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Review Article
Toxicity, Teratogenicity and Anti-cancer Activity of α-solanine: A Perspective on Anti-cancer Potential

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Abstract

The α-Solanine is a glycoalkaloid metabolite produced by solanaceae species, important plant food in the human nutrition. This α-solanine is highly toxic to animals and humans and has been indicated as a risk factor for developing congenital malformations. However, recent studies suggest that α-solanine possesses anti-microbial and anti-tumor activities. The aim of this review was to summarize the main properties of α-solanine, its toxicity and teratogenicity in animal models and the main findings reported about anti-cancer activity against various cancer cell lines in *in vitro* assays. Key α-solanine mechanisms of action are presented alongside arising interdisciplinary research, connecting agricultural sciences and medicine. Data presented in this review, may assisted in preventing toxic effects of α-solanine and promote research about its potential use in the treatment and management of human cancers.

Key words: α-Solanine, plant foods, teratogenicity, antitumor activities, glycoalkaloid metabolite, solanaceae species, anti-cancer activity

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INTRODUCTION

Solanaceae plant family includes numerous species that are important for human nutrition, such as peppers, aubergines, tomatoes and varieties of potatoes. Solanaceae species produce alkaloids such as α-, β-, γ-solanine, α-, β-, γ-chaconine, solanidine and tomatidenol[1,2]. The α-Solanine is a glycoalkaloid found mainly in potatoes (*Solanum tuberosum*) and other plant foods such as apples (*Malus domestica*), cherries (*Prunus avium*), eggplant (*Solanum melongena*) and tomatoes (*Solanum lycopersicum*). This glycoalkaloid was biochemically characterized in European black nightshade berries (*Solanum nigrum*) by Desfosses in 1820[3]. Since then, the concentration of α-solanine has been shown to vary in different plant parts, localizing in stems, leaves, husks and inside the tubers[4], where this glycoalkaloid exerts a protective effect against fungi, bacteria and insects[5].

The α-Solanine has been studied as a factor relevant for human health, mainly due to its toxicity and possible teratogenic effects in humans. Exposure to α-solanine has been linked to dozens of deaths in the 20th century in Germany and Britain[6] and numerous cases of intoxication have been reported in various countries[7,8]. Symptoms of α-solanine intoxication (respiratory distress, nausea, vomiting and diarrhea) are related to inhibition of acetylcholinesterase[9], however, the underlying mechanisms of action are still under study. Teratogenicity of α-solanine has been demonstrated in murine and amphibian animal models, where it induced embryonic malformations, mainly of the central nervous system, such as exencephaly, encephalocele and anophthalmia[10-12]. Recently, potential anti-cancer properties of α-solanine have received attention as it was shown to inhibit the growth of breast, pancreatic and melanoma cancer cells[13-15].

As α-solanine is present in widely consumed human foods such as potato tubers, this review aimed to describe aspects of this alkaloid of relevance to human health, including effects on embryogenesis of the central nervous system. Importance of the quantification of α-solanine in the consumption tubercle is highlighted, inviting inter-disciplinary research between agricultural sciences and human medicine. Data presented in this review, may assist in preventing toxic effects of α-solanine and promote its use in the treatment and management of human cancers.

TOXICITY, TERATOGENICITY AND ANTI-CANCER OF α-SOLANINE

Solanaceae species produce a wide variety of nitrogen-containing secondary metabolites, including alkaloids[16]. Alkaloids play an essential role in protecting the plant against infection as they possess anti-microbial and insecticidal properties including inhibition of bacterial growth[17], anti-fungal[18], larvicidal and anti-oviposition activity[18]. Most alkaloids are toxic to animals, including man[19].

Glycoalkaloid α-solanine is an organic, insoluble compound with a triterpenoid structure and is naturally found in plants of the Solanaceae family, mainly in stems, leaves, skin and inside the fruits. Mammals directly consume this compound in assorted dietary vegetables such as potatoes (*Solanum tuberosum*), tomatoes (*Solanum lycopersicum*), eggplant (*Solanum melongena*) and peppers (*Capsicum annuum*). Biochemically, α-solanineand other steroid alkaloids are derived from sterols, which are glycosylated to produce bitter-tasting steroidal glyco-alkaloids. Biosynthetic precursor of glyco-alkaloids is cholesterol. In plants, such as potatoes, cholesterol is cyclized to solanidine, which is subsequently glyco-sylated to α-solanine or α-chaconine[20]. Together, these two compounds form up to 95% of total glyco-alkaloids in potatoes. External factors encountered during post-harvest handling of potatoes, such as exposure to light, heat, wounds and stress, significantly increase glyco-alkaloid content of the tubers, increasing the risk of post-consumption toxicity in animals and humans[21,22].

Among external factors affecting the concentration of glyco-alkaloids, exposure to ultraviolet (UV) light is the most studied[23,24]. However, pathogenic factors such as infection by *Erwinia carotovora*, *Synchytrium endobioticum* and *Phytophthora infestans* are also relevant[25]. Glyco-alkaloid content also depends on the variety of the potato, the geographical location of the crop and the conditions of storage, transport and marketing[26]. Section of the potato tuber analyzed is also of importance as glyco-alkaloid concentration is lower in the meat than in green parts such as skin, eyes and shoots[26,27].

Several studies evaluated the concentration of glyco-alkaloids in different varieties of the tuber, analyzing crops in Pakistan[26,27], Denmark[27], Brazil[28], Ireland[29], Bolivia[30] and Canada[31]. Using high-performance liquid chromatography (HPLC) and reverse phase-based (RP-HPLC) techniques with UV detection (at 202 nm), these studies demonstrated that a typical tuber contains 12-20 mg kg^{-1} of glyco-alkaloids, whereas a green tuber contains[32] 250-280 mg kg^{-1}. Solanine concentration in commercial potato varieties should be and usually[28] is <200 mg kg^{-1}. However, some of the varieties analyzed in the afore-mentioned studies contained more than 200 mg kg^{-1} glyco-alkaloids, which is the safe upper limit for human consumption recommended by the Food and Agriculture Organization (FAO) and the World Health Organization (WHO)[26,28,33]. Finally, a synergic effect of the plant genotype and the environment was

observed on the glyco-alkaloid content of wild-type and commercial potato varieties[29].

Furthermore, quality of the tuber is determined, in part, by taste and color, parameters directly affected by the concentration of glyco-alkaloids because both bitter taste and green color are the result of glyco-alkaloid accumulation[34]. Cooking, frying, dehydration, irradiation and freezing are insufficiently effective in reducing the glyco-alkaloid toxicity[32,35] as these compounds are thermostable, bio-accumulate and remain active after cooking and processing the potato[32]. However, the concentration of glyco-alkaloids decreases by 70% if potato skin is removed and by $\leq$30% if the tuber is bleached or washed. Furthermore, glyco-alkaloid activity reduces by 92 and 83% at frying temperatures used for preparing French fries and pan-fried potatoes, respectively[36].

Acute toxicity of α-solanine: Acute α-solanine intoxication was characterized mainly by gastrointestinal symptoms (nausea, vomiting, diarrhea and gastrointestinal bleeding). In severe cases, a generalized rash is accompanied by neurological disorders, including cerebral edema, coma and death[19].

Outbreaks of α-solanine poisoning have been reported throughout the 20th century in several countries[37-39]. The characteristic taste of potatoes was attributed to glyco-alkaloids, although these same compounds at high concentrations cause bitterness and a burning sensation in the mouth, which may prevent food poisoning[29]. Most potatoes purchased commercially contain low concentrations of α-solanine (4-10 mg/100 g dry weight) but if α-solanine concentration is $\geq$20 mg/100 g, the tubers present a toxic hazard[40]. The maximum tolerated dose in humans is 1 mg kg^{-1} body mass, whereas acute doses of 2-5 and 3-6 mg kg^{-1} body mass had been reported as potentially lethal (Table 1)[29,39,41,42,10-12,43-48].

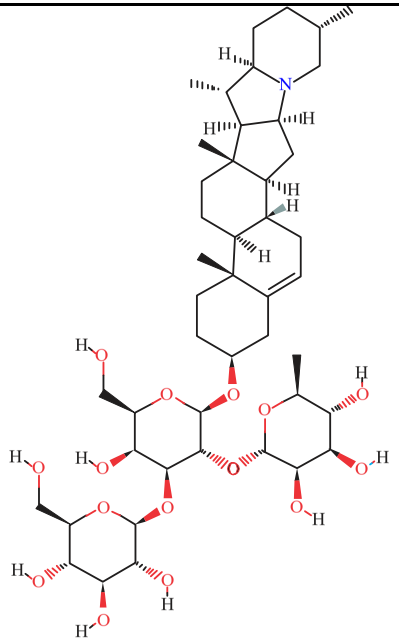
α-solanine teratogenicity: Potential teratogenic effects of glyco-alkaloids have been a cause of concern for public health since the 1970s, when specific congenital defects in humans, mainly neural tube defects (NTDs) were first associated with the ingestion of tubers producing these substances by Renwick *et al.*[49], based on a review of epidemiological data on anencephaly and spina bifida. Renwick *et al.*[49] postulated a link between the incidence of these neuronal dysplasias and consumption of potatoes stored during the winter and drawing from conclusions of previous studies, suggested that potatoes could become teratogenic as they get older or that a potato-infecting fungus could be a determining factor in the etiology of anencephaly and spina bifida. This hypothesis was based on overlapping geographical distributions of potato and NTDs[50]. Since then, teratogenic effects of α-solanine in the development of NTDs have been demonstrated in murine models[49] and in rabbits and pigs where this glyco-alkaloid caused defects in neurulation and anencephaly[51]. However, these teratogenic effects were not observed in non-human primates[47].

The estimated daily average consumption of potato glyco-alkaloids for a human is 12.75 mg (around 0.18 mg kg^{-1} b.wt.), which is approximately 1/5th of the acute toxic concentration in humans (1 mg kg^{-1} of b.wt.), making acute intoxication seemingly more relevant than a critical effect during embryo development. However as α-solanine is an insoluble substance that accumulates in the body up to 24 h after ingestion, the developing fetus could be affected by accumulation, not necessarily by acute exposure, making both the effects of acute intoxication and teratogenic impact of α-solanine accumulation worth considering. However, no existing evidence supported this hypothesis as teratogenic effects leading to NTDs manifest at critical points of development, not corresponding to a cumulative effect[52].

In murine models, in utero exposure of embryos to α-solanine has consistently resulted in the development of central nervous system abnormalities, such as exencephaly, encephalocele and anophthalmia[42]. The NTDs are characterized by neurulation defect in which the closure of the anterior or posterior neuropore fails[53]. It is hypothesized that the teratogenic threshold of α-solanine can be reached accumulatively or by exposure to increasing doses that impede cell differentiation, through alterations in cell morphology that inhibit aggregation. The α-solanine was shown to exhibit dose-dependent toxicity in rat stem cells, modifying cell morphology and causing decreased cell size and detachment of adherent cells in culture (decreased intercellular adhesion)[54], mechanisms that together could contribute to the closing defect of the neuropore.

In murine models, in addition to NTDs, fetal exposure to glyco-alkaloids such as α-solanine also resulted in alterations in the morphology of cardiac cells[55] and necrosis in the gastro-intestinal tract[56]. In Xenopus embryos, α-chaconine displayed a more pronounced teratogenic effect than α-solanine[43], however, these glyco-alkaloids altered the embryonic development of Xenopus synergistically, with their combination shown to be the primary factor increasing the risk of developmental abnormalities[12]. In fish embryos (*Oryzius latipes* or Japanese rice-fish and *Oncorhynchus mykiss* or rainbow trout), α-solanine increases mortality by inducing functional and structural defects of various organ systems. Additionally, *in vitro* exposure of cattle zygotes to α-solanine inhibits implantation and embryonic

Table 1: Physical properties of α-solanine, toxic doses and teratology animal models

			α-Solanine
			Physical properties of α-solanine[39,41] Molecular formula: C45H73NO15 Molecular weight: 868.071 g moL^{-1} Melting point: 285°C Water solubility: 1.380 mg L^{-1} (25°C) PubChem CID: 129627772
Toxicology	Safe potato concentration	Safe oral dose (humans)	Potential lethality
	<200 mg kg^{-1} in fresh potato	1 mg kg^{-1} body mass	2-5 mg kg^{-1} body mass to 3-6 mg kg^{-1} body mass
Teratology	Animal model	System affected	Phenotype
	Syrian hamsters	Central nervous system	Exencephaly, encephalocele and anophthalmia[42]
	Chick embryos	Central nervous system, cardiac system, somite development	*Cranioschisis, caudal regression syndrome, cardiac septal defects[10,11]
	Xenopus	Central nervous system, gastrointestinal system	**Microcephaly, anencephaly, abnormal gut coiling[12,43]
	Japanese rice fish (*Oryzius lutipes*)		Increased embryo mortality at high concentrations[44]
	Rainbow trout (*Oncorhynchus mykiss*)		Increased embryo mortality at high concentrations[44]
	***Pig (oocyte and embryo)	Oocyte maturation, embryonic development	Disturbed meiosis, reduced cleavage and blastocyst formation, decreased number of total and inner cell mass cells[45]
	Bovine (oocyte and embryo)		Inhibition of pre-implantation embryo development, reduced morula cleavage rates[46]
	Female rhesus monkeys and marmosets (before breeding and 6 weeks following conception)		Absence of neural tube defects, development of hydrocephalus in rhesus monkey infants[47]
	Drosophila melanogaster	Body size, thorax and abdomen	Decreased body size, deformed wings, smaller abdominal zone[48]

Molecule 2D structure taken from PubChem[41], *In experiments with potatoes infected with *Phytophthora infestans*, sub-germinal injection of α-solanine had the same effect as boiled potatoes infected with *Phytophthora*, **Interaction of α-chaconine and α-solanine, ***Blighted potato diet

development[46]. In contrast, glyco-alkaloids derived from *Solanum lycocarpum* (wolf apple) act as endocrinological disruptors[57,58].

This evidence indicated that developmental effects of α-solanine occur under particular circumstances, implying an all-or-nothing effect, similar to other drugs with teratogenic potential[59]. Impact on higher primates could be severe but clinically undetectable as NTDs if exposure occurs during early developmental stages and causes a premature loss of the embryo, whereas if the teratogenic threshold is not reached, development would not be significantly altered and would continue un-obstructed.

Increased consumption of foods with high folic acid content was shown to be an effective measure for preventing NTDs[60,61]. As folic acid inhibits the growth of pathogenic bacteria in potatoes such as *Erwinia* spp.[62], it has been suggested that bio-fortification of potato with folic acid would have a triple effect: Preventing potato diseases by inhibiting pathogen growth[62], decreasing α-solanine concentration as less alkaloid would be required to defend the tuber against pathogens and decreasing teratogenic potential[53]. Table 1 summarized teratologic effects of α-solanine in diverse animal models.

α-solanine and cancer: Alongside protective actions in the plant and potential teratogenic effects in animals, α-solanine has demonstrated *in vitro* and *in vivo* anti-cancer activity, with most studies identifying activation of apoptosis as the underlying mechanism of α-solanine anti-tumor activity[63].

Apoptotic effects of α-solanine have been demonstrated *in vitro* in HepG2 cells[2], in which α-solanine caused cell cycle arrest, decreased the duration of G phase[2] and increased the duration of S phase of the cell cycle as well as decreased the synthesis of anti-apoptotic regulatory protein[64] Bcl-2. Additionally, α-solanine induced HepG2 cellular morphological changes typical of apoptosis, inducing changes in the mitochondrial membrane potential, altered calcium gradients[65] and increased synthesis of reactive oxygen species (·OH and H_2O_2)[66]. Likewise, α-solanine decreased the synthesis of histone deacetylase 1 (HDAC1), which regulates cell growth, while stimulating the synthesis of apoptosis-inducing proteins ASK1 (apoptosis signal-regulating kinase 1) and TBP-2 (tetrahymena piggyBac transposase 2)[66], leading to decreased cell proliferation and increased rate of programmed cell death.

In models of colon cancer, induction of apoptosis is mediated mainly by activation of caspase-3 pathways and inhibition of phosphorylation of ERK1 and ERK2 (extracellular signal-regulated protein kinases 1 and 2)[67]. Caspase-3 is a pro-apoptotic kinase[68], whereas ERK1 and ERK2 participate in diverse cellular functions, including cell cycle progression, migration, survival, differentiation, metabolism, proliferation and transcription. In these models, exposure to α-solanine favored programmed cell death[69]. Additionally, increased rate of autophagy[70] was observed in pancreatic cancer cells exposed to α-solanine, in which the alkaloid suppressed the Akt/mTOR pathway (phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin)[63], involved in proliferation of diverse cancer cell types[71].

In prostate cancer, in both *in vitro* models and *in vivo* mouse models, α-solanine displayed apoptotic effects mediated by synergistic cyclin suppression, induction of reactive oxygen species and activation of P38. P38 is a protein belonging to the sub-family MAPK (mitogen-activated protein kinases)[72] that, similar to ERK1/2 proteins, regulates cell cycle, proliferation and intercellular interactions[73].

Neo-angiogenesis and vascular proliferation are fundamental mechanisms in tumor survival. The α-chaconine inhibits proliferation of endothelial cells by reducing the expression of MMP-2 (matrix metalloproteinase-2), a protein involved in angiogenesis[74]. Similarly, α-solanine intervenes in vascular remodeling, reversing the effects of AXIN (axis inhibition protein 1) and BMPR2 (bone morphogenetic protein receptor type-2) proteins involved in tumor proliferation and metastasis through vascular remodeling mediated by β-catenin[75].

More than one mechanism, triggered by induction of apoptosis may explain the effect of α-solanine on tumor proliferation as exemplified by α-solanine activity in melanoma cells, in which cell migration is inhibited by decreased activity of MMP-2, JNK (c-Jun N-terminal kinase) and PI3K/Akt, implying a mechanism combining increase in apoptosis and regulation of angiogenesis[14]. Similar mechanisms of action have been described in models of breast cancer[5]. Additionally, in lung adenocarcinoma and esophageal cancer cells, exposure to α-solanine increased radiosensitivity and expression of microRNA-138[76,77]. In conclusion, α-solanine shows promising pharmacological potential for the management of human cancers by stimulating apoptosis, inhibiting angiogenesis, regulating the cell cycle and increasing cellular sensitivity to radiotherapy. The Table 2 summarized physiological effects of α-solanine in different tissues and human diseases associated with animal models and *in vitro* assays analyzed[78-83], whereas Table 3 summarized the effect of α-solanine in different cancers[72,84,85,5,15,76,13,14,66].

Current results demonstrated that α-solanine produces structural changes and growth inhibition in Mensequimal

Table 2: Physiological effects of α-solanine in different experimental models and associated human diseases

	α-solanine			
System	Model	Physiological effects	Related disease	Genetic background
Vascular system	Monocrotaline-induced pulmonary arterial hypertension in mice	Reversed pulmonary vascular remodeling and vascular angiogenesis[78]	Pulmonary arterial hypertension	α-solanine reversed dysfunctional AXIN2, β-catenin and BMPR2 signaling
Gastrointestinal tract	Cultured epithelial cell lines of rat and human intestinal mucosa	Increased brush border permeability[79]	Inflammatory bowel disease	-
	Murine small intestine	Disruption of intestinal barrier integrity[80]	Inflammatory bowel disease	-
	Caco-2 monolayers	Cytotoxicity and disruption of intestinal tight junction integrity[81]	Intestinal autoimmune diseases	-
Immune system	*Plasmodium yoelii* 17XL infection in mice	α-chaconine showed a dose-dependent suppression of malaria infection. Simultaneous administration of α-chaconine and α-solanine did not show any synergistic effects[82]	Malaria	-
Immune system	LPS-induced septic shock in mice	Inhibition of the NF-κB signaling pathway[83]	Endotoxin-induced shock	Inhibition of LPS- activation of nuclear factor-κB (NF-κB) reduced translocation of p65, degradation of inhibitory κBα (IκBα) and phosphorylation of IκB kinase α/β (IKKα/β)

Table 3: α-solanine and cancer

Cancer type	Experimental model	α-solanine mechanisms of action
Prostate cancer	Cultured human prostate cancer cell line DU145	Inhibition of prostate cancer growth by blocking the expression of cell cycle proteins (cyclin D1, cyclin E1, CDK2, CDK4, CDK6 and P21) and inducing apoptosis via reactive oxygen species and activation of P38 pathway[72]
	Cultured human prostate cancer cell line PC-3	Inhibition of proliferation and induction of apoptosis of tumor cells by reducing mRNA levels of MMP-2, MMP-9 and extracellular inducer of matrix metalloproteinase (EMMPRIN) and increasing the expression of reversion-inducing cysteine-rich protein with Kazal motifs (RECK) and tissue inhibitors of metallo-proteinases 1 and 2 (TIMP-1 and TIMP-2)[84]
Esophageal carcinoma	Cultured human esophageal EC9706/Eca109 cancer cells	Reduced expression of MMP-2 and MMP-9 and increased apoptosis[85]
Breast cancer	Mice breast cancer	Decreased expression of anti-apoptotic Bcl-2 protein and increased expression of Bcl-2-like protein 4 (proapoptoticBax protein)[5]
		Reduced expression levels of Bax, MMP-2, MMP-9, mTOR and Akt[15]
Lung adenocarcinoma	Cultured A549 and H1299 cells	Inhibited cell migration and invasion ability and induced expression of miR-138[76]
Pancreatic cancer	Cultured human pancreatic cancer cells (PANC-1 cell line)	Inhibition of pancreatic cancer cells proliferation by decreased expression of VEGF and suppressed mRNA expression of MMP-2, MMP-9, ENOS, EMMPRIN, and CD44[13]
Melanoma	Human melanoma cell line A2058	Suppressed phosphorylation of JNK, PI3K and Akt[14]
Liver cancer	HepG2 cells	Increased expression of ASK1 and TBP-2, induced ROS production and inhibited expression of proliferation-associated proteins such as HDAC1, all contributing to elevated apoptosis rate[66]

stem cells (MSCs) in a dose-dependent manner, consistent with findings in other cell types, such as, colon (HT29, T84) and liver (HepG2) cancer cells[86]. In addition, an important finding obtained in present study is the fact that α-solanine can affect the adhesion capacity of MSCs as the dose increases, a phenomenon that can be directly associated with the reported morphological alterations.

Perspectives: Further evidence of potential teratogenic effects of α-solanine in humans is required before specific public health recommendations can be issued, however, as α-solanine has shown teratogenic effects in various animal models, it should not be ruled out as a risk factor for the development of congenital malformations, especially NTDs. α-solanine is a versatile substance, which, in addition to protecting the plant that produces it, shows anti-tumor activity and taking into account its effects on angiogenesis, may be beneficial in treating vascular disorders such as primary pulmonary hypertension[77].

Additionally, continued research of biological effects exerted by α-solanine in normal and cancer cells should establish mechanisms involved in toxicological and teratogenic effects of α-solanine and make further progress in preventing cancer progression. As natural sources of α-solanine are potatoes and other widely consumed solanaceae plants, research in this area is an opportunity for inter-disciplinary studies combining agricultural sciences and medicine. It should be noted that glyco-alkaloids are also found as a highly valuable raw material in the residues of the potato industry.

High variability of α-solanine concentration in potatoes and high tuber consumption rates highlight the importance of determining specific glyco-alkaloid concentrations in all native varieties of the tuber, different commercial forms (frozen, fried or dehydrated potato) and in new and improved potato varieties currently developed. Altitude, climate, storage and geographical location should be taken into account and levels of α-solanine correlated with diverse biological and environmental conditions. These recommendations become relevant in the light of the precautionary principle, which implies that strategies must be established to contain risks that to date do not have a complete scientific understanding[78,87]. Terato-genic potential of α-solanine falls under this principle as only indirect evidence of harmful effects of α-solanine on human embryonic development has been discovered.

CONCLUSION

The α-solanine is a glyco-alkaloid metabolite produced by Solanaceae species, mainly in potatoes, important plant foods in the human nutrition. It has been reported the α-solanine teratogenicity and toxicity in *in vitro* assays and *in vivo* animal model. Accordingly, further studies of α-solanine in humans to prevent harmful effects are needed. Research in this area could be an opportunity for inter-disciplinary studies that combine agricultural sciences and medicine. In addition, the continuous investigation of the biological effects exerted by α-solanine in normal and cancerous cells could establish the molecular mechanisms involved before promoting its possible use in the treatment and control of management cancer.

SIGNIFICANCE STATEMENT

This study discover and summarize the biological effects reported up to now of α-solanine and its anti-cancer potential. α-solanine is a metabolite produced by Solanaceae species, important plant foods of human consumption. This review article can be beneficial in the formation of a general concept about toxic and terato-genic effects of α-solanine to take into consideration in human nutrition. This study will help the researcher to uncover the critical areas of research about its potential use in the treatment and management of human cancers that many researchers were not able to explore. Thus a new theory on the beneficial properties of α-solanine may be arrived at.

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