



Solanum nigrum L. in COVID-19 and post-COVID complications: a propitious candidate

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Abstract

COVID-19 is caused by severe acute respiratory syndrome coronavirus-2, SARS-CoV-2. COVID-19 has changed the world scenario and caused mortality around the globe. Patients who recovered from COVID-19 have shown neurological, psychological, renal, cardiovascular, pulmonary, and hematological complications. In some patients, complications lasted more than 6 months. However, significantly less attention has been given to post-COVID complications. Currently available drugs are used to tackle the complications, but new interventions must address the problem. Phytochemicals from natural sources have been evaluated in recent times to cure or alleviate COVID-19 symptoms. An edible plant, *Solanum nigrum*, could be therapeutic in treating COVID-19 as the AYUSH ministry of India prescribes it during the pandemic. *S. nigrum* demonstrates anti-inflammatory, immunomodulatory, and antiviral action to treat the SARS-CoV-2 infection and its post-complications. Different parts of the plant represent a reduction in proinflammatory cytokines and prevent multi-organ failure by protecting various organs (liver, kidney, heart, neuro, and lung). The review proposes the possible role of the plant *S. nigrum* in managing the symptoms of COVID-19 and its post-COVID complications based on *in silico* docking and pharmacological studies. Further systematic and experimental studies are required to validate our hypothesis.

Keywords *Solanum nigrum* · COVID-19 · Post-COVID complications · SARS-CoV-2 Phytochemicals

Introduction

Coronavirus disease, commonly known as COVID-19, is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The first confirmed case was reported on December 31, 2019, in Wuhan, China. According to the WHO dashboard, 651,918,402 confirmed cases and 6,656,601 deaths were reported till December 23, 2023, with a 2% mortality rate. The global pandemic has baffled the world with its impact, and eventually, every group of society has been suffering economically, medically, and socially.

Clinical manifestations of COVID-19 include fever, cough, fatigue, loss of smell and taste, soreness in the throat, diarrhea, headache, rashes on the skin, and more severe manifestations include difficulty breathing or shortness of breath, chest pain or pressure, and hypoxia [2]. New symptoms are still emerging due to the mutations in the SARS-CoV-2 genome. It takes around 4–6 days for symptoms to appear and lasts up to 14 days [3, 4]. As of now, no particular treatment is available to tackle the disease, and currently available drugs are repurposed to control the disease. Acute respiratory infection is the prime manifestation of COVID-19 [5]. However, non-respiratory and post-treatment manifestations are also reported, suggesting that the virus has a long-term implication on host immunity and organs.

Patients who recovered from COVID-19 experienced multiple symptoms. There is no standardized term coined for that but most commonly, these symptoms are referred to as “post-COVID complications” or “long COVID” [6]. Any abnormal parameter or symptoms that exist 2 to 12 weeks after COVID-19 with negative real-time reverse transcription–polymerase chain reaction (RT-PCR) can be considered an acute post-COVID complications. By comparison,

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symptoms present beyond 12 weeks can be considered a chronic COVID complications. Many patients worldwide have reported different post-COVID complications through various platforms. Unfortunately, few clinical trials and meta-analyses have been carried out to streamline the different symptoms and abnormalities in clinical parameters. As many as 50 symptoms have been reported regarding post-COVID manifestation [7]. Although no particular guideline or treatment is available to tackle post-COVID complications due to the large and lacking data on symptoms, post-COVID complications have affected patients' quality of life as they are haunted by the fear of significant complications [8]. Patients with post-COVID complications also restrain themselves from interacting socially as they cannot carry out day-to-day activities [9].

Available oral antiviral medications, namely remdesivir, lopinavir, and ribavirin, produce multiple adverse effects like hyperuricemia, anemia, bradycardia, and gastrointestinal and hepatic dysfunctions [10]. Recently, on April 22, 2022, WHO strongly recommended “paxlovid” an oral antiviral combination of nirmatrelvir and ritonavir for severe COVID-19 and immunocompromised patients [11]. Besides oral therapeutic drugs, vaccines are being utilized to manage the pandemic, yet mild-to-moderate side effects like nausea, chills, fever, diarrhea, muscle pain, and fatigue are also associated [12, 13]. Among all of the vaccines, ten show good efficacy against SARS-CoV-2 infection and attained emergency use listing (EUL) by WHO in terms of quality, safety, and efficacy [14]. Till now, there are 119 vaccines in clinical trials and 49 have attained the final stage. Most vaccines that are approved are in phase three clinical trials and are being utilized in various countries for emergency use [15]. Besides all these successful attempts of COVID-19 rapidly developing vaccines, approximately, 40% of the world population choose to remain unvaccinated, and only 65% have completed their first dose [16]. According to the centers for disease control and prevention (CDC) report, 15% population of the US chooses to remain unvaccinated. A Household pulse survey (HPS) conducted by the US Census Bureau states that 42% of adults do not believe in COVID-19 vaccines [17]. Vaccine breakthrough infections are also happening worldwide as COVID-19 vaccines are not 100% effective [18]. Moreover, variants like delta and omicron also pose challenges to vaccines and therapeutics. Research is ongoing by thousands of scientists worldwide to better understand how new virus mutations and variants affects the effectiveness of different COVID-19 vaccines.

Medicinal plants and their bioactive constituents with high efficacy and minimal side effects play a major role in treating numerous viral diseases [19–24]. It is important to find phytochemicals in a single plant possessing antiviral, anti-inflammatory, and immunomodulatory activities. Recent studies suggest multiple medicinal plants and

formulations that have been reported to have these activities and could be explored against COVID-19. For instance, *Withania somnifera*, *Adhatoda vasica*, *Piper longum*, *Santalum album*, *Morus alba*, and *Momordica charantia* have been recommended for their immunomodulatory, antiviral, and anti-inflammatory action [25, 26]. Thus, one could say that medicinal plants and phytochemicals from natural sources may show an important role against SARS-CoV-2 infection. *Solanum nigrum* is an edible plant in India, Australia, Tanzania, Ethiopia, and Uganda [27, 28]. In countries like Australia and Tanzania, people use it as a vegetable, and leaves are boiled and eaten like spinach. In Ethiopia and Uganda, leaves and fruits (black or violet) are edible in their raw form [27]. Traditional practices suggest that various plant parts are useful in ulcers, fever, flatulence, vomiting, dyspepsia, wounds, swelling, and skin-related disorders. Some parts like leaves and roots are used for laxative, cardiogenic, digestive, and diaphoretic action. Moreover, these parts also showed their action against whooping cough, hepatitis, and asthma-related issues particularly in some regions [29, 30]. Decoction of berries is useful in treating pulmonary tuberculosis, bronchitis, diarrhea, hydrophobia, and rat bite [29]. Scientific studies provide pieces of evidence suggesting the medicinal importance of *S. nigrum* and its part in arthritis [31], cancer [32–34], oxidative stress [35], and disease caused by hepatitis C virus (HCV) and human immunodeficiency virus (HIV) [36, 37]. Moreover plant also possess pharmacological activities like anti-ulcer [38–40], hepatoprotective [41], and cardioprotective action [42, 43]. Phytochemical studies of *S. nigrum* show the presence of glycoalkaloids like solanine, solamargine [44], and solasodine [45] as the primary marker compounds (demonstrated in Fig. 1).

Flavonoids, namely quercetin, luteolin, malvidin, pelargonidin, rutin, naringenin, apigenin and kaempferol [46], were reported. Moreover, carbohydrates, saponins [47], and sterols [48] were also reported. A combination of these phytochemicals indicates *S. nigrum* could be a promising therapeutic option for the treatment of COVID-19 and post-COVID complications. *S. nigrum* was also included in the guidelines for Ayurveda practitioners for COVID-19 published by the Ministry of AYUSH, where the use of the plant is recommended as a vegetable in the diet for the management of COVID-19 [49]. Moreover, *in silico* findings of plant phytochemicals against multiple target proteins of SARS-CoV-2 (depicted in Table 1) strengthen our hypothesis.

Furthermore, pharmacological studies suggest the role of the plant as an immunomodulator, anti-inflammatory, and antiviral agent [25, 64] (demonstrated in Table 2).

Thus, the present review features the potentiality of *S. nigrum* in treating acute and chronic post-COVID-19 complications.

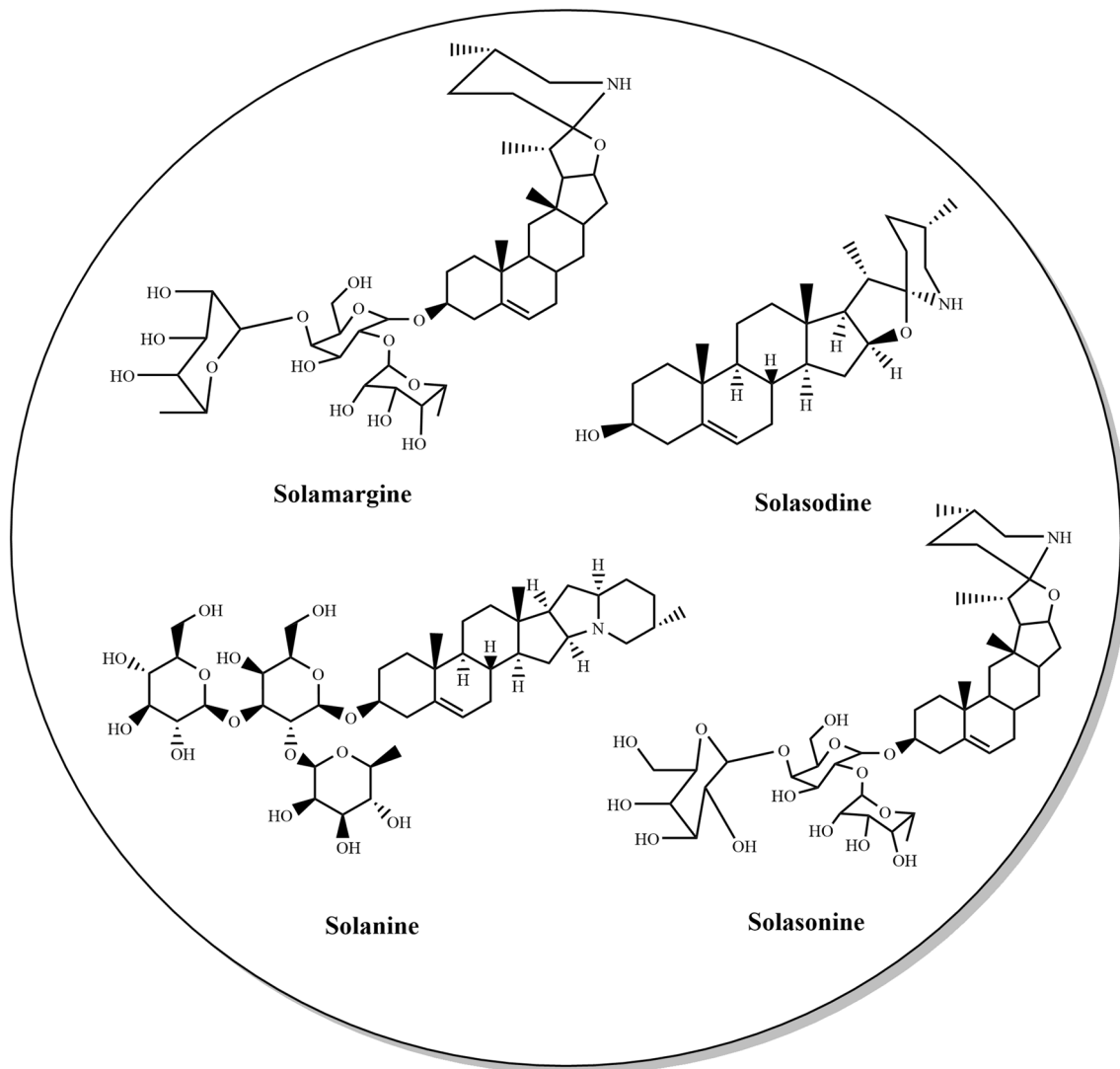


Fig. 1 Major phytoconstituents of *Solanum nigrum* L.

Table 1 *In silico* studies of phytoconstituents present in the *Solanum nigrum* L.

Sr. no	Phytoconstituent	Software Used	Spike (S)	ACE2	3CL ^{pro} /M ^{pro}	RdRp	PL ^{pro}	Reference
1	Kaempferol	Autodock Vina, Molecular Operating Environment software (MOE)	−8.5	−7.20	−7.8	−6.1	−5.2	[50–52]
2	Luteolin	Autodock, MOE, Autodock Vina	−8.0	−10.1	−8.17	−8.3	−7.1	[51, 53–57]
3	Naringenin	Autodock Vina, MOE, Glide (Schrödinger)	–	−6.05	−7.89	−6.4	−5.8	[53, 54, 57, 58]
4	Apigenin	Autodock 4.2, AutoDock Vina	−7.8	−6.5	−7.83	−5.5	–	[50, 53, 56]
5	Quercetin	AutoDock 4 and Auto-Dock Vina	−8.2	−6.0	−7.5	−7.4	–	[59, 60]
6	Myricetin	AutoDock 4.2, AutoDock Vina, Glide (Schrödinger)	–	−7.59	−7.3	−8.4	–	[61, 62]
7.	Rutin	Glide (Schrödinger), AutoDock Vina	−9.2	−11.5	−9.2	−9.0	–	[56, 58, 60]
8	Hesperetin	Autodock Vina, Autodock 4.2	−7.7	−7.45	–	–	–	[56, 61]
9	Solanine	Glide	−9.5	−6.0	−10.3	−6.1	–	[58, 62]
10	Solamargine	Glide	–	−5.6	–	−10.8	–	[58]
11	Solasodine	Glide	–	−4.8	–	−4.2	–	[58]
12	Solanocapsine	AutoDock Vina	–	–	−7.9	–	–	[63]

Table 2 Reported pharmacological activities of *Solanum nigrum* L. useful in COVID-19

Sr. no	Activity	Plant part	Extract	Conc/Dose	Model	Effect	Reference
1	Anti-inflammatory	Berries	MeOH	125, 250 and 375 mg/kg	Carrageenan induced rat paw edema	23.45% reduction in edema caused by carrageenan after 3 h	[65]
2		Berries	EtOH	100–300 mg/kg	Carrageenan induced rat paw edema	63% inhibition at the highest dose of 300 mg/kg	[66]
3		Fruits	EtOH	125–1000 mg/ml	TPA inflammation induction model using RAW264.7 cells	79.8% inhibition of NO production	[67]
4		Whole plant	MeOH	100 and 200 mg/kg	Carrageenan induced rat paw edema	44.81% inhibition in albino rats at the maximum dose	[68]
5		Whole plant	EtOH	100 and 200 mg/kg	Carrageenan induced rat paw edema	100 and 200 mg/kg exhibited 40.36% and 68.46% inhibition respectively	[69]
6		Berries	MeOH	2.5, 5, 10, 20, 40, 50 μ M	LPS-induced model	IC ₅₀ 11.33 to 49.35 mM	[70]
7	Antiviral Activity	Whole plant	MeOH	100 μ g/ μ l	Huh-7 cell lines	Methanolic extract of <i>S. nigrum</i> shows 37% inhibition	[37]
		Seeds	Chloroform			Chloroform extract shows 50% inhibition of HCV	
8		Aerial parts	Aqueous	100 μ g/ μ l	Human T-cell line	32.6% inhibition in HIV-PR 17.4% inhibition against HIV-1 RT	[36]
9	Immunomodulation	Whole plant	EtOH	90, 180, and 360 mg/kg	ELISA Method: IFN- α and IL-4 assay	Significant increase in the CD4+ and decrease in the percentage of CD8+ T lymphocyte	[71]
10		Whole plant	Aqueous	50, 100, and 200 mg/kg	H ₂₂ cell lines	IL-2 and IFN- γ levels increased significantly in H ₂₂ bearing mice	[72]
11		Dried stems	Aqueous	200 μ g/ml	ELISA, Flow cytometry	Increase in the CD4+/CD8+ lymphocyte ratio as well as the immune organ indexes	[73]

MeOH Methanol, EtOH Ethanol

Pathophysiology of COVID-19

Coronaviruses belong to the group of RNA viruses known to cause mild-to-severe respiratory infections in animals and humans. In the last two decades, three different variants of coronaviruses have caused severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and SARS-CoV-2 in humans [74, 75]. Like other coronaviruses, SARS-CoV-2 consists of spike glycoprotein (S), an

envelope protein (E), membrane protein (M), and a nucleocapsid protein (N). S, E, and M proteins make up the virus envelope, and the N protein holds the viral genome. The diameter of SARS-CoV-2 is around 50–200 nm in diameter [76]. It is still unclear about the transmission of the virus to humans, but the most likely hypothesis suggests the cross-transmission of the virus through bats and pangolin [77].

Viral entry and lung damage

SARS-CoV-2 enters the host through the nasal cavity and invades ciliated cells [78]. Angiotensin-converting enzyme 2 (ACE2) receptors are present in most cells, including the lungs, heart, kidney, and liver. The Spike protein of SARS-CoV-2 enters the cells through ACE2 receptors in the lungs. The entire process is carried out with the support of transmembrane protease serine 2 (TMPRSS2) [79]. Damage to the respiratory tract was due to excessive mucus and cell debris present in the respiratory tract, and the lungs are filled with fluid, fibrin, and hyaluronan [80].

In the beginning, the viral load remains high in the lower respiratory tract. The inflammatory response is initiated by infected cells and macrophages present in the alveolar, with the recruitment of neutrophils, lymphocytes, and monocytes [81]. Vasoactive peptide kinins are released with disease progression, activating endothelial kinin receptors, relaxing the vascular smooth muscle, and upregulating vascular permeability [82]. ACE2 controls this entire signaling cascade. Uncontrolled release of proinflammatory markers further results in pulmonary edema entering the alveolar, leading to hyaline membrane formation and acute respiratory distress syndrome (ARDS). The coagulation pathway leads to the formation of the microthrombi [81].

Lung Fibrosis

Pulmonary fibrosis is defined as a decrease in lung function that leads to respiratory failure [83]. Pro-fibrotic factors initiate lung fibrosis, mainly transforming growth factor- β (TGF- β). In a normal scenario, the release of TGF- β from the affected lung leads to tissue repair and damage correction due to an infection. However, excessive infection of COVID-19 leads to higher secretion of TGF- β , ultimately leading to the transition of cells like epithelial-to-mesenchymal transition [84, 85]. This transition leads to thickening of the inner wall of the lungs and eventually loss of efficacy of the lungs [86].

Coagulopathy

Thromboembolism of arteries and veins is one of the critical manifestations of severe COVID-19 infection [87, 88]. The exact cause of this phenomenon is unknown. However, some studies suggest that invasion of lung endothelial cells leads to an increase in D-dimer concentrations (3–50 times higher than normal concentrations), fibrinogen, an increase in prothrombin and thromboplastin time, and thrombocytopenia [89–91]. The circulating concentration

of D-dimer remains very high in severe COVID-19 than in general pneumonia patients.

Cytokine storm

Production of cytokines mainly depends upon two pathways: The first is direct viral detection by immune cells via pattern-recognition receptors, mainly Toll-like receptors (TLR-3, 7, 8, 9). The second pathway is by activating damage-associated molecular patterns (DAMPs) by damaged epithelial cells [92, 93]. When the injury occurs to different cells like endothelial, epithelial, and parenchymal, they tend to release a variety of inflammatory markers which activate an acute immune response [94]. Some studies showed circulating concentrations of proinflammatory markers like tumor necrosis factor (TNF), interleukin-6 (IL-6), monocyte chemoattractant protein 1 (MCP1), and macrophage inflammatory protein-1 α (MIP-1 α) were higher in patients with COVID-19 [95]. The exact pathophysiology of cytokine storm is debatable, but an increase in proinflammatory markers is proven in COVID-19 infection, although current evidence neither supports nor rejects the fact that proinflammatory response is due to the damage to the lungs only.

Current evidence regarding the pathophysiology of SARS-CoV-2 indicates that SARS-CoV-2 causes cold-like symptoms when present in the upper respiratory tract. When it settles down to the lower respiratory system, it causes severe pneumonia and breathing difficulties. Rather than alveolar infection, endothelial and epithelial infection appears too dominant [96, 97]. The destruction of the alveolar epithelial–endothelial barrier is essential for the development of severe pneumonia and acute respiratory distress syndrome (ARDS). The inflammatory response is atypical; although patients with COVID-19 have elevated circulating proinflammatory cytokines over a longer time than patients with influenza [98], for example, the concentrations seem to be significantly lower than are typical in non-COVID-19-related ARDS [99]. The inflammatory characteristics thus far observed in patients with COVID-19 suggest that either the systemic cytokine component is not a crucial contributor to COVID-19 severity or that the disease features its own unique, poorly understood, yet detrimental inflammatory profile. The inflammatory response remains highly unusual. Though proinflammatory markers are higher in COVID-19 patients, it is much lower than in non-COVID-19 patients with ARDS. The exact pathophysiology is still unknown, and scientists worldwide are working around the clock to understand how coronavirus affects the human body to develop new therapeutic drugs and approaches.

Post-COVID complications of COVID-19

Almost 80% of the patients who have recovered from COVID-19 infection complained about one or more symptoms since the beginning of the pandemic. Due to constant waves of infection shattering healthcare and research, very little importance has been given to post-COVID complications. But now, many prospective and retrospective studies have pointed out the seriousness of post-COVID manifestation. For example, a 6-month cohort study in Wuhan, China, showed that most patients have at least one of the following symptoms: fatigue or muscle weakness, sleep difficulties, and psychological problems, mainly depression. The study also pointed out that female survivors have higher stress levels and anxiety than males. The same study also found other complications such as abnormal pulmonary diffusion, renal dysfunction, newly diagnosed type-II diabetes, and venous thrombotic diseases [100]. In another prospective single health system, an observational cohort study examining severely ill COVID patients demonstrated that the intensity, frequency, and duration of the shortness of breath worsened after COVID-19. The study also observed severe psychological problems (20%) in patients who live alone [101]. Another meta-analysis showed altered diffusion capacity, restrictive pattern, and obstructive pattern in 39%, 15%, and 7% of patients [102]. The long-term complications that arise after COVID-19 infection are shown in Fig. 2.

Pulmonary complications

Invasion of lung epithelial cells barrier, systemic inflammatory response, and damage to the immune system plays an important role in pulmonary complications. Viral-dependent and independent mechanisms lead to disruption of the endothelial–epithelial layer of alveoli with monocyte and neutrophils infiltration in the alveolar space of the lungs. Fibrosis in the lungs is induced by proinflammatory cytokines such as TNF- α , IL-6, TGF- β , and superficial bacterial infection. Autopsy of lung tissue collected from five severe COVID-19-related pneumonia patients showed single-cell RNA patterns similar to end-stage pulmonary fibrosis without active COVID-19 infection, proving that some patients may suffer from pulmonary fibrosis even after recovering from the active infection. In addition, 20 to 30% of the recovered patients showed micro- and macrothrombosis, which is higher compared to any other disease condition indicating the role of COVID-19 infection even after the negative RT-PCR.

From dyspnea to pneumonia and lung fibrosis, pulmonary complications have been reported in COVID-19 survivors. After hospital discharge, abnormal pulmonary dysfunction has been reported in severe COVID-19 patients [103]. Severe patients showed a higher prevalence of diffusion capacity of carbon dioxide (DLCO) impairment and lower transfer factor of carbon dioxide (TLC) compared with non-severe patients after 30 days of discharge, indicating that severe patient requires more time to recover from pulmonary

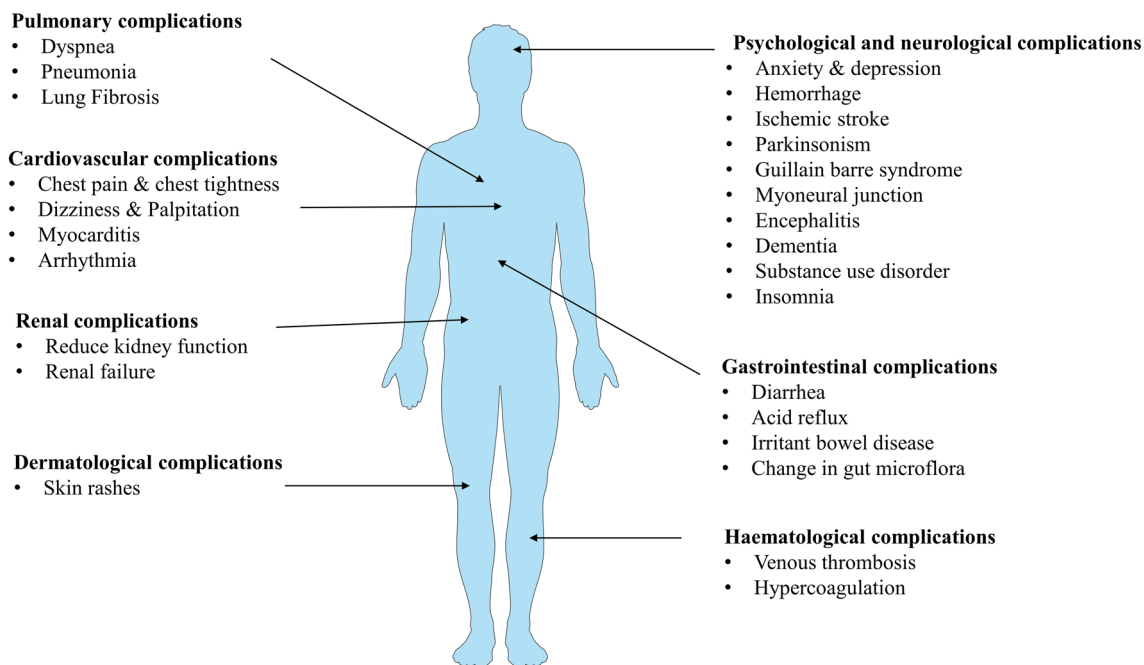


Fig. 2 Long-term complications associated with recovered COVID-19 patients

dysfunction [104]. A Swiss study has demonstrated that four months after SARS-CoV-2 infection, severe COVID-19 survivors were present with significant functional and radiological abnormalities, possibly due to small airway and lung parenchymal disease [105]. A 6-month follow-up CT study in severe COVID survivors found fibrotic-like changes in the lung within 6 months. Patients with fibrotic-like changes in the lung showed a 63% ARDS, also a predictor of fibrotic-like changes [106]. An almost similar result obtained in an Italian study was that 72% of the patient showed fibrotic-like changes after 6 months of CT [107]. A study on dyspnea and breathlessness in COVID survivors showed that 70% of previously hospitalized COVID-19 survivors experience fatigue and dyspnea 7 months after hospitalization. In addition, 45% of survivors found difficulties in day-to-day activities. It was found that gender difference, preexisting comorbidities, the number of symptoms present at hospital admission, and the number of days at the hospital were potential risk factors associated with fatigue and dyspnea [108]. An 8-month follow-up study in COVID-19 survivors showed that survivors with severe COVID-19 had higher incidences of DLCO impairment, persistent symptoms in daily life, dyspnea, and higher abnormal CT score as compared with mild cases [109]. 1-year prospective cohort study to evaluate lung abnormalities on serial computed tomography (CT) scans found that COVID-19 survivors showed continuous improvement on lung CT scans during 1 year. The study also showed that old age and the severity of COVID infection delay the recovery of lungs and require more comprehensive rehabilitation [110].

Cardiac complications

The mechanism involved in cardiac complications after COVID-19 infection includes downregulation of ACE2 receptors, lung fibrosis, and inflammatory and immune response affecting cardiac muscles, and the heart's conduction system. An autopsy study of 39 COVID-19 patients showed the presence of a virus in the heart. Inflammatory response and cytokine storm may lead to the death of cardiomyocytes and displacement of desmosomal proteins required for the cell adhesion process. Patients who recovered from COVID-19 exhibited more cardiometabolic demand after 6 months, leading to dysfunction of the renin-angiotensin system (RAS) and reduced cardiac reserve. Cytokines such as TNF- α and IL-6 lead to changes in ion exchange in cardiac myocytes leading to arrhythmias and cardiac myopathy.

Cardiovascular complications mainly occur in admitted severe or fatal cases of COVID-19 that have already developed ARDS. A 60-day cohort study on hospitalized COVID survivors found chest pain in 16.6% of patients, while 15.5% required rehospitalization [111]. Different perspectives and retrospective trials demonstrated persistent chest pain

ranging from 16 to 21% in severe COVID survivors after 60 days [112–114]. A 6-month Chinese cohort study found that 9% of survivors suffered from palpitation, while 5% suffered from chest pain [100]. A clinical study conducted on 287 hospitalized survivors in Egypt reported 28.9% chest discomfort, 1.4% myocarditis, and 0.3% arrhythmia after 20 days [115]. A half-year follow-up of patients recovering from severe COVID-19 in Wuhan, China, demonstrated that around 10% of survivors suffer from chest pain [116]. Based on the trial data, the most common cardiovascular complications were chest pain, dizziness, palpitation, chest tightness, and chest problem on exertion. At the same time, few people were diagnosed with myocarditis and arrhythmia.

Dermatologic complications

The multisystem inflammatory response (MSI) had been documented in many patients who recovered from COVID-19. Those patients who had negative RT-PCR reports and positive antibody status point out that MSI may be due to the host immune response rather than the COVID-19 infection or viral entry and downstream consequence. More study data are required to evaluate the possible mechanism behind the dermatological consequences of long COVID-19.

While the most common symptoms of COVID-19 involve fever, coughing, and cold, skin problems can occur in up to 20.4% of patients after suffering from COVID-19 [117]. Around ten female survivors at Montefiore Medical Center, New York, USA, complained about hair loss after three months. These patients who do not have any history associated with hair loss indicate the possible effect of viral infection [118]. Only 3% of patients reported a skin rash at 6-month follow-up in the post-acute COVID-19 Chinese study [100].

Hematologic complications

Coagulopathy has been documented in around 20–30% of patients with acute COVID-19 infection. The underlying cause of coagulopathy may be an aggressive proinflammatory response and hypercoagulable condition. The possible mechanism that leads to coagulopathy includes injury to the endothelial layer followed by activation of platelet and downstream signaling leading to platelet-leukocyte cross-talk, infiltration of neutrophils, inflammatory response, and disturbance in the coagulation pathway. Coagulation in COVID-19 infection follows a similar pathway as any other thrombotic event. The possible complications from hypercoagulation in the hyperinflammatory state and how long it persists, although very little data are available to conclude this statement.

Venous thromboembolism has always been a critical concern in patients with COVID-19. Patients admitted to COVID-19 frequently developed venous thromboembolism during their hospital stay, especially in critically ill patients. A prospective follow-up study of patients admitted to the hospital due to COVID-19 showed that at 6 weeks after discharge, one (1%) of 102 patients developed asymptomatic venous thromboembolism event by venous ultrasound [119]. A prospective study in China of patients discharged after a hospital stay due to COVID-19 reported no deep vein thrombosis of lower limbs in 390 participants by ultrasonography 6 months after illness onset [100]. In a root cause analysis involving 1877 hospital discharges associated with COVID-19, nine episodes of HA-VTE were diagnosed within 42 days, giving a postdischarge rate of 4.8 per 1000 discharges. In 1 year, 18,159 discharges were associated with a medical admission, out of which, 56 episodes of health-care-associated venous thromboembolism (HA-VTE) were identified within 42 days (3.1 per 1000 discharges) [120].

Neuropsychiatric complications

The mechanisms involved in neurological and psychiatric complication of COVID-19 includes direct viral infection, systemic inflammation, neuronal inflammation, thrombosis, and stressful event. Till now, no evidence has been found regarding COVID-19 presence in neurons. However, autopsy reports of COVID-19 patients have found a change in parenchyma and vessel of the brain, possibly due to a change in the coagulation system or blood along with persistent inflammation and the blood–brain barrier.

Psychological complications

More than 30% of patients hospitalized with COVID-19 may experience anxiety, depression, and cognitive impairment that last for months after discharge. These symptoms are even more prominent in intensive care patients [121]. A UK-wide surveillance study to assess psychiatric manifestation in 153 COVID-19 patients concluded that 31% of patients had altered mental status, including anxiety and depression encephalopathy, in younger patients [122]. A retrospective cohort study evaluated neurological and psychotic outcomes in 236,379 survivors of COVID-19 at 6 months. After 6 months, the following complications were identified: intracranial hemorrhage (0.56%), ischemic stroke (2.10%), parkinsonism (0.11%), Guillain barre syndrome (0.08%), the myoneural junction (0.45%), encephalitis (0.10%), dementia (0.67%), anxiety/depression (23.59%), substance use disorder (6.58%), and insomnia (5.42%). The study also reveals that the severity of COVID-19 had a clear effect on

subsequent neurological diagnoses [123]. An observational study of 58 COVID-19 patients in France reported a confused state of mind, agitation, depression, and anxiety [124].

Neurological complications

A UK-wide surveillance study to assess acute neurological manifestation in 153 COVID-19 patients concluded that 62% of patients suffered from cerebrovascular events [122]. An observational study of 58 COVID-19 patients in France reported encephalopathy and acute ischemic strokes [124]. The risk of ischemic stroke and intracranial hemorrhage was high after COVID-19, with the prevalence of ischemic stroke rising to almost one in ten in patients with encephalopathy. A higher risk of stroke in patients was identified in COVID-19 patients than in those who had a common cold or influenza [125].

Renal complications

Traces of SARS-CoV-2 have been found in renal tissue and necrosis of tubules in necropsies and autopsies of severe COVID-19 patients. As renal failure is associated with a high risk of APOL1 alleles, point out that SARS-CoV-2 can hit only susceptible patients in the same manner as human immunodeficiency virus (HIV). In addition, thrombosis and coagulopathy may also be significant contributors to renal complications.

Kidney involvement is most common in patients with SARS-CoV-2 infection, and chronic inflammation and injury may remain for many months, resulting in a progressive decline in kidney function that leads to kidney failure [126]. A US study from the Veterans Health Administration (VHA) conducted a comprehensive study of long COVID and reported that COVID-19 increased the risk of chronic kidney disease, and the chance was found to be higher who were severely ill [127]. A follow-up study in China found that 35% of patients had reduced kidney function 6 months after COVID-19 hospitalization. Moreover, 13% of patients who did not have AKI during hospitalization showed a reduction in GFR at a 6-month follow-up [100].

Gastrointestinal complications

Mild-to-moderate gastrointestinal complications have been reported in COVID-19 survivors. The presence of viral debris like ribonucleic acid has been documented in fecal after at the 11th day after negative RT-PCR results. COVID-19 can potentially change the gut microflora and lead to the accumulation of bacteria, which may lead to opportunistic

infection. The role of gut Microbiota in respiratory illness has been proven in influenza infection. Long COVID-19, patients have experienced irritable bowel syndrome and acid reflux problems. Diarrhea, one of the prominent symptoms of acute COVID-19 infection, typically wears off after 14 days and does not last long. No other serious complications were detected in COVID survivors, indicating no role of COVID in gastric complications.

Hepatic complications

Patients with chronic liver disease and cirrhosis have a low immune response and are more susceptible to COVID-19 infection. Elevated serum levels of ALT and AST were found in hospitalized COVID-19 patients who are not related to increased levels of inflammatory markers or muscle breakdown pointing out that increased liver markers were due to direct liver injury. Patients with very high serum ALT levels also had a high amount of CRP, D-dimer, ferritin, and IL-6. Most of the liver enzymes achieved normal levels after COVID-19 infection. As of now, no particular study is presently focusing on liver complications in long COVID-19. However, an injury sustained during COVID infection may affect the liver in the longer term.

Solanum nigrum in COVID-19 with special emphasis on its immunomodulatory, anti-inflammatory and antiviral action

Numerous medicinal plants and phytochemicals are being recommended to treat COVID-19 based on previous reports against coronaviruses [128–135]. Similarly, during the early pandemic crisis, the Ministry of AYUSH recommends a few Indian medicinal plant-based formulations possessing antiviral, anti-inflammatory, and immunomodulation action [25]. Thus, it is clear that to find a novel therapeutic agent to be effective against COVID-19 from natural sources, a medicinal plant must possess antiviral, anti-inflammatory, and immunomodulatory properties to treat COVID-19 and post-COVID effects as well.

S. nigrum is an edible, herbaceous plant belonging to the family Solanaceae. Commonly, it is known as black nightshade and garden nightshade. The whole plant and its various active constituents exhibit immunomodulatory, anti-inflammatory, and antiviral action, which is the main prerequisite for developing a therapeutic agent for COVID-19 (Table 1).

Immunomodulation

Polysaccharides of the plant *S. nigrum* are very well-known for immunomodulatory activity [72, 73, 136]. The aqueous

and alkali extract of *S. nigrum* containing polysaccharides at 50, 100, and 200 mg/kg doses reduces interleukin-10 (IL-10), and along with this action, it also shows anticancer potential by inhibiting mouse hepatoma 22 ascitic tumor (H22) cell growth and increases the weight of tumor-bearing mice [72]. In another study, polysaccharides from the *S. nigrum* stem showed anticancer and immunomodulatory activity. These polysaccharides activate the Toll-like receptor 4-myeloid differentiation primary response 88 (TLR4-MyD88) signaling pathway to promote immune activity and inhibit tumor growth [73]. Similarly, flavonoids like myricetin, rutin, quercetin, and kaempferol are also present in various plants and reported to significant immunomodulatory activity [60, 137]. It is stated that flavonoids can interfere with the mTOR pathway and induce CD4+ and T regulatory cells, thus possessing immunomodulatory action by limiting chronic inflammation [138].

Anti-inflammatory activity

It is investigated that patients with severe COVID-19 are also suffering from acute respiratory distress syndrome due to increased levels of proinflammatory cytokines [139]. *In vitro* and *in vivo* studies performed on different plant parts and active constituents of *S. nigrum* from berries, leaves, and stems prove anti-inflammatory activity [65, 67–70, 140]. Methanolic extract of *S. nigrum* fruits at 125, 250, and 275 mg/kg doses showed significant anti-inflammatory activity by inhibiting the edema caused by carrageenan [140]. A similar study performed at a dose of 375 mg/kg also indicated the anti-inflammatory action of plant berries [66]. At acute and sub-acute stages of inflammation, extract of the whole plant of *S. nigrum* (100 and 200 mg/kg) showed anti-inflammatory potential as compared to indomethacin (10 mg/kg) [69]. Ethanolic extract of the plant berries at 100, 200, and 300 mg/kg concentrations showed 28, 52, and 63% inhibition against carrageenan-induced paw edema. These dose-dependent results confirm the anti-inflammatory potential of plant berries [65]. Solanine, an active glycoalkaloid, was evaluated for anti-inflammatory activity in the croton-oil-induced skin-inflammation model. The alkaloidal fraction containing solanine showed 80% percentage inhibition to reduce ear edema in swiss mice and thus showed anti-inflammatory action [141]. Solasodine at doses of 5, 30, and 75 mg/kg can also produce anti-inflammatory action by inhibiting arachidonic acid, cyclo-oxygenase (COX), and the 5-lipoxygenase pathway, which ultimately reduces inflammation in carrageenan-induced paw edema [142]. Three steroidal glycosides from the plant demonstrated anti-inflammatory potential in LPS-induced RAW 264.7 macrophages. A significant inhibitory effect was seen against LPS-induced nitrous oxide (NO) production and thus proves the anti-inflammatory action of phytoconstituents of *S. nigrum* [70].

Kaempferol and other glycosides show anti-inflammatory action by inhibiting cytokine storm in SARS-CoV-2 infection [143–146]. Similarly, other constituents like apigenin, luteolin, rutin, and quercetin showed anti-inflammatory action through various pathways [147]. Moreover, these flavonoids are also included in various Traditional Chinese Medicine (TCM) formulations recommended to treat SARS-CoV-2 infection in China [148–150]. Evaluation of three selected TCM formulations through network pharmacology proves that they are beneficial in COVID-19 by reducing IL-6 levels [151]. It has also been proved that IL-6 inhibitors play a major role in the treatment and prevention of COVID-19 [152].

Antiviral activity

Antiviral *in vitro* culture assay using Huh-7 cell line and real-time quantitative RT-PCR of methanolic and chloroform extract of *S. nigrum* possesses 37% and 50% inhibition against HCV [37]. However, aqueous extract of aerial parts of *S. nigrum* at a dose of 100 µg/ml possesses antiviral action against HIV-1 protease and HIV-1 reverse transcriptase by showing 32.6% and 17.4% inhibition, respectively [36]. Both studies demonstrate that plants possess antiviral action against RNA-based viral diseases like HIV and HCV. So, it can be assumed that it could be a potential therapeutic agent against COVID-19 and other RNA-based viral diseases.

Thus, considering the plant's immunomodulatory, antiviral, and anti-inflammatory activities, we proposed that *S. nigrum* would be a potential candidate for the management of COVID-19 and post-COVID complications.

Role of *Solanum nigrum* in COVID-19: *in silico* studies

The major proteins that facilitate the entry mechanism of the novel SARS-CoV-2 virus into the host cell are spike S protein, angiotensin-converting enzyme-2 (ACE2), and human transmembrane serine proteases type-II (TMPRSS2). Similarly, 3C-like main proteases (CL^{pro}) and Papain-like proteases (PL^{pro}) are responsible for viral encoding. However, RNA-dependent RNA polymerase (RdRp) produces multiple copies of RNA and is thus involved in the infection cycle. Some lead molecules from natural sources can be used to target these different proteins of SARS-CoV-2 to control viral infection and post-COVID complications. Previous reports claim that certain phytochemicals such as catechins, polyphenols, and flavonoids are mainly responsible for inhibiting viral entry and replication [153–155]. Viral pathology suggests that virus proteins are required for the entry and multiplication of SARS-CoV-2. To identify active constituents of *S. nigrum* as potential inhibitors

of SARS-CoV-2 proteins, multiple *in silico* studies have been carried out. Molecular docking studies of flavonoids evidenced potent inhibitors of proteins involved in SARS-CoV-2 infection [56, 156–158]. For example, luteolin represents its potential against SARS-CoV-2 by binding with a spike (−8.149) (S), TMPRSS-2 (−7.4) ACE2(−10.1), M^{pro} (−8.17), and RdRp (−8.3) protein through *in silico* approach [53–55, 57, 159]. *In silico* docking analysis of rutin revealed excellent binding with a spike (−9.2), ACE2 (−11.5), M^{pro} (−9.2), and RdRp (−9.0) protein that suggest its potentiality towards SARS-CoV-2 [56, 58, 60]. Similarly, molecular docking of kaempferol showed maximum binding affinity towards spike and ACE2 protein with the binding score of −8.5 and −7.20, respectively [50, 52, 57]. Myricetin, an active flavonoid, docked against multiple SARS-CoV-2 proteins, including ACE2, CL^{pro}, and RdRp, and the result demonstrates a satisfactory binding score, i.e., greater than −7 kcal/mol [50, 61, 62]. Phytoconstituents like solamargine and solanine were also identified through molecular docking, and results revealed good binding affinities towards viral targets like a spike, M^{pro}, and ACE2, RdRp [58, 62]. Other alkaloids of *S. nigrum* like solasodine (−8.3), solanine (−9.0), solasurine (−9.1), and α-solamargine (−10.8) have good binding energies against 3CL^{pro} [160]. Active constituents present in *S. nigrum* targeting various stages of SARS-CoV-2 are shown in Fig. 3

Thus, available literature on molecular docking and other pharmacological reports indicates that *S. nigrum* could be used for inhibition of SARS-CoV-2 entry, replication, and suppression of COVID-19 symptoms.

Potential role of *Solanum nigrum* in post-COVID-19 complications

Pulmonary complications

Hospitalized COVID-19 patients suffer from lung fibrosis, pneumonia, chronic cough, and pulmonary embolism [161, 162]. *S. nigrum*, play a very important role in the treatment of respiratory disorders and the management of cough [163]. Petroleum ether, ethanol, and aqueous extracts of *S. nigrum* fruit show antiallergic and antihistaminic action by inhibiting contraction caused by histamine and resisting the increased leukocytes. Thus, berries of the plant represent a potential role in the treatment of asthma [164]. Furthermore, phytochemicals of *S. nigrum*, such as kaempferol, and luteolin, also have their effect on acute lung injury [165, 166], which is a beginning stage of ARDS [167]. Thus, the above findings conclude that fruit extract and phytochemicals of *S. nigrum* play an important role in controlling acute lung injury and pulmonary disorders, which ultimately suggests its potential in pulmonary complications of COVID-19.

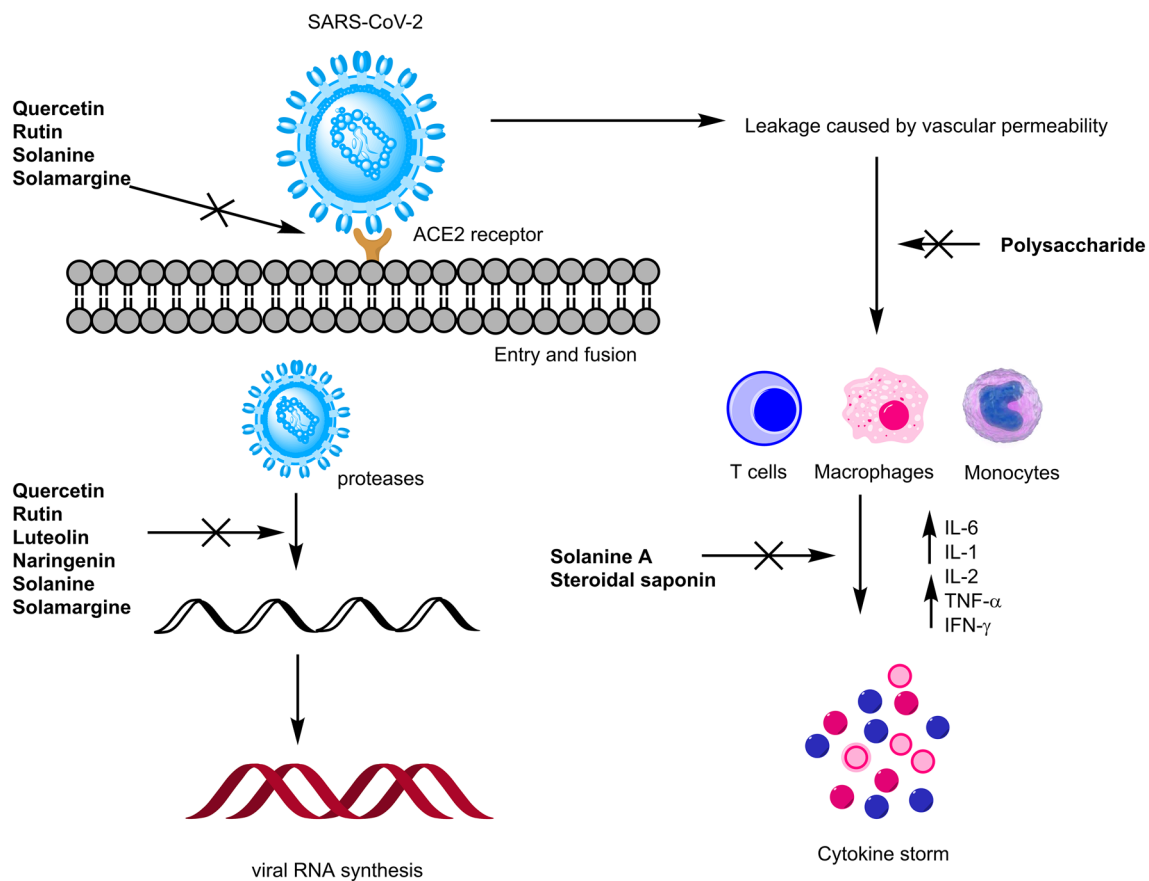


Fig. 3 Major targets of *Solanum nigrum* L. phytochemicals in SARS-CoV-2 infection (*in silico* and pharmacological)

Cardiac complications

Arrhythmia, myocardial infarction, heart failure, chest discomfort, and severe pain in the chest are the common consequences of COVID-19 after recovery. Traditionally, *S. nigrum* has been reported to have a potential role in treating multiple cardiac disorders [168]. A study conducted on isoproterenol-induced myocardial infarction rats showed the efficacy of *S. nigrum* as a cardioprotective agent. The hydroalcoholic extract of the whole plant at 75, 150, and 300 mg/kg was given to the albino rats and checked for cardioprotective and antioxidant activity. The *in vivo* study results have decreased QT interval (duration of ventricular electrical systole) and heart rate due to a decrease in myocardial damage. A reduction in biochemical parameters like triglyceride and cholesterol was also observed by the hydroalcoholic extract of the plant and thus confirms cardioprotective action [169]. Berries of the plant (2.5 and 5.0 mg/kg) also showed cardioprotective and antioxidant properties. The heart of male albino rats was isolated from estimating thiobarbituric acid reactive substances (TBARS), Myocardial Superoxide dismutase (SOD), reduced level of glutathione, and myocardial catalase content (CAT). Results

of this study expressed that myocardial TBARS was found to decrease ischemic reperfusion injury, and there was a significant increase in myocardial endogenous antioxidants enzymes (GSH, SOD, and CAT). Thus, fruit extract of *S. nigrum* shows a protective effect in ischemia–reperfusion-induced oxidative stress, which eventually indicates cardioprotective action [43]. Another study includes an aqueous extract of berries (1 g/kg) for cardioprotective action. In this *in vivo* study, doxorubicin (20 mg/kg i.p) was used to induce cardiac toxicity in rats, and carvedilol (30 mg/kg) was used as the standard. Results indicate a significant reduction in cardiac serum levels like cardiac serum markers creatinine phosphokinase (CKMB), lactate dehydrogenase (LDH), serum glutamate oxaloacetate transaminase (SGOT), and serum glutamate pyruvate transaminase (SGPT) and thus proved to produce cardioprotective effect [42]. Moreover, *S. nigrum* fruits have been proven to prevent vascular complications in streptozotocin-induced diabetic rats [170]. Hence, scientific research revealed the cardioprotective action of hydroalcoholic extract of the plant and its fruit that may help later in cardiac complications that arise after COVID-19.

Dermatologic complications

Hair loss is the most common symptom of a patient suffering from COVID-19 recovery. It has been reported that berries of the *S. nigrum* plant have been traditionally used for alopecia [171]. An herbal hair formulation containing berries extract of *S. nigrum* (0.5%), the flower of *Hibiscus rosa* (1%), and *Eclipta alba* (1%) was prepared on a laboratory scale and evaluated for effective herbal hair therapy. Phytoconstituents in this formulation showed effective action against 5- α -reductase and thus treated alopecia [172]. A recent study stated that *S. nigrum* could suppress proinflammatory cytokines in a model of 1-chloro-2,4-dinitrobenzene (DNCB)-induced atopic dermatitis (AD) and in TNF- α /IFN- γ -stimulated HaCaT cells. The *in vitro* and *in vivo* studies showed the efficiency of ethanolic extract of the plant in suppressing inflammatory cytokines, mitogen-activated protein kinase (MAPK), and nuclear factor- κ B (NF- κ B) in human adult low calcium high temperature (HaCaT) cells. Additionally, serum level of IgE and CD8+ and dermal thickness was also reduced in the DNCB model of AD [173]. A study also showed the efficacy of *S. nigrum* and *Azadirachta indica* in skin regeneration [174]. Hair loss is a serious concern after recovery from COVID-19. Furthermore, traditional and scientific reports suggest the plant's probable role in alopecia and other skin-related issues. Thus, *S. nigrum* could be useful in dermatological complications after COVID-19.

Neurological complications

Plants have been used for neurological disorders for so many years. *S. nigrum* also has a beneficial role in neurological diseases [175]. Two species of genus *Solanum*, namely *S. nigrum* and *S. macrocarpon*, at 2 mg/kg were given as dietary inclusions to rats for the evaluation of cognitive and neurochemical complications induced by scopolamine in rats, particularly in Alzheimer's disease. Increased level of acetylcholinesterase (AChE), monoamine oxidase (MAO), and butyrylcholinesterase (BChE) is reduced by both species [176]. Hence, this plant could be useful in the prevention of cognitive impairments for Alzheimer's involved after COVID-19 diseases. Leaves of the plant used as dietary inclusion at a dose of 0.1 to 1.0% w/v show a variety of benefits from protecting against aluminum-induced neurotoxicity [177] to preventing cerebral damage and behavioral changes by investigating carbonated alcoholic herbal beverage (CAHB). This *in vivo* study proves that aqueous leaves extract shows a constructive effect in CAHB-produced cerebellar edema, degeneration of Purkinje cells, vascular stenosis, and ulceration [178]. Phenolic constituents and aqueous leaves extract of the plant *S. nigrum* were reported to have ameliorative activity against superoxide dismutase

(SOD), glutathione-S-transferase (GST), TBARS, and glutathione levels [179]. Thus, results revealed that plant could be used for the prevention of free radicals caused by neurological diseases. Significant results of all the studies indicate the role of the plant in neurological diseases and eventually strengthen its role in the neurological complications of COVID-19.

Psychiatric complications

Although limited data are available to relate plant activity with psychiatric disorders. But a study showed the potential of aqueous extract of the leaves of *S. nigrum* at 30–60 mg/kg for anti-epileptic action in rats, mice, and chicks. Picrotoxin and pentylenetetrazol were used to induce seizures, and a 10–60 mg/kg dose was given to the animals. The extract showed dose-dependent inhibition and possessed anti-epileptic action [180]. Thus, the anti-epileptic activity of plant suggests that it could be useful in the psychiatric complication of COVID-19.

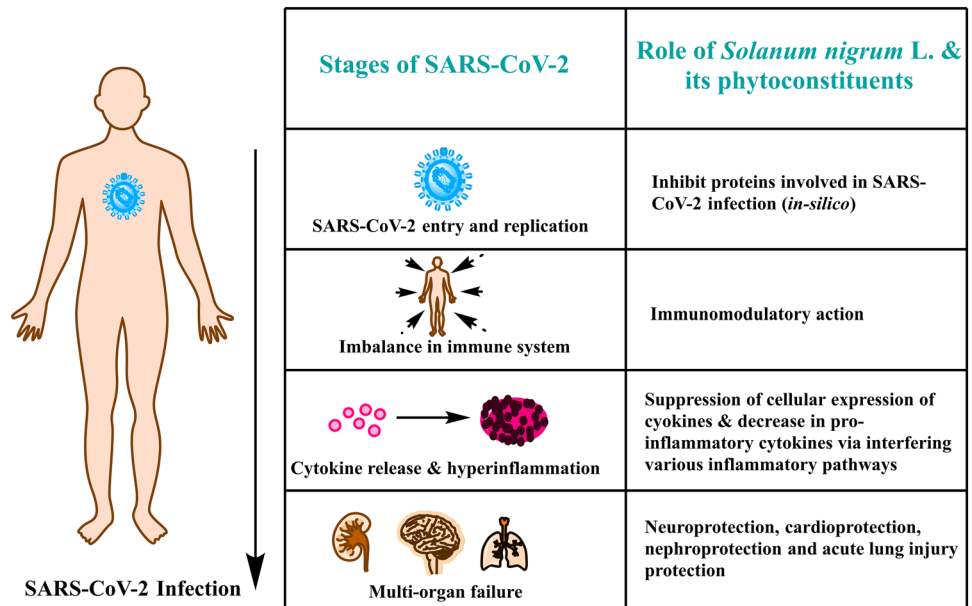
Renal complications

A report confirms the nephroprotective action of the plant *S. nigrum* based on its previous studies performed against kidney disorders. Histopathology studies showed that parameters such as ALP, ALT, AST, and bilirubin levels could be normalized by *S. nigrum*. The study also suggests the safer dose of *S. nigrum* is up to 5 ml/kg above which plant may be toxic [181]. Fruit extract of *S. nigrum* (200 mg/kg) shows nephroprotective action by showing significant reductions in blood urea nitrogen and serum creatinine. Results were compared with gentamicin-induced nephrotoxic rats [182]. A similar study performed by the same researcher, along with histopathology, proves the efficacy of plant fruits as a nephroprotective agent [183]. Hence, various renal studies performed on the plant disclose that *S. nigrum* is very effective in treating kidney disorders which indicates its possible role in the treatment of COVID-19-related renal complications.

Hematologic complications

Although *S. nigrum* does not play a major role in hematologic complications produced after COVID-19, it has been reported that the aqueous extract of leaves and fruit of the plant possesses hemopoietic and hematinic properties. Phenylhydrazine (10 mg/kg) produces anemia in Wistar rats, and aqueous extract of leaves and fruit of *S. nigrum* ultimately shows a defensive mechanism against anemia and significantly increases the red blood cell. The study also demonstrated the anti-bacterial and anti-parasitic properties of the aqueous extract of *S. nigrum* leaves [184].

Fig. 4 Possible therapeutic role of *Solanum nigrum* L. in long-term COVID-19 complications



Gastro complications

S. nigrum has proved its efficacy against ulcers. Methanolic leaves extract of *S. nigrum* at a dose of 500 mg/kg causes a reduction in ulcer index (77.85% in aspirin and 66.6% in CRS-treated groups) in the cold restraint stress model. The plant extract also showed an ameliorative effect on biochemical parameters and histological changes [38]. Another study on the methanolic extract of *S. nigrum* fruits proves its efficacy against gastric ulcers at 200 and 400 mg/kg doses [40]. Aqueous and hydroalcoholic extract of leaves and berries also showed a defensive mechanism against gastritis and ulcers in female albino rats. Ethanol and aspirin were used to induce gastritis and gastric ulcers, respectively. Aqueous extract of leaves (80 mg/kg and 250 mg/kg) and berries (50 mg/kg) significantly reduced ulcer index. Also, they showed an anti-gastritis effect by decreasing the concentration of Evans blue [185]. Recently, *Althaea officinalis* and *S. nigrum* demonstrated antioxidant and anti-ulcerogenic action on indomethacin-induced gastric ulcerated rats. *S. nigrum* is a gastro-protective agent as it can reduce TNF- α , IL-1 β , and gastric mucosal damage induced by indomethacin. Also, oral administration of plant extract causes a boost in the PG-E₂ level [39]. Hence, all these activities prove the efficacy of *S. nigrum* leaves and berries in gastritis and gastric ulcers which certainly suggests its role in gastric complications of COVID-19.

Hepatic complications

It has been proved that *S. nigrum* possesses hepatoprotective action *in vitro* and *in vivo* methods. Flavonoid-rich extract

of the plant at 100, 200, and 300 mg/kg doses showed a dose-dependent effect in CCl₄-induced hepatotoxic mice [186]. Similarly, aqueous extract of *S. nigrum* at the dose of 150 mg/kg also possesses hepatoprotective action against ethanol-induced hepatotoxicity by decreasing liver marker enzymes such as AST, ALT, ALP, and total bilirubin [187]. According to both studies, *S. nigrum* has proven efficacy against acute hepatic injury induced by CCl₄ and ethanol. A polyherbal extract containing three medicinal plants (*Andrographis paniculata*, *Tinospora cordifolia*, and *S. nigrum*) that have been known to treat liver disorders traditionally showed hepatoprotective action by showing reductions in triglycerides (TG) and low-density lipoproteins (LDL) at the dose of 500 mg/kg [188]. Hence, all these activities showed that *S. nigrum* could show hepatoprotective action, and it could be beneficial against hepatic complications that may arise after COVID-19.

Conclusions and future perspective

COVID-19 has changed the world scenario. Almost every drug failed to conquer the disease, while few drugs are successful only in minimizing or controlling the symptoms. Failure of currently available drugs to destroy the virus leads many scientists worldwide to find alternatives. Scientists successfully developed an mRNA vaccine quickly, but even after the vaccine, the threat of COVID-19 is still present among us. As a result, many critically ill patients are hospitalized for longer. Hospitalized patients had been treated with antiviral, anti-inflammatory, and steroidal drugs. Bombardment of drugs leads to many physiological changes in

the body, and patients recovering from COVID-19 face many complications, which were pointed out by many clinical and retrospective studies. The most prominent ones are headache, fatigue, anxiety, depression, difficulty in breathing, and neurological and cardiovascular complications. Post-COVID complications need to be addressed as they are also posing challenges to our day-to-day life.

Many healthcare professionals are working on revisiting the alternatives to standard drugs to tackle long-term complications. Many medicinal plants and their phytoconstituents possess the efficacy to treat the various complications of COVID-19. The traditional report indicates the role of *S. nigrum* in pulmonary tuberculosis, fever, bronchitis, and asthma-related issues. Moreover, overall literature on molecular docking and reported pharmacological activities confirms that *S. nigrum* has multiple potentialities in antiviral, anti-inflammatory, and immunomodulatory activity. A combination of these three activities is a necessity to develop a novel therapeutic agent for COVID-19.

Furthermore, developing therapies targeting major proteins in the viral life cycle would be a viable solution, and *S. nigrum* fulfills the need. Most adults who get SARS-CoV-2 infection experience several long-term symptoms that do not go entirely after several months. These complications are even more challenging than the SARS-CoV-2 infection because they cause diverse adverse effects on multiple organs. Pharmacological studies proved that *S. nigrum* plays a crucial role in protecting different body organs, i.e., nephroprotective, gastro-protective hepatoprotective, and neuroprotective action that will ultimately help in the post-COVID-19 complications (Fig. 4). However, further focused studies are required in this direction to place this herb as a solution to long-term post-COVID complications.

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Declarations

Conflict of interest The authors declared no conflicts of interest.

Ethical approval This article does not contain any studies with animal or human participants.

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