Chapter

Perspective Chapter: Integrated Network Pharmacology and Multiomics Approach to Elucidate the Repositioning of Fatal Food Toxins to Lifesaving Anticancer Drug

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Abstract

This research investigates repurposing potato glycoalkaloids as lifesaving anticancer drugs. There is integration of network pharmacology with multiomics. Solanine, chaconine, and their hydrolysis products' pharmacokinetics were tested using SwissADME. Solanine and chaconine targets were identified *via* reverse pharmacophore mapping. Through database mining, 26 solanine and chaconine targets were found in cancer genes. To understand gene function, KEGG and GO analyses were done. STRING was used to create a protein-protein interaction network to find similarities between chemicals and cancer. To find prognostic genes in various cancers, CytoHubba in Cytoscape identified hub genes and GEPIA2 did survival analysis. ADME testing for solanine and chaconine medication candidates failed. Their glycosylation boosted solubility and P-glycoprotein inhibition. Cancer targets shared by both drugs were elevated in cancer-related pathways such as Pi3k-Akt1 and HIF-1. Cell death control and programmed cell death genes were enriched in gene ontology study. We built a protein-protein interaction network with 26 nodes and 38 edges. The hub genes were STAT3, TLR4, FGF2, IL2, NFKB1, AR, CHUK, TRIM24, NOS3, and KDM1A. Survival research showed that these genes predict cancer prognosis. We found that solanine and chaconine may interact with cancer-related genes to fight cancer. Discovery of hub genes with prognostic significance sheds light on glycoalkaloids' anticancer processes.

Keywords: potato, glycoalkaloids, solanine and chaconine, network pharmacology, multiomics

1. Introduction

1.1 Drug repositioning

Drug repositioning or repurposing is an interesting way to reuse old drugs for new indications; For example, chloroquine, an old antimalarial drug, showed promising results for treating COVID-19, interfering with multidrug resistance (MDR) in several types of cancer, and chemo-sensitizing human leukemic cells. There is a great economic impact of drug repurposing on drug discovery for the treatment of many skin infectious diseases, neurological disorders, cancers, and orphan diseases [1]. In this aspect, the liver research laboratory (FAB-Lab, Faculty of Pharmacy, Mansoura University, Mansoura, and Egypt) has utilized several approaches for not only optimizing and enhancing the therapeutic effect of the commonly available natural products but also recognizing novel applications for them so that one therapeutic agent could be used for the treatment of several or complex conditions adopting different strategies for drug repositioning [2–12].

1.2 Food glycoalkaloids: toxic compounds in our daily foods

Glycoalkaloids are a family of chemical compounds that serve as secondary metabolites in plants, derived from alkaloids to which sugar groups are appended and naturally occurring in several plant species of the Solanaceae family, which are grown for ornamental or agricultural purposes. This includes widely consumed vegetables such as tomatoes, potatoes, eggplants, and peppers [13, 14].

The distribution of glycoalkaloids across plant species is influenced by genetic factors, environmental conditions, plant development stages, and postharvest practices [15]. The most common GA found in food plants are α-solanine and α-chaconine in potato, α-tomatine in tomato, and solamargine and α-solanine in eggplants [13, 16]. Glycoalkaloids have two main structural moieties: an aglycone moiety based on a 27 carbon atoms cholestane skeleton in addition to a ring containing nitrogen atom, thus shares both the steroidal and alkaloid chemical properties and pharmacological activities, and an oligosaccharide moiety [17]. The aglycone is derived from cholesterol and can be solasodine, solanidine, or tomatidine depending on the plant source. The oligosaccharide can vary in length and composition but usually contains glucose, galactose, rhamnose, or xylose units [15]. The glycoalkaloids are named according to their aglycone and oligosaccharide structure (**Figure 1**).

1.3 Biological activity

Glycoalkaloids play an important role in plants, serving as defense compounds against a variety of pathogens and herbivores. They can inhibit fungal growth, interfere with viral infection, disrupt insect feeding and development, and deter mammalian predators by their bitter taste and toxicity [18]. Glycoalkaloids can also affect plant-plant and plant-microorganism interactions in the soil by exuding or leaking from plant organs [3]. For example, glycoalkaloids from potato tubers can inhibit the germination of weed seeds and suppress the growth of soil-borne pathogens [3]. Glycoalkaloids can also modulate the expression of genes involved in plant stress responses and biosynthesis of other secondary metabolites [1]. Studies have shown that glycoalkaloids are involved in the regulation of plant growth and development, including the formation of roots, shoots, and leaves. They have also been reported

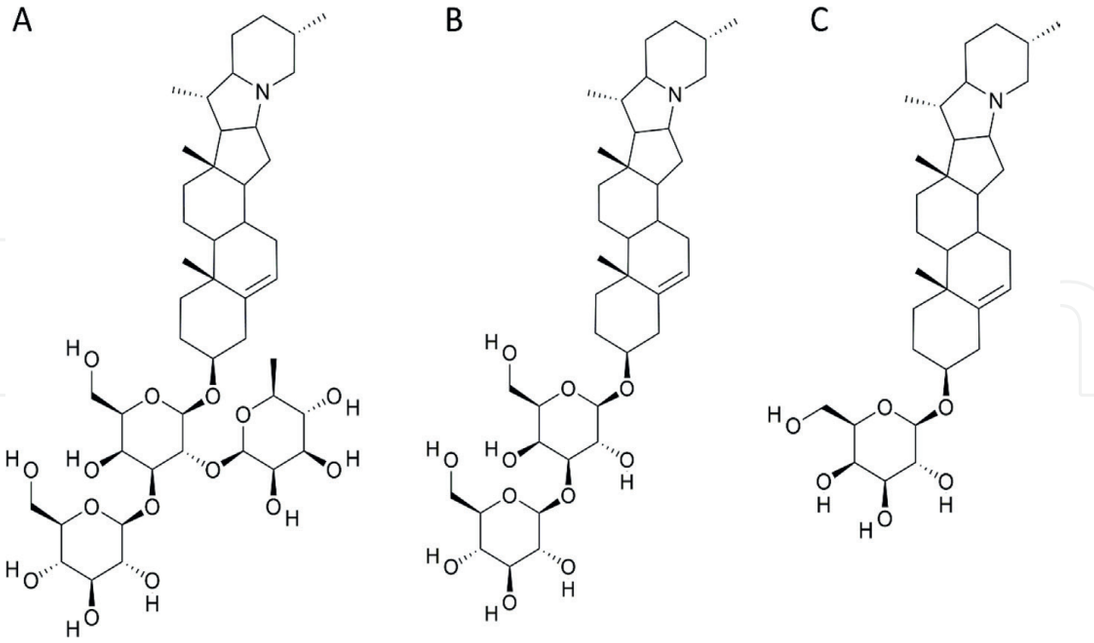

Figure 1.
Oligosaccharide can vary in length and composition. (A) α-solanine, 3 carbohydrate molecules, (B) β-solanine, 2 carbohydrate molecules and (C) γ-solanine, one carbohydrate molecules.

to have antioxidant properties, which can help protect plants from oxidative stress caused by environmental factors, such as UV radiation [19, 20].

1.4 Toxicity

Regarding human toxicity, sporadic outbreaks of poisoning may occur due to elevated levels of glycoalkaloids, as indicated by research studies, as they are largely resistant to home processing conditions such as baking, boiling, frying, and microwaving [21]. In humans, acute toxicity of potato glycoalkaloids causes gastrointestinal symptoms such as nausea, vomiting, and diarrhea. As a reference for risk assessment, the European Food Safety Authority established a lowest-observed-adverse-effect level of 1 mg total potato glycoalkaloids per kilogram of body weight per day [14]. The toxic effects of glycoalkaloids are due to their ability to inhibit cholinesterase activity, which can lead to symptoms such as nausea, vomiting, diarrhea, and even death at high doses [22]. The mechanism of toxicity consists of two processes: disturbance of membranes phospholipids bilayer [23] and inhibition of acetylcholinesterase [24], the latter can lead to a decrease in the activity of the central nervous system and the manifestation of neurological symptoms observed during poisoning (hallucinations, convulsions, depression etc.).

1.5 SAR of glycoalkaloids

The structure-activity relationship (SAR) of glycoalkaloids can be studied by analyzing the effects of modifications in the aglycone and the sugar moieties. The aglycone structure has a significant impact on the biological activity of glycoalkaloids. For example, solanine and solasonine differ only in their aglycone moieties; α-solanine has a solanidine aglycone, while solasonine has a solasodine aglycone. α-Solanine is more toxic than solasonine [25]. The teratogenic effect on hamsters when an alkaloid

is administered orally is more dependent on the presence or absence of unsaturation at C-5 and C-6 in the alkaloid rather than the specific molecular arrangement (stereochemistry) at C-22 or the position of the nitrogen atom in the ring [26, 27]. The biological activity of glycoalkaloids is influenced by the presence and type of sugar groups attached to them. Glycosylation can increase the solubility and stability of the aglycone, which may lead to better absorption by the body. Researchers examined the sensitivity of fungi to α-tomatine, its hydrolysis product β2-tomatine, and its aglycone tomatidine. The results showed that β2-tomatine was generally less toxic than α-tomatine, while the aglycone form was the least toxic, suggesting the role of the sugar in compound toxicity [28]. Enzymatic hydrolysis of one or more sugars from the tetrasaccharide moiety of α-tomatine has also been shown to restrict its binding to 3β-hydroxy sterols, thus reducing the toxicity of the compound [29].

In a cell model called RL95-2, it was discovered that α-chaconine has greater potential as an anticancer agent compared to α-solanine. Although both glycoalkaloids share the same aglycone component, they differ in their sugar groups, with α-chaconine containing chacotriose and α-solanine containing solatriose. This indicates that the higher toxicity of α-chaconine may be attributed to the presence of chacotriose in its sugar moiety [30]. Similarly, solamargine and solasonine are two glycoalkaloids that share the aglycone moiety while differ in the sugar moiety. Solamargine has chacotriose, while solasonine has solatriose. Solamargine exerted higher antiproliferative effect on all tested cancer and normal cell lines. Supporting that stronger toxicity is attributed to the chacotriose moiety [31]. More recently, a comparative study of solamargine and solasonine on Chinese hamster lung fibroblasts (V79) demonstrated that at a dose of 28.4 μg/ml of compounds the inhibition of proliferation for solamargine was more than 80%, while for solasonine did not exceed 40% [32].

When compared to α-solanine, α-chaconine, and solanidine, the glycoalkaloids extracted from potato sprouts demonstrated a higher level of inhibition of human serum cholinesterase, with inhibition level of 63%. The inhibition levels for α-solanine and α-chaconine were 52% and 41%, respectively, while solanidine showed no inhibition [33]. α-Solanine and α-chaconine show similar potential in their ability to inhibit the activity of bovine and human acetylcholinesterase (AChE). The aglycones solanidine, tomatidine, and solasodine do not have significant inhibitory effects. While the ability to disrupt cell membranes appears to be influenced by the sugar side chain, the structure of the steroid seems to play a more critical role in determining AChE inhibition. A sugar side chain is a necessary requirement for the inhibition of AChE to take place [23]. *In vitro* studies showed that solanidine demonstrated minimal estrogenic effects, while its parent glycoalkaloids α-chaconine and α-solanine did not exhibit such effects, suggesting the sugar moiety has a masking effect on the estrogenic activity of the aglycone [34]. Summary of SAR is presented in **Table 1**.

1.6 Potato glycoalkaloids

α-Solanine and α-chaconine are important cholestane glycoalkaloids sharing the solanidine residue (**Figure 2A**). The structures of α-chaconine and α-solanine are nearly identical, with the exception of their side chains. α-Solanine contains glucose, galactose, and rhamnose molecules in its side chains (**Figure 2B**), and α-chaconine is constituted of glucose and two rhamnose molecules (**Figure 2C**) [35, 36]. α-Solanine and α-chaconine are glycoalkaloids found in potatoes that have been shown to be toxic

Effector	Observed	Evidence	Ref.
Aglycone moiety (same sugar and different aglycone)	Solanidine is more active than solasodine	Solanine and solasonine differ only in their aglycone moieties. α-solanine has a solanidine aglycone, while solasonine has a solasodine aglycone. α-Solanine is more toxic than solasonine	[25]
	C-5 and C-6 unsaturation affect activity	The existence or lack of unsaturated bonds on carbon atoms five and six affects orally induced hamster teratogenicity	[26, 27]
Sugar moiety (same aglycone and different sugar)	A higher glycosylation state indicates higher activity	Fungi are more sensitive to α-tomatine than their hydrolysis product β2-tomatine and their parent aglycone tomatidine	[28]
		Enzymatic hydrolysis of one or more sugar residues from the tetrasaccharide moiety of α-tomatine restricts its binding to 3β-hydroxy sterols	[29]
		Solanidine could not inhibit the activity of cholinesterase compared to 52% inhibition for α-solanine and 41% inhibition for α-chaconine	[33]
	Chacotriose has more antiproliferative potency than solatriose	The antiproliferative potential of α-chaconine is higher than α-solanine	[30]
		The antiproliferative potential of solamargine is higher than solasonine	[31, 32]
	Solatriose has more cholinesterase inhibitory effect than chacotriose	52% cholinesterase inhibition for α-solanine and 41% for α-chaconine	[33]

Table 1.
Summary of structure activity relationship of glycoalkaloids.

to humans and animals if consumed in high doses [37]. α-Solanine and α-chaconine are biosynthesized from spirosolane glycoalkaloids, and a DOX family enzyme is involved in this process [38]. The types and distribution of glycoalkaloids identified in potatoes, as well as the factors affecting their rates of formation and biosynthesis, have been extensively discussed [39].

1.7 Anticancer potential of potato glycoalkaloids

Despite being considered potentially toxic, recent studies over the past decade suggest that glycoalkaloids may also have beneficial effects under certain doses and conditions of use. These potential applications include anticancer properties, anti-inflammatory [40–43], antinociceptive [44], antipyretic [40, 45], anticholesterol [25], antifungal, and antibacterial effects [46]. Many studies carried out on glycoalkaloids and their potential effects on cancer cell proliferation rate, cell cycle distribution, and apoptosis induction have confirmed these findings, for example, solasodine and solanidine on osteosarcoma cells [47]. The anticarcinogenic properties of pure α-chaconine and α-solanine obtained from potatoes were examined. The compounds reduced the proliferation of cervical, liver, lymphoma, and stomach cancer cells in a concentration-dependent manner. It is worth mentioning that α-chaconine was found more potent than α-solanine in terms of its anticarcinogenic effects [48].

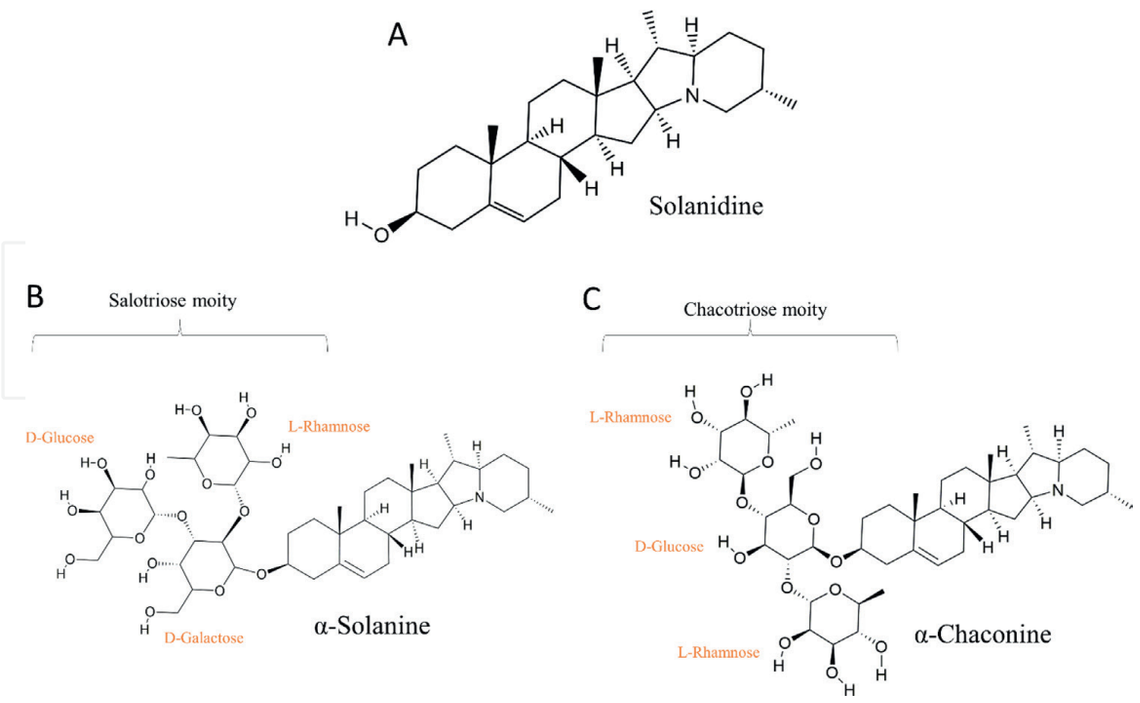

Figure 2.
(A) Structure of the parent structure of potato glycoalkaloids solanidine, (B) chemical composition of α-solanine, and (C) chemical composition of α-chaconine.

α-Chaconine demonstrated very potent activity against prostate and colon cancer cell lines and induced apoptosis *via* caspase-dependent and caspase-independent pathways [33, 49]. α-Chaconine is suggested to exert the cytotoxic effect through the suppression of PI3K/Akt and ERα signaling pathways. Research conducted on the RL95-2 human endometrial cancer cell line indicated that the genes encoding Akt and ERα exhibited reduced expression and activity [50].

Studies performed on AML-193 acute myeloid leukemia (AML) cells demonstrated that α-solanine induced morphological changes in cancer cells and regulated the expression of Bax and Bcl-2, well-established markers of apoptosis. Specifically, α-solanine increased the expression of Bax and miR-16. miR-16 is known to target Bcl-2, leading to an epigenetic regulation of Bcl-2 expression [51]. α-Solanine exhibited a more significant cytotoxic effect on human breast cancer MCF-7 and MDA-MB-231 cells compared to cycloheximide. Furthermore, α-Solanine can induce apoptosis and cell cycle arrest in the S phase in MCF-7 cells [52]. α-Solanine induced JNK-dependent apoptosis in HepG2 HCC cells while inhibited proliferation through downregulation of HDAC1 [53]. α-Solanine induces oxidative stress in hepatocellular carcinoma (HCC) HepG2 cells and regulates appropriate miRNAs controlling the NF-κB pathway, thus increasing NF-κB expression [53, 54].

The antiproliferative activity of glycoalkaloids is accompanied by anti-invasive properties. In the case of α-chaconine and α-solanine, they were found to exhibit an antimetastatic effect against melanoma, lung, and esophageal cancer cells. Both compounds achieved this by reducing the expression of MMP2/9 through targeting the primary oncogenic pathways [55–57]. What is particularly noteworthy is that in the case of A549 cells, a significant reduction in cell viability was observed when treated with doses higher than 1.5 μg mL^{-1} [56]. α-Chaconine exhibited anti-invasive and antiangiogenic effects in bovine aortic endothelial cells (BAECs) through reducing

MMP2 activity, this might be attributed to the downregulation of NF-κB levels, PI3K, and JNK phosphorylation [58]. α-Solanine exhibited similar effects and responses in human melanoma cell line A2058 [59].

1.8 Potato glycoalkaloids and drug discovery

There is currently a lack of research to support the use of glycoalkaloids as a cancer treatment target and the underlying biological mechanisms. As a result, further investigation and discussion on this topic are required. Network pharmacology is an interdisciplinary approach that integrates medicine, pharmacology, network biology, systems biology, and computer science. It exposes complex disease processes, which may be used to generate successful therapeutic approaches based on a thorough understanding of the systems involved [60–66]. Network pharmacology has been proven to be an effective tool for the acquisition of comprehensive and systematic insights into the polypharmacological properties of herbal medicines, and it is widely employed to investigate the therapeutic targets that are responsible for their pharmacological effects in diverse diseases, such as cancer [67–69]. Therefore, in this study, we adopted a network pharmacology approach to establish a network of the common α-solanine and α-chaconine cancer targets and their associated pathway. A network analysis of protein-protein interactions (PPI) was conducted to identify influential hub targets. Additionally, gene enrichment analysis of these target genes was performed using gene ontology (GO) and the Kyoto Encyclopedia of Genes and Genomes (KEGG).

2. Methods

2.1 Pharmacokinetic properties

The canonical SMILES (Simplified Molecular Input Line Entry System) format for solanidine, α-solanine, α-chaconine, β-solanine, β-chaconine, γ-solanine, and γ-chaconine was retrieved using the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). PubChem is a public database that provides access to chemical compounds and their associated information, including SMILES strings [70].

ADMET properties were tested for solanine, chaconine, and their parent molecule, solanodine using SwissADME [71]. All of the compounds were assessed for various properties, including lipophilicity measured by XLogP3, topological polar surface area (TPSA), hydrophobicity and solubility measured by Log S, saturation of carbons in sp3 hybridization (carbon fraction sp3), flexibility measured by rotatable bonds according to the Lipinski rule, ability to cross the blood-brain barrier (BBB), human intestinal absorption (HIA), potential interaction with P-glycoprotein (PGP), inhibition of cytochrome P450 isoenzymes, and skin permeation parameters.

2.2 Drug target prediction

The SMILES format if α-solanine and α-chaconine was imported to three computational tools for target prediction: (a) SuperPred (https://prediction.charite.de/index.php), a tool that predicts protein-ligand binding using a combination of machine learning models, including random forest and support vector machines [72]. Targets with both probability and model accuracy greater than 70% were selected.

(b) SwissTargetPrediction (http://www.swisstargetprediction.ch/), a tool that predicts drug targets based on a combination of bioinformatics and machine learning methods. Targets with a probability greater than zero were retrieved. (c) Similarity ensemble approach (https://sea.bkslab.org/), a method that predicts drug targets by comparing the chemical structure of compounds to known human protein structures. All human targets were retrieved from the similarity ensemble approach. The targets retrieved from each tool were normalized using the UniProt database (https://www.uniprot.org/) and merged for each compound. Duplicate targets were removed.

2.3 Cancer-related genes collection

This study collected cancer-related genes from Genecards database [73] (https://www.genecards.org/) and disease and gene network database [74] (DisGeNet: https://www.disgenet.org/). In DisGeNet, genes with gene-disease association (GDA) score equal or greater than 0.1 were obtained. In GeneCards genes with relevance score greater than 10 were obtained by using. The obtained genes from both databases were then combined, and duplicate genes were eliminated. The final dataset of cancer-related genes was used for further analysis.

2.4 Gene ontology and KEGG pathway analysis of cancer drug targets

Web-based gene set analysis toolkit (WebGestalt, http://www.webgestalt.org/option.php) is a web-based tool for functional interpretation of gene sets. It can be used to identify enriched biological themes, functional categories, and pathways among the input gene set, compare the input gene set with reference sets [75]. We employed WebGestalt to perform GO [76] and KEGG pathway analysis [77] for drug target genes in cancer. Gene ontology analysis was carried out to understand the biological process and molecular function of the drug target genes. Additionally, KEGG pathway analysis was also performed on these genes. Results with a false discovery rate (FDR) < 0.05 were considered significant.

2.5 PPI network construction and topology analysis

Protein-protein interaction (PPI) network was built using the Search Tool for the Retrieval of Interacting Genes/Proteins database [78, 79] (STRING v11.5; https://string-db.org/), a database that integrates diverse data sources to predict the presence and strength of functional associations between proteins. With a confidence score of 0.7, the PPI network was built then exported to Cytoscape v3.9.1 [80] for further analysis. Cytoscape is a software platform for visualizing molecular interaction networks and biological pathways. The topology of the network was analyzed using the Cytohubba plugin [81, 82], which is a Cytoscape plugin that measures the topological properties of the nodes in a network. The top 10 genes with the highest maximal clique centrality (MCC) were considered as hub genes.

2.6 Survival analysis

The overall survival (OS) and disease-free survival (DFS) of the target genes were analyzed by Gene Expression Profiling Interactive Analysis V.2 database (GEPIA2; http://gepia2.cancer-pku.cn/), which is an online tool used for the visualization, evaluation, and download of large-scale cancer-related genomics datasets. We

utilized this tool to generate a survival map that screened the prognostic value of the hub genes we selected in various cancers. "0.05" as the significance level, and "median" as the group cutoff.

3. Results

3.1 ADMET profiling

ADMET analysis is a challenging process in drug discovery. The SwissADME tool was applied to predict the pharmacokinetic properties of potato glycoalkaloids. Pharmacokinetic factors can be utilized to predict the absorption, distribution, metabolism, and elimination (ADME), as well as the toxicity of potential novel therapeutic compounds. The glycoalkaloids also have more rotatable bonds, hydrogen-bond acceptors and donors, and a larger TPSA than solanidine. These properties could be attributed to the polar nature of the glycosidic moiety, which can participate in hydrogen bonding and increase solubility in water. The lower lipophilicity of glycoalkaloids could also make them less permeable through biological membranes, as evidenced by the lower log Kp values.

The results show that the solubility and lipophilicity of the solanine and chaconine and their hydrolysis products vary based on their glycosylation state. In general, the glycosylated forms of solanine and chaconine have higher molecular weights and lower LogSw values compared to the aglycone solanidine. This suggests that the glycosylation of the compounds may affect their solubility and lipophilicity. Gastrointestinal (GI) absorption was found to be negatively correlated with the glycosylation states. Solanidine and the least glycosylated forms were found to be the higher GI absorption. Similarly, only solanidine is permeable across the blood-brain barrier (BBB), while none of the glycosylated solanines or chaconines can penetrate the BBB. This could be due to the larger size of the glycosylated molecules. All of the compounds, except for solanidine, are P-glycoprotein (Pgp) substrates, meaning they are recognized and effluxed by this membrane transporter, which might be the cause of their anticancer activity. None of the compounds are inhibitors of the various cytochrome P450 enzymes (**Table 2**).

Compounds with fewer Lipinski and Leadlikeness violations, higher bioavailability scores, are more likely to become successful drugs. Alpha and beta forms of solanine and chaconine have more Lipinski and Leadlikeness violations, lower bioavailability scores, compared to the gamma form and solanidine. This suggests that solanine and chaconine may have lower drug-likeness compared to solanidine. It seems that the presence of multiple glycosylation moieties in solanine and chaconine may contribute to their lower drug-likeness properties. The glycosidic moiety can influence the pharmacokinetics of the compound by affecting its absorption, distribution, metabolism, and excretion (ADME) properties (**Table 2**).

3.2 Drug targets in cancer

We aimed to identify potential drug targets for α-solanine and α-chaconine in cancer using SEA, SwissTargetPrediction, and Superpred online tools. We applied specific criteria and identified a total of 59 α-solanine targets and 62 α-chaconine targets. 46 targets were shared between both drugs (**Figure 3A**), so we focused our analysis on these genes to explore the common mechanism. We further researched

	Solanidine	α-Solanine	β-Solanine	γ-Solanine	α-Chaconine	β-Chaconine	γ-Chaconine
MW	397.64	868.06	721.92	559.78	852.06	705.92	559.78
Fraction Csp3	0.93	0.96	0.95	0.94	0.96	0.95	0.94
#Rotatable bonds	0	8	6	3	7	5	3
#H-bond acceptors	2	16	12	7	15	11	7
#H-bond donors	1	9	7	4	8	6	4
TPSA	23.47	240.69	181.77	102.62	220.46	161.54	102.62
Silicos-IT LogSw	−4.14	0.75	−0.54	−2.37	0.16	−1.12	−2.37
Silicos-IT solubility (mg/ml)	2.86E−02	4.84E+03	2.11E+02	2.42E+00	1.24E+03	5.39E+01	2.42E+00
Silicos-IT solubility (mol/l)	7.19E−05	5.57E+00	2.92E−01	4.32E−03	1.45E+00	7.64E−02	4.32E−03
Silicos-IT class	Moderately soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble
GI absorption	High	Low	Low	High	Low	Low	High
BBB permeant	Yes	No	No	No	No	No	No
Pgp substrate	No	Yes	Yes	Yes	Yes	Yes	Yes
CYP1A2 inhibitor	No	No	No	No	No	No	No
CYP2C19 inhibitor	No	No	No	No	No	No	No
CYP2C9 inhibitor	No	No	No	No	No	No	No
CYP2D6 inhibitor	No	No	No	No	No	No	No
CYP3A4 inhibitor	No	No	No	No	No	No	No
log Kp (cm/s)	−4.4	−10.31	−8.64	−6.53	−10.26	−8.19	−6.53
Lipinski #violations	1	3	3	1	3	3	1
Bioavailability Score	0.55	0.17	0.17	0.55	0.17	0.17	0.55
Leadlikeness #violations	2	2	1	2	1	1	2

Table 2.
ADME profile of main potato glycoalkaloids.

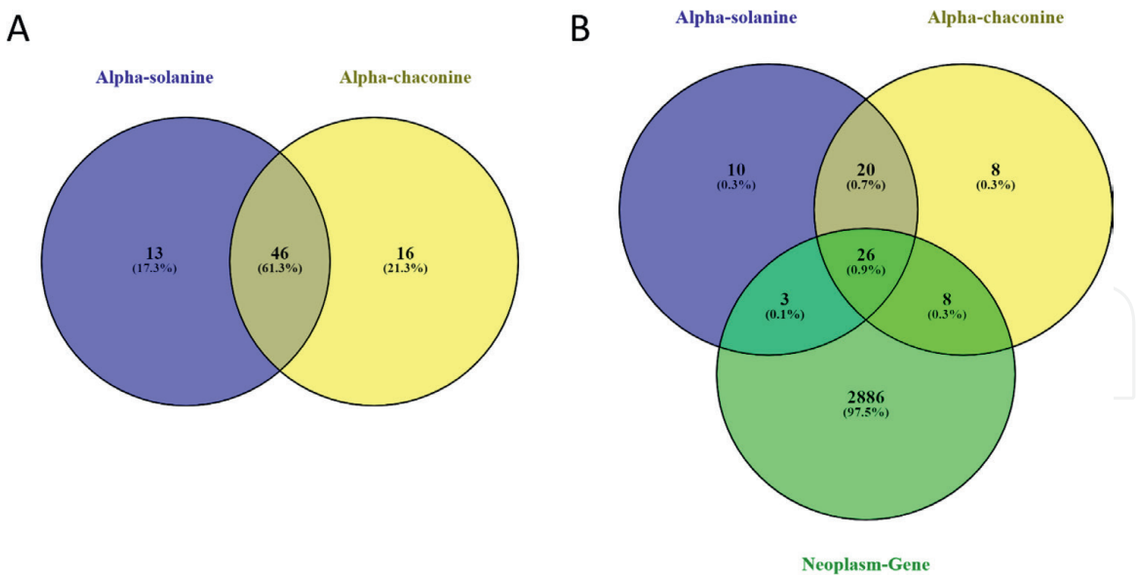

Figure 3.
(A) Common targets between alpha-solanine and alpha chaconine and (B) neoplasm related targets shared between alpha-solanine and alpha-chaconine.

these targets by looking at disease-related genes from Genecards, which resulted in 1458 genes, and using DisGeNet, we found 2510 targets related to cancer. After eliminating duplicates, we were left with 2925 targets that were relevant to cancer. These targets were then cross-referenced with known drug targets, resulting in a final list of 26 targets that were considered as potential drug targets for cancer treatment (**Figure 3B**). These targets were then chosen for further examination.

3.3 PPI network construction and topology analysis

We used the 26 drugs predicted targets in cancer to build a protein-protein interaction (PPI) network using the STRING database. The resulting PPI network consisted of 26 nodes and 38 edges, with an average node score of 2.92. PPI enrichment analysis revealed a P value of 3.65E−05 (**Figure 4A**). We then applied the MCC algorithm in Cytohubba to identify the top 10 hub genes in the network, which were found to be STAT3, TLR4, FGF2, IL2, NFKB1, AR, CHUK, TRIM24, NOS3 and KDM1A (**Figure 4B**).

3.4 Gene ontology and pathway analysis

We performed KEGG and GO pathway analysis on drug predicted targets imported to WebGesTalt. For KEGG analysis, PI3K-Akt1 pathway, HIF-1 pathway, and Th17 cell differentiation were among the most enriched pathways that are closely related to cancer development, progression, and drug resistance [83–90] (**Figure 5A**). Potential target genes in Pi3k-Akt1 and HIF-1 signaling pathways are visualized in **Figure 5B** and **C**. Among the enriched BP related to cancer, cellular response to oxygen-containing compound, cellular response to endogenous stimulus, regulation of cell death, regulation of programmed cell death, and regulation of intracellular signal transduction (**Figure 5D**). In addition, three molecular functions were identified, namely, signaling receptor binding, transcription factor binding, and chromatin binding (**Figure 5E**).

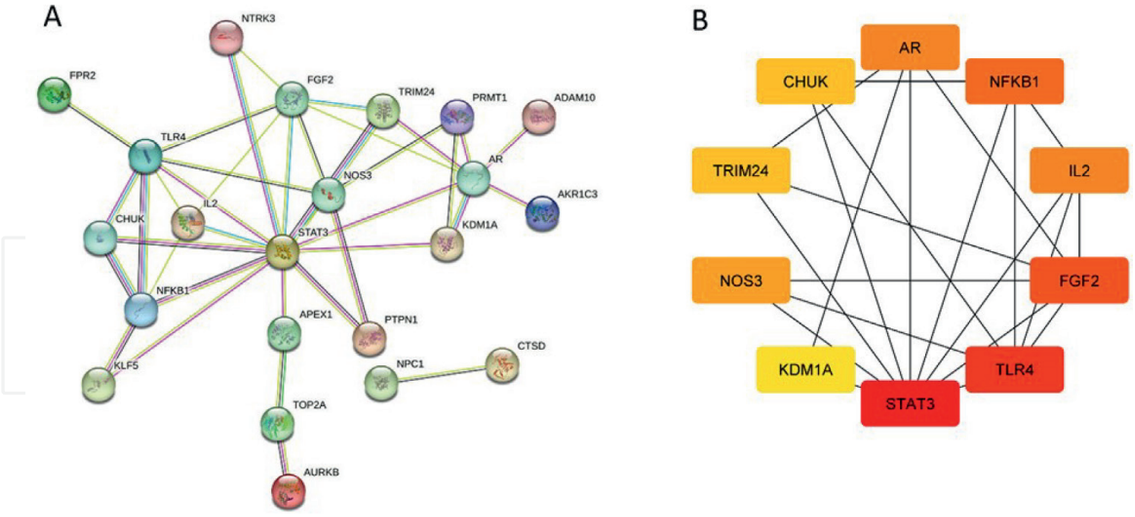

Figure 4.
PPI and topology analysis. (A) Original PPI obtained from STRING and (B) top 10 hub genes according to MCC algorithm in cytohubba.

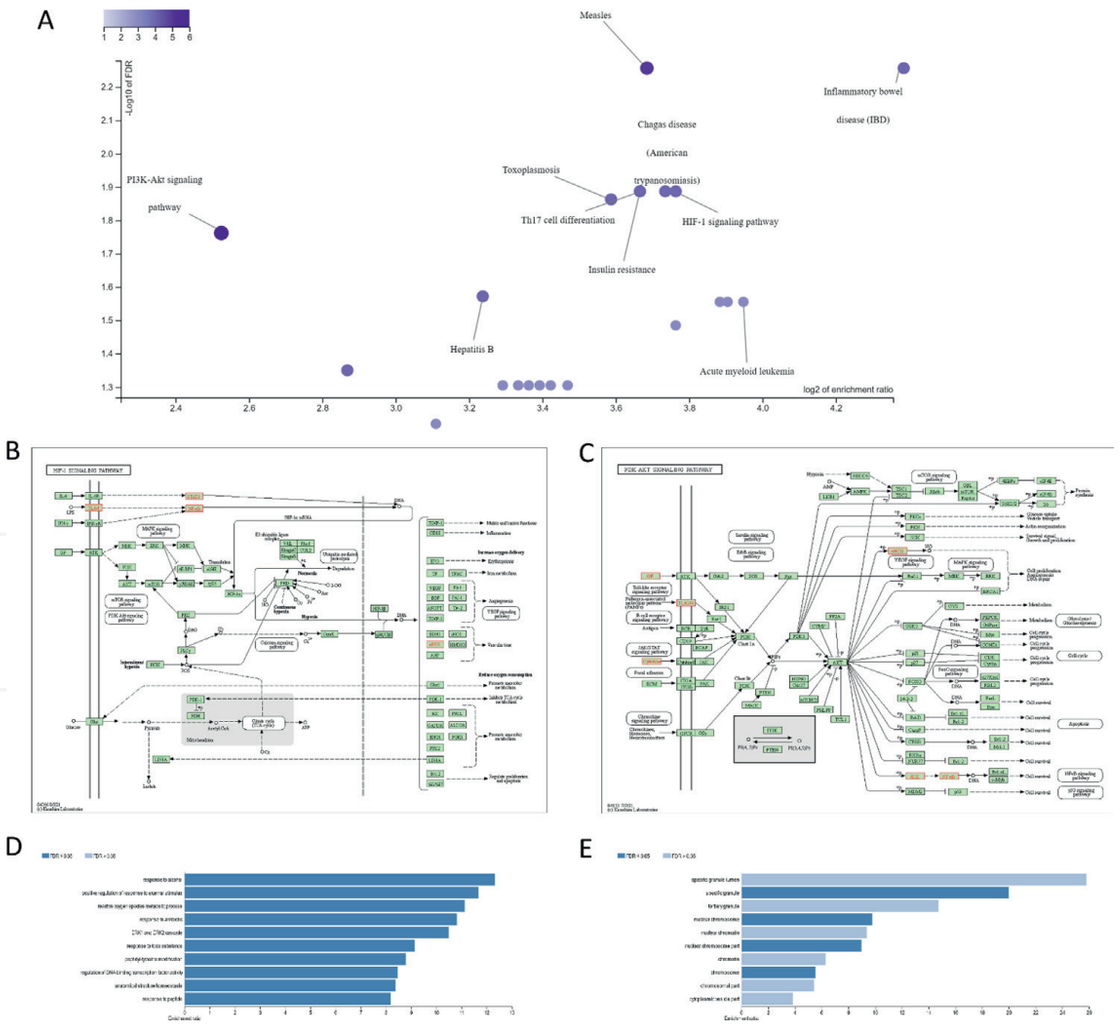

Figure 5.
KEGG pathway and gene ontology analysis of common target genes. (A) Enriched KEGG pathways according to WebG2estalt database. Darker node colors indicate higher significance, (B) target genes mapped to the PI3K-Akt1 pathway, (C) target genes mapped to the HIF-1 pathway, (D) enriched gene ontology biological processes and (E) enriched gene ontology molecular function.

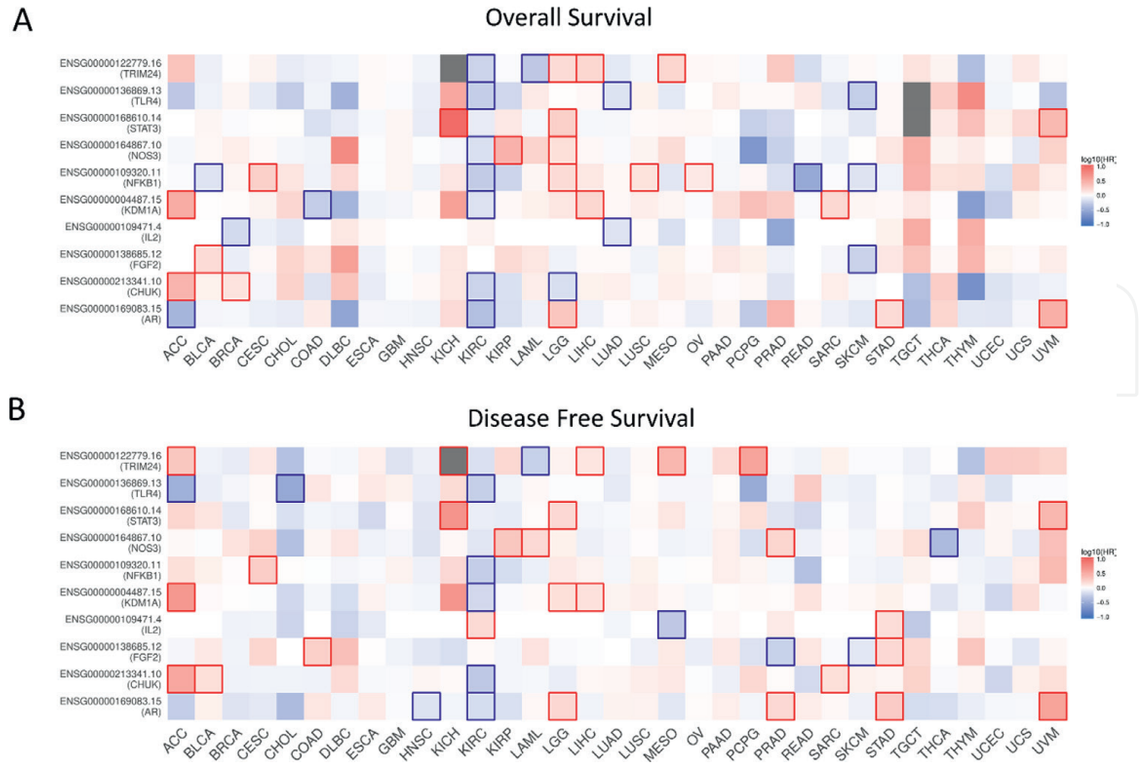

Figure 6.
Survival analysis of hub genes. (A) Pan-cancer overall survival and (B) pan-cancer disease free survival.

3.5 Survival analysis

To investigate the prognostic significance of hub genes identified from the network analysis, we performed pan-cancer survival analysis using the GEPIA2 database. We found that expression levels of several hub genes were significantly associated with patient survival in multiple cancer types. Notably, low expression levels of seven out of the 10 hub genes were associated with poor overall survival (OS) in kidney renal carcinoma (KIRC) (**Figure 6**). These findings suggest that the drug predicted targets may have potential therapeutic implications in cancer, and the enriched terms and pathways may provide insights into the underlying biological mechanisms.

4. Discussion

The conventional drug design approach follows the "one drug, one target" principle, whereas network pharmacology focuses on the relationship between drugs and diseases using a multi-targeted therapy approach [61]. This approach is innovative because it employs systems biology, network analysis, connectivity, and redundancy. Natural product studies have been effective in identifying new targets and uncovering unknown signaling pathways that interact with compounds [91]. The approach of network pharmacology offers fresh perspectives on the interconnectedness of therapeutic targets and diseases as a whole. It is a potent and encouraging method for understanding disease mechanisms at a systemic level and identifying possible bioactive ingredients [92]. The current study created a new network that provides an overview of the molecular mechanisms involved in the most prevalent potato glycoalkaloids.

A compound's ADME features predict its disposition inside an organism, contributing to its pharmacological (or toxicological) action [93, 94]. The study investigated the impact of glycosylation on the pharmacokinetic properties of potato glycoalkaloids using the SwissADME tool. The glycosylated forms of solanine and chaconine had higher molecular weights, lower LogSw values, and lower lipophilicity compared to the aglycone solanidine. The glycosylation state was negatively correlated with gastrointestinal (GI) absorption, and none of the glycosylated solanines or chaconines could penetrate the blood-brain barrier (BBB). The compounds were recognized and effluxed by P-glycoprotein (Pgp), which might be the cause of their anticancer activity. The glycosylation moieties also influenced the drug-likeness properties of the compounds (**Table 2**).

In the present study, drug targets were collected based on structure similarity and reverse pharmacophore mapping, 46 shared targets were discovered shared between both compounds. Cancer-related genes were collected by mining public databases, and 2925 unique genes were screened after removing duplicates. Among the drug targets and disease-related genes, 26 genes were shared between both datasets. GO and KEGG analysis identified several pathways and related diseases/disorders associated with the selected genes. The GO enrichment analysis showed the direct involvement of bioactive in the regulation of BC.

KEGG pathway analysis proved that PI3K-Akt1 pathway, HIF-1 pathway, and Th17 cell differentiation were among the most enriched pathways that are closely related to cancer development, progression, and drug resistance [83–90]. This helps to support that potato glycoalkaloids may be used for cancer treatment. For the GO analysis, enriched BP were cellular response to oxygen-containing compound, cellular response to endogenous stimulus, regulation of cell death, regulation of programmed cell death, and regulation of intracellular signal transduction, suggesting the property of glycoalkaloids as multi-target compounds.

To gain mechanistic insight into the drug targets, we used STRIG database to build PPI. The resulting PPI network consisted of 26 nodes and 38 edges, with an average node score of 2.92. PPI enrichment analysis revealed a P value of 3.65E−05 (**Figure 4A**). Applying the MCC algorithm in Cytohubba, we screened the top 10 hub genes in the network, namely, STAT3, TLR4, FGF2, IL2, NFKB1, AR, CHUK, TRIM24, NOS3, and KDM1A (**Figure 4B**). Survival analysis of hub genes identified several genes having prognostic significance in several types of cancers (**Figure 6**).

5. Conclusion

Our study suggests that solanine and chaconine, two glycoalkaloids found in potatoes, may have potential anticancer effects through their interactions with cancer-related genes. Despite the unpromising results of ADME testing, the glycosylation of solanine and chaconine increased their solubility and probability of inhibiting P-glycoprotein.

Our analysis identified 26 cancer targets common to both compounds, which were enriched in cancer-related pathways such as Pi3k-Akt1 and HIF-1 signaling pathways. Further analysis revealed that these genes were enriched in the regulation of cell death and programmed cell death. A protein-protein interaction network was constructed, and hub genes were identified as STAT3, TLR4, FGF2, IL2, NFKB1, AR, CHUK, TRIM24, NOS3, and KDM1A. Survival analysis indicated that these genes have prognostic value in one or more types of cancer.

Overall, our findings provide valuable insights into the potential mechanisms underlying the anticancer effects of solanine and chaconine and highlight the potential therapeutic applications of these glycoalkaloids in cancer treatment. The identification of hub genes with prognostic value suggests that they may serve as potential targets or biomarkers for diagnosis, prognosis, or treatment response in cancer. Further, research is needed to validate these findings and explore the full potential of solanine and chaconine in cancer therapy.

6. Future perspective

The potential of solanine and chaconine as cancer treatment requires further clinical validation. Studies should be designed to evaluate the efficacy, safety, and pharmacokinetics of these glycoalkaloids in different types of cancers. Furthermore, as predicted and validated, glycosylation enhances the solubility of this family of compounds, opening the gate to a new era of nano-based therapies of glycoalkaloids based on this fact. Mechanistic studies are needed to further validate the interaction between the compounds and screened targets to establish the connection between drugs and their anticancer potential. SAR analysis of the structures infers that structural modifications of these compounds might enhance their pharmacokinetic properties, alter their physicochemical properties, reduce their toxicity to normal cells, and potentiate their toxicity against cancer cells.

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Conflict of interest

There are no conflicts of interest associated with this publication, and the manuscript has been read and approved by all named authors.

List of abbreviations

AChE	acetylcholinesterase
ADME	absorption, distribution, metabolism, and excretion
AML	acute myeloid leukemia
AR	androgen receptor
BAECs	bovine aortic endothelial cells
Bax	Bcl-2-associated X protein
BBB	blood-brain barrier
Bcl-2	B-cell lymphoma 2
BP	biological processes

CHUK	conserved helix-loop-helix ubiquitous kinase
DFS	disease-free survival
FDR	false discovery rate
FGF2	fibroblast growth factor 2
GDA	gene dosage analyzer
GEPIA2	gene expression profiling interactive analysis 2
GI	gastrointestinal
GO	gene ontology
HCC	hepatocellular carcinoma
HDAC1	histone deacetylase 1
HIA	human intestinal absorption
HIF-1	hypoxia-inducible factor 1
IL2	interleukin 2
JNK	c-Jun N-terminal kinase
KDM1A	lysine demethylase 1A
KEGG	Kyoto encyclopedia of genes and genomes
MCC	maximal clique centrality
MDR	multidrug resistance
MMP2/9	matrix metalloproteinase 2 and 9
NFKB1	nuclear factor kappa B subunit 1
NF-κB	nuclear factor-kappa B
NOS3	nitric oxide synthase 3
OS	overall survival
PGP	P-glycoprotein
PPI	protein-protein interaction
RL95–2	endometrial adenocarcinoma.
SAR	structure-activity relationship
SEA	similarity ensemble approach
SMILES	simplified molecular input line entry system
STAT3	signal transducer and activator of transcription 3
STRING	search tool for the retrieval of interacting genes/proteins
Th17	T-helper 17 cells
TLR4	Toll-like receptor 4
TPSA	topological polar surface area
TRIM24	tripartite motif containing 24
V79	V79 Chinese hamster lung fibroblast cell line

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