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REVIEW

Therapeutic Potential of *Solanum* Alkaloids with Special Emphasis on Cancer: A Comprehensive Review

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Abstract: Cancer has emerged as a formidable global health challenge, with treatment methods like chemotherapy and radiation often exacerbating the situation due to their associated side effects. Opting for natural sources like plants as a safer and environmentally friendly alternative seems promising. Historically, plants have served as valuable sources for treating diverse health conditions, attributable to their rich composition of therapeutic phytochemicals. Within this array of phytochemicals, alkaloids, especially those found in the *Solanaceae* plant family, are notably prominent. Alkaloids from *Solanaceae* plant family called *Solanum* alkaloids demonstrate noteworthy anti-tumour characteristics and exert a potent inhibitory influence on cancer cell proliferation. They trigger programmed cell death in cancerous cells through various molecular pathways, whether administered alone or combined with other medications. S*olanum* alkaloids act upon cancer cells via multiple mechanisms, including apoptosis induction, suppression of cell growth and migration, as well as inhibition of angiogenesis. This review provides insights into the anti-cancer attributes of *Solanum* alkaloids found in various *Solanum* plant species, along with a brief overview of their other medicinal properties.

Keywords: *Solanum* alkaloids, anticancer, apoptosis, molecular mechanism, structure function relationship, therapeutic values

Introduction

Cancer, categorized as a non-communicable disease, stands as a pressing worldwide issue and ranks as the primary cause of death across the globe. The incidence of cancer cases is persistently increasing, with the estimation that it will reach 21 million by the year 2030.[1–5] Within the realm of cancer, ordinary cells undergo a transformation into malignant ones, driven by genetic instability and alterations that prompt uncontrolled cell proliferation. Numerous external factors, including radiation, smoke, water pollution, specific metals, dietary elements, air quality, chemicals, and infectious agents, are known to contribute to cancer. Internally, hormonal imbalances, immune system anomalies, and genetic mutations also play roles in cancer development. Genetic instability, a fundamental factor contributing to cancer development, involves oncogene mutations like Bcl-2, MYC, RAF, and RAS (known as biological accelerators), as well as tumour suppressor genes like NF1, NF2, p53, and RB (recognized as biological brakes). It also encompasses repair genes of DNA such as p53, p22, p27, p21, p51, and factors regulating integrity of DNA, alongside genes controlling cellular metabolism and growth. Cancer manifests in diverse forms affecting individuals of all age groups.[6–8]

Cancer treatment involves various methods, including surgical procedures, radiation therapy, chemotherapy, immunotherapy, cancer vaccines, stem cell therapy, or combinations of these approaches. The selection of therapeutic interventions for cancer patients is influenced by variables including the tumour's anatomical site, clinical stage, and histological type. Nevertheless, certain treatment methods and drugs may lead to adverse effects such as toxicity,

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restricted bioavailability, lack of specificity, rapid elimination, and constraints in addressing metastasis.[9,10] For example, chemotherapy has shown potential in managing different types of cancers, yet it faces obstacles including side effects, expensive costs, complexity, and negative environmental consequences. Chemotherapeutic drugs, including topoisomerase inhibitors, doxorubicin, alkylating agents, and microtubule-targeting agents like vincristine, vinblastine, docetaxel, and paclitaxel, are examples of such treatments.[11,12] Research studies have highlighted certain phytochemicals sourced from various plants as potential candidates for anticancer drugs. At this juncture, plants and plant-derived medications emerge as promising contenders for cancer treatment due to their safety, reduced toxicity, eco-friendliness, and cost-effectiveness when compared to conventional treatments. Additionally, medicinal plants offer a sustainable approach to healthcare by harnessing naturally occurring therapeutic compounds, thereby reducing reliance on synthetic drugs and promoting ecological balance. The extensive range of plant species has been investigated for their potential in combating cancer. Given the limited understanding of the molecular mechanisms and complexity of this disease, there is a necessity to seek out new biomarkers for targeting. Several studies have focused on utilizing compounds sourced from the Himalayan flora, employing nanocarriers for drug delivery to minimize side effects and enhance targeted treatment.[13] This strategy highlights the significance of conserving biodiversity for ongoing medical breakthroughs and improvements in healthcare.

Hence, medicinal plants represent a valuable natural resource bestowed upon humanity for the betterment of health. Bioactive compounds present in the plant source have been used in the treatments for a range of ailments.[14] Despite the vast diversity of plant species around 250,000, only around 10% of these species have been explored for their medicinal properties. In various parts of plants, including roots, flowers, fruits, rhizomes, stigmas, seeds, pericarps, sprouts, stems, leaves, embryos, and barks, numerous phytochemical compounds like primary and secondary metabolites are present. These phytochemicals play a crucial role in inhibiting cancer cells. Furthermore, they enhance the production of protective enzymes and trigger antioxidant responses. These diverse mechanisms contribute to the potent anticancer effects of these phytochemicals, affecting proteins, enzymes, and signaling pathways, thereby enhancing their efficacy.[15–17]

Among these phytochemical compounds, alkaloids emerge as a significant category present in numerous plant species, possessing remarkable medicinal properties. In 1803, the initial alkaloid isolated was narcotine, succeeded by morphine in 1806, both originating from plants. Alkaloids present in plants act as a defense mechanism against pests, herbivores, and pathogens. They are predominantly present in angiosperms, followed by other plant forms with certain animals and microbes also capable of producing alkaloids. Remarkably, various plant cells within the same taxonomic group may contain a wide array of alkaloids. Two alkaloids have been isolated from plant source. The first alkaloid being narcotine in 1803 and the next being morphine in 1806. Alkaloids found in plants serve as a defense mechanism against pests, herbivores, and pathogens. Interestingly, different plant cells within the same taxonomic group may harbor diverse alkaloids.[18,19] One noteworthy subgroup of alkaloids is steroidal alkaloids, which can be found in plant families like *Solanaceae, Buxaceae, Apocynaceae, and Liliaceae*. These natural steroidal alkaloids contain a nitrogen atom and a steroidal framework, exhibiting dual roles as both alkaloids and steroids. The pharmaceutical sector has utilized steroidal alkaloids as primary compounds for developing new steroidal medications. Prior studies have revealed that steroidal alkaloids exhibit a diverse array of medicinal benefits, encompassing anticancer, anti-inflammatory, antimicrobial, and analgesic effects.[20–23] Steroidal alkaloids from the Veratrum, Petilium, and Korolkovia genera have been shown to have varying pharmacological activities, with some being effective in decreasing blood pressure, with its action as anti-inflammatory, analgesic, anti-platelet aggregation, and antitumor agents.[24] Other well-known plant alkaloids include caffeine, cocaine and nicotine.[25] In this review paper, we discuss the alkaloids found in various species of *Solanum* plant, focusing on their prospective efficacy as agents in cancer treatment. Several studies have demonstrated that *Solanum* plants possess not only ethnopharmacological properties but also other beneficial traits. Notably, the *Solanum viarum* species has been found to accumulate heavy metals in its aerial parts, making it a potential candidate for phytoremediation in the treatment of metal-polluted soils.[26]

Solanum Alkaloids and Their Multifaceted Biological Activities

Numerous investigations have indicated that *Solanum* species boast a wealth of alkaloids. Both in vitro and in vivo studies have unveiled encouraging biological properties associated with steroidal alkaloids found in various *Solanum*

Table 1 Therapeutic Potential of Derivatives of Solanum Alkaloids

Alkaloid	*Solanum* species	Biological activity	Reference
Solanidine	*Solanum tuberosum*	Teratogenicity	[28]
Solasodine	*Solanum leucocarpum; Solanum trilobatum*	Cholinergic	[29,30]
Tomatidine	*Solanum arboretum*	Toxicity study; neuritogenic and ngf-enhancing activities.	[31,32]
Solamargine	*Solanum palinacanthum; Solanum lycocarpum*	Anticancer	[33]
Solanopubamine	*Solanum schimperianum*	Anticancer and antimicrobial	[28]
Chaconine	*Solanum tuberosum*	Cytotoxicity studies	[34]
Solanine	*Solanum nigrum; Solanum tuberosum*	Cytotoxicity studies	
Solasonine	*Solanum melongena, Solanum lycocarpum, Solanum nigrum*	Anticancer	[35]

species. Remarkably, out of approximately 350 *Solanum* species, nearly 90 distinct alkaloid structures have been documented.[22] These *Solanum* species have a longstanding tradition of being employed in the treatment of various ailments. Some research endeavors have utilized crude plant extracts, while others have isolated specific phytochemicals, such as alkaloids, and assessed their therapeutic potential, as summarized in Table 1. In the plant species *S. tuberosum*, the primary alkaloid compounds are α-chaconine and α-solanine. *S. melongena* contains solamargine and solasonine. *Lycopersicon esculentum*, or tomato, is known to synthesize α-tomatine and dehydrotomatine, both belonging to the spirosolane-type glycoalkaloid category. Additionally, *S. tuberosum* yields α-chaconine and α-solanine. In tomato species, α-tomatine and dehydrotomatine are found, differing solely in the double bonds within the ring structure. Notably, potatoes contain α-solanine and α-chaconine as their primary glycoalkaloids. Solanine, a toxic glycoalkaloid, is present in the leaves, fruits, and tubers of both tomato and potato plants.[22,27]

Amid the myriad of phytochemicals found in plant species, the extraction, purification, fractionation, and identification of alkaloids remain relatively straightforward processes. Various methods are employed depending on the nature of the compounds. However, the alkaloid extracts obtained through these techniques often contain numerous impurities. To refine them, the mixture must undergo further processing, involving extraction with acids, precipitating reagents, or chromatographic methods such as partition chromatography, column chromatography, and ion-exchange chromatography. Subsequently, the fractionated alkaloids are subjected to processes like fractional distillation, fractional crystallization, or chromatographic techniques like column chromatography, HPTLC (High-Performance Thin-Layer Chromatography), ion-exchange chromatography and/or HPLC (High-Performance Liquid Chromatography). Finally, fractionated alkaloids are identified using techniques such as NMR (Nuclear Magnetic Resonance) spectroscopy or X-Ray crystallography.[36–38] Several studies have successfully extracted and identified *Solanum* alkaloids structure because of the structure is related to its function as anticancer compounds. Some research studies have suggested that the number and nature of carbohydrate moieties present in *Solanum* alkaloids may alter their binding specificity to cancer cell receptors. This binding can regulate gene expression in various ways, which is crucial for the cytotoxic and apoptotic properties of *Solanum* alkaloids.[39]

Anticancer Studies of Solanum Alkaloids

Numerous phytochemicals have undergone extensive research to assess their potential as anticancer agents. Among these are many alkaloids like vinblastine and camptothecin, terpenoids, anthranilic acid derivatives, polyphenols and lignans. Alkaloids and their analogues constitute a significant portion of clinically used anticancer drugs.[21,40] In recent years, steroidal alkaloids derived from *Solanum* species have garnered increased attention for their cancer treatment potential due to their unique chemical structures and potent activity. One such compound is α-chaconine, an aglycone solanidine derivative which had displayed significant inhibitory effects on the proliferation, invasion, and migration of A549 cells (lung adenocarcinoma cells) and bovine aortic endothelial cells (BAECs). These effects are linked to the suppression of the JNK and Akt pathways (Figure 1). Additionally, α-chaconine reduces the presence of NF-kB factor and the expression of enzyme MMP-2 (MMP-matrix metalloproteinase) in BAECs (Bovine Aorta Endothelial Cells) and MMP-2/-9 in A549 cells with MMP-2 contributing in angiogenesis.[41,42] Another study revealed the combination of α-chaconine and gallic acid which is effective against PC-3

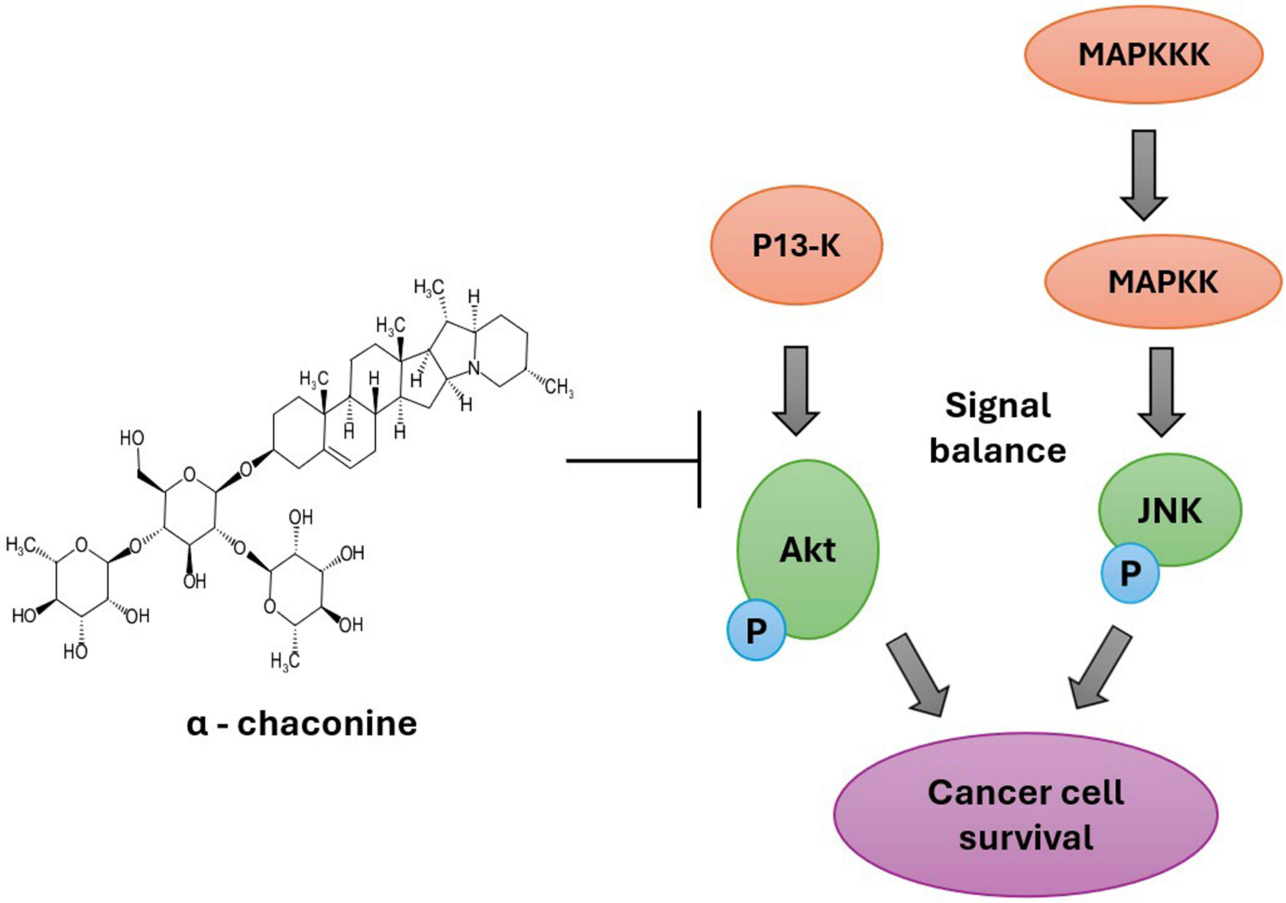

Figure 1 Apoptotic effect of α-chaconine inhibiting the phosphorylation of JNK and AKT pathways in cancer cell.
Abbreviations: P13-K, phosphatidylinositol 3-kinase; Akt, protein kinase B; MAPKKK, mitogen-activated protein kinase kinase kinase; MAPKK, mitogen-activated protein kinase kinase; JNK, c-Jun N-terminal kinase; P, phosphorylation.

and LNCaP (prostate cancer cell lines). This combination triggers the cyclin-dependent kinase enzyme inhibitor p27 in both prostate cancer cell lines (LNCaP and PC-3) and caspase-dependent apoptosis only in one cell line (LNCaP). The synergistic action of α-chaconine and gallic acid resulted in the apoptotic effect by the activation of JNK pathway.[43]

Solanidine, another alkaloid, has shown the ability to prevent the proliferation in MCF-7 cancer cell lines in vivo.[44] Additionally, soladulcidine, a steroidal alkaloid, isolated from *Solanum dulcamara*, has exhibited antiproliferative effects against prostate cancer cells (PC-3).[45] β-solamarine, extracted from *Solanum dulcamara*, showed potential for inhibiting tumours against Sarcoma 180 in mice. Additionally, solasonine, sourced from the fruit of *Solanum lycocarpum*, was investigated for its inhibitory effects on various tumor cell lines. Among the evaluated cell lines, HepG2 exhibited the highest susceptibility, with an IC_{50} of 6.01 μg/mL.[46] Research on solasonine, a steroidal alkaloid isolated from the entire plant of *S. nigrum*, has shown its anticancer properties against human gastric cancer SGC-7901 cells. Solasonine effectively inhibited the growth of SGC-7901 cells in a manner dependent on dosage. The IC_{50} value of solasonine against SGC-7901 cells after 24 hours was 18 μM, closely comparable to cisplatin (17.5 μM). Flow cytometry analysis showed a comparable apoptotic rate in SGC-7901 cells treated with 18 μM solasonine (40.4%) and 17.5 μM cisplatin for 24 hours (44%). This reaffirmed the comparable in vitro inhibitory effects of these two agents against gastric cancer cells. Solasonine triggered cell cycle arrest at the G2 phase and decreased the protein expression of Bcl-2 and Caspase-3 while decreasing Bax and BClxL protein expression in SGC-7901 cells (Figure 2). Thus, solasonine exhibited a similar inhibitory impact on the proliferation of human gastric cancer SGC-7901 cells as cisplatin, triggering apoptosis in these cells via both mitochondrial and endoplasmic reticulum stress pathway.[47]

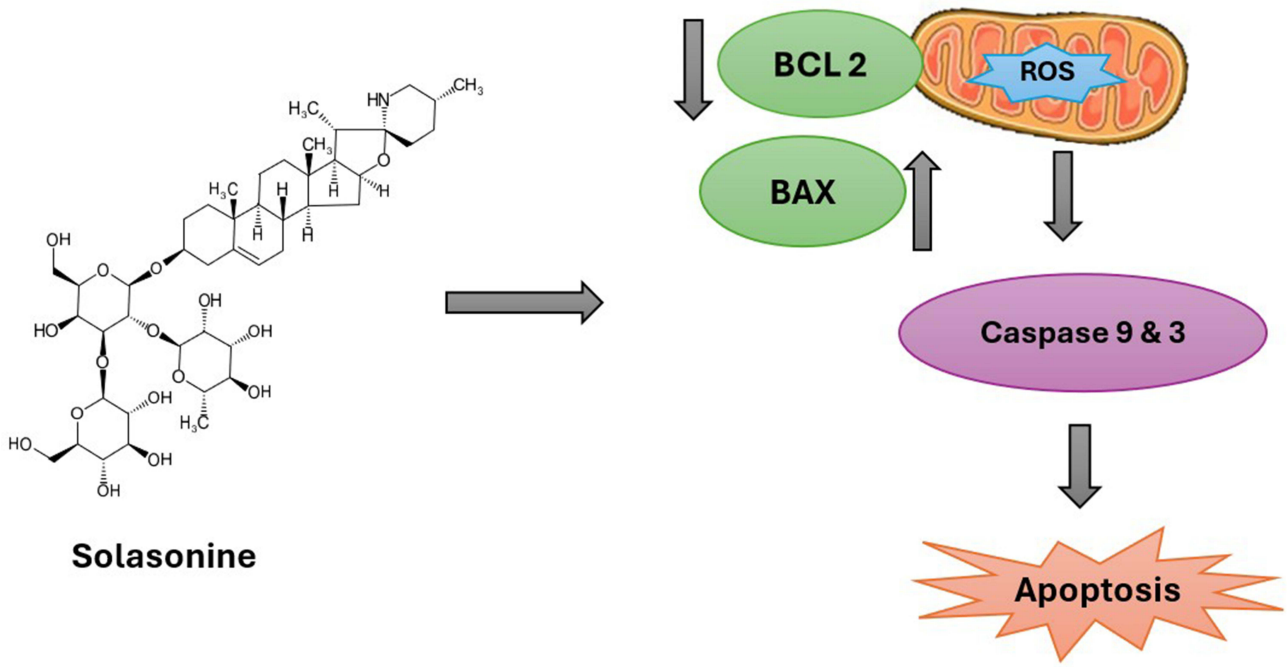

Figure 2 Antiproliferative effect of Solasonine induces cancer cell apoptosis.
Abbreviations: BCL2, b cell lymphoma 2; BAX, bcl2-like protein; ROS, reactive oxygen species.

In a separate study focusing on solasonine, a steroidal alkaloid extracted from the *Solanum nigrum* plant, it was discovered that it induces apoptosis in pancreatic cancer cell lines CFPAC-1 and PANC-1 while also impeding their migration, proliferation, and invasion. Through Cell Counting Kit-8 (CCK-8) assays, it was noted that solasonine inhibited cell growth in a dose-dependent manner, with its suppressive effects notably pronounced at the 72-hours. Likewise, clone formation assays illustrated that solasonine, at concentrations of 25 and 50 mM, impeded the proliferation of both PANC-1 and CFPAC-1 cells. Flow cytometry and propidium iodide (PI) staining indicated that solasonine (at concentrations of 25 and 50 mM) induced cell apoptosis within 24 hours. Additionally, after being treated with solasonine, the levels of drug resistance-related proteins (MRP1 and Pgp) decreased. Studies utilizing mouse xenograft and metastasis models of PANC-1 and CFPAC-1 further corroborated that solasonine significantly impeded both tumor growth and metastasis. Metabolomics analysis further validated solasonine's influence on glutathione metabolism and ferroptosis mediated by SLC7A11 (solute carrier family 7 member 11). Molecular docking studies confirmed the direct binding of solasonine to TFAP2A, resulting in reduced level of proteins. Bioinformatics analysis and luciferase assays revealed the binding of TFAP2A to the OTUB1 promoter region, consequently enhancing its transcription. In essence, solasonine impedes the TFAP2A/OTUB1 SLC7A11 axis, triggering ferroptosis activation and mitigating pancreatic cancer cell advancement.[48]

Solasonine has shown antitumor properties by inhibiting the growth of acute monocytic leukemia cell lines (THP-1 and MV4-11) in laboratory settings. With increasing concentrations of solasonine, the inhibition of cell growth was evident in both THP-1 and MV4-11 cell lines at 24 and 48 hours. In contrast to the cells in the control group, those exposed to solasonine showed decreased in number, and with increased solasonine concentrations, a percentage of cells displayed apoptosis-specific alterations, like fragmentation and nuclear shrinkage in both cell lines. This suggests that solasonine stimulates apoptosis and triggers cell cycle arrest in the G2/M phase. A correlation between solasonine and upregulated gene expression within the AMPK/FOXO3A pathway was noticed in the RNA sequencing data.[49] In a study involving solamargine, a steroidal alkaloid from *Solanum nigrum* L., it exhibited potent cytotoxic effects against human K562 leukemia cells. Within a span of 2 hours, solamargine was noted to cause lysosomal rupture, leading to the cathepsin B release into the cytosol. Following this, subsequent mitochondrial impairment was identified, which included

permeabilization of mitochondrial membrane, as demonstrated by a reduction in membrane potential and cytochrome c release from mitochondria. Solamargine of concentration 10 μM was exposed to cells for 30 mins. It showed an increase in the concentration of calcium which is seven times more compared to control treatment. Downregulation of Bcl-2, upregulation of Bax, and activation of caspase-3 and caspase-9 were also observed, indicating that solamargine's cytotoxicity is associated with a lysosomal-mitochondrial death pathway.[50]

Another study on Solamargine from *Solanum nigrum* demonstrated its antiproliferative effect against SMMC-7721 and HepG2 cells. Solamargine exhibited significant cytotoxicity, as evidenced by low IC_{50} values. When treated with solamargine for 72 hours, the IC_{50} values were 9.21 μg/mL for SMMC-7721 cells and 19.88 μg/mL for HepG2 cells, indicating that solamargine had antitumor efficacy on SMMC-7721 cells and apoptosis was triggered by the activation of caspase-3 enzyme which caused G2/M phase arrest. Solamargine's antiproliferative activity was more pronounced in SMMC-7721 cells compared to HepG2 cells.[51] Moreover, research studies indicated that solamargine is specific in its action and effectively inhibits the growth of two melanoma cell lines (WM239 and WM115) which were metastatic, but it caused minimal impact on WM35 cell lines which were normal and benign. Cell necrosis was triggered by solamargine in WM115 and WM239 cell lines which were malignant, by swiftly inducing permeabilization of lysosomal membrane, as evidenced by the increased levels of cathepsin B. This in turn caused cytochrome c release and TNFR1 upregulation by inducing apoptotic pathway originating from the extrinsic activation of mitochondria. This subsequently triggered the extrinsic mitochondrial death pathway, marked by the release of cytochrome c and upregulation of TNFR1. Additionally, it caused hILP/XIAP downregulation, caspase-3 enzyme cleavage, BclxL and Bcl-2 upregulation, and Apaf-1 and Bax downregulation in WM115 and WM239 melanoma cell lines. Thus, in vitro studies demonstrated solamargine with greater effectiveness against melanoma cells in the vertical growth phase.[52]

A glycoalkaloid compound solanine present in *Solanaceae* plant family is recognized for its pesticidal and fungicidal properties, serving as a natural defense mechanism.[53] Various research studies have highlighted solanine's ability to impede the growth of neoplastic cells via molecular pathways and induce apoptosis in diverse cancer cell types, including skin, colon, liver, and gastric cancers (Figure 3).[37,42,54] The outcomes of in vitro investigations have spurred further exploration into solanine's potential through in vivo studies. One such study assessed solanine's toxicity using a standard animal model for breast cancer. Solanine notably inhibited 4T1 cancer cell proliferation in a dose dependent and time-dependent manner. Solanine with IC_{50} value for the 4T1 cancer cell line was determined to be 34 μM within 24 hours, which decreased to 17 μM after 48 hours. A minimal effect of solanine was observed on human fibroblast normal cell lines. From the results, it was evident that significant chemotherapeutic and chemoprotective effect of solanine was observed against breast cancer cells via apoptosis induction, cell proliferation inhibition, and angiogenesis suppression.[55] Three steroidal alkaloids like khasianine, solamargine, and solasodine were employed to investigate the function of carbohydrate moieties in the mechanism of apoptosis, and their cytotoxicity was assessed, with IC_{50} values of 2.0, 2.7, and 3.0 μg/mL, respectively. Solasodine and solamargine demonstrated strong cytotoxicity against human hepatoma Hep3B cells. These studies suggested a connection between the carbohydrate moieties of steroidal alkaloids and the regulation of gene expression for apoptosis in cancer cells.[37] Moreover, derivatives of solamargine, ursolic acid, and solasodine demonstrated noteworthy cytotoxicity against in vitro human liver cancer cell lines (PLC/PRF/5). The ursolic acid with aliphatic acid esterification significantly improved their cytotoxic effects against the same cell lines (PLC/PRF/5) in vitro.[56]

Solasodine and solanidine, two steroidal alkaloids that resemble structurally similar to diosgenin, underwent testing for their physiological impacts on human osteosarcoma 1547 cell lines. Variations in its activity were investigated in terms of rate of proliferation, cell cycle distribution, and apoptosis initiation. The correlation between empirical and theoretical findings underscored the hetero-sugar moiety's significance and 5.6-double bond presence in biological activities such as apoptosis induction and arrest of cell cycle in human 1547 osteosarcoma cell line.[57] Tomatine was found to trigger growth inhibition and apoptosis induction in HL-60 human myeloid leukemia (MLL) cells in a manner dependent on the dosage. Tomatine demonstrated cytotoxic effects by disrupting the cell membrane and inducing necrosis, primarily attributed to its capacity to bind to cholesterol.[57] Tomatine also suppressed proliferation, autophagy inhibition, and apoptosis induction in ovarian cancer (OC) cell lines (Skov3). Additionally, tomatine inhibited the PI3K/Akt/mTOR pathway.[21] Neoplastic cells release matrix metalloproteinases (MMP), crucial factors in tumor metastasis. Studies have shown that tomatine triggers programmed cell death and inhibits MMP-9, MMP-2, and MMP-9/NGAL

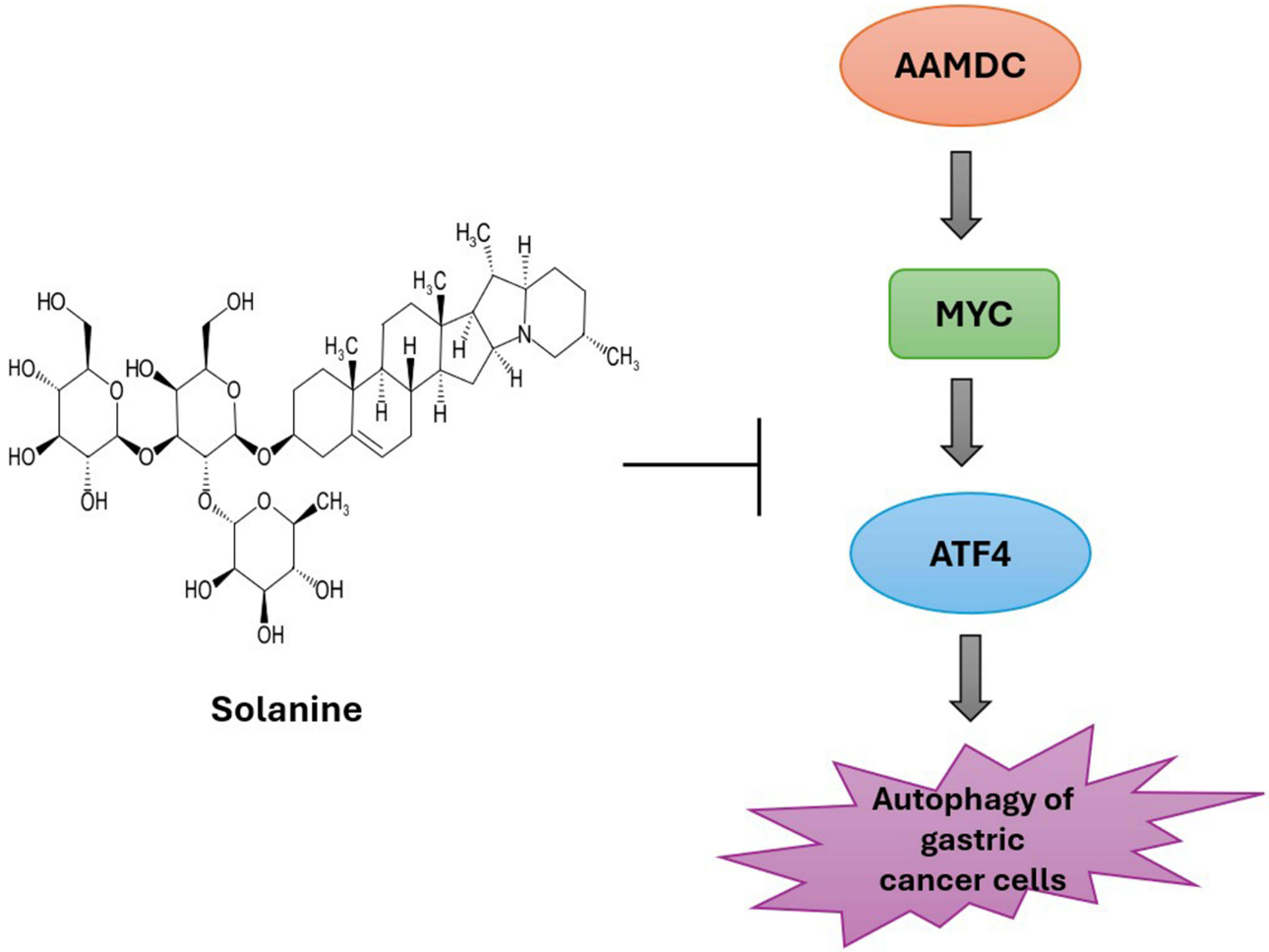

Figure 3 Autophagic effect of Solanine by downregulating AAMDC resulting in the deactivation of the MYC-ATF4 pathway in gastric cancer cells.
Abbreviations: AAMDC, Adipogenesis Associated Mth938 Domain Containing; MYC, MYC Proto-Oncogene; ATF4, Activating Transcription Factor 4.

activation in the human MCF-7 breast cancer cell lines.[58] Some studies have suggested that the potential of tomatine as an anticancer agent can be used when it is combined with other compounds (Figure 4). The combination of tomatine with curcumin more effectively inhibited the in vitro growth of prostate adenocarcinoma PC-3 cell lines and induced apoptosis. Additionally, in cancer cells, tomatine-curcumin combination reduced phospho-Akt and phospho-ERK1/2 levels which is involved in the regulation of cell proliferation and apoptosis.[59]

Recently, three new Solasodine-type glycoalkaloids, named solanigrinosides A–C, were isolated from *Solanum nigrum,* and their cytotoxicity was studied. These compounds, particularly solanigrinoside B, demonstrated significant cytotoxicity against LU-1, Hep-G2, and MCF-7 cells with IC_{50} values ranging from 4.6 μM to 56.2 μM.[60] Another research study isolated six new solanidane steroidal alkaloids, lyrasolanosides A–F, from *Solanum lyratum* among which Lyrasolanoside B showed significant cytotoxicity against A549 cells, inhibiting cell migration, invasion, and adhesion by downregulating the JAK2/STAT3 pathway and modulating E-cadherin, N-cadherin, and vimentin expression, thereby suppressing lung cancer metastasis. These studies underscore the importance of natural compounds in cancer treatment and contribute valuable insights into the efficacy of plant-derived bioactive molecules for drug.[61] Moreover, in a seminal study, the first systematic evaluation of phytochemical profiling, quantification, and bioactivities of polyphenolics and glycoalkaloids in different parts of *Solanum nigrum* L. was conducted. Remarkably, glycoalkaloids distributed throughout the plant exhibited significant cytotoxic activity against PC-3 prostate cancer cells. Although leaf extracts demonstrated the highest cytotoxicity, the specific glycoalkaloids responsible remain to be fully characterized. This significant

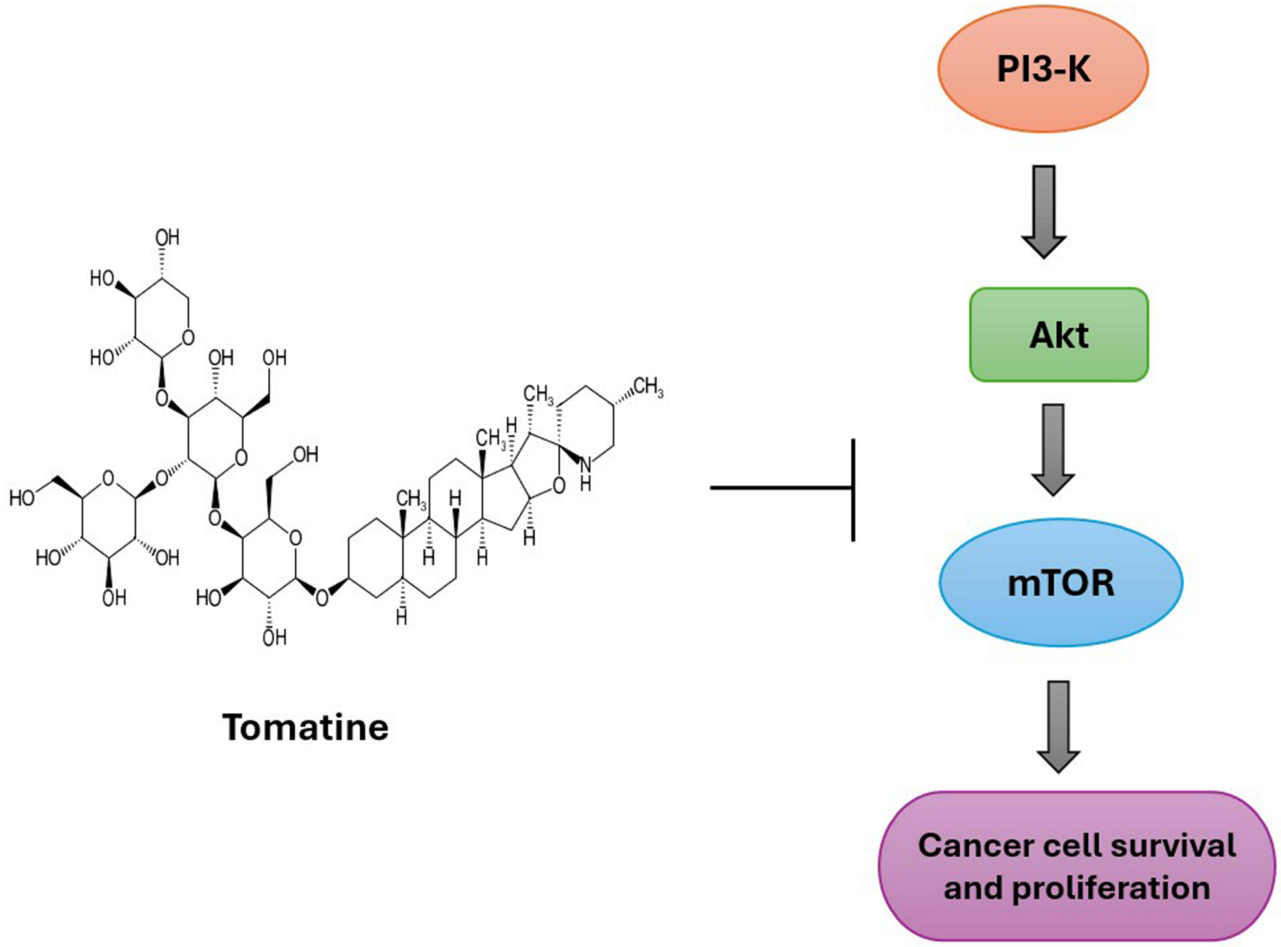

Figure 4 Tomatine alkaloid inhibiting PI3K/AKT/mTOR signaling pathway of cancer cells.
Abbreviations: PI3-K, phosphatidylinositol 3-kinase; Akt, protein kinase B; mTOR, mammalian target of rapamycin.

discovery underscores the untapped potential of *Solanum nigrum* L. as a source of novel bioactive compounds, particularly its glycoalkaloids, urging further exploration for their promising anticancer properties.[62]

Other Medicinal Properties

Solanum alkaloids have been traditionally used for a long period of time for treating various disorders. Researchers have explored *Solanum* species through studies involving crude extracts as well as isolated phytochemical compounds. Investigations into *Solanum* alkaloids have revealed their activity in the regulation of nervous system at lower dose levels. For example, solasodine was evaluated for its neuroprotective effects in rats against ischemia. The assessment revealed a reduction in lipid peroxidation (LPO) and nitric oxide (NO), as well as an increase in glutathione (GSH), catalase (CAT), and thiols. Histopathology studies indicated the protection of neurons in the coronal region of the brain after Solasodine administration.[63] In the case of β-solamarine, it did not influence acetylcholinesterase at lower doses but caused membrane damage at higher doses. Additionally, studies have indicated the possibility of synthesizing an optimal acetylcholinesterase inhibitor from solanocapsine and its derivatives Alzheimer's disease treatment.[64,65] A combination of alkaloids such as demissidine, tomatidine, solasodine, and dihydrosolacongestidine from *Solanum leucocarpum* exhibited bactericidal activities.[66] Solacasine from *Solanum pseudocapsicum* has been reported to possess antibacterial properties.[67] Solacongestidine alkaloid exhibited antifungal properties against various fungal strains, displaying Minimum Inhibitory Concentration (MIC) values and demonstrating efficacy through time-kill analysis.[68] Furthermore, solamargine and solasonine in 1:1 combination ratio exhibited potent inhibition and effectiveness against

the fungus *Rhizoctonia solani*.[69] Additionally, alkaloids such as α-solanine, solanidine, and α-chaconine were identified as compounds with anti-inflammatory properties. Research studies demonstrated that in Con A-induced Jurkat cells, α-chaconine and solanidine compounds markedly inhibited the generation of crucial inflammatory molecules, such as interleukin-2/8. Moreover, treatment with α-solanine and solanidine led to a notable decrease in the production of nitric oxide in raw macrophage cell lines where the inflammation is induced with lipopolysaccharide (LPS).[70] Anabasine alkaloid has been explored for its potential use as a biomarker for the assessment of tobacco in individuals undergoing nicotine replacement therapy.[71]

Desacetylsolaphyllidine and solaphyllidine alkaloids extracted from the plant *Solanum oblongifolium* were studied to evaluate their impact on locomotor activity. These alkaloids were found to decrease sleep duration, while solaphyllidine enhanced locomotor activity.[72] Additionally, the in vitro hepatoprotective activity of the khasianine alkaloid notably mitigated liver damage induced by carbon tetrachloride (CCl_4).[73] Extracts from various *Solanum* species have demonstrated potent antioxidant properties in DPPH, H_2O_2, FRAP and ABTS assays. The antioxidant activity was positively correlated with its alkaloid content, suggesting the potential of these alkaloid compounds as radical scavengers. However, the precise mechanism of their scavenging action through cytokine stimulation still requires further clarification.[74] In a comparative investigation of *Solanum* alkaloids, tomatidine and solasodine were evaluated for their effectiveness against LPS-stimulated inflammation in macrophages. It was observed that tomatidine exhibited greater efficacy compared to solasodine in suppressing inflammation. Tomatidine demonstrated more effective attenuation of NF-κB and JNK signaling molecule expression, thereby mitigating inflammation. This indicates that tomatidine possesses potent antimicrobial properties against *Staphylococcus aureus*, making it potential for the drug development against microbial infections either independently or in conjunction with conventional antibiotics.[75] Notably, germicidal properties were observed in solaverbascine, a novel alkaloid derived from *Solanum verbascifolium*.[76] An equimolar combination of solasonine and solamargine demonstrated increased leishmanicidal activity against *Leishmania amazonensis* (protozoa).[59] Peng et al reported that polyphenols derived from *S. nigrum* could serve as anti-obesity agents, promoting lysis of lipids in the liver, reducing triacylglycerides and LDL-cholesterol levels in the blood serum, thus inhibiting fatty acid synthesis.[77]

Recent research conducted explores the potential of *Solanum incanum* L. in malaria treatment, focusing on host-directed therapy (HDT). Extract fractions from S. incanum leaves exhibit prophylactic antimalarial activity, particularly the ethyl acetate fraction, which reduces δ-ALAD expression associated with Plasmodium growth. Phytochemical analysis reveals high terpenoids, flavonoids, and phenol levels in ethyl acetate and aqueous extracts. While alkaloids are moderate and quinones are high in crude extract, saponins are prevalent in all fractions. GC-MS analysis identifies compounds like 2-methyloctacosane, tetracosane, and decane.[78] Another research delved into *Solanum dasyphyllum* Schumach and Thonn's potential as an alternative antivenom against Naja nigricollis-induced toxicity, addressing limitations of conventional treatments. Phytochemical screening revealed tannins, cardiac glycosides, saponins, flavonoids, and alkaloids in the plant extract. In vivo studies on mice demonstrated the extract's ability to neutralize venom activity, lower mortality rates, and reduce lipid peroxidation and acetylcholinesterase activity. These studies demonstrate encouraging results, emphasizing the need for further research to fully harness the therapeutic benefits of the *Solanum* alkaloids.[79]

Conclusion

Cancer remains a leading cause of death worldwide, with its incidence expected to rise significantly by 2030. Traditional cancer treatments, though varied, often come with severe side effects and limitations. Consequently, there is a growing interest in plant-based compounds, especially phytochemicals, for their potential anticancer properties due to their safety, reduced toxicity, and cost-effectiveness. Phytochemicals, which are plant-derived compounds used in drug development studies, represent a highly effective and promising research area in healthcare sector. Among these phytochemicals, alkaloids from *Solanum* species stand out as having significant efficacy, making them ideal candidates for drug design. These alkaloids, including solasonine, solamargine, and α-chaconine, demonstrate potent anticancer activities through various mechanisms, like cell proliferation inhibition, apoptosis induction, and suppression of tumour metastasis. The efficacy of these compounds, combined with their traditional medicinal uses and easy methods for extraction and purification, make it a valuable resource in the treatment of cancer. These steroidal heterocyclic alkaloids interact with different signaling pathways, such as AKT, JNK, and P13, influencing cancer cells through various mechanisms,

including changes in caspase-3 expression, modulation of Bax and BCl-2 expression, regulation of ROS signaling, and inhibition of MMP (matrix metalloproteinase). These alkaloids can be utilized either alone or combining with other therapies or drugs which will improve their mechanism of action and efficacies. Alongside their anticancer potential, *Solanum* alkaloids also exhibit various medicinal properties, including antioxidant, anti-inflammatory, cholesterol-lowering, locomotor-enhancing, and antimicrobial activities. The future research should prioritise on studying the precise mechanism, comparative efficacy, potency, preclinical, toxicity studies, bioavailability, combination therapies, formulation and drug development of *Solanum* alkaloids. These continued research and exploration of *Solanum* alkaloids could lead to significant advancements in developing more effective and safer anticancer therapies, highlighting the critical importance of preserving plant biodiversity for medicinal applications.

Disclosure

The authors report no conflicts of interest in this work.

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