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Review Article

Exploring Nature's Invigorating Power: Phytotherapy for SARS-CoV-2

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Abstract

Covid-19 is a respiratory disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that spreads by person-to-person contact. The virus is thought to have a zoonotic origin. It mainly affects the respiratory system, resulting in fever, cough, shortness of breath, headaches, diarrhea, throat infections, and myalgia. It takes over the host's cell via the angiotensin-converting enzyme-2 receptors (ACE2). Despite the development of multiple vaccinations via diverse techniques, there is no scientifically significant therapy to combat SARS-CoV-2 infection. However, research into current therapeutic strategies' potential safety and effectiveness is in progress. This review briefly discusses the epidemiology of SARS-CoV-2, its pathophysiology, and the challenges of current treatment for SARS-CoV-2. The significance the medicinal plants and their extracts are discussed at length. Available literature suggests that aloe vera, senna, black cumin, and fenugreek have the potential to be effective antivirals against SARS-CoV-2. Many of these plants also have immunomodulatory, antiasthmatic, antipyretic, anti-tussive, and antiviral effects. Bioactive compounds such as quercetin, curcumin, epigallocatechin gallate, baicalin, andrographis, glycyrrhizin, and resveratrol have also been shown to relieve Covid-19 symptoms. We suggest that these medicinal plants may serve as a source of phytocompounds with safer and more potent antiviral agents against SARS-CoV-2 and should be investigated further in detail.

Keywords: Coronavirus, Covid-19, SARS-CoV-2, phytochemicals, antiviral, herbal treatment, medicinal plants.

1. Introduction

Cardiovascular disorders Coronaviruses are named for the crown-like spikes on their surface. They belong to a family of enveloped RNA viruses (positive single-stranded). In late 2019, a new strain of coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was discovered in Wuhan, China. SARS-CoV-2 has contributed to the worldwide outbreaks, and WHO declared it a public health emergency. SARS-CoV-2 is a member of the β-family of 4 known genera (α, β, γ, and δ) of coronavirus (Runfeng et al. 2020, Zhang et al. 2023). It shares 79.6% sequence similarity with SAR-CoV; recent research shows that both strains share the same ACE2 receptors to infect human cellular machinery(Zhang et al. 2023). SARS-CoV is still a major health concern globally owing to continuous evolution in its strain and subsequent production of various variants(Pan et al. 2023). Since no definite and target-specific antiviral therapy for Covid-19 is currently available, symptomatic treatment, supportive care, control, and prevention are major therapeutic strategies. Medicinal plants with considerable anti-inflammatory and antiviral activity present a remarkable opportunity to treat this deadly disease (Kaul and Paul 2021).

This article will discuss the effectiveness of various plants and their constituents as antiviral

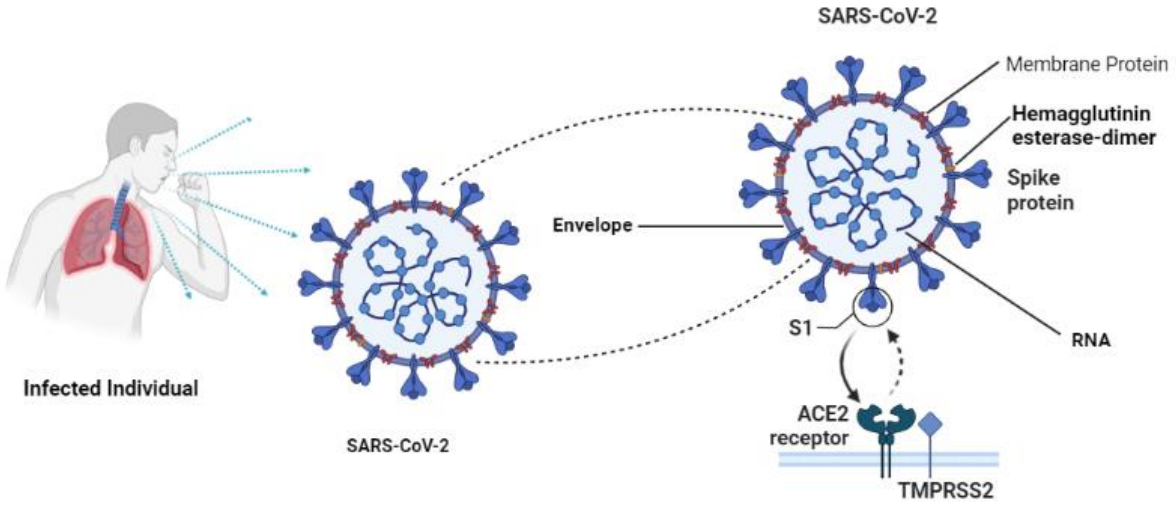

Figure 1: Representation of SARS-CoV-2 structure and its receptor binding. Enveloped, ++SS RNA virus with structural proteins, spike (S), membrane protein, and envelope protein. Created in Biorender.com

agents. Moreover, this literature review will provide insight for future research and development in using medicinal plants, phytochemicals, and extracts as a possible therapy for coronaviruses.

2. Epidemiology

Covid-19 is a highly contagious viral disease and it has had a disastrous effect on public health, resulting in more than six million casualties worldwide. As per WHO, the outbreak of viral diseases is a major risk to global public health. SARS-CoV-2 spread all over the world, which led to over 690 million cases of infection and over 6.8 million deaths globally. It was declared a worldwide pandemic by WHO in early 2020. The United States reported over 1 million causalities, followed by Brazil and India. WHO estimated that 2.2% is the global case fatality rate (GCFR) for the Covid-19 pandemic. The death rate was higher in older adults (with a median age of 80 years) and people with underlying health conditions. However, it may be influenced by several factors, including gender, age, severity of illness, and comorbidities, and considerably varies from country to country(Cascella et al. 2023).

3. Pathophysiology of SARS-CoV-2

SARS-CoV-2 predominantly attacks humans' respiratory tract by invading host cells and binding to the ACE2 receptors through its spike proteins. After hijacking a host's cellular machinery, the virus replicates and releases viral particles to adjacent tissues, leading to cell destruction. This destruction activates the immune system, which causes the generation of pro-inflammatory and inflammatory mediators, along with cytokines and chemokines, at the site of infection for the recruitment of immune cells. This immune response can sometimes be unwanted and outrageous, leading to hypercytokinemia (cytokine storm) and severe tissue damage, and organ collapse (Florindo et al. 2020).

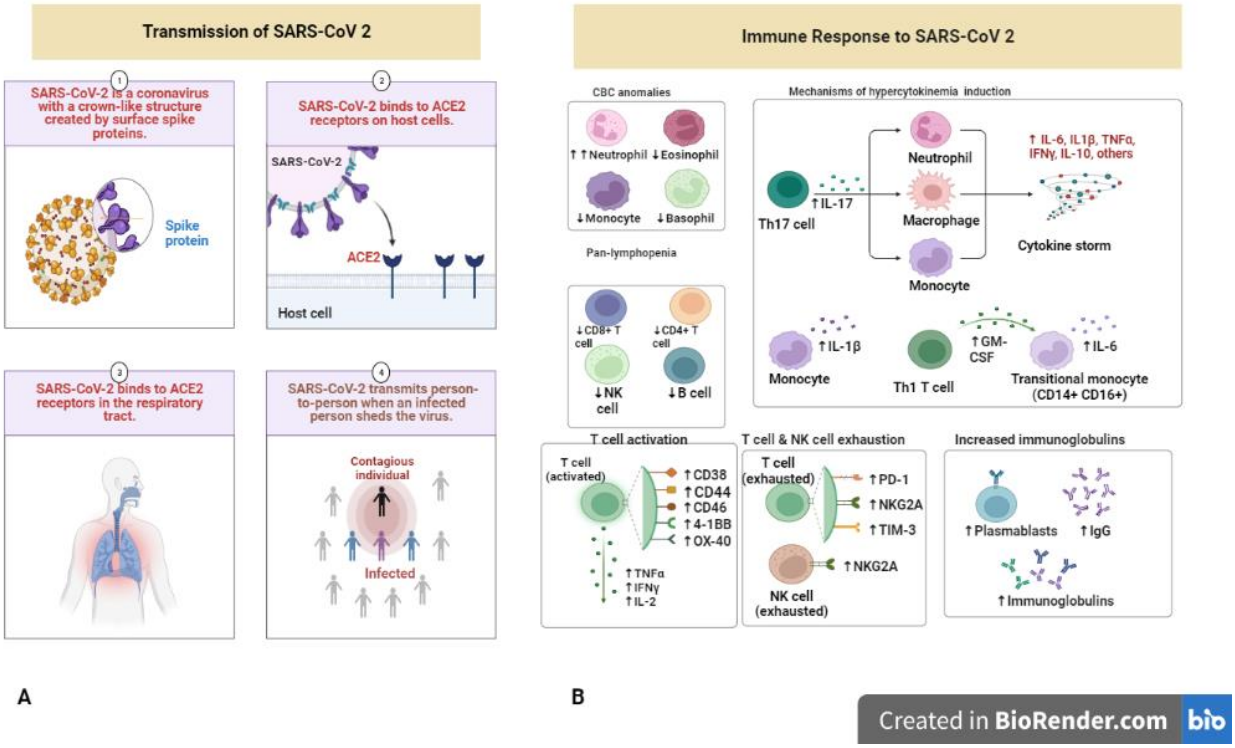

Figure 2: Transmission of SARS-CoV 2 (A), Immune action/cytokines storm to SARS-CoV 2 (B). Created in BioRender.com

4. Current Treatments and Challenges in Developing New Treatments

The biggest challenge in developing new treatments for SARS-CoV-2 is the dearth of knowledge because it's a novel illness. The therapeutic strategy for SARS-CoV-2 varies with the severity of the viral infection. Typically, the treatment involves a combined approach of antiviral, anti-inflammatory drugs, and supportive therapies. The antiviral therapy includes Remdesivir, which the FDA approved for emergency use for the treatment of SARS-CoV-2. Favipiravir and molnupiravir have also demonstrated promising results for treating SARS-CoV-2. Corticosteroids, such as dexamethasone, were found to decrease mortality in patients with severe SARS-CoV-2 infection(Group 2021). Montelukast and leukotriene receptor antagonists are also helpful in dealing with symptoms like shortness of breath (Nhean et al. 2023, McCarthy 2023). Treatment with the interleukin-6 receptor antagonist (tocilizumab and sarilumab) improved outcomes in critically ill patients in intensive care units(Investigators 2021). Supportive care includes mechanical ventilation, increased supplemental oxygen, electrolyte, and fluid management. Low molecular weight heparin fraction, enoxaparin, and heparin were found to reduce the risk of blood clotting in hospitalized patients with SARS-CoV-2 infection(Di Micco et al. 2021, Angelini et al. 2022).

Several limitations to the development of SARS-CoV-2 therapy include the requirement for large-scale clinical trials, the urgency of finding effective medicines, the variety in prognosis, and the severity of the infection in an individual. The currently used medicines are mostly preexisting antiviral drugs such as those used in influenza, HIV, or some other viral infections(Slomski 2022). However, various medicinal plants and their extracts have shown promising results in cell culture and animal models(Colunga Biancatelli et al. 2020). The rapid evolution and mutation of the

SARs-CoV-2 make it difficult to develop an effective treatment, as mutations in virus structure make it resistant to existing antiviral drugs. However, medical plants and their extracts are effective against a wide range of viral mutations(Benarba and Pandiella 2020, Adhikari et al. 2021). With the current treatments, the severity of the disease may not be addressed, and immunocompromised people or older adults with underlying health conditions are more prone to severe viral infection even if the treatment is available. However, phytochemicals with immune-boosting effects prevent serious illness(Demeke, Woldeyohanins, and Kifle 2021). Availability and cost-effectiveness put further limitations on synthetic compound drug development.

Meanwhile, medicinal plants and their extracts are often affordable and more accessible than conventional treatments(Lim, Teh, and Tan 2021). Many concerns regarding the virus remain unresolved, including the long-term impact of the infection, the role of asymptomatic carriers in propagating the virus, and events that lead to severe illness. Clinical studies for SAR-SCoV-2 therapeutics that can modify the immune response without completely inhibiting it are among the major challenges (Robinson et al. 2022, Hamidi et al. 2023).

5. Medicinal Plants as Natural Antivirals Against SARS-CoV-2

Due to their natural origin, medicinal plants are thought to possess less harmful effects and are preferred over synthetic medications. Medicinal plants are known to be a great source of natural chemicals that could potentially be used to synthesize antibacterial and antioxidant drugs in the modern era. Plants have been associated with various beneficial characteristics, notably antibacterial, anti-inflammatory, anticonvulsant, and antipyretic actions. Polyphenols (e.g., kaempferol and quercetin) found in medicinal plants are beneficial in treating various medical conditions(Daglia et al. 2023, Di Pierro et al. 2021). Herbal substances have particular traits, such as their ability to prevent SARS-CoV-2 virus entrance into host cells and interfere with inflammatory responses, limiting its pathogenicity. This review aims to identify medicinal herbs that may be used to prevent SARS-CoV-2 infection by targeting cellular and molecular processes.

5.1. Aloe vera L. (*Aloe barbadensis Miller*)

Aloe barbadensis Miller, a member of the family Aloaceae, vernacularly known as Aloe vera L. The name 'aloe' originated from the Arabic word 'Halal' or 'Alloeh', which means "shiny bitter **not sour** material," and 'vera' originated from a Latin phrase that means 'truth'. The aloe vera plant contains approximately 200 bioactive compounds that comprise amino acids, saponins, anthraquinones, lignin, carbohydrates, enzymes, vitamins, and minerals. The pharmacological significance aloe vera plant suggests that it might be utilized to alleviate Covid-19 symptoms(Astuti et al. 2017). *Table 1* lists the active compounds in aloe vera and their effects on cellular processes for disease prevention.(Ahmed et al. 2023).

5.2. Black cumin, Kalonji (*Nigella sativa*)

Nigella sativa (NS) belongs to the family Ranunculaceae. It has been utilized in the treatment of conditions such as asthma, colds, headaches, and nasal congestion. It has multiple therapeutic effects, notably antioxidant, anticancer, immunomodulator, antibacterial, antiasthmatic, and bronchodilator(Biswas et al. 2021). Since NS has antiviral, immunomodulatory, antipyretic, and broncho-dilatory properties, it is considered a useful herb for treating SARS-CoV-2-infected individuals.

Multiple biologically active compounds, including terpenes, flavonoids, coumarins, tannins, phenolic compounds, cardiac glycosides, alkaloids, volatile oils, saponins, fatty acids, dithymoquinone (DTQ), terpenes (e.g., TQ), limonine, p-cymene, indazole alkaloids like nigellicine, and nigellidine and isoquinoline alkaloids including nigellicimine, nigellicimine-N-oxide and α-hederin are found in

Kalonji *(Table 2)*. In addition, bioactive ingredients such as alpha -hederin and nigellidine are also considered to be effective in SARS-CoV-2 treatment(Bibi et al. 2021, Usmani et al.). *Table 1* lists the active compounds in NS and their effects on cellular processes.

Table 1: List of active compounds in Aloe vera and Nigella sativa (Black Cumin), and their effects on cellular processes for disease prevention.

Plant	Biological Activity(s)	Active Compounds	Mechanism of action	Reference
Aloe barbadensis	Antiviral Antibacterial Immune-modulatory	Aloe emodin	Breakdown of 3-c like protease inhibits in corona (SARS) virus.	(Ahmed et al. 2023, Morin 2008)
		Lectins	Cell-loaded carboxymethylcellulose (CMC) proliferator inhibitor. Generates cytokines and triggers an immune response	(Ahmed et al. 2023, Hamman 2008)
		Acemannan	Block reproduction of viruses (Herps, AIDs Virus)	(Ahmed et al. 2023)
		Aloin	Integration into the viral envelope. Destruction of phospholipid double layer	(Ahmed et al. 2023, Lewis et al. 2022)
		Uronic acid	Preventing association of Ribosome with the aa-***t***-RNA. Protein synthesis inhibited	(Ahmed et al. 2023, Rezazadeh et al. 2016)
		Zinc ionophores	Stops viral replication	(Ahmed et al. 2023, Skalny et al. 2020)
		Lignin	Decrease body temperature	(Ahmed et al. 2023, Sakagami et al. 2022)
Nigella sativa	Antiviral Antiasthma Immune-modulatory Anti-histaminic	Nigellidine	Inhibitor of SARS & SARS-CoV 2 virus.	(Bouchentouf and Missoum 2020, Ahmed et al. 2023)
		Thymoquinone	Elevate T-lymphocytes and natural killers (NK) cells in immune responses. Inhibits the production of several leukotrienes	(Ahmed et al. 2023, Badary, Hamza, and Tikamdas 2021)
		Nigellone	Suppression of mast cells' histamine release.	(Bouchentouf and Missoum 2020, Ahmed et al. 2023)
		Volatile-oil	Improve intratracheal pressure and breathing rate	(Ahmed et al. 2023, Şakalar and Ertürk 2023)

5.3. Fenugreek (*Trigonella foenum graecum*)

Trigonella foenum-graecum commonly referred to as fenugreek, is a member of the family Leguminosae. It gets its name from an ancient Greek phrase that means "3-angled"(Wani and Kumar 2018). Many countries worldwide use it as an herb (leaves) and a spice (seed), as well as for medicinal uses. Fenugreek has long been used to cure a variety of ailments, notably influenza, head colds, asthmatic bronchitis, respiratory infections, throat inflammation, tuberculosis, allergies, hay fever, and sinusitis. Trigonelline, an antiviral molecule derived from nicotinic acid and a primary alkaloid, is found in the seeds of the Fenugreek plant (Hwa et al. 2019).

Furthermore, the plant features flavonoids such as apigenin and orientin, which have antiviral characteristics (Table 2). Apigenin has been

observed to decrease viral internal ribosome entry sites (IRES)-driven translational activity against the foot and mouth disease (FMD) virus. This action initiates cap-independent viral genome translation(Patch et al. 2011), which apigenin blocks. On the other hand, Orientin can bind to the overlapping amino acid in the SARS-CoV-2 spike model to a place responsible for receptor GRP78 binding. Thus, orientin binding may prevent the SARS-CoV-2 mutant protein from interacting with the host's receptor GRP78, thus decreasing viral infection (Aanouz et al. 2021, Khan et al. 2021, Hwa et al. 2019, Pastick et al. 2020).

5.4. Senna (*Cassia angustifolia*)

The drought-resistance herb *Cassia angustifolia,* commonly knowns as the Senna plant, belongs to the family of Leguminosae(Gagnon et al. 2016). Senna is notably served to treat respiratory disorders, mainly asthma, bronchitis, and gastrointestinal disorders like constipation, ameboid dysentery, and fever. Glycosides (Sennoside A and B) present in the senna plant serve as laxatives. Isorhamnetin in senna possibly interferes with the ACE2 receptor site, blocking viral entry and preventing SARS-CoV-2 infection in human lung cells expressing ACE2 (*Table 2*). For this purpose, Isorhamnetin is considered the potential novel drug for SARS-CoV-2 treatment as a protein interaction inhibitor of ACE2(Yang et al. 2020, Bibi et al. 2022, Zhou et al. 2020, Islam et al. 2021).

Table 2: List of active compounds in Trigonella foenum-graecum and Cassia angustifolia, and their effects on cellular processes for disease prevention.

Plant	Biological Activity(s)	Active Compounds	Mechanism of action	Reference
Trigonella foenum-graecum	Antiviral Antiasthma Immune-modulatory Anti-histaminic Antipyretic Anti-tussive	Kaempferol	Blocking of the 3-a protein ion-channels & prevention of viral production.	(Zakaryan et al. 2017, Ahmed et al. 2023)
		Apigenin	Decreases the translational activity of viral IRES	(Patch et al. 2011, Ahmed et al. 2023)
		Orientin	Competence to associate overlapping amino acid residues in the SARS-CoV 2 mutant model	(Patch et al. 2011, Pastick et al. 2020, Ahmed et al. 2023)
		Luteolin	Blocks mucus buildup in the respiratory tract by blocking the GABAergic pathway	(Bai et al. 2016, Ahmed et al. 2023)
		Chlorogenic	Antipyretic properties	(Chen et al. 2010, Ahmed et al. 2023)
		Saponin	Antitussive characteristics	(Li et al. 2021, Ahmed et al. 2023)
Cassia angustifolia	Antiviral Immune-modulatory	Kaempferol	Blocking of the 3-a protein ion channels and prevention of viral production. In PRV-infected mice inhibits the replication of the virus.	(Zhao et al. 2018)
		Isorshamnetin	Inhibit interaction of ACE2 spike pro-teins.	(Yang et al. 2020)

6. Plant extracts as promising agents against SARS-CoV-2

Several plant extracts have proven their potential in the treatment of Covid-19; these botanical extracts can be consumed in a variety of ways, involving nutritional supplements, natural remedies, and traditional medications. Plant extracts have been shown to halt viral replication. Plant-derived compounds, including quercetin, curcumin, EGCG, baicalin, and resveratrol, can hinder viral replication by restricting viral entry, limiting virus-specific protein expression, and initiating host antiviral responses. Several herbal extracts have shown efficacy in the treatment of coronavirus. However, it is necessary to highlight that more investigation is required to fully comprehend the benefits and their adverse consequences. *Table 3* summarizes certain aspects of the most prominent recent research on natural plant extracts in treating Covid-19 infection.

Table 3: Plant extracts and traditional Chinese medicine (TCM) as promising agent against SARS-CoV-2 infection.

Extract	Biological Activity	Mechanism of action	Reference(s)
Quercetin	Antioxidant Anti-inflammatory	Blocks of viral replication. Prevents viral entrance to cell, halts viral protein expression.	(Derosa et al. 2021, Di Pierro et al. 2021)
Curcumin	Anti-inflammatory Antiviral	Halts of viral replication. Prevents viral entrance to cell, halts viral protein expression, and triggers host antiviral response.	(Vahedian-Azimi et al. 2022, Shojaei et al. 2023)
Epigallocatechin gallate (EGCG)	Anti-inflammatory Antiviral	Blocks viral replication by preventing viral entrance to cell, halts viral protein expression, and triggers host antiviral response.	(Ohishi et al. 2022)
Baicalin	Anti-inflammatory Antiviral	Prevents viral entry and replication by inhibiting angiotensin converting enzyme-2 receptor and protease activity of virus.	(Wang and Li 2023, Song et al. 2023)
Andrographis	Anti-inflammatory Antiviral Immune-boosting	Prevents replication and inflammation by improving interferon production and triggering the immune response.	(Shavira, Handayani, and Fatmaria 2023, Komaikul et al. 2023)
Glycyrrhizin	Anti-inflammatory Antiviral	Alters lipid bilayer membrane of virus, increasing nitric oxide production in macrophages, halting viral protein expression.	(Banerjee et al. 2023)
Resveratrol	Anti-oxidant Anti-inflammatory	Blocks viral replication by suppressing viral protein expression enhances autophagy and lowers the expression of pro-inflammatory mediators. Regulates immune response and arrests the thrombotic events in SARS-CoV 2 infected patient.	(Domi et al. 2022)
Lianhuaqingwen (Traditional Chinese Medicine, TCM)	Anti-inflammatory Antiviral	In vitro studies shown significant action in inhibiting covid-19 virus replication, alter viral morphology, and show anti-inflammatory action.	(Fan et al. 2022)

7. Conclusions & Future Directions

Medicinal plants come with various limitations, such as the exact mechanisms by which many phytochemical and herbal extracts exert their effects against SARS-CoV-2 are still unknown. They sometimes may lead to potentially harmful interactions, which must be addressed before clinical use. Depending on the cultivation conditions, harvesting techniques, and processing methods, medicinal plants may lack standardization. Large-scale cultivation and provision of extracts worldwide is still a challenge. Moreover, patient compliance is also a big hurdle, as many are reluctant to take phytochemicals or extracts as therapeutic agents. These challenges associated with medicinal plants and their extracts can be addressed with standardized extracts, standardized doses, more research, and data

safety. In this review, we concluded that various medicinal substances such as aloe vera, senna, black cumin, fenugreek, and bioactive substances like quercetin and curcumin are able to regulate pro-inflammatory cytokine synthesis and release, interfere with viral replication within host cells, and influences particular pathological pathways, making them beneficial in the battle against Covid-19.

However, we recommend patients seek the advice or supervision of a healthcare professional before taking medications containing the aforementioned compounds to prevent or treat Covid-19 infection. Furthermore, medical professionals should exercise caution when administering herbal medicines to patients due to the dearth of consistent data on their safety and potential side effects. Limited preclinical or clinical trials evaluating the efficacy of these herbal agents for Covid-19 have been conducted, further emphasizing the need for additional research into their safety profiles and therapeutic potential. Although medicinal plants can possibly serve as a promising synthetic route for preclinical trials, more rigorous and reliable investigations must be conducted to determine the efficacy of these plants and their extracts in the therapeutic management of SARS-CoV-2 infection.

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Conflict of interest

There was no conflict of interest.

Study Approval

NA

Consent Forms

NA

Data Availability

All the data related to this manuscript including research articles that were analyzed for this review are available with the authors**.**

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Author Contributions

Main idea and conceptualization, and initial draft by FB, literature collection, and review by AI & BR, graphics, language and grammar by AK, analysis and proofreading by QUA, review editing, ebuttals and final draft by TZ.

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