frontiers | Frontiers in Pharmacology

Solanum nigrum Linn.: An Insight into Current Research on Traditional Uses, Phytochemistry, and Pharmacology

Xufei Chen[1†], Xufen Dai[2†], Yinghai Liu[1], Yan Yang[3], Libang Yuan[1], Xirui He[3]* and Gu Gong[1]*

[1]Department of Anesthesiology, The General Hospital of the Western Theater Command, Chengdu, China, [2]Shaanxi Institute for Food and Drug Control, Xi'an, China, [3]Department of Bioengineering, Zhuhai Campus, Zunyi Medical University, Zhuhai, China

*Correspondence:
Xirui He
xiruihe6105194@163.com
Gu Gong
gonggu68@163.com

[†]These authors have contributed
equally to this work

Solanum nigrum Linn., is a common edible 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. Traditionally, it has been used to treat various cancers, acute nephritis, urethritis, leucorrhea, sore throat, toothache, dermatitis, eczema, carbuncles, and furuncles. Up to now, 188 chemical constituents have been identified from *S. nigrum*. Among them, steroidal saponins, alkaloids, phenols, and polysaccharides are the major bioactive constituents. Investigations of pharmacological activities of *S. nigrum* revealed that this edible medicinal herb exhibits a wide range of therapeutic potential, including antitumor, anti-inflammatory, antioxidant, antibacterial, and neuroprotective activities both *in vivo* and *in vitro*. This article presents a comprehensive and systematic overview of the botanical, traditional uses, phytochemical compositions, pharmacological properties, clinical trials, and toxicity of *S. nigrum* to provide the latest information for further exploitation and applications of *S. nigrum* in functional foods and medicines.

Keywords: traditional use, phytochemistry, pharmacology, toxicology Taylor and Francis, *Solanum nigrum Linn.*

INTRODUCTION

The genus *Solanum* (Solanaceae family) consists of more than 2,000 species, which are distributed worldwide in tropical and subtropical regions. They mostly have beautiful flowers and fruits. In China, 39 species and 14 varieties of *Solanum* exist (Editorial Committee of Flora of China, 1979). *Solanum nigrum* Linn. (**Figure 1**), also known as *Solanum nigrum* var. *virginicum* L. and "龙葵" (in Chinese). *S. nigrum* is distributed in almost every province in China and is commonly found near the fields, wastelands, and villages. It is also widely distributed in the temperate to tropical regions of Europe, Asia, and America (The Plant List, 2013; Xiang et al., 2019). In China, the plant is known under local names, such as "Yelahu", "Yehaijiao", "Heixingxing", "Heitiantian", "Kukui", "Kucai", "Heidoudou", and "Yesanzi" (Flora of China, 2007).

S. nigrum can be used as a medicine and tastes bitter, is of cold property and slightly toxic, and belongs to the lung and kidney meridians. In Chinese folk medicine and traditional Chinese medicine (TCM), people have accumulated rich clinical experience in the use of *S. nigrum*. The whole plant of *S. nigrum* has good effects of dispersing blood stasis and detumescence, clearing away heat, as well as detoxification and has been commonly used for the treatment of canker sores, skin eczema, urinary tract infections, bacterial dysentery, prostate, and chronic bronchitis, etc. for thousands of years (Gao et al., 2021). In addition, in modern clinical practice, *S. nigrum* is commonly combined with other drugs for the treatment of cancers, such as lung cancer, cervical

GRAPHICAL ABSTRACT |
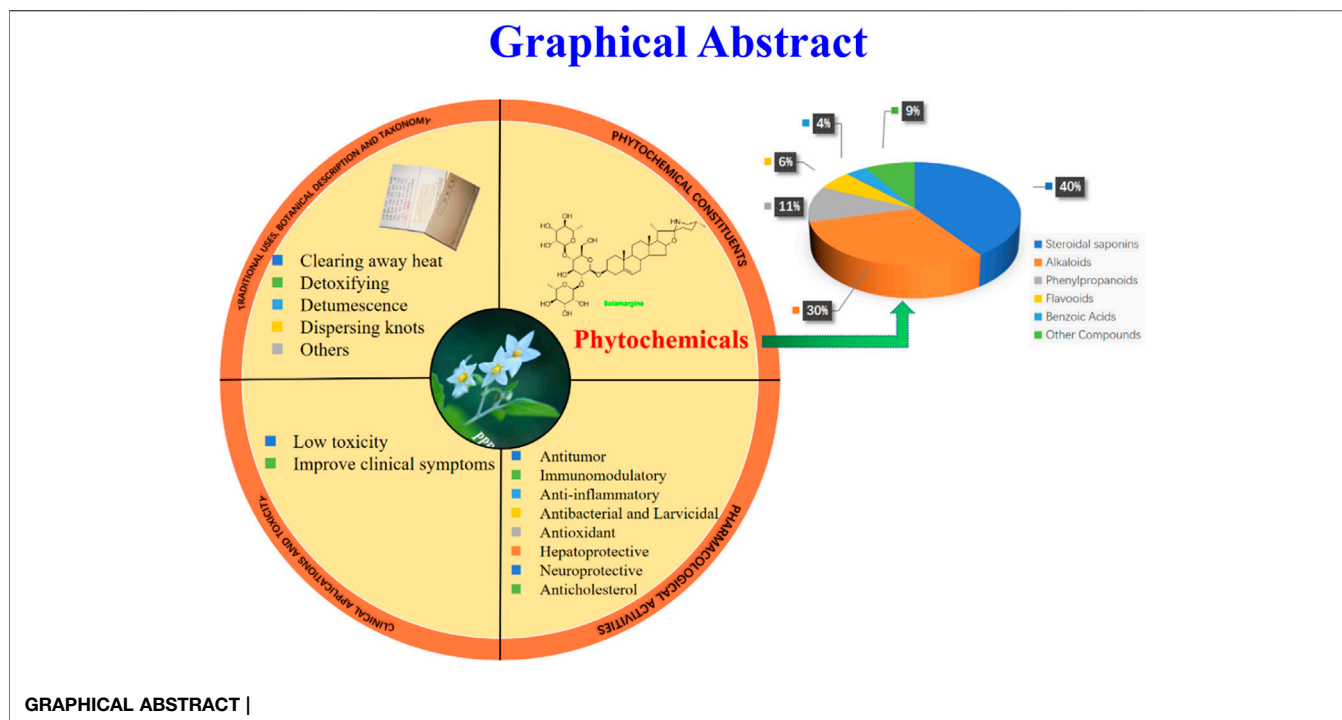
cancer, breast cancer, esophageal cancer, stomach cancer, liver cancer, and bladder cancer. In other Asian countries, such as Japan and India, it has also been documented for the treatment of tumors. Ripe berries of *S. nigrum* are sweet and salty and were reported to have been used as a famine food in China in the 15th century. In India, the leaves and berries of this plant are commonly consumed as food or vegetable after cooking (Wang, 2007; Zhao, 2010; Wang et al., 2017). In the past few decades, phytochemical research has confirmed that the whole *S. nigrum* herb contains steroidal saponins, steroidal alkaloids, flavonoids, coumarin, lignin, organic acids, volatile oils, polysaccharides, and other ingredients. The crude extract of *S. nigrum* and some of the above-mentioned compounds have been confirmed to have various effects, including antitumor, antioxidative, anti-inflammatory, hypotensive, neuroprotective, immunomodulatory, antibacterial, and liver protective effects. Especially the antitumor effect of steroidal saponins and steroidal alkaloids is a research hotspot, and drug researchers expect to find antitumor lead compounds from these components.

In view of the increasing interest in steroid derivatives obtained from *S. nigrum* due to their significant pharmacological activity, this review provides a systematic summary and criticism of the traditional uses, phytochemistry, pharmacological activity, and safety of *S. nigrum* based on the literature obtained from databases, with emphasis on the pharmacological activity and potential applications of *S. nigrum* in TCM. We believe that this review is of great significance for the further research or development of antioxidant functional foods, and novel antitumor drugs based on *S. nigrum* and its active compounds.

RESEARCH METHODOLOGY

The literature of this review (until March 2022) was obtained from various important databases, such as Google Scholar, Baidu Scholar, Web of Science, SciFinder Scholar, PubMed, published classic texts of Chinese herbal medicines (e.g., *Sheng Ji Zong Lu*), the China Knowledge Resource Integrated Database from the China National Knowledge Infrastructure (CNKI), publications in peer-reviewed journals, Ph.D. and M.Sc. theses, as well as other web sources, such as Flora of China, the Plant List, and YaoZh website (https://db.yaozh.com). Keywords used in the literature search were: "*Solanum nigrum* Linn.", "Long Kui/龙葵", "phytochemistry", "pharmacology", "biological activity", "traditional uses", "secondary metabolites", "safety", "toxicology", and "clinical trial". After reviewing a total of 576 scientific publications on *S. nigrum*, excluding some irrelevant content, we mainly focused on 120 documents. ChemDraw Ultra 15.0 software was used to draw the chemical structures.

BOTANICAL DESCRIPTION AND TAXONOMY

Botanical Description

S. nigrum is an annual erect herbaceous plant with 0.25–1 m in high. It has a taproot system with a well-developed main root and is often lignified. The stem has no inconspicuous edges, is green or purple in color, and nearly glabrous or puberulent. The leaf is ovate, 2.5–10 cm long, and 1.5–5.5 cm wide, and its apex is shortly pointed. The cuneate is base wedge shaped to broad and descending to the petiole, with irregular wavy coarse teeth throughout or on each side and smooth or sparse, soft, and hairy
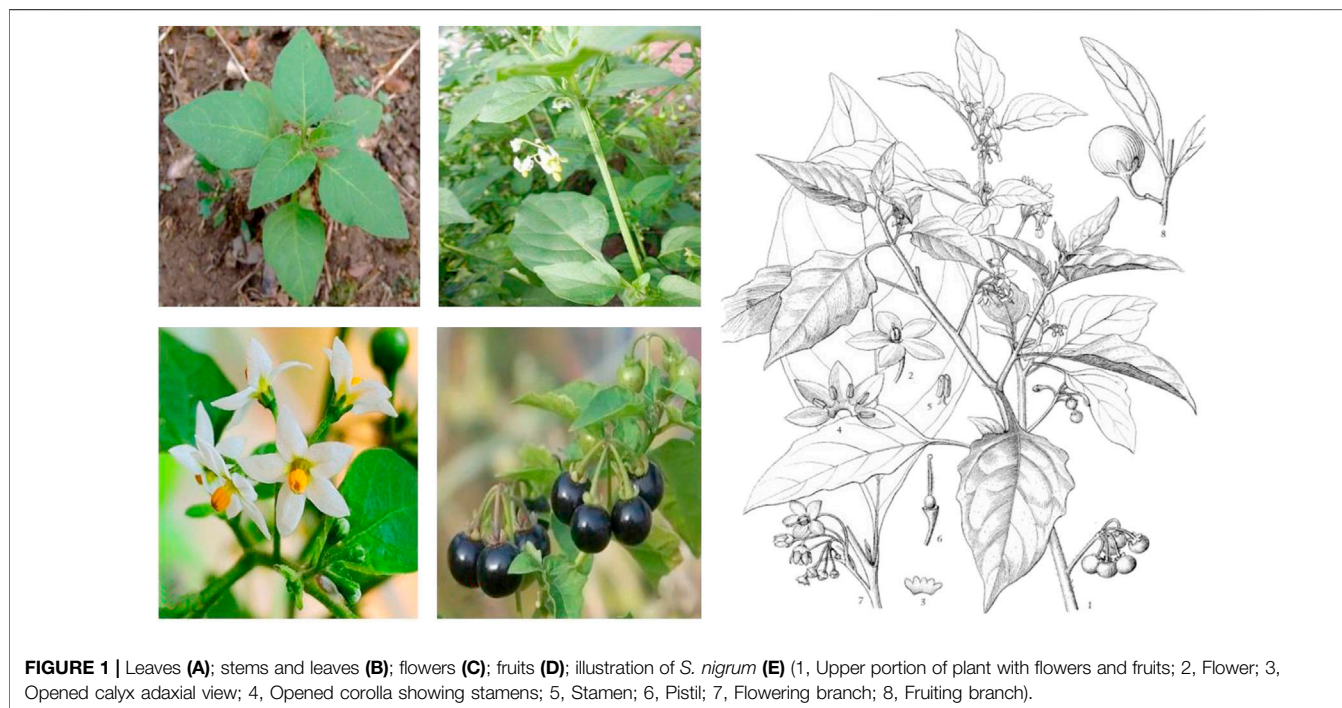
FIGURE 1 | Leaves **(A)**; stems and leaves **(B)**; flowers **(C)**; fruits **(D)**; illustration of *S. nigrum* **(E)** (1, Upper portion of plant with flowers and fruits; 2, Flower; 3, Opened calyx adaxial view; 4, Opened corolla showing stamens; 5, Stamen; 6, Pistil; 7, Flowering branch; 8, Fruiting branch).

on both sides with five to six veins on each side, and the petiole is about 1–2 cm long. The scorpion-tailed inflorescence is extra-axillary and composed of 3-6-(10) flowers. The total pedicel is about 1–2.5 cm long, and the pedicel is about 5 mm long and nearly glabrous or pubescent. The calyx is small, shallow cup shaped, and about 1.5–2 mm in diameter, and the teeth are oval, the tip is round, and the junction between the two teeth at the base is angled. The corolla is white, the tube is hidden in the calyx and less than 1 mm in length, and the 5-parted crown is about 2.5 mm in length. The lobes are ovoid and about 2 mm long. The filaments are short, the anthers are yellow, about 1.2 mm long, and about four times the length of the filaments, and the apical hole is inward. The ovary is ovoid and about 0.5 mm in diameter, and the style is about 1.5 mm long. The lower part of the middle part is covered with white hairs, the stigma is small, and the head is shaped. The berry is spherical, about 8 mm in diameter, and black when ripe. The seeds are mostly nearly ovoid, about 1.5–2 mm in diameter, and compressed on both sides (Flora of China, 2007).

Taxonomy

S. nigrum in botanical classification as Plantae, Angiospermae, Magnoliopsida, Solanales, Solanaceae, Solanum. Solanaceae is a family of plants with about 80 genera and 3,000 species, widely distributed in tropical and temperate regions, mainly in tropical America. Solanum occupies an important weight in the Solanaceae family, with about 2,000 species, among which the well-known varieties are *Solanum melongena* L., *Solanum tuberosum* L., *S. nigrum*, etc. (The Plant List, 2013; Flora of China, 2007). The spherical berries of *S. nigrum* are dark purple when ripe. Both the berries and the leaves are edible, but the leaves contain high amounts of alkaloids that must be cooked to detoxify.

TRADITIONAL USES

The first known record describing the medicinal use of *S. nigrum* was found in *Yao Xing Lun* (药性论, Tang Dynasty) (Editorial Committee of State Administration of traditional Chinese Medicine, 1999). Since then, the medicinal use of *S. nigrum* was increasingly reported in many other well-known classical TCM monographs, including *Xin Xiu Ben Cao* (新修本草, Tang Dynasty), *Shi Liao Ben Cao* (食疗本草, Tang Dynasty), *Ben Cao Tu Jing* (本草图经, Song Dynasty), *Jiu Huang Ben Cao* (救荒本草, Ming Dynasty), *Dian Nan Ben Cao* (滇南本草, Ming Dynasty), *Ben Cao Gang Mu* (本草纲目, Ming Dynasty), *Dian Nan Ben Cao Tu Shuo* (滇南本草图说, Ming Dynasty), and *Ben Cao Gang Mu Shi Yi* (本草纲目拾遗, Qing Dynasty). In these classical books of TCM, it is recorded that *S. nigrum* has the functions of clearing away heat, detoxification, detumescence, and dispersion of knots (Editorial Committee of Nanjing University of Chinese Medicine, 2006). In all of these major TCM monographs, *S. nigrum* has different medicinal properties, including the treatment of sore carbuncle swelling poison, skin eczema, poor urination, chronic bronchitis, excessive leucorrhea, prostatitis, and dysentery. Many TCM herbs or classical prescriptions containing *S. nigrum* have been used in the form of decoction, powders, granules, tablets, and pills. The traditional and modern prescriptions of *S. nigrum* commonly used in China are presented in **Table 1**. For example, according to *Sheng Ji Zong Lu*, *S. nigrum* (30 g) is compatible with other herbs such as

TABLE 1 | The traditional and modern prescriptions of *S. nigrum* in China.

Preparation name	Composition	Route of administration	Dosage form	Indications for use	References
Longkui san	***S. Nigrum***, *Hylotelephium erythrostictum* (Miq.) H. Ohba, *Coptis chinensis* Franch., *Os Draconis* (FossiliaOssiaMastodi), *Boswellia carterii* Birdw., *Momordica cochinchinensis* (Lour.) Spreng., *Abelmoschus manihot* (Linn.) Medicus	External use	Making into powder	Malignant sores	"*Sheng Ji Zong Lu*" (Song Dynasty, A.D. 1117)
Longkui san	***S. Nigrum***, *Boswellia carterii* Birdw., *Prunus armeniaca* L., *Coptis chinensis* Franch	External use	Making into powder	Malignant sores	"*Sheng Ji Zong Lu*" (Song Dynasty, A.D. 1117)
Longkuigeng san	***S. Nigrum***, *Moschus berezovskii* Flerov	External use	Making into powder	Back sore	"*Sheng Ji Zong Lu*" (Song Dynasty, A.D. 1117)
Longkui gao	***S. Nigrum***, *Hyoscyamus niger* Linn., *Allium sativum* L., *Coriandrum sativum* Linn., *Prunus armeniaca* L.	External use	Making into cream	Malignant prickling sore pain	"*Tai Ping Sheng Hui Fang*" (Song Dynasty, A.D. 992)
Xinlikang capsules	*Scutellaria barbata* D. Don, ***S. Nigrum***, *Duchesnea indica* (Andr.) Focke, *Astragalus membranaceus* (Fisch.)Bge., *Panax ginseng* C. A. Meyer, *Saussurea involucrata* (Kar. et Kir.) Sch.-Bip., *Angelica sinensis* (Oliv.) Diels, *Curcuma longa* Linn., *Salvia miltiorrhiza* Bunge	Take orally	Decocting with water, and then making into granules	Invigorate qi and nourish blood, remove blood stasis and detoxify, cancer	Liu et al. (2019a)
Compound Tianxian capsules	*Trichosanthes kirilowii* Maxim., *Clematis chinensis* Osbeck, *Hedyotis diffusa* Willd., *Bos taurus domesticus* Gmelin, ***S. Nigrum***, *Arisaema heterophyllum* Blume, *Boswellia carterii* Birdw., *Commiphora myrrha* (Nees) Engl., *Panax ginseng* C. A. Meyer, *Astragalus membranaceus* (Fisch.)Bge., *Polyporus umbellatus* (Pers.) Fr., *Elphe taeniura* Cope, *Cinnamomum camphora* (L.) Presl, *Moschus berezovskii* Flervo	Take orally	Making into capsules	Supervened after esophageal cancer and stomach cancer, peptic ulcer	Kang et al. (2014)
Loulian capsules	*Hedyotis diffusa* Willd., *Semiaquilegia adoxoides* (DC.) Makino, *Polygonum onrientale* L., *Paris polyphylla* Smith. var. *yunnanensis* (Franch.) Hand.-Mzt., *Amyda sinensis* (Wiegmann), *Curcuma zedoaria* (Christm.) Rosc., *Lobelia chinensis* Lour., *Steleophaga Plancyi* (Boleny), *Whitmania pigra* Whitman, *Panax ginseng* C. A. Meyer, *Fallopia multiflora* (Thunb.) Harald., ***S. Nigrum***	Take orally	Making into capsules	Hepatitis, liver cirrhosis, liver cancer, breast cancer, hemangioma	Zhang, (2015)
Baiying qinghou decoction	*Solanum lyratum* Thunberg, ***S. Nigrum***, *Duchesnea indica* (Andr.) Focke, *Scutellaria barbata* D. Don, *Armeniaca mume* Sieb	Take orally	Decocting with water	Laryngeal cancer	"*Qiu Yuan Ying Fang*"
Kaizhi longgu san	*Os draconis* (FossiliaOssiaMastodi), *Asarum sieboldii* Miq., *Gypsum Fibrosum*, *Ligusticum sinense* Oliv., ***S. Nigrum***, *Angelica dahurica* (Fisch. ex Hoffm.) Benth. et Hook. f., *Gypsum Rubrum*, *Salt*	External use	Making into powder	Bad breath	"*Pu Ji Fang*" (Ming Dynasty, A.D. 1390)
Lingxian longcao decoction	*Clematis chinensis* Osbeck, ***S. Nigrum***, *Prunella vulgaris* Linn., *Smilax glabra* Roxb., *Trichosanthes kirilowii* Maxim., *Clematis terniflora* DC., *Iphigenia indica* Kunth, *Wikstroemia indica* (Linn.) C. A. Mey	Take orally	Decocting with water	Phlegm scrofula, breast mass, wheezing, vomiting	"*Yan Fang Xuan Bian*" (A.D. 1959)

Hylotelephium erythrostictum (Miq.) H. Ohba (30 g), *Coptis chinensis* Franch. (30 g), *Momordica cochinchinensis* (Lour.) Spreng. (15 g), and *Abelmoschus manihot* (Linn.) Medicus (15 g) for the treatment of malignant sores (https://db.yaozh.com). For the treatment of carbuncles, swelling, and poisoning, *S. nigrum* can be externally applied for washing and smashing. It can also be combined with TCM, such as *Corydalis bungeana* Turcz., *Chrysanthemum indicum* L., and *Taraxacum mongolicum* Hand.-Mazz., for decoction and subsequent oral administration to treat sore throats. In addition, *S. nigrum* has a diuretic effect and can be used together with *Alisma plantago-aquatica* Linn., *Akebia quinata* (Houttuyn) Decaisne, and other drugs to treat edema, adverse urination and other diseases (Editorial Committee of Nanjing University of Chinese Medicine, 2006). In recent years, it has been commonly used together with *Duchesnea indica* (Andr.) Focke, *Hedyotis diffusa* Willd.,

TABLE 2 | Chemical components structurally identified from *S. nigrum*.

No	Chemical constituents	Molecular formula	CAS	Extracts	References
	Steroidal saponins				
1	Diosgenin	$C_{27}H_{42}O_3$	512-04-9	MeOH	Gao et al. (2021) Tsuyoshi et al. (2003)
2	Degalactotigonin	$C_{50}H_{82}O_{22}$	39941-51-0	EtOH	Wang (2007)
3	Stigmasterol	$C_{29}H_{48}O$	83-48-7	EtOH	Zhao (2010)
4	Pterosterone	$C_{27}H_{44}O_7$	18089-44-6	EtOH	Zhao (2010)
5	12-keto-porrigenin	$C_{27}H_{42}O_5$	189014-45-7	EtOH	Zhao (2010)
6	28-*O*-β-ᴅ-glucopyranosyl betulinic acid 3β-*O*-β-D glucopyranoside	$C_{42}H_{68}O_{13}$		EtOH	Yang (2014)
7	β-daucosterol	$C_{35}H_{60}O_6$	474-58-8	EtOH	Yang (2014)
8	(25*R*)-5α-furost-3β, 22α-diol-12-one-26-carboxylicacid-3-*O*-β-D-glucopyranosy-(1→4)-[*O*-β-ᴅ-glucopyranosyl-(1→2)]-*O*- β-ᴅ-glucopyranosyl-(1→4)-*O*-β-ᴅ-galactopyranoside	$C_{47}H_{76}O_{20}$		EtOH	Li (2010b)
9	Tigogenin3-*O*-β-ᴅ-glucopyranosyl-(1→2)-[*O*-β-ᴅ-xyloyranosyl-(1→3)]-*O*-β-ᴅ-glucopyranosyl-(1→4)-*O*-β-ᴅ-galactopyranoside	$C_{52}H_{86}O_{21}$		EtOH	Li (2010b)
10	Uttroside A	$C_{57}H_{96}O_{28}$	82003-86-9	EtOH	He et al. (2015), Zhou (2006)
11	Uttroside B	$C_{56}H_{94}O_{28}$	88048-09-3	EtOH	He et al. (2015), Zhou (2006)
12	(22α, 25*R*)-26-*O*-(β-ᴅ-glucopyranosyl)-22-methoxy-furost-Δ5-3β, 26-diol-3-*O*-β-ᴅ-glucopyranosyl -(1→2)-*O*-[β-ᴅ-xylopyranosyl-(1→3)]-*O*-β-ᴅ-glucopyranosyl-(1→4)-*O*-β-ᴅ-galactopyranoside	$C_{57}H_{94}O_{28}$		EtOH	He et al. (2015), Zhou (2006)
13	(22α, 25*R*)-26-*O*-(β-ᴅ-glucopyranosyl)-22-hydroxy-furost-Δ5-3β, 26-diol-3-*O*-β-ᴅ-glucopyranosyl-(1→2)-*O*-[β-ᴅ-xylopyranosyl-(1→3)]-*O*-β-ᴅ-glucopyranosyl-(1→4)-*O*-β-ᴅ-galactopyranoside	$C_{57}H_{92}O_{28}$		EtOH	He et al. (2015), Zhou (2006)
14	(5α, 22α, 25*R*)-26-*O*-(β-ᴅ-glucopyranosyl)-22-methoxy-furostan-3β, 26-diol-3-β-ᴅ-glucopyranosyl-(1→2)-*O*-[β-ᴅ-glucopyranosyl-(1→3)]- *O*-β-ᴅ-glucopyranosyl-(1→4)-*O*-β-ᴅ-galactopyranoside	$C_{58}H_{98}O_{29}$	108886-03-9	EtOH	He et al. (2015), Zhou (2006)
15	(5α, 22α, 25*R*)-26-*O*-(β-ᴅ-glucopyranosyl-22-hydroxy-furost-3β,26-diol-3-β-ᴅ-glucopyranosyl-(1→2)-*O*-[β-ᴅ-glucopyranosyl-(1→3)]-*O*-β-ᴅ-glucopyranosyl-(1→4)-*O*-β-ᴅ-galactopyranoside	$C_{57}H_{96}O_{29}$		EtOH	He et al. (2015), Zhou (2006)
16	Solanigroside I	$C_{62}H_{104}O_{31}$		EtOH	He et al. (2015), Zhou (2006)
17	Solanigroside J	$C_{61}H_{102}O_{31}$	1354759-80-0	EtOH	He et al. (2015), Zhou (2006)
18	Solanigroside K	$C_{57}H_{94}O_{28}$		EtOH	He et al. (2015), Zhou (2006)
19	Solanigroside L	$C_{57}H_{92}O_{28}$		EtOH	He et al. (2015), Zhou (2006)
20	Solanigroside M	$C_{57}H_{92}O_{28}$		EtOH	He et al. (2015), Zhou (2006)
21	Solanigroside N	$C_{57}H_{94}O_{28}$		EtOH	He et al. (2015), Zhou (2006)
22	Solanigroside R	$C_{50}H_{84}O_{23}$		EtOH	He et al. (2015), Zhou (2006), Tai et al. (2018)
23	Solanigroside S	$C_{50}H_{86}O_{23}$		EtOH	He et al. (2015), Zhou (2006)
24	Solanigroside T	$C_{45}H_{84}O_{22}$		EtOH	He et al. (2015), Zhou (2006)
25	Hypoglaucin H	$C_{39}H_{60}O_{15}$	50773-43-8	EtOH	Zhou (2006)
26	5α-pregn-16-en-3β-ol-20-one-lycotetraoside	$C_{44}H_{70}O_{21}$		EtOH	He et al. (2015), Zhou (2006)
27	Solanigroside A	$C_{49}H_{78}O_{24}$	1029362-42-2	EtOH	He et al. (2015), Zhou (2006)
28	Solanigroside B	$C_{45}H_{72}O_{22}$	1029362-44-4	EtOH	He et al. (2015), Zhou (2006)
29	(5α, 20*S*)-3β, 16β-dihydroxy pregn-22-carboxylic acid (22, 16)-lactone-3-*O*-β-ᴅ-glucopyranosyl-(1→2)-*O*-[β-D-xylopy ranosyl-(1→3)]-*O*-β-ᴅ- glucopyranosyl-(1→4)-*O*-β-ᴅ-galactopyranoside	$C_{45}H_{72}O_{22}$		EtOH	He et al. (2015), Zhou (2006)
30	Solanigroside U	$C_{50}H_{80}O_{25}$		EtOH	He et al. (2015), Zhou (2006)
31	Solanigroside V	$C_{50}H_{80}O_{25}$		EtOH	He et al. (2015), Zhou (2006)
32	Solanigroside W	$C_{45}H_{70}O_{22}$		EtOH	He et al. (2015), Zhou (2006)
33	Solanigroside X	$C_{45}H_{72}O_{23}$		EtOH	He et al. (2015), Zhou (2006)
34	Nigrumnin I	$C_{55}H_{90}O_{25}$		EtOH	He et al. (2015), Zhou (2006)
35	Solanigroside C	$C_{51}H_{82}O_{26}$	905914-27-4	EtOH	He et al. (2015), Zhou (2006)
36	Solanigroside D	$C_{55}H_{88}O_{27}$	905914-28-5	EtOH	He et al. (2015), Zhou (2006)
37	Solanigroside E	$C_{55}H_{88}O_{28}$	905914-29-6	EtOH	He et al. (2015), Zhou (2006)
38	Solanigroside F	$C_{56}H_{92}O_{28}$	905914-30-9	EtOH	He et al. (2015), Zhou (2006)

(Continued on following page)

TABLE 2 | (*Continued*) Chemical components structurally identified from *S. nigrum*.

No	Chemical constituents	Molecular formula	CAS	Extracts	References
39	Solanigroside G	$C_{50}H_{82}O_{23}$	905914-31-0	EtOH	He et al. (2015), Zhou (2006)
40	Solanigroside O	$C_{51}H_{86}O_{23}$		EtOH	He et al. (2015), Zhou (2006)
41	Nigroside A	$C_{56}H_{94}O_{29}$	386747-86-0	EtOH	He et al. (2015), Zhou (2006)
42	Tigogenin/(25R)-5α-spirostan-3β-ol	$C_{27}H_{44}O_3$		EtOH	Wu (2011)
43	(25R)-26-O-β-D-glucopyranosyl-cholest-5(6)-en-3β, 26-diol-16,22-dione-3-O-α-L-rhamnopyranosyl -(1→2)-[β-D-glucopyranosyl-(1→3)]-β-D-galactopyranoside	$C_{51}H_{86}NO_{23}$		MeOH	Xiang et al. (2018)
44	(25R)-26-O-β-D-glucopyranosyl-cholest-5(6)-en-3β, 26-diol-16,22-dione-3-O-α-L-rhamnopyranosyl -(1→4)-β-D-glucopyranoside	$C_{45}H_{76}NO_{18}$		MeOH	Xiang et al. (2018)
45	(25S)-26-O-β-D-glucopyranosyl-cholest-5(6)-en-3β, 26-diol-16, 22-dione-3-O-α-L-rhamnopyranosyl -(1→2)-[α-Lrhamnopyranosyl-(1→4)]-[β-D-glucopyranosyl-(1→6)]-β-D-glucopyranoside	$C_{57}H_{96}NO_{27}$		MeOH	Xiang et al. (2018)
46	(25R)-26-O-β-D-glucopyranosyl-(1→2)-β-D-glucopyranosyl-cholest-5(6)-en-3β, 26-diol-16, 22-dione-3-O-α-Lrhamnopyranosyl-(1→2)-[α-L-rhamnopyranosyl-(1→4)]-[β-D-glucopyranosyl-(1→6)]-β-D-glucopyranoside	$C_{63}H_{106}NO_{32}$		MeOH	Xiang et al. (2018)
47	(25S)-26-O-β-D-glucopyranosyl-cholest-5(6)-en-3β, 26-diol-16, 22-dione-3-O-β-D-glucopyranosyl -(1→6)-β-D-glucopyranosyl-(1→3)-[α-L-rhamnopyranosyl-(1→2)]-β-D-galactopyranoside	$C_{57}H_{96}NO_{28}$		MeOH	Xiang et al. (2018)
48	(25R)-26-O-β-D-glucopyranosyl-(1→2)-β-D-glucopyranosyl-cholest-5(6)-en-3β, 26-diol-16, 22-dione-3-O-α-L-rhamnopyranosyl-(1→2)-[β-D-glucopyranosyl-(1→3)]-β-D-galactopyranoside	$C_{57}H_{96}NO_{28}$		MeOH	Xiang et al. (2018)
49	(25R)-26-O-β-D-glucopyranosyl-cholest-5α-3β, 26-diol-16, 22-dione-3-O-β-D-glucopyranosyl-(1→2)-[β-D-glucopyranosyl-(1→3)]-β-D-glucopyranosyl-(1→4)-β-D-galactopyranoside	$C_{57}H_{98}NO_{29}$		MeOH	Xiang et al. (2018)
50	Stigmast-5, 22-dien-3β-ol	$C_{29}H_{48}O$		EtOH	Sharma et al. (2012)
51	Inunigroside A	$C_{50}H_{82}O_{23}$	1427934-51-7	MeOH	Ohho et al. (2012)
52	Solanigroside Y1	$C_{51}H_{82}O_{26}$	2098576-14-6	MeOH	Wang et al. (2017)
53	Solanigroside Y2	$C_{51}H_{82}O_{26}$	2098576-15-7	MeOH	Wang et al. (2017)
54	Solanigroside Y3	$C_{51}H_{80}O_{26}$	2098576-16-8	MeOH	Wang et al. (2017)
55	Solanigroside Y4	$C_{45}H_{70}O_{21}$	2098576-17-9	MeOH	Wang et al. (2017)
56	Solanigroside Y5	$C_{57}H_{94}O_{28}$	2098576-18-0	MeOH	Wang et al. (2017)
57	Solanigroside Y6	$C_{57}H_{94}O_{27}$	2098576-19-1	MeOH	Wang et al. (2017)
58	Solanigroside Y7	$C_{63}H_{106}O_{34}$	2098576-20-4	MeOH	Wang et al. (2017)
59	Solanigroside Y8	$C_{62}H_{104}O_{33}$	2098576-21-5	MeOH	Wang et al. (2017)
60	Solanigroside Y9	$C_{62}H_{104}O_{33}$	2098576-22-6	MeOH	Wang et al. (2017)
61	(25R)-26-O-β-D-glucopyranosylfurost-5(6)-ene-3β, 22α, 26-triol-3-O-β-D-glucopyranosyl-(1→2)-[β-D-glucopyranosyl-(1→3)]-β-D-glucopyranosyl-(1→4)-β-D-galactopyranoside	$C_{57}H_{96}O_{30}$		MeOH	Wang et al. (2017)
62	(25R)-26-O-β-Dglucopyranosylfurost-5(6)-ene-3β, 22α, 26-triol-3-O-α-L-rhamnopyranosyl-(1→2)-[α-L-rhamnopyranosyl-(1→4)]-β-D-glucopyranoside	$C_{57}H_{92}O_{25}$		MeOH	Wang et al. (2017)
63	(25R)-26-O-β-D-glucopyranosylfurost-5(6)-ene-16α-methoxy-3β, 26-diol-3-O-α-L-rhamnopyranosyl -(1→2)-[α-L-rhamnopyranosyl-(1→4)]-β-D-glucopyranoside	$C_{39}H_{60}O_{16}$		MeOH	Wang et al. (2017)
64	(25R)-26-O-β-D-glucopyranosyl-5α-furost-3β, 22α, 26-triol-3-O-β-D-glucopyranosyl-(1→2)-[β-D-glucopyranosyl-(1→3)]-β-D-glucopyranosyl-(1→4)-β-D-galactopyranoside	$C_{57}H_{94}O_{30}$		MeOH	Wang et al. (2017)
65		$C_{57}H_{94}O_{30}$		MeOH	Wang et al. (2017)

TABLE 2 | (*Continued*) Chemical components structurally identified from *S. nigrum*.

No	Chemical constituents	Molecular formula	CAS	Extracts	References
	(25S)-26-O-β-D-glucopyranosyl-5α-furost-3β, 22α, 26-triol-3-O-β-D-glucopyranosyl-(1→2)-[β-D-glucopyranosyl-(1→3)]-β-D-glucopyranosyl-(1→4)-β-D-galactopyranoside				
66	(25R)-26-O-β-Dglucopyranosyl-22α-methoxy-5α-furost-3β, 26-diol-3-O-β-D-glucopyranosyl-(1→2)-[β-D-glucopyranosyl-(1→3)]-β-D-glucopyranosyl-(1→4)-β-D-galactopyranoside	$C_{57}H_{96}O_{30}$		MeOH	Wang et al. (2017)
67	Uttroside B ((25R)-26-O-β-D-glucopyranosyl-5α-furost-3β, 22α, 26-triol-3-O-β-D-glucopyranosyl-(1→2)-[β-D-xylopyranosyl-(1→3)]-β-D-glucopyranosyl-(1→4)-β-D-galactopyranoside)	$C_{56}H_{94}O_{28}$	88048-09-3	MeOH	Wang et al. (2017)
68	β-sitosterol	$C_{29}H_{50}O$	83-46-5	EtOH	Yang (2014)
69	β-carotene glycosides	$C_{35}H_{58}O_6$		EtOH	Yang (2014)
70	Tigogenin	$C_{27}H_{44}O_3$	77-60-1	EtOH	He et al. (2015), Zhou (2006)
71	Uttronin A	$C_{50}H_{82}O_{22}$	39941-51-0	EtOH	He et al. (2015), Zhou (2006)
72	Uttronin B	$C_{39}H_{62}O_{12}$	84955-03-3	EtOH	He et al. (2015), Zhou (2006)
73	Dumoside	$C_{40}H_{62}O_{16}$	221526-58-5	EtOH	He et al. (2015), Zhou (2006)
74	Nigrumnin II	$C_{55}H_{88}O_{27}$		EtOH	He et al. (2015), Zhou (2006)
75	Solanigroside H	$C_{51}H_{82}O_{22}$	905914-32-1	EtOH	He et al. (2015), Zhou (2006)
76	Cholesterol	$C_{27}H_{46}O$	57-88-5	EtOH	Geng et al. (2020)
Alkaloids					
77	β1-solasonine	$C_{39}H_{63}NO_{11}$	73069-18-8	EtOH	He et al. (2015), Zhou (2006)
78	β2-solasonine	$C_{39}H_{63}NO_{12}$	73069-19-9	EtOH	He et al. (2015), Zhou (2006)
79	Solamargine	$C_{45}H_{73}NO_{15}$	20311-51-7	EtOH	He et al. (2015), Zhou (2006), Wang (2007)
80	β2-solamargine	$C_{39}H_{63}NO_{11}$	32449-98-2	EtOH	He et al. (2015), Zhou (2006) Wang (2007)
81	Solanigroside P	$C_{39}H_{63}NO_{12}$	1446029-15-7	EtOH	He et al. (2015), Zhou (2006)
82	Solanigroside Q	$C_{45}H_{69}NO_{15}$		EtOH	He et al. (2015), Zhou (2006), Tai et al. (2018)
83	(3β, 12β, 22α, 25R)-3, 12-dihydroxy-spirosol-5-en-27-oic acid	$C_{27}H_{41}NO_5$		EtOH	He et al. (2015), Zhou (2006)
84	Solaoiacid	$C_{44}H_{83}NO_{19}$		H_2O	Shi et al. (2019)
85	(25R)-22αN-4-nor-spirosol-5(6)-en-3β-ol-6-al-3-O-L-rhamnopyranosyl-(1→2)-[α-L-rhamnopyranosyl-(1→4)]-β-D-glucopyranoside	$C_{45}H_{72}NO_{16}$		MeOH	Xiang et al. (2019)
86	(25R)-22αN-spirosol-5(6)-en-3β-ol-7-oxo-3-O-L-rhamnopyranosyl-(1→2)-[α-L-rhamnopyranosyl-(1→4)]-β-D-glucopyranoside	$C_{45}H_{72}NO_{16}$		MeOH	Xiang et al. (2019)
87	(25R)-22αN-spirosol-4(5)-en-3β-ol-6-oxo-3-O-α-Lrhamnopyranosyl-(1→2)-[α-L-rhamnopyranosyl-(1→4)]-β-D-glucopyranoside	$C_{45}H_{72}NO_{16}$		MeOH	Xiang et al. (2019)
88	Solasodine	$C_{27}H_{43}NO_2$	126-17-0	EtOH	He et al. (2015), Zhou (2006)
89	N-methylsolasodine	$C_{28}H_{45}NO_2$	7604-92-4	EtOH	He et al. (2015), Zhou (2006)
90	Tomatidenol	$C_{27}H_{43}NO_2$	546-40-7	EtOH	He et al. (2015), Zhou (2006)
91	Solanocapsine	$C_{27}H_{46}N_2O_2$	639-86-1	EtOH	Liu et al. (2020), Zhou (2006)
92	Solanaviol	$C_{27}H_{43}NO_3$	74131-93-4	EtOH	He et al. (2015), Zhou (2006)
93	Solasodine-3-O-β-D-glucopyranoside	$C_{33}H_{53}NO_7$		EtOH	Chang et al. (2017)
94	12β-hydroxysolasodine β-solatrioside	$C_{45}H_{73}NO_{17}$		EtOH	He et al. (2015), Zhou (2006)
95	12β, 27-dihydroxy solasodine β-chacotrioside	$C_{45}H_{73}NO_{17}$		EtOH	He et al. (2015), Zhou (2006)
96	23-O-acetyl-12β-hydroxysolasodine	$C_{29}H_{45}NO_{15}$	117803-97-1	EtOH	He et al. (2015), Zhou (2006)
97	(3β, 22α, 25R)-spirosol-5-en-3yl-O-α-L-Rhamanopyranosyl-(1-2)-[O-β-D-glucopyranosyl(1–3)]-O-β-D-galactopyranoside	$C_{39}H_{85}NO_{15}$	101009-59-0	EtOH	Yang (2014)
98	15α-hydroxysolasodine	$C_{27}H_{43}NO_3$	10009-88-8	EtOH	Wu (2011)
99	α-Solanine	$C_{45}H_{73}NO_{15}$	20562-02-1	EtOH	Huang et al. (2020)
100	Solasonine	$C_{45}H_{73}NO_{16}$	19121-58-5	EtOH	He et al. (2015), Zhou (2006)
101	Leptinine I	$C_{45}H_{73}NO_{15}$		EtOH	Gao et al. (2021)
102	(7R, 8S)-1-(4-hydroxy-3-methoxyphenyl)-2-{4-{2-[N-2-(4-hydroxyphenyl)ethyl]Carbamoylehenyl-2-methoxyphenoxyl}}-1, 3-propanodiolnamed	$C_{28}H_{32}NO_8$		EtOH	Li et al. (2019)
103	(7S, 8R)-1-(4-hydroxy-3-methoxyphenyl)-2-{4-{2-[N-2-(4-hydroxyphenyl)ethyl]Carbamoylehenyl-2-methoxyphenoxyl}}-1, 3-propanodiolnamed	$C_{28}H_{32}NO_8$		EtOH	Li et al. (2019)

TABLE 2 | (Continued) Chemical components structurally identified from S. nigrum.

No	Chemical constituents	Molecular formula	CAS	Extracts	References
104	(7R, 8R)-1-(4-hydroxy-3-methoxyphenyl)-2-{4-{2-[N-2-(4-hydroxyphenyl)ethyl] Carbamoylehenyl -2-methoxyphenoxyl}}-1, 3-propanodiolnamed	$C_{28}H_{32}NO_8$		EtOH	Li et al. (2019)
105	(7S, 8S)-1-(4-hydroxy-3-methoxyphenyl)-2-{4-{2-[N-2-(4-hydroxyphenyl)ethyl] Carbamoylehenyl-2-methoxyphenoxyl}}-1, 3-propanodiolnamed	$C_{28}H_{32}NO_8$		EtOH	Li et al. (2019)
106	7′S, 8′R-7-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-N^2, N^3-bis(4-hydroxyphenethyl)-6-methoxy -1, 2-dihydronaphthalene-2, 3-dicarboxamide	$C_{36}H_{37}N_2O_8$		EtOH	Li et al. (2019)
107	7′R, 8′S-7-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-N^2, N^3-bis(4-hydroxyphenethyl)-6-methoxy -1, 2-dihydronaphthalene-2, 3-dicarboxamide	$C_{36}H_{37}N_2O_8$		EtOH	Li et al. (2019)
108	7′R, 8′S-7-(4-hydroxy-3, 5-dimethoxyphenyl)-3′-hydroxymethyl-1′-[N-7″-(4″-hydrxyphenyl)ethyl] carbamoylethenyl-3′-methoxybenzodihydrofuran	$C_{29}H_{31}NO_8$		EtOH	Li et al. (2019)
109	7′S, 8′R-7-(4-hydroxy-3, 5-dimethoxyphenyl)-3′-hydroxymethyl-1′-[N-7″-(4″-hydrxyphenyl)ethyl] carbamoylethenyl-3′-methoxybenzodihydrofuran	$C_{29}H_{31}NO_8$		EtOH	Li et al. (2019)
110	(7′R, 8′R)-2-(4-Hydroxy-3-methoxyphenyl)-3-[N-2-(4-hydroxyphenyl)ethyl] carbamoyl-5-[N-2-(4-hydroxyphenyl)ethyl]carbamoylethenyl-7-methoxybenzodihydrofurn	$C_{36}H_{36}N_2O_8$		EtOH	Li et al. (2019)
111	(7′S, 8′S)-2-(4-Hydroxy-3-methoxyphenyl)-3-[N-2-(4-hydroxyphenyl)ethyl] carbamoyl-5-[N-2-(4-hydroxyphenyl)ethyl]carbamoylethenyl-7-methoxybenzodihydrofurn	$C_{36}H_{36}N_2O_8$		EtOH	Li et al. (2019)
112	Cannabisin F	$C_{36}H_{36}N_2O_8$	163136-19-4	EtOH	Li et al. (2019)
113	Adenine	$C_5H_5N_5$	73-24-5	MeOH	Gao et al. (2021)
114	Pyroglutamic acid	$C_5H_7NO_3$	98-79-3	MeOH	Gao et al. (2021)
115	Nicotinic acid	$C_6H_5NO_2$	59-67-6	MeOH	Gao et al. (2021)
116	9-aminononane-1,3,9-tricarboxylic acid	$C_{12}H_{21}NO_6$		MeOH	Gao et al. (2021)
117	Glutarylcarnitine	$C_{12}H_{21}NO_6$	102636-82-8	MeOH	Gao et al. (2021)
118	(6S)-3-((1H-imidazol-4-yl)methyl)-6-amino-1, 4-diazocane-2, 5, 8-trione	$C_{10}H_{13}N_5O_3$		MeOH	Gao et al. (2021)
119	3-Indoleacrylic acid	$C_{11}H_9NO_2$		MeOH	Gao et al. (2021)
120	6-Hydroxypurine	$C_5H_4N_4O$	68-94-0	MeOH	Gao et al. (2021)
121	Uridine	$C_9H_{12}N_2O_6$	58-96-8	MeOH	Gao et al. (2021)
122	Ethyl 4-glycylbenzoate	$C_{11}H_{13}NO_3$		MeOH	Gao et al. (2021)
123	Adenosine	$C_{10}H_{13}N_5O_4$	58-61-7	MeOH	Gao et al. (2021), Wang (2007)
124	Dihydrocapsaicin	$C_{18}H_{29}NO_3$	19408-84-5	MeOH	Gao et al. (2021)
125	Choline	$C_5H_{14}NO$	62-49-7	MeOH	Gao et al. (2021)
126	Betaine	$C_5H_{11}NO_2$	107-43-7	MeOH	Gao et al. (2021)
127	Allantoin	$C_4H_6N_4O_3$	97-59-6	MeOH	Gao et al. (2021)
128	Uracil	$C_4H_4N_2O_2$	66-22-8	MeOH	Gao et al. (2021)
129	Trigonelline	$C_7H_7NO_2$	535-83-1	MeOH	Gao et al. (2021)
130	(2-acetoxyethyl)trimethylammonium	$C_7H_{16}NO_2^+$		MeOH	Gao et al. (2021)
131	Glycyl-L-leucine	$C_8H_{16}N_2O_3$		MeOH	Gao et al. (2021)
132	GABA	$C_4H_9NO_2$	56-12-2	MeOH	Gao et al. (2021)
133	FMoc-Asn(Trt)-OPfp	$C_{44}H_{31}F_5N_2O_5$		MeOH	Gao et al. (2021)
Phenylpropanoids					
134	Trans-4-Hydroxycinnamic acid	$C_9H_8O_3$	501-98-4	EtOH	Liu et al. (2019b)
135	Cis-4-Hydroxycinnamic acid	$C_9H_8O_3$	4501-31-9	EtOH	Liu Z et al. (2019)
136	Ethyl 3, 4-dihydroxycinnaMate	$C_{11}H_{12}O_4$	102-37-4	EtOH	Liu et al. (2019a)
137	Cis-caffeic acid ethyl ester	$C_{11}H_{12}O_4$	74257-25-3	EtOH	Liu et al. (2019b)
138	Trans ferulic acid	$C_{10}H_{10}O_4$	537-98-4	EtOH	Liu Z et al. (2019)
139	Cis-ferulic acid	$C_{10}H_{10}O_4$	1014-83-1	EtOH	Liu et al. (2019a)
140	Caffeic acid	$C_9H_8O_4$	331-39-5	MeOH	Gao et al. (2021)
141	4-(4-hydroxyphenyl)-2-methylenebutyrolactone	$C_{11}H_{10}O_3$		EtOH	Liu et al. (2019b)
142	Chlorogenic acid	$C_{16}H_{18}O_9$	327-97-9	MeOH	Gao et al. (2021)
143	3-caffeoylquinic acid methyl ester	$C_{17}H_{20}O_9$	123483-19-2	MeOH	Xiang et al. (2019)
144	Scopoletin	$C_{10}H_8O_4$	92-61-5	EtOH	Zhao (2010), Wang et al. (2007), Wang (2007)
145	(–)-5′-methoxyisolariciresinol-3α-O-β-D-glucopyranoside	$C_{27}H_{36}O_{12}$		MeOH	Xiang et al. (2019)
146	(+)-isolariciresinol-3α-O-β-D-glucopyranoside	$C_{26}H_{34}O_{11}$		MeOH	Xiang et al. (2019)
147	Cinnacassoside A	$C_{26}H_{36}O_{12}$	1691248-24-4	MeOH	Xiang et al. (2019)

(Continued on following page)

TABLE 2 | (*Continued*) Chemical components structurally identified from *S. nigrum*.

No	Chemical constituents	Molecular formula	CAS	Extracts	References
148	Pinoresinol	$C_{20}H_{22}O_6$	81446-29-9	EtOH	Zhao (2010)
149	Pinoresinol-4-*O*-β-D-glucopyranoside	$C_{26}H_{32}O_{11}$	69251-96-3	EtOH	Wang et al. (2007), Wang (2007)
150	Syringaresinol	$C_{22}H_{26}O_8$	487-35-4	EtOH	Zhao (2010)
151	Syringaresinol-4-*O*-β-D-glucopyranoside	$C_{28}H_{36}O_{13}$	137038-13-2	EtOH	Wang et al. (2007), Wang (2007)
152	Medioresinol	$C_{21}H_{24}O_7$	40957-99-1	EtOH	Zhao (2010)
153	Acanthoside D	$C_{34}H_{46}O_{18}$	573-44-4	MeOH	Xiang et al. (2019)
154	(+)-medioresonol-di-*O*-β-D-glucopyranoside	$C_{33}H_{44}O_{17}$		MeOH	Xiang et al. (2019)
Flavonoids					
155	Quercetin	$C_{15}H_{10}O_7$	117-39-5	EtOH	Yang (2014)
156	Quercitrin	$C_{21}H_{20}O_{11}$	522-12-3	EtOH	Yang (2014)
157	Isoquercitrin	$C_{21}H_{20}O_{12}$	21637-25-2	EtOH	Yang (2014)
158	Quercetin-3-*O*-β-D-glucopyranosyl(1-2)-β-D-glucopyranoside	$C_{27}H_{30}O_{17}$		EtOH	Yang (2014)
159	Quercetin-3-*O*-β-D-galactopyranosyl-(1→6)-β-D-glucopyranoside	$C_{28}H_{32}O_{17}$		MeOH	Xiang et al. (2019)
160	Quercetin-3-gentiobioside	$C_{27}H_{30}O_{17}$	7431-83-6	EtOH	Wu (2011)
161	Quercetin-3-O-α-L-rhaopyranosyl(1→4)-*O*-β-D-glucopyranosyl-(1→6)-*O*-β-D-glucopyranoside	$C_{28}H_{32}O_{17}$		EtOH	Li (2010b)
162	6-Hydroxyluteolin 7-sophoroside	$C_{27}H_{30}O_{17}$		MeOH	Gao et al. (2021)
163	Kaempferol	$C_{15}H_{10}O_6$	520-18-3	EtOH	Liu Z et al. (2019)
164	(8-hydroxy-3′-β-D-galactosyl-isoflavone)-2′-8″-(4‴-hydroxy-flavone)-biflavone	$C_{36}H_{28}O_{11}$		EtOAc	Sabudak et al. (2017)
165	2′, 3′, 5-trihydroxy-5″-methoxy-3″-O- α-glucosyl-3-4‴-O-biflavone	$C_{36}H_{30}O_{15}$		EtOAc	Sabudak et al. (2017)
Benzoic acids					
166	Gallic acid	$C_7H_6O_5$	149-91-7	MeOH	Gao et al. (2021)
167	2, 4-Dihydroxybenzoic acid	$C_7H_6O_4$	89-86-1	MeOH	Gao et al. (2021)
168	Protocatechuic acid	$C_7H_6O_4$	99-50-3	EtOH	Zhao (2010)
169	Vanillic acid	$C_8H_8O_4$	121-34-6	EtOH	Zhao (2010)
170	4-Hydroxybenzoic acid	$C_7H_6O_3$	99-96-7	EtOH	Liu et al. (2019a)
171	Salicylic acid	$C_7H_6O_3$	69-72-7	EtOH	Liu et al. (2019b)
172	2, 5-Dihydroxybenzoic acid	$C_7H_6O_4$	490-79-9	MeOH	Gao et al. (2021)
Other compounds					
173	Galacturonic acid	$C_6H_{10}O_7$	14982-50-4	MeOH	Gao et al. (2021)
174	Pyruvic acid	$C_3H_4O_3$	127-17-3	MeOH	Gao et al. (2021)
175	Formic acid	CH_2O_2	64-18-6	MeOH	Gao et al. (2021)
176	Succinic acid	$C_4H_6O_4$	110-15-6	MeOH	Gao et al. (2021)
177	Fumaric acid	$C_4H_4O_4$	110-17-8	MeOH	Gao et al. (2021)
178	Ursolic acid	$C_{30}H_{48}O_3$	77-52-1	EtOH	Zhao (2010)
179	Linolenic acid	$C_{18}H_{30}O_2$	463-40-1	MeOH	Gao et al. (2021)
180	Oleic acid	$C_{18}H_{34}O_2$	112-80-1	EtOH	Wang (2007)
181	Linoleic acid	$C_{18}H_{32}O_2$	60-33-3	EtOH	Wang (2007)
182	Palmitic acid	$C_{16}H_{32}O_2$	57-10-3	EtOH	Wang (2007)
183	1-monolinolenin	$C_{21}H_{36}O_4$	75685-85-7	EtOH	Zhao (2010)
184	Lignoceric acid	$C_{24}H_{48}O_2$	557-59-5	EtOH	Zhao (2010)
185	(*E*)-docosyl-3-(4-hydroxy-3-methoxyphenyl)acrylate	$C_{32}H_{54}O_4$		EtOH	Zhao (2010)
186	α-carotene	$C_{40}H_{56}$	432-70-2	EtOH	Wu (2011)
187	β-carotene	$C_{40}H_{56}$	7235-40-7	EtOH	Wu (2011)
188	Xanthophyll	$C_{40}H_{56}O_2$	127-40-2	EtOH	Wu (2011)

Solanum lyratum Thunberg, etc. in clinic for the treatment of cancer (Liu et al., 2019a).

In Libya, *S. nigrum* is often used as folk medicine, and its berries are used as diuretics, antispasmodic, and emetics, and to treat diarrhea, fever, and eye problems, as well as bleeding. In addition, *S. nigrum* leaves are used as a sedative, cholagogic, and anesthetic for the treatment of insomnia, convulsions, and dysentery as well as the external treatment of wounds and itching. In Italy, the aboveground part of *S. nigrum* is used as an antispasmodic, sedative, and analgesic drug. In Yemen, *S. nigrum* is used to dispel phlegm and treat diarrhea and bleeding. In Jordan, *S. nigrum* fruit is used as an antispasmodic drug. Moreover, *S. nigrum* is used as an important plant in traditional

Indian medicines for the treatment of dysentery, stomach complaints, and fever (Aburjai et al., 2014).

PHYTOCHEMICAL CONSTITUENTS

S. nigrum is a rich source of natural compounds with varying structural patterns and beneficial properties. To date, approximately 188 phytochemical compounds have been separated and identified from *S. nigrum*, containing steroids, alkaloids, organic acids, flavonoids, phenylpropanoids and their glycosides, as well as other compounds. Steroidal compounds consist of steroidal saponins (**1–76**) and steroidal alkaloids
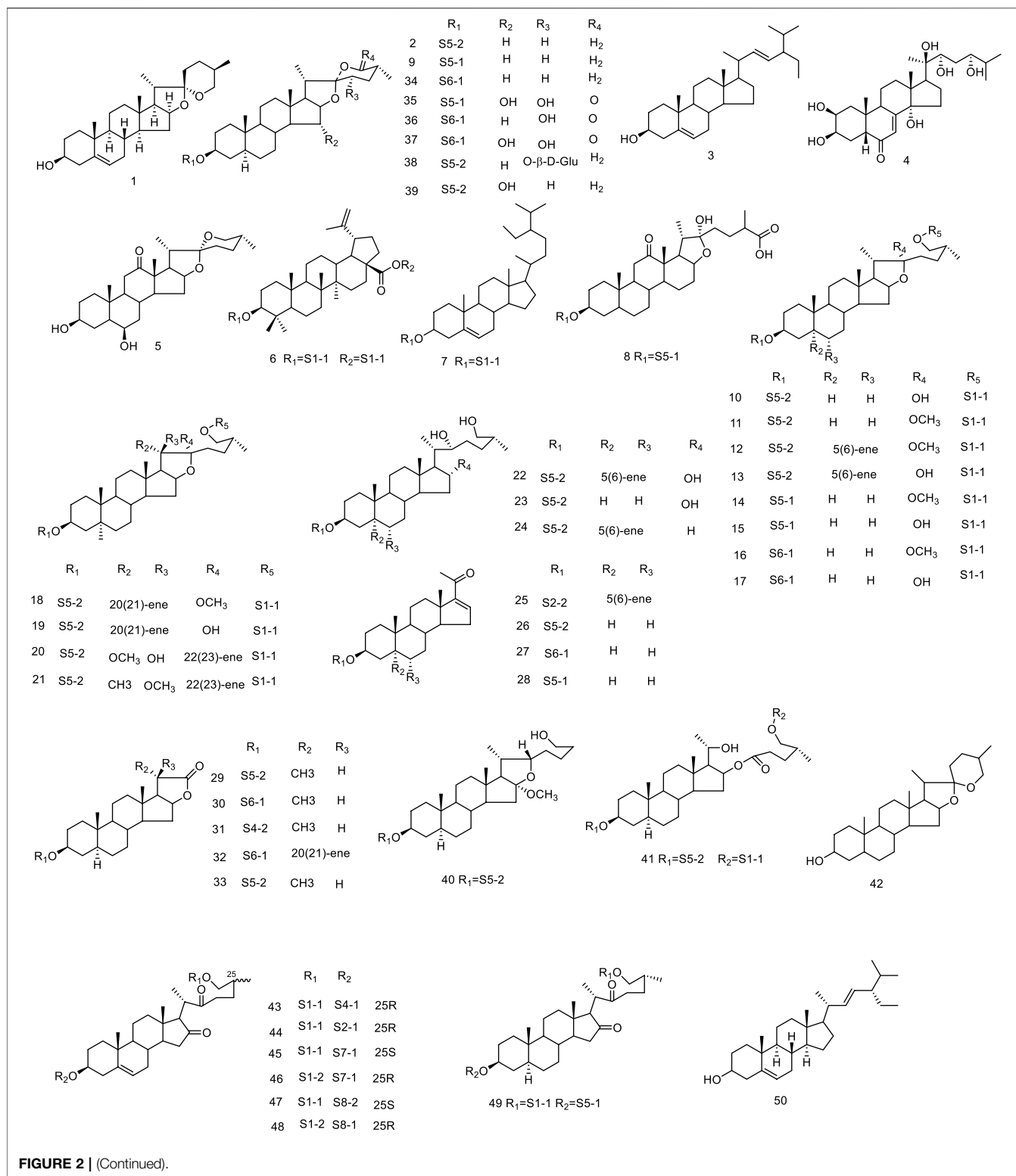
FIGURE 2 | (Continued).

(77–101) and are considered to be the main bioactive components of *S. nigrum*, exhibiting various pharmacological activities, such as antitumor, anti-inflammatory, and antiviral activities. The compounds isolated from *S. nigrum* are documented and listed in **Table 2**, and their chemical structures are drawn and presented in **Figure 2**. In addition, *S. nigrum* is rich in a large number of polysaccharides, which is a material basis for its various pharmacological activities, such as
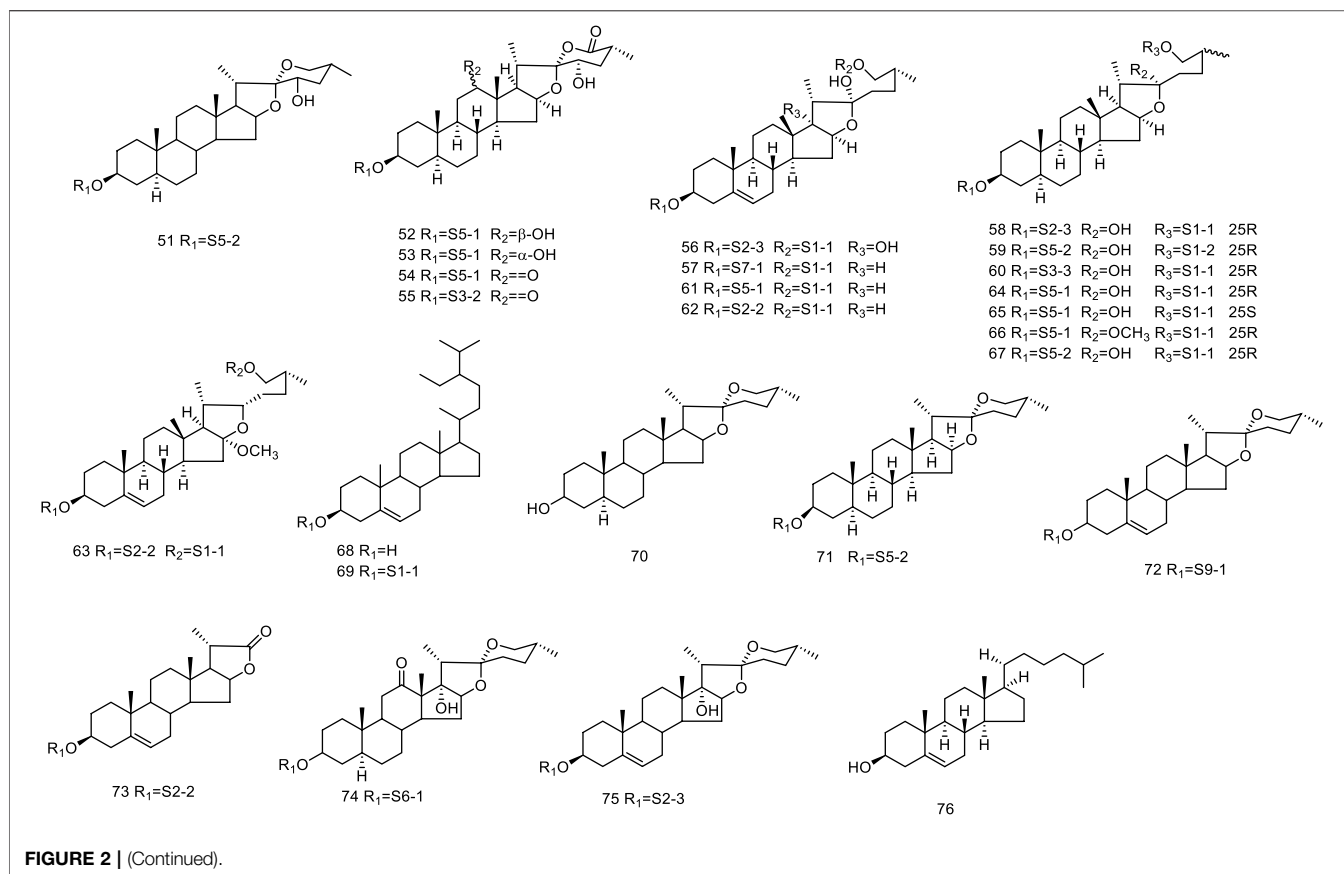
FIGURE 2 | (Continued).

Steroidal Saponins

Steroidal saponins are an important class of secondary metabolites and pharmaceutical resources distributed in higher plants and some marine organisms, showing good pharmacological activities. Modern research suggests that steroidal saponins are the major pharmacologically active constituents of *S. nigrum*. Until now, 76 steroidal saponins (**1–76**) have been isolated and identified. Current research on the pharmacological activity of *S. nigrum* is mainly focused on the antitumor and anti-inflammatory activities, and research on the corresponding chemical compositions is mainly focused on the various types of steroidal saponins. In 2006, 22 new steroidal saponins (Solanigroside A-O, Solanigroside R-X) were isolated from the whole plant of *S. nigrum*, and structure-activity analysis of the steroidal saponins in *S. nigrum* showed that the cytotoxic activities of spirostanol saponins and progesterone saponins were stronger than those of furostanol saponins and cholesteric saponins (Zhou, 2006). In 2017, Wang et al. (2017), isolated nine new steroidal saponins from the berries of *S. nigrum* of which Solanigroside Y1 showed significant anti-inflammatory activity. Subsequently, Xiang et al. isolated seven new steroidal saponins (**61–67**) with a new cholestane 16, 22-dione skeleton from immature *S. nigrum* berries, and some of these compounds

exhibited moderate anti-inflammatory activity (Xiang et al., 2018). The contents of the steroidal saponins are shown in **Table 2**, and their structures are presented in **Figure 2**.

Alkaloids

Until now, the alkaloids contained in *S. nigrum* reported in the literature are mainly steroidal alkaloids, and most of them are present in the form of glycosides in the fruits, stems, leaves, and roots of the plant. The immature fruit of *S. nigrum* has the highest content of steroidal alkaloids of up to 4.2%, which gradually decreases as the plant grows. This phenomenon may explain the self-protective effect of the plant, as the toxicity of *S. nigrum* alkaloids prevents the young leaves and fruits from being eaten by other animals and promotes the survival of the species. The steroidal alkaloids contained in *S. nigrum* are also the basis of the antitumor activity of *S. nigrum*. Among the steroidal alkaloids contained in *S. nigrum*, solasonine (**100**) and solamargine (**79**) make up to 0.2% and 0.25%, respectively, and the glycoside of solasonine and solamargine formed after alkaline hydrolysis is solasodine (**88**) (He et al., 2015). Solamargine (**79**) is the main component of the total alkaloids of *S. nigrum*, and pharmacological studies have shown that solamargine (**79**) has strong inhibitory activity against liver cancer, cervical cancer, lung cancer, laryngeal cancer, cholangiocarcinoma, esophageal cancer, etc (Wang 2007; Sun et al., 2010; Ding et al., 2012a; Zhang, 2018; Xiang et al., 2019). In addition, β_2-solasonine (**78**),
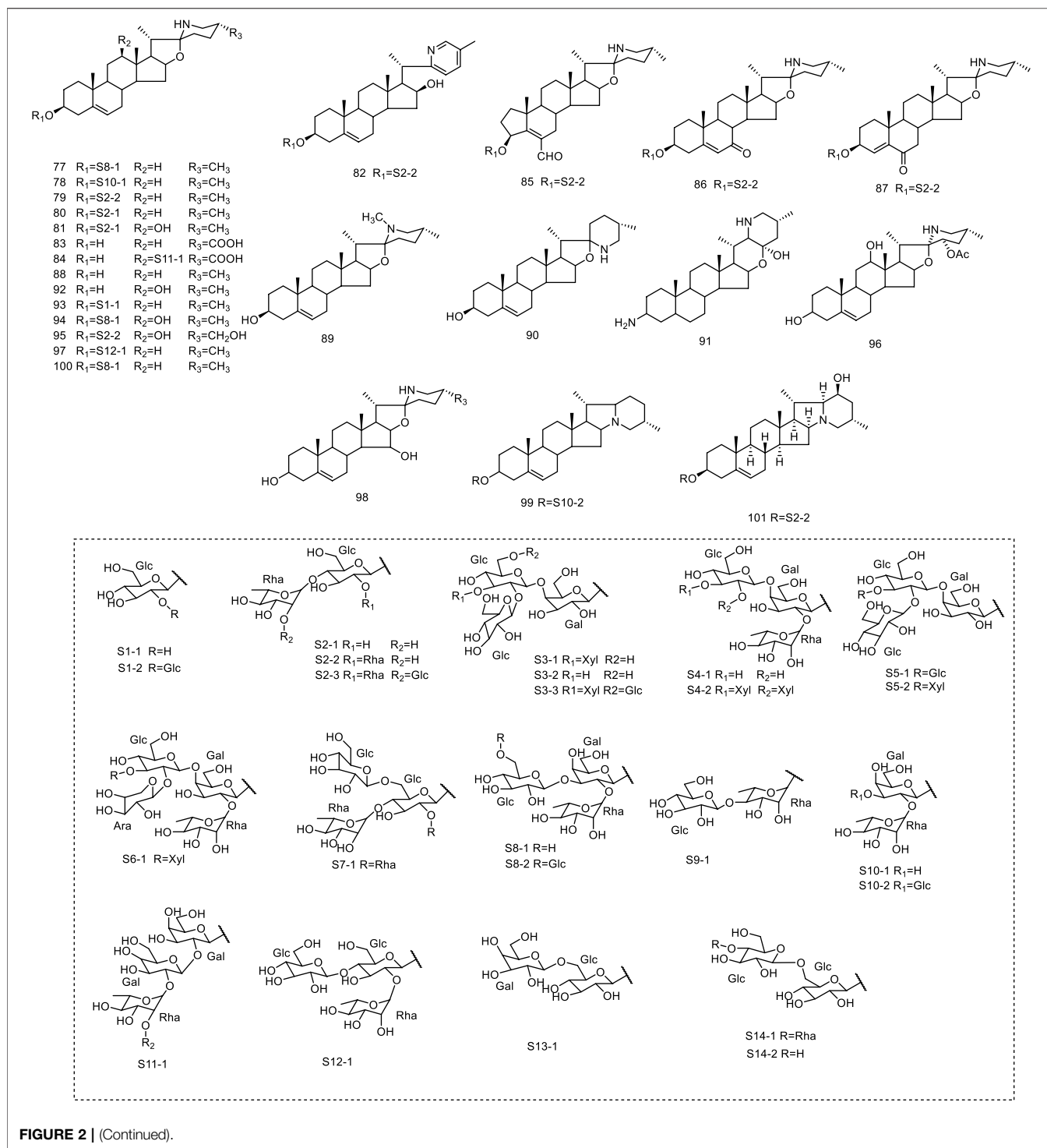
FIGURE 2 | (Continued).

solaoiacid (**84**), (25*R*)-22*α*N-4-nor-spirosol-5(6)-en-3*β*-ol-6-al-3-*O*-L-rhamnopyranosyl-(1→2)-[*α*-L-rhamnopyranosyl-(1→4)]-*β*-D-glucopyranoside (**85**), and solasonine (**100**) showed antitumor and anti-inflammatory activities (Xiang et al., 2019; Li et al., 2020; Zhang et al., 2021).

In addition to steroidal alkaloids found in *S. nigrum*, other types of alkaloids have also been identified in *S. nigrum*.

Lignanamides are a rare kind of natural product defined as blignans bearing amide groups, displaying diverse biological activities, including neuroprotective, anti-inflammatory, and insecticidal effects. Findings indicated that cannabisin F (**112**) isolated from the above-ground parts of *S. nigrum* has significant neuroprotective activity against MPP$^+$-induced SH-SY5Y cell injury models at doses of 12.5, 25, and 50 μM (Li et al., 2019).
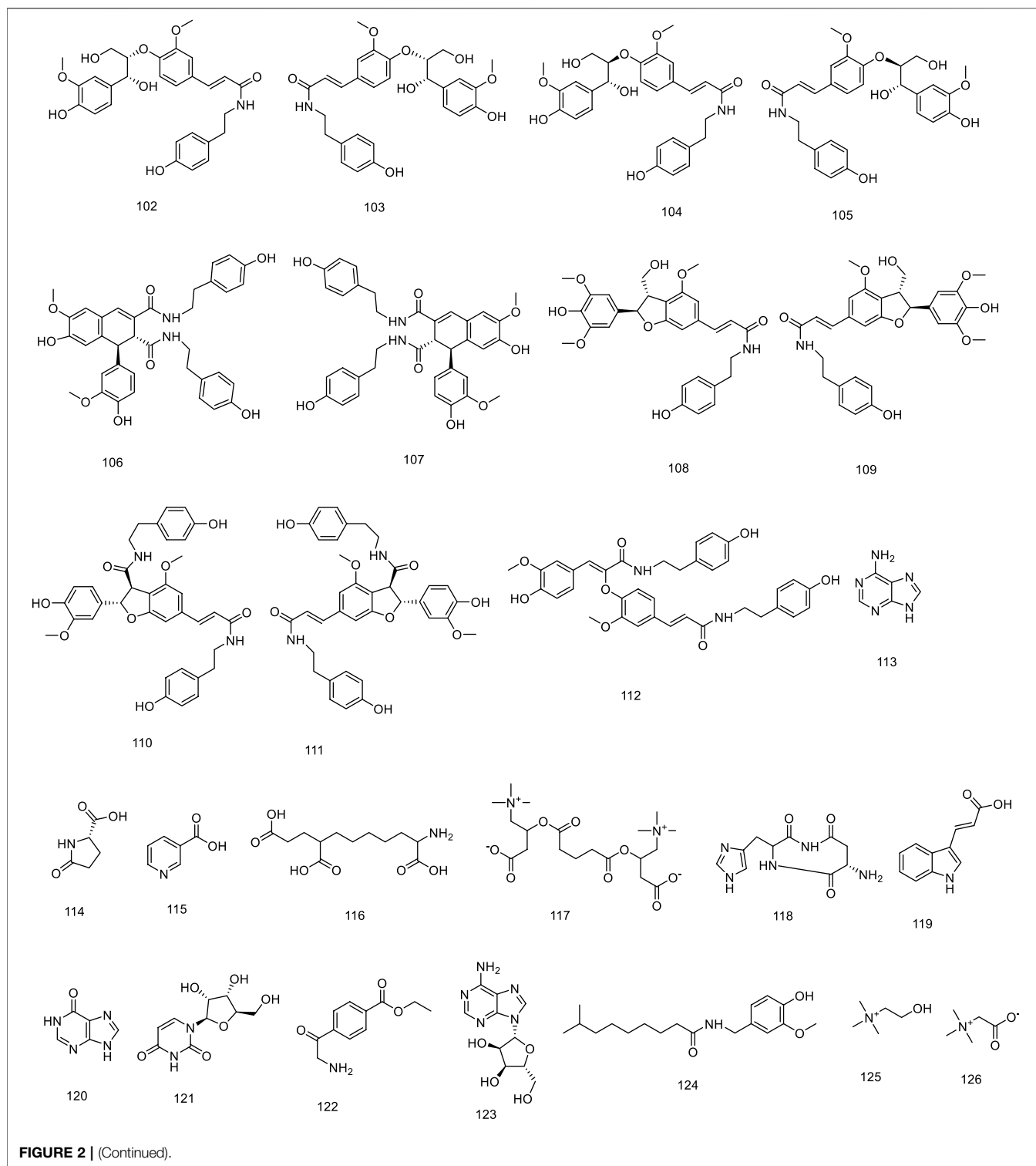
FIGURE 2 | (Continued).

In 2021, Gao et al. analyzed the chemical constituents of *S. nigrum* using LC-MS and NMR, and identified 89 compounds, mainly including adenine (**113**), nicotinic acid (**115**), 9-aminononane-1, 3, 9-tricarboxylic acid (**116**), adenosine (**123**), allantoin (**127**), and dozens of alkaloids (Gao et al., 2021).

Phenylpropanoids

Phenylpropanol is a naturally occurring compound composed of a benzene ring connected to three straight-chain carbons (C_6-C_3 groups). It has a phenol structure and is a phenolic substance. In the biosynthesis, most of these compounds are formed by a series

FIGURE 2 | (Continued).
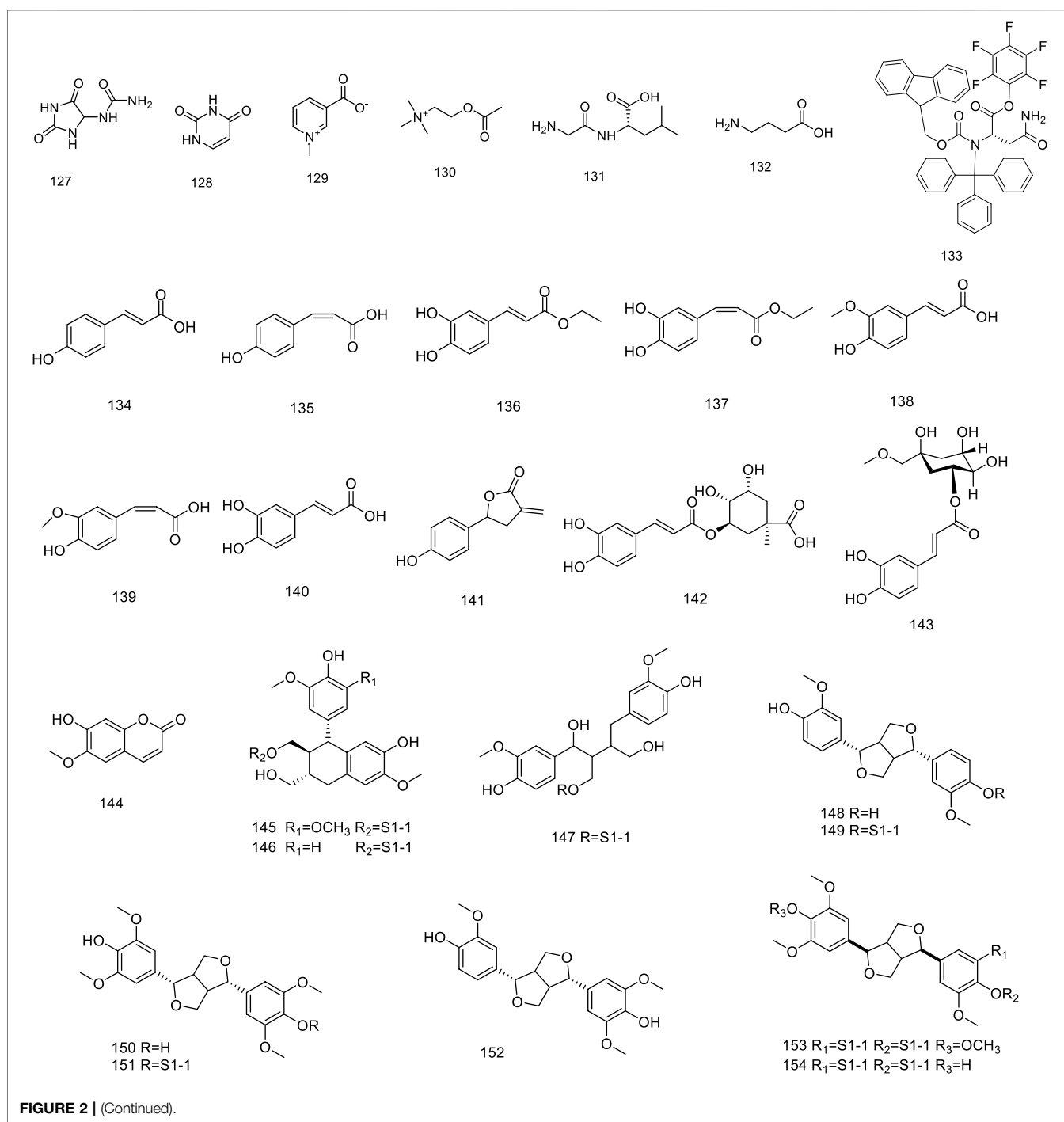
of reactions such as deamination and hydroxylation of shikimic acid through aromatic amino acids, such as phenylalanine and tyrosine. Until now, 21 phenylpropanoids (**134–154**), including 10 phenylpropionic acid and their esters (**134–143**), 1 coumarin (**144**), and 10 lignans (**145–154**), have been successfully separated and chemically identified by spectroscopic analysis, including 1H-NMR and 13C-NMR, of the whole plants of *S. nigrum*. Scopoletin (**144**) is widely distributed in *S. nigrum*, and

current studies have shown that it has various pharmacological activities, such as antitumor, anti-inflammatory, hypoglycemic, hypotensive, and anti-neurodegenerative effects (Chu et al., 2019).

Flavonoids

Flavonoids are a class of secondary metabolites that account for over half of the plant phenolics, with various pharmacological

FIGURE 2 | Chemical structures of compounds isolated from *S. nigrum*.
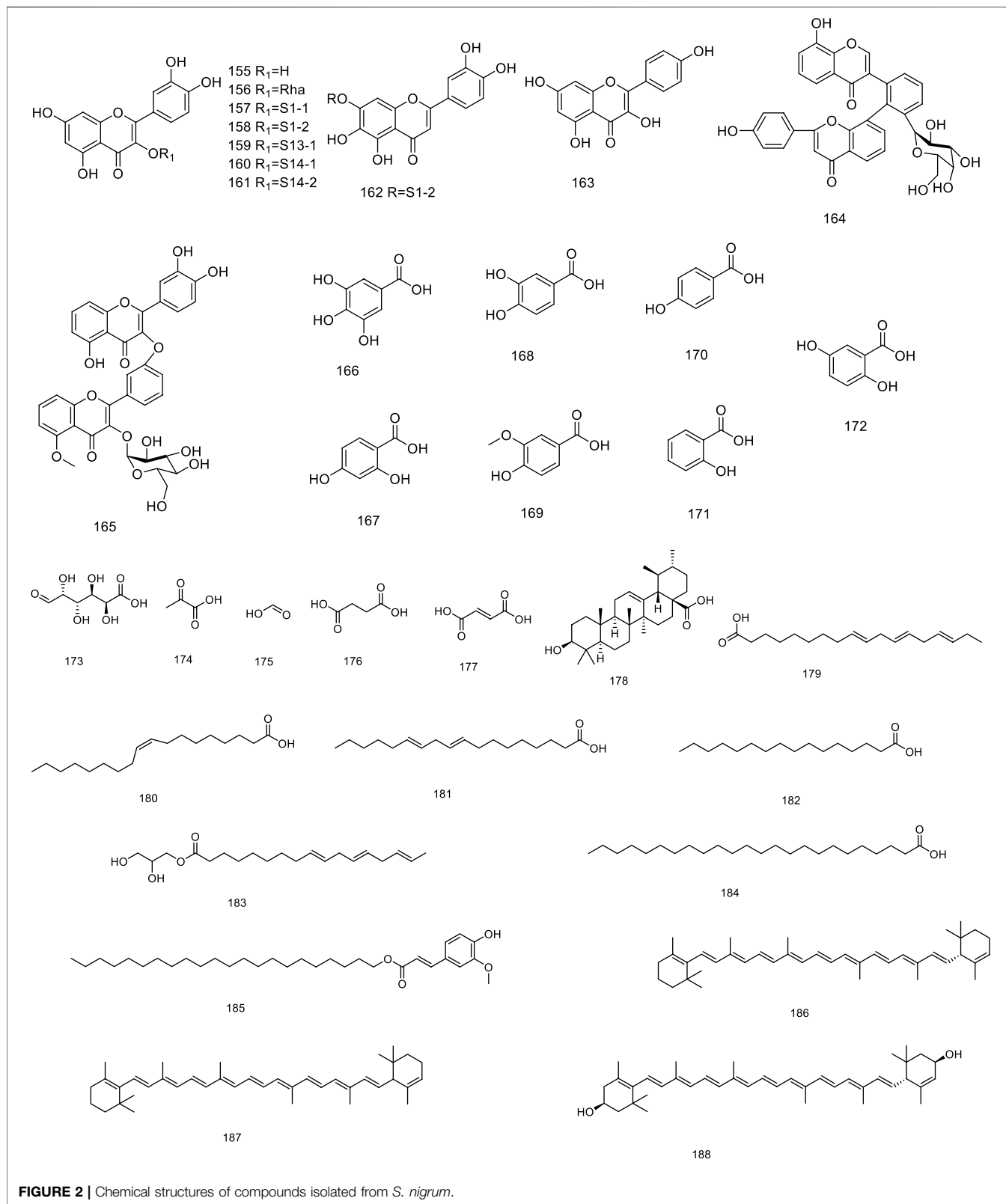
activities such as antioxidant and anti-inflammatory activities. In 2014, Yang et al. isolated and identified one flavone (**155**) and

three flavone glycosides (**156–158**) from the whole plant of *S. nigrum* (Yang, 2014). In 2017, compound (**164**) and (**165**) were

TABLE 3 | Monosaccharides composition, molecular weight, structures, and bioactivities of polysaccharides purified from *S. nigrum*.

No.	Polysaccharides	Monosaccharide composition	M.W. (Da)	Structures	Bioactivities	References
1	S1	mannose, glucose, galactose, arabinose in a ratio of 1.00: 8.32: 6.72: 2.90	5.44×10^4	ND	Prebiotic effects	Yao et al. (2020)
2	S2	rhamnose, galacturonic acid, glucose, galactose, arabinose in a ratio of 1.00: 0.76: 4.57: 7.25: 4.49	7.22×10^4	ND	Prebiotic effects	Yao et al. (2020)
3	SNL-1	rhamnose, xylose, arabinose, glucose in a ratio of 4.9: 1: 2. 4: 13	5.30×10^3	α-glycosidic and β-glycosidic linkages	ND	Xiao and Zeng (1998)
4	SNL-2	glucose, arabinose in a ratio of 13.3: 1	1.12×10^4	α-glycosidic and β-glycosidic linkages	ND	Xiao and Zeng (1998)
5	SNL-3	xylose, mannose, glucose, galactose in a ratio of 75.7: 9.2: 4.9: 10.2	2.37×10^4	1, 3 xyl residue linkage	Immunomodulatory activity	Xiao and Zeng (2000)
6	SNL-4	xylose, mannose galactose in a ratio of 89.4: 1.7: 8.9	4.77×10^4	1, 3 xyl residue linkage	Immunomodulatory activity	Xiao and Zeng (2000)
7	SNL-WP-1	galactose, glucose, mannose, arabinose in a ratio of 1.8: 1: 1.2: 2	1.41×10^4	β-glycosidic linkages	Antitumor activity	Li (2010a)
8	SNL-WP-2	galactose, glucose, mannose, xylose, arabinose in a ratio of 5.4:10.4: 1.4: 1: 1.6	9.12×10^3	ND	Antitumor activity	Li (2010a)
9	SNL-AP-1	galactose, glucose, mannose, xylose, arabinose in a ratio of 28: 1: 6: 51: 13	$>1.6 \times 10^6$	β-glycosidic linkages	Antitumor activity	Li (2010a)
10	SNL-AP-2	galactose, glucose, mannose, xylose, arabinose in a ratio of 5.8: 1: 1.3: 2.6: 2	$>1.6 \times 10^6$	β-glycosidic linkages	Antitumor activity	Li (2010a)
11	SNLBP	xylose, mannose, glucose, galactose in a ratio of 82.2: 7.4: 3.8: 6.6	ND	β-glycosidic linkages	Immunomodulatory activity	Liu (2003)
12	SNL-P1a	rhamnose, xylose, arabinose, glucose	ND	β (1→3) glycosidic bond	Immunomodulatory and antitumor activity	Li (2009)

isolated and identified from *S. nigrum*, showing that their cholinesterase inhibitory activity was weaker than that of their ethyl acetate extract of *S. nigrum*, presumably due to the synergistic effect between these compounds (Sabudak et al., 2017). The antioxidant activity of *S. nigrum* is closely related to its flavonoid content, and the research on the flavonoids of *S. nigrum* should be increased to provide the basis for the development and utilization of functional foods of *S. nigrum*.

Benzoic Acids

In addition, seven benzoic acids with phenolic hydroxyl substituents have been identified from *S. nigrum*, including gallic acid (**166**), 2, 4-dihydroxybenzoic acid (**167**), protocatechuic acid (**168**), vanillic acid (**169**), 4-hydroxybenzoic acid (**170**), salicylic acid (**171**), and 2, 5-dihydroxybenzoic acid (**172**) (Wang et al., 2007; Liu et al., 2019b; Gao et al., 2021). Most of these compounds have anti-inflammatory, antioxidant, antibacterial, and antiviral activities, providing broad application prospects and important pharmaceutical intermediates for disease treatment.

Polysaccharides

Polysaccharides are one of the four substances that form the basis of life activities. More and more research results show that some plant polysaccharides have many special biological activities, such as immune regulative, antifatigue, antioxidative, antiradiative, blood sugar-lowering, antiviral, antitumor, and liver-protective effects (Yang, 2014). At present, 12 kinds of polysaccharides have been successfully isolated and purified from *S. nigrum*, which are reported to have antitumor, immunomodulatory, and liver-protective activities (Liu, 2003; Liu, 2005; Yao et al., 2020).

The monosaccharide composition, molecular weight, structural characteristics, and biological activities of the polysaccharides purified from *S. nigrum* are summarized and presented in **Table 3**.

Other Compounds

In addition to the above-mentioned compounds, a few compounds (**173–188**) have been identified from *S. nigrum* until now, and the corresponding chemical structures are shown in **Figure 2**. Compounds (**173–177**) were identified as organic acids. Ursolic acid (**178**) is a famous antitumor triterpene, and compounds (**179–184**) are aliphatic compounds. Compound (**185**) is a ferulic acid ester, which are compounds that are, in addition to α-carotene (**186**), β-carotene (**187**), and xanthophyll (**188**), essential nutrients for people and of great significance to the health of human eyes and skin (Wang, 2007; Zhao, 2010; Gao et al., 2021).

PHARMACOLOGICAL ACTIVITIES

Numerous studies have reported the pharmacological activities of *S. nigrum* in the past decades. Various solvent extracts and isolated bioactive compounds of *S. nigrum* have exhibited many pharmacological properties including antitumor, antioxidant, anti-inflammatory, immunomodulatory, antihypertensive, antimicrobial, and antiviral activities (Yang et al., 2016; Veerapagu et al., 2018; Tian et al., 2019; Guo et al., 2020; Sivaraj et al., 2020). These pharmacological studies have been summarized in **Table 4**, and the reported effects and mechanisms will be discussed in detail in the following

TABLE 4 | Biological activity of bioactive compounds and extracts of *S. nigrum*.

Biological activities	Extracts/ compounds	Types	Testing subjects	Doses/duration	Mechanisms/effects	References
Antitumor activity						
	SNPE	*In vitro*	HepG$_2$ cells	0.5, 1.0 and 2.0 mg/ml for 24 h	IC$_{50}$ value was 0.75 mg/ml, arrested the cell cycle at the G2/M phase and CDK1, Bcl-2 and Bid protein expression levels ↓	Wang et al. (2010)
	SNPE	*In vivo*	HepG$_2$ tumor-bearing mice	1 or 2 µg/ml for 35 days	Tumor weight and tumor volume ↓	Wang et al. (2011)
	SNWE SNPE	*In vitro*	HepG$_2$ cells	0.05–2 mg/ml for 24 h	The IC$_{50}$ of SNWE and SNPE was 2.18 and 0.86 mg/ml, respectively, inhibited TPA-induced HepG$_2$ migration, TPA-induced PKCα and p38 protein expression levels ↓	Yang et al. (2010)
	SNWE SNPE	*In vitro*	HUVEC and HepG$_2$ cells	0.1–2 mg/ml for 24, 48, 72, and 96 h	Suppression of the VEGF-induced activation of AKT and mTOR	Yang et al. (2016)
	SNWE SNPE	*In vivo*	HepG$_2$ tumor-bearing mice	0–2% for 35 days	Reduced the volume and weight of the tumors, and CD31 protein expression levels ↓	Yang et al. (2016)
	SNEE	*In vitro*	A549 cells	100 µg/ml for 16 h	Exhibited specifically stat3-suppressing activity in A549 cells through the decrease of Bcl-xL expression	Park et al. (2014)
	SNTA	*In vitro*	RPMI-8226 cells	12.5, 25, and 50 mg/kg for 14 days	Inhibited I κB-α Phosphorylation and NF-κB/IRF4 signaling pathway to induce apoptosis	Liu et al. (2021)
	SNFME	*In vitro*	C6 cells	0.025–0.4 mg/ml	IC$_{50}$ value was 0.23 mg/ml, attenuated cell cloning, migration and invasion	Li et al. (2021)
	SNWE	*In vitro*	TG-elicited peritoneal macrophages	10–500 mg/ml for 12 h	Decreased NO production and increased the expression of iNOS protein	An et al. (2005)
	SNLP-1	*In vivo*	Lung Cancer Bearing Mice	200 mg/kg/day	Played an antitumor role by enhancing the function of the immune system in the body	Pu (2020)
	SNCE	*In vitro*	786-O cells	40 mg/ml	Inhibited proliferation and promoted apoptosis by inhibiting the activation of PI3K/Akt signaling pathway	Liao et al. (2020)
	2	*In vitro*	Human hepatoma cancer cell line (HepG$_2$ cell)	3.125, 6.25, 12.5, 25, 50, and 100 µM	IC$_{50}$ value against HepG2 cell was 0.245 µg/ml	Wang (2007)
	2	*In vitro*	Human tumor cells lines (NCI-H460, SF-268, MCF-7, HepG$_2$ Cell)	3.125, 6.25, 12.5, 25, 50, and 100 µM for 48 h	IC$_{50}$ values against four tumor cells were 4.4, 3.1, 1.5, and 0.2 µM, respectively	Zhou (2006)
	26	*In vitro*	Human tumor cells lines (NCI-H460, SF-268, MCF-7, HepG$_2$ Cell)	3.125, 6.25, 12.5, 25, 50, and 100 µM for 48 h	IC$_{50}$ values against four tumor cells were 31.8, 34.7, 29.1, and 19.6 µM, respectively	Zhou (2006)
	28	*In vitro*	Human tumor cells lines (NCI-H460, SF-268, MCF-7, HepG$_2$ Cell)	3.125, 6.25, 12.5, 25, 50, and 100 µM for 48 h	IC$_{50}$ values against four tumor cells were 52.3, 260.4, 64.7, and 48.6 µM, respectively	Zhou (2006)
	78	*In vitro*	Human tumor cells lines (NCI-H460, SF-268, MCF-7, HepG$_2$ Cell)	3.125, 6.25, 12.5, 25, 50, and 100 µM for 48 h	IC$_{50}$ values against four tumor cells were 22.9, 34.2, 42.2, and 19.2 µM, respectively	Zhou (2006)
	79	*In vitro*	Human tumor cells lines (K562, KB, K562/A02, and KB/VCR)	NW	IC$_{50}$ values against four tumor cells were 8.0, 7.8, 5.4, and 7.1 µM, respectively	Zhao (2010)
	79	*In vitro*	HepG$_2$	3.125, 6.25, 12.5, 25, 50, and 100 µM	IC$_{50}$ value against HepG2 cell was 19.2 µg/ml	Wang (2007)
	79	*In vitro*	Human tumor cells lines (HL-60, U-937, Jurkat, K562, and HepG$_2$)	NW	Exhibited the most potent cytotoxicity to all the cell lines with IC$_{50}$ values of 3.53, 9.31, 2.72, 8.75, 5.36 µM, respectively	Xiang et al. (2019)
	79	*In vitro*	Human tumor cells lines (MDA-MB-231, A549, Hep3B, PC3)	30 and 100 µM	IC$_{50}$ values against 4 tumor cells were 1.86, 2.24, 0.78, 5.13 µM, respectively	Tai et al. (2018)
	79	*In vitro*	Human tumor cells lines (NCI-H460, SF-268, MCF-7, HepG$_2$)	3.125, 6.25, 12.5, 25, 50, and 100 µM for 48 h	IC$_{50}$ values against 4 tumor cells were 21.4, 25.1, 15.2, and 7.6 µM, respectively	Zhou (2006)
	79	*In vitro*	K562 cells	5, 7.5 and 10 µM for 0, 2, 4, 6, 8, and 24 h	Induced tumor apoptosis by initiating an early lysosomal destabilization pathway	Sun et al. (2010)
	79	*In vitro*	SMMC-7721 cells	0, 5, 10, 15 µg/ml for 72 h	The IC$_{50}$ values were 9.21 µg/ml	Ding et al. (2012a)

TABLE 4 | (*Continued*) Biological activity of bioactive compounds and extracts of *S. nigrum*.

Biological activities	Extracts/ compounds	Types	Testing subjects	Doses/duration	Mechanisms/effects	References
	79	*In vitro*	QBC939 cells	0–10 μM	The IC_{50} value was 9.81 μM, Inhibited the metastasis and invasion by inhibiting the expression of PI3K/Akt signal pathway	Zhang (2018)
	84	*In vitro*	Lung cancer A549 cells	1–20 μmol/L for 24 h	IC_{50} values against A549 cells were 2.36 μM, respectively	Shi et al. (2019)
	99	*In vitro*	PANC-1 cells	0, 2, 4, 6 μg/ml	N-cadherin, vimentin, MMP2 expression level ↓; E-cadherin expression level ↑	Kong et al. (2020)
	99	*In vitro*	RKO and HCT-116 cells	13–32 μM in RKO cells, 11–28 μM in HCT-116 cells	IC_{50} were 20.84 and 20.32 μM respectively. The expression levels of cyclin D1 and cyclin-dependent kinase 2 in RKO cells↓; production of ROS in RKO cells ↑; inhibited the migration and invasion of HCT-116 cells	Yan et al. (2020)
	99	*In vitro*	HCT-116 cells	4–32 μmol/L for 48 h	Inhibited proliferation and clone, induced apoptosis by activating Caspase-3	Hu et al. (2019)
	99	*In vitro*	SK-OV3 cells	5–15 μmol/L for 24, 48, 72 h	Inhibited proliferation and induced apoptosis by regulating the expression of p-Akt, cleaved Caspase-3 and p53 protein	Zhu et al. (2019)
	99	*In vitro*	RKO cells	NW	Induced apoptosis by activation of Caspase-3, the increase of intracellular ROS level and the inhibition of FAK phosphorylation	Yan and Hu (2019)
	99	*In vitro*	U87 cells	2.5–30 μg/μl	Inhibited proliferation and induced apoptosisby by down-regulating the expression of Ki-67, PCNA and Bcl-2 protein and up-regulating the expression of Bax protein	Zhao et al. (2019)
	99	*In vitro*	SGC-7901 cells	25, 50, 100 μg/ml for 48, 72 h	Inhibited proliferation and promoted apoptosis by up-regulating the expression of mir-140 and down-regulating the expression of MACC1	Huang et al. (2020)
	99	*In vitro*	EC9706, KYSE30 cells	4 μmol/L	Enhanced the drug sensitivity of esophageal cancer cell lines EC9706 and kyse30 to 5-fluorouracil and cisplatin via	Wu (2019)
	99	*In vivo*	ACHN-induced tumor-bearing mice	20 mg/kg for 28 days	Inhibited tumor growth through HIF-1α pathway to affect the expression and activity of key enzymes of glycolysis	Wang et al. (2019)
	100	*In vitro*	THP-1, MV4-11, NB-4, HL-60, HEL cells	NW	IC_{50} were 11.19, 12.50, 15.45, 15.87, 17 mM, promoted apoptosis and caused less cell cycle arrest in the G2/M phase through the activation of the AMPK/FOXO3A Axis	Zhang et al. (2021)
	100	*In vitro*	HepG2 and QGY-7703 cells	0–50 μM for 24, 48, 72 h	The proliferation of hepatoma cells was inhibited by activating mir-375-3p, ccat1, Sp1 and IRF5 protein expression levels ↓	Zhang et al. (2021)
	100	*In vitro*	A549 cells	0, 15, 20, 25 μmol/L for 24, 48, and 72 h	Induced apoptosis by inhibiting the expression of p65 and Bcl-2 protein, enhancing the expression of bik and Bak protein, and activating Caspase-3 pathway	Li et al. (2020)
	100	*In vitro*	Human tumor cells lines (NCI-H460, SF-268, MCF-7, $HepG_2$)	3.125, 6.25, 12.5, 25, 50, and 100 μM for 48 h	IC_{50} values against four tumor cells were 97.5, 113.5, 75.7, and 48.9 μM, respectively	Zhou (2006)
	100	*In vitro*	Human tumor cells lines (HL-60, U-937, Jurkat, K562, and $HepG_2$)	NW	IC_{50} values against five tumor cells were 33.32, 39.16, 12.85, 26.83, and 17.33 μM, respectively	Xiang et al. (2019)
	180	*In vitro*	$HepG_2$	3.125, 6.25, 12.5, 25, 50, and 100 μM	IC_{50} value was 62.3 μg/ml	Wang (2007)
	181	*In vitro*	$HepG_2$	3.125, 6.25, 12.5, 25, 50, and 100 μM	IC_{50} value was 57.5 μg/ml	Wang (2007)
Anti-inflammatory activity						
	SNCFE	*In vitro*	Peritoneal macrophages			Kang et al. (2011)

(Continued on following page)

TABLE 4 | (*Continued*) Biological activity of bioactive compounds and extracts of *S. nigrum*.

Biological activities	Extracts/compounds	Types	Testing subjects	Doses/duration	Mechanisms/effects	References
	SNFEE	*In vivo*	Acute ear edema mouse model	0–200 µg/ml for 4 and 24 h	NO, TNF-α and IL-6 levels ↓; p38, JNK and ERK1/2 expression levels ↓	Yeom et al. (2019)
				0.125, 0.250, 0.500, and 1.000 mg/ml	The cell viability below 0.5 mg/ml was about 90%, alleviating edema and decreased thickness of ear tissue	
	SNEE	*In vivo*	Acute and sub-acute rat model	100 and 200 mg/kg	The pathological changes of granuloma, kidney, liver and stomach were lighter than those in the model group	Aryaa and Viswanathswamy (2017)
	SNWE	*In vitro*	Patients with thoracic malignant tumor after radiotherapy	NW	PDGF, TGF-β1, IL-6,TNF-α expression level ↑	Che (2018)
	SNFPEFE	*In vitro*	Hyaluronidase, lipoxygenase	100–1,000 µg/ml	The IC$_{50}$ values of hyaluronidase and lipoxygenase were 810.67 and 781.28 µg/ml	Guo et al. (2020)
	43	*In vitro*	LPS-induced RAW 264.7 cells	2.5, 5, 10, 20, 40, and 50 µM	NO inhibition (IC$_{50}$ = 40.11 µM)	Xiang et al. (2018)
	44	*In vitro*	LPS-induced RAW 264.7 cells	2.5, 5, 10, 20, 40, and 50 µM	NO inhibition (IC$_{50}$ = 72.39 µM)	Xiang et al. (2018)
	45	*In vitro*	LPS-induced RAW 264.7 cells	2.5, 5, 10, 20, 40, and 50 µM	NO inhibition (IC$_{50}$ = 33.00 µM)	Xiang et al. (2018)
	46	*In vitro*	LPS-induced RAW 264.7 cells	2.5, 5, 10, 20, 40, and 50 µM	NO inhibition (IC$_{50}$ = 48.75 µM)	Xiang et al. (2018)
	47	*In vitro*	LPS-induced RAW 264.7 cells	2.5, 5, 10, 20, 40, and 50 µM	NO inhibition (IC$_{50}$ = 50.77 µM)	Xiang et al. (2018)
	48	*In vitro*	LPS-induced RAW 264.7 cells	2.5, 5, 10, 20, 40, and 50 µM	NO inhibition (IC$_{50}$ = 63.66 µM)	Xiang et al. (2018)
	49	*In vitro*	LPS-induced RAW 264.7 cells	2.5, 5, 10, 20, 40, and 50 µM	NO inhibition (IC$_{50}$ = 11.33 µM)	Xiang et al. (2018)
	52	*In vitro*	LPS-induced RAW 264.7 cells	12.5 and 25.0 µM for 24 h	NO inhibition (IC$_{50}$ = 9.7 µM)	Wang et al. (2017)
	53	*In vitro*	LPS-induced RAW 264.7 cells	12.5 and 25.0 µM for 24 h	NO inhibition (IC$_{50}$ = 17.8 µM)	Wang et al. (2017)
	54	*In vitro*	LPS-induced RAW 264.7 cells	12.5 and 25.0 µM for 24 h	NO inhibition (IC$_{50}$ = 14.0 µM)	Wang et al. (2017)
	56	*In vitro*	LPS-induced RAW 264.7 cells	12.5 and 25.0 µM for 24 h	NO inhibition (IC$_{50}$ = 38.3 µM)	Wang et al. (2017)
	57	*In vitro*	LPS-induced RAW 264.7 cells	12.5 and 25.0 µM for 24 h	NO inhibition (IC$_{50}$ = 41.0 µM)	Wang et al. (2017)
	59	*In vitro*	LPS-induced RAW 264.7 cells	12.5 and 25.0 µM for 24 h	NO inhibition (IC$_{50}$ = 48.5 µM)	Wang et al. (2017)
	60	*In vitro*	LPS-induced RAW 264.7 cells	12.5 and 25.0 µM for 24 h	NO inhibition (IC$_{50}$ = 44.0 µM)	Wang et al. (2017)
	63	*In vitro*	LPS-induced RAW 264.7 cells	12.5 and 25.0 µM for 24 h	NO inhibition (IC$_{50}$ = 22.1 µM)	Wang et al. (2017)
	85	*In vitro*	LPS-induced RAW 264.7 cells	NW	NO inhibition (IC$_{50}$ = 23.42 µM)	Xiang et al. (2019)
	164	*In vitro*	BChE assay	NW	moderate BChE inhibitory activity (IC$_{50}$ = 195.2 µg/ml)	Sabudak et al. (2017)
	165	*In vitro*	BChE assay	NW	Moderate BChE inhibitory activity (IC$_{50}$ = 299.1 µg/ml)	Sabudak et al. (2017)
Antioxidant activity						
	SNFME	*In vitro*	DPPH and hydrogen peroxide radicals	25, 50,100, 150, and 200 µg/ml	The IC$_{50}$ value of 70.73 µg/ml for DPPH radical scavenging and IC$_{50}$ 59.72 µg/ml for hydrogen peroxide scavenging activity	Veerapagu et al. (2018)
	SNFEE	*In vitro*	DPPH and hydroxyl radical	0–2.4 mg/ml	The scavenging rate on DPPH, hydroxyl radical scavenging assay were 68.45% and 49.12%, respectively	Teng et al. (2014)
	SNFP	*In vitro*	DPPH and hydroxyl radicals	0–1.2 mg/ml	The IC$_{50}$ values were 65.43 µg/ml and 0.33 mg/ml for DPPH, hydroxyl radical scavenging assay	Chen et al. (2020)
	SNFEAE	*In vitro*	FRAP and DPPH· scavenging assays			Guo et al. (2020)

TABLE 4 | (*Continued*) Biological activity of bioactive compounds and extracts of *S. nigrum*.

Biological activities	Extracts/ compounds	Types	Testing subjects	Doses/duration	Mechanisms/effects	References
	SNFEE	*In vitro*	DPPH and ABTS radical	100–2,500 µg/ml for FRAP 50–1,000 µg/ml for DPPH 0–120 µg/ml	The IC_{50} values were 119.43 µg/ml and 2.674 µg/ml, FeSO4/L for DPPH and FRAP scavenging activity Showed moderate free radical scavenging activity against DPPH and ABTS$^+$ free radical with the IC_{50} were 81.02 and 35.56 µg/ml, respectively	Sivaraj et al. (2020)
Immunoregulatory activity						
	SNLWP-1 SNLAP-1 SNLAP-2	*In vivo*	H22-bearing mice	50, 100, and 200 mg/kg for 10 days	IL-2, IFN-c levels ↑; IL-10 levels↓	Ding et al. (2012b)
	SNCP	*In vivo*	Male BALB/C mice	200, 400, 800 mg/kg for 28 days	B.T, NK cell activity ↑	Tian et al. (2019)
	SNLP-1	*In vivo*	Lung Cancer Bearing Mice	200 mg/kg/day	CD4+/CD8+of T lymphocytes levels ↑; Th1 cytokines levels ↑	Pu (2020)
Hepatoprotective activity						
	SNWE	*in vivo*	CCl$_4$-induced chronic hepatotoxicity in rats	0.2, 0.5, and 1.0 g/kg for 6 weeks	GOT, GPT, ALP, total bilirubin, superoxide , hydroxyl radical levels↓; GSH, SOD, GST Al, GST Mu levels ↑	Lin et al. (2008)
	SNFBFE	*in vivo*	D-GalN-induced hepatic fibrosis rats	16 and 25 mg/kg for 10 days	ALT, AST, ALP enzymes, GSH, SOD, and CAT levels↓	Chester et al. (2019)
	SNWSP	*in vivo*	CCl$_4$-induced acute injury in rats	100, 200, 400 mg/kg for 7 days	ALT, AST, ALP, MDA levels↓; SOD, GSH-Px, CAT levels ↑	Yang et al. (2014)
	SNWE	*in vivo*	Ethanol-induced liver injury in rats	100, 150, 200 mg/kg for 7 days	ALT, AST, GSTA1, MDA levels↓; SOD, GSH, GSH-Px ↑	Han (2014)
Antibacterial activity						
	SNFEE	*in vitro*	*Aspergillus's Niger, Fusarium oxysprum*	250–1,000 µg/ml for 24 h	Highest antifungal zone was 32.42 and 28.16 mm against *Aspergillus's Niger* and *Fusarium oxysprum*	Mazher et al. (2017)
	SNFEE	*in vitro*	*Escherichia coli*	250–625 µg/ml	The maximum zone of inhibition was 25 mm for *Escherichia coli* at 625 µg/ml concentration	Sivaraj et al. (2020)
	SNEE	*in vitro*	*Staphylococcus aureus Escherichia coli Aeromona sobria*	12.5–200 mg/ml	The maximum zones of inhibition were 16.88, 11.33, and 19.25 mm for *Staphylococcus aureus, Escherichia coli, Aeromona sobria* at 200 mg/ml concentration	Ge (2019)
	SNEE	*in vitro*	*Alternaria solani Cladosporium cucumerinum Fusarium oxysporun Rhizoctonia solani*	NW	The EC_{50} values of *Rhizoctonia solani* and *Fusarium oxysporun* were 1,629 and 1,262 ppm	Cai (2003)
	93	*in vitro*	*Candida albicans*	0, 8, 16, 32, and 64 mg/ L for 12, 24, 36, 48 h	Inhibited the activity of *Candida albicans* via regulating Ras-cAMP-PKA signaling pathway and reducing the intracellular cAMP content	Li et al. (2015)
	93	*in vitro*	*Candida albicans*	32, 64 µg/ml	Alkalizing the intracellular vacuole of *Candida albicans* and causing hyper-permeability of the vacuole membrane	Chang et al. (2017)
Insecticidal activity						
	SNLME	*in vitro*	2nd instar larvae of CPB	5, 10,15, 20, 25, 30, 35, 40, and 45 mg/ml	Caused 50% mortality for 2nd instar CPB larvae at concentration of 5 ppm and foliar consumption was decreased by 74%	Ben-Abdallah et al. (2019)
	SNLCME	*in vitro*	Cx. vishnui group and An. subpictus	25, 45, 60 mg/L for 24, 48, and 72 h	Showed 100 percent larval mortality against early 3rd instar of An. subpictus at 60 mg/L	Rawani et al. (2017)
	SNFMWE	*in vitro*	*Galba truncatula*	NW	The hydro-methanol LC_{50} = 3.96 mg/L, LC_{90} = 7.49 mg/L	Hammami et al. (2011)
	SNLEAE	*in vitro*	*Culex quinquefasciatus*	10–50 ppm for 24–72 h	LC_{50} values of ethyl acetate extracts were 17.04 ppm	Rawani et al. (2010)
	SNLEE	*in vitro*	Green Peach Aphid Myzus persicae Sulzer	4.24 mg/ml for 24, 48, and 72 h	Caused 28.54%, 56.8%, and 57.42% mortality rates after 24, 48, and 72 h exposure	Madanat et al. (2016)

TABLE 4 | (*Continued*) Biological activity of bioactive compounds and extracts of *S. nigrum*.

Biological activities	Extracts/ compounds	Types	Testing subjects	Doses/duration	Mechanisms/effects	References
	SNLME	*in vitro*	*Culex quinquefasciatus*	6.25–1,000 ppm	Methanol leaves extract causing 90% mortality rate	Rahuman et al. (2009)
Neuroprotective activity						
	SNL	*in vivo*	SCOP-induced cognitive impairment rats	5% and 10% leaf inclusions	ChEs levels↑; restored the impaired memory function	Ogunsuyi et al. (2018)
	SNL	*in vivo*	AlCl$_3$-induced neurodegeneration in *Drosophila melanogaster*	0.1% and 1.0% pulverized vegetable for 7 days	GST, MAO, ChE, ROS, TBARS levels ↓; Athletic, memory ability ↑	Ogunsuyi et al. (2020)
	SNL	*in vivo*	AlCl$_3$-induced neurodegeneration in *Drosophila melanogaster*	0.1% and 1.0% pulverized vegetable for 7 days	ROS, GST, Hsp70, Jafrac1, reaper and NF-κB/Relish ↓; cnc/Nrf2 and FOXO ↑	Ogunsuyi et al. (2021)
	112	In vitro	MPP+-induced SH-SY5Y cells	12.5, 25, and 50 μM for 1 h	Induced protective autophagy to protect SH-SY5Y cells from MPP+-induced apoptosis, the cell viability of which improved by 12% at 25 μM	Li et al. (2019)
Gastroprotective activity						
	SNEE	*in vivo*	Ethanol-induced gastric ulcer mice	5–500 mg/kg	At dose of 500 mg/kg, the extract was as effective as lansoprazole in reducing all parameters of peptic ulcer in both models	El-Meligy et al. (2015)
	SNFME	*in vivo*	Gastric ulcer rats	200 and 400 mg/kg	Gastric secretory volume, acidity, pepsin secretion ↓	Jainu and Devi (2006)
Hypoglycemic activity						
	SNFWE	*in vivo*	Streptozotocin-induced Diabetic rats	1 g/L for 8 weeks	Ca/Mg ratio, plasma glucose, HDL, LDL, VLDL, cholesterol, triglyceride ↓	Sohrabipour et al. (2013)
Antimalarial activity						
	79	*in vivo*	*Plasmodium yoelii*-infected mice	7.5 mg/kg for 4 days	At a dose of 7.50 mg/kg, the parasitemia suppressions of solamargine were 64.89%, respectively	Chen et al. (2010)
	100	*in vivo*	*Plasmodium yoelii*-infected mice	7.5 mg/kg for 4 days	At a dose of 7.50 mg/kg, the parasitemia suppressions of solasonine were 57.47%, respectively	Chen et al. (2010)
CNS-depressant activity						
	SNFEE	*in vivo*	Wistar rats and CD1 mice	51, 127.5, and 255 mg/kg	Exploratory and aggressive behavior↓; locomotor activity↓; pentobarbital-induced sleeping time ↑	Perez et al. (1998)
Hypolipidemic activity						
	SNWE	*in vitro*	3T3L1 cells model	0.3, 0.4, 0.5 mg/ml	PPARα, CPT-1 ↑; FaS, HMG-CoR↓; amount and lipid content of adipocytes ↓; inhibiting lipogenesis	Peng et al. (2020)
	SNSEE	*in vivo*	Triton-induced hyperlipidemic rats	200 and 400 mg/kg	Total cholesterol, triglycerides, LDL cholesterol ↓; HDL cholesterol ↑	Sohrabipour et al. (2013)

Note: NM, not mentioned; SNWE, water extracts of S. nigrum; SNPE, polyphenol extracts of S. nigrum; SNEE, ethanol extracts of S. nigrum; SNTA, total alkaloids of S. nigrum; SNFME, Methanol extracts of S. nigrum fruits; SNCE, chloroform Extracts of S. nigrum; SNFEE, ethanol extracts of S. nigrum fruits; SNFP, Polysaccharide from S. nigrum fruit; SNFEAE, Ethyl acetate extracts of S. nigrum fruit; SNCFE, chloroform Fraction extracts of S. nigrum; SNFPEFE, Petroleum ether fraction extracts of S. nigrum fruit; SNCP, Crude Polysaccharides from S. nigrum; SNFBFE, n-butanol fraction extracts of S. nigrum fruit; SNWSP, water-soluble polysaccharides from S. nigrum; SNLME, methanol extracts of S. nigrum leaves; SNLCME, chloroform: methanol (1:1 v/v) extracts of S. nigrum leaves; SNFMWE, methanol-water (8:2 v/v) extracts of S. nigrum fruit; SNLEAE, Ethyl acetate extracts of S. nigrum leaves; SNLEE, ethanol extracts of S. nigrum leaves; SNFWE, water extracts of S. nigrum fruits; SNL, S. nigrum leaves; SNSEE, ethanol extracts of S. nigrum seeds.

paragraphs. A variety of proprietary Chinese medicines in which *S. nigrum* extract is one of the medicinal ingredients have been widely used in clinical practice. Some of the patents containing *S. nigrum* can be found in **Table 5**, the pharmacological activities are mostly found in the field of treatment of tumors and skin diseases, mostly in the form of combination with other herbs.

Antitumor Activity

Crude extracts and isolated compounds of *S. nigrum* have exhibited significant antitumor potential *in vitro* and *in vivo*. The underlying mechanism of the antitumor activity of the crude

extracts or bioactive substances of *S. nigrum* is presented in **Table 4** and **Figure 3**.

Crude Extract

In vitro studies showed that different solvent extracts of *S. nigrum* significantly inhibited the growth of various cancer cell lines, such as human breast cancer cell line MCF-7, renal cell carcinoma cell line 786-O, esophageal cancer cell line ECA-109, human liver cell lines SMMC-721 and HepG$_2$, gastric cancer cell line MGC-803, human colorectal carcinoma cell lines HT-29, HCT-116, and DLD-1, and human lung cancer cell line A549 (He et al., 2015). Specifically, the treatment with the water extract of *S. nigrum*

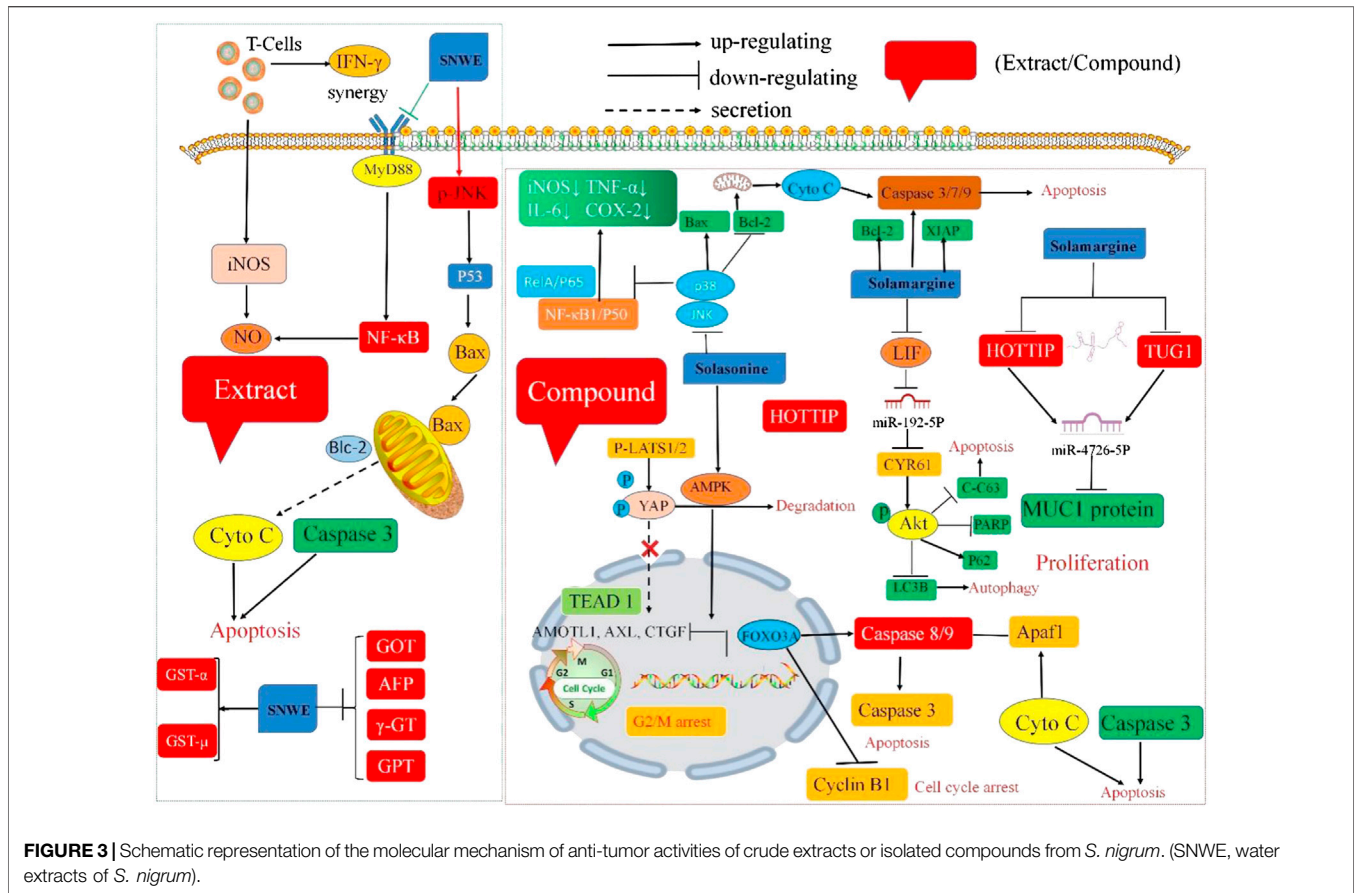**TABLE 5 |** Patents list of products containing *S. nigrum* and their claimed pharmacological properties.

Application	Main composition	Pharmacological properties	Publish number
Herbal preparation	*Fritillaria thunbergii* Miq., *Hedyotis diffusa* Willd., **S. nigrum**, *Paris polyphylla* Smith, *Scutellaria barbata* D. Don, *Adenophora stricta* Miq., *Prunella vulgaris* Linn., etc.	Treating pulmonary fibrosis	CN111991507A
Herbal preparation	*Coix lacryma-jobi* Linn., *Amygdalus persica* Linn., *Carthamus tinctorius* Linn., *Scutellaria baicalensis* Georgi, *Sophora flavescens* Alt., *Rehmannia glutinosa* Libosch., **S. nigrum**, etc.	Treating lung and colon cancer	CN113398215A
Bacteriostatic agent	**S. nigrum**, *Artemisia argyi* Levl. et Van., *Syzygium aromaticum* (L.) Merr. Et Perry, *Cynanchum paniculatum* (Bunge) Kitagawa, Carbomer, Salicylic acid, etc.	Treating skin diseases	CN113368193A
Herbal preparation	*Cordyceps Sinensis* (Berk.) Sacc., **S. nigrum** extract, *Taxus chinensis* (Pilger) Rehd. extract	Treating lung cancer	CN113332358A
Herbal preparation	**S. Nigrum**, *Pteris multifida* Poir., *Lithospermum erythrorhizon* Sieb. et Zucc., *Angelica dahurica* (Fisch. ex Hoffm.) Benth. et Hook. f., *Dioscorea polystachya* Turczaninow	Treating psoriasis	CN110368445A
Herbal preparation	**S. Nigrum**, *Astragalus membranaceus* (Fisch.)Bge., *Panax ginseng* C. A. Meyer, *Atractylodes macrocephala* Koidz., *Hedyotis diffusa* Willd., *Curcuma zedoaria* (Christm.) Rosc., etc	Treating stomach cancer	CN112717097A
Herbal preparation	**S. Nigrum**, *Cinnamomum cassia* Presl, *Dioscorea polystachya* Turczaninow, *Asarum sieboldii* Miq., *Scrophularia ningpoensis* Hemsl., *Cornus officinalis* Sieb. et Zucc., etc	Treating glaucoma	CN108210683A
Herbal preparation	**S. Nigrum**, *Hedyotis diffusa* Willd., *Verbena officinalis* Linn., *Lithospermum erythrorhizon* Sieb. et Zucc., *Reynoutria japonica* Houtt., *Angelica dahurica* (Fisch. ex Hoffm.) Benth. et Hook. f., etc	Treating vaginitis and cervicitis	CN111991481A
Herbal preparation	**S. Nigrum**, *Bidens pilosa* Linn., *Hedyotis diffusa* Willd., *Verbena officinalis* Linn., *Taraxacum mongolicum* Hand.-Mazz., *Plantago asiatica* L., etc	Treating cholecystitis	CN111529631B
Herbal preparation	**S. Nigrum**, *Gentiana scabra* Bunge, *Gardenia jasminoides* Ellis, *Paeonia suffruticosa* Andr., *Angelica sinensis* (Oliv.) Diels, *Pinellia ternata* (Thunb.) Breit., etc	Treating leukemia	CN106822558B

Abbreviation: A549, human alveolar basal epithelial cells; ABTS, 2, 2'-azino-bis-(3-ethylbenzenthiazoline-6-sulphonic) acids; AChE, acetylcholinesterase; AFP, Alpha-FetoProtein; AKT, proteinkinase B; ALP, alkaline phosphatase; AMPK, 5-AMP activated protein kinase; AP-1, activator protein-1; Bax, bcl-associated X protein; Bcl-2, B-cell CLL/lymphoma 2; Caspase 3, cysteinyl aspartate-specific proteinase-3; Caspase 7, cysteinyl aspartate-specific proteinase-7; CAT, catalase; CDC25, recombinant cell division cycle protein 25; CDK1, recombinant cyclin dependent kinase 1; c-JUN, c-Junamino-terminalkinase; COX-2, cyclooxygenase-2; DLD-1, human colorectal adenocarcinoma epithelial cells; DPPH, 1,1-Diphenyl-2-picrylhydrazyl free radical; GOT, glutamic-oxal(o)acetic transaminase; GPT, glutamic pyruvate transaminase; GPx, glutathione peroxidase; GSH, L-glutathione; GST-α, glutathione S-transferase-α; GST-μ, glutathione S-transferase-μ; H22, mouse H22 hepatocellular carcinoma cells; HAase, Human Hyaluronidase; HCT-116, human colorectal adenocarcinoma cells; HDL, high-density lipoprotein; HEL, human erythorleukemia cell line; HepG2, liver hepatocellular cells; HL-60, Leukemia Myeloidcells; HT-29, human conlon carcinoma cells; IC50, half maximal inhibitory concentration; IFN-γ, Interferon-gamma; IL-17, interleukin-17; IL-1β, interleukin-1β; IL-2, interleukin-2; IL-6, interleukin- 6; iNOS, inducible nitric oxide synthase; c-JNK, Jun N-terminal kinase; LC3, microtubule associated proteins 1A/1B light chain 3; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; LT, leukotriene; MACC1, human metastasis associated in colon cancer 1; MCF-7, human breast adenocarcinoma cell line; MDA, malondialdehyde; MIC, minimum inhibitory concentration; mTOR, molecular target of rapamycin; MV4-11, Human acute monocytic Leukemia cells; MyD88, myeloid differentiation primary response protein; NB4, acute promyelocyte cells; NF-κB, nuclear factor kappa-B; NO, nitric oxide; Nrf2, Nuclear Factor erythroid 2-Related Factor 2; PDTC, pyrrolidine dithiocarbamate; PG, prostaglandin; PKCα, recombinant protein kinase C Alpha; ROS, reactive oxygen species; SGC-7901, human gastric cancer cells; SMMC-721, human hepatocellular carcinoma cells; SOD, superoxide dismutase; TG, thioglycollate; THP-1, human monocytic leukemia cells; TLR4, toll like receptor 4; TNF, tumor necrosing factor; TNF-α, tumor necrosis factor -α; TRAF-6, TNF receptor associated factor 6; VEGF, vascular endothlial growth factor; XTT, 2, 3-bis(2-methoxy-4-nitro-5-sulfophenyl)-5-[(phenylamino)carbonyl]-2H-tetrazolium hydroxide; γ-GT, γ-glutamy transpeptidase.

(SNWE) induced apoptosis in HepG$_2$ cells by increasing the mitochondrial release of cytochrome C, and activating Caspase-3, and inducing autophagy through implicating the levels of LC3, Bcl-2, and Akt (Lin et al., 2007). Nitric oxide (NO) is an antitumor molecule produced by activated macrophages. Harvesting thioglycollate (TG)-elicited peritoneal macrophages from mice followed by incubation with different concentrations of SNWE (10–500 mg/ml) alone or with recombinant interferon-γ (rIFN-γ) (20 U/ml) for 6 h showed that the extract dose-dependently induced NO production and iNOS expression, which was highly strengthened in combination with rIFN-γ. Further mechanism research demonstrated that pyrrolidine dithiocarbamate (PDTC), an NF-κB inhibitor, inhibited the synergistic effect of *S. nigrum* and rIFN-γ on the NO production and iNOS expression. These results suggested that *S. nigrum* increased the NO production through NF-κB activation (An et al., 2005). Furthermore, 1% and 2% SNWE prominently reduced hepatic carcinogenesis to 40% and 20% and significantly increased the survival rate to 90% and 100%, respectively, in AAF/NaNO$_2$-induced hepatoma rats (Hsu et al., 2009). SNWE also caused 43% cytotoxicity, inhibited migration, and suppressed the activities of hexokinase and

pyruvate on the of human breast cancer cell line (MCF-7) by about 30% and 40% at a concentration of 10 g/L, respectively (Ling et al., 2019).

Wang et al. reported that the IC$_{50}$ value of the polyphenolic extract of *S. nigrum* (SNPE) was 0.75 mg/ml and the cell viabilities of HepG$_2$ cells were 85%, 27%, and 6% at concentrations of 0.5, 1.0, and 2.0 mg/ml, respectively. Furthermore, SNPE arrested the cell cycle at the G2/M phase (21.13%, 24.53%, and 31.62% at 0.5, 1.0, and 2.0 mg/ml, respectively) by regulating the activity of the CDC25 family and CDK1 and reactivated apoptosis via decreasing protein expression of Bcl-2 and Bid. Moreover, SNPE decreased the tumor weight and tumor volume after feeding HepG2 tumor-bearing mice daily with 5 g basal diet containing 1 or 2 μg/ml (w/v) SNPE for 35 days (Wang et al., 2010). Yang et al. (2010) also revealed that SNPE significantly reduced the viability of HepG$_2$ cells (IC$_{50}$ = 0.86 mg/ml). The mechanism of action study showed that SNPE inhibited TPA-induced HepG2 migration and invasion via blocking the expression of PKCα and attenuated p38 and p38/ERK activation (Yang et al., 2010). Moreover, SNPE inhibited the viability of HepG$_2$ cells through the suppression of the VEGF-induced activation of AKT and mTOR *in vitro* and reduced the volume and weight

FIGURE 3 | Schematic representation of the molecular mechanism of anti-tumor activities of crude extracts or isolated compounds from *S. nigrum*. (SNWE, water extracts of *S. nigrum*).
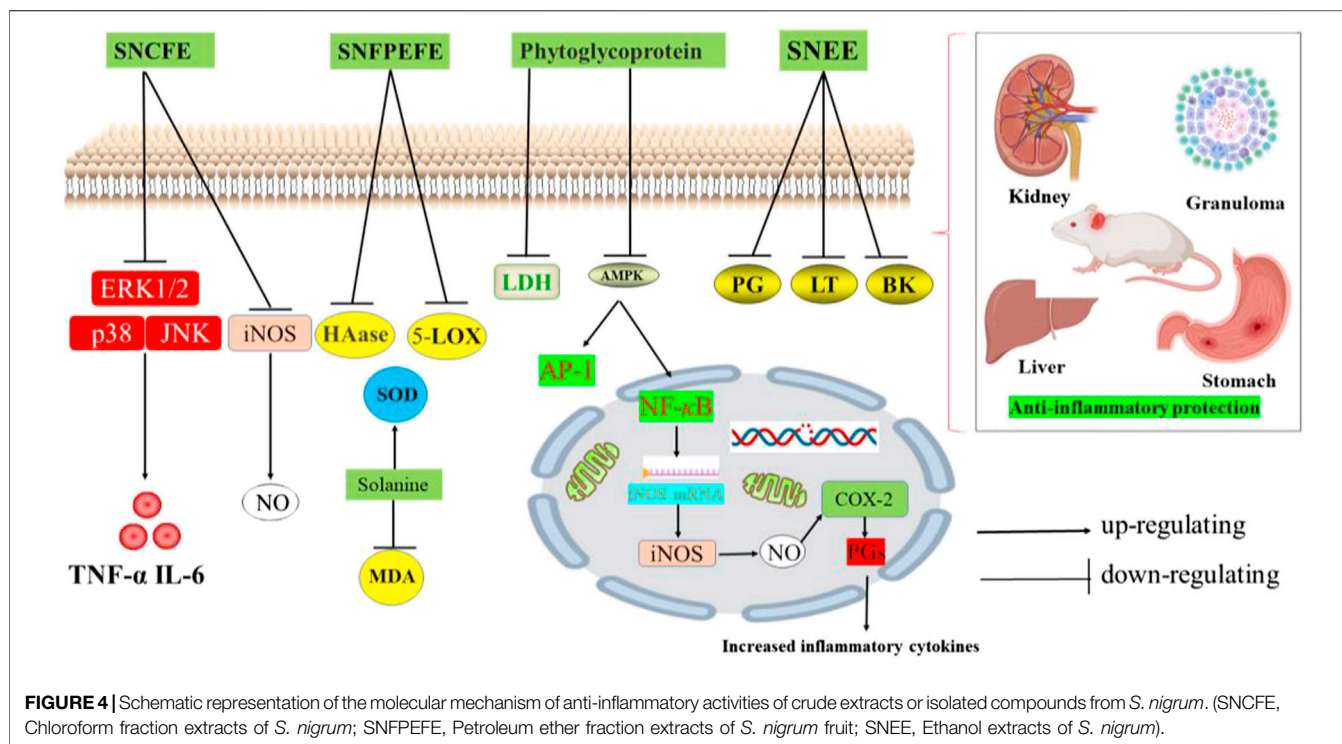
of the tumors in the HepG$_2$ tumor-bearing mouse model (Yang et al., 2016).

According to relevant literature reports, different solvent extracts (water, ethanol, chloroform, and n-Butanol) extracts of *S. nigrum* show strong broad-spectrum antitumor activity. It has been demonstrated that the ethanol extract of *S. nigrum* fruit (SNCE) could arrest the cell cycle in the S phase and continue to the G2/M phase, inhibiting MCF-7 proliferation (IC$_{50}$ = 40.77 μg/ml) and inducing apoptosis 43.31% (Churiyah et al., 2020). The n-Butanol extract of *S. nigrum* inhibited the growth of human colorectal cancer SW480 cells in a dose-dependent manner via blocking cells in the G2/M phase and increasing the expression of Caspase-3 (Ye and Gao, 2019). These studies indicated that different solvent extracts of *S. nigrum* could be promising candidates for the treatment of cancer.

Isolated Compounds

Furthermore, compounds isolated from *S. nigrum* also displayed multiple antitumor effects. α-solanine (**99**) is a chemical component that widely exists in potatoes, tomatoes, eggplants and other Solanaceae plants. Pharmacological studies have shown that it has antitumor and insecticidal activities, but it also showed toxic effects on humans in overdose. Treatment of the human gastric cancer cell line (SGC-7901) with different concentrations of α-solanine (25, 50, 100 μg/ml) for 24 or 48 h inhibited proliferation and promoted apoptosis of cells by upregulating

the expression of miR-140 and downregulating the expression of MACC1 (Huang et al., 2020). Furthermore, α-solanine exhibited antitumor properties by regulating the expression of p-Akt, cleaving Caspase-3 and p53 protein, increasing the intracellular ROS level, and inhibiting FAK phosphorylation and the expression of miR-138 and the survivin protein (Wu, 2011; Zhu et al., 2019). The IC$_{50}$ values of solasonine (**100**) against five tumor cells (THP-1, MV4-11, HL-60, NB4, HEL) were 11.19, 12.50, 15.87, 15.45, and 17.00 mM, respectively. Moreover, solasonine promoted apoptosis and caused less cell cycle arrest in the G2/M phase through the activation of the AMPK/FOXO3A Axis. In the THP-1-induced xenograft model, all the mice were intraperitoneally injected with 4, 8, and 16 mg/kg solasonine once a day for 14 days, and the pharmaceutical and immunoblotting results showed that solasonine inhibited tumor growth with increasing solasonine concentration and induced the nuclear translocation of FOXO3A, upregulated the expression of Bax and P-CDK1, and downregulated the expression of Bcl-2 and Cyclin B1 (Zhang et al., 2021). Solasonine induced apoptosis by inhibiting the expression of the proteins p65 and Bcl-2, enhancing the expression of the proteins Bik and Bak, and activating the Caspase-3 pathway (Li et al., 2020). Zhang et al. showed that solamargine (**79**) induced apoptosis by decreasing the mitochondrial membrane potential, upregulating the expression of pro-apoptotic protein, and downregulating the

FIGURE 4 | Schematic representation of the molecular mechanism of anti-inflammatory activities of crude extracts or isolated compounds from *S. nigrum*. (SNCFE, Chloroform fraction extracts of *S. nigrum*; SNFPEFE, Petroleum ether fraction extracts of *S. nigrum* fruit; SNEE, Ethanol extracts of *S. nigrum*).

expression of anti-apoptotic protein with an IC_{50} value of 9.81 μM (Zhang, 2018). In 2022, Yin et al. found that solamargine induces apoptosis and autophagy in liver cancer cells by regulating the LIF/miR-192-5p/CYR61/Akt signaling pathway at high doses, thereby inhibiting tumor cell proliferation. Solamargine at low doses regulates the biological function of immune cells by inhibiting the LIF/Stat3 signaling pathway, reshaping the tumor microenvironment, and inhibiting the process of tumor cell heterogeneity, thereby exerting a synergistic antitumor effect. This provides a scientific basis for its wide application in modern clinical treatment (Yin et al., 2022). In the clinic, adjuvant therapies, such as radiotherapy, endocrine therapy, chemotherapy, and targeted therapy, are administered to patients with advanced or metastatic tumors, but subsequent side effects usually result in treatment failure and increased mortality. Hence, the need for drugs with strong efficacy but minimal side effects and toxicity is great. Degalactotigonin (**2**) isolated from *S. nigrum* can inhibit the proliferation, invasion, migration and tumorigenicity of renal cell carcinoma cells. It can be used as an effective drug for the treatment of advanced renal cell carcinoma (Wang et al., 2020). This provides strong evidence that TCM can be better applied in the clinic.

Immunomodulatory Activity

S. nigrum crude polysaccharides SNLP-1 displayed obvious immunoregulatory activity for macrophages by promoting the release of NO and the secretion of cytokines (TNF-α and IL-6) *in vitro*, and further mechanistic studies have indicated that SNLP-1 improves the gene and protein expression levels of TLR4 and its key nodes MyD88, TRAF-6, NF-κB, and c-JUN

in the pathway. Establishing a lung cancer mice model and oral administration with 200 mg/kg/day SNLP-1, SNLP-1 not only reduced the tumor weight of lung cancer mice, but also increased the index of thymus and spleen. Flow cytometry revealed that the ratio of T lymphocyte subsets $CD4^+/CD8^+$ and the concentrations of serum Th1 cytokines (IFN-γ, IL-2, TNF) in mice were increased by SNLP-1. This indicated that the homogeneous polysaccharide fraction SNLP-1 can enhance the function of the body's immune system *in vivo* and *in vitro* (Pu, 2020). Similarly, prepared and cultured mouse spleen lymphocytes with LPS and ConA, thymus and spleen index, B and T lymphocyte proliferative transformation, and NK cell activity were significantly higher in three groups than in the control group after daily oral administration of 800, 400 or 200 mg/kg crude polysaccharides of *S. nigrum* for 28 days (Tian et al., 2019). Compared with the control group, *S. nigrum* water extract polysaccharide (SNLWP-1) and alkali extract polysaccharide (SNLAP-1 and SNLAP-2) significantly increase the weight of immune organs and serum IL-2 and IFN-γ in H22 tumor bearing mice (Ding et al., 2012b). Other extractions protocols, including decoction also exhibited immunomodulatory activity in clinical studies. Treatment with commissioned Longkui Yinxiao Tablet for 8 weeks resulted in higher $CD4^+/CD8^+$ and $CD4^+$ levels in the psoriasis treatment group and lower $CD8^+$ and cytokines TNF-α, IL-6, and IL-17 levels compared with the control group (Dai et al., 2018).

The above literature indicated that *S. nigrum*, especially polysaccharides, has immunomodulatory activity *in vitro* and *in vivo*. However the immunomodulatory mechanism of *S. nigrum* is limited to the level of inflammatory factors, and there is a lack of in-depth exploration of its

immunomodulatory mechanism. Research on effective immunomodulatory components mainly focuses on polysaccharides, but more attention should be paid to other effective components.

Anti-Inflammatory Activity

Inflammation is the immune system's response of the body to pathogenic factors and their damaging effects, and it is a self-protective response to help the body recover and resist infection, disease and pain. Relevant studies have confirmed the anti-inflammatory activity of crude extracts of *S. nigrum* in various inflammation related models and explained the possible related mechanisms, and a possible mechanism of action is shown in **Figure 4**. Chloroform extract of *S. nigrum* showed 80% inhibition of the NO and iNOS production stimulated by LPS at a concentration of 50 μg/ml. TNF-α and IL-6 are cytokines, which are responsible for the pathogenesis of many inflammatory disorders. Thus, the levels of TNF-α and IL-6 measured by ELISA on LPS-induced peritoneal macrophages have been determined, and the results showed that the chloroform fraction reduced the TNF-α and IL-6 levels in a dose-dependent manner and inhibited the phosphorylation of p38, JNK and ERK1/2, which may account for the anti-inflammatory mechanism of the *S. nigrum* chloroform fraction (Kang et al., 2011). Yeom et al. showed in the TPA-induced acute ear edema mouse model that the cell viability in fruit extract of *S. nigrum* in 80% ethanol was 51.35% at the concentration of 0.125 mg/ml. The NO production in *S. nigrum* fruit extract in 80% ethanol decreased to 4.1%, 16.1%, 61.0%, and 79.8% at concentrations of 0.125, 0.250, 0.500, and 1.000 mg/ml, respectively, and could also relieve edema and decrease the thickness of ear tissue *in vivo*, probably accounting for the abundance of alkaloid and flavonoid (Yeom et al., 2019). Similar results in acute and subacute rat models, and the hydroalcoholic extracts of *S. nigrum* showed less deposition of macrophages and more deposition of collagen fibres and exhibited organ protection properties (liver, stomach, and kidney), perhaps owing to the presence of steroidal alkaloids and steroidal saponins of *S. nigrum* (Aryaa and Viswanathswamy, 2017). Self-made *S. nigrum* suppository promoted the repair of damaged epithelial tissue and restored prostatic secretion through the decrease of the rat prostate wet quality and the white blood cell count and the increase in the density of lecithin corpuscle (Xu et al., 2015). Likewise, self-made *S. nigrum* could increase the SOD activity and decrease the MDA content to exhibit anti-inflammatory activity in the rabbit synovium after the rabbit knee joint was coated with self-made *S. nigrum* ointment for 1.5 h per day for 6 days in total in an electroacupuncture-made rabbit knee synovitis model (Li J et al., 2021). In 2017, Wang et al., isolated nine new steroidal saponins from berries of *S. nigrum*, Among these steroidal saponins, solanigrosides Y1 (**52**) significantly inhibited the NO production with an IC$_{50}$ value of 9.7 μM, and some compounds exhibited significant inhibitory effects on the LPS-induced IL-6 and IL-1β production (Wang et al., 2017). In 2018, Xiang et al. isolated seven previously undescribed steroidal glycosides from the unripe berries of *S. nigrum*, and all seven compounds

exhibited inhibitory activities on the NO production with IC$_{50}$ values ranging from 11.33 to 49.35 μM (Xiang et al., 2018). Overall, the extracts and other preparations from *S. nigrum* deserve more studies related to inflammatory diseases.

Antibacterial and Larvicidal Activity

So far, bacterial and fungal infections and multidrug resistance have been great threats to human health and are important challenges that need to be urgently solved. Pharmacological studies have demonstrated that the antifungal activities of different parts of *S. nigrum* prepared in four solvents (ethanol, chloroform, petroleum ether, and distilled water) to struggle against five fungal strains viz. *Aspergillus's Niger*, *A. flavors*, *Saccharomyces cervisae*, *Alternaria alternate*, and *Fusarium oxysprum*. The MIC was found to be in the range of 250–1,000 μg/ml, and the zone of inhibition was measured in the range of 9.3 mm of stem extract in distilled water against *A. flavus* and 32.42 mm of fruit extract in chloroform against *A. niger* (Mazher et al., 2017). The maximum zones of inhibition of ethanol extract of *S. nigrum* were 16.88, 11.33, and 19.25 mm for *Staphylococcus aureus*, *Escherichia coli*, and *Aeromona sobria* at a concentration of 200 mg/ml, respectively (Ge, 2019). The isolated compound, solasodine-3-*O*-β-D-glucopyranoside (**93**) displayed potent fungicidal activity against both *azole-sensitive* and *azole-resistant Candida albicans* strains in spider medium with the MIC value of 32 mg/ml, which may be attributed to the essential role of the glucosyl moiety. Subsequent pharmacological mechanism studies found that solasodine-3-*O*-β-D-glucopyranoside alkalized the intracellular vacuole and elicited vacuole permeability to contribute to cell death in *C. albicans* (Chang et al., 2017). Another study showed that solasodine-3-*O*-β-D-glucopyranoside could attenuate the virulence of *Candida albicans* through inhibiting adhesion and yeast-to-hyphal morphological transformation, and the results of the XTT reduction assay showed that solasodine-3-*O*-β-D-glucopyranoside could inhibit biofilm formation of *C. albicans* at concentrations of 16 mg/L or above. Next, downregulation of adhesion-related genes such as ALS3, EAP1, and HWP1 with the addition of 1 mM cAMP rescued the growth rate of solasodine-3-*O*-β-D-glucopyranoside-treated biofilm from 27.11% to 77.15%. The results suggested that solasodine-3-*O*-β-D-glucopyranoside inhibits the activity of *C. albicans* via regulating the Ras-cAMP-PKA signaling pathway and reducing the intracellular cAMP content (Li et al., 2015).

After exposition to graded concentrations (2.5, 5, and 10 ppm) of the synthesized silver nanoparticles (AgNPs) to fight against third instar larvae of *C.quinquefasciatus* and *An. Stephensi*, the IC$_{50}$ and IC$_{90}$ values of dry leaf, fresh leaf, and berry extracts of *S. nigrum* for *An. Stephensi* were 1.33, 1.59, and 1.56 ppm and 3.97, 7.31, and 4.76 ppm, respectively. The IC$_{50}$ and IC$_{90}$ values of dry leaf, fresh leaf and berry extracts of *S. nigrum* for *C.quinquefasciatus* were 1.26, 1.33, and 2.44 ppm and 14.38, 38.04, and 13.42 ppm, respectively (Rawani et al., 2013). To explore the acaricidal activity of crude extracts of *S. nigrum* for *Tetranychus cinnabarinus*, Chen et al. conducted slide-dip and leaf-dip assays and glasshouse experiments, revealing LC$_{50}$ and LC$_{90}$ values of 3.50, 3.99, 4.70, 12.15, 13.99, and 14.92 g/L

after 1, 3, and 7 days of treatment, respectively. (Chen and Dai, 2016). The methanol leaf extract possessed the highest larvicidal activity (mortality rate of 90%) against the early fourth-instar larvae of *C. quinquefasciatus* at 1,000 ppm (Rahuman et al., 2009). Leaf extract from *S. nigrum* caused mortality rates of 28.54%, 56.8%, and 57.42% of the green peach aphid after exposure for 24, 48, and 72 h (Madanat et al., 2016). In addition, the active compounds solamargine and solasonine isolated from *S. nigrum* were found to fight against *Plasmodium yoelii* 17XL in mice, and the parasitemia suppressions of solamargine and solasonine were 64.89% and 57.47%, respectively (Chen et al., 2010). However, there is a lack of research on the mechanism underlying the insecticidal effect.

Antioxidant Activity

Excessive accumulation of free radicals in the body may cause aging and tissue damage. Oxidative stress is the pathogen of many human diseases, such as atherosclerosis, ischemic reperfusion injury, inflammation, cancer, aging, and neurodegenerative diseases. Antioxidants are the only weapon against the oxidizing and damaging effects of free radicals on the body's vital chemicals and cells. Various studies focus on the antioxidant activity of the bioactive compounds or extracts of *S. nigrum* using *in vitro* and *in vivo* assays. Sivaraj et al. carried out DPPH radical, superoxide radical, ABTS$^+$ radical cation, phosphomolybdenum reduction, and Fe^{3+} reducing power assays of the fruit extract of *S. nigrum*. The maximum DPPH radical scavenging activity was 73.16% at 120 µg/ml (IC$_{50}$ = 81.02 µg/ml), the maximum superoxide radical scavenging activity was 60.06% at 120 µg/ml (IC$_{50}$ = 57.82 µg/ml), the maximum ABTS$^+$ radical cation scavenging activity was 67.70% at 60 µg/ml (IC$_{50}$ = 35.56 µg/ml), the maximum phosphomolybdenum reduction was 96.77% at 120 µg/ml (RC$_{50}$ = 21.25 µg/ml), and the maximum Fe^{3+} reduction was 72.10% at 120 µg/ml (RC$_{50}$ = 63.74 µg/ml). These results indicated that two compounds, flavone and oleic acid, may be one of the reasons for the antioxidant property of the fruit extract of *S. nigrum* (Sivaraj et al., 2020). GSH and ROS levels determined in primary rat astroglial cell cultures showed that the leaf extract of *S. nigrum* could increase intracellular GSH levels and decrease ROS levels, which indicated that the leaf extract of *S. nigrum*. could restore the oxidative status by using glutamate as a stressor, prevent the increase in the glutamate uptake, and inhibit the excitotoxicity of glutamate (Campisi et al., 2019). According to the hydroxyl radical scavenging assay, 60% ethanol crude extract of *S. nigrum* had DPPH scavenging a rates of 68.45% and 49.12% (Teng et al., 2014). Lunasin peptide, purified from *S. nigrum*, inhibited oxidative DNA damage in a dose dependent manner by blocking the Fenton reaction between Fe^{2+} and H$_2$O$_2$ by chelating Fe^{2+} suggesting that lunasin peptide may play an important role in the chemoprevention for oxidative carcinogenesis (Jeong et al., 2010). After the treatment with glucose oxidase or xanthine oxidase alone or in combination with 0.01, 0.1, 1, 10, and 20 µg/ml of glycoprotein for 4 h, the viabilities of the NIH 3T3 cells were 40.4%, 47.3%, 53.0%, 68.2%, and 85.3%, respectively, compared with 33.3% of the control group (glucose oxidase). The viabilities were 75.1%, 79.3%, 83.2%, 86.0%, and 95.1%, respectively, compared with 71.2% of the

control group (xanthine oxidase) (Heo and Lim, 2004). Overall, the extracts and compounds from *S. nigrum* may be suitable antioxidants for the further investigations.

Hepatoprotective Activity

The water extract of *S. nigrum* (SNWE) demonstrated the potential to protect the liver against diseases. Administration of SNWE at dosages of 0.2, 0.5, and 1.0 g/kg for 6 weeks in CCl$_4$-induced chronic hepatotoxic rats reversed the body and organ weights and caused cloudy swelling, necrosis, cytoplasmic vacuolization and fatty degeneration determined by both qualitative and quantitative histopathological examinations. Furthermore, SNWE also reduced the levels of serum liver enzyme markers (GOT, GPT, ALP, and total bilirubin), superoxide and hydroxyl radicals and restored the GSH and SOD contents to the normal level especially at high doses of 0.5 and 1.0 g/kg (Lin et al., 2008). In AAF-induced liver damage rats, the liver/body weight ratios were 3.1- and 2.9-fold of that of the control group for 1% and 2% SNWE supplement, respectively. SNWE also decreased the levels of the serum biomarkers GOT, GPT, γ-GT, and AFP and induced the expression and the activation of both GSTs (GST-α, and GST-µ), which were responsible for the metabolism of a broad range of xenobiotics and carcinogens. Moreover, the treatment of SNWE regulated the level of Nrf2 and the level of downstream antioxidant enzymes regulated by Nrf2, including GPx, SOD-1, and catalase (Hsu et al., 2009). Chester et al. reported that the hydroalcoholic extract (250 mg/kg) of *S. nigrum* showed a significant decrease in hepatic GSH, SOD, and CAT and considered this as an index of the antioxidant status of tissues in D-galactosamine-induced hepatic fibrosis rats. Histopathological study also showed that the crude extract had a protective effect on the liver due to the antioxidant properties of the plant (Chester et al., 2019). Polysaccharides, extracted from *S. nigrum*, alleviated liver swelling, increased the levels of SOD, GSH, and CAT, decreased the content of MDA (Yang et al., 2014).

Neuroprotective Activity

With the development of modern medicine, there are increasing investigations to illustrate the mechanisms of the bioactive constituents isolated from *S. nigrum*, promoting the research and applications in clinic in turn. Regarding the central nervous system, Ogunsuyi et al. investigated the neuroprotective effect of *S. nigrum* on an oscopolamine-induced cognitive impairment model in rats. Pretreatment with 10% *S. nigrum* inclusions could also significantly restore the impaired memory function, decrease the AChE activity, MDA content, and BChE activity, and increase the brain GSH content (Ogunsuyi et al., 2018). In 2019, Ogunsuyi et al. continued to study the neuroprotective effect of *S. nigrum* in *Drosophila melanogaster*, and the results also showed that the impaired behavioral physiology and enzyme activities (glutathione-S-transferase, monoamine oxidase, cholinesterase) were ameliorated in Al-treated flies after the daily administration of pulverized vegetables for 7 days (Ogunsuyi et al., 2020). In 2021, Ogunsuyi et al. proved that 1% dietary inclusions of *S. nigrum* could decrease the survival rate and ROS levels and increase the total thiol contents *in vivo* (Ogunsuyi et al., 2021).

Anticholesterol Activity

Polyphenols derived from S. nigrum were reported to be an antiobesity agent, which could promote hepatic lipolysis, decrease serum triacylglyceride, cholesterol, and low-density lipoprotein (LDL)-cholesterol and inhibit lipogenesis (Peng et al., 2020). In addition, the oral administration of an ethanolic extract or chloroform fraction of S. nigrum (200 and 400 mg/kg) for 5 days to triton-induced hyperlipidemic rats reversed the elevation of the serum of total cholesterol, triglycerides and LDL cholesterol level and the reduction of the HDL cholesterol level (Sharma et al., 2012).

CLINICAL EFFECTIVENESS IN HUMANS

As a folk medicine widely used around the world, S. nigrum has been widely reported clinically in recent years. The application of decoction of the whole herb or fruit of S. nigrum and its compound preparations for the treatment of liver cancer, lung cancer, cervical cancer, esophageal cancer, breast cancer, nasopharyngeal cancer, and other malignant tumors has attracted the attention of scholars at home and abroad for its remarkable clinical efficacy (Mei et al., 2011).

Liver cancer is currently the fourth most common malignant tumor and the second leading cause of cancer death in China, which seriously threatens the life and health of the Chinese people. In an open, prospective, randomized clinical trial conducted from 2012 to 2015, the clinical efficacy of S. nigrum tablets in the treatment of liver cancer was evaluated. Eighty-two patients with liver cancer were divided into observation group and control group according to the random number table method. The patients in the control group were treated with sorafenib, and the patients in the observation group were treated with S. nigrum tablets on the basis of the control group. The clinical efficacy, liver function recovery, inflammatory factor levels and survival rate were compared between the two groups. Results: The complete remission rate and total effective rate in the observation group were 14.63% (6/41) and 43.90% (18/41), which were significantly higher than those in the control group (2.44% (1/41) and 14.63% (6/41); the number of patients with liver function recovery in the observation group at 3 months, 6 months, and 1 year of treatment were significantly higher than those in the control group; after treatment, the IL-1, IL-6 and TNF-α levels were significantly lower than those in the control group. The 1-year survival rate and 2-year survival rate of the observation group were significantly higher than those of the control group. These research results show that S. nigrum tablet has a significant effect in the treatment of liver cancer, can effectively promote the recovery of liver function, improve the level of inflammatory factors, and improve the survival rate of patients (Yang et al., 2017). In addition, another clinical experimental study showed that the treatment of patients with advanced primary liver cancer with S. nigrum mixture can improve the clinical symptoms, liver function and immune function of the patients, effectively improve the quality of life of the patients, and is expected to prolong the survival period (Huang and Guan, 2013). In view of the diverse in vitro and in vivo pharmacological activities of S. nigrum, larger-scale randomized, double-blind, and controlled trials are needed to verify its clinical efficacy.

TOXICITY

Although S. nigrum has been used as a drug or food for thousands of years and a large number of pharmacological activities have been reported, there are limited reports on the safety and side effects of the plant and its bioactive components. In 2005, Lai et al. studied the acute toxicity and genotoxicity assay of S. nigrum. The highest gavage dose of 21.5 g/kg was administered to mice, and no signs of toxicity and death were observed and recorded for 14 days of continuous gavage. In the genotoxicity test, the short-term mutagenicity of S. nigrum juice was investigated by the mouse sperm deformation test, micronucleus test, and Ames test. The results of these three tests were all negative, indicating no genotoxic effect (Lai et al., 2005). In 2014, Mo et al. experimentally confirmed the maximum dose of 494.4 g/kg of aqueous decoction of S. nigrum in mice. When normal people take the commonly used amount of S. nigrum (30–60 g), toxic and side effects are rarely observed. However, overdose can cause poisoning, resulting in symptoms such as headache, abdominal pain, vomiting, diarrhea, pupil dilation, arrhythmia, coma, and other symptoms (Mo et al., 2014).

Modern research showed that S. nigrum mainly contains active chemical ingredients such as alkaloids, saponins, and polysaccharides. Among these active ingredients, steroidal alkaloids have antitumor, liver and kidney protective, antipyretic, analgesic, anti-inflammatory, and expectorant effects. The steroidal alkaloids in S. nigrum not only have a wide range of pharmacological activities but also have some toxicity. Representative compounds are solasonine and solamargine, both of which are steroidal alkaloids composed of solanidine as an aglycon. Solanine causes strong irritation to gastrointestinal mucosa (Li, 2019). In addition, other toxicological tests have also confirmed that solanine can affect the embryonic development, causing miscarriage and stillbirth. The results of solanine on the bone marrow cell cycle of male mice showed that the ratio of cells in G0/G1 phase increased with increasing dose, while the ratios of S phase and G2/M phase decreased, and cells were blocked in G0/G1 phase. Affect the synthesis of DNA, and then affect the G2/M phase, so that the number of cells entering this phase is reduced. The incidence of micronucleus and sperm deformity increased gradually with the dose. Therefore it has potential mutagenic effects and certain genetic toxicity (Ji et al., 2009). However, the content of solanine in the leaves, stems and fruits of S. nigrum will gradually decrease as the plant grows. Preliminary toxicological studies of S. nigrum showed less toxicity and a certain impact on the liver and kidney function. In the future, a large amount of clinical and animal data will be needed to verify the safety of S. nigrum for better use as medicine in the field of clinical and health care and in food homologous products.

CONCLUSION AND FUTURE PERSPECTIVES

This review systematically summarizes the latest findings on the botany, traditional uses, phytochemistry, pharmacology, clinical trials, and toxicity of *S. nigrum*. Regarding the use as a medicinal and edible plant, there are records in the dietary histories of China and India that the leaves and fruits of *S. nigrum* were cooked as food. *S. nigrum* has been used to treat various cancers, diarrhea, fever, itchy skin, dysentery, edema, and other diseases in the indigenous peoples of China, India, Italy, Turkey, Yemen, Jordan, and Libya for more than a thousand years. Regarding the research on the phytochemical constituents of *S. nigrum*, 188 small molecule compounds and dozens of polysaccharides have been isolated and identified. Through systematic analysis, polysaccharides, steroidal saponins, and alkaloids were identified as the representative active components of *S. nigrum* with numerous pharmacological activities, which have been demonstrated in *in vitro* and *in vivo* investigations. Steroidal alkaloids represented by compounds **79** and **100** and polysaccharides represented by SNL-P1a have been considered to be biologically active components with extensive biological properties, including antitumor, anti-inflammatory, immunomodulatory, antimalarial, antibacterial, and antiviral effects. A large number of pharmacological studies have shown that **79** is a very promising candidate for the treatment of cancer. The content of vitamin C in the *S. nigrum* fruit is quite high, which has good nutritional and health value. The antitumor effect of *S. nigrum* polysaccharide is mainly through improving the immunity of the body. To sum up, as a food and medicinal resource, *S. nigrum* has a good health care function and important edible and medicinal value, and deserves more development and research.

However, a number of points also need to be improved: 1) A large number of studies on the *in vitro* and *in vivo* activities of *S. nigrum* extracts are listed in **Table 3**, but the material basis for the pharmacological activities of these crude extracts is still unknown. A large number of compounds have been isolated from *S. nigrum*, but current research on these compounds may be just the tip of the iceberg. Research on the chemical composition of *S. nigrum* mainly focuses on saponins, alkaloids, and polysaccharides, while the research on organic compounds, such as phenolic acids represented by flavonoids, is relatively rare. Therefore, research aimed at clarifying the active ingredients in *S. nigrum*, and the mechanism of action of the active ingredients should be further elucidated. For the trace active components in *S. nigrum*, its structure and activity mechanism can be studied through new technologies such as efficient preparation, computer virtual screening, and target fishing. 2) The composition and content of steroidal saponins and steroidal alkaloids in *S. nigrum* will change with the plant growth. To further explore the material basis of its active components, the composition and content of *S. nigrum* at different growth stages should be identified, and the biosynthetic pathway should be explored. 3) Toxicological studies are critical to assess the safety of herbal medicines, but data on the toxicology of *S. nigrum* remain scarce. It has been reported that

the unripe *S. nigrum* fruit has a certain toxicity and can cause human poisoning and harm to human health. Therefore, it is necessary to carry out systematic toxicity and safety assessment studies on *S. nigrum* extracts and active ingredients to ensure full utilization of drug resources, meet Western standards of evidence-based medicine, and provide accurate evidence for clinical application. By studying the metabolites and metabolic mechanisms of drugs in the body, new drugs with higher biological activity and safer can be found. Therefore, pharmacokinetic, pharmacodynamic, and toxicological research are equally important in the process of drug development. Research on the drug metabolism of *S. nigrum* should be increased. 4) Since the *S. nigrum* plant contains potentially toxic compounds such as compound **79**, reliable analytical methods are required for proper quality control of product development to ensure that potentially toxic components in *S. nigrum* products are kept below tolerated levels. 5) *S. nigrum* fruit is rich in vitamin C and polysaccharides with immunomodulatory effects. The processed products of *S. nigrum* need further research, exploration, and utilization, especially as a formula for fruit juice, fruit wine, and cosmetics.

Taken together, *S. nigrum* has attracted great interest as a medicinal and edible herb because of its rich nutrition and wide range of pharmacological activities. It has great development potential in the fields of functional food and TCM, and also provides resources for the lead compound library in the process of new drug development. However, in addition to providing opportunities, the application of *S. nigrum* also exhibits challenges. Facing the weak links and specific problems of the development of TCM, more time and research efforts need to be devoted to the high-quality development of TCM. We believe that this review can provide a valuable reference for the future development and utilization of *S. nigrum*.

AUTHOR CONTRIBUTIONS

YL and LY obtained the literatures. XC, YY, and XD wrote the manuscript and finalized the paper. XH and GG gave ideas and edited the manuscript. All authors approved the paper for publication.

FUNDING

REFERENCES

Aburjai, T. A., Oun, I. M., Auzi, A. A., and Hudaib, M. M. (2014). Volatile Oil Constituents of Fruits and Leaves of Solanum nigrumL. Growing in Libya. *J. Essent. Oil Bear. Plants* 17 (3), 397–404. doi:10.1080/0972060X.2014.895194

An, H. J., Kwon, K. B., Cho, H. I., Seo, E. A., Ryu, D. G., Hwang, W. J., et al. (2005). Solanum nigrum Produces Nitric Oxide via Nuclear Factor-kappaB Activation in Mouse Peritoneal Macrophages. *Eur. J. Cancer Prev.* 14 (4), 345–350. doi:10.1097/00008469-200508000-00006

Aryaa, A., and Viswanathswamy, A. H. (2017). Effect of *Solanum nigrum Linn* on Acute and Sub-acute Models of Inflammation. *J. Young. Pharm.* 9 (4), 566–570. doi:10.5530/jyp.2017.9.108

Ben-Abdallah, S., Cáceres, L. A., Wang, Z., Renaud, B. J., Lachâal, M., Karray-Bouraoui, N., et al. (2019). Host Plant Defenses of Black (*Solanum nigrum* L.) and Red Nightshade (*Solanum Villosum* Mill.) Against Specialist *Solanaceae* Herbivore *Leptinotarsa decemlineata* (Say). *Arch. Insect Biochem. Physiol.* 101 (2), e21550. doi:10.1002/arch.21550

Cai, Y. D. (2003). *Studies on the fugicidal activity and formulation processing of taraxacum mongolicum. and* Solanum nigrum L. Gansu: Master, Gansu Agricultural University.

Campisi, A., Acquaviva, R., Raciti, G., Duro, A., Rizzo, M., and Santagati, N. A. (2019). Antioxidant Activities of *Solanum nigrum L.* Leaf Extracts Determined in *In Vitro* Cellular Models. *Foods* 8 (2), 63. doi:10.3390/foods8020063

Chang, W., Li, Y., Zhang, M., Zheng, S., Li, Y., and Lou, H. (2017). Solasodine-3-O-β-d-glucopyranoside Kills Candida Albicans by Disrupting the Intracellular Vacuole. *Food Chem. Toxicol.* 106, 139–146. doi:10.1016/j.fct.2017.05.045

Che, Y. F. (2018). Effect of *Solanum nigrum* Fruit on Acute Radiation-Induced Lung Injury after Tumor Radiotherapy and its Effect on Serum Related Inflammatory Cytokines. *World Latest Med. Inf.* 18 (84), 151–152. doi:10.19613/j.cnki.1671-3141.2018.84.126

Chen, Y. J., and Dai, G. H. (2016). Effect of the Extract and Compound from *Solanum nigrum Linn* on Tetranychus Cinnabarinus. *J. Appl. Entomol.* 141, 458–469. doi:10.1111/jen.12358

Chen, Y., Li, S., Sun, F., Han, H., Zhang, X., Fan, Y., et al. (2010). *In Vivo* antimalarial Activities of Glycoalkaloids Isolated from Solanaceae Plants. *Pharm. Biol.* 48 (9), 1018–1024. doi:10.3109/13880200903440211

Chen, Y., Song, Z. K., and Zhang, H. Y. (2020). Optimization Extraction and Antioxidant Activity of Polysaccharide from *Solanum Nigrum* Fruit by Response Surface Methodology. *Food Sci. Tech-Brazil* 45 (07), 209–215. doi:10.13684/j.cnki.spkj.2020.07.036

Chester, K., Zahiruddin, S., Ahmad, A., Khan, W., Paliwal, S., and Ahmad, S. (2019). Bioautography-Based Identification of Antioxidant Metabolites of *Solanum nigrum L.* and Exploration its Hepatoprotective Potential Against D-Galactosamine-Induced Hepatic Fibrosis in Rats. *Pharmacogn. Mag.* 15, 104–110. doi:10.4103/pm.pm_359_18

Chu, Z. X., Lu, M., and Xiong, S. (2019). Research Advances on Pharmacological Activities and Pharmacokinetics of Scopoletin. *Chem. Res.* 30 (14), 434–440. doi:10.14002/j.hxya.2019.04.017

Churiyah, C., Ningsih, S., and Firdayani, F. (2020). The Cytotoxic, Apoptotic Induction, aand Cell Cycle Arrest Activities of *Solanum nigrum L.* Ethanolic Extract on MCF-7 Human Breast Cancer Cell. *Asian Pac J Cancer Prev.* 21 (12), 3735–3741. doi:10.31557/APJCP.2020.21.12.3735

Dai, S., Li, M., Fei, J. R., Ni, H., Huang, Z. W., and Ding, P. J. (2018). Curative Effect of Longkui Yinxiao Tablet Combined With Liangxue Huayu Decoction in the Treatment of Psoriasis and Its Influence on Serum Level of Related Factors. *J. Liaoning Univ. Tradit. Chin. Med.* 20 (12), 198–201. doi:10.13194/j.issn.1673-842x.2018.12.057

Ding, X., Zhu, F. S., Li, M., and Gao, S. G. (2012a). Induction of Apoptosis in Human Hepatoma SMMC-7721 Cells by Solamargine From *Solanum nigrum L. J. Ethnopharmacol.* 139, 599–604. doi:10.1016/j.jep.2011.11.058

Ding, X., Zhu, F., and Gao, S. (2012b). Purification, Antitumour and Immunomodulatory Activity of Water-Extractable and Alkali-Extractable Polysaccharides From *Solanum nigrum L. Food Chem.* 131, 677–684. doi:10.1016/j.foodchem.2011.09.060

Editorial Committee of Flora of China (1979). *Chinese Academy of Sciences. Flora of China*, 67. Beijing: Science Press, 76.

Editorial Committee of Nanjing University of Chinese Medicine (2006). *Dictionary ofChinese Materia Medica*. second ed. Shanghai: Science & Technology Press, 873–874.

Editorial Committee of State Administration of traditional Chinese Medicine (1999). *Zhonghua Bencao*, 7. Shanghai: Science and Technology Press, 309–311.

El-Meligy, R. M., Awaad, A. S., Soliman, G. A., Bacha, A. B., Alafeefy, A. M., and Kenawy, S. A. (2015). Prophylactic and Curative Anti-Ulcerative Colitis Activity and The Possible Mechanisms of Action of Some Desert Plants. *J. Enzyme Inhib. Med. Chem.* 30 (2), 250–258. doi:10.3109/14756366.2014.915394

Flora of China (2007). *Flora of China*. Available at: http://www.iplant.cn/info/Solanum%20nigrum?t=z..

Gao, S. H., Su, Z. Z., Yang, L. J., and Li, Z. Y. (2021). Chemical Components From Stems of *Solanum nigrum* by LC-MS and NMR. *Chin. Tradit. Herb. Drugs.* 52 (5), 1263–1273. doi:10.7501/J.issn.0253-2670.2021.05.006

Ge, J. Q. (2019). Inhibitory Effects of Plants Extract of *Trapa pinosa* and *Solanum Nigrum* on Pathogenic Bacteria. *J. Jingling, Tech.* 35 (1), 88–92. doi:10.16515/j.cnki.32-1722/n.2019.01.019

Geng, Q. S., Zhu, Z. J., Wang, W. B., Shen, Z. B., Li, L. F., Xue, W. H., et al. (2020). Study on the Biological Mechanism of the Action of Nightshade Against Lung Cancer by Using Network Pharmacology. *Chin. J. Clin. Pharmacol.* 36 (11), 1588–1591. doi:10.13699/j.cnki.1001-6821.2020.11.051

Guo, R., Li, Y., and Wang, P. (2020). Evaluation on Antioxidant and Anti-Inflammation *In Vitro* of extracts of three *Solanum Nigrum L.* Berries. *Mod. Food Sci. Technol.* 36 (2), 94–101. doi:10.13982/j.mfst.1673-9078.2020.2.014

Hammami, H., Mezghani-Jarraya, R., Damak, M., and Ayadi, A. (2011). Molluscicidal Activity of Various Solvent Extracts from *Solanum nigrum* var. villosum L. aerial Parts Against *Galba truncatula. Parasite* 18, 63–70. doi:10.1051/parasite/2011181063

Han, Q. (2014). *Analysis of GSTA1 on Ethanol Induced Mice Hepatocytes Injury and Hepatoprotective Role of* Solanum nigrum Linn. Heilongjiang: Master, Northeast Agricultural University.

He, J., Zhou, C. D., Ma, B. Z., Liu, F., Liu, X., and Zhao, T. (2015). Research Progress on Chemical Constituents and Antitumor Pharmacological Activities of *Solanum nigrum. China Pharm.* 26 (31), 4433–4436. doi:10.6039/j.issn.1001-0408.2015.31.37

Heo, K. S., and Lim, K. T. (2004). Antioxidative effects of Glycoprotein Isolated from *Solanum nigrum L. J. Med. Food* 7 (3), 349–357. doi:10.1089/jmf.2004.7.349

Hsu, J. D., Kao, S. H., Tu, C. C., Li, Y. J., and Wang, C. J. (2009). *Solanum nigrum* l. Extract Inhibits 2-Acetylaminofluorene-Induced Hepatocarcinogenesis Through Overexpression of Glutathione s-Transferase and Antioxidant enzymes. *J. Agric. Food Chem.* 57, 8628–8634. doi:10.1021/jf9017788

Hu, B., An, H. M., Yan, X., Zheng, J. L., Huang, X. W., and Li, M. (2019). Effects of Solanine on Proliferation and Apoptosis of Colorectal Cancer HCT116 Cells. *Acta Chin. Med. Pharmacol.* 47 (1), 61–63. doi:10.19664/j.cnki.1002-2392.190016

Huang, D. B., and Guan, J. (2013). Clinical Study of *Solanum nigrum* Mixture on Quality of Life and Immune Function in Patients with Advanced Liver Cancer. *Lishizhen Med. Mater. Med. Res.* 24 (07), 1676–1678. doi:10.3969/j.issn.1008-0805.2013.07.058

Huang, M. M., Liu, M. Y., Li, B. H., and Li, K. (2020). Solanine Regulates Proliferation and Apoptosis of Gastric Cancer Cells By Targeting miR-140/MACC1 pathway. *Chin. J. Clin. Pharmacol.* 36 (16), 2440–2443. doi:10.13699/j.cnki.1001-6821.2020.16.017

Jainu, M., and Devi, C. S. (2006). Antiulcerogenic and Ulcer Healing Effects of *Solanum nigrum (L.)* on Experimental Ulcer Models: Possible Mechanism for the Inhibition of Acid Formation. *J. Ethnopharmacol.* 104 (1-2), 156–163. doi:10.1016/j.jep.2005.08.064

Jeong, J. B., De Lumen, B. O., and Jeong, H. J. (2010). Lunasin Peptide Purified from *Solanum nigrum* L. Protects DNA From Oxidative Damage by Suppressing the Generation Of Hydroxyl Radical Via Blocking Fenton Reaction. *Cancer Lett.* 293, 58–64. doi:10.1016/j.canlet.2009.12.019

Ji, B. Y., Wu, P., and Lang, L. (2009). Progress in Toxicological Research of Solanine. *Chin. Tradit. Herb. Drugs.* 40, 29–31.

Kang, H., Jeong, H. D., and Choi, H. Y. (2011). The Chloroform Fraction of Solanum Nigrum Suppresses Nitric Oxide and Tumor Necrosis Factor-α in

LPS-Stimulated Mouse Peritoneal Macrophages Through Inhibition of p38, JNK and ERK1/2. *Am. J. Chin. Med.* 39 (6), 1261–1273. doi:10.1142/S0192415X11009548

Kang, M., Wang, R. S., Liu, W. Q., and Tang, A. Z. (2014). Research on the Inhibition of Nasopharyngeal Carcinoma Cells Growth by Compound Tianxian Capsule Drug-Containing Serum *In Vitro. Chin. J. Mod. Med.* 24 (1), 5–9.

Kong, H. R., Dai, S. J., Chen, H., Lou, B., Ni, X. F., and Sun, H. W. (2020). α-Solanine Inhibits Epithelial-Mesenchymal Transition in Trichostatin A-Resistant Human Pancreatic Cancer Cells Through The WNT Signaling Pathway. *J. Hepatopancreatobiliary Surg.* 32 (2), 89–96. doi:10.11952/j.issn.1007-1954.2020.02.006

Lai, Y. H., Ma, Z. C., Yan, H. Y., and Mao, H. X. (2005). Acute Toxicity and Genetic Toxicity Tests of *Solanum Nigrum L* Juice. *Carcinog. Teratog. Mutagen.* 17 (3), 54–58. doi:10.3969/j.issn.1004-616X.2005.01.018

Li, Y., Chang, W., Zhang, M., Ying, Z., and Lou, H. (2015). Natural Product Solasodine-3-O-β-D-Glucopyranoside Inhibits the Virulence Factors of Candida Albicans. *Fems Yeast Res.* 15. doi:10.1093/femsyr/fov060

Li, C. X., Song, X. Y., Zhao, W. Y., Yao, G. D., Lin, B., Huang, X. X., et al. (2019). Characterization of Enantiomeric Lignanamides From Solanum Nigrum l. And their Neuroprotective Effects Against MPP$^+$-Induced SH-SY5Y Cells Injury. *Phytochemistry* 161, 163–171. doi:10.1016/j.phytochem.2019.01.001

Li, L. M., Huang, J. P., He, W. F., Li, Q. P., Wu, W. G., and Long, S. K. (2020). Molecular Mechanism of Apoptosis Induced by Solasonine Extracted from *Solanum nigrum* in A549 Cells. *Tradit. Chin. Drug Res. Clin. Pharmacol.* 31 (12), 1422–1427. doi:10.19378/j.issn.1003-9783.2020.12.006

Li, J. H., Li, S. Y., Shen, M. X., Qiu, R. Z., Fan, H. W., and Li, Y. B. (2021). Anti-Tumor Effects of Solanum Nigrum l. Extraction on c6 High-Grade Glioma. *J. Ethnopharmacol.* 274 (1), 114034. doi:10.1016/j.jep.2021.114034

Li, N., Li, D. P., Ding, J. X., Xie, X. W., Zheng, X. L., Yao, X. Q., et al. (2021). Effects of External Application of *Solanum nigrum* ointment on Serum SOD, MDA and Synovial Morphology in Rabbits With Knee Synovitis. *J. Gansu Univ. Med.* 38 (1), 16–20. doi:10.16841/j.issn1003-8450.2021.01.04

Li, J. (2009). *Study on Anti-Cervical Cancer And Immunomodulating Effects of Sub-Fraction 1a of Polysaccharides From* solanum nigrum linne. Hebei: Doctor, Yanshan University.

Li, G. Y. (2010a). *Studies on Isolation, Purification, Structural Identification And Anti-H22 Tumor Activity of Polysaccharides From* Salanum nigrum L. Jiangsu: Master, Nanjing Agriculture University.

Li, X. C. (2010b). *Studies on chemical constituents of* Solanum nigrum L. Jilin: Master, Jilin University.

Li, C. (2019). *Effect of α-Solanine on Migration and Invasion of Human Trophoblast Cell.* Changsha: Master, Hunan Agriculture University.

Liao, C., Liang, H., Zhang, R. M., Sun, C., Wu, X. L., Li, L., et al. (2020). Effect of chloroform extract from *Solanum nigrum L* on clear renal cell carcinoma. *J. Clin. Urol.* 36 (6), 454–457. doi:10.13201/j.issn.1001-1420.2020.06.008

Lin, H. M., Tseng, H. C., Wang, C. J., Chyau, C. C., Liao, K. K., Peng, P. L., et al. (2007). Induction of autophagy and apoptosis by the extract of *Solanum nigrum Linn* in HepG2 cells. *J. Agric. Food Chem.* 55, 3620–3628. doi:10.1021/jf062406m

Lin, H. M., Tseng, H. C., Wang, C. J., Lin, J. J., Lo, C. W., and Chou, F. P. (2008). Hepatoprotective effects of *Solanum nigrum Linn* extract against CCl(4)-induced oxidative damage in rats. *Chem. Biol. Interact.* 171, 283–293. doi:10.1016/j.cbi.2007.08.008

Ling, B., Xiao, S., Yang, J., Wei, Y., Sakharkar, M. K., and Yang, J. (2019). Probing the antitumor mechanism of *Solanum nigrum l.* Aqueous extract against human breast cancer mcf7 cells. *Bioeng. (Basel)* 6 (4), 112. doi:10.3390/bioengineering6040112

Liu, S., Song, Y. J., Wang, W. W., Zou, S. H., Li, H. J., Wang, C. H., et al. (2019a). Phenols from *Solanum nigrum. Chin. Tradit. Pat. Med.* 41 (4), 828–831. doi:10.3969/j.issn.1001-1528.2019.04.023

Liu, S., Hu, X. S., and Lin, H. S. (2019b). Mechanism of Xinlikang Capsule inhibiting the proliferation of lung cancer A549 cells and the analysis of its effective componets. *Chin. J. Cancer Prev. Treat.* 26 (9), 613–618. doi:10.16073/j.cnki.cjcpt.2019.09.003

Liu, J. H., Lyu, D. Y., Zhou, H. M., Kuang, W. H., Chen, Z. X., and Zhang, S. J. (2020). Study On Molecular Mechanism Of Solanum Nigrum In Treatment Of Hepatocarcinoma Based On Network Pharmacology And Molecular Docking.

Zhongguo Zhong Yao Za Zhi 45 (1), 163–168. doi:10.19540/j.cnki.cjcmm.20190807.401

Liu, K., Wang, Y., Nie, T., Hao, J. Q., Huang, R., and Jiang, J. B. (2021). Effects of Total alkaloids of *Solanum nigrum* on mice plasma cell myeloma through NF-κB/IRF4 signaling pathway. *West. J. Tradit. Chin. Med.* 34 (2), 9–13. doi:10.12174/j.issn.2096-9600.2021.02.03

Liu, Z., Ma, C., Tang, X., Tang, Q., Lou, L., Yu, Y., et al. (2019). The Reciprocal interaction between LncRNA CCAT1 and miR-375-3p contribute to the downregulation of IRF5 gene expression by Solasonine in HepG2 human hepatocellular carcinoma Cells. *Front. Oncol.* 9, 1081. doi:10.3389/fonc.2019.0108

Liu, Y. (2003). Study on the composition of polysaccharices from *Solanum Nigrum L. J. Chang. Univ. Sci. Technol. Nat. Sci.* 15 (4), 20–21.

Liu, T. (2005). *The studies on the extraction, purifieation and determination of active compositions in* solanum nigrum L. Hunan: Master, Central South University.

Madanat, H. M., Al Antary, A., and Abu Zarqa, M. H. (2016). Toxicity of six ethanol plant extracts against the green peach aphid *myzus persicae* sulzer (homoptera: aphididae). *Fresen Environ. Bull.* 25 (3), 706–718.

Mazher, M., Anjum, M., Mushtaq, W., Noshad, Q., and Malik, Z. N. (2017). Antifungal assay of *Solanum nigrum Linn.* fruit, leaves and stems extracts in different solvents. *Int. J. Biosci.* 10 (4), 380–385. doi:10.12692/ijb/10.4.380-385

Mei, Q. X., Zhang, Z. Q., Lin, H., Guan, J., Jiang, Q. M., and Li, H. N. (2011). Research progress on the pharmacological effects and clinical application of *Solanum nigrum* in the treatment of tumors. *China Pharm.* 23 (39), 3735–3737. doi:10.6039/j.issn.1001-0408.2012.39.31

Mo, L. J., He, D., Zhou, C. R., and Ling, L. L. (2014). Experimental study on acute toxicity of raw *Solanum nigrum* and *Solanum nigrum* juice. *China health care Nutr.* 5, 2889–2890. doi:10.3969/j.issn.1004-7484(x).2014.05.610

Ogunsuyi, O. B., Ademiluyi, A. O., Oboh, G., Oyeleye, S. I., and Dada, A. F. (2018). Green leafy vegetables from two Solanum spp. (*Solanum nigrum L* and *Solanum macrocarpon L*) ameliorate scopolamine-induced cognitive and neurochemical impairments in rats. *Food Sci. Nutr.* 6, 860–870. doi:10.1002/fsn3.628

Ogunsuyi, O. B., Oboh, G., Özek, G., and Göger, F. (2020). Solanum vegetable-based diets improve impairments in memory, redox imbalance, and altered critical enzyme activities in *Drosophila melanogaster* model of neurodegeneration. *J. Food Biochem.* 45 (3), e13150. doi:10.1111/jfbc.13150

Ogunsuyi, O. B., Olagoke, O. C., Afolabi, B. A., Oboh, G., Ijomone, O. M., Barbosa, N. V., et al. (2021). Dietary inclusions of Solanum vegetables mitigate aluminum-induced redox and inflammation-related neurotoxicity in *drosophila melanogaster* model. *Nutr. Neurosci.*, 1–15. doi:10.1080/1028415X.2021.1933331

Ohno, M., Murakami, K., El-Aasr, M., Zhou, J.-R., Yokomizo, K., Ono, M., et al. (2012). New spirostanol glycosides from *Solanum nigrum* and S. *jasminoides. J. Nat. Med.* 66, 658–663. doi:10.1007/s11418-012-0637-z

Park, J. S., Bang, O. S., and Kim, J. (2014). Screening of Stat3 inhibitory effects of Korean herbal medicines in the A549 human lung cancer cell line. *Integr. Med. Res.* 3, 67–73. doi:10.1016/j.imr.2013.10.004

Peng, C. H., Cheng, J. J., Yu, M. H., Chung, D. J., Huang, C. N., and Wang, C. J. (2020). *Solanum nigrum* polyphenols reduce body weight and body fat by affecting adipocyte and lipid metabolism. *Food Funct.* 11, 483–492. doi:10.1039/c9fo02240f

Perez, R. M., Perez, J. A. J. A., Garcia, L. M., and Sossa, M. H. (1998). Neuropharmacological activity of *Solanum nigrum* fruit. *J. Ethnopharmacol.* 62, 43–48. doi:10.1016/s0378-8741(98)00059-2

Pu, Y. W. (2020). *Extraction and isolation of* Solanum nigrum *polysaccharide and its immunomodulatory mechanism.* Chongqing: Master, Chongqin Medical University.

Rahuman, A. A., Bagavan, A., Kamaraj, C., Vadivelu, M., Zahir, A. A., Elango, G., et al. (2009). Evaluation of indigenous plant extracts against larvae of *Culex quinquefasciatus* Say (Diptera: Culicidae). *Parasitol. Res.* 104, 637–643. doi:10.1007/s00436-008-1240-9

Rawani, A., Ghosh, A., and Chandra, G. (2010). Mosquito larvicidal activities of *Solanum nigrum L.* leaf extract against *Culex quinquefasciatus* Say. *Parasitol. Res.* 107, 1235–1240. doi:10.1007/s00436-010-1993-9

Rawani, A., Ghosh, A., and Chandra, G. (2013). Mosquito larvicidal and antimicrobial activity of synthesized nano-crystalline silver particles using leaves and green berry extract of *Solanum nigrum L.* (Solanaceae: Solanales). *Acta Trop.* 128, 613–622. doi:10.1016/j.actatropica.2013.09.007

Rawani, A., Ray, A. S., Ghosh, A., Sakar, M., and Chandra, G. (2017). Larvicidal activity of phytosteroid compounds from leaf extract of *Solanum nigrum* against Culex vishnui group and Anopheles subpictus. *BMC Res. Notes* 10 (1), 135. doi:10.1186/s13104-017-2460-9

Sabudak, T., Ozturk, M., and Alpay, E. (2017). New bioflavonoids from *Solanum nigrum* L. by anticholinesterase and anti-tyrosinase activities-guided fractionation. *Rec. Nat. Prod.* 11 (2), 130–140.

Sharma, B. K., Iyer, D., and Patil, U. K. (2012). Bioactivity guided fractionation in experimentally induced hyperlipidemia in rats and characterization of phytoconstituent from *Solanum nigrum*. *J. Herbs, Spices Med. Plants* 18, 257–267. doi:10.1080/10496475.2012.688933

Shi, F., Wang, C., Wang, L., Song, X., Yang, H., Fu, Q., et al. (2019). Preparative isolation and purification of steroidal glycoalkaloid from the ripe berries of Solanum nigrum L. by preparative HPLC-MS and UHPLC-TOF-MS/MS and its anti-non-small cell lung tumors effects *In Vitro* and *In Vivo*. *J. Sep. Sci.* 42, 2471–2481. doi:10.1002/jssc.201801165

Sivaraj, C., Yamini, S., Yahavi, A., Kumar, R. P., Arumugam, P., and Manimaaran, A. (2020). Antioxidant, antimicrobial activities and GCMS analysis of fruit extract of *Solanum nigrum* L. *J. Pharmacogn. Phytochem.* 9 (4), 1114–1121.

Sohrabipour, S., Kharazmi, F., Soltani, N., and Kamalinejad, M. (2013). Effect of the administration of *Solanum nigrum* fruit on blood glucose, lipid profiles, and sensitivity of the vascular mesenteric bed to phenylephrine in streptozotocin-induced diabetic rats. *Med. Sci. Monit. Basic Res.* 19, 133–140. doi:10.12659/MSMBR.883892

Sun, L., Zhao, Y., Li, X., Yuan, H., Cheng, A., and Lou, H. (2010). A lysosomal-mitochondrial death pathway is induced by solamargine in human K562 leukemia cells. *Toxicol vitro* 24, 1504–1511. doi:10.1016/j.tiv.2010.07.013

Tai, B. H., Van Doan, V., Yen, P. H., Nhiem, N. X., Cuc, N. T., Trang, D. T., et al. (2018). Two new steroidal alkaloid saponins from the whole plants of *Solanum nigrum*. *Nat. Product. Commun.* 13 (11), 1934578X1801301–1460. doi:10.1177/1934578x1801301111

Teng, F., Yuan, C. P., and Wang, P. (2014). Study on antioxidant activity of extracts from *Solanum nigrum* L.berries and analysis of the active ingredients. *J. Anhui Agric. Sci.* 42 (19), 6217–6219. doi:10.13989/j.cnki.0517-6611.2014.19.040

Version 1.1 The Plant List (2013). The Plant List. Available At: http://www.theplantlist.org/.

Tian, H. L., Yu, S. W., Pei, Y., Shen, Z. D., Dong, R. J., and Kang, D. Z. (2019). Effects of crude polysaccharide from *Solanum nigrum* L. on immune system of mice. *J. Yanbian Med. Coll.* 42 (1), 8–11. doi:10.16068/j.1000-1824.2019.01.003

Tsuyoshi, I., Hidetsugu, T., Takehiko, H., and Toshihiro, N. (2003). Cytotoxic activity of steroidal glycosides from solanum plants (Pharmacognosy). *Biol. Pharm. Bull.* 26 (8), 1198–1201.

Veerapagu, M., Jeya, K. R., Sankaranarayanan, A., and Rathika, A. (2018). *In Vitro* antioxidant properties of methanolic extract of *Solanum nigrum* L. fruit. *Pharma Innovation J.* 7 (5), 371–374.

Wang, L. Y., Wang, N. L., and Yao, X. S. (2007). Non-Saponins from Solanum nigrum L. *Zhong Yao Cai* 30 (7), 792–794. doi:10.13863/j.issn1001-4454

Wang, H. C., Chung, P. J., Wu, C. H., Lan, K. P., Yang, M. Y., and Wang, C. J. (2010). *Solanum nigrum* L. polyphenolic extract inhibits hepatocarcinoma cell growth by inducing G2/M phase arrest and apoptosis. *J. Sci. Food Agric.* 91, 178–185. doi:10.1002/jsfa.4170

Wang, Y., Xiang, L., Yi, X., and He, X. (2017). Potential anti-Inflammatory steroidal saponins from the berries of *solanum nigrum* L. (European black nightshade). *J. Agric. Food Chem.* 65 (21), 4262–4272. doi:10.1021/acs.jafc.7b00985

Wang, P., Wang, Y. D., Zhao, W. B., Zhang, S. S., and Qi, X. M. (2019). Effects of *Solanum nigrum* alkaloids combined with curcumone on energy metabolism of renal cell carcinoma cells. *Chin. Rem. Clin.* 19 (18), 3213–3215. doi:10.1186/s12935-019-0981-0

Wang, Y., Hong, T., Chen, L., Chu, C., Zhu, J., Zhang, J., et al. (2020). The natural extract degalactotigonin exerts antitumor effects on renal cell carcinoma cells through repressing YAP. *Transl. Cancer Res.* 9 (12), 7550–7561. doi:10.21037/tcr-20-1864

Wang, L. Y. (2007). *Continue study on cytotoxic active constituents and study on quality control of* Solanum nigrum L. Liaoning: Master, Shenyang Pharmaceutical University.

Wu, X. W. (2011). *A virtual screening research for the antitumor activity of the ingredients in LSYQD*. Henan: Master, Zhengzhou University.

Wu, J. B. (2019). *Solanine promotes the drug sensitivity of esophageal cancer cells to 5-FU/DDP by inducing the expression of microRNA-138*. Henan: MasterZhengzhou University.

Xiang, L., Wang, Y., Yi, X., and He, X. (2018). Anti-inflammatory steroidal glycosides from the berries of *Solanum nigrum* L. (European black nightshade). *Phytochemistry* 148, 87–96. doi:10.1016/j.phytochem.2018.01.019

Xiang, L., Wang, Y., Yi, X., and He, X. (2019). Steroidal alkaloid glycosides and phenolics from the immature fruits of *Solanum nigrum*. *Fitoterapia* 137, 104268. doi:10.1016/j.fitote.2019.104268

Xiao, G. W., and Zeng, H. P. (1998). Isolation, purification and identification of polysaccharides from black nightshade (*Solanum nigrum*). *Chin. J. Pharm. Biotechnol.* 5 (3), 157–160. doi:10.19526/j.cnki.1005-8915.1998.03.008

Xiao, G. W., and Zeng, H. P. (2000). Isolation, purification and identification of polysaccharides from black nightshade (*Solanum nigrum*) (II). *Chin. Tradit. Herb. Drugs.* 31 (3), 162–164.

Xu, H. Y., Kong, L. X., and Ni, G. L. (2015). Effects of longkui suppository treating experimental chronic prostatitis rats. *Hebei J. Tradit. Chin. Med.* 37 (1), 70–72+163. doi:10.3969/j.issn.1002-2619.2015.01.027

Yan, X., and Hu, B. (2019). "Effect and mechanism of solanine on anoikis and apoptosis of colorectal cancer RKO cells," in Abstracts of the 17th National Cancer academic conference of integrated traditional Chinese and Western Medicine.17

Yan, X., Li, M., Chen, L., Peng, X., Que, Z. J., An, H. M., et al. (2020). α-Solanine inhibits growth and metastatic potential of human colorectal cancer cells. *Oncol. Rep.* 43, 1387–1396. doi:10.3892/or.2020.7519

Yang, M. Y., Hsu, L. S., Peng, C. H., Shi, Y. S., Wu, C. H., and Wang, C. J. (2010). Polyphenol-rich extracts from Solanum nigrum attenuated PKC alpha-mediated migration and invasion of hepatocellular carcinoma cells. *J. Agric. Food Chem.* 58, 5806–5814. doi:10.1021/jf100718b

Yang, Y., Hu, X. X., Zhou, L. L., Gao, S. L., and Ding, X. (2014). Protective effect of *Solanum nigrum* polysaccharide on CCl_4 induced acute liver injury in mice. *Chin. Tradit. Pat. Med.* 36 (12), 2602–2605. doi:10.3969/j.issn.1001-1528.2014.12.036

Yang, M. Y., Hung, C. H., Chang, C. H., Tseng, T. H., and Wang, C. J. (2016). *Solanum nigrum* suppress angiogenesis-mediated tumor growth through inhibition of the AKT/mTOR pathway. *Am. J. Chin. Med.* 44 (16), 1273–1288. doi:10.1142/S0192415X16500713

Yang, X. F., Wen, Q. X., and Zhang, J. R. (2017). To investigate the effect of morel on prevention and treatment of liver cancer. *Chin. J. Integr. Tradit. West. Med. Liver Dis.* 27 (06), 353–355. doi:10.3969/j.issn.1005–0264.2017.06.012

Yang, Y. (2014). *The therapeutic basis and hepatoprotective activities of* Solanum nigrum L. Jiangsu: Master, Nanjing agricultural University.

Yao, H., Wang, L., Tang, X., Yang, Z., Li, H., Sun, C., et al. (2020). Two novel polysaccharides from *Solanum nigrum* L. exert potential prebiotic effects in an *In Vitro* fermentation model. *Int. J. Biol. Macromol.* 159, 648–658. doi:10.1016/j.ijbiomac.2020.05.121

Ye, L. F., and Gao, Z. W. (2019). Study of *Solanum nigrum* n-butanol extract on the proliferation of human colorectal cancer SW480 and its mechanism. *World J. Integr. Tradit. West Med.* 14 (3), 356–358+363. doi:10.13935/j.cnki.sjzx.190315

Yeom, Y.-E., Kim, M. A., Kim, J., and Lee, C.-M. (2019). Anti-inflammatory effects of the extract of *Solanum nigrum* L. on an acute ear edema mouse model. *Mater. Technol.* 34 (14), 851–857. doi:10.1080/10667857.2019.1638671

Yin, S., Jin, W., Qiu, Y., Fu, L., Wang, T., and Yu, H. (2022). Solamargine induces hepatocellular carcinoma cell apoptosis and autophagy via inhibiting LIF/miR-192-5p/CYR61/Akt signaling pathways and eliciting immunostimulatory tumor microenvironment. *J. Hematol. Oncol.* 15 (32), 1–6. doi:10.1186/s13045-022-01248-w

Zhang, H., Tian, F., Jiang, P., Qian, S., Dai, X., Ma, B., et al. (2021). Solasonine suppresses the proliferation of acute monocytic leukemia through the activation of the AMPK/FOXO3A axis. *Front. Oncol.* 10. doi:10.3389/fonc.2020.614067

Zhang, L. M. (2015). Clinical observation of entecavir combined with Loulian Capsules in the treatment of HBeAg liver cirrhosis in decompensated stage. *Med. Inf.* 045, 50–51.

Zhang, X. H. (2018). *Effect of solamargine extracted from* Solanum Nigrum *on growth and metastasis on the mechanism of cholangiocarcinoma cells*. Jiangsu: Doctor, Nanjing University of Chinese Medicine.

Zhao, S. Y., Lei, Y. J., Ma, S. M., and Gao, M. (2019). *Solanum nigrum* combined with KLF16 gene synergistically inhibit glioma cell proliferation and induce apoptosis. *J. Mol. Diagn Ther.* 11 (4), 303–309.

Zhao, Y. (2010). *Chemical constituents of two solanum species, microbial transformation and biological activities*. Shandong: Doctor, Shandong University.

Zhou, X. L. (2006). *Study on anticancer active component of* Solanum nigrum. Liaoning: Doctor, Shenyang Pharmaceutical University.

Zhu, J. Y., Ma, F. H., and Xu, Y. H. (2019). *Solanum nigrum* inhibits proliferation and promote apoptosis of ovarian cancer cells through regulates the expression of p-AKT, cleaved Caspase-3 and p53 protein. *Shaanxi J. Tradit. Chin. Med.* 40 (5), 556–560. doi:10.3969/j.issn.1000-7369.2019.05.004

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.