have antimicrobial, anticancer, anti-hyperlipidaemic, anti-inflammatory, anti-paracites and cardiac activities. In this review, we have discussed medicinal properties, important sources, pharmacological activities and analytical aspects of solanidine. From the above mentioned facts, we can conclude that solanidine have very bright future as it could be used as a leading precursor molecule for the synthesis of various steroidal drugs.

1. Introduction

Alkaloids are one of main phytochemical ingredient of plants and related species in the form of secondary metabolite and have various medicinal effects. There are various sources of the alkaloids in the nature as they are present in almost all types of plants, their parts and related species. The parts of plants and their derived product such as seeds, fruits, stems, roots, flowers, latex and leaves are the best examples of alkaloids[1]. Alkaloids have various roles in the plants such as they play important role in the defense mechanism against pests, animals and pathogens[2]. In the nature, there are so many examples of the alkaloidal class drugs which are having toxic reaction in the human being and other animals due to their poisonous nature. Some alkaloids of original plants cause serious injury and illness in the human being and in some cases, it could be lethal[3,4]. There are various types of alkaloids which are available from the nature and we can categorize them on the basis of the biogenetic pathway, chemical class and pharmacological activities and steroidal glycoalkaloids (SGAs) are one of alkaloids which are found in the plants belonging to Solanaceae family like eggplant, tomato and potato. SGAs are N based compounds and have cholestane moiety and produced by glycosylation of the alkamine steroidal skeleton at C-3b position. There are various important pharmacological activities of SGAs such as insecticidal, antimicrobial and fungicidal. SGAs play an important role in the defense system of the various species and also provide resistance

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against several pests, insect and herbivores animal[1].

2. An introduction of glycoalkaloids

Glycoalkaloids are secondary metabolites having N moiety in their basic chemical structure, and present in the various plants and related species. So far, more than 100 different types of glycoalkaloids have been isolated from various *Solanum* species. Concentration of active constituents in the plants varies and mainly depends upon the climatic variation and soil content. Moreover, glycoalkaloidal contents mainly depend upon the plants species and their different parts. In the plants, glycoalkaloids protect themselves against various types of microbes and act as a key intermediate in their defense mechanism. So far, various pharmacological activities of glycoalkaloids have been mentioned in the various literature and these are antimicrobial, insecticidal and fungicidal. We are very much familiar about the toxicity of the alkaloidal class chemical as in the early days, they are used as an arrow poison for hunting purpose. The toxicity of glycoalkaloidal compounds is mainly due to their disruption of potential of cell membranes and anticholinesterase activity. Further glycoalkaloidal class chemical also has various severe toxicities like teratogenicity, embryotoxicity and genotoxicity[1]. *Solanum* species contain various types of SGAs which are mainly responsible for their toxicity in human being and other species. Chaconine and solanine are the other examples of the naturally occurring SGAs, which are mainly found in the sprouts, vines and green potato tuber[5]. SGAs are naturally present in the various species of Solanaceae family, which protect plants from insect and other pests, however higher concentration could affect the quality of drugs. There are various factors such as diseases, insect attack, light, genetic and stress factors, maturity, storage temperatures and mechanical damage which can affect the quality and quantity of the glycoalkaloids. Further, it was also found that the small immature tubers are generally containing higher amount of glycoalkaloids compared to the fully grown[6]. The basic mechanism behind the toxicity of the glycoalkaloidal compounds is nothing but inhibition of acetylcholinesterase enzymes and disruption of phospholipid membranes[7]. Regarding to the toxicity of glycoalkaloidal compounds, we can observe two common symptoms related to neurological effects and depression of the central nervous system[8]. During the biological testing of these toxic substances, we need lots of animal and other organism but now, we are using *Escherichia coli* generated recombinant antibodies to solanidine glycoalkaloids for the same purpose[9]. From the various literatures database of the last two decades, we can also conclude that these compounds are also having antimicrobial, antinociceptive, anticancer and anti-inflammatory activities[10].

3. The biosynthesis of glycoalkaloidal compounds

For the synthesis of the different types of the phytochemistry, plants need different basic metabolic pathway and for the biosynthesis of steroidal compounds, they need acetate-mevalonate pathway[11,12]. However, still we don't know the complete synthetic pathway from cholesterol to solanidine[13]. There are various types of the alkaloidal compounds in the potato, but potato glycoalkaloids are structurally similar compounds which have same aglycone moiety solanidine but there are different carbohydrate moiet in these structures. The biosynthesis of α-solanine is catalysed by the enzyme uridine diphosphate (UDP)-galactose: solanidine galactosyltransferase from UDP-galactose and solanidine. The biosynthesis of c-chaconine from UDP-glucose and solanidine is catalysed by the enzyme UDP-glucose: solanidine glucosyltransferase. The biosynthesis of both α-solanine and α-chaconine is catalysed by the enzyme UDP-rhamnose: β-SGA rhamnosyltransferase[6]. There is the presence of the low concentrations of solanidine in potatoes, which might be because of the rapidly glycosylation and this probably occurs through separate glucosyl, galactosyl and rhamnosyl-transferase[14].

4. An overview of potatoes alkaloid

SGAs are one of the main secondary metabolite of *Solanum* species plants. These compounds are basically used as a precursor moiety or material for the synthesis of various steroidal class drugs, therefore nowadays there is increasing interest in the SGA. There are the different sources of SGA in the nature but various species of *Solanum* are one of the best sources. *Solanum khasianum, Solanum lyratum* (*S. lyratum*)*, Solanum xanthocarpum, Solanum nigrum, Solanum gracile, Solanum tuberosum* (*S. tuberosum*) and *Solanum laciniatum* are some of the species which contain significant concentration of the steroidal glycoalkloids[1]. Potato tubers contain good amount of steroidal triglycosides and α-solanine and α-chaconine accounted more than 95% of the total glycoalkaloidal content. Further α-solanine and α-chaconine have the same basic aglycone moiety *i.e.* solanidine with different sugar moieties[15]. In the worldwide, people know potatoes it's not because of their medicinal properties but as a food material. Potatoes are the major source of energy and protein for human being and more than 350 million tons of potatoes are produced in the world. The primary compounds present in the commercial cultivated potatoes are α-solanine and α-chaconine and both are triglycosides of solanidine[16]. There are some other uses of potatoes and their derived products that potato protein concentrate (PPC) is among one of them which is mainly used as a protein supplement for fish, pigs and broilers[17].

5. An overview of solanidine

Solanidine is a steroidal aglycon of potato glycoalkaloids which is an important precursor for the synthesis of pharmacologically active hormones[18]. Solanidine is basically obtained after the hydrolysis of solqnine and solanine and has the molecular formula C_{27} H_{43} NO and molecular weight of 397.62[19]. Unlike other steroidal drugs, solanidine also has the nitrogen moiety in their basic heterocyclic chemical structure[20]. For the production of pure glycoalkaloids, proteins were firstly separated from the starch during the refining process and then protein fraction is subjected to a number of refining processes for the separation of glycoalkaloids. Solanidine could be converted into an industrially attractive way to 16-dehydropregnenolone acetate, which is the key intermediate for the industrial synthesis of progesterone and cortisone derivatives[21]. Solanidine is found in the nature in the form of aglycone and their glycoside derivatives, but it has also been demonstrated that solanidine is much less toxic than its glycoside derivatives[22]. From the literature sources, we have found that α-solanidine has different biological activities including antihyperlipidemic[23].

6. Pharmacological activities of solanidine

6.1. Effect of solanidine on microorganism

Trypanothione reductase (TryR) is a key enzyme in the metabolism of *Trypanosoma cruzi*. A molecular docking procedure using a Lamarckian Genetic Algorithm was implemented to examine the protein-ligand binding interactions of inhibitors. A set of natural alkaloids including solasodine was assessed computationally against *Trypanosoma cruzi* TryR and the study confirms that (22R,25S)-solanidine, and (22R,25R)-solasodine could be the TryR inhibitors[24]. Antifungal effects of α-solanine, α-chaconine, solanidine and caffeic acid, alone or in combined form were tested and results suggested that the sterol pattern of fungi was related to their resistance to potato glycoalkaloids[25].

6.2. Effect of solanidine on skins pruritus

Single-blind prospective study on patients responding to a solanaceae-free diet on scar pruritus were performed to cross check the believe that alkaloids in solanaceae might be the actual pruritogens. Solanidine and tomatidine have been applied to each scar and investigated whether they have pruritogenic effect or not. A total of 18 patients were responded for developing pruritus and the triggering aglycone was coincided with that prevailing in the pruritogenic food. So from these data it can conclude that solanaceae aglycones are directly involved in the pathogenesis of scar pruritus[26].

6.3. Effect of solanidine on cardiovascular system

Two solanidine-type veratrum alkaloids (VAs) isolated from *Veratrum taliense* exhibited strong cardiovascular toxicity. A pathophysiological study indicated that these VAs blocked sodium channels NaV1.3–1.5 and exhibited the strongest ability to inhibit NaV1.5, which is specifically expressed in cardiac tissue and plays an essential role in cardiac physiological function. This result revealed that VAs exert their cardiovascular toxicity via the NaV1.5 channel. The effects of VAs on NaV1.3 and NaV1.4 may be related to their analgesic effect and skeletal muscle toxicity, respectively[27].

6.4. Effect of solanidine on inflammation

The potato glycoalkaloids, α-solanine, α-chaconine and solanidine, along with potato peel extracts were investigated for their anti-inflammatory effects using stimulated Jurkat and macrophage models with concanavalin A and lipopolysaccaride. Solanidine and α-chaconine significantly reduced interleukin-2 and interleukin-8 productions in concanavalin A-induced Jurkat cells. In lipopolysaccaride-stimulated raw macrophages, α-solanine, solanidine and two potato peel extracts significantly reduced induced NO production[28].

6.5. Effect of solanidine on cancer

Effect of exposure of cancer cells to glycoalkaloids produced by potatoes, eggplants and tomatoes or their hydrolysis products and the aglycones solanidine, solasodine and tomatidine inhibits the growth of the cells in culture[29]. A set of solanidine analogs with antiproliferative properties were synthetized from pregnenolone acetate and six of these compounds elicited the accumulation of a hypodiploid population of HeLa cells, indicating their apoptosis-inducing character, and another one caused cell cycle arrested at the G2/M phase[30]. Antiproliferative effects of three synthetic solanidine analogs on HL-60 human leukemia cells were characterized. The three compounds exerted similar cytostatic effects and the most effective one was selected for further investigations. Further antiproliferative effect of the test compound on the non-cancerous human lung fibroblast cell line (MRC-5) was significantly weaker than that on the leukemia cells[31].

6.6. Effect of solanidine on plant metabolites

Concentrations of the primary or secondary metabolite of any plant mainly depends upon the natural climate, composition of the soil and the genetic variation of the plant. In the present study, allelic sequences spanning coding regions of four candidate genes were obtained from two potato species differing in their SGAs contents and composition. Knowledge of the genetic factors influencing SGAs contents in potato could be used for the development of the better pest resistance species[32]. Natural variation in five candidate genes of the SGA metabolic pathway and whole-genome single nucleotide polymorphism genotyping were studied in six wild cultivated potato species with contrasting levels of SGAs[33]. Quantitative RT-PCR was used to estimate relative steady-state transcript levels of SGAs-related genes in leaves of the transgenic plants compared to nontransgenic plants[34].

6.7. Effect of solanidine on general metabolic pathway

Effect of diets containing soybean meal and PPC in 22 females and 22 males on two reproductive cycles was investigated. The SGAs content in PPC was found to be 2316 mg/kg. Result showed that diets containing potato protein did not affect pregnancy rate, the number and conformation of neonates and number of pups weaned but it reduces their body weight. From these observation, we can conclude that giving moderate amounts of high-glycoalkaloid PPC does not harm reproductive cycle and performance and does not induce any malformation in pups but inhibits the foetal and postnatal growth rate[35].

6.8. Effect of solanidine on plant tissue culture techniques

Plant tissue culture techniques are one of the best techniques for the production of the secondary metabolite outside the plant by using plant tissue. There are the various types of drugs available from the markets which are mainly obtained through plant tissue culture techniques. Plant cell and tissue culture of *S. lyratum* are able to produce various steroidal alkaloids which could be useful as a precursor molecule for the production of various supplements and drugs. Effect of the different phytohormones such as auxin-type phytohormones including indole-3-acetic acid, naphthaleneacetic acid, 2,4-dichlorophenoxyacetic acid and indole-3-butyric acid on the cell and callus cultures of *S. lyratum* for the production of solanidine, solanine and solasodine were studied and found that 2,4-dichlorophenoxyacetic acid induced calli from roots of the *S. lyratum* produces significant amount of solanine production[36].

6.9. Poisoning cases of solanidine in human being

SGAs showed various types of toxicity and poisoning cases in human being and other animal species and microorganism. Here, an interesting cases of poisoning of susumber berries was presented. A 54-year-old woman admitted in the emergency department showed emesis, speech, vision, gait changes and diffuse myalgias. The physical examination demonstrated a lucid mental status, intact, opsoclonus, miosis, dysmetria, severe dysarthria, mild extremity, weakness, tenderness and inability to ambulate. Moreover, solasonine and solanidine were also found to be present in the serum[37]. In another patient case study, ingestion of *Veratrum viride* showed vomiting, bradycardia, nausea and hypotension. Moreover, we also found that patient's serum contained digoxin. Further, gas chromatography (GC)/ mass spectrometry (MS) techniques also identified several steroidal alkaloid in the *Veratrum viride* samples and among all the components, solanidine was also present in the human being[38].

7. Analytical methods for the detection of solanidine

For the determination of active constituents in the plants and other species, there are the various analytical methods available from the literature. Like other phytoconstituents, we have different traditional and modern analytical methods for α-solanidine. Thin layer chromatography, colorimetry, GC, immunoassays and high-performance liquid chromatography are the methods for the determination of α-solanidine in different samples. Current methodology for the analysis of potato glycoalkaloids includes extraction, separation and purification of samples before measurements[16]. An ultra-high performance liquid chromatographic-tandem mass spectrometry method was developed for the quantification of potato steroidal alkaloids *i.e.* solanidine, α-solanine, α-chaconine and demissidine. Three different columns *i.e.* hydrophilic lipophilic interaction, ethylene bridged hybrid C18, and amide chromatographic columns were tested and developed for the quantification of various glycoalkaloids and result showed that the ethylene bridged hybrid C18 column was found to be the most effective in term of separation and sensitivity[39]. Pressurized liquid extraction was found to be more effective compared to other conventional solid-liquid extraction process to get higher yield of glycoalkaloids in potato peels[40]. Some time, production of secondary metabolites in the plants occurs because of the microbial and pathogens attack. The ability of ambient mass spectrometry was used to determine the plant metabolic glycoalkaloids in response to pathogen invasion. The variation of the phytoconstituents in the sprouted potatoes infected by the phytopathogen *Pythium ultimum* was measured through imprint imaging desorption electrospray ionization mass spectrometry and found that intensity of solanidine was increased after 8 days from the inoculation[41]. For the extraction of the plant active constituents and different metabolites, we use different types of the solvents depending on the nature of the component extracted. Solid liquid extraction and ultrasound assisted extraction using methanol were used for the extraction of the steroidal alkaloids from the potato peel and optimized the conditions for ultrasound assisted extraction of α-chaconine, α-solanine, demissidine and solanidine. From the result, it was found that ultrasound assisted extraction process I was better for steroidal alkaloids from potato peel waste compared to the other one[42]. Centrifugal partition chromatography techniques were used for the preparative isolation of solanidine from fresh *S. tuberosum*. Hydrolysis of the glycoalkaloids from the skin and sprouts of *S. tuberosum* was first developed and then its isolation was carried out by the centrifugal partition chromatography. The purity of the isolated solanidine was found to be more than 98% and thus this techniques will be used for the extraction of the very high purity of the solanidine of *S. tuberosum* biomass in large quantities[43]. GC/MS with Fourier transform ion cyclotron resonance/mass spectrometry and bioinformatics were used for the study of interactions in the potato sprout-*Rhizoctonia solani* pathosystem and fluctuations[44]. Foliar alkaloid analysis and GC-MS analysis of potato genotype *i.e. Solanum chacoense* Bitt were performed and showed that in addition to leptinidine, solanidine and acetyl-leptinidine, there is the presence of another new aglycone in the potato[45]. Phytochemical investigation of the fresh bulbs of *Fritillaria anhuiensis* resulted in the isolation of a known 22S-solanidine-type steroidal alkaloids discovered from nature[46]. Abiotic and microbial degradation of the compounds in groundwater was investigated and found that degradation was primarily microbial and the glycoalkaloids were degraded within 21–42 days[47]. Liquid chromatography-electrospray ionization time-of-flight mass spectrometry technique was used for determination and quantification of potato glycoalkaloids and their metabolites in aqueous soil extracts[48]. Two SGAs (α-chanonine and β 2-chanonine) were isolated from *Solanum distichum* and the structures of the isolated compounds were studied by 1D and 2D nuclear magnetic resonance techniques and fast atom bombardment mass spectrometry analysis[49]. GC, high performance liquid chromatography, thin layer chromatography and GC/MS are the techniques which are mainly used for the determination of the nature and content of several *Solanum* species widely used in potato breeding and hybridization programs[50].

8. Discussion

Food material and herbal medicine are the two most important aspects of the healthy human life. For the better healthcare, we got various medicines from the natural sources. As we are dependent upon the plants, animal and other macro- or micro-organism for the daily need, they are also providing us some of the best medicine for the treatment of various critical diseases such as cancer and diabetes *etc*. There is the increasing rate in the herbal medicine sector, as most of the populations from the developing country to the developed countries rely on the herbal medicine for their primary healthcare and the general needs. Further popularity of the herbal medicine in the modern system of medicine is also due to it's easily availability and fewer side effects. Some of the most important drugs of the modern system of medicine were derived from plants, microorganism, mineral and marine sources[51]. Phytoconstituents play an important role in the health care system due to the health promoting activity so it is our duty to check and validate its potential in terms of the quality, safety and efficacy before it is consumed. For the quality check, we use both instrumental and non- instrumental techniques and in the last few decades, high performance liquid chromatography and high performance thin layer chromatography technique have gained much popularity. For the past few years, there has been an exponential growth in the field of herbal medicine as many medicines were derived mainly from medicinal plants, minerals and organic matter. The World Health Organization has provided the data of 21 000 medicinal plants, which are used throughout the world due to its beneficial effect[52,53]. SGAs naturally occurred secondary metabolites that are found in plants, foods, potatoes and tomatoes. The most common potato species *i.e. S. tuberosum* contains α-solanine and α-chaconine (glycoalkaloids). However, wild-type potatoes contain less amount of glycoalkaloids[50]. In the present review, we have collected all the information of SGAs including the most important one *i.e.* solanidine regarding its pharmacological activities, general usage, medicinal importance and analytical techniques for quantification of solanidine in various samples. In the future, this review will be helpful to the researcher, analyst, scientist and medical person to know the hidden potential of solanidine. Moreover, these data will be also used to enhance our knowledge and understand steroidal alkaloids and their contribution to the plants, human and other microorganism.

Conflict of interest statement

We declare that we have no conflict of interest.

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