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Review Article

Scientific Evidence for the Herbal Remedies Used in the Treatment of COVID-19

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Abstract

The recent outbreak of coronavirus in December 2019, now officially named SARS-CoV-2 caused severe acute respiratory syndrome. The lack of significant targeted therapy options led to treating the pandemic symptomatically through the use of antivirals, anti-inflammatory agents, immunoglobulins, and low molecular weight heparins. Non-replicating viral vector vaccines have been manufactured by some organizations however the cure has still not been discovered. Herbal remedies have been used to treat a multitude of illnesses over time and have been the foundation for uncovering the cure for some diseases. This review delves into the scientific evidence of herbs such as *Curcuma longa*, *Glycyrrhiza glabra,* and *Zingiber officinale* having a therapeutic effect against SARS-CoV-2 by binding to various crucial sites on the virus rendering it ineffective. Many of these phytocompounds were found to have a distinguished mechanism of action showing anti-SARS-CoV-2 activity as shown in Figures 1 and 2. Some of them have also exhibited anti-inflammatory properties. The following figure illustrates how the natural compounds mentioned in this article act on SARS-CoV-2 during its various stages of life.

Keywords: SARS-CoV-2, Herbal Remedies, Complementary medicine, Anti-viral, Coronavirus, Phytocompounds, Immunomodulators, ACE-2

1. Introduction

The highly communicable Coronavirus disease 19 (COVID-19) was declared a public health emergency by the World Health Organization (WHO) in December 2019. The first cases of this zoonotic virus were reported in Wuhan, China (Qu et al. 2020). It is a large family of highly variant, positive-sense, single-stranded, and enveloped RNA viruses. The virus infects symptomatically and asymptomatically. The major clinical manifestations include dry cough, fever, dyspnea, myalgia, and fatigue (He, Deng, and Li 2020). Belonging to the family Coronaviridae and subfamily Orthocoronavirinae; coronaviruses are further classified into Alpha, Beta, Gamma, and Delta coronavirus (Payne 2017). SARS-CoV-2 is found to be very similar to the beta subdivision (Mohamadian et al. 2021). Seven human coronaviruses (HCoVs) have been discovered so far that are prevalent worldwide: HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1, SARS-CoV, MERS-CoV, and SARS-CoV-2, all majorly infecting the upper respiratory tract (Mohamadian et al. 2021) (Zhu et al. 2020).

The structurally distinct element of SARS-CoV-2 that explains its name, is its envelope spike proteins that mediate the receptor binding to the angiotensin-converting enzyme-2 (ACE-2) receptors (Strauss et al. 2021). Consequently, disturbances such as alveolar collapse, vasoconstriction, and thrombosis occur (Strauss et al. 2021). A study conducted in 2021 concluded that mild cases reported a loss of smell or taste or manifested at least 2 of the main SARS-CoV-2 symptoms. Moderate infection presented as rapid or difficulty breathing, dyspnea, and chest tightness while severe cases were subjected to hospitalization (Maier et al. 2022).

Initially, about 5 million cases were reported worldwide with over 300,000 deaths by May 20, 2020 (Ciotti et al. 2020). By February 6, 2021, it augmented to 100 million cases with more than 2.5 million deaths (Yusuf et al. 2021). It further rose to over 170 million diagnosed cases and 3.5 million deaths by June 1, 2021 (Saragih et al. 2021). Excess death rates were estimated to be 1.4 million in China and 14.83 million globally (Raphson and Lipsitch 2024) (Msemburi et al. 2023).

2. Treatment

The rapid spread of SARS-CoV-2 required an urgent solution. Vaccines were available within a year but during this one-year, desperate for relief, people opted for various local remedies. Many of the people, especially in rural areas of both developed and developing world pinned their hopes on local medicinal plants. While some plants may have demonstrated antiviral or immune-modulating properties in laboratory studies, translating these findings into safe and effective treatments for COVID-19 requires rigorous clinical testing. It's crucial to note that misinformation and unverified claims about the effectiveness of certain herbs or medicinal plants against COVID-19 have circulated. The WHO and other health authorities have emphasized the importance of relying on evidence-based treatments and vaccines for COVID-19. Research into potential treatments, including those derived from medicinal plants, continues, but rigorous scientific evidence is necessary before any treatment can be recommended. Here in this review, we gather evidence from the literature for the use of several medicinal plants in treating COVID-19 and the scientific rationale for its use.

3. Natural Remedies

A significant portion of the world population has historically relied upon medicinal plants for treating various illnesses, such as *Andrographis paniculata* (Nees), which is used to treat fever and the common cold (Murugan, Pandian, and Jeyakanthan 2021). During the last few years, medicinal plants have been used extensively in various capacities for treating COVID-19. Some medicinal plants and their compounds have demonstrated antiviral properties in laboratory studies. Certain medicinal plants may have immunomodulatory effects, influencing the immune system. In COVID-19, the immune response is crucial, and maintaining a balanced immune reaction is essential for recovery. Inflammation is also an important component of the immune response, and severe cases of COVID-19 are associated with an inflammatory response sometimes referred to as a cytokine storm. Some medicinal plants are known for their anti-inflammatory properties, and research is ongoing to explore their potential role in managing inflammation in COVID-19. Certain plants may provide symptomatic relief for common cold-like symptoms associated with respiratory infections, including COVID-19.

3.1. Turmeric

Curcuma longa (turmeric) has been known for its use in treating many issues including chronic inflammation, gastric complications, and oxidative stress since before the use of modern medicine (Sharifi-Rad et al. 2020). Computational studies show that compounds found in *C. longa*, such as cyclo curcumin and curcumin, can bind to the active site of SARS-CoV-2 main protease (Mpro) (5R82). The highest binding affinity was recorded with cyclo curcumin (−6.77 kcal/mol) and curcumin (−6.13 kcal/mol), revealing the formation of hydrogen bonds in the binding site. It has, therefore, been suggested that daily intake of *C. longa* can be beneficial against viral replication of SARS-CoV-2 (Rajagopal et al. 2020).

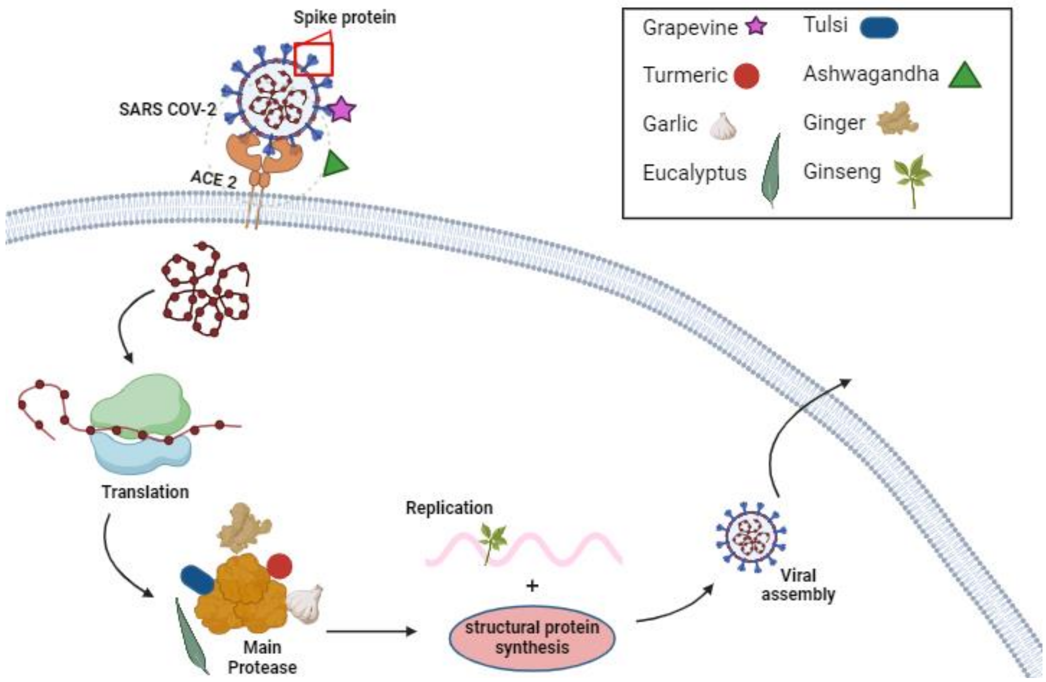

Figure 1. Target sites of Natural compounds on the SARS-CoV-2.

Since SARS-CoV-2 binds with ACE-2, hypertensive patients are more susceptible to developing severe COVID-19 (Fang, Karakiulakis, and Roth 2020). Curcumin can be used in hypertensive patients, as it has been shown to reduce hypertension by preventing the expression of angiotensin-1 (AT_1) receptors, which are a binding site for angiotensin-II, which is a product of ACE-2 (Yao et al. 2016).

In a clinical trial in India, the administration of curcumin with piperine was investigated in COVID patients. Piperine is known to improve curcumin absorption. The control group (C3 group) and study group (non-C3 group) were administered probiotics, curcumin, and piperine, respectively, along with the standard of care. Each group consisted of 70 COVID-19-positive patients. Each group was further divided into subgroups of mild, moderate, and severe symptoms. The C3 group had a regimen of 14 days consisting of 525 mg curcumin and 2.5 mg piperine twice daily. Vital monitoring was done multiple times every day. The authors observed that patients in the C3 group had more significant symptomatic management, which included fever, sore throat, and cough, while also being able to maintain an oxygen saturation of more than 94% (Pawar et al. 2021).

3.2. Huangqin

The root of *Scutellaria baicalensis* Georgi has been long used in Traditional Chinese Medicine for its heat-clearing, detoxifying, and hemostatic properties. The Chinese pharmacopeia has now included *S. baicalensis* as an antiviral, antimicrobial, and anti-inflammatory herb. 3C-like protease is an important target site of SARS-CoV-2 to inhibit viral reproduction. This activity has been shown by baicalein, the main component of huangqin. Data collected from an *in vitro* study demonstrated a positive correlation between the increase in the concentration of baicalein and the percentage of reproductive inhibition of SARS-CoV-2. The crude drug revealed inhibitory effects at IC_{50} 8.5 μg/ml while the constituents baicalin and baicalein had IC_{50} 83.4 μM and 0.39 μM respectively (Liu et al. 2021). In a separate study, 0.1-0.3 μM of baicalein was sufficient to provide a barrier to cell injury when a sample of baicalein and SARS-CoV-2 was added to the cells after 1 hour of incubation. In this study, Vero E6 cells were used to test the concentrations of baicalein needed to overcome cell injury caused by SARS-CoV-2 (Song et al. 2021).

3.3. Grapevine

Vitis vinifera (grapevine) is known to have many bioactive compounds that have antibacterial, antifungal, and antiviral activity. Leaf extracts of grapevine have demonstrated antiviral activity against SARS-CoV-2. Polyphenol extraction from 25mg of leaf samples was performed with one-hour incubation at room temperature in a 75% (v/v) methanol and 0.05% (v/v) trifluoroacetic acid solution. Different concentrations were tested in 4 scenarios to determine the most effective approach to treatment. Over 80% inhibition was seen across concentrations of 10 – 500 µg/mL. These results demonstrate that *V. vinifera* can block the entrance of the virus into the host cell while also decreasing the expression of spike proteins, weakening the virus (Zannella et al. 2021).

3.4. Licorice

The therapeutic benefits of *Glycyrrhiza glabra* (licorice) have been recorded over thousands of years. The main component responsible for its therapeutic abilities is glycyrrhizin and its metabolite glycyrrhetinic acid. *G. glabra* has been shown to reduce the cellular uptake of SARS-CoV-2 due to decreasing expression of ACE-2 receptors. Glycyrrhetinic acid inhibits 11-beta-hydroxysteroid dehydrogenase type 2 enzyme which then allows cortisol to bind to mineralocorticoid receptors. The pathway causes a secondary effect which is the reduction of ACE-2 expression. Animal studies in rats demonstrated a lower protein and mRNA expression of ACE-2 in the small intestines. Hence, there is reduced entry of SARS-CoV-2 since fewer ACE-2 proteins are available to carry out this cell invasion (Jezova et al. 2021).

G. glabra also reduces the severity of SARS-CoV-2 infection. In a clinical trial comprising 213 COVID-19 patients, administration of licorice syrup containing 1.21 ± 0.003 mg/ml of glycyrrhizic acid, showed a hospital admission time of 5.24 days, a 25% increase in O_2 saturation in 94.5% of patients, three deaths and five transfers into the intensive care unit. These results suggest that *G. glabra* helps in the management and recovery of COVID-19 (Soleiman-Meigooni et al. 2022).

Glycyrrhizin also exhibits anti-inflammatory effects, which are beneficial in lowering the severity of COVID-19. It takes place with the binding of glycyrrhizin onto High Mobility Group Box 1 (HMGB1); a damage-associated molecular pattern protein. This reduces the inflammatory response by inhibiting cytokine release from macrophages and lowering expression of ACE-2 protein which also decreases SARS-CoV-2 entry into cells. A decrease in HMGB1 activity with the addition of 1 mM glycyrrhizin was observed. These effects were demonstrated in malignant lung tumor cells using glycyrrhizin (Gowda et al. 2021).

3.5. Nees

Owing to its diverse range of pharmacologically active phytochemicals exhibiting anti-viral, antioxidant, anticancer, and hepatoprotective properties, *Andrographis paniculata* (Nees) is regarded as the 'King of Bitters' and has been used traditionally to treat fever and common cold. Among the several phytochemicals constituents of *A. paniculata*, andrographolide showed the most excellent affinity towards 3 L main protease (3CLpro) and spike-ACE-2 in docking studies conducted to predict the binding affinities of these constituents with SARS-CoV-2, implying the potential for inhibition of SARS-CoV-2 activity by blocking the main sites of action of the virus (Murugan, Pandian, and Jeyakanthan 2021).

In vitro investigations using human lung epithelial cells (Calu-3) as host cells to test the antiviral effects of *A. paniculata* extract and andrographolide also demonstrated significant activity. Various concentrations of extract and chemical constituent ranging from 0.05-50 µg/mL, incubated for 48 hours with Calu-3 cells previously infected with SARS-CoV-2 showed significant inhibition with post-infection treatment at IC_{50} of 0.036 µg/mL and 0.034 µM for

A. paniculata extract and andrographolide respectively (Sa-Ngiamsuntorn et al. 2021).

A clinical trial investigating the effect of *A. paniculata* extract on COVID-19 patients showed no patients developed pneumonia, 34.5% of patients with COVID-19 on Day 5. None of the patients had C-reactive protein >10 mg/L. In contrast, the placebo group had three patients who developed pneumonia, 57.1% of patients who had COVID-19 on Day 5, and 5 patients with >10 mg/L C-reactive protein (showing inflammation). The treated group consisted of 29 patients who received 60 mg of andrographolide three times a day for five days, and the placebo group consisted of 28 patients. Both groups were also given standard supportive care. These results support the use of *A. paniculata* to manage COVID-19 (Wanaratna et al. 2021).

3.6. Garlic

Allium sativum (garlic) has been used for thousands of years as a spice and medicine. In medicine, it is commonly used for treating influenza and colds. A computational study, investigating 17 compounds present in *A. sativum* for a molecular match against ACE-2 protein, which serves as the host for SARS-CoV-2 and PDB6LU7, which is the Mpro protein of SARS-CoV-2, showed that diallyl tetrasulfide had the strongest binding effect with ACE-2 protein (-14.06 kcal/mol) while ally trisulfide binds SARS-CoV-2 protease (-15.02 kcal/mol). This demonstrates that *A. sativum* can form strong bonds, and therefore, capable of anti-SARS-CoV-2 properties (Thuy et al. 2020).

3.7. Eucalyptus

The essential oils of Eucalyptus species have proven useful in the management of respiratory illness while also exhibiting antiviral effects. Computational investigations show binding energies of several phytocompounds from *Eucalyptus globulus* (eucalyptus) with the Mpro of SARS-CoV-2. Among those, cuniloside showed the most significant result, demonstrating a potential target to be further investigated on its antiviral property against SARS-CoV-2 (Fitriani et al. 2020). A similar computational investigation was performed for *E. globulus* essential oils. Eucalyptol, the most abundant component in *E. globulus* showed the highest binding energy of -5.86 kcal/mol towards the Mpro, demonstrating possible inhibition of SARS-CoV-2 viral replication due to binding via strong hydrogen bonds (Panikar et al. 2021).

3.8. Purple Coneflower

Echinacea purpurea (purple coneflower) has been shown in previous studies to possess antifungal, antibacterial, and antiviral properties (Oniszczuk et al. 2019). *E. purpurea* also aids in the prevention of SARS-CoV-2 and the reduction in the duration of the disease. A 5-month intake of *E. purpurea* extract has resulted in a significant reduction in the number of patients catching SARS-CoV-2. The extract was given at a dose of 800mg, three times a day, to 120 patients of intervals of 2, 2, and 1 month with a one-week gap in between the intervals. Fourteen patients in the control group contracted SARS-CoV-2, while five patients in the *E. purpurea* extract group were detected. These results suggest a 63% reduction in the risk of contracting SARS-CoV-2 for patients receiving prior *E. purpurea* extract (Kolev et al. 2022).

3.9. Willow bark

Willow bark (*Salix* extract) has been in use for centuries, mainly for its use in fever, inflammation, and pain relief. *Salix* extract can be used to reduce one of the many symptoms of COVID-19, such as inflammation (Le et al. 2021). The anti-inflammatory effect of *Salix* extract may be through reducing prostaglandin E2 (PGE2) formation. This hypothesis was tested on human peripheral blood mononuclear cells already infected by SARS-CoV-2. Infected cells resulted in about a 150% increase in PGE2 production. *Salix* extract was added to the infected cells for 24 hours and showed a reduction of 50%, which is much lower than the 150% increase observed in untreated cells. *Salix* contains salicin which might be responsible for this anti-inflammatory effect (Le et al. 2021).

3.10. Umckaloabo

Found primarily in South Africa, *Pelargonium sidoides* (umckaloabo) is useful for treating a range of diseases and symptoms including respiratory infections, diarrhea, and dysentery. *P. sidoides* extract was also found beneficial in an investigation in which the human lung cell line Calu-3 was used to determine the antiviral effects of the extract on SARS-CoV-2. Cells were treated with the extract before the addition of SARS-CoV-2. Viral growth was seen to be inhibited by the addition of 10-100 μg/mL of *P. sidoides* extract. It was observed that when cells were only infected with SARS-CoV-2, interleukin production (Interleukin-1β and interleukin-6) was high, leading to inflammation. However, after treatment with *P. sidoides* extracts at 100 μg/mL, these same inflammatory modulatory were reduced in concentration (Papies et al. 2021).

In vitro studies involving Vero E6 cells showed that *P. sidoides* extract caused a 50% reduction in SARS-CoV-2 activity at 87.25 μg/mL concentration. Computational investigation of the four constituents, catechin, gallic acid, umckalin, and scopoletin shows good binding affinities on the targeted sites of SARS-CoV-2, catechin being the most potent. These results demonstrate promising capabilities of the antiviral effects that can be used to target SARS-CoV-2 (Alossaimi et al. 2022).

3.11. Ginger

Zingiber officinale (ginger) has been used to manage respiratory illnesses and clear nasal passages according to its use in Ayurvedic Medicine. Grid-based Ligand Docking with Energetics was used to see whether constituents of *Z. officinale* would be able to bind to SARS-CoV-2 spike proteins. Results indicated that adenine and xanthin showed binding affinities towards the target site. It would interact with the viruses' ability to invade host cells, reducing its effect (Haridas et al. 2021).

Z. officinale has been shown to boost immunity, which facilitates recovery from COVID-19. Patients from different areas of Burdwan Municipality, India, were tested from March 17, 2020, to March 31, 2020. A powdered form of *Z. officinale* was used to make diluted preparations. *Z. officinale* was given to the patients 4-6 times per day, along with standard nutritional care. This consisted of 5-10 drops of the diluted preparations mixed into warm drinking water, tea, or milk. The study consisted of patients from different age groups, Senior (60 - 99 years), Middle (20 -59 years), and Early (0 – 19 years). A high rate of recovery was seen in all three age groups. In the Senior, Middle, and Early age groups, COVID-19 recovery was seen in 74/97 patients, 100/153 patients, and 100/271 patients, respectively (Datta 2021).

Forty-two chemical constituents of *Z. officinale* were screened for their binding affinity on the 6LU7 binding site of SARS-CoV-2. The results were narrowed down to 10 constituents showing binding affinity, with shogasulphonic acid A showing the most excellent affinity. These constituents can be further investigated to tackle SARS-CoV-2 (Prasanth et al. 2020).

3.12. Ashwagandha

Being part of the ancient Ayurvedic system, *Withania somnifera* (Ashwagandha) has shown numerous properties like anti-tumor, neuroprotective, cardioprotective, anti-inflammatory, and anti-microbial. *W. somnifera* has been used in Ayurveda as an immunomodulator. Since it's known for its anti-inflammatory properties, docking studies were conducted to observe its effect on the main protease of SARS-CoV-2. A 3-dimensional structure of COVID-19 was obtained via the Protein Data Bank. Twenty-eight compounds of *W. somnifera* were tested using Auto Docked software. It resulted in 2 compounds showing that Withanoside V (10.32 kcal/mol) and Somniferine (9.62 kcal/mol) had the most significant binding affinity towards the Mpro (Shree et al. 2022).

Another set of docking studies was done on the main protease of SARS-CoV-2. It revealed that another constituent of *W. somnifera*, Winthanone, could bind to the target site with -4.42 kcal/mol (Kumar et al. 2021).

SARS-CoV-2 attaches to ACE-2 receptors via its receptor binding domain, which was the target for this docking study. The following components of *W. somnifera* demonstrated binding at the receptor binding domain and ACE-2 receptor interface, weakening the virus's bond on the receptor. Withanone (-9.4 kcal/mol), Withanolide A (-9.6 kcal/mol), Withanolide B (-9.4 kcal/mol), and Withaferin A (-9.1 kcal/mol) can all serve as candidates for further studies into COVID-19 management (Balkrishna et al. 2020). *W. somnifera* has continuously proven to have the ability to tackle COVID-19.

3.13. Guduchi (Giloy)

In Ayurvedic medicine, there have been many herb-mineral combinations used to target respiratory diseases, playing a role to manage rhinitis, asthma, and overproduction of mucus. One of the many on the list is *Tinospora cordifolia* (Giloy). 59 COVID-19 patients were admitted to COVID-19 centers in Ahmedabad, Gujrat, India, between May 2020 and June 2020. They were divided into two groups where one was only given Ayurvedic herbs (18 patients) while the other was given a combination of Ayurvedic herbs and medication (41 patients). Among the few Ayurvedic herbs given, 2g *T. cordifolia* was also administered daily. The proceeding two months were a period of data collection. Various symptoms were being monitored, including headache, nasal congestion, difficulty breathing, fatigue, and body temperature. Results showed that in the first 13 days, the Ayurvedic group had more symptomatic relief of 88.33% as compared to the other group showing 48.76%, demonstrating a shorter recovery time with the use of Ayurvedic herbs alone (Balkrishna et al. 2021).

In the National Capital Region, Gurgaon, India, a combination of *T. cordifolia* and *Piper longum* was given to COVID-19 patients in addition to standard medication. Two groups were made, each containing 30 patients. One group received only standard medicinal therapy (SOC) and had a mean age of 29.7 years, while the other received both medical and Ayurvedic treatment (SOC + Ayurveda), having a mean age of 38.7 years. The SOC group remained in the hospital for about one day (mean: 6.9 days) more than the SOC + Ayurveda group (5.5 days). The SOC group had more significant patients discharged on days six and nine after administration, and the SOC + Ayurveda group showed more substantial amounts of discharges on day 5 and day 8. The addition of Ayurveda in the treatment of COVID-19 has been demonstrated to help speed up recovery time. Patient follow-ups took place three months after discharge to monitor the effects on quality of life after treatment. These follow-ups revealed that the SOC + Ayurveda group reported more excellent general health, lower impact on daily work activities, and lower amounts of cardiac, respiratory, and dermatological challenges compared to the SOC group (Kataria et al. 2022).

3.14. Huang Qi

Astragalus membranaceous (Huang Qi) has a high content of *Astragalus* polysaccharide, which is known to have antiviral immunomodulatory properties (Yeh et al. 2022). ARDS and multiorgan failure are complications of viral genome-induced cytokine release syndrome (Tan, Komarasamy, and Rmt Balasubramaniam 2021). *A. membranaceous* is a therapeutic and preventive intervention for SARS-CoV-2 owing to its Qi-tonifying effects. SymMap database (FDR-BH < 0.01) revealed 64 potential target genes for *Astragalus* polysaccharide (APS) and APS-L were the two extract preparations of *A. membranaceous.* 1mg/ml extracts of each sustained an endurance rate of more than 80% and could upregulate innate miRNAs favorable in treating COVID-19. APS enhanced the level of let-7a by 1.2 folds as well as miR-148b and miR-146a approximately two times. 1.5 folds was the increment rate of APS-L for let-7a and 3 folds for miR-148b and miR-146a. The in vivo investigation was verified using BEAS-2B cells (normal bronchial epithelium of a non-cancerous human). Lipopolysaccharide (LPS) was used to stimulate the inflammatory environment of a cytokine syndrome. The in-silico analysis of

APS-L exceptionally inhibited tumor necrosis factor-α (TNF-α), a factor upregulated in the diseased patients in a time and dose-dependent manner. SARS-CoV-2 Mpro is another potential target for the therapeutic intervention of anti-SARS-CoV-2. With IC_{50} of 536.21 ± 38.74 μg/ml, APS-L remarkably repressed the Mpro activity. Moreover, APS and APS-L suppressed the binding affinity of SARS-CoV-2 S protein and ACE-2 to some extent (Yeh et al. 2022).

3.15. Honeysuckle

Lonicera japonica (Honeysuckle), belonging to Traditional Chinese Medicine has a history of being used to treat viruses such as hepatitis B, dengue, and influenza A virus, due to having anti-inflammatory effects in its flower and dry bud. Owing to its safety profile, *L. japonica* was investigated in silico and in vitro to evaluate its anti-SARS-CoV-2 activity. The screening of the probable targets of *L. japonica* from the SymMap database (FDR-BH < 0.01) found 66 target genes. Enhanced expression of the miRNAs, let-7a, miR-148b, and miR-146a proved beneficial to the treatment of SARS-CoV-2. A greater than 80% viability rate was attained for honeysuckle aqueous extract (honeysuckle-H_2O) at the highest safe dose of 500 μg/ml. 1.6 folds expression of let-7a and 1.4 folds expression of miR-148b was instigated by honeysuckle ethanol extract (honeysuckle-EtOH) at the dose of 50 μg/ml, whereas 1.2 folds and 1.4 folds were the enhancement rate of miR-148b and let-7a respectively when treated with the highest dose of 500 μg/ml. Gradual upregulation of miR-148b and miR-146a by 50 and 500 μg/ml of honeysuckle-H2O was at the rate of 1.4 and 1.6-fold and 1.2 and 1.4-fold, respectively. Administering *L. japonica* to mice and human subjects showed a pronounced expression of the mRNAs, let-7a, and miR-148b. BEAS-2B cells were used for further validation. The LPS-stimulated model was used for assessing the efficacy of *L. japonica* in the cytokine storm. The higher dose of honeysuckle-EtOH significantly downregulated the LPS-induced IL-6 secretion more than the lower dose. The binding of the SARS-CoV-2 spike protein to the ACE-2 receptor and syncytia formation was lessened by honeysuckle-EtOH (500 μg/ml) at the rate of 30% and 25%, respectively, whereas, for the honeysuckle-H2O (500 μg/ml) treatment group, both estimations were about 40% of the control group. Furthermore, the honeysuckle-EtOH presented 25-40% more repression of binding affinity than the honeysuckle-H_2O with doses of 2, 4, and 8 mg/ml. Additionally, the western blot assay analysis of the honeysuckle-EtOH (500 μg/ml) treated Calu-3 cells exhibited downregulated ACE-2 expression. The co-administration of *L. japonica* and *A. membranaceous* could be a potent anti-SARS-CoV-2 remedy through various combined mechanisms (Yeh et al. 2022).

3.16. Tulsi

Ocimum sanctum (Tulsi) is part of the Ayurveda system of medicine. Ayurvedic scriptures mention its role as an anti-inflammatory, antimicrobial, and immunomodulator. Docking studies were performed on chemical constituents in *O. sanctum* (Tulsi), against the Mpro enzyme of SARS-CoV-2, which was taken from the Protein Data Bank. A total of 46 constituents were tested, and 3 showed a strong binding affinity. The following constituents were Vicenin (8.79 kcal/mol), Isorientin 4′-O-glucoside 2″-O-p-hydroxybenzoate (8.55 kcal/mol), and Ursolic acid (8.52 kcal/mol) (Shree et al. 2022).

3.17. Ginseng

The use of *Panax ginseng* (ginseng) can be traced back over centuries, being widely used as an agent that facilitates the regulation of bodily functions. SARS-CoV-2 infected Vero E6 cells were used to explore the antiviral effects of fermented black color ginseng (FBCG), keeping remdesivir and chloroquine phosphate as the positive control. FBCG exhibited a dwindle in the intra and extracellular viral RNA replication in a dose-dependent manner, and the outcome was comparable to the positive control of remdesivir when cured with 25 μg/mL of the drug (Han et al. 2021).

Table 1. The table shows various medicinal remedies, their chemical constituents, doses, binding energies, and potential cellular targets.

Name	Family	Scientific Name	Part	Chemical Constituent	Dose/ Binding Energy	Extract	Study Type/Target	Citations
Turmeric	Zingiberaceae	*Curcuma longa*	Root	Curcumin and Cyclocurcumin	− 6.13, − 6.77 kcal/mol	Not applicable	In-silico/main protease	(Rajagopal et al. 2020)
Huangqin	Lamiaceae	*Scutellaria baicalensis*	Root	Baicalin and Baicalein	IC50 (μM), 83.4, 0.39	70% Ethanol extract	In-vitro/ 3C-like protease	(Liu et al. 2021)
Grapevine	Vitaceae	*Vitis vinifera*	Leaf	Polyphenols and Flavonoids	10 – 500 μg/mL	75% (*v/v*) methanol and 0.05% (*v/v*) trifluoroacetic acid	In-vitro/ Spike proteins	(Zannella et al. 2021)
Licorice	Fabaceae	*Glycyrrhiza glabra*	Whole Plant	Glycyrrhizic acid	1.21 mg/ml	Glycyrrhizic acid salt in water	In-vivo/ symptomatic management	(Soleiman-Meigooni et al. 2022)
Nees	Acanthaceae	*Andrographis paniculata*	Extract	A. paniculata extract and andrographolide	IC50 of 0.036 μg/mL and 0.034 μM	Not applicable	In-vitro/ virions production	(Sa-Ngiamsuntorn et al. 2021)
Garlic	Liliaceae	*Allium sativum*	Essential oil	Diallyl tetrasulfide, Trisulfide, 2-Propenyl Propyl, Allyl Disulfide, Allyl Trisulfide	-14.47, -14.36, -15.32, -15.02 kcal/mol,	Essential oils	In-silico/ main protease	(Thuy et al. 2020)
Eucalyptus	Myrtaceae	*Eucalyptus globulus*	Leaf	Eucalyptol, Alpha-pinene, *o*-Cymene, d-Limonene	-5.86, -5.43, -4.99, -5.18 kcal/mol	Essential oils	In-silico/ main protease	(Panikar et al. 2021)
Purple Coneflower	Asteraceae	*Echinacea purpurea*	Extract	Cichoric acid, Caffeic acid, Alkyl Amides, and Polysaccharides	2,400 mg/day	Aqueous, methanolic tablets	In-vivo/ infection management	(Hemmati and Mojiri-Forushani 2022; Kolev et al. 2022)
Willow bark	Salicaceae	*Salix* species	Bark	Salicin	1 μg/mL	Not applicable	In-vitro/ PGE2	(Le et al. 2021)
Umckaloabo	Geraniaceae	*Pelargonium sidoides*	Root	Gallic acid, Catechin, Scopoletin, and umckalin	IC50 of 96.41, 58.55, 17.79, 311.6 μM	Ethyl acetate extract	In-vitro/ Vero E6 cells	(Alossaimi et al. 2022)
Ginger	Zingiberaceae	*Zingiber officinale*	Root	Cyclosativene, Zingiberene, Camphor	-5.8l, -5.0, -4.6 kcal/mol	Not applicable	In-silico/ main protease	(Prasanth et al. 2020)
Ashwagandha	Solanaceae	*Withania somnifera*	Root	Withanone, Withanolide A, Withanolide B, Withaferin A	-9.4, -9.6, -9.4, -9.1 kcal/mol	Reversed-phase HPLC of root extract	In-silico/ ACE2 – receptor binding complex	(Balkrishna et al. 2020)
Guduchi (Giloy)	Menispermaceae	*Tinospora cordifolia*	Whole plant	Tinocordiside, Tinosporine	2 g	Tablets	In-vivo/ symptomatic treatment	(Chavda et al. 2022; Balkrishna et al. 2021)
Huang Qi	Fabaceae	*Astragalus membranaceous*	Root	Polysaccharides, saponins, flavonoids	1 mg/ml	Alcoholic precipitation	In-vitro/ viral inhibition	(Yeh et al. 2022)
Honeysuckle	Caprifoliaceae	*Lonicera japonica*	Flower buds	Luteolin, chlorogenic acid, linalool	50 μg/mL	Heat with 95% ethanol	In-vitro/ viral inhibition	(Yeh et al. 2022)
Tulsi	Lamiaceae	*Ocimum sanctum*	Leaves	Vicenin, Isorientin, 4′-O- Glucoside 2″-O-p-Hydroxybenzoagte, Ursolic Acid,	8.97 kcal/mol, 8.55 kcal/mol, 8.52 kcal/mol	Not applicable	In-silico/ main protease	(Shree et al. 2022)
Ginseng	Araliaceae	*Panax ginseng*	Root	Saponins	25 μg/mL	Fermented ginseng	In-vitro/ RNA replication	(Han et al. 2021)

4. Future Implications and Challenges

Despite being remarkably efficient in maintaining and enhancing immunity in the event of a disease, herbal drugs pose certain challenges that make it necessary to limit their use and approach with caution. The lack of infrastructure and regulatory policies that govern the standardization of herbal preparations for quality, purity, and safety is a primary barrier to the use of medicinal herbs. Moreover, testing and analysis for quality control following Good Manufacturing Practices; proper labeling, marketing, and post-marketing surveillance practices are also insufficient. Financial constraints also greatly compromise the improvement of the system. Extensive investigation of the complicated clinical designs is still needed. While medicinal herbs may contribute to the national and global economy, pharmaceutical companies may not earn a significant market investment (Saggar et al. 2022).

5. Conclusion

COVID-19 is the disease caused by SARS-CoV-2 which has taken over most of the world due to its rapid transmission, leaving healthcare providers with little time in trying to design effective therapeutic regimens for all types of patients. Variations in disease symptoms and severity have been presented amongst all patient populations. This review focuses on finding evidence-based natural remedies to help alleviate this malady by mediating the immune response. Numerous studies have been conducted to explore the potential of herbal plants as a treatment for SARS-CoV-2. These studies have ranged from in silico and docking studies to clinical trials and have identified various chemical constituents that may effectively treat the virus. *W. somnifera* and *V. vinifera* block the ACE-2-mediated SARS-CoV-2 activity. Furthermore, *Z. officinale, C. longa, A. sativum, O. sanctum,* and *E. globulus* act on Mpro, inhibiting the viral structural protein synthesis and replication. Similarly, *P. ginseng* also stops replication. These constituents have been added to the list of potential treatment options based on their affinity levels towards SARS-CoV-2 target sites. Most of the current findings can be seen as taken from Traditional Chinese Medicine, including herbal plants, essential oils, capsules, and decoctions. While the therapeutic benefits of the discussed phytocompounds are numerous, their clinical application still proves to be a challenge. Further extensive research is required to establish a definitive protocol to prescribe and monitor the therapeutic regimen of these compounds.

Conflict of Interest

The authors declare that they have no competing interests.

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Data Availability

All the data related to this manuscript are available with the authors**.**

Author Contributions

Main idea and conceptualization, initial draft by AH, literature collection, and review by HS & EA, graphics, language, and grammar by HHB, analysis and proofreading by AH, HS, and EA, review editing, rebuttals, and final draft by HHB.

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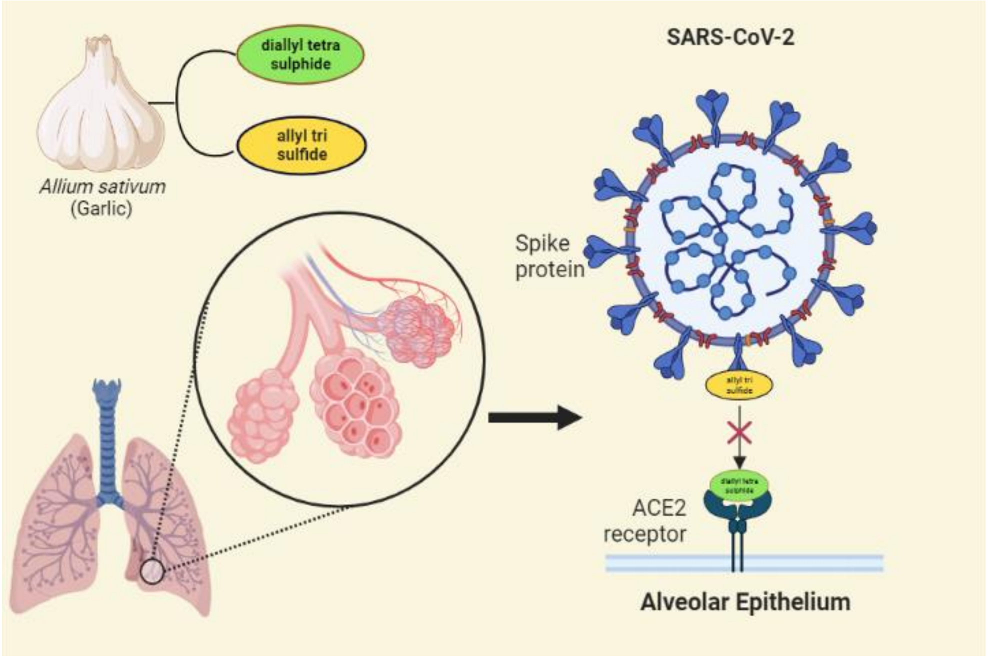

Figure 2. Mechanism of action of *A. sativum* constituents, diallyltetrasulfide and allyltrisulfide, against SARS-CoV-2

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