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A Review: on Advances in Anticancer Effect of Solanum Nigrum as a Prospective Chemotherapeutic Treatment Against Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is one of the most common and fatal types of liver cancer, with poor therapeutic efficacy because of high recurrence rates, drug resistance, and toxicity of conventional chemotherapeutic agents. Over the past years, natural products have emerged as promising alternatives or adjuncts in cancer treatment. Solanum nigrum, a medical plant used traditionally in Asian and African medicine, has shown considerable pharmological activities, especially its anti-tumor activity. This review focuses on phytochemical profile & pharmological activity of Solanum nigrum against cancer, particularly its activity against. The principal bioactive components, which are steroidal saponins and alkaloids such as solanine, solasonine, and solamargine, have strong anticancer activity through pathways such as induction of apoptosis, cell cycle inhibition, metastasis inhibition, anti-angiogenesis, and pathway modulation of important signaling pathways. In addition, its anti-

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inflammatory, antioxidant, antimicrobial, hepatoprotective, and therapy of liver cancer. Overall, Solanum nigrum is likely to be developed into a new chemotherapeutic agent for treatment of hepatocellular carcinoma.

Keywords: Hepatocellular carcinoma; Solanum nigrum;Pharmological activity; Antioxidant; anticancer

I. Introduction

Cancer continues to be a major cause of death globally [1].In 2020, there were approximately 19.3 million new cancer cases and 10 million cancer-related deaths worldwide [2,3].The ACS (American Cancer Society's) Cancer Facts & Figures 2023 report anticipates over 1.9 million new cancer diagnoses and around 609,820 cancer deaths in the United States in 2023 [4].Additionally, global forecasts suggest a 50% rise in the cancer burden by 2040 compared to 2020, largely due to an ageing population [5].Liver cancer, with HCC accounting for about 95% of cases, ranks as the third most common causeof cancer deathin the world. Due to its high relapse rate, considering an overall survival rate after five years of around 3-5%, HCC has a very harmful prognosis [6,7].Therefore, developing new agents to effectively treat and prevent HCC recurrence is crucial. A significant portion of human cancers (approximately 80-90%) is linked to environmental factors [8].However, removing carcinogenic elements from the environment is challenging. While modern surgical techniques have significantly lowered cancer mortality, additional treatments like radiotherapy and chemotherapy have only achieved a 5% reduction in death rates [8]. Consequently, there is a continuous effort to find better control and prevention strategies to reduce cancer mortality and associated side effects. Cancer has emerged as a significant cause of mortality, influenced by various risk factors such as Hepatitis B and C viruses’smoking, infections,

alcoholic cirrhosis, fatty liver disease, iron deficiency, obesity, aflatoxin B1, malnutrition, and poor dietary habitsshown in figure 1. Treatment protocols for HCC include immunotherapy,chemotherapy and combination therapies shown in figure 2. However, these treatments are limited due to side effects, resistant to chemotherapeutic agents and surgicalchallenges. Sorafenib, approved by the FDA, is used for HCCtreatment. In 2017, nivolumab and regorafenib were also approved, followed by Lenvatinib in 2018. Despite these options, challenges such as rapid resistance development and drug toxicity remain, highlighting the need for modern drug combination that target various signaling pathways to reduce the likelihood of resistance in cancer cells. Numerous studies are currently focused on identifying natural compounds that can inhibit or prevent carcinogenesis [9].Cancer treatment presents a paradox: it involves delivering potent toxicity to tumours while also spreading toxicity throughout the body. The side effects of such treatments can sometimes be fatal before the cancer itself. Biological response modifiers are compounds that uniquely affect physiological functions, potentially reducing the side effects of cancer treatments while enhancing their effectiveness [10].

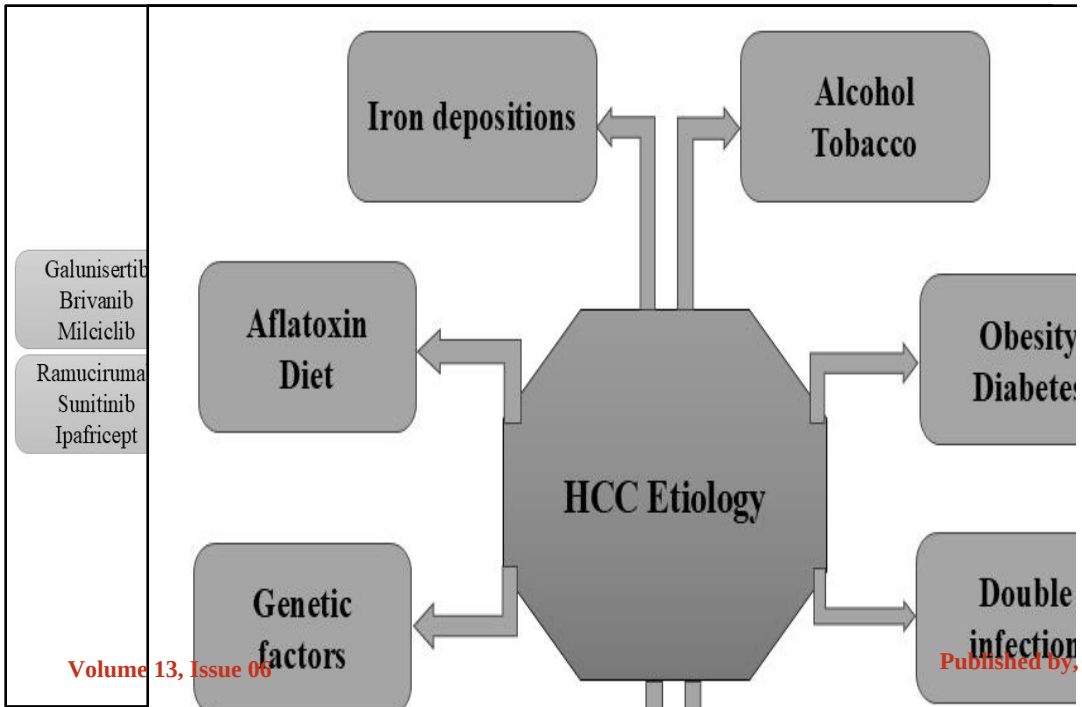

Figure 1: Etiological factors of HCC

Figure 2: Current treatment approaches in HCC.

The Solanum genus, part of the Solanaceae family, includes over 2,000 species that are found globally in tropical and subtropical areas. These plants are often noted for their attractive flowers and fruits. *Solanum nigrum* Linn. is a herbaceous species commonly seen in temperate zones and grows naturally in various parts of the world [11].In traditional Chinese medicine, *Solanum nigrum*consumes for medicinal purposes for centuries, believed to have a cold, bitter, and slightly toxic flavour that is associated with the lung and kidney meridians [12].It is very familiar for its anti-inflammatory, diuretic, and fever-reducing properties. Recently, the plant has gained attention for its anti-tumor capabilities, and it is used in combination with other herbs to treat several cancer types. In

contemporary clinical settings, it is frequently employed to address cancers of theliver, bladder, lung, breast, stomach and esophagus, among others.*Solanum nigrum* contains 4 polysaccharides, 8 phenolics, 16 steroidal alkaloids, and 38 steroid saponins, according to earlier chemical compound analyses. [13,14].The whole plant works well for detoxifying, lowering swelling,dispersing blood stasis and removing heatand has been traditionally used for treating canker sores, bacterial infection, prostate problems, skin eczema, chronic bronchitis for millennia and urinary tract infections etc [5].Additionally, in current therapeutic practice, *Solanum nigrum* is often combined with other drugs to treat cancers like,stomach, oesophageal, bladder breast, cervical, lungand liver cancers. It has also been used in other Asian countries, including India and Japan, for the treatment of cancers.Phytochemical investigations have revealed that *Solanum nigrum*contains a wide spectrum of bioactive compounds, including steroidal alkaloids, saponins, flavonoids, polysaccharides, and phenolics. These constituents are believed to contribute to the plant's anti-inflammatory, hepatoprotective, and antitumor activities, thus supporting its traditional reputation as a versatile medicinal agent. The antitumor potential of steroidal saponins and steroidal alkaloids is particularly noteworthy, drawing significant attention from drug researchers who aim to discover antitumor lead compounds within these substances. Chemicals or biopharmaceuticals/materials are used in chemotherapy to prevent or delay the onset of certain diseases, particularly tumors. Previous scientific research has shown that inclusion of vegetable connections in nutrition can reduce the risk of cancer. Currently, chemotherapy prevention is extensively used to mitigate the likelihood of colon cancer. As a result, phytochemical conditions from food and their derivatives serve as valuable sources of anticancer compounds. Flavonoids form a broad group among these. Due to structural diversity, it continues to be divided into anthocyans, flavones,

flavanols, Flav flavones or chalcones, flavanones, and exists in following types like, glycoside is a byproduct or as free aglycones. These compounds play a dynamic role in human nutrition and are commonly found in natural sources like, fruits, vegetables, grains, tea, and wine [5]. Flavonoids show the following biological properties, such as anti-angiogenic, antioxidant anti-inflammatory effects, which are very significant for their efficacy in chemotherapy [15,16].

II. Chemical composition of *Solanum nigrum*

By 2022, researchers have identified 188 distinct chemicals in *Solanum nigrum,* including polyphenols, lignins, organic acids, glycoproteins, steroidal saponins, polysaccharides and steroidal alkaloids[17].The primary active ingredients contributing to its antitumor effects are both(steroidal saponins andsteroidal alkaloids).The steroidal alkaloids mainly include three compounds:solamargine, solasonine, and solanines which are predominantly found in the plant's unripe fruits and have been a significant focus in natural product studies [14]. The herb *Solanum nigrum* is rich in steroidal alkaloids, all of which share the basic steroidal skeleton of gonane (cyclopentanoperhydrophenanthrene). The potential of this structural characteristic as an anticancer agent is currently the subject of intensive research [18]. The fruits of *Solanum nigrum* are mostly abundant in steroidal alkaloids, with the leading concentration in the green, unripe fruits. When the fruits grow, the alkaloid content diminishes due to compositional changes. Initial research in the early 1980s led to the isolation of solasonine and solamargine using ethanol extraction techniques from the unripe berries [19].Since then, several other structurally related alkaloids have been reported, including derivatives such as hydroxylated and glycosylated forms. These complex molecules often consist of solasodine aglycones linked to various sugar residues, forming highly bioactive glycosides [20,21].

Table 1: Several crucial elements of Solanum nigrum show antitumor activities.

S.NO	Compounds	Cell line	Tumor type	Concentration	Animal dose	Mechanisms	References
1	Solamargine	HepG2	Hepatoma	0-6 μM	4-8 (mg/kg)	Bcl-2/Bax and caspase pathway, LIF/p-Stat3, LIF/miR-192-5p/CYR61/Akt, and suppression of MUC1 gene activity	[28]
2	Solanine	HepG2	Hepatoma	0-20 μM	37.5 (mg/kg)	The synthetic Signalling pathways, including MMP-2, MMP-9, miR-21, TGFb/Smad, regulatory cell inhibition, caspase, and ROS	[27]
3	Solasonine	HepG2,	HCC	0-50 μM	10-100 (mg/kg)	miR-375-3p and the mortalin-p53 signalling pathway	[29]
4	Solamargine	HepG2	Liver cancer	-	-	Both MMP-2 and MMP-9 expression and activity decreased in HepG2 cells. Blocking the EMT method.	[30]
5						Iron death is triggered when the GSH redox pathway is disrupted by inhibition of GSS and GPX4 expression.	[31]
6						By upregulating miR-4726-5p, downregulating the lncRNAs HOTTIP and TUG1 suppressed the MUC1 protein.	[32]
7						HepG2 cells induce autophagy caused by the LIF/miR-192 5p/CYR61/AKT axis.	[33]
8	Solasonine	HepG2	Liver cancer	-		The miR-375-3p, CCAT1, SP1, and IRF5 axis inhibits cell growth.	[34]
9	Daucosterol					Daucosterol suppresses HCC cell migration and invasion via the Wnt/β-catenin pathway.	[35]
10	β-sitosterol					Caspase-3 and −9 activation causes apoptosis.	[36]

11	Uttrosi de B				To induce apoptosis, the caspase pathway is activated and the MAPK and mTOR signalling pathways are regulated.	[37]

III. Pharmacological activity of *Solanum nigrum*

Recent pharmacological research has shown that extracts of *Solanum nigrum*, when derived using various solvents, produce different pharmacological outcomes. As a case study, thewater-based extract of *Solanum nigrum* has been reported to inhibit angiotensin-II-induced ventricular hypertrophy and improve cardiac function [22].Additionally, this extract can suppress the proliferation of ovarian, liver, and breast cancer cells by affecting the expression of several tumour-related genes [23,24].Research has indicated that solamargine has inhibitory effects on cancers like,gastric, lung, and liver etc[25, 26].Particularly, uttroside B, a saponin extracted from *Solanum nigrum*, has shown greater HCC effectiveness compared to sorafenib, a leading drug that targets angiogenesis for anticancer and antitumor treatment[27]. *Solanum nigrum* has been used in cancer treatment for a long time, through its extracts showing notable pharmacological antitumor activities. Therefore, furtherinvestigationinto theextraction and purification of *Solanum nigrum's* anticancer active components is of great importance. *Solanum nigrum* has exhibited numerous therapeuticcharacters, for exampleantimicrobial,anti-inflammatory, antihypertensive, antioxidant,immunomodulatory, antitumor, analgesic, hepatoprotective, anti-HCV, cardioprotective, and antidiarrheal activities, among others[12].These pharmacological studies are summarized in a table 1, with reported effects and mechanisms explained in detail in the following paragraphs. Various unique Chinese medicines in which *Solanum nigrum* extract is a medical element were used in detail in therapeutic practice. Some patents, including *Solanum nigrum*, are listed on the table 2, so that pharmacological activities are primarily focused on the tumour and skin disease treatment,often combined with other herbs.

Table 2: Isolated phytoconstituents and therapeutic activities of Solanum nigrum.

S. No	Plant parts	Plant sources	Compounds	Biological properties	References
1	Fruit		Inunigroside A	Antiviral	[38]

2	Whole	*Solanum nigrum*	γ-Solamargine	Antibacterial, molluscicidal	[39]
3	Whole		Solamargine	Anticancer	[39]
4	Leaf		Quercetin	Anticancer	[40]
5	Leaf		Quercetin	Anticancer	[41]
6	Leaf		Quercetin	Anticancer	[42]
7	Leaf		Rutin	Anticancer	[41]
8	Leaf		Kaempferol	Anticancer	[43]
9	Whole		Pinoresinol	Anti-inflammatory	[44]
10	Whole		Pinoresinol 4-O-β-d-glucoside	Anti-inflammatory	[12]
11	Whole		Medioresinol	Anti-inflammatory	[44]
12	Whole		Syringaresinol-4′-O-β-d-glucoside	Anti-inflammatory	[12]

1) Antitumor activity of *Solanum nigrum*

Solanum nigrum's crude extracts and isolated compounds have demonstrated notable antitumor effects both in vitro and in vivo. The table outlines the mechanisms behind the antitumour activity of these extracts or bioactive substances. In vitro experiments revealed that various solvent extracts of Sun nigrum significantly suppressed the proliferation of several cancer cell lines, including the MCF-7(Human breast cancer cell line), 786-O, (Renal cell carcinoma cell line),ECA-109(Esophageal cancer cell line),SMMC-721, (Human hepatocyte cell line), MMC-803 (Hujal hepatocyte cell line) and MMC-803 (Gastric cancer cell line) and A549 (Human lungcancer cell line) etc. [12]. *In vitro* analyses have demonstrated that

treatment with S. nigrum extracts can induce apoptosis in HCC(HepG2) cells by disrupting mitochondrial integrity and increasing the cytochrome C release and triggering the caspase-3 mechanism. Additionally, changes in the expression of autophagy-related proteins such as LC3 and regulatory markers like Bcl-2 and Akt suggest a dual mechanism involving both apoptosis and autophagy[22]. According to Wang et al. (2011), Polyphenolic extracts from *Solanum. nigrum* have been shown to induce cell cycle arrest at the G2/M phase, accompanied by downregulation of cell division cycle regulators like CDK1 and the CDC25 family. These effects result in decreased cell viability in a dose-dependent manner.Furthermore, SNPE reduced HepG2 cell viability by suppressing VEGF-induced AKT and mTOR activation in vitro and decreased tumour volume and weight in the HepG2 tumour-bearing mouse model [45]. Several chemicals obtained from Solanum nigrum from, including solamargine, solasonine, and solasodine, have demonstrated selective cytotoxicity against tumor cells while sparing healthy tissues. Notably, a saponin known as uttroside B, derived from *Solanum nigrum*, has exhibited greater anti-hepatocellular malignance efficacy than sorafenib, a commonly used chemotherapeutic agent [24].

2) Antioxidant activity of *Solanum nigrum*

Antioxidant activities of the methanol-based extract from the berries of *Solanum nigrum* were assessed through a biochemical antioxidant profile of tissue. The extract demonstrated aimportant antioxidant capacity, as indicated by thecardiovascular tissue biochemical antioxidant profile, and this activity was not dependent on the dose. The methanol-based extract from the berries of *Solanum nigrum* showed antioxidant activity [46]. Additionally, the cytotoxic and antioxidant properties of ethanol extracts from dried Solanum nigrum fruits wereinvestigated. Free radicals were detected by the

coil in the extract in a qualitative antioxidant test using DPPH (1.1 diphenyl-2-picrylhydrazyl)[47].

3) Anti-inflammatory activity of *Solanum nigrum*

Inflammation is the body's immune response to harmful factors and their detrimental effects, serving as a protective mechanism to aid in recovery and combat infection, disease, and pain. Research has validated the anti-inflammatory properties of crude extracts from *Solanum nigrum* in several inflammation-related models, elucidating potential mechanisms involved. *Solanum nigrum* chloroform extract reduced iNOS and NO production by 80% at 50 µg/ml of lipopolysaccharide (LPS).TNFand IL-6 is a cytokine involved in the development of many inflammatory diseases. The results revealed that tumor necrosis factor alpha (TNF-±) and interleukin 6 (IL-6) levels were assessed using ELISA in peritoneal macrophages with LPS inserted and that chloroform fractions reduced TNF-INEE in the catch method and inhibited P38 linking. Anti-inflammatory effects of Solanum-Nigrum-Chloroform ion[48]. Animal model studies have demonstrated that ethanol or hydroalcoholic extracts of *Solanum nigrum*reduce tissue inflammation and edema, particularly in TPA-induced mouse ear edema and synovitis models. These outcomes are attributed to the presence of bioactive compounds such as steroidal alkaloids and flavonoids, which enhance antioxidant enzyme activity and decrease oxidative stress markers like malondialdehyde (MDA) [49]. Similar outcomes were observed in acute and subacute rat models, where hydroalcoholic extracts of Solanum nigrum showed reduced macrophage deposition and increased collagen fibre deposition, exhibiting protective effects on organs such as the liver, stomach, and kidneys, possibly due to the presence of steroidal alkaloids and saponins in *Solanum nigrum*[50]. A self-made Solanum nigrum suppository facilitated the repair of damaged epithelial tissue and restored prostatic secretion by reducing the rat prostate wet weight and white blood cell count

while increasing lecithin corpuscle density [51]. Homemade Solanum-nigrum Soopsotory facilitated repair of damaged epithelial tissue, reducing the wet weight of Ratte-Prostata and the number of white blood cells, while simultaneously increasing the density of the lecithin membrane [51]. Similarly, homemade sun-nigrum ointment increased SOD activity and reduced MDA[52]. Isolated steroidal glycosides from the plant have also exhibited concentration-dependent inhibitory effects on NO production in stimulated immune cells, reinforcing their role as promising anti-inflammatory agents [53]. Collectively, these findings suggest that Solanum nigrumcontains multiple constituents capable of modulating inflammatory responses, supporting its traditional use and highlighting its therapeutic potential in inflammatory diseases.

4) Antidiarrheal and Analgesic activity of *Solanum nigrum*

The ethanolic extract derived from the dried fruits of *Solanum nigrum* Linn. was evaluated for its antidiarrheal properties. Fruit extract showed significant antidiarrheal effects ($P<0.01$ and $P<0.001$) ondiarrhoea induced by mousecastor oil as they expanded thefrequency of defecation and increased the average latency period of body weight of 250 mg/kg and 500 mg/kg[54]. Ethanolic extracts of *Solanum nigrum* were also tested for analgesic properties. The analgesic effects ofextract were assessed for both central and peripheral pharmacological effects using Eddy's hot plate or acetic acid-induced properties. This study was conducted at oral doses of 100, 250, and 500 mg/kg. At a dose of 500 mg/kg, the extract showed significant analgesic activity ($P < 0.01$) compared to the standard drug diclofenac sodium (50 mg/kg) (Kaushik et al., 2008).Ethanolic extract of the dried fruit of *Solanum nigrum* Linn. was further evaluated for analgesic activity. In the acetic acid-induced writhing test in mice,ethanolic extract at doses of 250 and 500 mg/kg significantly inhibited the writhing reflex by 51.39% and

66.67%, respectively, compared to the standard diclofenac sodium, indicating positive analgesic activity [54].

5) Cardioprotective and Anti-HCV activity of *Solanum nigrum*

The cardioprotective effects of the methanolic extract from *Solanum nigrum* berries were assessed through global in vitro ischemia-reperfusion injury, using doses of 2.5 and 5.0 mg/kg administered six days a week over a 30-day period. The findings reveal that the extract demonstrated significant ($p<0.001$) cardioprotective properties against global in vitro ischemia-reperfusion injury, and this effect was not dependent on the dose. The methanolic extract from Solanum nigrum berries showed cardioprotective activity [54]. In addition to its cardiovascular benefits, *Solanum nigrum* has demonstrated antiviral activity against HCV. Extracts prepared from the plant's seeds using methanol and chloroform showed notable inhibition of HCV replication at concentrations that were non-toxic to host cells. Specifically, the chloroform extract was effective in reducing the expression and activity of the viral *Solanum nigrum 3* protease a key enzyme necessary for viral replication—without affecting the expression of housekeeping genes like GAPDH. These findings point to the potential of *Solanum nigrum* as a source of bioactive compounds with anti-HCV activity.Moreover, the combination of *Solanum nigrum* extracts with existing antiviral therapies, such as interferon, may enhance therapeutic outcomes and offer a synergistic approach to managing chronic HCV infections [55].

IV. Conclusion

Solanum nigrum exhibits a wide spectrum of pharmacological effects that support its use as a potential chemotherapeutic and chemopreventive agent for hepatocellular carcinoma. The presence of potent steroidal saponins and alkaloids in its phytochemical makeup underpins its anticancer efficacy, primarily through

induction of apoptosis, inhibition of tumor proliferation, and modulation of oncogenic pathways. Additionally, its antioxidant, anti-inflammatory, hepatoprotective, and immunomodulatory properties provide complementary benefits that are crucial for the supportive treatment of cancer. While current evidence is highly encouraging, further rigorous research, including pharmacological standardization and clinical trials, is imperative to fully harness the therapeutic potential of *Solanum nigrum*. This natural agent holds promise as an effective and safer alternative in the evolving landscape of liver cancer treatments.

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