



Review Article

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Recent developments in the therapeutics of SARS-CoV-2 infection

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly transmittable respiratory virus that causes COVID-19 disease. Since its emergence in the early 2000s, SARS has posed significant public health challenges and continues to be a concern. This review provides an overview of current treatment strategies for SARS-CoV and explores the potential utility of herbal molecules in combating this viral infection. The primary treatment approach for SARS-CoV has historically centered on supportive care, which includes oxygen therapy, mechanical ventilation, and antipyretic medications to manage symptoms. However, with the ongoing advancement of medical research and our evolving understanding of the virus, several antiviral drugs have been developed and repurposed to target SARS-CoV. Recent developments in the field of herbal medicine have drawn attention to the potential efficacy of natural compounds in the management of viral infections, including SARS. Herbal molecules, characterized by their diverse bioactive constituents, exhibit antiviral properties that could be harnessed to mitigate SARS symptoms and inhibit viral replication. *Ocimum sanctum*, *Tinospora cordifolia*, *Zingiber officinale*, *Curcuma longa*, *Panax ginseng*, and *Aloe vera* have been identified for their immunomodulatory effects. This review highlights promising herbal molecules such as quercetin, and curcumin, which have demonstrated antiviral effects *in-vitro* and in some preclinical studies. While current treatment strategies for SARS primarily rely on supportive care and antiviral medications, the exploration of herbal molecules presents an exciting avenue for potential adjunctive therapies. Further research is required to validate their efficacy, safety profiles, and mechanisms of action. A holistic approach that combines conventional medicine with herbal remedies may offer new insights into the treatment of SARS and other viral respiratory illnesses.

KEYWORDS: SARS-CoV-2; Repurposed drugs; Herbal molecules; COVID-19; Quercetin; Immune booster

1. Introduction

December 2019 witnessed a burst of highly contagious respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which then rapidly spread all over the world, causing significant loss of life and wreaking havoc on global economies[1]. It was initially discovered as a probable root of baffling and untreated pneumonia but was eventually found to be a coronavirus disease. Oropharyngeal and nasopharyngeal swab testing revealed that SARS-CoV-2 predominantly infects patients' respiratory systems[2]. The initial incubation phase, which starts when a person is exposed to the virus and symptoms appear, lasts between one to fourteen days. Cough, rise in body temperature, and squatness of breath are the common symptoms of COVID-19, which eventually impairs the patient's respiratory system[3]. Patients infected with SARS-CoV-2 infection can be categorized into three groupings, namely, asymptomatic circumstances with or devoid of detectable virus, non-severe or insignificant symptomatic cases with the virus, and patients with elevated infection rates, multi-organ failure, and primarily respiratory failure who need medical attention[4].

Recent reports of the WHO suggest that over 775 million cases of COVID-19 have been reported accounting for over seven million deaths[5]. It has been discovered that among the three strains reported, novel coronavirus (nCoV-2019) SARS-CoV, and

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Middle East respiratory syndrome coronavirus (MERS-CoV), were extremely pathogenic in people and cause severe sickness. These viruses cause a variety of respiratory tract infections, including pneumonia, bronchiolitis, strep throat, a cold, sinusitis, and other symptoms like intermittent diarrhea[6].

Infants, the aged, and individuals with severe illnesses are more likely to get lower respiratory tract infections besides COVID-19 disease. SARS-CoV-2 is not restricted to the respiratory tract and has the potential to invade several other tissues of the human body, including the central nervous system[1]. Accumulated data suggest that a wide number of patients infected with SARS-CoV-2 have mild or moderate illnesses, but between 5% and 10% have severe or even life-threatening infections[7]. SARS-CoV-2 infection not only causes complications in the patients during the infection period, but accumulated evidence suggests that the post-COVID-19 complications, every so often stated to as extensive COVID or post-acute sequelae of SARS-CoV-2 infection be able to manifest in individuals who have recovered from the acute phase of the virus. These complications can vary widely but may include fatigue, shortness of breath, cognitive symptoms, joint and muscle pain, chest pain, headaches, loss of smell and taste, cardiovascular issues, gastrointestinal problems, mental health challenges, sleep disturbances, respiratory problems, hair loss[1]. Therefore, it's crucial to create SARS-CoV-2 control methods, considering the post-SARS-CoV-2 infection complications that are now being reported at a higher rate[7].

The COVID-19 vaccine program is already being used worldwide, but successful treatment is yet anticipated, especially in areas where vaccination rates are stagnant and vaccine resistance is a worry[8]. Additionally, roughly people may not counter well to COVID-19 vaccinations, including those who are immunocompromised, cancer patients getting chemotherapy, and others with hematologic malignancies[9]. Since the emergence of COVID-19, numerous readings and clinical trials have been conducted to find a medication for the condition, however, the majority are still in the early stages[10].

Numerous drugs were repurposed and other treatments like vaccines were authorized and constructed on an emergency usage sanction procedure to combat the pandemic[11]. Herbal medicine has indeed gained attention as a potential adjunct therapy in managing infectious diseases like COVID-19. While modern medicine remains the primary approach for treating such illnesses, herbal remedies are being explored for their possible benefits. It is essential to approach these alternative treatments with caution, relying on scientific evidence and expert recommendations. Apart from this, various foods and nutraceuticals have been recognized for their potential to combat viruses and regulate the immune system. *Glycyrrhiza glabra*, *Pelargonium sidoides*, *Atropa belladonna*, *Ocimum sanctum*, *Tinospora cordifolia*, *Zingiber officinale*, *Curcuma longa*, *Panax ginseng*, and *Aloe vera* have been identified for their

immunomodulatory effects. Currently, immunoglobulin therapy, antivirals, anti-inflammatories, cell therapy, convalescent plasma therapy, nutraceutical supplementation, and monoclonal antibodies are among the potential therapeutic approaches that are discussed in the present review to highlight recent developments in COVID-19 research, with prime focus on prospective treatment approaches that could be used to manage COVID-19-related problems.

2. The lifecycle of coronavirus in the host cell

The peak common approach to SARS-CoV-2 transmission is over respiratory droplets, near contact with infected individuals, and contaminated items that then come into contact with the nose, mouth, or eyes of healthy individuals[8]. SARS-CoV-2 principally marks lung epithelial cells, while also affecting immune cells, cerebral neuronal cells, and epithelial renal tubules to varying degrees[12]. Structurally, coronavirus contains four main proteins, which include spike, membrane, envelop proteins, and lately nucleocapsid protein (Figure 1). The envelope of coronavirus is dotted with glycoproteins in addition to the nucleoprotein, and the membrane protein is encircled by a core enclosed in single-stranded RNA. The host cell's adherence to the virus is controlled by the envelope glycoproteins. Seven genes (*E*, *ORF1A*, *M*, *ORF1B*, *S*, *ORF3*, and *N*) are located in the 5' to 3' orientation of the RNA genome. The *ORF1A* and *ORF1B* genes create two viral replicas of polyproteins (pp1a in addition to pp1ab). Non-structural proteins break down the polyproteins to form the replicase transcriptase complex[13].

The SARS-CoV-2 virus primarily targets cells in the respiratory tract that express the Angiotensin-converting enzyme 2 (ACE-2) receptor. When the virus enters the body through the respiratory system, its spike proteins bind to these ACE-2 receptors on target cells[14]. This binding helps clear mucus and bacteria from the lungs, but it also allows the virus to enter and infect these cells. ACE-2 protein is found in various organs, including the lungs, gastrointestinal system, and the brain, creating these structures susceptible to SARS-CoV-2 infection. ACE-2 is particularly common in type-2 pneumocytes, which are crucial for gas exchange in the alveoli[15]. Furthermore, SARS-CoV-2 can disrupt the normal functioning of the renin-angiotensin system (RAS) by attacking ACE-2 receptors in the kidneys. The virus can also enter the brain because ACE-2 receptors are present in brain tissues. When the virus's spike-like protein attaches to ACE-2 receptors on these organs, it interferes with the regulation of angiotensin II, leading to abnormal functioning of ACE-2-producing tissues. Additionally, the virus relies on the cofactor transmembrane serine protease 2 to facilitate its access into cells, which promotes viral replication and infection[16,17].

Upon exposure to SARS-CoV-2, the immune system is activated

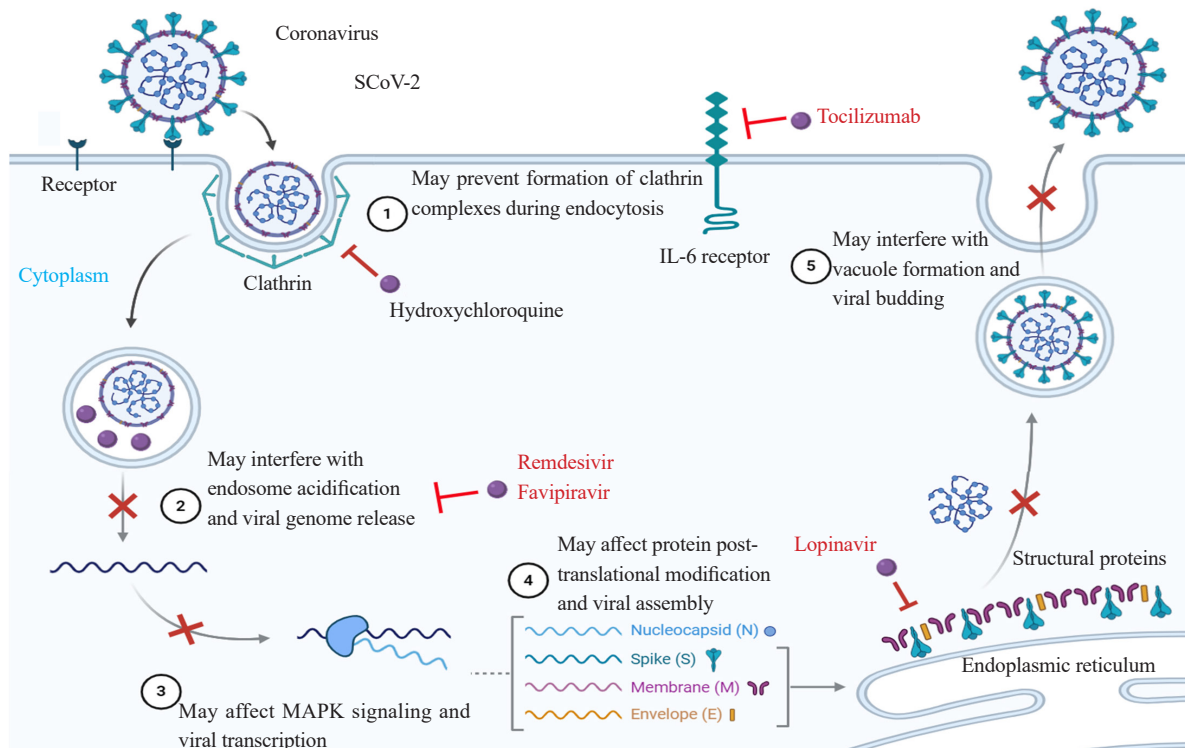


Figure 1. Sites of repurposed drug action for the management of SARS-CoV-2 infection.

in the host, and inflammatory cytokines are released into the systemic circulation[18]. Inflammation, fever, a drop in blood pH, and pleural outflow are all caused due to the excessive generation of cytokines and other protected cells, which include lymphocytes and neutrophils. The immune response thus generated is responsible for initiating the sequence of events leading to the development of lung injury. Data accumulated from the deceased individuals suggest that there is a significantly higher level of pro-inflammatory mediators such as IL-6 and TNF- α in patients suffering from SARS-CoV-2 infection[19].

Individuals initially confirmed as positive for SARS-CoV-2 through molecular diagnostic tests like polymerase chain reaction (PCR) and antigen tests can be categorized into different infection severity levels based on their symptoms and clinical assessments. Those with a mild infection, typically exhibit symptoms such as fever, cough, headache, or muscle pain but do not show signs of shortness of breath, dyspnoea, or uncharacteristic chest imaging[20]. In contrast, individuals with moderate infection maintain an oxygen saturation level of $\geq 94\%$ while showing clinical signs of lower respiratory disease. Severe infection, encompasses individuals with respiratory frequencies exceeding 30 breaths per minute, oxygen saturation levels $< 94\%$, a proportion of arterial partial pressure of oxygen (PaO_2) to a portion of inspired oxygen (FiO_2) < 300 mmHg, or lung infiltrates covering more than 50% of the lung area[21]. Critically infected patients experience severe respiratory failure, multiple organ failures, and septic shock, while in pediatric cases, especially neonates, hypoxia is a crucial criterion used to define

severe illness.

One of the most common and severe complications is acute respiratory distress syndrome, where the lungs become severely inflamed, leading to difficulty in breathing and reduced oxygen levels in the blood. This can result in the need for mechanical ventilation and can be life-threatening. COVID-19 can also lead to the formation of blood clots in the lungs (pulmonary embolism) or other parts of the body, increasing the risk of complications such as stroke or heart attack. Beyond the respiratory system, COVID-19 can affect the cardiovascular system, leading to myocarditis (inflammation of the heart muscle), arrhythmias (irregular heart rhythms), and even heart failure[20]. Neurological complications, such as stroke, encephalitis, and Guillain-Barré syndrome, have also been reported, highlighting the virus's ability to affect the nervous system[1]. Furthermore, COVID-19 can cause systemic inflammation and immune dysregulation, leading to a cytokine storm, a severe immune response that can damage multiple organs and tissues throughout the body. This heightened inflammatory state can contribute to multi-organ failure and significantly increase the risk of mortality. Additionally, individuals with underlying health conditions, such as diabetes, obesity, hypertension, or immunocompromised states, are at higher risk of developing severe complications from COVID-19. Understanding these complications is crucial for healthcare providers in effectively managing and treating COVID-19 patients, as well as for public health efforts aimed at preventing and controlling the spread of the virus[21].

Due to the limited number of individuals infected with SARS-CoV-2 at the beginning of the endemic, the number of “mutant” variant viruses was modest[22]. Numerous SARS-CoV-2 variations have developed since then as a result of the enormous number of illnesses, including extended infection in immunocompromised persons. The following variants have just received new names from the WHO: Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2).

3. Management and available therapeutics for SARS-CoV-2 infection

Currently, there is no precise treatment available for SARS-CoV-2 contamination and its related pathophysiology. Although vaccinations are being utilized to counter SARS-CoV-2 infection, the success rate is yet to be determined. The majority of therapeutic strategies currently being employed are merely supportive and focus on symptom management. The discovery of a novel drug is a time-consuming, and perilous procedure; the pandemic's emergency mandated that attempts to identify suitable cures among approved or marketed drugs be made first[23,24]. To identify therapeutic possibilities for SARS-CoV-2 infection in a short time, drug repurposing was the ideal method. In addition, researchers were developing antiviral medications to treat COVID-19 patients, some of which have previously been used to treat other conditions[9].

At present, treatment strategies involve the use of antiviral drugs, repurposed drugs, and traditional drugs. These drugs focused primarily on targeting the viral replication cycle and managing the disease's symptoms[25].

4. Repurposed drugs

The Food and Drug Administration (FDA) has licensed remdesivir for the handling of SARS-CoV-2[26]. It was previously cast off for the handling of Ebola and Marburg virus contaminations and has been exposed to *in-vitro* and *in-vivo* activity against SARS-CoV-2 by inhibiting viral replication. Several *in-vitro* studies have confirmed the potency of remdesivir against SARS-CoV-2 infection[27]. The results of a retrospective review of data from a COVID-19 active surveillance study revealed that remdesivir was well tolerated and had an acceptable safety profile[28]. Remdesivir should be administered intravenously once at 200 mg followed by once daily for four days at 100 mg for the management of SARS-CoV-2 infection[29]. However, if no appreciable clinical improvement has occurred by day 5, the course of treatment may be prolonged to 10 days[29]. In some patients, at hand is scarce evidence to endorse either for or in contradiction of the routine use of Remdesivir in patients through reasonable COVID-19 who do

not require supplemental oxygen[30]. According to a meta-analysis of those trials, there is a significant improvement in infected individuals, although most likely by enhancing clinical output and lessening severe adverse effects in individuals who are hospitalized due to severe SARS-CoV-2 infection[31]. The clinical outcome was 84% cure and improvement rate, with greater improvement in patients aged 60 years and using standard low-flow oxygen, and a 6.77% mortality rate[32]. Paxlovid is a fixed-dose combination of two antiviral drugs, Nirmatrelvir and Ritonavir. Nirmatrelvir inhibits duplicating the virus by inhibiting SARS-CoV-2 proteins, and Ritonavir breaks down nirmatrelvir and permits it to break in the body for lengthier at higher absorptions[33]. Favipiravir, also known as AVIFAVIR, is an RNA polymerase inhibitor that is used as a second-line handling for novel or re-emerging influenza outbreaks in Japan (Avigan) and China (Favilavir)[34]. Favipiravir is also classified as a possible experimental treatment by the WHO as a broad-spectrum antiviral[35]. The Russian Ministry of Health gave AVIFAVIR provisional marketing approval following the Phase II/III clinical trial, making it the only oral medicine approved for the treatment of mild SARS-CoV-2 infection to date[36]. Another repurposed medication being utilized in the treatment of SARS-CoV-2 infection is the combination of lopinavir and ritonavir (Kaletra)[37]. Both of these drugs block the SARS-CoV-2 protease enzyme, thereby inhibiting viral replication and life cycle in the host cells[26]. Molnupiravir is an N-hydroxycytidine ribonucleoside prodrug with promising achievement counter to SARS-CoV-2 and other RNA viruses with a significant resistance development barrier[38]. N-hydroxycytidine circulates systemically after molnupiravir treatment and is phosphorylated intracellularly to N-hydroxycytidine triphosphate[39]. Viral RNA polymerase integrates N-hydroxycytidine triphosphate into viral RNA, which then misdirects viral polymerase to include either guanosine or adenosine during viral replication[40]. A total of 716 patients of the 1433 patients studied were randomized to receive molnupiravir, while 717 were given a placebo[41]. The results of the subgroup examination were generally similar to these overall findings; however, in several subgroups, such as those with diabetes, low baseline viral loads, and patients with indication of prior SARS-CoV-2 infection, the point estimate for the difference favored placebo. Through day 29, nine deaths were reported in the placebo group and 1 in the molnupiravir group. In the molnupiravir group, adverse actions were reported by 216 of 710 participants (30.4%) and by 231 of 701 (33.3%) in the placebo group[42].

Chloroquine is an anti-parasitic medication (antimalarial) that is known to suppress the pH-dependent replication of viruses. Multiple studies have been conducted on it since the COVID-19 epidemic to examine the possible antiviral properties of chloroquine and hydroxychloroquine[43]. Comparing the effectiveness of chloroquine to that of other antiviral medications, particularly,

penciclovir, nafamostat, favipiravir nitazoxanide, and ribavirin, *in vitro* studies have shown that chloroquine is more effective at suppressing SARS-CoV-2 infection[44]. Clinical investigations in hospitals revealed that chloroquine and hydroxychloroquine were significantly effective against SARS-CoV-2, and they prevented pneumonia predisposing factors, lowered viral conversion to the dangerous kind, and decreased the duration of the illness without causing any adverse effects[45]. Patients with unadorned SARS-CoV-2 infection have diminished IFN-I activity, increased T cell apoptosis, and amplified inflammatory response[46]. However, the regulatory consequence of chloroquine and hydroxychloroquine taking place the immune response is deficient to stop the over-activation of the innate immune system[47]. There was no statistically substantial transformation in the in-hospital mortality rates among the various treatment groups, according to a retrospective multicentre cohort analysis of data from SARS-CoV-2 infected patients at New York hospitals[48]. Corticosteroids are frequently administered to hospitalized patients with pulmonary viral infections, such as those brought on by MERS-CoV and SARS-CoV-2, to minimize lung inflammation and the risk of pulmonary damage[49]. Given that the use of corticosteroids in these patients is already debatable, with ongoing clinical trials addressing the issue, corticosteroids can depress immunological responses, which can hinder viral allowance as was witnessed in some MERS-CoV patients[50]. Since the onset of combating this disease, numerous drugs like chloroquine, Lopinavir, Darunavir, Ribavirin, Remdesivir, Favipiravir, and Paxlovid have been introduced into clinical trials. However, some are still under investigation, and for others, their effectiveness has been discounted. Nonetheless, the safety and potential efficacy of many remain uncertain[51].

5. Immunomodulators and monoclonal antibodies (mAbs)

Various immune system components, including the innate and adaptive immune systems, can be activated, inhibited, or modulated by immunomodulatory drugs[52]. It is frequently advised to use immune stimulants, to enhance the immune system's response to pathogenic infections[53]. Targeting cytokine signaling during SARS-CoV-2 infection using immunomodulatory approaches minimizes overall hyperinflammation in such individuals since the rate and severity of inflammation are significantly correlated with severity and mortality in infected patients[54]. mAbs class of unconventional antibodies, produced by a particular β cell subset, recognizes a well-defined epitope on a specific antigen[55]. With the proper therapeutic intervention, a wide variety of functions can imitate, block, or change exact pathways to offer a very specific treatment for illnesses. In the fight to control severe COVID-19, researchers are actively investigating mAbs that can calm the immune system and disrupt

pathways crucial for SARS-CoV-2 infection[56]. The inflammatory mediators IL-1, IL-2, IL-6/IL-6R, TLR3, IL-8, IL-12/IL-23, IL-17, TNF, IP-10/CXCL10, and complement component-5 are all blocked by monoclonal antibodies in this situation[57].

Tocilizumab is an IL-6 receptor-targeted monoclonal antibody that has been studied extensively for its ability to lower the inflammatory response in patients with unembellished SARS-CoV-2. It has been approved by the FDA to suppress severe cytokine release syndrome during SARS-CoV-2[10]. According to a meta-analysis of SARS-CoV-2 RCTs (randomized controlled trials), tocilizumab was linked to a decreased death rate[58]. High doses of a medication called Anakinra have been given to some patients with serious infections caused by viruses like Epstein-Barr virus (EBV), influenza H1N1, and Ebola. Anakinra is a man-made protein that blocks the activity of a molecule involved in inflammation. Anakinra's impact on patients with SARS-CoV-2 infection's hyperinflammatory state was examined in a recent cohort research. According to reports, early findings indicate anakinra could be a potential therapy for severe COVID-19, reducing mortality and reliance on mechanical ventilation[59]. The IL-17-specific mAb, secukinumab, is presently the subject of phase 2 clinical investigation (NCT04403243). In one study, netakimab was administered to patients with severe SARS-CoV-2 infection and it was found to be associated with clinically significant improvements, a decrease in inflammatory biomarkers, and an upgrade in oxygenation intensities without noteworthy side effects[60]. Several monoclonal antibodies have been approved by the FDA for emergency use as a treatment for mild or moderate COVID-19. These treatments are intended for high-risk, non-hospitalized patients who have a confirmed case of COVID-19 and are at increased risk of severe illness or hospitalization[61]. Bamlanivimab and etesevimab developed by Eli Lilly have been suggested for the treatment of the patient population infested with the delta (δ) variant of SARS-CoV-2 as an intravenous infusion[62].

Several drugs called mAbs, including cilgavimab and tixagevimab (AstraZeneca), casirivimab and imdevimab (Regeneron), regdanvimab (Celltrion), and sotrovimab (GSK and Vir), are used to treat COVID-19 infection[63]. Intravenous immunoglobulin (IVIG) is a source of therapeutic, naturally occurring IgG obtained from the plasma of a large donor pool (thousands of healthy individuals). 29 clinical trials have been carried out to date to assess how IVIG affects patients with severe SARS-CoV-2 infection. The benefits of IVIG therapy for SARS-CoV-2 infection remain debatable[64]. A meta-analysis was recently carried out to evaluate the effectiveness of IVIG therapy for COVID-19 patients. This meta-analysis analyzed data from a total of seven studies, consisting of four clinical trials and three cohort studies, comprising a cohort of 825 hospitalized patients. They concluded that IVIG confirmed clinical value on critically hostile patients with COVID-19[65].

6. Convalescent plasma therapy

It has emerged as an effective treatment preference for managing SARS-CoV-2 infection[66]. Convalescent plasma has received FDA approval for use as an alternative handling for patients with serious or life-threatening disorders, including SARS-CoV-2 infection. Convalescent plasma exhibits encouraging outcomes in several instances, however, there is yet insufficient data to justify its efficient use in the management of SARS-CoV-2 infection[67]. The addition of convalescent plasma to antiviral therapy may have several weeks to month's long-lasting protective effect[68]. Convalescent plasma transfusion is a safe treatment that can help critically ill patients by lowering their viral load and improving their chances of survival[69]. While the reduction in the mortality of disappointingly sick patients is not statistically significant, convalescent plasma has therapeutic implications, including easing clinical complaints[70]. More than 50 patients receiving this therapy were included in a randomized experiment, and just two negative events were reported[71]. The efficiency of the treatment was evaluated using the viral load and the qRT-PCR tests. It was demonstrated that the viral load dropped following the transfusion and turned negative after a few days[72]. According to a clinical study, the impermanence rate for patients with usual convalescent plasma transfusion after one week of hospitalization was less compared to 30% for patients who did not get plasma. Patients who got plasma treatment within one week of admission did not experience any mortality[73].

Table 1. List of SARS-CoV-2 vaccines.

Types of vaccines	Target	Company	Names of vaccines	Preclinical study	Age groups	Side effects	References
Inactivated Virus	Whole virus	Sinopharm	BBIBP-CorV	Rats, guinea pigs, mice, rabbits, monkeys	≥18 years	Pain in Injection site, headache, fatigue, fever	[80–82]
		Sinovac Biotech	CoronaVac	Monkey, mice, wistar rats		CoronaVac- Pityriasis rosea, reactive arthritis	[83]
		Bharat Biotech	Covaxin	Hamsters, monkeys, mice, rats, rabbits		Covaxin-Booster shots may be required	[84]
Viral vector	S protein	University of Oxford and AstraZeneca	AZD1222 (Chimpanzee adenoviral vector)	Monkeys, guinea pigs	≥18 years	AZD1222 headache, fatigue, muscle pain, nausea, anaphylaxis, thrombosis and	[85]
		Johnson & Johnson	Ad26.COV2.S from (Human adenoviral vector)	Monkeys, hamsters		thrombocytopenia syndrome, cerebral venous sinus thrombosis, , myocarditis	[86]
		Gamaleya	Sputnik V(Human adenoviral vectors serotypes-2)	Monkeys, ferrets		Sputnik V- Hyperthermia, headache, Guillain–Barré syndrome asthenia, muscle pain	[87, 88]
RNA	S protein	Moderna and NIAD	mRNA-1273 (mRNA)	Monkeys	≥18 years	Local injection-site reactions, fever, fatigue, headache	[89]
		Pfizer and BioN Tech	BNT162b2 (mRNA)	Monkeys, mice	≥16 years		
DNA	S protein	Zydus Cadila	ZyCoV-D	Hamsters	≥18 years	Local injection-site reactions, fever, fatigue, headache	[90]
Subunit	S protein	Novavax and CEPI	NVX-CoV-2373 (Protein Subunit)	Monkeys, mice, baboons	≥18 years	Tenderness, fatigue, headache, muscle pain	[91]

7. Vaccines

Vaccines continue to be the backbone of infection prevention[74]. The present vaccines may not be enough to protect the populations, despite the quick development and distribution of vaccines, as several new strains coming from different parts of the world are constantly being identified. To stop the spread of the present worldwide pandemic, it is crucial to understand how the current vaccinations are made and to look into fresh research for potential new vaccines and therapies. SARS-CoV-2 vaccines are currently available in various forms, which include a DNA vaccine that can be administered intramuscularly and contains a plasmid DNA cloned with the SARS-CoV-2 spike protein[75]. The spike protein open reading frame is cloned into the adenovirus genome using viral vector platforms to create a virulent recombinant virus that will be injected intramuscularly for the development of immunity against SARS-CoV-2 infection[76]. In an mRNA vaccine, SARS-CoV-2 spike mRNA is chemically generated which is subsequently encapsulated with lipid nanoparticles and administered into the human body[77]. In protein vaccines, the entire spike protein, or a portion of it in the form of a subunit is combined with a particular adjuvant before being administered to humans[78]. In the inactivated vaccine, the SARS-CoV-2 is chemically inactivated and combined with a precise adjuvant and administered intramuscularly[79]. Many organizations have provided efficacy information for their

vaccines such as AstraZeneca-University of Oxford, Pfizer-BioNTech, Moderna, AstraZeneca–Johnson & Johnson Gamaleya, Sinovac Biotech, Sinophar, Novavax, and Bharat Biotech[77].

Bharat Biotech created the whole virion incapacitated SARS-CoV-2 vaccine, BBV152, also recognized as Covaxin, using Vero cells[92]. A phase-III clinical trial in India revealed that BBV152 is 65.2% protective in contradiction of the δ variant and 78 % effective against symptomatic cases[93]. Beijing Institute of Biological Products, a subsidiary of Sinopharm, developed BBIBP-CorV, an inactivated vaccine[94]. In Vero cells, a sample of the WT virus (HB02 strain) was grown before being chemically inactivated by propiolactone and combined with an adjuvant made of aluminum[95]. The phase-III study's interim analysis showed that the vaccine had a 78.1% success rate in contradiction of symptomatic SARS-CoV-2 infections[96]. In a study involving 282 subjects from Sri Lanka who received the vaccine formulation, it was observed that the neutralizing antibody titers against the β and δ variants of the SARS-CoV-2 virus were reduced by a factor of 10 and 1.38, respectively, when compared to the titers against the reference strain of the virus[95]. SinoVac, a pharmaceutical company, manufactures the potential inactivated COVID-19 vaccine known as CoronaVac[97]. However, it has been observed that the effectiveness of this vaccine serum in neutralizing certain SARS-CoV-2 variants is reduced. Specifically, when tested against the B.1.1.7 and B.1.351 variants, the neutralizing antibody (nAb) activity of the vaccine serum was significantly diminished by a factor of 5.27, and 3.92 respectively[98]. These findings suggest that this vaccine may be less effective in generating neutralizing antibodies against these specific variants. The non-replicating adenovirus vaccine vector AZD1222, also known as ChAdOx1 nCoV-19, was developed by Oxford-AstraZeneca and is based on a chimpanzee adenovirus vector (ChAdOx1)[99]. This vaccine includes an adjuvant sequence in addition to the full-length S protein of the SARS-CoV-2 virus. The adjuvant sequence is incorporated to enhance the immune response elicited by the vaccine and improve its effectiveness in generating protective immunity[99]. The AZD1222 vaccination was 81.3% effective for avoiding symptomatic SARS-CoV-2 infection in participants who had around two doses separated within 12 weeks[100]. AZD1222 confers maximum protection against α and 67.0% protection against δ variants[101]. It is made up of a non-replicating adenoviral vaccine (adenovirus serotype 26, Ad26) that encodes a prefusion-stabilized SARS-CoV-2 S glycoprotein and has two proline stabilizing mutations in addition to a mutation at the furin cleavage site[102]. The phase-III trial's interim analysis revealed a 66% effectiveness rate against symptomatic illness[103]. It was

observed that nAb activity against the β strain was reduced by five times and that of the γ strain by three times when compared to the original strain[104].

The Gamaleya Research Institute of Epidemiology in addition to Microbiology produced Sputnik V, the two adenoviral vectors (one is Ad26 and the second is Ad5) harboring the gene encoding the full-length of protein S that makes up the adenovirus-based vaccination[105]. Developers of Sputnik V declared at the end of June 2021 that the vaccine was roughly 90% effective against the δ strain[106]. The phase-III study's interim analysis revealed that Sputnik V's efficacy against symptomatic COVID-19 was 91.6%[107]. It effectively neutralized the S protein of the B.1.1.7 variation and the B.1 lineage[108]. The same sera, however, displayed significantly decreased neutralizing activity against the S protein of the β strain and somewhat decreased neutralizing activity against the S protein of the γ variation bearing the E484K mutation single-handedly[109].

Moderna as well as the National Institute of Allergy and Infectious Diseases created the mRNA-1273 vaccine. The full-length antigen S, which has a transmembrane anchor and an S1–S2 cleavage site, is encoded by the mRNA, which is enclosed in lipid nanoparticles (LNPs). To stabilize the S protein in its prefusion shape and hence increase its immunogenicity, two proline subunits were added to the S2[110]. BioNTech developed BNT162b2 with assistance from Pfizer. The complete spike protein is encoded by the mRNA, which is packed in LNPs. Two prolines were added to one of the subunits to stabilize the prefusion conformation and boost the protein's immunogenicity[111]. Phase II/III clinical studies' preliminary results showed that BNT162b2 was 95% effective at preventing symptomatic SARS-CoV-2 infections[112].

An effective method to generate neutralizing antibodies that stop the virus from attaching to the ACE-2 receptor and entering host cells is thought to be an RNA vaccine that codes for the S protein. Targeting the S protein may be a limitation if SARS-CoV-2 can enter cells using a mechanism besides ACE-2[113]. RNA-based vaccines face additional technical hurdles, including ensuring mRNA stability, efficient cellular uptake, and proper release from nanoparticles within the cell cytoplasm to enable target protein production[114].

Preparedness Innovations Foundation and the American biotechnology company Novavax together produced the COVID-19 vaccine NVX-CoV2373. The baculovirus SF9 insect cell expression technology was used to create the recombinant subunit vaccine. It comprises a saponin-based Matrix M adjuvant that stabilizes the full-length S glycoprotein in the prefusion conformation[115]. The

Phase-IIa/ IIb clinical studies showed that NVX-CoV2373 provided protection in contradiction of β variants during the predominance of B.1.351 in South Africa[116](Table 1).

8. Herbal medicines and nutraceuticals

Traditional drugs could efficiently relieve signs and symptoms of SARS-CoV-2 infections such as fever, fatigue, and cough, and lessen the possibility of patients mounting critical conditions. Recent *in-silico* investigation has revealed that several natural compounds are very effective at inhibiting the enzymatic activity and cell wall receptors of the human Coronavirus. These bioactive compounds may be used in milder quantities to prevent or at least halt the spread of SARS-CoV-2[117]. In addition to many other researched herbs, *Glycyrrhiza glabra* and *Pelargonium sidoides* may be beneficial in treating SARS-CoV-2 infection. They have been demonstrated to stop the release of the SARS-infected cells' HMGB1 nuclear protein (high motility group box protein 1)[118]. But even though some herbal remedies might not be enough as the primary therapy for SARS-CoV-2 infection, they might be introduced successfully as supplementary medications. On April

14, 2020, the three patent herbal drugs were approved by Chinese officials to improve the symptoms of SARS-CoV-2 infection. These included Lianhuaqingwen capsules and Jinhuaqinggan granules for minor circumstances, and Xuebijing in parenteral form for unembellished conditions. They decrease the level of IL-8, TNF- α , IL-10, IL-1 β , IL-6, and other cytokines, causing the inhibition of lung inflammation or acute lung injury[119]. Lianhuaqingwen capsules inhibited SARS-CoV-2 replication in Vero E6 cells and decreased the level of pro-inflammatory cytokine (TNF- α , IL-6, and CXCL-10/IP-10)[120]. Additionally, the hospitalization rate is greatly decreased by jinhua qinggan granules. Faster recovery attained by a suitable complementary therapy is particularly significant since it assists in relieving viral load in patients[121]. Additionally, treating severe SARS-CoV-2 infection remains complicated, thus herbal medications, even when utilized as an experimental therapy, may be highly helpful in clinical settings. Since the ACE-2 receptor is pivotal in viral entry to the cells, by blocking the viral attachment to the host ACE-2, many flavonoids have shown beneficial effects against SARS-CoV-2 infection[122]. Totally 447 participants were included in a successful clinical open-labeled randomized research with quercetin therapy (NCT04377789)[123](Table 2).

The foremost features of viral infections can now be treated using

Table 2. List of herbal molecules and nutraceuticals for SARS-CoV-2.

Herbal molecules/ Nutraceuticals	Mechanisms	References
Curcumin (<i>Curcuma longa</i>)	Significantly decreased IL-6 and IL-1 β secretion during COVID-19	[124]
Berberine (<i>Berberis berberidaceae</i>)	Trafficking of viral receptors ACE2	[125]
Resveratrol and pterostilbene	Inhibited SARS-CoV-2 viral replication	[126]
Polysaccharides of <i>Malva sylvestris</i> and <i>Salvia officinalis</i> L.	Antitussive activity	[127]
Polysaccharide of <i>Aloe barbadensis</i>	Antitussive activity	[127]
Cynaroside (<i>Cynara scolymus</i> L.)	ACE inhibition	[128]
Anthocyanins (<i>Hibiscus sabdariffa</i> L.)	ACE inhibition	[129]
Phaitanthrin D, sinigrin, aloe emodin, hesperetin, and sinigrin	SARS-3CLpro inhibition	[130]
(<i>Isatis indigotica</i>)		
Hirsutenone (<i>Alnus japonica</i>)	PLpro inhibition	[131]
Amentoflavone (<i>Torreya nucifera</i>)	SARS-3CLpro inhibition	[132]
Psoralidin, bavachinin, corylifol A (<i>Psoralea corylifolia</i>)	PLpro inhibition	[133]
Capillarisin (<i>Artemisia capillaries</i>)	Decreased TNF- α , IL-1 β , and IL-6 during COVID-19	[134]
Arabinogalactan (<i>Glycyrrhiza glabra</i>)	Spasmolytic activity	[135]
Aqueous extract of <i>Allium sativum</i>	Inhibited virus penetration and proliferation in cell culture	[136]
Aqueous extract of <i>Zingiber officinalis</i>	Anti-avian influenza virus H9N2 activity in both chick embryos and cell models	[137]
Ginseng powder capsule (<i>Panax ginseng</i>)	Modulated CD69-expressing immune cells and exhibited a significant enhancement of influenza virus-specific IgA antibody in mice lungs	[138]
Eucalyptus oil (<i>Eucalyptus polybractea</i>)	Inhibited avian influenza virus H11N9 in aerosol and vapor form	[139]
Probiotics strain of <i>Lactobacillus</i> and <i>Bifidobacterium</i>	Increased the number of key immune cells, T-helper cells, cytotoxic T cells, and T suppressor cells	[140]
Vitamin calcifediol	Reduced the need during hospitalization in COVID-19	[141]
Vitamin C	Lowered the incidence of thrombosis	[142]
Combination therapy of Vitamins	The combination therapy significantly decreased inflammatory cytokines, TNF- α , IL-6, and C-reactive protein was significantly decreased in COVID-19	[143]
Zinc	Zn2+ inhibits SARS-CoV	[144]

herbal antiviral preparations[145]. Countless Chinese medicinal herbs were screened, and it was discovered that extracts from, *Artemisia annua*, *Lindera aggregata*, and *Lycoris radiata* had an anti-SARS-CoV-2 impact. Factually, homeopathy has supposedly been used for prevention during the epidemics of Cholera, Spanish Influenza, Yellow fever, Scarlet fever, Diphtheria, Typhoid, etc[146]. The all-inclusive approach of Ayurveda, Unani, Yoga, Naturopathy Siddha, and Homeopathy systems of medicine emphasizes prevention through daily lifestyle adjustment, nutritional supervision, prophylactic involvements for enhancing immunity and simple preparations based on management of the indicators[147]. The Siddha system of medicine in India uses Kabasura Kudineer, a polyherbal preparation, to treat clinical manifestations that resemble SARS-CoV-2[148].

Due to its antibacterial properties and widespread use as a seasoning in Indian culture and other cultures around the globe, turmeric is a popular Ayurvedic medicine. Curcumin, turmeric's primary ingredient, could combat SARS-CoV-2 infection by having antibacterial, antiviral, and anti-inflammatory properties[149]. It could also be of importance in preventing the "cytokine storm" that is brought on when too many pro-inflammatory mediators and molecules, including IL-1, IL-6, IL-8, and IL-10, TNF- α , cytokines, cyclooxygenase enzymes, and bradykinin, are secreted simultaneously[150]. Additionally, research suggests that curcumin might inhibit the 3-chymotrypsin-like protease enzyme in Vero cells, preventing cellular replication-an essential mechanism for viral cellular replication-and thereby gradually lowering the body's viral load[151]. *Scutellaria lateriflora* flavones, scutellarein, may have inhibited SARS-CoV-2 helicase protein *in-vitro* by blocking nsP13's adenosine triphosphatase (ATPase) activity[152]. SCoV 3CL protease activity was significantly reduced in rhizomes of *Rhizoma cibotii*, dried rhizomes of *Cibotium barometz*, rhizomes of *Dioscoreae*, and tubers of *Dioscorea batatas*. Herbaceous, rhoifolin, amentoflavone, and pectolinarin are some examples of flavonoids whose anti-SARS-CoV 3CLpro action has been proven[153]. Nutraceuticals, which combine elements of both nutrients and pharmaceuticals, offer a unique approach to health maintenance and disease prevention. These products provide both medicinal benefits and essential nutrition necessary for various metabolic processes and the regulation of bodily functions. By serving as dietary supplements, nutraceuticals support overall body health while also aiding in the prevention and treatment of diseases. They contribute to physical health and strengthen the immune system, promoting longevity and normalizing bodily functions. Moreover, nutraceuticals offer several advantages over synthetic drugs. They can help reduce the high production costs associated with pharmaceuticals, particularly by utilizing natural ingredients.

Since COVID-19 is already known to be the cause of flu-like symptoms, one method to prevent it is by boosting immunity with a variety of nutritional supplements, such as zinc, vitamins C, D,

and B, and probiotics[154]. Several nutraceuticals have been reported to potentially reduce symptoms associated with dermatological infections, including those related to COVID-19. Some important nutraceuticals in this regard are resveratrol, hesperidin, lactoferrin, vitamins A, and K, zinc, quercetin, and omega-C fatty acid. According to experimental and controlled trials, ginseng increases the production of inflammatory mediators such as IFN- γ and interleukins, which have an impact on the activation and control of the immune system, as well as B-lymphocyte proliferation. Additionally, it contains anti-inflammatory qualities and prevents the spread of viruses[155,156]. On April 28, 2020, a study was registered at ClinicalTrials.gov (NCT04366180) to examine if dietary supplementation with *Lactobacillus coryniformis* K8 can aid in preventing healthcare workers from developing SARS-CoV-2 infection[157]. While the exact mechanism by which *Lactobacillus coryniformis* K8 may prevent SARS-CoV-2 infection is not fully understood, it possesses several important activities such as enhancing gut barrier function, increasing immunoglobulin synthesis, preventing virus replication, and increasing white blood cell phagocytic activity.

9. Conclusions and future prospects

In conclusion, this manuscript has provided a comprehensive overview of the potential therapeutics for SARS-CoV-2 infection. The global scientific community has examined a wide array of therapeutic strategies, ranging from antiviral drugs and monoclonal antibodies to repurposed medications and innovative vaccine technologies. *Glycyrrhiza glabra*, *Pelargonium sidoides*, *Atropa belladonna*, *Ocimum sanctum*, *Tinospora cordifolia*, *Zingiber officinale*, *Curcuma longa*, *Panax ginseng*, and *Aloe vera* have been identified for their potential role for the management of the COVID-19. The evolving landscape of SARS-CoV-2 therapeutics underscores the resilience and adaptability of scientific research in the face of an ongoing and challenging public health emergency.

While much progress has been made in identifying and developing treatments for COVID-19, it is crucial to acknowledge that the field continues to evolve rapidly. Ongoing research, clinical trials, and collaborative efforts across the globe hold the promise of discovering even more effective therapies and advancing our understanding of the virus. As we move forward, the pursuit of safe, accessible, and efficacious treatments remains paramount. Additionally, our manuscript underscores the importance of multidisciplinary collaboration, data sharing, and transparency to accelerate the development and deployment of therapeutic options. The pursuit of these goals offers hope in our collective endeavour to mitigate the impact of SARS-CoV-2 and protect the health and well-being of individuals and communities worldwide.

Conflict of interest statement

The authors claim there is no conflict of interest.

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Data availability statement

The data supporting the findings of this study are available from the corresponding author upon request.

Authors' contributions

Nagu P and Sharma P performed literature search, and wrote the first draft of the manuscript. Parashar A and Mehta V read the manuscript, made corrections to the manuscript, reviewed, and edited the content of the entire manuscript. All authors approved the final copy of the manuscript before submission.

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