Review of: "[Review Article] A Comprehensive Overview on Pharmacological and Therapeutic Insights of Solanum nigrum Linn"

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Potential competing interests: No potential competing interests to declare.

An Extensive Examination of The Pharmacological And Therapeutic Properties of Solanum nigrum Linn.of *Solanum nigrum* Linn.

Abstract

Solanum nigrum Linn., is a common medicinal herb of the Solanaceae family which is native to Southeast Asia and is now widely distributed in temperate to tropical regions of Europe, Asia, and America. *Solanum nigrum*, commonly known as black nightshade, boasts a rich repository of 188 chemical constituents. Among these, steroidal saponins, alkaloids, phenols, and polysaccharides stand out as the primary bioactive components. The exploration of its pharmacological potential has unveiled a diverse array of therapeutic benefits, including antitumor, anti-inflammatory, antioxidant, antibacterial, and neuroprotective properties, both in laboratory settings and animal studies. Traditional Indian medicine recognizes its efficacy as a hepatoprotective agent. This article presents a comprehensive and systematic overview of the phytochemical compositions, pharmacological properties, clinical trials, and therapeutic insights of *S. nigrum* to provide the latest information for further exploitation and applications of *S. nigrum* in functional foods and medicines.

Introduction

Solanum nigrum (black nightshade) is a medicinal plant member of the Solanaceae family of plants. This family consists of more than 2,000 species, which are distributed worldwide in tropical and subtropical regions and comprises many genera, well known for their therapeutic properties.

S. nigrum has been extensively used traditionally to treat various ailments such as pain, inflammation, and fever (1,2). The plant finds application in Oriental medical systems for diverse purposes, and as an antitumorigenic, antioxidant (3), anti-inflammatory (2), hepatoprotective (4), diuretic (2), and antipyretic agent (2). Various compounds have been identified which are responsible for assorted activities.

The major active components of *S.nigrum* are glycoalkaloids, glycoproteins, and polysaccharides. It also contains steroidal saponins, steroidal alkaloids, flavonoids, catechin, epicatechin, protocatechuic acid (PCA), coumarin, lignin, organic acids, volatile oils, polysaccharides, and other ingredients (5). The crude extract of *S. nigrum* and some of the above-mentioned compounds have been confirmed to have various effects, including antitumor, anticancer, antioxidant, antidepressant, antihypertensive, anti-inflammatory, hypolipidemic, hypoglycemic, anti-obesogenic, antidiabetic,

neuroprotective, immunomodulatory, antibacterial, and liver protective effects (6). Especially, drug researchers expect to find antitumor lead compounds from steroidal saponins and steroidal alkaloids.

The glycoalkaloids include solamargine, solasonine, and solanine, which belong to the tropane group of compounds. They comprise 95 percent of the total alkaloid concentration present in the plant and are found naturally in any part (7). One of the primary natural defenses of the plant lies in its toxicity, even in minute quantities.

We believe that this review is of great significance, therapeutic insight, and awareness for the further research or development of functional foods and bioactive molecules based on *S. nigrum.*

1. Chemical Composition of *Solanum nigrum*

As of 2022, analysis has revealed that *Solanum nigrum*, commonly known as black nightshade, contains a comprehensive array of 188 chemicals. These include steroidal alkaloids, steroidal saponins, glycoproteins, glycoalkaloids, organic acids, lignins, polysaccharides, and a variety of polyphenols. Among the polyphenols identified are gallic acid, catechin, protocatechuic acid (PCA), caffeic acid, epicatechin, rutin, and naringenin (8). In *Solanum nigrum*, the steroidal alkaloids mainly comprise three glycosides: solanines, solasonine, and solamargine (SM). Extensive research in the field of natural products has focused on the study of these glycosides, primarily found in immature fruits of *Solanum nigrum* (9). The majority of alkaloids identified throughout the entirety of the *Solanum nigrum* herb belong to the category of steroidal alkaloids. These compounds share a common fundamental structure known as cyclopentanoperhydrophenanthrene. Researchers are currently conducting widespread investigations into this structural motif as a promising candidate for antitumor activity (10).

As early as 1982, Japanese researchers utilized ethanol for the isolation of two steroidal alkaloids, solasonine and solamargine, from immature fruits. These glycosides are connected by glycosidic bonds and share the same glycoside, solasodine. (11). Since then, numerous steroidal alkaloids have been discovered in *S. nigrum* fruits, including compounds like 7a-OH-kekasianine, 7a-OH SM, 7a-OH solasonine, 12b,27-dihydroxy solanine-3-O-b-D-glucopyranoside, and 27-solasonine-3-O-b-D-glucopyranosyl-(1→4)-a-L-rhamnopyranoside-(1→2)-[a-L-rhamnopyranoside-(1→4)]-b-D-glucopyranoside (12,13).

In addition to these, in 2010, the anti-inflammatory and anticonvulsant activity of the ethanolic extract of *S. nigrum* was assessed using carrageenan paw edema and supramaximal electric shock (MES) methods, with three varying doses (100, 200, and 300 mg/kg b.w) administered. The ethanolic extract of *S. nigrum* demonstrated a notable dose-dependent anti-inflammatory effect ($P < 0.01$) and anticonvulsant effect ($P < 0.05$). The presence of flavonoids in the berries could potentially account for this observed activity (14).

2. Pharmacological Activity

2.1. Anti-diabetic Activities

Solanum nigrum Linn. is a common medicinal plant possessing a wide variety of pharmacological activity. Current

treatment of diabetes mellitus has plenty of adverse effects, necessitating the search for alternate drugs.

This study aimed to investigate the potential antidiabetic and nephroprotective effects of*Solanum nigrum* Linn. Fruit (SNE) in diabetic rats. Nine groups of animals were divided into two experimental protocols, including nondiabetic controls (NDCs) and diabetic rats induced with streptozotocin. Diabetic rats were treated with SNE (D-SNE), insulin (D-I), or left untreated (D) for 8 weeks. Additionally, four groups were examined for diabetic nephropathy (DN) over 16 weeks. Blood urea nitrogen (BUN), creatinine (Cr), magnesium, nitric oxide (NO), and malondialdehyde (MDA) levels were assessed, and kidney samples were analyzed for MDA, NO levels, and renal damage.

Fariba et al. have demonstrated that SNE effectively reduced blood glucose levels in diabetic rats and was more effective than insulin (15). Moreover, SNE decreased levels of blood urea nitrogen (BUN), creatinine (Cr), kidney weight, and damage after 8 and 16 weeks of administration. Levels of nitric oxide (NO) and malondialdehyde (MDA) in both plasma and kidney also decreased (15). These findings suggest that SNE may be beneficial in managing diabetes and preventing diabetic nephropathy (DN).

In a study conducted in 2017, the antidiabetic effect of the Aqueous Extract of*Solanum nigrum* Linn Berries (AESNB) was evaluated in alloxan-induced diabetic Wistar rats. The study involved five groups of rats: normal control, diabetic control, AESNB (at doses of 200 mg/kg/day and 400 mg/kg/day), and a standard group treated with glimepiride (at a dose of 0.1 mg/kg/day). Diabetes was induced using alloxan. Glimepiride and AESNB were administered orally. Fasting blood glucose levels were measured on days 0, 1, 7, 14, and 21. After 21 days, pancreases were histopathologically analyzed post-sacrifice. Statistical analysis was conducted using one-way ANOVA.

The aqueous extract of *Solanum nigrum* Linn berries at doses of 200 mg/kg/day and 400 mg/kg/day significantly reduced blood glucose levels, with the higher dose showing a highly significant reduction starting from day 7 (16). Glimepiride, the standard drug, normalized blood glucose levels by day 21. Additionally, histopathological examination revealed pancreatic beta cell regeneration in the AESNB group.

The aqueous extract of *Solanum nigrum* Linn berries possesses antidiabetic activity (16).

2.2. Anti-inflammatory Activity

Inflammation represents a transient reaction of the immune system, often addressed through the use of conventional anti-inflammatory medications. In recent years, due to the adverse effects of the drugs, the demand for alternative inflammation treatments with fewer side effects is increasing. Exosomes, being extracellular vesicles released by most eukaryotic cells, have garnered attention as a potential avenue for cell-free therapy in inflammatory conditions owing to their immunomodulatory and anti-inflammatory attributes. Recent trends in exosome research have shifted focus from those derived from animal cells towards plant-derived exosome-like nanoparticles (PDENs).

In a study conducted in 2024, Emmanuela et al. investigated the anti-inflammatory potential of plant-derived exosome-like nanoparticles (PDENs) obtained from black nightshade berries (*Solanum nigrum* L.). PDENs were found to be internalized by the RAW264.7 macrophage cell line within 2 hours of exposure without inducing any cytotoxic effects up to a

concentration of 2.5 µg/mL (17). Notably, treatment with PDENs significantly reduced the expression of the pro-inflammatory cytokine gene IL-6 and IL-6 protein levels by up to 97.28% in LPS-stimulated RAW264.7 cells (17). The results of this study also demonstrated the anti-inflammatory activity of PDEN by suppressing the production of IL-6 in LPS-stimulated RAW264.7 cells.

2.3. Anti-cancer Activities

L-asparaginase is used in chemotherapy for acute lymphoblastic leukemia and other cancers. L-asparaginase derived from a bacterial source triggers immune responses. This study explores *Solanum nigrum* as a new source of L-asparaginase to mitigate immune responses triggered by bacterial-derived L-asparaginase, commonly used in chemotherapy for various cancers, including acute lymphoblastic leukemia. The antitumor activity of *Solanum nigrum* methanol extract was evaluated using the potato disc assay. Through purification, the enzyme was obtained to homogeneity with a recovery rate of 61.99% (18). Optimal conditions for enzyme activity were determined, resulting in a high L-asparaginase titer. Molecular weight analysis revealed a size of 32 ± 5 kDa. The fruit extract exhibited significant anti-tumorigenic efficacy and demonstrated potent antifungal and antibacterial properties (18). Molecular docking studies provided insights into the structural motifs and interactions underlying the activity of L-asparaginase. *Solanum nigrum* is suggested as a promising source of L-asparaginase and phytochemicals, offering potential for the development of novel anticancer drugs.

Traditional chemotherapy is being reconsidered due to its systemic toxicity. Combination chemotherapy, which involves administering multiple chemotherapeutic drugs targeting different biochemical or molecular pathways, has emerged as a promising approach to enhance efficacy and mitigate adverse effects across various cancer types. However, there is a growing interest in exploring natural-based alternatives with lower toxicity. Experimental evidence suggests that herbal extracts like *Solanum nigrum* and *Claviceps purpurea*, as well as isolated herbal compounds such as curcumin, resveratrol, and matairesinol, when combined with anti-tumoral drugs, may help overcome resistance to cancer therapy and provide chemoprotective effects (19). Nevertheless, it's important to acknowledge that plant products carry risks, including herb-drug interactions and adverse effects, which need to be carefully considered.

In a study conducted in 2018, the anti-oral cancer properties of*Solanum nigrum*, a Chinese herb known for its potential in suppressing various cancer types, particularly oral squamous cell carcinoma (OSCC), were investigated. Human oral squamous cancer cells (SCC-4) were utilized to assess the effects of aqueous extracts of *Solanum nigrum* (AESN) on cancer cell proliferation, cell cycle, mitochondrial function, and apoptosis. The results indicated that AESN significantly increased the production of reactive oxygen species, activated caspase-9 and caspase-3, and triggered the mitochondrial apoptotic pathway in SCC-4 cells (20). Moreover, AESN treatment led to a dose-dependent inhibition of glucose uptake, resulting in mitochondrial fission (20). These findings suggest that AESN may have potential as a functional food in adjuvant chemotherapy for treating human oral cancer by suppressing mitochondrial function.

In another study, six isolated fractions (ethyl acetate, petroleum ether, chloroform, n-butanol, ethanol, and aqueous) from *Solanum nigrum* were investigated for their cytotoxic effects on various cell lines, including HepG2, HeLa, and baby hamster kidney (BHK) cells. Cell viability assays were conducted to assess the cytotoxicity of the fractions, and lactate

dehydrogenase and vascular endothelial growth factor assays were performed on the most active fraction to further analyze its cytotoxicity. HPLC analysis was also conducted to examine the biological activity of compounds in the most active fractions. The ethyl acetate fraction of *S. nigrum* exhibited potent cytotoxic activity against HepG2 cells, with an IC_{50} value of 7.89 µg/mL (21). Other fractions also demonstrated significant anticancer activity against HepG2 and HeLa cells, while showing no cytotoxicity in BHK cells. These findings highlight the high antiproliferative potential of the ethyl acetate fraction of *S. nigrum* against HepG2 cells and suggest the potential therapeutic application of S. nigrum fractions in cancer treatment, with minimal toxicity to normal cells.

In a study by Zhang et al., the anti-cancer effect of solamargine, an active ingredient of *Solanum nigrum*, was investigated in human cholangiocarcinoma QBC939 cells. The results showed that solamargine inhibited cell viability in a dose-dependent manner and induced apoptosis in QBC939 cells. Additionally, solamargine altered the mitochondrial membrane potential and modulated the expression of apoptosis-related genes and proteins. Specifically, it decreased the mRNA levels of anti-apoptotic genes such as Bcl-2 and increased the mRNA levels of pro-apoptotic genes like Bax. Western blot analysis further confirmed these findings, showing inhibition of Bcl-2 and poly ADP ribose polymerase (PARP) expression, and promotion of Bax, cleaved PARP, caspase 3, cleaved caspase 3, and caspase 7 expression by solamargine. (22). These results suggest that solamargine induces apoptosis via the mitochondrial pathway and alters the expression of apoptosis-associated proteins in cholangiocarcinoma cells. Overall, this in vitro study suggests that solamargine could be a promising chemotherapeutic agent for cholangiocarcinoma in clinical practice.

Nath et al. present the remarkable efficacy of uttroside B, a potent saponin derived from *Solanum nigrum* Linn, against liver cancer, which has not been reported before. Isolated from the leaves of *Solanum nigrum* Linn, a plant widely used in traditional medicine, uttroside B is known for its anticancer properties. It exhibits ten times higher cytotoxicity against the liver cancer cell line HepG2 compared to sorafenib, the only FDA-approved drug for liver cancer. Importantly, uttroside B induces cytotoxicity in all liver cancer cell lines, regardless of their HBV status, while sparing normal hepatocytes. Mechanistically, it induces apoptosis in HepG2 cells by down-regulating the activation of MAPK and mTOR pathways.(23). In animal studies, uttroside B significantly reduces HepG2-xenograft tumor size in NOD-SCID mice, and its safety is confirmed through acute and chronic toxicity studies in Swiss albino mice (23). These findings underscore the potential of uttroside B as a promising therapeutic agent against liver cancer, particularly in cases where current chemotherapeutic options are limited.

2.3.1. Breast Cancer

Chemotherapy, while the primary approach for treating advanced and recurrent carcinoma, is hindered by low response rates, drug resistance, and adverse effects impacting patient quality of life. Recent studies have explored a connection between epithelial-mesenchymal transition (EMT) and chemotherapy resistance. Researchers have identified the aqueous extract of *Solanum nigrum* (AESN) as a key component in traditional Chinese medicine formulas for cancer treatment, demonstrating anti-tumor effects (24). They examined AESN's ability to suppress EMT in MCF-7 breast cancer cells and observed significant inhibition of cell viability through apoptosis induction, cell cycle arrest, and mitochondrial dysfunction. AESN treatment led to decreased expression of EMT markers and mitochondrial fission (24). These findings suggest

AESN's potential in treating breast cancer cells and warrant further investigation for integrative cancer therapy targeting breast cancer proliferation, metastasis, and migration.

In a study conducted in 2020, the aim was to evaluate the cytotoxic, cell cycle arrest, and apoptotic induction effects of a 70% ethanol extract obtained from the fruit of *Solanum nigrum* L. on MCF-7 human breast cancer cells. The fruit was processed into a semisolid extract, which was then analyzed for phytochemical composition. Cytotoxicity was evaluated using MTT assays on MCF-7 cancer and Vero normal cells, while apoptotic and cell cycle arrest analyses were conducted using flow cytometry. Results showed the extract contained phenolic and flavonoid compounds, with glycitin being the most abundant isoflavone. The extract selectively inhibited MCF-7 cell proliferation with an IC_{50} value of 40.77±4.86 µg/mL, while showing lower cytotoxicity towards Vero cells (IC_{50}: 298.96 ± 27.28 µg/mL) (25). Cell cycle analysis indicated arrest in the S phase, progressing to the G2/M phase at half the IC50 value. Apoptosis induction was observed in MCF-7 cells (43.31 %), comparable to doxorubicin (59.14 %). (25). Solamargine was identified as a potential active anticancer compound. Overall, the ethanolic-70% extract of *S. nigrum* fruit exhibited cytotoxicity against MCF-7 cells and minimal toxicity to Vero cells, suggesting its potential as an anticancer agent for breast cancer treatment.

2.3.2. Gastric Cancer

Solasonine, a steroidal glycoalkaloid found in *Solanum nigrum* Linn., has demonstrated efficacy against various human cancers, but its activity against gastric cancer has not been extensively studied. A study conducted in 2022 aimed to investigate the impact of solasonine on human gastric cancer SGC-7901 cells. Results revealed that solasonine inhibited SGC-7901 cell proliferation in a dose-dependent manner and induced cell cycle arrest at the G2 phase (26). Treatment with solasonine led to significant downregulation of Bcl-2 and Caspase-3 protein expression, while reducing Bax and Bcl-xL protein expression in SGC-7901 cells. Additionally, solasonine exhibited a comparable inhibitory effect on SGC-7901 cell proliferation compared to cisplatin and induced apoptosis through both the endoplasmic reticulum stress pathway and the mitochondrial pathway (26). These findings suggest that solasonine holds promise as a potential therapeutic agent for gastric cancer treatment.

2.3.3. Cytotoxic Activities

In this study, the cytotoxic effects of hydro-alcoholic extracts from*Cucurbita pepo* (*C. pepo*) and *Solanum nigrum* (*S. nigrum*) were investigated on both normal (Chinese hamster ovarian cells and rat fibroblast) and cancer (HepG2 and CT26) cell lines. The IC_{50} values of the extracts were determined for each cell line using a clonogenic assay method. Results indicated that the IC50 value of the *S. nigrum* extract was significantly lower than that of the C. pepo extract for all four cell lines ($P < 0.05$). Additionally, the IC50 value of the *S. nigrum* extract was significantly higher than that of Taxus baccata and cisplatin, which served as positive control anticancer compounds, on all four cell lines ($P < 0.05$). Thus, it was concluded that the *S. nigrum* extract exhibits cytotoxicity similar to that of the T. baccata extract on cancer cells.

2.3.4. Hepatocellular Carcinoma

The effectiveness of chemotherapy in treating advanced and recurrent hepatocellular carcinoma (HCC) is hindered by low

response rates, drug resistance, and significant adverse effects, leading to a diminished quality of life for patients. In a study conducted in 2015, the efficacy of combining *Solanum nigrum* extract (AE-SN), a component of traditional Chinese medicine, with standard chemotherapy drugs cisplatin or doxorubicin in the treatment of hepatocellular carcinoma (HCC), was investigated. Results indicated that integrating AE-SN with cisplatin or doxorubicin enhanced their cytotoxic effects on HCC cells, triggering apoptotic cell death via caspase-7 cleavage and autophagic cell death through LC-3 A/B II accumulation (28). This suggests that AE-SN could complement standard chemotherapy, potentially offering a promising approach for treating HCC patients.

In a study conducted in 2015, the protective effects of*Solanum nigrum* against alcoholic liver damage were aimed to be assessed in both primary hepatocytes and mice using glutathione S-transferase alpha 1 (GSTA1) as a marker. Results indicated that the presence of *S. nigrum* aqueous extracts (100 mg/mL) prevented hepatocytic damage induced by ethanol, with GSTA1 showing greater sensitivity compared to alanine aminotransferase and aspartate aminotransferase (29). Mice treated with *S. nigrum* aqueous extracts (150 mg/kg) alongside ethanol exhibited significant mitigation of ethanol-induced hepatotoxicity, as evidenced by reduced serum transaminases and variations in hepatic oxidative indices and GSTA1 levels compared to the model group and mice receiving higher doses of *S. nigrum* extracts (200 mg/kg). These effects were significantly different from the model group and comparable to the positive drug group, suggesting that *S. nigrum* confers hepatoprotective effects against ethanol-induced injury both in vitro and in vivo by preserving hepatocyte integrity and reducing liver GSTA1 release, thereby enhancing liver detoxification.

The aim of this study was to investigate the immunohistochemical and histopathological changes, as well as the chemoprotective effects of aqueous and alcoholic extracts of *Solanum nigrum* on a rat model of N-nitrosodiethylamine (NDEA)-induced hepatocellular carcinoma (HCC). Eighty-two male Wistar rats weighing 200-250 g and aged 15 weeks were divided into ten groups. HCC was induced in specific groups using NDEA and phenobarbitone for 16 weeks. Various treatment regimens were administered orally for 28 days. Liver samples were collected to assess gross and histopathological lesions, as well as the activity of cleaved caspase-3 and the chemopreventive effects of *Solanum nigrum* extracts on HCC. Results indicated that administration of the alcoholic extract of *Solanum nigrum* and sorafenib reduced the severity of liver lesions in NDEA/phenobarbital-treated rats. Immunohistochemical analysis revealed limited caspase-3-positive cells in hepatocytes treated with a higher dose of the alcoholic extract of *Solanum nigrum*, comparable to sorafenib (30). Oral administration of *Solanum nigrum* extracts for 28 days led to significant rejuvenation in liver structure in a dose-dependent manner in rats.

2.3.5. Colon Cancer

This study utilized network pharmacology and molecular docking techniques to investigate the components and mechanisms of *Solanum nigrum* L. (SNL), or Longkui, a Chinese herb, for its potential in treating colon cancer.

The study gathered components of *Solanum nigrum* L. (SNL) from various databases, including TCMSP, ETCM, HERB, and NPASS. Target proteins of these components were identified or predicted using databases such as TCMSP, SEA, SwissTargetPrediction, and STITCH, while colon cancer-related target genes were sourced from the TCGA and GTEx databases. Interaction networks were constructed using Cytoscape 3.7.2, and Gene Ontology and KEGG pathways were

enriched using the David 6.8 online tool. Molecular docking was employed to verify the binding of key components and targets, and the efficiency of apigenin and kaempferol binding to the AURKB protein in CT26 cells was assessed using the cellular thermal shift assay (CETSA).

A total of 37 components of *Solanum nigrum* L. (SNL), 796 SNL targets, 5,356 colon cancer genes, and 241 shared targets between SNL and colon cancer were identified. Through topology analysis, 43 key targets were identified, involved in various biological processes such as signal transduction, drug response, and protein phosphorylation. Additionally, 104 signaling pathways, including pathways in cancer, human cytomegalovirus infection, and the PI3K-Akt signaling pathway, were implicated. Molecular docking confirmed the binding of four key components (quercetin, apigenin, kaempferol, and luteolin) to these targets. CETSA results demonstrated the ability of apigenin and kaempferol to bind to the AURKB protein, thus exhibiting anti-colorectal cancer effects (31)

Quercetin, apigenin, kaempferol, and luteolin are primary components of *Solanum nigrum* L. (SNL) used in colon cancer treatment (31). SNL influences various biological processes through signaling pathways, including those involved in cancer, PI3K-Akt, and cell cycle regulation.

2.3.6. Prostate Cancer

A study conducted in 2016 investigates the inhibitory effects of solanine, a naturally occurring steroidal glycoalkaloid found in nightshade (*Solanum nigrum* Linn.), on cancer development both in vivo and in vitro using cultured human prostate cancer cells (DU145). Results demonstrate that solanine injection significantly suppresses tumor cell growth in xenograft athymic nude mice and regulates the protein levels of key cell cycle regulators. (32). In cultured DU145 cells, solanine inhibits cell growth, with the administration of NAC reducing solanine-induced cell death. Furthermore, inhibition of ROS by NAC inactivates the P38 pathway, suggesting that solanine-induced apoptosis may occur via ROS and activation of the P38 pathway. These findings suggest the therapeutic potential of solanine for suppressing prostate cancer growth.

In another study, it is demonstrated that a polyphenolic extract obtained from ripe berries of*Solanum nigrum* (SN) selectively induces cell cycle arrest and apoptosis in various human prostate cancer cells without affecting normal prostate epithelial cells. Using virally transformed normal human prostate epithelial PZ-HPV-7 cells and their cancer counterpart CA-HPV-10 cells, we evaluated the growth-inhibitory effects of the SN extract. Treatment with SN (5-20 µg/ml) led to modest growth inhibition in PZ-HPV-7 cells but significantly increased cytotoxicity, reduced cell viability, and induced apoptosis in CA-HPV-10 cells. (33). Similar effects were observed in the human prostate cancer cell lines LNCaP, 22Rv1, DU145, and PC-3, irrespective of disease stage and androgen association, with notable reductions in cell viability and induction of apoptosis. Cell cycle analysis revealed dose-dependent G2/M phase arrest and subG1 accumulation in CA-HPV-10 cells but not in PZ-HPV-7 cells upon SN treatment (5-20 µg/ml). These findings highlight the selective inhibitory effects of the SN extract on cellular proliferation and apoptotic events in prostate cancer cells, suggesting its potential as a promising therapeutic or preventive agent against prostate cancer.

2.3.7. Pancreatic Cancer

In a study conducted in 2018, degalactotigonin and three other steroidal compounds were isolated from *Solanum nigrum* methanolic extract, and their chemical structures were determined through spectroscopic analyses. Among these compounds, only degalactotigonin exhibited significant cytotoxicity against human pancreatic and lung cancer cell lines. It induced apoptosis in pancreatic and lung cancer cells and inhibited EGF-induced proliferation and migration in a dose-dependent manner. (34). Additionally, degalactotigonin induced cell cycle arrest at G0/G1 phase by regulating cyclin D1 and p21 expression, and it inhibited EGFR phosphorylation and downstream signaling pathways involving Akt and ERK.

2.3.8. Leukemia

In a study conducted in 2012, *Solanum nigrum* extracts from both organic solvent and aqueous sources were evaluated for their antiproliferative effects on leukemic cell lines Jurkat and HL-60. Cell viability was assessed using the MTT assay, showing increased cytotoxicity with higher extract concentrations. The methanol extract exhibited the lowest 50% inhibitory concentration value on both cell lines compared to other extracts (35).

It has been reported that the anti-tumor effect of Solanine in Jurkat cells and its molecular mechanism. Solanine, the main extract of *Solanum nigrum* Linn, demonstrated dose- and time-dependent inhibition of Jurkat cell proliferation. It induced apoptosis in Jurkat cells, evidenced by flow cytometry. Solanine modulated the mRNA levels of Bcl-2 and Bax, with a significant increase in Bax and decrease in Bcl-2 expression confirmed by western blot analysis (36). Solanine also enhanced the chemosensitivity of Jurkat cells to Adriamycin. Overall, these findings suggest that Solanine's anti-tumor activity involves inhibiting cell proliferation, inducing apoptosis, and increasing Adriamycin cytotoxicity, indicating its potential as a novel treatment for acute lymphocytic leukemia.

2.4. Anti-tumor Activities

In 2013, the anti-tumor effect of polysaccharides extracted from *Solanum nigrum* Linne and their impact on the immune function of tumor-bearing organisms was investigated. MTT assay was utilized to observe the influence of different doses of these polysaccharides on lymphocyte proliferation in tumor-bearing mice. ELISA assay was employed to measure IL-2 levels in mice, and laser scanning confocal microscopy was used to assess the effect of the polysaccharides on intralymphocytic free calcium ion concentration in tumor-bearing mice. Various doses of *Solanum nigrum* Linne polysaccharides significantly inhibited the growth of mouse H22 solid tumors, prolonged the survival time of tumor-bearing mice, enhanced lymphocyte proliferation, increased IL-2 levels, and raised the concentration of calcium ions in lymphocytes. (37) These findings suggest that polysaccharides from Solanum nigrum Linne possess anti-tumour properties, which are associated with the regulation of cellular immune function in the body.

The aim of this study was to investigate the impact of *Solanum nigrum* polysaccharides (SNPs) on tumor growth in mice bearing H22 hepatocarcinoma cells, focusing on the regulation of caspase-3 and bcl-2 expression. Fifty mice bearing H22 cells were randomly divided into five groups: Model group, cyclophosphamide group (CTX, 30 mg/kg), and SNP groups with low, medium, and high doses of SNP (30, 60, and 120 mg/kg). Twenty-four hours after H22 cell inoculation, CTX or SNP was administered by gavage once daily for 10 days. Tumor growth was monitored, and tumor inhibition rate as well as spleen and thymus indexes were calculated. Immunohistochemical analysis was performed to determine caspase-3

and bcl-2 expression in tumor tissue. SNP administration (30, 60, and 120 mg/kg) dose-dependently reduced average tumor weight compared to the model group, with tumor inhibition rates of 37.73%, 38.24%, and 42.60%, respectively (38). Additionally, SNP dose-dependently increased the thymus index compared to the CTX group. Immunohistochemistry results revealed higher caspase-3 protein expression but lower bcl-2 expression in SNP groups compared to the model group in a dose-dependent manner. SNP inhibited tumor growth in H22-bearing mice and protected immune organs (38). The mechanism underlying tumor inhibition may involve upregulation of caspase-3 and downregulation of bcl-2.

In a study conducted in 2023, the aim was to investigate the effectiveness of α-solanine, a compound found in the traditional Chinese herb *Solanum nigrum* L., in treating gliomas and to understand its mechanisms. Using network pharmacology, molecular docking, and molecular biology experiments, the study identified potential targets of α-solanine and their interactions. Through various analyses, including Gene Ontology and pathway analysis, 11 hub genes were identified, and it was revealed that α-solanine affects signaling pathways like MAP kinase and PI3K-Akt. In vitro experiments confirmed that α-solanine inhibits glioma cell proliferation and migration while promoting apoptosis (39). Moreover, STAT1 was highlighted as a potential mediator of α-solanine's effect on glioma prognosis. These findings suggest that α-solanine could be a promising candidate for developing novel anti-glioma therapies.

2.5. Antioxidant activity

The aim of the study conducted in 2018 was to assess the antioxidant effects of two leaf extracts of *Solanum nigrum* L. (SN), a medicinal plant commonly used in soups worldwide. Both extracts, SN1 (methanolic/water (80:20)) and SN2 (water), were prepared and analyzed for their polyphenolic content. The study evaluated their ability to restore oxidative status in astrocytes exposed to glutamate, showing significant antioxidant properties. SN1 and SN2 extracts effectively quenched radicals and prevented glutamate-induced cell damage, highlighting their potential therapeutic use (40).

In another study, the protective effects of *Solanum nigrum* fruit extract (SNFEt) against ethanol-induced toxicity in rats were investigated, focusing on its antioxidant and antihyperlipidemic properties. Rats were exposed to ethanol for 30 days, resulting in elevated levels of oxidative stress markers and disrupted lipid profiles. However, supplementation with SNFEt effectively reversed these effects, restoring antioxidant levels and normalizing lipid profiles (41). The study also compared these effects to the standard drug silymarin. Overall, the findings indicate that *Solanum nigrum* fruit extract exhibits significant antioxidant and antihyperlipidemic activities, providing protection against ethanol-induced toxicity.

2.7. Antimalarial Activity

In a study conducted in 2022, the crude extract and fractions of S. nigrum L. (Solanaceae) leaves were aimed to be evaluated for their antimalarial activity against P. berghei infection in mice. Both prophylactic and suppressive models were employed to assess the antimalarial activity of extracts from *Solanum nigrum* L. Male mice were randomly divided into eleven groups, and various doses of the plant extract were administered. Chloroquine was used as a reference drug. Statistical analysis was performed using one-way ANOVA followed by post hoc Tukey’s multiple comparison test. Results showed significant chemosuppressive and chemoprophylactic effects of the plant extract fractions compared to the negative control. The ethyl acetate fraction exhibited the highest suppression rates in both models, with no observed

acute oral toxicity at a dose of 2 g/kg (42). This suggests that *Solanum nigrum* L. possesses promising antimalarial activity, supporting its traditional medicinal use.

2.8. Antimicrobial Activity

In a study conducted in Pakistan in 2022, the antimicrobial activity of fruit extracts from two Solanaceous plants indigenous to Pakistan, *Solanum nigrum* and *Solanum xanthocarpum*, was investigated. Various solvents, including petroleum ether, chloroform, dichloromethane, ethyl acetate, acetone, methanol, and water, were employed for extraction, with water yielding the highest percentages of polar components. Antimicrobial activity was assessed using the hole-plate diffusion method against selected Gram-positive bacteria, Gram-negative bacteria, and fungi. Methanolic extracts at concentrations of 5, 10, and 15 mg/mL exhibited significant inhibition zones against most tested bacteria and fungi, although not as potent as standard antibiotics such as ampicillin or amphotericin B (43). This study highlights the potential antimicrobial and antifungal activities of fruit extracts from these plants.

2.9. Anti-viral Activity

Hepatitis C is a major health problem that causes liver cirrhosis, hepatocellular carcinoma, and death. Javed et al. investigated the potential of medicinal plants in Pakistan for their anti-HCV properties. They collected ten medicinal plants and evaluated their anti-HCV activity by infecting liver cells with HCV 3a. Among these, methanol and chloroform extracts from *Solanum nigrum* (SN) seeds showed significant inhibition of HCV, with the chloroform extract exhibiting more than 50% inhibition at non-toxic concentrations (44). Furthermore, the antiviral activity of SN seeds extract against HCV NS3 protease was assessed by transfecting liver cells with an HCV NS3 protease plasmid. The findings revealed that the chloroform extract of SN seeds reduced the expression or function of HCV NS3 protease in a dose-dependent manner, while GAPDH levels remained constant. These findings indicate that SN extract harbors promising antiviral agents against HCV. Combining SN extract with interferon may represent a more effective option for treating chronic HCV.

COVID-19, caused by SARS-CoV-2, has led to widespread mortality and various complications affecting multiple organ systems. Post-COVID complications, including neurological, psychological, renal, cardiovascular, pulmonary, and hematological issues, have persisted in some patients for over 6 months. Despite the gravity of these complications, they have received limited attention. Current drugs are used to address these complications, but novel interventions are needed. Phytochemicals from natural sources, such as *Solanum nigrum*, have shown promise in alleviating COVID-19 symptoms (45). S. nigrum exhibits anti-inflammatory, immunomodulatory, and antiviral properties against SARS-CoV-2 infection and its complications.

2.10. Anti-obezite Activity

It has been reported that *Solanum nigrum* exhibits anti-obesity effects in animal models induced by a high-fat diet. This study aimed to investigate the mechanism behind the anti-obesity effects of *Solanum nigrum* aerial part (SNAP), which has been shown to inhibit lipid droplet accumulation in 3T3-L1 cells. It was found that SNAP reduced the expression of adipogenic proteins while increasing the expression of lipolytic proteins (46). Additionally, SNAP treatment led to elevated levels of free glycerol and phosphorylation of AMP-activated protein kinase. Furthermore, SNAP increased the expression

of thermogenic and autophagic proteins. These findings suggest that SNAP inhibits lipid droplet accumulation by suppressing adipogenesis and promoting lipolysis, thermogenesis, and autophagy.

2.11. Atopic Dermatitis Activity

Hong et al. investigated the potential of *Solanum nigrum* L. in alleviating symptoms of atopic dermatitis (AD) induced by 1-chloro-2,4-dinitrobenzene (DNCB) and in TnF-α/iFn-γ-stimulated HaCaT cells. AD, a chronic inflammatory skin condition, presents symptoms like erythema, edema, pruritus, and eczema. Steroids, commonly used for inflammation, have limitations due to side effects. Thus, alternative treatments are needed. While *Solanum nigrum* has shown efficacy against oxidants and cancer, its effects on AD were unknown. The study evaluated *Solanum nigrum* ethanol extract on DNCB-induced AD model and stimulated HaCaT cells (47). Results showed *Solanum nigrum* reduced cytokine levels in stimulated HaCaT cells, inhibited p-p38 levels, and regulated NF-κB activation. Additionally, *Solanum nigrum* reduced serum IgE levels, dermal thickness, and mast cell and CD8 infiltration in the mouse model of DNCB-induced AD. This suggests *Solanum nigrum* has anti-inflammatory effects both in vitro and in vivo by modulating the immune system.

2.12. Oral Mucositis Activity

Oral mucositis, a severe side effect of chemotherapy and chemoradiotherapy, can greatly impact patient well-being. Although *Solanum nigrum* leaves have been used in traditional Indian medicine for treating oral ulcers, their pharmacological effects remained unexplored. In this study, an aqueous extract of *Solanum nigrum* leaves (AESN) was prepared and subjected to phytochemical screening. HPLC analysis of the ethyl acetate fraction was also conducted. The protective effects of AESN (at doses of 100 and 200 mg/kg) were evaluated in two rat models of oral mucositis induced by chemoradiotherapy and chemotherapy. Various parameters, including changes in body weight, food intake, and mortality, were assessed. AESN demonstrated protective effects in both models of oral mucositis, with the higher dose showing greater efficacy in chemotherapy-induced mucositis. Treatment groups showed a reduction in oral mucositis score ($p < 0.05$) and significant improvement in food intake ($p < 0.05$) (48). These findings suggest that the aqueous extract of *Solanum nigrum* leaves has a protective effect against chemotherapy and chemoradiotherapy-induced oral mucositis in rats.

2.13. Neuroprotective Activity

In a study conducted in 2018, the effects of dietary inclusion of black nightshade (*Solanum nigrum* L.) and African eggplant (*Solanum macrocarpon* L.) leaves on cognitive function and neurochemical parameters in rats treated with scopolamine, an inducer of cognitive impairment, were investigated. Rats were assessed for spatial working memory and levels of critical enzymes and antioxidants in the brain. Results demonstrated that both black nightshade and African eggplant leaves reversed spatial memory impairment induced by scopolamine and normalized levels of acetylcholinesterase, butyrylcholinesterase, monoamine oxidase, and antioxidant enzymes (49). These findings suggest that these vegetables may offer protection against cognitive impairment and could potentially serve as functional foods or nutraceuticals for conditions like Alzheimer's disease.

2.14. Antioxidative Activity

Under cadmium (Cd) stress, *Solanum nigrum* demonstrated a threefold increase in Cd accumulation in its leaves, displaying tolerance to Cd, whereas *Solanum torvum*, a low Cd-accumulating relative, experienced reduced growth and oxidative damage. However, the physiological mechanisms underlying the differential Cd accumulation and tolerance between the two Solanum species remain largely unknown. This study assessed the involvement of antioxidative capacity and the accumulation of organic and amino acids in response to Cd stress in both Solanum species. *Solanum nigrum* exhibited higher antioxidative capacity than S. torvum under Cd toxicity (50). Metabolomics analysis revealed that Cd treatment significantly increased the production of several organic and amino acids in *S. nigrum*. Pretreatment with proline and histidine increased Cd accumulation, while pretreatment with citric acid increased Cd accumulation in leaves but decreased it in roots, suggesting a potential role in Cd long-distance transport and accumulation in leaves. These findings provide novel metabolite evidence supporting the enhancement of citric acid and amino acid biosynthesis in Cd-treated S. nigrum, indicating their contribution to Cd tolerance and accumulation and offering insights into stress adaptation in other Solanum species.

2.15. Anti-osteoporotic Activity

In a study conducted in 2021, it was investigated whether the potential anti-osteoporotic effects of *Solanum nigrum* line (SI), a medicinal plant with known pharmacological effects. Using a postmenopausal osteoporosis model in Sprague-Dawley rats and an osteoclast model treated with receptor activator of NF-κB ligand (RANKL) on murine RAW 264.7 macrophages, the study assessed SI's impact on bone density and osteoclast differentiation and function. In vivo experiments showed that SI reduced bone mineral density loss, improved bone microstructure, and inhibited the expression of osteoclast-related markers (51). In vitro, SI suppressed RANKL-induced osteoclast differentiation and bone resorption ability by targeting key transcription factors involved in osteoclast differentiation. (51). These findings suggest that SI may serve as an alternative treatment for osteoporosis by regulating abnormal osteoclast activation.

2.16. Tyrosinase Inhibitory Activity

In a study conducted in 2018, methanolic extracts of berries from two different species of the Solanaceae family, Withania somnifera (WS) and *Solanum nigrum* (SN), were fractionated using solvents of varying polarity to analyze their phytochemical composition and investigate their antioxidant and tyrosinase enzyme inhibition capacities. Chemical analysis and biological activity evaluation were conducted on the methanolic extract and n-hexane, ethyl acetate (WSEA, SNEA), and aqueous fractions. The highest levels of total flavonoids and total phenolics were found in the WSEA and SNEA fractions. High-performance liquid chromatography with diode array detection (HPLC-DAD) analysis revealed the presence of polyphenols and flavonoids in the ethyl acetate fractions of WS and SN. WSEA and SNEA fractions exhibited the highest scavenging activity against 2,2-diphenyl-2-picryl hydrazyl (DPPH) radicals, total antioxidant capacity, and iron-reducing power (52). Furthermore, WSEA and SNEA demonstrated significant inhibition of tyrosinase enzyme activity. These findings underscore the medicinal potential of *Withania somnifera* and *Solanum nigrum* berry extracts as natural

antioxidant sources, likely attributed to their polyphenol and flavonoid content.

2.17. Anti-ulcer Activity

This study aimed to investigate the gastro-protective and antioxidant potential of Althaea officinalis and *Solanum nigrum* extracts in rats with pyloric-ligation/indomethacin-induced gastric ulceration. Rats were divided into six groups, including normal control, gastric ulcer control, and groups receiving standard pretreatments with omeprazole or misoprostol, as well as test pretreatments with Althaea officinalis and *Solanum nigrum*. Pretreatments were administered orally for 14 days, followed by induction of gastric ulceration. Results showed that the administration of pyloric-ligation/indomethacin led to significant ulceration and alterations in various biomarkers associated with gastric ulceration (53). However, pretreatment with omeprazole, misoprostol, *Althaea officinalis*, or *Solanum nigrum* effectively protected against ulceration and restored biomarker levels, suggesting potential therapeutic benefits in clinical settings.

3. Conclusion

Based on extensive literature review and analysis of experimental results, it can be concluded that *Solanum nigrum*, a traditional remedy for ulcers, hepatotoxicity, and cancer, possesses diverse immunological applications in cancer and other conditions. The plant demonstrates efficacy in preventing liver toxicity and cytotoxicity, thereby enhancing liver function. In addition to its anti-inflammatory, antimalarial, antimicrobial, and anti-ulcer effects, it also offers significant benefits on cognitive and psychological functions. Given its numerous beneficial properties, *Solanum nigrum* emerges as a safe and highly valuable medicinal plant for the broader population.

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