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- Review Article

A COMPREHENSIVE REVIEW ON BLACK NIGHTSHADE (*SOLANUM NIGRUM*): CHEMICAL CONSTITUENTS, PHARMACOLOGICAL ACTIVITIES AND ITS ROLE IN COVID-19 TREATMENT

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Abstract

Three-fourths of the world's population uses 30% of all plant species as a safe source of disease control and treatment. Similarly, *Solanum nigrum* (Black nightshade), a therapeutic herb with small, spherical berry fruits, is used as an herbal remedy to treat many different diseases, including respiratory diseases. According to recent research, this plant can aid in the management of COVID-19. Alkaloids, flavonoids, steroids, glycoproteins, tannins, polysaccharides, polyphenolic compounds etc. are found in this plant. Among them, polyphenolic compounds are mostly responsible for showing various pharmacological activity. Anti-tumor, antioxidant, anti-diabetic, anti-inflammatory, anti-seizure, immunostimulant, hepatoprotective, antimicrobial activities are shown by *S. nigrum* according to multiple studies. The aim of this article is to compile different aspect of this plant like plant description, uses, chemical constituents, pharmacological activities and especially its role in the management of COVID-19 and probable mechanism behind this role.

Keywords: Solanum nigrum, Black nightshade, Phytochemical analysis, Pharmacological activities, COVID-19, Pathogenesis.

Introduction

Pharmaceutical lead compounds have been obtained from medicinal plants since the early days. They are considered rich sources of traditional remedies, and also many modern medicines are derived from them. Dating back to the prehistoric period, plants are utilized for medical purposes. Early human beings, depending only on their instinct, taste and experience, used plants to treat their illnesses. Herbs were described in ancient Egyptian papyrus, Unani texts, and Chinese writings. There is evidence that people have

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used plants as medicine for more than 4000 years, including Indian Vaids, Unani Hakims, and people from European and Mediterranean cultures (Khan 2016; Khan *et al.,* 2009; Dar 2017). According to published data, plants and plant extracts are the basic source of health care for almost 75% of the global population. And more than 30% of all plant species have been used for medical reasons at one time or another. The usage of medicinal plants is seen to be relatively safe, as there is no or very few side effects. The fact that these medicines are in touch with nature is the best thing. In addition, herbal medicines are used by people of all ages and genders (Khan, 2016; Silori and Badola, 2000). There is a bright future for medicinal plants, as there are over half a million plants on the planet, the majority of which have not yet been investigated for their medicinal properties, and their hidden medicinal potential could play significant role in present and future studies (Dar, 2017).

S. nigrum, generally known as black nightshade in English, Makoi in Hindi and Bengali local name is Kakmachi, is a dicot weed which belongs to the Solanaceae family. This medicinal plant has long been utilized for a range of diseases such as liver disorder, inflammation, chronic skin problems, painful periods, diarrhea, fever, eye infections, hydrophobia, and so forth. And for these medicinal purposes leaves, whole plant and roots are used whereas black colored fruits of *S. nigrum* cannot be used as they possess toxicity (mainly because of high concentration of solanine). This plant is mostly seen in the Europe, Africa and Indian continent. Only few countries semi-cultivate this plant, but generally it grows spontaneously on waste lands, beside fences and roads and as weeds in cultivated lands (Jain *et al.,* 2011; Saleem *et al.,* 2009; Chauhan *et al.,* 2012; Zhou *et al.,* 2006).

S. nigrum is an annual herb, which is 25 to 100 cm long, erect, bifurcately branched, suffrutescent and pubescent. It has ovate or oblong or lanceolate, toothless or sinuate-toothed, glabrous and dull dark green color leaves. The plant contains 3-8 small white flowers with a little petiole and five petals in extra-axillary umbels. Generally, black and reddish brown berries are the two types of fruit found in two varieties of *S. nigrum*. They are small, globose and only 8-10 mm in diameter. They turn black when ripe and these black colored ones are toxic (Saleem *et al.,* 2009; Chauhan *et al.,* 2012; Zhou *et al.,* 2006).

A large amount of chemical compounds is present in *S. nigrum* and they show various pharmacological activities. The main chemical constituents are alkaloids, flavonoids, steroids, glycoproteins, tannins, polysaccharides, and polyphenolics such as caffeic acid, catechin, gallic acid, protocatechuic acid, rutin, epicatechin, etc. The major acid

constituents of *S. nigrum* are citric acid, malic acid, acetic acid, and tartaric acid. This plant also contains some important minerals like Mg, K, Ca, Fe, Na, Mn, Zn etc. Also, some researchers discovered that the fruit and root of this plant contains ascorbic acid and the fruit contains the highest concentration. Whereas, the seeds are rich of lipid content and have moderate amount of protein (17.63%). The phytochemical analysis of the plant gives us some important qualitative value such as, ash values for leaf, fruit and stem are 3.928%, 6.723% and 11.90%, respectively, whereas crude fibre values are 8.42%, 15.19% and 14.73%, respectively. Solanine, a deadly glycoalkaloid present throughout most of the plant as a natural defense system, accounts for 95% of the total alkaloid content of *S. nigrum*. Although, the raw fruit has the highest quantity of solanine, the concentration decreases eventually with fruit maturation (Jain *et al.,* 2011; Saleem *et al.,* 2009; Chauhan *et al.,* 2012; Zhou *et al.,* 2006; An *et al.,* 2006). Researchers identified six novel steroidal saponins, which are collectively known as solanigrosides, and one known saponin, degalactotigonin. Again two new disaccharides and steroidal saponins, called nigrumnins I and II have been isolated from *S. nigrum* (Saleem *et al.,* 2009; Chauhan *et al.,* 2012; Akubugwo *et al.,* 2007). Like other *Solanum* species, *S. nigrum* possesses diverse pharmacological activities like anti-tumorigenic, antioxidant, anti-inflammatory, anti-diabetic (in Sprague Dawley rats and albino rats), anti-HCV, anti-cancer (on HeLa cell line), anti- diarrheal, immunostimulant, hepatoprotective (against CCl4 induced liver damage in rats), cardioprotective, analgesic, diuretic, antipyretic agent, antimicrobial, anti-convulsant, antiulcerogenic etc (Lin *et al.,* 2008; Jainu and Devi, 2006; Parez *et al.,* 1998). Also, studies revealed that *S. nigrum*'s fruits have neuropharmacological activities. It showed a potent CNS-depressive effect in animal studies (Parez *et al.,* 1998).

As this plant possesses various pharmacological activities *S. nigrum* has been broadly used in the oriental medicine. For example, leaves are used for the cure of skin problems, rheumatic gout, dropsy and nervous disorders. Flowers and berries extracts are used for the treatment of cough, erysipelas, diarrhea, opthalmopathy and rabies. Even roots are employed in opthalmopathy, otopathy, hepatitis and rhinopathy. Mostly, people from different parts of Africa and India follow these traditional ways to treat diseases (Jain *et al.,* 2011; Saleem *et al.,* 2009; Chauhan *et al.,* 2012; Atanu *et al.,* 2011). A lot of studies have already proved that various illnesses, particularly respiratory conditions, can be treated using *Solanum* species (including *S. nigrum*). Recent studies revealed that some polyphenolic compounds specifically glycoalkaloids such as quercetin, kaempferol and apigenin, which are present in *S. nigrum*, had shown interaction with SARS-CoV-2 protease. Here stated quercetin is a strong natural antioxidant and two quercetin

glycosides are present in *S. nigrum*. Moreover, the immunostimulant activity of this plant can help in the regulation of Covid-19 (Mbadiko *et al.,* 2020; Nallusamy *et al.,* 2020).

Methods and Materials

Several procedures were followed to ensure a high quality review of the literature on the medicinal plant, *S. nigrum*. At first, an extensive literature searches of peer-reviewed journals, but not conference paper or reports, was conducted based on a wide range of key words like, medicinal plant, *S. nigrum*, phytochemical analysis and therapeutic functionality of *S. nigrum* in COVID-19 treatment etc. The search engines and journal websites used in this step are Google Scholar, PubMed, Researchgate, ScienceDirect, International Journal of Pharmacy and Pharmaceutical Sciences, World Journal of Pharmacy and Pharmaceutical sciences, and others. Second, the reference section for each article found was also searched to find additional articles. And the pictures of the plant were taken from website. Word 2016 installed in HP Probook 450 G5 device was used to write this review and to prepare the tables. PowerPoint 2016 has been used to prepare the figure. And ChemDraw pro 12.0 was used to draw the phytochemical constituents. All the valuable information, most importantly the pharmacological activity, therapeutic role and medicinal uses of the plant are mentioned in this paper.

Findings and Discussion

S. nigrum is one of the mostly utilized medicinal plants in Indian continent. Numerous chemical constituents are responsible for a number of pharmacological activities. It is popular for its use in respiratory diseases.

Taxonomical Classification

Kingdom: Plantae, **Subkingdom:** Tracheophyta, **Superdivision:** Spermatophyta, **Division:** Angiospermae, **Class:** Dicotyledonae, **Subclass:** Asteridae, **Order:** Solanales, **Family:** Solanaceae, **Genus:** *Solanum*, **Species:** *Solanum nigrum L* (Saleem *et al.* 2009; Rani *et al.,* 2017).

Chemical Constituents

Different chemicals have been extracted from various areas of the plant and researchers reported about the variability of concentration of these compounds depending upon maturation time and place. The phytochemical analysis of *S. nigrum* extracts shown that there were tannins, flavonoid, phytosterols, and fixed oils and fats in benzene and hexane

extracts. While the *S. nigrum* berries' aqueous and ethanolic extracts included alkaloids, coumarins, tannins, saponins, phenols, phytosterols, and carbohydrates (Atanu *et al.,* 2011; Ravi *et al.,* 2009). Many steroidal alkaloids, steroidal glycosides, steroidal oligoglycosides (such as solasonine, solamargine, solasdamine, solavilline, and solanine), flavonoids, glycoprotein and steroidal saponins, and many polyphenolic compounds are found in *S. nigrum*, which can be clearly seen from the phytochemical screening shown in Table-1. There have also been claims of proteins, carbohydrates and coumarins, polyphenols, crude polysaccharides, luteolin, gentisic acid, kaempferol, apigenin, and anthocyanidin. The anti-tumor activity of steroidal alkaloids and glycoproteins has been discovered (Jain *et al.*, 2011).

S. nigrum whole plant Berries of *S. nigrum*

Fig. 1. Berries and whole plant of *S. nigrum*
(Pictures are taken from https://www.indiamart.com/proddetail/solanum-nigrum-extract-makoi-extract-16684056088.html)

Glycoalkaloids

The glycoalkaloids present in *S. nigrum* include solasonine, solamargine, solanigrine, solasodine and solanine (Table 2) from the tropane group of compounds. Solanidine with MW=397.62 and formula: $CH_{43}NO$, can be obtained by hydrolysing solanine and solasonine, is less toxic in nature. These glycoalkaloids have anticancer activity across an array of tumor cell lines. According to studies, the alkaloidal concentration of plant sections changes as it develops. Over the period of leaf development, the quantity of alkaloid per leaf rises, but the concentration decreases. Small green *S. nigrum* fruits

contained a high amount of solasodine, but as the fruit matures, both the concentration and absolute amount of solasodine per fruit decrease (Atanu *et al.,* 2011).

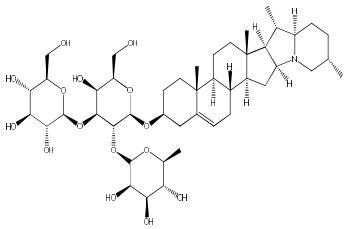
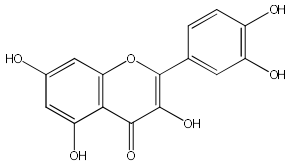
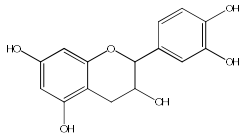
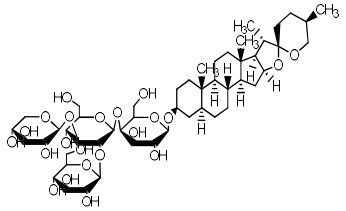
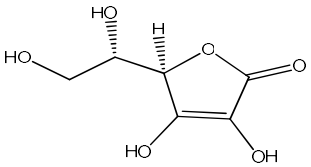
Table 1. Phytochemical screening of crude extract of *S. nigrum* (Ewais *et al.*, 2015).

Name of chemical groups	Test conducted	Result	Inference
Alkaloids	Wagner's test	+ve	Present
	Dragndorrf test	+ve	Present
Glycosides	Glycosides test	+ve	Present
	Modified borntrager's test	+ve	Present
Phenolic compound	Ferric chloride test	+ve	Present
Saponins	Foam test	+ve	Present
Sterol	Salkawskis test	-ve	Absent
	Libermannburchard's test	-ve	Absent
Flavonoids	NaOH test	+ve	Present
Tannins	Gelatin test	+ve	Present
	Lead acetate test	+ve	Present

Phenolics

Caffeic acid, gallic acid, catechin, quercetin (Table 2), protocatechuic acid (PCA), epicatechin, rutin, naringenin and flavonoids are the polyphenolic compounds found in *S. nigrum.* Phenolics are the most significant antioxidants found in plant materials. Among the largest groups of molecules that operate as principal antioxidants or free radical scavengers is contributed by them. Flavonoids are a class of natural chemicals that are diverse in their chemical and biological properties, including the ability to scavenge free radicals. Total phenolic and flavonoid concentrations were determined to be 3222.66 mg/g gallic acid equivalents and 2262.81 mg/g quercetin equivalents, respectively (Jain *et al.,* 2011; Atanu *et al.,* 2011; Jasim *et al.,* 2015; Prasath 2016).

Table 2. Most abundant chemical constituent found in *S. nigrum* (Jain *et al.,* 2011; Jasim *et al.,* 2015; Atanu *et al.,* 2011; Prasath, 2016; Saleem *et al.,* 2008; Chauhan *et al.,* 2006)

Constituent Name	Description	Structure
Solanine	Solanine makes up 95% of the overall amount of alkaloid in the plant and can be found in any part but unripe berries contain the highest portion. Because it is toxic even in minute amounts, it is among the most essential defense mechanisms of the plant. It is made up of an aglycone, solanidine, and three sugar molecules linked to the third position of the aglycone (glucose, galactose, and rhamnose, together known as solatriose). Its chemical formula is C45H73NO15, and its molecular weight is 868.04 g/mol. Although it is most frequently found as α-solanine, it can also be hydrolyzed into β- and γ-solanine.	
Quercetin	Quercetin is one of the most powerful antioxidants present in nature. Quercetin 3-O-(2Gal-α- rhamnosyl)-β-glucosyl(1→6)-β-galactoside and quercetin 3-O-α-rhamnosyl(l→2)-β-galactoside are two quercetin glycosides found in Sn. Quercetin 3-glucosyl(l→6)galactoside, 3-gentiobioside, 3-galactoside and 3-glucoside are also present in this plant.	
(+)-Catechin	Catechin is one of the phenolic compounds found in *S. nigrum.*	
Degalactotigonin	It is a saponin identified in *S. nigrum* by spectroscopic analysis, chemical degradation	
Vitamin C	Vitamins are present in *S. nigrum* in sufficient amount. Both the leaves and seeds of the plant contain vitamins in the following order: vit C > vit B > vit E > vit A. Ascorbic acid is mostly present in fruits of *S. nigrum.*	

Glycoprotien

S. nigrum glycoproteins are extracted by precipitating them with 80 percent ammonium sulphate. Fruits, stems, and leaves contain SNL glycoprotein II of 210 kDa and SNL glycoproteins I of 150 kDa and 100 kDa. Glycoproteins are composed of carbohydrate (69.74%) and protein (30.26%), with the majority of the amino acids being hydrophobic, such as glycine and proline. In HCT-116 cells, it has been found that a 150 kDa phytoglycoprotein that was found in seeds using affinity chromatography and ammonium sulphate precipitation exhibits anticancer, diuretic, and antipyretic properties (Jain *et al.,* 2011).

Saponins

Spectroscopic analysis, chemical degradation, and derivatization of *S. nigrum* instigated the discovery of six new steroidal saponins known as solanigrosides, as well as one known saponin degalactotigonin. Sn was used to characterize a pair of steroidal saponins known as nigrumins I and II. Nigrumnin I, also known as (25R)-5alpha-spirostan-3beta-ol 3-O-betaD-xylopyranosyl- (1-->3)-[alpha-L-arabinopyranosyl-(1–>2)]-beta-D-glucopyranosyl-(1—>4)-[alpha-L-rhamnopyranosyl(1-->2)] -beta-D-galactopyranoside and nigrumnin II was identified as (25R)-3beta, 17alpha-dihydroxy-5alpha- spirostan-12-one 3-O-beta-D- xylopyranosyl-(1-->3)-[alpha-L-arabinopyranosyl-(1-->2)] -beta-D-glucopyranosyl-(1—>4)-[alpha-L-rhamnopyra-nosyl-(1-->2)]- beta-D-galactopyranoside. In addition, five non-saponins were discovered: 6-methoxycoumarin, syringaresinol-4-O-beta-D-glucopyranoside, pinoresinol-4-O-beta-D-glucopyranoside, 3, 4-dihydroxhbenzoic acid (IV), p-hydroxybenzoic acid, and 3-methoxy-4-hydroxyienzoic acid (Atanu *et al.* 2011).

Other Pharmacological Activities

S. nigrum has also shown several other pharmacological actions that are not displayed in Table 3, such as, antimicrobial, immunomodulatory, anti-ulcer, anti-HCV, cardio-protective, analgesic activity etc.

Antimicrobial activity

Antimicrobial activity of *S. nigrum* is evaluated against various types of gram-positive and gram-negative bacteria, along with fungus by using different extractions of the plant and disc diffusion method. Potential of the extract as antimicrobial agent is assessed on the basis of zone of inhibition. It is clear form Table 4 that different bacteria had different levels of susceptibility to crude extracts according to the microorganism and extracting solvent. The active components that are responsible for this antimicrobial activity of *S.*

nigrum have been identified as saponins (Chauhan *et al.,* 2012; Atanu *et al.,* 2011; Zubair *et al.,* 2011).

Table 3. Therapeutic Activities of *S. nigrum* on different models (Jain *et al.,* 2011; Son *et al.,* 2003; Zhao *et al.,* 2018; Dong *et al.,* 2021; Patel *et al.,* 2009; Atanu *et al.,* 2011; Loganayaki *et al.,* 2010; Muthuvel *et al.,* 2020; Alam *et al.,* 2012; Chauhan *et al.,* 2006; Lin *et al.,* 2008; Prasath 2016; Cai *et al.,* 2010; Parez *et al.,* 1998; Aali *et al.,* 2010; Sugunabai *et al.,* 2014)

Therapeutic activity	Preparation types	Constituent name	Dose	Mechanism of action	Model
Anticancer Activity	Methanolic extracts	Diosgenin	0.0196-10 mg/mL	By interfering with the tumor cell membrane's constitution and function, disturbing DNA and RNA synthesis, and obstructing the NF-kappaB anti-apoptotic pathway.	*In vitro*
Antioxidant Activity	Methanolic Extract	Polyphenols	IC_{50}: 120.22 µg/mL; IC_{50}: 301.99 µg/mL; IC_{50}: 194.98 µg/mL	1, 1-diphenyl-2- picrylhydrazyl (DPPH) radicals, hydroxyl radical (OH), and superoxide anion (O^{2-}) scavenging activity	*In vitro*
Hepatopro-tective Activity	Methanolic Extract	Polyphenols, alkaloids and saponins	0.2, 0.5, and 1.0 g /kg bw	By modulating detoxification enzymes (GSTs) and antioxidant enzyme (SOD) and ultimately by blocking the oxidative stress	Sprague-Dawley (SD) rats
Anti-inflammatory Activity	Ethanolic extract	(E)-ethyl caffeate; 150 kDa glycoprotein	100, 250 & 500 mg/kg bw	By lowering nitric oxide synthesis, lactate dehydrogenase release, and thiobarbituric acid reactive substances concentrations; Also, through controlling the expression of the iNOS and COX-2 enzymes.	Rats; A/J mouse
Anti-convulsant Activity	Aqueous extract	Flavonoid	30-60 mg/kg bw; 10-40 mg/kg bw	The mode of action of the extract is yet unknown.	Rats and mice; Chicks
Antidiabetic activity	Aqueous and hydro-alcoholic extracts	Alkaloids and solanines	200,250 and 400 mg/kg bw	Most likely by increasing Insulin secretion from pancreatic beta cells.	Albino rat

Mechanism of Action /Clinical Indication

Diverse therapeutic activities of *S. n5igrum* with their mechanism of actions are demonstrated in Table 3.

Immunostimulant activity

It was observed *in vivo* that treatment with crude polysaccharide extracted from *S. nigrum* enhanced the ratio of CD4/Cd8 and T-lymphocyte subpopulations in peripheral blood. Additionally, SNL-P therapy led to a notable decline in IL-α ($p < 0.05$, 360 mg/kg bw.) and a considerable increase in IFN-α ($p < 0.01$, 90, 180, and 360 mg/kg bw.), both of which were evaluated using the ELISA method. From these data, we can say that SNL-P is a potential immunostimulant which can help to fight infection and tumor (Atanu *et al.,* 2011).

Cardioprotective activity

A worldwide *in vitro* ischemia-reperfusion injury model was used to assess the cardioprotective activity of methanolic extract of *S nigrum* berries. The experiment was conducted using dosages of 2.5 and 5.0 mg/kg six days a week for 30 days. This experiment's findings imply that the extract has considerable cardioprotective properties (Chauhan *et al.,* 2012).

Table 4. Antimicrobial activity of different extracts of fruits of *S. nigrum* (dose level = 20mg/ml) (Abbas *et al.*, 2014).

No	Microorganisms	Zones of inhibition (mm) ± SE(Standard error)				
		Chloroform	Ethyl acetate	Acetone	Methanol	Water
1	**Gram positive organisms**					
	Micrococcus luteus	9.2±1.25	6.5±3.2	7.6±1.3	3.4±2.1	13.5±3.4
	Staphylococcus aureus	8.5±2.12	7.2±2.0	8.3±2.0	15.2±3.5	14.7±2.4
2	**Gram negative organisms**					
	Escherichia coli	6.7±1.4	7.5 ± 2.3	7.9 ± 2.1	14.3 ± 2.6	16.4±3.0
	Salmonella typhi	7.6±1.8	6.7±2.5	6.5±2.0	15.2±3.3	15.3±3.2
3	**Fungal species**					
	Candida albicans	5.8±2.6	6.7±1.3	5.3±1.0	7.6±1.0	4.8±2.10

Analgesic activity

Using Eddy's hot plate and acetic acid-induced writhing method, the analgesic activity of ethanolic extracts of *Solanum nigrum* was assessed. 100, 250, and 500 mg/kg orally administered dosages were employed in the trial. The result is that noteworthy pain-relieving effect was observed at the dose of 500 mg/kg ($P<0.01$) (Chauhan *et al.,* 2012).

Traditional Uses

For its various important pharmacological activity *S. nigrum* has been taken as folk remedy all across the world. Some of its uses are shown in Table-5.

Table 5. Overview of traditional uses of *S. nigrum* in different parts of the world (Jain *et al.,* 2011; Saleem *et al.,* 2008; Rani *et al.,* 2017; Atanu *et al.,* 2011; Khan, 2016).

Country	Plant Part	Preparation	Condition
Tamil Nadu, India	Leaf paste	Applied directly	Rabies; wound healing; rheumatic and gouty joints
	Complete plant	As food item	Cold
Himalayan region, India	Leaf	-	Indigestion; liver excitant
Assam, India	Roots	Extraction of root juice	Whooping cough and Asthma
Thar Desert, India	Roots	Boiling roots with a little sugar	Boost female fertility
Tanzania, Africa	Leaf	Pounded leaves are applied topically	Treatment of infection with ringworm
	Leaf	The crushed and broiled leaves	Used as a wart dressing
	Fruit	Ripe fruits	Provided to children in order to prevent bedwetting
United Republic of Congo, Africa	Whole plant	Maceration	Snake bite or poisonous animal's sting
Tunisia, Africa	Sap	-	Erysipelas (acute Streptococcus bacterial infection)
Algeria, Africa	Fruit	Diluted infusion of berries	Blindness; glaucoma; conjunctivitis; trachoma; cataract
	Whole plant	Decoction	Burns and skin problems

Toxicity of *S. nigrum*

Despite of the fact that *S. nigrum* is famous for its use in the traditional medicine it can be very toxic. In fact, the majority of species in the Solanaceae family are toxic to both people and animals. Tropane alkaloids are found, for example, in deadly nightshade. The classic anticholinergic poisoning is the symptom of tropane alkaloids-containing plant toxicity. The glycoalkaloid solanine, which causes varying levels of toxicity with dose-dependent effects, is primarily responsible for *S. nigrum*'s toxicity. Solanine poisoning can cause a variety of symptoms in humans, including diarrhea nausea, vomiting, headaches, vertigo, chills, speaking impediment, perspiration, blindness, arrhythmia, mental confusion, seizures, coma, and death. Consuming nightshade plants including tomato, potato, and eggplant is known to aggravate joint pain. According to reports, the solanine found in these plants' green parts is probably to blame. However, ripe fruits and cooked plants of this family are safe to eat as the toxic compound is reduced or destroyed (Jain *et al.,* 2011).

***S. nigrum* in management of COVID-19**

COVID-19 is one of the most lethal pandemics the world has seen. The world has been startled by the rapid spread of this lethal virus, which presents a challenge to worldwide medical and scientific communities (Sikander *et al.* 2020) Natural plant chemicals are being studied for their ability to suppress the SARS-CoV-2, the source of COVID-19, in order to combat the current pandemic. Natural products, such as antiviral chemicals of very little toxicity, are employed by the pharmaceutical industry because of their pharmacological activities, could be a useful resource in the formulation of COVID-19 treatments. They are taken into consideration since they have already made contributions to the research and development of medications that treat viruses like HIV, influenza, and MERS-CoV (da Silva Antonio *et al.,* 2020; Teli *et al.,* 2021). The potential of flavonols, flavanols, and flavanones as anti-SARS-CoV-2 agents, moreover the reason that angiosperm plants contain a lot of these substances, have given hope to the people of the world. However, critical problems regarding their absorption and real efficacy in vivo remain unresolved (da Silva Antonio *et al.,* 2020). The plant *S. nigrum* containing some of these compounds like solanine, quercetin, kaempferol, apigenin etc can also be an option for the treatment. The main reason for choosing this plant as an option is been previous record of antiviral and immunomodulatory activity. With limited but systematic clinical studies, some formulations can be developed using this plant, it is intended to establish a presence on the global market and offer up new avenues for the study of COVID-19 and related illnesses (Goyal *et al.,* 2021).

Pathogenesis of COVID-19

For a better knowledge of how natural compounds or phytomolecules might successfully combat new coronavirus, it is crucial to identify the structural characteristics, pertinent targets, and receptors associated with these viruses. To build a COVID-19 therapeutic natural-sources-based regimen, it may also be helpful to comprehend the action mechanism of classical antiviral medications and possible drug development targets (Patel *et al.,* 2021). Coronaviruses are members of the Coronaviridae family. The average size of coronaviruses, which range from 60 nm to 140 nm in diameter and under electron microscopy display a crown-like appearance, varies considerably depending on their genotype and phenotype. They have single-stranded RNA and are positive sense enveloped viruses. Although it is thought to have been transmitted by bats, the exact origins of SARS-CoV-2, enzootic transmission patterns, and animal reservoir are unknown. SARS-CoV-2 is made up of four basic structural proteins: membrane protein (M), spike protein (S), envelop protein (E), and helically symmetrical nucleocapsid protein (N), as well as non-structural proteins like nsp12-RNA-dependent RNA polymerase (RdRp), Nsp5- 3C-like main protease, Nsp3-Papain-like proteinases, and nsP13 SARS-CoV helicase (Patel *et al.,* 2021; Mirzaie *et al.,* 2020, Khan and Al-Balushi 2021).

Inoculation and Replication

The SARS-CoV-2 virus infects healthy cells by attaching to the ACE2 receptor on the host cells, which is widely present in the heart, kidney, lungs, intestine, and blood vessels. This process is carried out by the viral spike (S) protein. After adherence of the S protein to the ACE2, the virus employs infected cell receptors (TMPRSS2) to reach the cytoplasm of the host cell. And after being uncoated, the cytoplasm is where the viral gRNA is discharged. Viral proteins are created by the protein synthesis mechanism of the host cell, and they are subsequently broken down by viral proteases and then transported to the replicase complex. Using its RdRP, the virus produces viral RNA. Additionally, viral assembly and structural proteins are produced, allowing for the finalization of the assemblage and the exocytosis-mediated discharge of viral progeny. β-CoVs generate pp1a and pp1ab through the translation of genomic RNA. Main protease (Mpro) and papain-like protease break them into structural and non-structural proteins (PLpro). The virion assembly will be discharged from the host cell once it is complete (Khan and Al-

Balushi, 2021). The ACE converts angiotensin I to angiotensin II while converting angiotensin 1-9 to angiotensin 1-7. Vasoconstriction, fibrosis, inflammation, prothrombotic, and arrhythmogenic actions are brought on by angiotensin II's binding to AT1 receptors in the body. Also Angiotensin II protects tissues by acting on AT2 receptors. Angiotensin 1-7 binds to the MAS receptor and has anti-proliferative, anti-inflammatory, antifibrotic, and antithrombotic properties (Goyal *et al.,* 2020).

Inflammatory Response

Cellular reactions are triggered by viral replication. This resulting in invasion of many inflammatory cells, which include both innate and adaptive immune cells. The intrinsic immune cells chiefly responsible for lung damage are neutrophils. The majority of adaptive immune cells are T cells, specifically cytotoxic CD8+T cells, that not only destroy viruses but also harm the lungs. Overall result is the systemic inflammatory reaction, which causes a surge in cytokines such as TNF, IL1, IL6, IL10, and others, which is known as cytokine storm. It is one of the suggested mechanisms of SARS-CoV-2-induced lung damage. Increased levels of various cytokines cause Type-1 and Type-2 cells in the lungs to enlarge and die. This hinders oxygen delivery which causes cell death in the lungs' alveoli and producing Acute Respiratory Distress or syndrome (ARDS). Increased levels of circulating pro-inflammatory cytokines, including interferon, interleukin (IL-1, IL-6, and IL-12), and chemokines (CXCL10 and CCL2), are associated with pulmonary inflammation and the pathogenesis of ARDS. This is because inflammatory damage to the blood–air barrier causes an increase in lung permeation and the secretion of protein-rich respiratory edema fluid into the air passages. It eventually causes respiratory failure and the consequences that lead to multiple organ failure. When SARS-COV2 binds to open reading frames (ORFs), particularly the ORF8 proteins, iron dissociates from the 1-beta chain of hemoglobin, which subsequently binds to the membrane glycoprotein porphyrin, results in the internal respiration failure. Weak immune system along with cytokine storm is the major cause of reduced cellular oxygen at the alveolar level, which is thought to be the major factor in demise in COVD-19 (Patel *et al.,* 2021).

Strategy for developing treatment

The SARS-CoV-2 genome sequence was used to identify the crucial proteins and enzymes associated with the virus's inoculation and multiplication. Its genomic sequence has79.5% resemblance with SARS-CoV-1 and 96% similarity with a coronavirus strain that is only communicable in bats. According to genomic evidence, three proteins and enzymes are principally responsible for SARS-CoV-2 infection and viral proliferation in humans (Fig. 2). The papain-like protease (ACE2), 3 chymotrypsin-like proteases (3CLpro) and spike protein (TMPRSS2) are the proteins in concern (da Silva Antonio *et al.,* 2020).

The virus is a necessary intracellular parasite which depends on host metabolic components as well as the environment for reproduction and proliferation. So, the challenge in developing an antiviral medicine is to create one that is both effective and selective in its toxicity against viruses rather than the host. Since SARS-CoV-2 binds to ACE2, which is also implicated in the pathogenesis of cardiovascular, pulmonary, and gastrointestinal dysfunction, and is the site of virus proliferation, inhibiting ACE2 has been the main focus of anti-COVID-19 research, despite the fact that it is probably not the best choice of action to act on such a central control system. The virus's trimeric spike glycoprotein (TMPRSS2), which is a transmembrane protease serine type 2 (TMPRSS2), attaches to host cells and is a major objective for future treatments and diagnostics. In each spike monomer, the SARS-CoV-2 S2 subunit reportedly has a transmembrane domain, a fusion peptide, and a cellular domain that is very constrained and may be an antiviral drug target (anti-S2). Also, the virus polypeptide is proteolytically broken down by the 3CLpro into 11 non-structural proteins that are crucial in the virus' growth. The 3CLpro, which is unique to SARS-CoV-2 and absent from the host cell., attracted interest as a possible target for COVID-19 therapy development (Patel *et al.,* 2021; Goyal *et al.,* 2020).

Phytomolecules produced by many plants can be employed to approach these viral targets, as they have been for other viral infections such as SARS, HIV, HCV, and others. Antiviral plants with anti-inflammatory effects that protect the lungs from infections can also be examined as a synergetic therapy. Based on the above mentioned strategies, a search for possible plants with the following features may assist in the establishment of natural plant-derived antiviral medicines to combat the pandemic disease (Patel *et al.,* 2021; da Silva Antonio *et al.,* 2020).

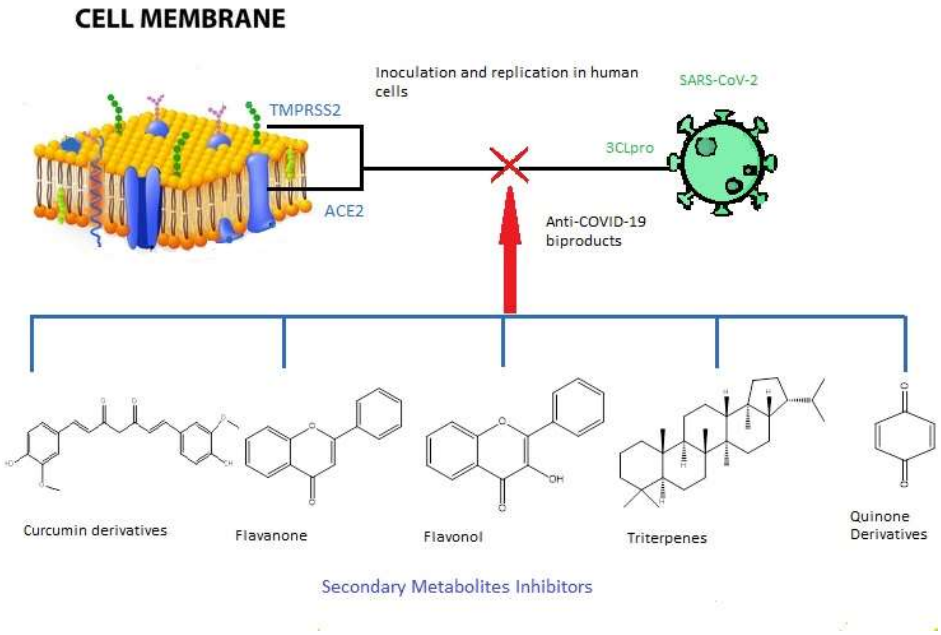


Fig. 2. Invasion of SARS-CoV-2 in human cell and action of some anti-COVID-19 compounds

Natural Therapeutic Options for COVID-19

Generally, developing bioactive natural cures for a particular ailment, such as COVID-19, should be faster than developing vaccines but it becomes a challenging process because of the variety of natural compounds, their extraction and chemical complexity. Fortunately, as an efficient method for comprehending and forecasting druggability in the early stages of drug development, in silico analysis by molecular docking technologies has expanded study fields and gained widespread acceptance. This is mainly used to predict how bioactive compounds bind with receptor proteins. Docking studies were conducted on flavonoids (flavones, flavonols, isoflavones, xanthones, flavanone, flavan 3-ols), tannins, phenolics, anthraquinones, alkaloids, lignans, and coumarins (simple, complex) targeting the papain-like protease (ACE2), 3 chymotrypsin-like proteases (3CLpro) and spike protein (TMPRSS2). The results demonstrate that flavonoids may attach to the S protein of the SARS-CoV-2 virus, a viral membrane glycoprotein necessary for early attachment and incorporation into host cells. Flavonoids such as luteolin, apigenin, quercetin, epigallocatechin (EGC), gallocatechin gallate (GCG),

amentoflavone, and kaempferol have been shown to suppress the proteolytic activity of SARS-CoV 3CLpro and 3a channel protein of the coronavirus. ACE2 inhibitory action was found in flavonoids such as luteolin, rutin, quercetin, apigenin and kaempferol. Furthermore, Mpro and spike glycoprotein inhibitors such as procyanidin A1, A3, A4, B2, acetoside, solanine, quercitrin, rutin, and theaflavin 3,3′-digallate can be subjected to future investigations in order to identify specific treatments to combat COVID-19 (da Silva Antonio *et al.,* 2020; Sulaiman *et al.,* 2021; Khan and Al-Balushi, 2021).

Natural ACE2 Inhibitors

The most effective method for COVID-19 therapy and prevention may involve limiting host cell entry by the virus. SARS-CoV-2 enters the cell via endocytosis after attaching to the ACE2 on the host cell membrane. Nucleoside analogs that inhibit viral replication and small compounds that target virus-host cell interaction, such as ACE2 in SARSCoV-2, are possible treatments for this viral illness. Similar to the mechanism seen with SARS-CoV-1 inhibitors, ACE and ACE2 inhibitors engage with the protein through amphiphilic molecule structures that typically have an aromatic component (Goyal *et al.,* 2020). As a component of the renin-angiotensin system, ACE2's primary job is to transform angiotensin II, a potent vasoconstrictor, into angiotensin (structural forms I, III, IV, V, VI, and VII), a vasodilator that helps to maintain and lower blood pressure by balancing ACE. Risks about coronavirus infections arise when ACE inhibitors (ACEIn) are used to treat diabetes and hypertension on a long-term basis. They make the patients more susceptible to COVID-19 by upregulating the activation of ACE2. Because of this, the vast bulk of COVID-19 identified patients had comorbid conditions, mainly diabetes or high blood pressure. As the level of angiotensin I increases as a function of ACE inhibition, ACE2 mRNA rises to balance. This is assumed to be caused by the reduced ability of ACE inhibitors to cleave angiotensin I. There are several compounds that function as both ACE2 inhibitors and Ace inhibitors, such as phenolics such as myricetin and glycosylated derivatives of quercetin. The molecular docking of several plant metabolites with the ACE2 against SARS-CoV-2 revealed 11 natural compounds that could block it. Baicalin (baicalein-7-O-glucuronide), hesperetin, scutellarin, glycyrrhizin, nicotianamine, naringin, neohesperidin, hesperidin, naringenin, and nobiletin are some of the naturally occurring metabolites reported as probable bioactive compounds against SARS-CoV-2. Natural ACE2 inhibitors, like ACE inhibitors, are classified as alkaloids, flavanones, flavonols, limonoids, terpenes, phenolic acids, lignans, tannins, terpenoids,

and fatty acids. Flavonoids, such as naringenin and naringin, were the main focus of the in silico studies of anti-COVID-19 natural compounds conducted at the primary stage. However, recent research indicates that glycosylated derivatives of quercetin have promising inhibitory activities with binding energies less than 8.3 kcal mol^{-1}. Quercetin 3-vicianoside and quercetin-3-glucuronide-7-glucoside and are two of these flavonoids (da Silva Antonio *et al.,* 2020).

Natural TMPRSS2 inhibitors

Flavonoids, terpenes, and peptides are all natural TMPRSS2 inhibitors. In in silico analyses against COVID-19, the flavonoids baicalin and baicalein were identified, which have earlier been described as expression-suppressing agents for TMPRSS-2. Molecular docking investigations have suggested that baicalein is also an ACE2 inhibitor. In fact, the proposed metabolite's bioactivity in vivo would be greatly increased if it could be employed to interact with a number of virus binding sites. Along with known human TMPRSS2 inhibitors, in silico investigations showed that iridoids, lignans and diterpenes, are possible anti-SARS-CoV-2 compounds that interact with TMPRSS2 (Khan and Al-Balushi, 2021). The researchers proposed 12 natural compounds such as silybin, geniposide, microcarpin, isogemichalcone B, withaferin A, excavatolide M, citocoline, (-)-epicatechin 3-o-(3'-o-methyl gallate) etc. with TPMRSS2 binding energies ranging from 11.06 to 14.69 kcal mol^{-1}. The geniposide was the natural metabolite with the highest inhibitory potential. Their inhibitory values are higher than previously mentioned ACE2 inhibition molecular docking (da Silva Antonio *et al.,* 2020).

Natural 3CLpro inhibitors

Researchers are focusing their attention more to 3CLpro's inhibition, which is the main protein of SARS-CoV-2, because it might restrict the virus from infecting the host. Procyanidin A3, acetoside, rutin, solanine, procyanidin A4, procyanidin B4, hypericin, quercetagetin, procyanidin, and astragalin were discovered to have highly excellent docking scores against 3CLpro of SARS CoV-2. An acetoside with α, β-unsaturated carbonyl group can attach covalently to the Cys145 residue of 3CLpro. These flavonoids' anti-SARS-CoV-2 action is beneficial due to the fact that they are easily found and abundant in angiosperm plant families. Apart from flavonoids, specialized metabolites called volatile terpenoids have some really promising early results that suggest their potential use. Geraniol, linalool, (E)-farnesene, and (E)-nerolidol, are themono and

sesquiterpenes, showed 3CLpro binding energy of 24.71, 24.05, 27.56, and 26.44 kcal mol^{-1}, respectively. These chemicals are present in a variety of plant species that have long been used as meals, medicines, and aromatics (da Silva Antonio *et al.,* 2020).

Inhibitory Phytoconstituents of Spike Glycoprotein

Acetoside binds to the spike glycoprotein RBD having a strong affinity (8.528 kcal/mol). Additionally, solanine has a great attraction for the spike glycoprotein RBD, which was similar to 3CLpro, and had a docking score of 9.501 kcal/mol. The H-bonding with Tyr449 (2.64Å) involved the oxygen atom of a glycosidic bond linked to a steroidal backbone. Rutin, quercitrin, epitheaflavin monogallate, procyanidin, procyanidin A1, procyanidin B2 also demonstrated considerable binding affinity with spike glycoprotein RBD (Khan and Al-Balushi, 2021).

RNA polymerase inhibitors

This process includes a very particular mechanism to inhibit virus proliferation using the RNA polymerase inhibitors. RNA-dependent RNA polymerase (RdRp), also called the nonstructural protein 12 (nsp12) has become a new target for therapeutic development against COVID-19. ACE2 or TMPRSS2 inhibitors, which attach to the host cell, are likely to be more harmful than metabolites having this feature. Though it's the safer option, its application in the treatment of coronavirus is still not very known. Hesperidin, naringin, apigenin-7-O-glucoside, hesperetin, quercetin, kaempferol, apigenin, solanine, solamargine, and other phytoconstituents are potential lead molecules for developing new RdRp inhibitors (da Silva Antonio *et al.,* 2020; Goyal *et al*., 2020).

***Solanum nigrum* as a COVID-19 treatment option**

In consideration of COVID19's pathophysiology, medicinal plants with significant anti-inflammatory, antiviral and immunomodulatory properties are a promising candidate for developing COVID-19 treatments. As the plant *S. nigrum* has all these properties, it may become a natural solution for this deadly disease. Again, this plant has shown inhibitory HIV reverse transcriptase activity which also indicates its possible effectiveness against SARS-CoV-2. From the phytochemical investigation we already know that the plant contains flavonoids, steroidal glycoalkaloids, triterpenoids, flavonoid glycosides and other compounds of different classes. Different components of these classes has already

shown great inhibitory potential against SARS-CoV-2 (Table 6). Among them solanine, quercetin, quercitrin, apigenin, kaempferol, rutin, leteolin, naringenin and m coumarins showed great potency (Patel *et al.,* 2021).

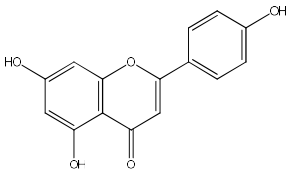
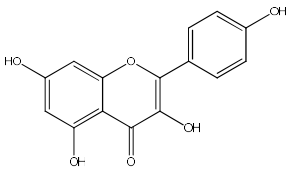
Table 6. Phytoconstituents found through molecular docking against SARS-CoV-2 (da Silva Antonio *et al.,* 2020; Khan and Al-Balushi 2021; Goyal *et al.,* 2020).

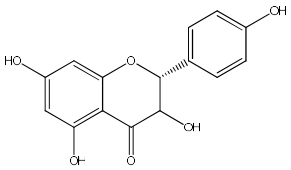
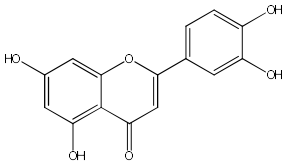
Phytoconstituent	Binding Energy (kcal mol^{-1})	Phytoconstituent	Binding Energy (kcal mol^{-1})
Binding with ACE2		**Binding with TMPRSS2**	
Quercetin 3-glucosyl-(1,4)-rhamnoside	−6.50	(−)-Epicatechin 3-*O*-(3′-*O*-methyl) gallate	−13.10
Quercetin	−8.664	Silybin	−11.928
Apigenin	−7.10	Geniposide	−14.69
Kaempferol	−7.20	Microcarpin	−13.31
Epicatechin-4-epigallocatechin	−7.20	5-Methoxyhydnocarpin	−13.92
Isoquercitrin	−7.80	Citocoline	−13.96
Silybin	−10.57	Withaferin A	−11.24
Solanine	−6.0	Excavatolide M	−14.38
Solasodine	−4.8	Dictyosphaeric acid A	−14.02
Solasonine	−2.6	Isogemichalcone B	−13.07
Quercetin 3-glucosyl-(1,4)-rhamnoside	−9.90	Solanine	−9.50
Apigenin	−7.80	Acetoside	−8.53
Kaempferol	−7.80	Rutin	−7.91
Isoquercitrin	−8.20	Quercitrin	−7.15
Quercetin	−8.47	Epitheaflavin monogallate	−7.52
Acetoside	−11.97	Procyanidin B2	−7.48
Rutin	−11.19	Theaflavin 3,3'-digallate	−7.02
Solanine	−10.30	Procyanidin A1	−6.84

Solanine is a glycoalkaloid found in European black nightshade (*S. nigrum*), tomato (*Solanum lycopersicum*), potato (*Solanum tuberosum*), and eggplant (*Solanum melongena*). Highest amount is found in *S. nigrum* berries. Fungicidal, antibacterial, and pesticidal activities are shown by this compound. At physiological pH, the nitrogen atom of solanine formed a salt bridge with Glu166 (4.87Å) and H-bonding with Glu166 (1.93Å). L-rhamnopyranose's hydroxyl group made an H-bond with Glu166 (2.64Å). The H-bonding with Tyr449 (2.64Å) involved the oxygen atom of a glycosidic bond linked to a steroidal backbone. Ser494 (1.92Å) demonstrated H-bonding with the methylene hydroxyl group of glucopyranose, which is connected to a steroidal backbone. Solanine had a strong binding affinity for the spike glycoprotein RBD, which was similar to 3CLpro, and had a docking score of 9.501 kcal/mol against PDB ID 6M0J (Khan and Al-Balushi, 2021).

Quercetin, a flavonoid containing five hydroxyl groups found in *S. nigrum*, has been shown antimicrobial, antitumour, anti-inflammatory, and antioxidant activities. Quercetin also possesses immunostimulatory properties, promoting the emergence of various important genes and the generation of Th-1-derived interleukin 1 (IFN-) while suppressing Th-2-derived interleukin 4. (IL-4). In addition, quercetin is thought to be a general inhibitor of immune cell buildup and activation, preventing chronic inflammation. It has evident antiviral effects on numerous respiratory and common cold viruses because of its capacity to decrease viral localization, proliferation, and load *in vitro*, as well as inflammatory responses and airway hyper-responsiveness in vivo. Quercetin-3-galactoside was found to block MERS-CoV 3CLpro's enzymatic activity *in vitro* and to inhibit a protease necessary for SARS-CoV viral multiplication. It has a stronger inhibitory effect on Angiotensin-Converting Enzyme than rutin, kaempferol, rhoifolin, and apigenin K flavonoids, as evidenced by their IC50 values (43 64 178 183 and 196 M, respectively). Furthermore, it has been demonstrated that the SARS-CoV 3CLpro's proteolytic activity is blocked (Khan and Al-Balushi, 2021, Khalil and Tazeddinova, 2020). Some other components having great inhibitory potential against SARS-CoV-2 are demonstrated in Table 7.

Table 7. Chemical constituents of *S. nigrum* that showed inhibitory potential against SARS-CoV-2 (Khalil and Tazeddinova 2020; Schwarz *et al.*, 2014).

Constituent Name	Description	Structure
Apigenin	*S. nigrum* contains a naturally occurring flavone molecule called apigenin (4′,5,7-trihydroxyflavone). It has a diverse array of biological actions, including powerful anti-inflammatory, antioxidant, antibacterial, and antiviral properties, as well as blood pressure lowering properties. Apigenin activates anti-inflammatory pathways such as p38/MAPK and PI3K/Akt, suppresses NF-B nuclear translocation, inhibits COX-2 activity, and significantly lowers IL-6, TNF-, and IFN- levels. It has demonstrated antiviral activity against adenoviruses (ADV) and the hepatitis B virus *in vitro*, blocking of the production of viral proteins by inhibiting viral IRES activity of picornaviruses, the African swine fever virus (ASFV) by inhibiting viral protein biosynthesis and reducing ASFV yield by 3 logs, and altering the viral RNA of enterovirus-71, and blocking of the production of viral proteins by inhibiting viral IRES (EV71). Apigenin, along with other flavonoids, has been demonstrated to reduce the enzymatic action of SARS-CoV 3CLpro, and the antiviral effect is assumed to be related to the suppression of SARS-CoV 3CLpro's activity.	
Kaempferol	Kaempferol, also known as 3,4′,5,7-tetrahydroxy-flavone, is a flavonoid seen in several medicinal plants, including *S. nigrum*. With its potent anti-inflammatory and antioxidant capabilities, kaempferol reduced LPS-induced TNF- and IL-1 production by raising the number of phagocytic cells and blocking NF-B moving inside the nucleus, so blocking the inflammatory cascade pathway. Kaempferol has been demonstrated to be a successful treatment for lung damage and inflammation brought on by the H9N2 influenza virus both *in vitro* and in vivo. Treatment with kaempferol reduced pulmonary edema, pulmonary capillary permeability, myeloperoxidase (MPO) activity, and inflammatory cell counts. Kaempferol glycosides and acylated kaempferol glucoside, two derivatives of kaempferol have already showed significant antiviral activity against the SARS coronavirus through inhibiting 3a channel protein. Kaempferol not only inhibits virus generation by blocking the 3a channel, but also affects the other stages of the viral life cycle, which indicates its potential as multi-target drugs.	

Naringenin	Naringenin, which is mainly 4′,5,7-trihydroxytlavanone, is a component of *S. nigrum*. Numerous pharmacological effects of naringenin include antidiabetic, anticancer, immunomodulatory, DNA protective, anti-inflammatory, hypolipidemic, antioxidant, antiasthmatic, antibacterial, antiviral, and PPAR activator. Through its antioxidant, anti-inflammatory, anti-nitrosative, and antitumor capabilities, it prevents the proliferation of various viruses in human cells, including dengue, chikungunya, and zika. It also offers significant protection against acute lung damage caused by LPS. Naringenin has the potential to be utilized to treat pneumonia linked with the spread of COVID-19 owing to its powerful anti-inflammatory and anti-oxidant properties.	
Luteolin	Luteolin, also known as 3′,4′,5,7-tetrahydroxyflavone, is a natural yellow dye found in a wide range of plants, notably *Solanum nigrum*. Like other flavonoid compounds, it has several pharmacological actions like immunostimulatory, anti-inflammatory, cytotoxic, antimicrobial, anti-oxidant, antiviral, anti-allergic, and neuroprotective activities. Using a wild-type SARS-CoV infection system, the anti-SARS-CoV effects of two small compounds, tetra-O-galloyl-d-glucose (TGG), and luteolin, were established. TGG and luteolin both efficiently inhibited the entry of HIV-luc/SARS pseudotyped virus into its host at the same potencies, suggesting that these two compounds could be used clinically as anti-SARS medicines. As it has significant antiviral and anti-inflammatory effects during infection, luteolin could be used as an alternate treatment as well as body immunity booster against COVID19 infection.	

Conclusions

With the emergence of the COVID-19 pandemic, several scientists and physicians attempted to propose viable medications for treating the disease. Natural substances have been utilized to treat infectious diseases for decades. Natural medications and their active constituents may be advanced as a promising therapeutic candidate against SARS-CoV-2 according to past experiences with coronavirus outbreaks like SARS-CoV in 2002 and MERS-CoV in 2012, seasonal epidemics brought on by several viruses, and the therapeutic efficacy of natural ingredients in treating HCV, HIV, and influenza. So, they might be essential in overcoming the global crisis. In COVID-19 patients, medicinal herbs could be utilized to alleviate symptoms including fever and coughing, as well as enhance immunity. Among these medicinal plants *S. nigrum* was the point of interest for

this review. This review demonstrates that *S. nigrum* has a wide range of therapeutic characteristics. The plant could be utilized to make an oral medicine to treat respiratory infections, but further research is needed to isolate the bioactive components from the crude extract for optimal drug development. In addition to having effects on cardiovascular targets rather than the renin-angiotensin system, phytoconstituents must exhibit anti-inflammatory, antioxidant, and antiviral action to be beneficial for treating COVID-19, ACE-2 being the main target. From the review we can see that the plant possesses all of these properties. To summarize, *S. nigrum* may contain bio-active compounds that can be employed as an anti-SARS-CoV-2 drug to cure COVID-19 disorders with no adverse effects (Patel *et al.,* 2021; Khan and Al-Balushi 2021).

Authors' contribution

MSA has conceived the original idea. FAS, MRT and FA extensively consulted the literature and prepared the initial manuscript and arranged the reference section. JAC, AAC and SK critically reviewed the overall activities. MSA supervised the whole activity. All the authors read the review article meticulously and agreed to submit the article.

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Conflict of interest

There is no conflict of interest, according to the authors.

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