

Review

THE TOXIC SAPONIN - SOLANINE AND ITS PROPERTIES

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Received: 10.03.2025 / Revised: 21.04.2025 / Accepted: 21.04.2025 / Published online: 06.08.2025

ABSTRACT

α -Solanine is a steroidal glycoalkaloid naturally occurring in plants of the *Solanaceae* family, such as potatoes, tomatoes, and eggplants. Due to its toxicity, it serves a protective function by deterring herbivores. High concentrations of this compound are found in the green parts of potato tubers. Due to the widespread occurrence of α -solanine in nature, it is often unknowingly consumed by a large number of people. Ingesting this compound in large amounts can lead to poisoning, which manifests as gastrointestinal and neurological symptoms. In extreme cases, excessive solanine consumption can be fatal. Despite documented cases of poisoning, α -solanine exhibits potentially beneficial pharmacological properties. This compound is being investigated for its anticancer and anti-inflammatory effects, as well as its potential use in the treatment of osteoarthritis and neurodegenerative diseases. However, its toxicity significantly limits its possible applications as a therapeutic agent. The objective of this study was to provide an overview of the biological properties of solanine and its potential applications in medical sciences.

KEYWORDS: solanine, phytochemical, *Solanum tuberosum*, toxicity, biological properties.

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1. α -Solanine

1.1. α -Solanine and Its Properties

α -Solanine belongs to a class of steroidal alkaloid saponins in which the aglycone moiety is steroid. This compound consists of a trissaccharide solatriose (D-glucose, D-galactose, L-rhamnose) attached to the aglycone part, solanidine. α -Solanine's molecular formula is $C_{45}H_{73}NO_{15}$ and it has a molecular weight of 868.1 g/mol. It is relatively poorly soluble in water [1]. In its pure form, it appears as a white crystalline solid with a melting point of 271-273°C and a bitter taste [2]. In cells it is mostly located in cytoplasm as well as the membranes. It is also found extracellularly [3-5].

Three types of solanine can be distinguished: α -solanine, β -solanine, and γ -solanine. Among these, α -solanine is the most common and will be the primary focus of this review. α -Solanine composes of solanidine and three sugar molecules: D-glucose, D-galactose, L-rhamnose (Fig. 1). β -Solanine has different molecular linkage than α -solanine and γ -solanine is the rarest out of them all, having a different arrangement of sugar molecules [6,7].

α -Solanine was isolated for the first time from European black nightshade (*Solanum nigrum*) in 1820. Over the years, it has had multiple uses such as a natural pesticide thanks to its toxicity as well as in some traditional medicines [8,9].

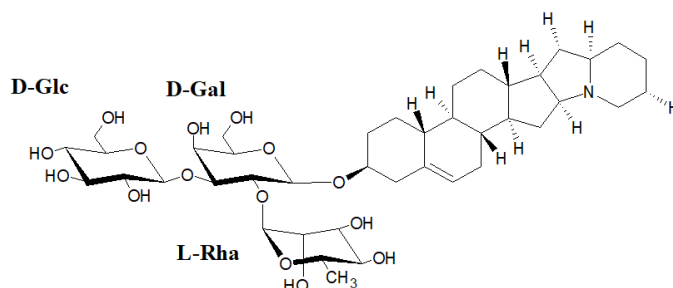


Fig. 1. Structure of α -solanine (D-Glc, D-glucose; D-Gal, D-galactose; L-Rha, L-rhamnose).

1.2. α -Solanine in Plants

This substance is naturally occurring primarily in the green parts of plants, such as leaves, stems or unripe fruits and it has been found in various plants such as tomatoes, eggplants and green peppers in trace amounts (Table 1). α -Solanine along with α -chaconine is found in plants of the *Solanaceae* family. α -Solanine production in plants is connected with their natural defense mechanisms serving to deter insects and other animals, causing symptoms such as nausea, diarrhoea, vomiting, heart arrhythmia and many others [7].

However, it has been most strongly associated with potatoes (*Solanum tuberosum* L.), where it accumulates in the skin and below it. It is responsible for the toxicity and teratogenicity of sprouting potatoes. The α -solanine level in potatoes varies depending on factors such as temperature or light. Green coloring under the skin of potatoes after they were exposed to light is caused by the accumulation of chlorophyll, which by itself is harmless, however, it indicates a heightened α -solanine build-up. This, along with a bitter taste, are possible indicators of toxicity and consumers are strongly advised against consumption of potatoes exhibiting those symptoms [2,10].

There has been a study that looked into accumulation of α -solanine in the soil. This topic requires further investigation, and limited information is currently available. However, there are some residual traces of α -solanine in all tested environments even at the end of the experiment. Nevertheless, the risk of α -solanine leaking into groundwater appears to be unlikely [11].

Table 1. Glycoalkaloid concentration (including α -solanine) in selected plants from the *Solanaceae* family.

Species	Part of the plant	Concentration [mg/g]	
<i>S. tuberosum</i>	Sprouts	2.0 - 7.3	[12]
	Flowers	2.15 - 5.0	
	Leaves	0.23 - 1.0	
	Stems	0.023 - 0.033	
	Roots	0.18 - 0.4	
	Tuber	0.01 - 0.15	
	Tuber peel	0.15 - 1.068	
<i>S. dulcamara</i>	Leaves	0.0008 - 0.004	[13]
<i>S. melongena</i>	Fruit skin	0.107	[14]
	Fruit flesh	0.626	

1.3. Biosynthesis of α -Solanine

As mentioned before, biosynthesis of α -solanine in plants is stimulated when stems or other parts of the plants are exposed to light, although the process is still not fully understood. The whole process occurs as a defense mechanism to prevent the exposed parts from being eaten by animals [15]. Biosynthesis of α -solanine begins with cholesterol and it involves many enzymes, some of which have yet to be identified. First, cholesterol is converted into the steroidal alkaloid solanidine through a series of chemical reactions, including hydroxylation, followed by oxidation into an aldehyde intermediate, and then transamination. It is suggested that the cyclization of solanidine occurs as a next step. The final part of the

biosynthesis of α -solanine involves glycosylation of solanidine (Fig. 2) [3-5].

2. α -Solanine Toxicity

2.1. Intoxication and Cases

Although α -solanine is widespread in nature, poisoning from it is rare but well-documented. This rarity is largely attributed to general public awareness of the potential toxicity of the green parts of certain plants, particularly potatoes [10,13].

Symptoms observed in humans include gastrointestinal distress (nausea, diarrhea, vomiting, and cramps) as well as neurological effects associated with the anticholinergic toxidrome (headaches, delirium, convulsions, pupil dilation and fever) [10,13-17]. Observations in poisoned animals have shown that α -solanine, in high doses, causes weight loss due to reduced food intake, and a significant increase in water consumption [21]. α -Solanine also reduces spontaneous locomotor activity in animals and increases sleep duration [18]. In some rare cases, intoxication can be fatal.

Pharmacokinetic studies of α -solanine have shown that it is only partially absorbed in the gastrointestinal tract. Some molecules can be hydrolyzed into the more readily absorbable aglycone, solanidine. The maximum tolerated dose of α -solanine in humans is 1 mg/kg body weight, whereas acute doses of 2-6 mg/kg body weight may be lethal. For comparison, most commercially available potatoes contain low concentrations of α -solanine, ranging from 4 to 10 mg per 100 g of dry weight [7].

During the first 12 hours after ingestion, a rapid increase in the concentration of α -solanine and its metabolites is observed in the liver, kidneys, spleen, and adipose tissue. After 72 hours, the highest levels of α -solanine are found in the kidneys [18]. Blood tests have shown a slight increase in sodium and urea levels, as well as a significant increase in glucose and creatinine concentrations (approximately twofold or even threefold). Conversely, albumin levels and alkaline phosphatase activity are reduced [21].

The most common sources of α -solanine poisoning are *Solanum tuberosum* (potatoes), particularly green tubers, sprouts, and potato berries. According to official statistics, α -solanine poisoning from potatoes has resulted in at least 30 deaths and over 2,000 cases of varying severity [22]. Plants contain a mixture of glycoalkaloids, including α -solanine, which makes it important to consider that poisonings may arise from the combined effects of several compounds rather than a single substance [20,21]. No cases of poisoning from the pure substance have been reported in the literature.

The first documented fatal case dates back to 1859 and describes a 14-year-old girl who consumed unripe "potatoe [sic] berries." [25]. She experienced severe abdominal pain and vomiting. Despite being treated with ipecacuanha and cathartics, her condition deteriorated, and she died three days after ingestion. Another fatal case from 1928, involving two victims, similarly indicated severe gastrointestinal symptoms - epigastric pain, nausea, diarrhea, and vomiting. Symptoms such as apathy, indifference, and exhaustion were noted, although fever

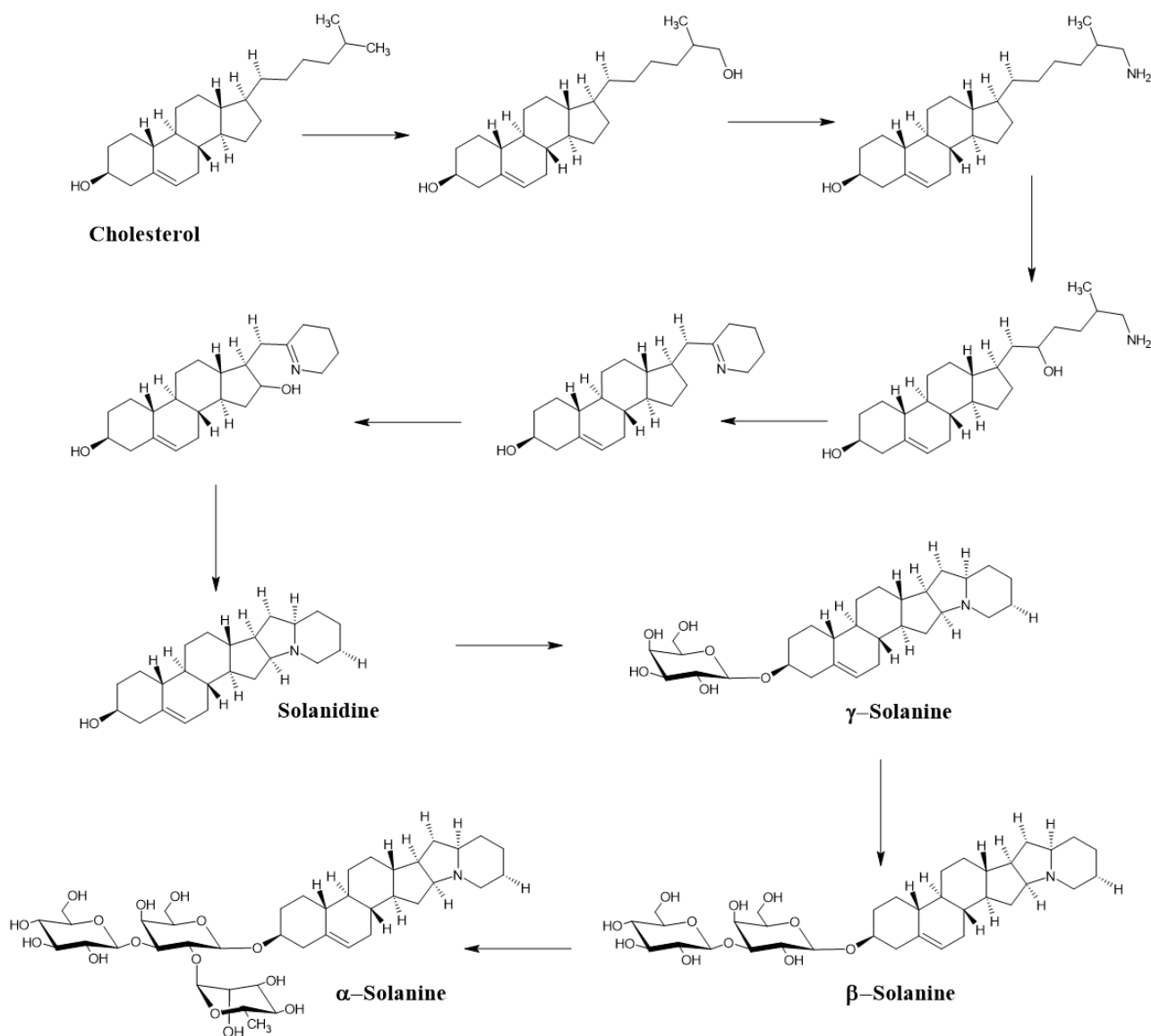


Fig 2. Biosynthesis of α-solanine.

was absent [26]. Cases of mass *Solanum* sp. poisoning have also been recorded: 56 soldiers in Berlin and 673 soldiers in Strasbourg in 1899, as well as 61 people in Glasgow in 1917 [16].

There have also been isolated cases of poisoning from other *Solanum* spp. rich in α-solanine. A case of a 4-year-old girl who ingested berries of *S. dulcamara* (woody nightshade) was reported. She exhibited symptoms consistent with the anticholinergic toxidrome. Treatment involved the administration of activated charcoal with sorbitol and physostigmine, an acetylcholinesterase inhibitor [28]. Another case involved a 75-year-old man who suffered α-solanine poisoning after consuming juice from *S. elaeagnifolium* (velvet nightshade) berries. He was diagnosed with anticholinergic toxidrome and was treated only with oxygen supplementation. The patient was discharged after 4 days without any neurological complications [29].

Kees et al. described a case of a Labrador Retriever puppy that consumed *S. dulcamara* berries. The animal exhibited severe poisoning symptoms, including strong

muscle tremors, fever, tachycardia, and tachypnea. Seizures were alleviated with phenobarbital and propofol, while diazepam and midazolam proved ineffective [30].

Other *Solanum* spp. such as *S. elaeagnifolium* (silverleaf nightshade) and *S. dimidiatum* (western horse nettle), grow in pastures and meadows, where they can be consumed by cattle or horses. Symptoms occurring in these animals include gastrointestinal irritation, abdominal pain, anorexia, excessive salivation, and urinary retention. Norman et al. describe a case of horses that, in addition to *Solanum* spp. poisoning, had previously been treated with ivermectin paste. *Solanum* toxins likely enhanced ivermectin absorption and reduced its excretion in the mammalian body, resulting in its toxic effects on the central nervous system [31].

Gastric necrosis, renal infarcts and hemorrhages of the small intestine were also observed in hamsters that were fed with potato sprout material. Baker et al. concluded that the cause of death was gastrointestinal damage (septicemia and fluid accumulation in the small

intestine), rather than changes in acetylcholinesterase levels, which were found to be too minor to account for the observed toxicity [32].

2.2. Mechanism of Toxic Action

α -Solanine has two primary mechanisms of toxic action.

The first mechanism affects the nervous system. First of all, solanine and its aglycone, solanidine, act as inhibitors of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). This property has been repeatedly confirmed by *in vitro* [33-35] and *in silico* studies [36], as well as *in vivo* experiments [14,34]. It has also been noted that cholinesterase activity is more significantly reduced in plasma than in erythrocytes [17]. Furthermore, plasma AChE activity does not exhibit dose-dependent inhibition, unlike brain AChE activity [37]. However, some studies have found no significant difference in AChE or BuChE activity in plasma or brain, even after exposure to high doses of solanine [18,35]. At the same time, the symptoms affecting the nervous system are clearly consistent with an anticholinergic toxidrome. This may suggest the ability to block cholinergic receptors. Therefore, solanine may act in a dual manner on the nervous system [13,16,17,23,25,27,28].

The second mechanism of α -solanine toxicity involves its effect on the integrity of phospholipid membrane. Solanine has been observed to decrease mitochondrial membrane potential, thereby impairing the function of the entire organelle [39-41]. The proposed mechanism involves the insertion of the aglycone part into the bilayer, followed by interactions between the sugar moieties of glycoalkaloids, leading to the formation of a stable complex. These processes disrupt membrane structure and function [42]. Potassium channels open, allowing Ca^{2+} ions to escape from mitochondria into the cytoplasm, ultimately causing cell damage [37,40]. This results in reduced cell proliferation [41] or even cell lysis [44]. *In vitro* studies have confirmed that solanine induces hemolysis of erythrocytes [45-47]. Additionally, it disrupts sodium ion transport across cell membranes [48].

Moreover, solanine has been found to stimulate hepatic ornithine decarboxylase activity in rats. This phenomenon may serve as a biomarker for glycoalkaloid toxicity in food [49].

2.3. Teratogenic Properties

Solanine also exhibits teratogenic properties. Its teratogenicity primarily affects the central nervous system, cardiovascular system, and gastrointestinal tract [50-53]. Higher doses may lead to embryonic death [48,49,51]. Solanine has also been observed to affect the maturation of oocytes [55], the development of somites, and the cleavage rate of morulae [54]. A particularly interesting case in primates involved the development of hydrocephalus in offspring of *Macaca mulatta* [56]. In *Drosophila melanogaster*, decreased body size and deformed wings were observed [57].

3. Biological Properties

3.1. Anticancer Activity

Several *in vitro* and *in vivo* studies have demonstrated the anticancer properties of α -solanine. The substance's

anti-tumor effects have been confirmed in cancer cells from various organs, including the lungs, esophagus, liver, pancreas, colon, prostate, skin (melanoma), bone marrow (acute lymphocytic leukemia), endometrium, and breasts tissue [55,56].

Due to its toxicity, it is necessary to adjust the dosage to avoid side effects. A study in mice showed that doses above 20 mg/kg cause liver and kidney damage, while a dose of 5 mg/kg proved to be safe. A spontaneous mammary tumor was implanted subcutaneously, and tumor growth was slowed in the α -solanine-treated group compared to mice treated with a placebo and those treated with doxycycline and cyclophosphamide [60].

The anticancer effects of α -solanine were tested on human colorectal cancer cell lines (RKO and HCT-116). In a scratch assay, Transwell invasion assay, and cell adhesion assay, α -solanine was shown to inhibit tumor cell proliferation, induce apoptosis, and reduce metastatic potential. It also reduced the expression of metalloproteinases. In a mouse model implanted with RKO cells, α -solanine inhibited tumor cell proliferation and increased the percentage of apoptotic cells [61].

A study on lung cancer cell lines (A549 and PC-9) demonstrated that solanine disrupted cell energy metabolism. It inhibited cancer cell growth by disrupting the glycolytic pathway, leading to decreased cell proliferation and migration, along with increased apoptosis [62].

Research on a prostate cancer cell line (PC-3) showed that α -solanine inhibited cell metastasis and invasion by blocking the epithelial-mesenchymal transition (EMT). Additionally, the compound altered the expression of metalloproteinase genes responsible for extracellular matrix degradation [63].

The antitumor effect of α -solanine may involve cell cycle arrest. Inhibition of cell proliferation has been confirmed in numerous studies [8,58,61]. Furthermore, it promotes apoptosis and increases the production of reactive oxygen species (ROS) [62,63].

Ma et al. (2024) demonstrated that α -solanine induces cell death via ferroptosis in colon cancer cell lines (HCT116 and SW480). Its administration led to increased ROS levels, lipid peroxidation, and cell membrane disruption [67].

In liver cancer patients, an increase in T regulatory lymphocytes (T_{reg}), as well as elevated IL-2 and IL-10 levels, have been observed. Additionally, cancer cells secrete more TGF- β than healthy cells. Given the anti-tumor effects of solanine, researchers examined its impact on suppressor T cells. A mouse xenograft tumor model was developed by subcutaneously implanting a murine hepatocellular carcinoma cell line (H22). α -Solanine significantly reduced TGF- β levels and Foxp3 expression, leading to a decrease in T_{reg} numbers in both cell cultures and tumor tissues. The treatment slowed tumor growth and reduced metastasis, especially when combined with a TGF- β inhibitor. Additionally, α -solanine attenuated the activation of the TGF- β /Smad signaling pathway, thereby potentially enhancing the body's immune response to the tumor. These findings suggest that solanine may serve as an adjunct agent in immune therapy for liver cancer [68].

Research on pancreatic cancer also showed positive effects of α -solanine both *in vitro* and *in vivo*. Rats implanted with tumor cells (PANC-1) and treated with α -solanine exhibited reduced tumor growth. The substance inhibited proliferation, angiogenesis, and metastasis by decreasing the expression of MMP-2/9, PCNA, and VEGF [69].

α -Solanine also enhances the radiosensitivity of cancer cells. Studies on prostate cancer cells (PC-3 and DU145) showed that combining the drug with irradiation had a synergistic effect, increasing apoptosis and phosphorylation of H2AX (γ -H2AX), which indicates an increase in DNA double-strand breaks [70]. A similar effect was observed in esophageal cancer (EC9706 and KYSE30) [71].

α -Solanine has been investigated as an active compound in various drug delivery systems. Chitosan has been proposed as a polymeric carrier [72]. Another strategy to enhance drug solubility was the dendrosomal formulation of α -solanine [73].

3.2. Anti-Inflammatory Activity

Research on the anti-inflammatory effects of α -solanine is limited. A compound extracted from potatoes was tested *in vitro* on RAW 264.7 macrophages and *in vivo* in a mouse model of sepsis induced by lipopolysaccharide (LPS). The compound inhibited the expression of pro-inflammatory enzymes and cytokines, with its mechanism of action involving inhibition of the NF- κ B pathway. In the sepsis model, the drug increased the survival rate of mice [74].

Another study conducted on the same cell line showed that α -solanine inhibits the production of nitric oxide and prostaglandin E2 in LPS- and gamma interferon-stimulated macrophages. Additionally, inhibition of mRNA expression of pro-inflammatory chemokines was observed. An *in vivo* study conducted on three different inflammation models (xylene-induced ear edema, carrageenan-induced paw edema, and agar-induced granuloma formation) demonstrated that α -solanine exhibited anti-inflammatory effects. It reduced swelling, inflammatory cell infiltration, and tissue congestion in mice given intraperitoneal injections of 5 mg/kg [75].

The anti-inflammatory properties of α -solanine were also tested in mice with dermatitis induced by croton oil. When applied to irritated skin, solanine reduced inflammation in a dose-dependent manner. However, dexamethasone exhibited a stronger anti-inflammatory effect than solanine [76].

3.3. Other Activities

Due to its promising effects, Zhou et al. (2024) investigated the impact of α -solanine administration on osteoarthritis (OA). A study on a mouse model of OA induced by destabilization of the medial meniscus (DMM) examined how intra-articular drug administration influenced disease progression. Mice were divided into four groups: control, DMM only, DMM treated with a low dose (0.5 μ mol/L), and DMM treated with a high dose (2 μ mol/L). α -Solanine was administered 10 days after treatment, twice a week for 8 and 12 weeks. The substance was found to attenuate OA progression by inhibiting extracellular matrix degradation. Interestingly, shorter administration periods were more effective. α -Solanine also inhibited chondrocyte pyroptosis and NF- κ B pathway signaling in these cells, while reducing pathological blood

vessel and nociceptor proliferation in the subchondral bone. These findings suggest that α -solanine may have therapeutic potential in OA treatment [77].

An *in silico* study of the affinity of solanine and its derivatives for acetylcholinesterase indicated that this compound can block its activity. Inhibitors of this enzyme are used in the treatment of Alzheimer's disease [36].

α -Solanine also affects cell morphology. Exposure of rat mesenchymal stem cells to the drug at concentrations of 2-6 μ M for 24 hours induced morphological changes, including an increase in the number of nuclei, suggesting enhanced protein synthesis, and the formation of cytoplasmic protrusions. Additionally, α -solanine reduced the number of adherent cells and colony formation. However, the biological basis of these changes remains unclear [78].

4. Conclusions

Research on α -solanine has been ongoing for approximately a century and a half. During this time, numerous studies have been conducted by various researchers, exploring different aspects of this compound. The plants containing α -solanine and its biosynthetic pathway have been identified. Despite extensive research on α -solanine toxicity, its precise toxicological mechanisms remain incompletely understood. α -Solanine affects the nervous system by inhibiting cholinesterases; however, the symptoms of solanine poisoning are often associated with an anticholinergic crisis. In addition, this compound has strong irritating effects on the gastrointestinal tract and can lead to cell lysis, including erythrocyte destruction. α -Solanine exhibits both anticancer and anti-inflammatory activities. It inhibits cancer cell proliferation and limits their ability to metastasize. Additionally, it may have beneficial effects in managing inflammatory conditions. Some evidence suggests that α -solanine could be effective in the treatment of osteoarthritis and Alzheimer's disease. However, the high toxicity of α -solanine significantly limits its practical applications. Further comprehensive studies are required to assess whether its toxic effects outweigh the therapeutic potential of α -solanine in clinical settings.

Author Contributions: Conceptualization, K.B., M.K. and J.K.; methodology, K.B., M.K. and J.K.; writing—original draft preparation, K.B., M.K. and J.K.; writing—review and editing, K.B., M.K. and J.K.; supervision, K.B., M.K. and J.K.; project administration, K.B., M.K.; and J.K. All authors have read and agreed to the published version of the manuscript.

Funding: This review paper did not receive any financial support.

Conflicts of Interest: The authors declare no conflict of interest.

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