REVIEW ARTICLE

Anticancer Activity and New Drug Discovery in *Solanum* species: A review

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Abstract

The ever-increasing incidence of cancer occurrence in world populations is a cause to worry amongst the scientific fraternity. It has been noted that most of the patients with cancer use some form of complementary and alternative medicine. A genus from the family Solanaceae that has received the most attention for its anticancerous properties is *Solanum*. All parts of the plants from this genus are used in cancer and related conditions as medication amongst the indigenous populations in many parts of the world. Several species of the genus showed antitumor and antiproliferative activity owing to the presence of high content of secondary metabolites. Many new types of biomolecules were detected in recent years in different parts of the plant and revealed their importance in the formulation of anticancer medication. Mostly *in-vitro* or in some cases, *in-vivo* models provide evidence of the pharmacological activity of solanaceous compounds towards cancer. However, new biomolecules are regularly being searched and their activities are still unknown. Also, more sophisticated and planned experiments, clinical trials and toxicological analysis are required to elucidate the possible anticancer mechanism of these molecules. Further studies are also necessary to prepare different herbal formulations against this disease. This review on the anticancer potential of *Solanum* will provide a boost towards an exploration of anticancerous agents and augment further research in the discovery of anticancer drugs.

Keywords: Anticancer, Antioxidant, Antiangiogenic, Antimutagenic, *Solanum* species, Drug discovery.

Highlights

- Solanaceous plants have many types of phytochemicals, some of which show anticancerous effects.
- Usually, the fruits have shown the most anticancer potential, but studies also revealed some effects in the leaf, stem, root and flowers.
- More scientific studies are required to elucidate the mode of action of these anticancerous agents.
- Toxicological studies are necessary before making therapeutic formulations.
- Solanaceous plants can be used in making herbal formulations.

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Introduction

Cancer is a major health concern in both developed and developing countries. It is a diseased condition in which the cells in the human body multiply uncontrollably, thereby forming tumors. They can turn metastatic and consequently invade nearby tissues to spread to distant regions of the body. There are several types of cancer; most of them are named after the organs they affect, e.g., colon cancer, bladder cancer, blood cancer, liver cancer, breast cancer, thyroid cancer and pancreatic cancer (NCI, 2021).

Every year, a large number of people are diagnosed with malignant growth all over the world, and the vast majority of the patients eventually succumb to it. In many nations, malignant growth positions the second most common reason for death following cardiovascular illnesses. With critical improvement in therapy and counteraction of cardiovascular illnesses, the disease has emerged as the primary killer in many parts of the world (Ma and Yu, 2007).

There are several causes of cancer, including environmental and genetic factors, which are not preventable. However, in the current scenario, it has become more of a lifestyle disease that happens due to excessive weight gain, alcohol consumption, improper nutrition and a sedentary lifestyle, to name a few (Blackadar, 2016). Presently, the most significant unpreventable threat is age. Although being a dreaded disease, it can be cured if diagnosed at an early stage (NCI, 2021). The cause-and-effect relationship of cancer-causing agents and cancer is depicted in Fig. 1.

Cancer is one of the several diseases that many research groups are currently targeting and constant efforts are being made globally with a lot of development in cures and preventative therapies. Several attempts have been made to develop an effective remedy for cancer. Natural products prove to be an alternative to synthetic drugs that have profound side effects. Quite a lot of natural biomolecules have been reported for the treatment of various diseases for thousands of years

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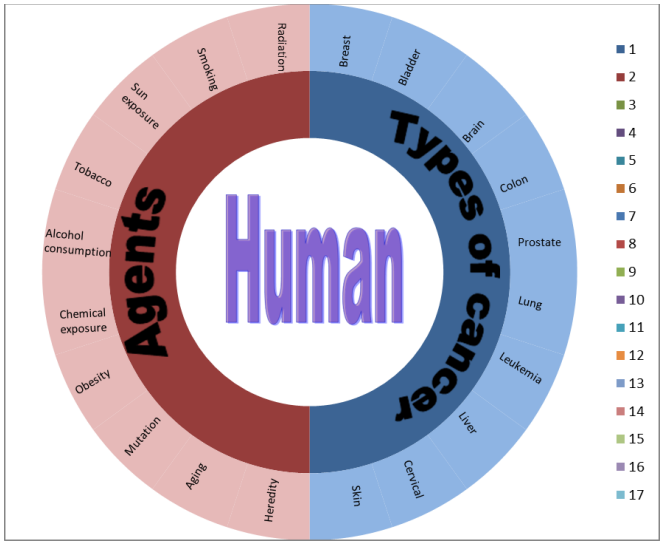

Fig. 1: Cause and effect relationship of cancer-causing agents and cancer

(Greenwell and Rahman, 2015). Ayurvedic medicine system is the main treatment strategy based on plant products. In the current review, we have explored the recent reports that have utilized *Solanum* species for their cytotoxic, antiproliferative, antioxidant and antimutagenic activities. Different aspects of the anticancer potential of *Solanum* have been highlighted in the present investigation.

The family Solanaceae comprises approximately 21 tribes, 100 genera and 2,500 species (Hunziker, 2001; Olmstead and Bohs, 2007). It is commonly known as the nightshade family. This family consists of many important and economically significant crops (e.g., potatoes, tomatoes, eggplant and chili peppers etc.). *Solanum* is one of the most important genera of the family Solanaceae. There are several other plant species belonging to this family that grow in a wild condition and have tremendous pharmacological potential e.g., *Nicotiana plumbaginifolia* Viv., *Datura wrightii* Regal, *Withania somnifera* (L.) Dunal, *Atropa belladonna* L., *Physalis minima* L. etc. The genus *Solanum* encompasses 2000 species widely distributed throughout the world Kaunda and Zhang, 2019. India alone has 122 species of Solanaceae; among them, 49 species belong to the genus *Solanum* (Venkatappa, 2011).

To prepare a comprehensive review on the anticancer activity of the plants of genus *Solanum*, the corresponding data were studied and integrated in this report. Searches were performed by using key terms like *Solanum* anticancer, antioxidant, antiproliferative, apoptotic, cytotoxic, DNA-damage activity; and antiangiogenic activity in authorized scientific search engines Research Gate, Scopus, Pubmed, Google Scholar and Science Direct databases to organize this review paper. Papers published in recent decades by publishers such as Elsevier, Springer, Taylor& Francis and Wiley have been systematically reviewed and a total of 59 articles were found valuable for the study and preparation of manuscript. Some of the valuable species were also identified in nature and authenticated with The Plant List (2013), IPNI (International Plant Name Index) and scientific literature available in the Department of Botany, DDU Gorakhpur

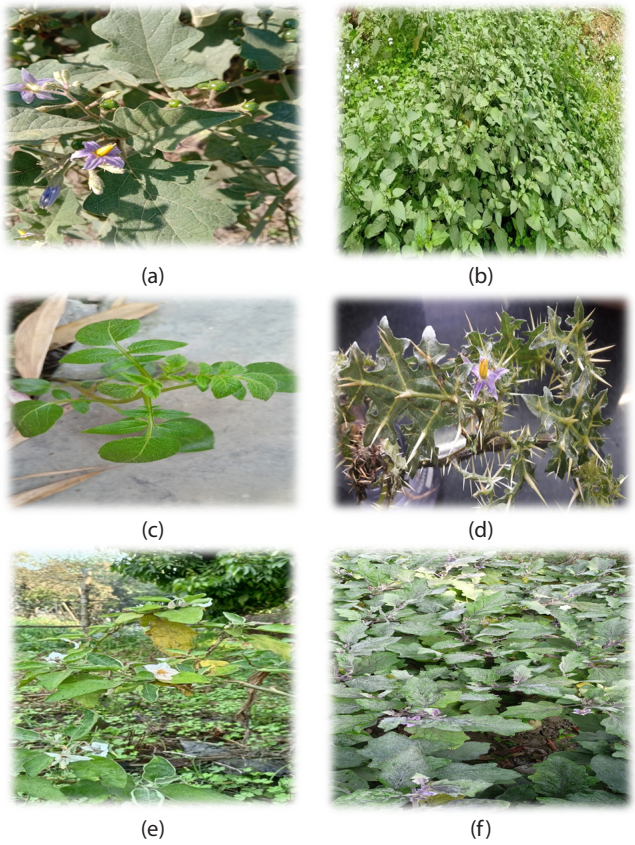

Fig. 2: *Solanum* species (a) *Solanum violaceum* Ortega, (b) *Solanum nigrum* L., (c) *Solanum tuberosum* L., (d) *Solanum xanthocarpum* Schrad, (e) and (f) *Solanum melongena* L.

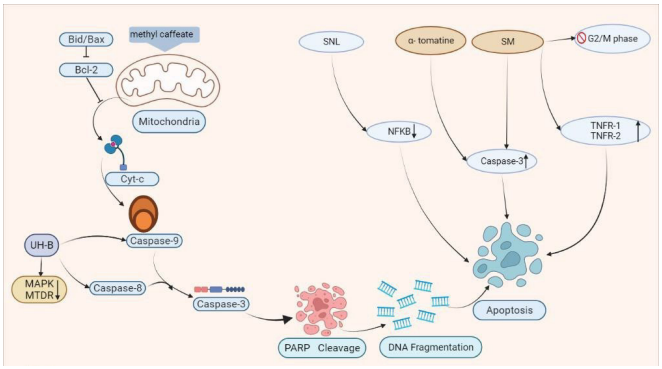

Fig. 3: Mechanism of action of SNL, Alpha-tomatine, Solamargine (SM) and Methyl Caffeate in apoptosis process

University, Gorakhpur, India. Synonyms were removed and only authenticated accepted name of the plant species were used during the preparation of literature. The photographs of *Solanum* species are given in Fig. 2. Anticancerous activities of molecules are mentioned in Table 1 and newly discovered phytomolecules are presented in Table 2. The mechanism of action of some phytomolecules are illustrated in Fig. 3.

Traditional Uses of the *Solanum* Species

Solanum species have ancient connection with the human civilization and journey of *Solanum* commences with the augment

Table 1: Anticancerous molecules in *Solanum* species and their activities

S. No.	*Plant species*	*Plant Part used*	*Type of Solvent*	*Responsible Biomolecules*	*Activity*	*Cell Lines/ Model*	*Type of Cancer*	*Reference*
1.	*Solanum aculeastrum* Dunal	Berries	Water, toluene and HCl mixture	Tomatidine and solasodine	Anticancer	HeLa MCF7 HT29	Cervical cancer	Kodoru *et al.,* 2008
2.	*S. nigrum* L.	Fruit	Methanol	-	Cytotoxic	HeLa Vero	Cervical cancer	Patel *et al.,* 2009
3.	*S. incanum* L.	Fruit	-	Solamargine	Anticancer	Hep3B	Hepatic cancer	Kuo *et al.,* 2000
4.	*S. tuberosum* var. vitelotte	Tuber	Acid-ethanol	Anthocyanin (Malvidin 3-o-p-coumaroyl rutinoside-5-o-glucoside, Petudinidin 3-o-p-coumaroyl-rutinoside-5-o-glucoside)	Antiproliferative, antiapoptotic	NB4 MCF7 HeLa LNCaP U937 MDA-MB231		Bontempo *et al.,* 2013
5.	*S. xanthocarpum* Schrad.	Fruit	Hexane, benzene, Chloroform, ethylacetate	Flavonoid content	Cytotoxic/ antioxidant	THP-1 HOP-62	Leukemia/lung	Kumar and pandey, 2014
6.	*S.* erianthum D. Don *S.* macranthum Mill.	Leaf Fruit	Aqueous	essential oil	Cytotoxic	PC-3 Hs578T	-	Essien *et al.,* 2011
7.	*S. lyratum* Thumb.	Whole plant	Ethanol 70%	-	Antiangiogenic	Tumor derived vascular endothelial cell	-	Han *et al.,* 2019
8.	*S.* nigrum L.	Fruit	Ethanol	Glycoprotein	Cytotoxic Antioxidant	HT-29	Colon cancer	Heo *et al.,* 2004
9.	*S.* nigrum L.	Leaf	Aqueous	-	Anticancer	Human SCC-4	Oral cancer	Uen *et al.,* 2018
10.	*S. sessiliflorum* Dunal	Fruit	-	-	Cytotoxic, genotoxic, antigenotoxic	Rat (male wistar)	-	Hernandes *et al.,* 2014
11.	*S. surattense* Burm.f.	Leaf	Ethanol	Phenolic content	Antioxidant	-	-	Muruhan *et al.,* 2013
12.	*S. xanthocarpum* Schrad.	Whole plant	Methanol	Sugar moieties of *Solanum* compounds	Cytotoxic Apoptosis (Necrosis)	HCT-116	Colon cancer	Bhutani *et al.,* 2010
13.	*S. septemlobum* Phil.	Whole plant	Ethanol	*Septemlobins* A-C	Cytotoxic	P-388 HONE-1 HT-29		Zhang *et al.,* 2015
14.	*S. melongena* L.	Sepal	Ethanol 70%	-	Cytotoxic	HeLa	Cervical cancer	Zhao *et al.,* 2020
15.	*S. melongena* L.	Fruit	Methanol, Water, Petroleum-ether fraction of Acetone extract	Lutein and Pheophorbide Tannin, Pheophytin	Antimutagenic			Yoshikawa *et al.,* 1996
16.	*S. melongena* L.	Fruit (skin)	Aqueous	Phenolic content	Antioxidant, DNA protective activity	Cattle blood DNA		Somawathi *et al.,* 2016
17.	*S. melongena* L.	Seed	Ethanol 95%	-	Cytotoxicity	SGC7901 and SW480	Antitumor	Chen *et al.,* 2021

18.	*S. melongena* L.	Skin	Acidulated alcohol	Anthocyanin (Delphinidin)	Antimutagenicity	Male Swiss Mice	-	Azevedo *et al.,* 2007
19.	*S. nigrum* L.	Whole plant	-	Solamargine	Apoptosis	SMMC-7721,HePG2	Hepatic Cancer	Ding *et al.,* 2012
20.	*S. lyratum* Thunb.	Whole plant	Ethanol (70%)	Steroidal glycoalkaloid & SA-1	Antitumor Antipro-angiogenic	A549 derived exosome	Lung adenocarcinoma	Du *et al.,* 2020
21.	*S. nigrum* L.	Fruit	Ethanol	Glycoprotien	Cytotoxic	MCF-7	Breast cancer	Heo et al., 2004
22.	*S. nigrum* L.	Seed	Distilled water	Lunasin peptide	Oxidative DNA damage	φX-174 RF I Plasmid DNA	-	Jeong *et al.,* 2010
23.	*S. lyratum* Thunb.	Whole plant	$CHCl_3$, Ethyl acetate fraction of Ethanolic extract	Solajiangxins F and G	Cytotoxic	P-388, HONE-1, HT-29	-	Li *et al.,* 2013
24.	*S. torvum* Sw.	Aerial part	60% Ethanol	Torvoside M, N	Cytotoxic	MGC-803, HepG2, A549, MCF-7	-	Lu *et al.,* 2009
25.	*S. nigrum* L.	Immature fruit	70% Methanolic fraction	Compound 4(Steroidal glycosides)	Cytotoxic	HL-60, U-937, Jurkat, K562 and HepG2	-	Xiang *et al.,* 2019
26.	*S. lyratum* Thunb.	Whole plant	75% Ethanol	Compound 6	Cytotoxic	SGC7901, BEL-7402	Gastric and liver cancer	Ling *et al.,* 2018
27.	*S. nigrum* L.	Whole plant	Water extractable fraction SNLWP-1 and alkali extractable fraction SNLAP-1and SNLAP-2	 galactose, arabinose - xylose,galactose, arabinose	Antitumor, Immunomodulatory	ICR mice	-	Ding *et al.,* 2012
28.	*S. nigrum* L.	Leaf	Methanol	Saponin Uttroside B	Cytotoxic, Apoptotic	HepG2 Hep3B SK-Hep1 Huh-7	Liver cancer	Nath *et al.,* 2016

of *S. tuberosum* L. in the Andes Mountains of Peruvian region (Bradshaw and Ramsay, 2009). The ethnobotany of *Solanum* evolves with the primates, especially with the *Homo sapiens*. Therefore, *Solanum* has pros and cons biomolecules for health and welfare of human beings. Many of *Solanum* species are used traditionally in the form of food, medicine or both as food and medicine. These species are important in the treatment of various ailments of ethnic people in the form of powder, paste and, decoction etc. *Solanum aculeastrum* Dunal fruits and leaves are used in making decoction for cancer treatment by the local people of South African Eastern Cape province (Koduru *et al.,* 2008). It is locally known as Itunga or Umthuma and is used in breast cancer (Sagbo and Otang-Mbeng, 2021). Leaves of *S. americanum* Mill. are used in myoma and fruits and leaves of *S. paniculatum* L. are used for internal tumors by natives of Brazil (De Melo *et al.,* 2011). The leaves and fruits of *S. nigrum* L., locally known as *Hidi*, is used against painful swellings of fingers in the form of paste by the Oromo community of Eastern Ethiopia (Bussa and Belayneh, 2019). The Kurd tribe of Ilam province of Iran uses *S. nigrum* L. (local name *Roarazak*) fruits in wound healing and in skin diseases (Pirbalouti *et al.,* 2013). The Baluchi tribes of South Eastern Iran used *S. nigrum* L. as *Angourtoulak* fruits and aerial parts in cancer (Maleki and Akhani, 2018). The fruits, roots and leaves of *S. incanum* L. (Nhundurwa) are used in skin, breast and blood cancer by traditional practitioners of Masvingo and Manicaland province of Zimbabwe (Matowa *et al.,* 2020). Fruits of *S. nigrum* L. have been used as a blood purifier by the *Tharu* tribes in the forest areas of Indo-Nepal border of Maharajganj District of Uttar Pradesh, India. Thus, this genus represents important ethnobotanical use by the local communities for the treatment of different types of cancers throughout the world.

Anticancerous Attributes of the *Solanum* Species

Anticancerous Activity

Several plants in the genus *Solanum* have been explored for their anticancerous properties. *S. nigrum*, commonly known as 'makoi' or black nightshade, is a potent herbal alternative as

an anticancer agent. The methanolic and chloroform extracts of stem and leaves of *S. nigrum* were tested for anticancerous effects on two cancer cell lines viz. PC3 and Hela (Moglad *et al.,* 2014). The cytotoxicity of *S. nigrum* was also investigated on the 3T3 NIH mouse embryo fibroblast cell line and CC-1 Wistar rat hepatocyte cell line and confirmed by MTT assay. The extracts exhibited anticancerous activity on PC3 and Hela cancerous cell lines while having a non-toxic effect on 3T3 and CC-1. These results portray that *S. nigrum* can be used as an anticancer agent in prostate cancer and cervical cancer. This also approves the traditional use of *S. nigrum* in the treatment of cancer in Sudan (Moglad *et al.,* 2014). α-tomatine displays tremendous antitumor action in colon disease cells by means of focusing on their membranous compartments and inciting both necroptosis and apoptosis Rudolf and Rudolf, 2016. Compound Solamargine, from *Solanum,* has been reported to have anticancer effects by inducing apoptosis in human hepatoma cells and may come out as a new drug for cancer treatment (Kuo *et al.,* 2000). Similarly, Mohesinikia *et al.,* (2013) reported that solanine has chemoprotective and chemotherapeutic effects on an animal model of breast cancer, both *in-vivo* and *in-vitro* conditions by inducing apoptosis, inhibiting cell growth, and inhibiting angiogenesis. Solanine increased proapoptotic Bax protein expression and reduced Bcl-2 expression in mouse breast tumors compared to the control group at $p > 0.05$.

The berries of *S. aculeastrum* yielded two steroidal glycosides, tomatidine and solasodine, which were identified using spectroscopic techniques. The effects of these chemicals on cell proliferation were examined using cancer cell lines HeLa, MCF7, and HT29. The IC_{50} results confirmed that tomatidine and solasodine had the strongest inhibitory effects on HeLa cells, with the combined compounds' IC_{50} being lower than that of solasodine and unaltered from that of tomatidine. However, the combined IC_{50} values of these two compounds were lower than that of IC_{50} values of the individual compounds in HT29 and MCF7 cells. The exposure of these two compounds for 24 hours resulted in cell cycle arrest in G0 or G1 phase. The compounds showed quite low cytotoxic value when flow cytometry was used to label them with annexin V–FITC/PI (Koduru *et al.,* 2007). Choudhary *et al.*, (2019) have investigated the effect of *S. xanthocarpum* whole plant extract on rat liver hepatoma (N1S1 cancerous cell line). The study suggested that *S. xanthocarpum* Schrad., possesses anticancer activity in a dose-dependent manner. Cytotoxic activity of *S. nigrum* fruit methanolic extract was evaluated on two cell lines viz. Hela and Vero by using SRB and MTT assay. Trypan blue dye exclusion method revealed 70 to 72% and 81.13% viability for Hela and Vero cell lines, respectively. In the concentration range of 10 to 0.0196 mg/mL, fruit extract showed cytotoxic activity in both the assay against HeLa cell lines with IC_{50} value of 847.8 and 265.0 for SRB and MTT assay, respectively. Vero cell lines demonstrated fluctuation in cytotoxicity and cell growth inhibition in both the assay. Methanolic fruit extract from this plant can be used in anticancer medication in cervical cancer (Patel *et al.,* 2009). In the Chinese medicine system, *S. nigrum* has been traditionally used to treat various types of cancers. Uen *et al.,* (2017) evaluated the anticancerous activity of aqueous extract of *S. nigrum* fruit against oral cancer cell line (SSC)-4. The extract triggered the caspase-9 and caspase-3 activation and promoted mitochondrial apoptosis. This study suggests the use of *S. nigrum* fruit in suppressing mitochondrial fission. *S. trilobatum* methanolic extract (STME) treatment ameliorated the level of hepatic injury in DEN-stimulated Wistar albino rats. The chemopreventive mechanism of extract involved in the reduction of nodule growth and tumor incidence and also downregulated the TBARS and upregulated the binding affinity of antioxidant enzymes with GSH. The result suggested that STME would be a potent chemopreventive agent inhibiting chemically induced hepatic cancer (Shahjhanet *et al.,* 2005). Similarly, the ethanolic extract of *S. trilobatum* also possesses antioxidant activity and anticancer activity in the lung stimulated by benzo(a)pyrene (Venugopal *et al.,* 2014).

Antioxidant activity

Antioxidants are also known as free radical scavengers (FRS). Free radicals are extremely reactive molecules that can cause cell damage. Antioxidants neutralize these free radicals and protect cells from their harmful effects. They are produced naturally in the body and involved in a variety of typical cellular functions. On the other hand, they can be harmful to the body in excessive concentrations, causing damage to all major components of cells, including DNA, proteins and cell membranes. Free radical damage to cells, particularly DNA damage, could have a role in the development of cancer. Among the traditional disease therapies, chemotherapy is the most often used therapy to treat dangerous malignant growth rather than surgical medical procedures and radiotherapy (Huy *et al.,* 2008). Anticancer medications, on the other hand, are related to plenty of secondary effects. Each drug, within each class, has its own set of side effects that can lead to patient noncompliance and a decline in quality of life. One of the significant reasons for unfavorable responses, particularly for drugs focusing on DNA, is the over-creation of reactive oxygen species (ROS) and, resulting in oxidative stress (Singh *et al.,* 2018). Antioxidants protect cells by interacting with and removing oxidative free radicals, making them useful in adjuvant chemotherapy.

There are comprehensive varieties of plant-based phytochemicals that exhibit antioxidant behavior. *S. surratense* leaf has been reported to have antioxidant activity owing to the presence of a variety of phytochemicals. The free radical scavenging activity of the obtained plant extracts was found to be concentration-dependent. For the superoxide radical scavenging assay (O_2^-), the IC_{50} value was 145.22 µg/mL, while in the H_2O_2 scavenging study, the IC_{50} value was reported as 147.23 µg/mL (Muruhan *et al.,* 2013). Another study was aimed to evaluate the genotoxicity of the *S. sessiliflorum* fruit as maná-cubiu, which has a peculiar flavor in salads and juices and enjoyed by the indigenous people of Northern Brazil (Hernandes *et al.,* 2014). The genotoxicity assay was performed in *in-vivo* conditions in the wistar rats along with oxidative stress study in the heart and liver. The test results revealed that the fruit pulp of *S. sessiliflorum* was not genotoxic and it was also observed that it decreased DXR-induced DNA damage. This fruit's antioxidant activity may contribute to the fruit's antigenotoxic effects. *S. sisymbrifolium* is an invasive herb that is used in traditional folk medicine for the treatment of various kinds of diseases. The

Table 2: Newly isolated biomolecules from *Solanum* species

S. No.	Plant name	New biomolecules	Type of biomolecules	References
1.	*S. melongena*	melongoside R-S (compound 1-2), melongoside T-V (compound 3-5)	Cholestane-type steroidal saponins, furostanol-type steroidal saponins	Chen *et al.,* 2021
2.	*S. lyratum*	Solalyraine A-G; Compound 1[(3β,5α,20S,22S,23R,25S)-16,22-epoxy-23,26-imino-cholestan-3-ylO-β-D-glucopyranosyl-(1 → 2)- O-β-D-glucopyranosyl-(1 → 4)-β-D-galactopyranoside], compound 2[e (3β,20S,22S,23R,25S)-16,22- epoxy-23,26-imino-cholestan-5-en-3-ylO-β-D-glucopyranosyl-(1 → 2)- O-β-D-glucopyranosyl-(1 → 4)-β-D-galactopyranoside], compound 3[16,23-epoxy-22,26-imino-cholestan-5,22(N),23,25(26)-tetraene3β-ol-3-O-β-D-glucopyranosyl-(1 → 2)-β-D-glucopyranosyl-(1 → 4)-β-Dgalactopyranoside], compound 4 [(3β,25R)-16,23-epoxy-23,24- imino-cholestan-5,16,20,23(N)-tetraene-3β-ol-3-O-β-D-glucopyranosyl- (1 → 2)-β-D-glucopyranosyl-(1 → 4)-β-D-galactopyranoside], compound 5 [(3β,5α,25R)-16,23-epoxy-23,24-iminocholestan-16,20,23(N)-triene-3β-ol-3-O-β-D-glucopyranosyl-(1 → 2)-βD-glucopyranosyl-(1 → 4)-β-D-galactopyranoside], compound 6 [15β-hydroxyl-(3β,5α,25R)-16,23-epoxy-23,24-imino-cholestan-16,20,23(N)-triene-3β-ol-3-O-β-D-glucopyranosyl-(1 → 2)-β-D-glucopyranosyl-(1 → 4)-β-D-galactopyranoside], compound 7 [15β-hydroxyl-(3β,25R)-16,23-epoxy-23,24-imino-cholestan5,16,20,23(N)-tetraene-3β-ol-3-O-β-D-glucopyranosyl-(1 → 2)-β-D-glucopyranosyl-(1 → 4)-β-D-galactopyranoside]	Steroidal glycoalkaloids	Du *et al.,* 2020
3.	*S. lyratum*	solajiangxins F and G	Eudesmane-type Sesquiterpenoids	Li *et al.,* 2013
4.	*S. torvum*	Solanolactosides A, B; Torvosides M, N	Steroidal lactone saponins; Spirostanol glycosides	Lu *et al.,* 2009
5.	*S. nigrum*	Compound 1[s (25R)-22αN-4-norspirosol-5(6)-en-3β-ol-6-al-3-O-α-L-rhamnopyranosyl-(1 → 2)-[α-Lrhamnopyranosyl-(1 → 4)]-β-D- glucopyranoside], compound 2[s (25R)-22αN-spirosol-5(6)-en-3β-ol-7-oxo-3-O-α-Lrhamnopyranosyl-(1 → 2)-[α-L-rhamnopyranosyl-(1 → 4)]-β-D-glucopyranoside], compound 3 [s (25R)-22αN-spirosol-4(5)-en-3β-ol-6- oxo-3-O-α-L-rhamnopyranosyl-(1 → 2)-[α-L-rhamnopyranosyl-(1 → 4)]- β-D- glucopyranoside]	Steroidal Alkaloid glycosides	Xiang *et al.,* 2019
6.	*S. lyratum*	16, 23-epoxy-22, 26 epimino-cholest-22(N), 23, 25(26)-trien-3β-ol-3-O-β-D-glucopyranosyl-(1→2)-β-D-glucopyranosyl-(1→4)-β-D-galactopyranoside, 26-O-β-D-glucopyranosyl-(25R)-5α-furost-20(22)-en-3β, 26-diol	Steroidal compound	Ling *et al.,* 2018
7.	*S. septemlobum*	Septemlobins A-B Septemlobins C	Eudesmane type Sesquiterpenoids Vetispirane-type Sesquiterpenoids	Zhang *et al.,* 2015
8.	*S. melongena*	Melongenaterpenes M-T	Sesquiterpenoids	Zhao *et al.,* 2020

crude extract of the plant was reported to have free radical scavenging activity. The aerial portions of this plant contain a moderate number of bioactive constituents which may be associated with the antioxidant effect (Gupta *et al.,* 2014). The aqueous extract of *S. melongena* was found to be an efficient scavenger of reactive oxygen species. The antioxidant effect of brinjal differed depending on skin color (Somawathi *et al.,* 2016). A glycoprotein extracted from *S. nigrum* L. has been reported to exhibit free radical scavenging activity in a dose-dependent manner (Heo *et al.,* 2004).

Cytotoxic Activity

Cytotoxicity is an important aspect for the determination of the impact of biomolecules on the cell lines. Cytotoxic activity

was evaluated for the biomolecules isolated from *S. erianthum* and *S. macranthum.* The essential oils isolated from the leaves of *S. erianthum* exhibited potent inhibitory properties against PC-3 (prostate tumor cells) and Hs 578T (Human breast cells) cell lines (Essien *et al.,* 2012). Two new compounds belonging to sesquiterpenoids were isolated from the whole plant of *S. lyratum* in ethanol. These compounds were named Solajiangxins F and G and both of them expressed cytotoxicity against HT-29, P-388, and HONE-1 cell lines (Li *et al.,* 2013). Similarly, eight new and nine known sesquiterpenoids have been isolated from the 70% ethanolic extract of the sepals of *S. melongena.* These molecules displayed cytotoxicity against HeLa, Ishikawa and MGC-8 cancer cells (Zhao *et al.,* 2020). Another group has isolated three new sesquiterpenoids from the whole plant of *S. septemlobum.* These compounds belonged to *Septemlobins* A-B and vetispirane-type Septemlobin-C and all three compounds exhibited cytotoxic activities with IC_{50} values in the range of 3.8 to 7.5 µm (Zhang *et al.,* 2015). The newly discovered biomolecules are listed in Table 2. *In-vitro* cytotoxic activity of the modified *S. tuberosum* aspartic protease was evaluated by Munoz *et al.,* (2014) where the aspartic protease 3 (stAP3) has been modulated by mono-PEG forms. This aspartic protease exhibits cytotoxic properties against various ranges of pathogens but they did not affect human red blood cells and human T-cells and thus, they may act as promising agent against various forms of cancer.

Apoptotic activity

Another compound extracted from the unripe fruit of *S. torvum* displayed significant cytotoxic activity against MCF-7 cells. The extracted methyl caffeate compound promoted the expression of Bid, Bax, Caspase-3 and PARP while it downregulated Bcl-2 expression, indicating activation of the mitochondria-mediated cell apoptosis pathway (Balachandran, 2015). Saraspogenin and diosgenin derived chain of steroidal constituents have been isolated from *S. xanthocarpum* and *Asparagus racemosus* and evaluated for their apoptotic and cell death mechanism on colon carcinoma cells. They concluded that the steroidal molecules from both plants had the ability to induce cell death (Bhutani *et al.,* 2010). A new saponin molecule uttroside B was isolated from the methanolic extract of *S. nigrum* leaves and was found tenfold more effective (IC_{50} 0.5µM) than the FDA-approved medication Sorafenib (IC_{50} at 5.8 µM) against HepG2 hepatocellular carcinoma. Uttroside B activated cleavage of procaspase 9, procaspase 8 and procaspase 7 in a dose-dependent manner and also promoted PARP cleavage. The apoptotic effect of uttroside B was found due to downregulation of MAPK and m-TOR signaling pathways (Nath *et al.,* 2016).

Antitumor activity

The methanolic extract of unripe fruit of *S. pseudocapsicum* exhibits strong cytotoxic activity with a CTC_{50} 12.01 µg/mL for the vero cell line, 6.32µg/ml for Hep-2 cell line and 1.65µg/ml for RD cell line (Vijayan *et al.,* 2002). No colony formation was seen up to 25 µg/mL concentration in the colonogenic assay. The whole alkaloid fraction of extract showed maximum cytotoxicity against RD cell line among all tested cell lines and in long-term (Hep-2) and short-term (DLA cells) studies the isolated fraction also showed antitumor activity against cancer cell line growth. Ding *et al.,* (2012) investigated the effect of polysaccharides extracted from *S. nigrum* in water and alkaline medium for antitumor activity. They reported excellent antitumor activity in SNLWP-1, SNLAP-1 and SNLAP-2 polysaccharide fractions of extract. The compositional analysis of alkali extracted fractions revealed high amounts of 5 and 6 carbon monosaccharide xylose and galactose, respectively. It was imagined that the monosaccharide composition could regulate the activity of polysaccharide fractions.

Antiangiogenic activity

Angiogenesis is the formation of new blood vessels from existing blood vessels. Compounds extracted from the *Solanum* species were tested for their antiangiogenic activity against cancerous cells. Three new with one known glycoalkaloids isolated from *S. lyratum* have been evaluated to have antiangiogenic potential. These compounds were investigated *in-vitro* for invasion, migration, and repression in tumor-originated endothelial cells (Han *et al.,* 2019). All glycoalkaloids exhibited antiangiogenic properties.

Antiproliferative Activity

Pigments belonging to the anthocyanins class are responsible for the attractive color of fruits, flowers and leaves. *S. tuberosum* var. vitelotte potato, used for food consumption by human beings, is a good source of anthocyanins. Anthocyanins from this plant were evaluated for antiproliferative and antioxidant potential. DPPH and FRAP techniques were used to assess antioxidant activity; the extract exhibited remarkable free radical scavenging capacity with 1.42 ± 0.2 and 4.25 ± 0.4 mmol Trolox/L, respectively for DPPH and FRAP and in antiproliferative activity, it was found that anthocyanins decrease cell proliferation and increase apoptosis in different solid and hematological cancer cell lines in a dose-dependent trend (Bontempo *et al.,* 2013). Solamargine, a major steroidal alkaloid glycoside isolated from *S. nigrum* , significantly inhibits the growth of human hepatoma SMMC-7721 cells and HepG2 cells and promotes cell apoptosis. When the complete cell cycle was analyzed, it was found that solamargine enhanced caspase-3 expression and checked cell cycle at the G2 and M phases (Ding *et al.,* 2012). The antiproliferative potential of *S. capsicoides* All seeds of methanolic extract replaced as methanolic seeds extract and isolated compound Carpesterol were investigated on different types of cancer cell lines. The methanolic extract showed its potent activity against leukemia, while carpesterol had significant activity against breast, glioma, kidney, ovary, lung and leukemia cancer cells. The toxicological studies demonstrated no harmful effect on any tested cell lines (Petreanu *et al.,* 2016). The steroidal glycosides from the *S. nigrum* unripe fruit were also tested for their antiproliferative activity against cancer cell lines with compound 4 solamargine was found effective in all cell lines examined. However, novel compounds 1-3 did not show any anticancerous activity (Xiang *et al.,* 2019).

Neuroprotective Activity

Neurodegenerative disorders are marked by gradual neuronal malfunction and death. Neuroprotection is a condition that allows the nervous system, its cells, structure and function to be salvaged, recovered or rebuilt (Ellison and Dementias, 2000; White, 1999). Neuroprotective activity was evaluated

for biomolecules derived from *S. nigrum* L. in SH-SY5Y (neuroblastoma cells) injured by MPP+. Among all the tested compounds, compound 6, which is Cannabisin F exhibited profound neuroprotective effect by the mechanism of protective autophagy (Li *et al.,* 2019).

DNA-Damage Activity

The DNA-binding activities of TPA-stimulated NF-κB and AP-1 are inhibited by *S. nigrum* glycoprotein, while NO generation is enhanced, both of which are crucial in the cytotoxic effect of *S. nigrum* in MCF-7 cells (Heo *et al.,* 2004). The pretreatment with delphinidin obtained from aqueous extract of *S. melongena* peel, which is a major source of anthocyanins, showed antimutagenic activity in cyclophosphamide-induced swiss mice *in-vivo* in single-cell (comet) and micronucleus assay (Azevedo *et al.,* 2007).

Chemical Structure and Function of *Solanum* Biomolecules

Solanum species possess various kinds of biomolecules like solamargine, uttroside B, tomatidine, solasonine, and melongenaterpene etc. Their structures are depicted in Fig. 4

Discussion

Solanaceous plants are important food plants with immense therapeutic potential owing to the presence of a diverse range of phytomolecules in the root, stem, leaf, flower, fruit and seed. Genus *Solanum* is one of the widely distributed genera of solanaceae and includes both commonly consumed and wild species. Biomolecules residing in the species of *Solanum* are not only the source of energy but also give therapeutic benefits. This review discusses the enormous diversity of *Solanum* species and its anticancer potential (Table 1). Cancer has a high mortality rate throughout the world. Only a few *Solanum* species like *S. nigrum*, *S. torvum*, *S. melongena*, *S. xanthocarpum*, *S. tuberosum*, *S. pseudocapsicum* have been evaluated for their anticancer activity and majority of species have remained untouched. The studies that have been done are also on the preliminary stage and only *S.nigrum* has got some attention. The anticancer activity is mainly evaluated on different types of cancer cell lines and shows promising results. The biomolecules responsible for activity are tomatidine, solasodine, solamargine, delphinidin, cannabisin F, carpesterol, methyl caffeate, diosgenin, saraspogenin and septemlobins (Table 2, Fig 4). However, solamargine, a glycoalkaloid, has been studied in some detail and other potent biomolecules need to be explored. These biomolecules can be isolated in different types of polar and non-polar solvents and the plant extracts show potent activity. New phytomolecules are now being regularly searched due to the advent of sophisticated techniques and these biomolecules have remained to be tested for their therapeutic potential. The biomolecules show anticancer activity mainly through their cytotoxic, antioxidant, antimutagenic, antiangiogenic, antitumor and antiproliferative effects (Table 1, 2 and Fig. 4). More sophisticated and decorated studies are required to support and validate the present scientific literature. The solanaceous biomolecules demonstrate their potential as antitumor agents against different types of malignancies as evident from the current literature and there is a need to test them against more types of cancer. Antioxidants are molecules needed to protect cellular machinery from the damaging effects of free radicals and solanaceous biomolecules have immense antioxidant potential. However, further research is needed to concrete these findings. The biomolecules illustrate the antitumor effect via the promotion of cell death through apoptosis. Multiple mechanisms are used to promote apoptosis and further research is required to elucidate the mode of action of these therapeutic agents. There is a lack of research in the field of toxicological studies and, which should be addressed before going further in clinical studies.

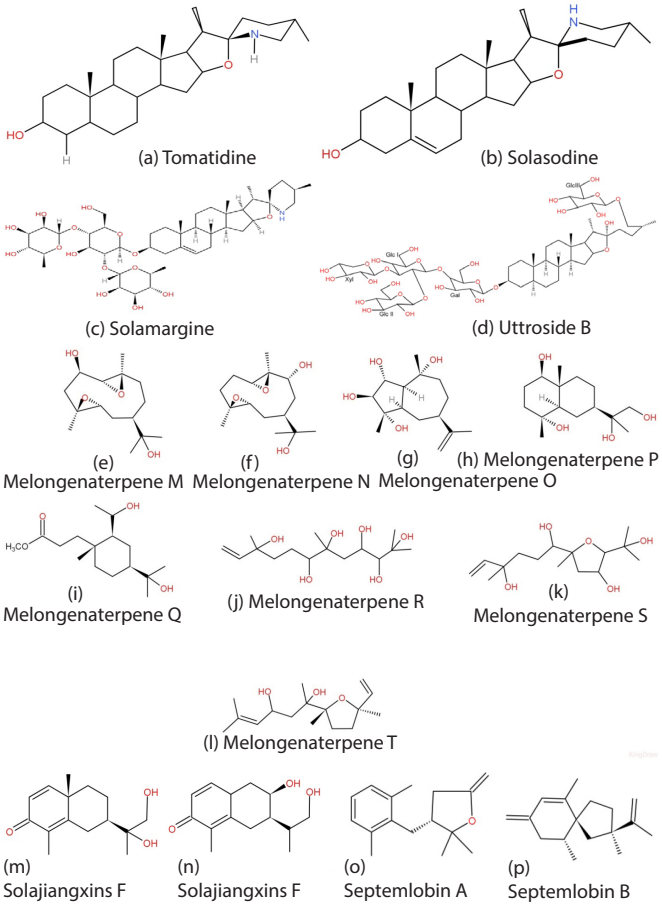

Fig. 4: (a-p). Some functional molecules of *Solanum* species

Future Prospects

The growing population of the world is now being exposed to many lethal diseases, out of which cancer is the leading cause of death. The increasing cost of drugs and the side effects on their prolonged consumption is necessary to address. Many regions of the developing world have populations that are not rich enough to rely on synthetic drugs. Traditional healthcare system supports the major populations for their healthcare needs. Plants are not only important for food but also have proven therapeutic potential. A large number of herbal formulations are present in the market for the treatment and prevention of diseases and many scientific works showed the importance of *Solanum* species as anticancer agents. *Solanum* species Wild and cultivated species of *Solanum* have different types of biomolecules residing in

leaves, fruits, seeds, flowers and fruit peels. *S. nigrum, S. torvum, S. xanthocarpum, S. tuberosum, S. aculeastrum* and *S. lyratum* have reportedly shown anticancer potential in both *in-vivo* and *in-vitro* studies. Other than that, many *solanum* species like *S. sisymbrifolium, S. trilobatum* also showed some anticancer properties but there are few reports on these species. Majority of species that belongs to genus *Solanum* have been unexplored with respect to their antitumor potential. These species are widely distributed in natural habitats and can easily be explored for their commercial value and therapeutic potential.

The biomolecules found in the member of genus *Solanum* fall into various categories and can be extracted with different organic and non-organic solvents. Solamargine, solanine, and tomatidine are few known biomolecules from *Solanum* plants that have shown anticancer efficacy. However, there are wide arrays of new biomolecules belonging to different phytochemical classes that have not been explored yet as indicated by new scientific literature. Advanced scientific tools and software have promoted the exploration of novel phytochemicals in solanaceous plants and these biomolecules have not yet been studied for their anticancerous properties. Preliminary studies revealed the cytotoxic potential of newly discovered biomolecules. There are few reports on mechanistic details of anticancer properties of the biomolecules and more studies are required on the mode of action of these phytomolecules. The data on the anticancer activity of *Solanum* species is based primarily on cell line studies. There is a serious dearth of knowledge on the preclinical and clinical efficacy of these species. Clinical studies must be done to support the incorporation of solanaceous compounds as anticancer agents. The active principles present in different plant parts promote apoptosis through multiple mechanisms and need to be investigated thoroughly before making anticancerous drugs. Very few studies provide toxicological insights and researchers should focus on toxicity analysis of different plant parts along with their anticancer activity. Herbal formulations have fewer side effects and different combinations of solanaceous plants may prove beneficial in this respect.

Conclusion

Solanaceous plants have immense potential as antiproliferative and anticancerous agents. Different extracts such as aqueous, ethanolic, methanolic and ethyl acetate extracts of these species have shown promising results. However, few studies have been done on the components that are responsible for the anticancer properties of these species and more research is required in the future to give a clear conception of the active components in *Solanum* species responsible for their anticancer potentials so that *Solanum* species can be exploited for making different drug formulations.

Ethics Approval And Consent To Participate

Not applicable.

Consent For Publication

Not applicable.

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Author Contribution

Ms Gunjan Pandey is the sole author of the paper. Mr. Kishan Kumar Prajapati and Ms Lalsa Shukla assisted partially in the research work and analysis. Ms Vartika is assisting in the collection of materials and online data. Prof. V. N. Pandey and Dr. Rakesh Pandey conceptualized the work and reviewed the paper.

Conflict Of Interest

There is no conflict of interest.

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