

## Therapeutic potential of selective medicinal plants and their phytoconstituents in respiratory diseases: A review with an emphasis on COVID-19

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### ABSTRACT

Respiratory diseases, spanning from mild illnesses like the common cold to more serious problems like pneumonia and COVID-19, pose significant challenges to global health and contribute significantly to morbidity and death. The emergence of COVID-19 has increased the need for efficient therapeutic approaches. This review article examines the potential of specific medicinal plants, namely Black Cumin, Licorice, and Echinacea, and their phytoconstituents in the management of respiratory diseases, with a specific emphasis on COVID-19. It synthesizes extant knowledge on the therapeutic efficacy of these plants, which have been used traditionally in Unani, Ayurvedic, and Chinese medicine to alleviate respiratory symptoms and boost immune functions. This review also discusses the immunomodulatory and antiviral properties of these three specific medicinal plants, as well as their function in the treatment of a number of life-threatening diseases. Incorporating insights from ethnomedicine and contemporary scientific research, this review highlights the urgency of exploring herbal medicines as complementary therapies for respiratory diseases and offers perspectives on incorporating these natural remedies into contemporary treatment paradigms, particularly in the perspective of combating COVID-19.

### INTRODUCTION

Respiratory diseases encompass a spectrum of conditions, varying in severity from mild and self-limiting disorders like the common cold to more severe and potentially life-threatening conditions such as pneumonia, tuberculosis, and pulmonary hypertension. These diseases have consistently posed a persistent challenge in the realm of global health [1,2]. Annually, the respiratory disorder causes 2.2 million fatalities. As a result, the treatment for acute respiratory tract infection costs more than 20 billion dollars [3]. Moreover, the appearance of the novel coronavirus (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has



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imposed an unparalleled strain on healthcare systems globally. First detected in Wuhan, China, in December 2019, the COVID-19 global pandemic has had a devastating impact on nearly every country across the entire world. The Chinese Centre for Disease Control and Prevention (CCDC) determined the causative agent from throat swab samples on January 7, 2020, and classified it as SARS-CoV-2[4]. The SARS-CoV-2 genes exhibit less than 80% nucleotide identity and almost 90% nucleotide similarity with SARS-CoV genes [5]. The vital target of infection is the lower respiratory tract [6]. The predominant signs of COVID-19 encompass fever, parched cough, and fatigue. Less prevalent however nonetheless detectable symptoms of the condition include anosmia (loss of taste or smell), rhinorrhea (nasal congestion), conjunctivitis (red eyes), pharyngitis (sore throat), cephalalgia (headache), myalgia or arthralgia (muscle or joint pain), diverse forms of dermatitis (skin rash), emesis (nausea or vomiting), diarrhea, rigors (chills), or vertigo (dizziness). In addition to these mild symptoms, certain individuals have presented with severe complications such as organ failure, septic shock, severe pneumonia, dyspnea, anorexia, cognitive impairment, persistent thoracic pain or pressure, high fever (above 38°C), and acute respiratory distress syndrome (ARDS) [7]. Given the increased focus on respiratory disorders, it is imperative to prioritize research on innovative and efficacious therapeutic approaches.

The utilization of medicinal plants for disease treatment and public health maintenance is recognized across various countries and cultural contexts worldwide [1]. Previous research in the field of ethnomedicine has demonstrated that the utilization of plant-derived medicines has the potential to alleviate chest and nasal congestion, providing relief to inflamed airways and mitigating symptoms [2]. Multiple studies have documented the existence of antihistamine and antioxidant properties in herbal remedies, which are essential in alleviating respiratory ailments [8,9]. Concurrently, technological advancements have equipped us with the tools to more comprehensively understand the molecular pathways that explain the therapeutic benefits of these plant-derived treatments, enabling a seamless integration of traditional and modern approaches.

The scientists' tireless efforts resulted in the discovery of some vaccines for the COVID-19. Although helpful in managing the pandemic, current antiviral medications and vaccination efforts have limitations. Vaccine hesitancy, variable efficacy against emerging strains, and the possibility of adverse reactions motivate the search for additional interventions. In another sense, the COVID-19 pandemic increases the urgency of investigating alternative therapies [10]. Natural products and herbal medicines have a crucial role in drug discovery. Several studies indicated that natural products and their derivatives have significant antiviral activity and potential of inhibiting viral replication [11,12]. Furthermore, nutritional interventions are important to boost up the host immune system against different infections or diseases. Mortality and morbidity associated with measles, diarrhea, measles-related pneumonia, human immunodeficiency viruses (HIV), and malaria can be reduced through the use of vitamin A supplements. Vitamin C boosts up immune functions and shows the potentiality against SARS coronavirus, atypical pneumonia, and lower respiratory tract infections. In addition, individuals suffering from conditions such as diabetes, hypertension, cardiovascular disease (CVD), and cancer can develop a resistance to SARS-CoV-2 by consuming adequate amounts of vitamin D and vitamin E [13]. Zinc and pyrithione, when used together at a specific dosage, effectively suppress the replication of SARS-CoV [14].

Along with the availability of several medicines or vaccinations for COVID-19, it is crucial to discover new approaches to manage the transmission of this disease and

inhibit its replication. There is solid attestation in favor of medicinal plants being utilized for fortifying body immune functions and treating different diseases in prehistoric systems of Unani, Ayurvedic, and Chinese traditional medicine. The objective of this review is twofold: first, to provide a concise overview of the existing knowledge concerning the three medicinal plants e.g., Black Cumin (*Nigella sativa* L.), Licorice (*Glycyrrhiza glabra*), and Echinacea (*Echinacea spp.*) and their phytoconstituents that demonstrate therapeutic potential in the treatment of respiratory disorders; and second, to investigate the relevance of these findings in the context of COVID-19. By bringing together various lines of research, this review seeks to pave the way for the effective introduction of herbal medicine into modern therapy regimens for respiratory diseases, with a particular focus on COVID-19.

## METHODOLOGY

An extensive literature search was carried out through the well-recognized web databases (Web of Science, PubMed, Science Direct, Elsevier, Google Scholar, Wiley Online Library, Taylor and Francis, Springer, ACS, etc.) and different books using suitable keywords. The current review only includes articles published in English-language journals that meet the required information standards of quality. The information was structured and analyzed with Microsoft Excel (2010) software prior to being organized into tables and figures. The online botanical databases 'The Plant List' (Royal Botanic Gardens, Kew, UK and Missouri Botanical Garden, USA) and 'Tropicos' (Missouri Botanical Garden, USA) were used for taxonomic treatment of the documented plant species. Table 1 presents the comprehensive procedure of this approach.

**Table 1.** Finding information for therapeutic properties of three medicinal plants.

Sources	Keywords	Search results
Google Scholar	Medicinal plants and COVID-19	87,900
	Medicinal plants and respiratory diseases	300,000
	<i>Nigella sativa</i> for COVID-19	5,090
	Echinacea for COVID-19	3,990
	Licorice for COVID-19	7,490
	Thymoquinone	24,500
	Glycyrrhizin	35,000
Science Direct	Cytokine storm	271,000
	COVID-19 vaccines	46,755
	Medicinal plants	151,444
	COVID-19	247,537
	Glycyrrhizic acid	3,238
PubMed	Active constituents of black cummin	1,283
	Cytokine storm	20,990
	Developing COVID-19 vaccines	14,500
	Respiratory illness children	16,566
	COVID-19	405,141
Wiley Online Library	Glycyrrhizic acid	2,722
	Autophagy	83,593
	COVID-19	103,487
	Medicinal plants	19,71,199
Taylor and Francis	Active constituents of black cummin	1,146
	Antiviral properties of medicinal plants	32,146
	COVID-19	79,972
Springer	Medicinal plants	970,350
	COVID-19	254,924
MDPI	Medicinal plants	126,192
	Antiviral properties of medicinal plants	7,951
		135

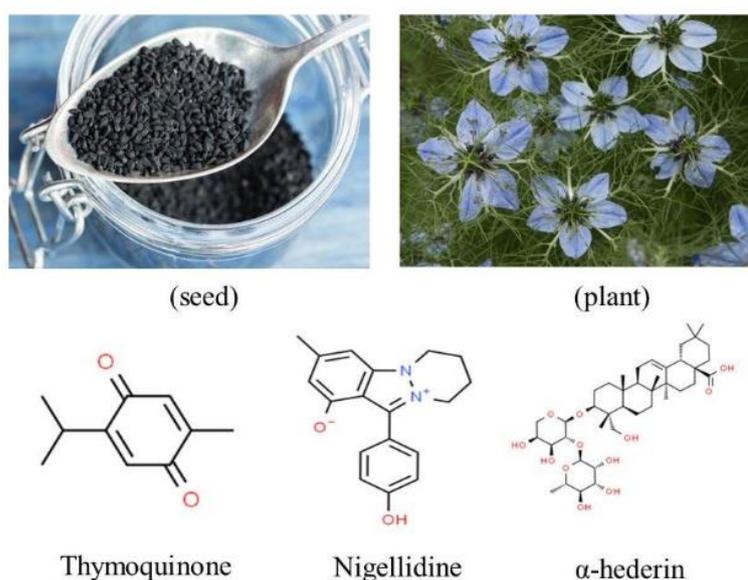
## PHARMACOLOGICAL POTENTIALS OF MEDICINAL PLANTS IN RESPIRATORY DISORDERS

COVID-19, emerging from the SARS-CoV-2 virus, is predominantly a respiratory disease. A respiratory disease and COVID-19 share similar modes of transmission, infected organs, complications, and symptoms. Individuals diagnosed with chronic respiratory diseases (CRDs), including chronic respiratory failure (CRF), asthma, chronic obstructive pulmonary disease (COPD), interstitial lung diseases (ILDs), pulmonary hypertension, sarcoidosis, or cystic fibrosis (CF), were promptly identified as being susceptible to experiencing severe symptoms of COVID-19 [15]. Various viral respiratory diseases are widely recognized for their tendency to induce serious respiratory consequences, such as ARDS, mainly in vulnerable elderly adults and those with significant underlying health conditions (such as obesity, diabetes, or heart or respiratory failure) [16]. Based on available information and clinical expertise, people of any age who have severe underlying medical conditions like diabetes, CVD, asthma etc. might be at higher risk [17,18]. Alongside containment strategies, the regular treatment for COVID-19 consisted of symptomatic and respiratory support based on the patient's diagnosis. Severe atypical pneumonia is the main cause observed for the death in this disease. The infected patients are usually observed with symptoms of mild upper respiratory tract infection, which has similarities with the common cold attack. Prognosis refers to the predominant symptoms of COVID-19 comprised of fever (88-98%), nasal congestion, non-productive cough, exhaustion, pharyngitis, dyspnea, diarrhea, myalgia, and gastrointestinal disturbances [7,19]. Herbal treatment can be considered as a substitute for conventional medicines for more than a few reasons, including easy access and availability, minimum or no side effects, and economic. Indigenous knowledge about various kinds of medicinal plants often offers great insight into the way of drug development for an emerging disease. Moreover, an adaptive and powerful immune system is undoubtedly essential for the human body to defend against SARS-CoV-2 as well as respiratory infections [20]. The use of these plants can be helpful to prevent the onset of this disease by strengthening the body's immune system [21]. Medicinal plants have curative potentials along with different complex chemical substances as secondary metabolites of different composition. Medicinal herbs and spices can positively be antimicrobial without being anti-life. Furthermore, these plants can be useful against viruses and fungal infections and support the ecosystem of the human body. The body's immune system plays a great role in defending the body from autoimmune disorders, cancers, and seasonal allergies as it is one of the best defense mechanisms for a human body. Clinical trials and numerous scientific research on the use and efficacy of herbal plants and spices are on the rise now-a-days [22]. Maximizing the natural immunity of the body is crucially important as the host environment is supposed to be a governing factor for the attacking organism. Furthermore, throughout history, medicinal plants and their extracts have been used to treat a variety of respiratory and viral diseases. The first Chinese medicine (CM) oriented hospital started its function in Wuhan since February 2020 and the first recovery in Beijing came from the treatment with the IM [23]. In addition, plant-based, traditional, and home remedies can be used as a form of primary treatment. Numerous investigations have documented the inhibitory properties of extracts derived from medicinal plants and botanicals against the replication of various viruses, including SARS [24]. Additional studies have focused on investigating the antiviral properties of various plant extracts against strains of viruses that are unresponsive to traditional antiviral treatments. This led us to proactively investigate the antiviral properties of naturally occurring medicinal herbs. Based on these findings, it is reasonable to state that the use of medicinal plants, in addition to other types of

drugs, should be addressed in order to combat or manage the respiratory diseases and COVID-19.

### Black cumin (*Nigella sativa* L.)

For more than 2000 years, black cumin (Figure 1) has been used as an anti-microbial treatment as a popular and well-known medicinal food. The Prophet Muhammad (PBUH) specifically referred to black cumin as a remedy for all diseases, with the exception of death. It is also specified within the list of natural medication of 'Tibb-e-Nabavi', or "Medicine of the Prophet (Muhammad PBUH)" [25]. *N. sativa* has been shown to have a wide range of actions, such as diuretic, immunomodulatory, analgesic, gastroprotective, antioxidant, hepatoprotective, anti-inflammatory, and spasmolytic properties [26]. It has been suggested strongly for combating the COVID-19 based on recent computational findings and its therapeutic potentials against autophagy dysfunction, immune disturbance, CVD, viral, and bacterial infections [27].



**Figure 1.** Black cumin and its active constituents for COVID-19 and respiratory diseases treatment options.

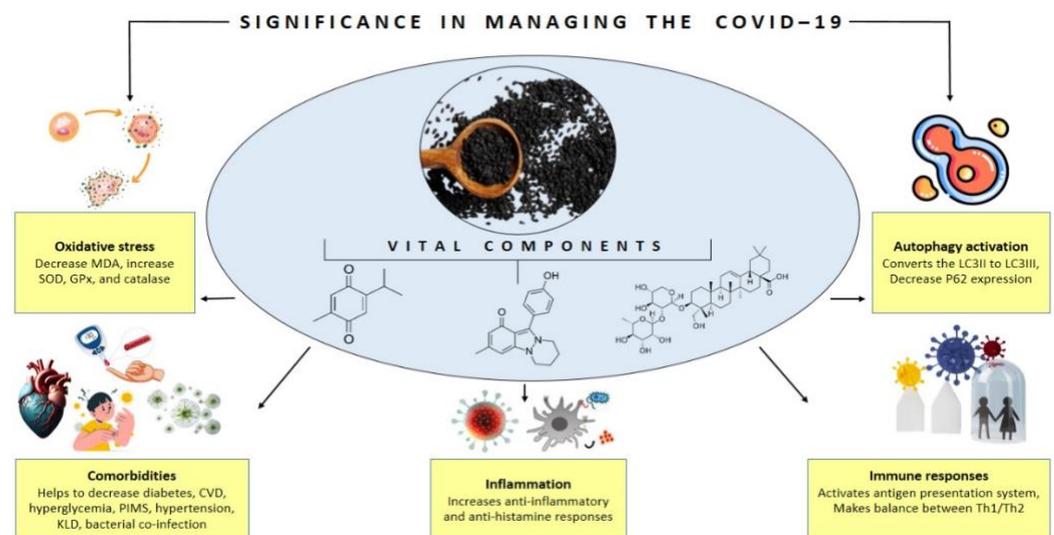
#### *Thymoquinone*

Thymoquinone (TQ) has a significant antioxidant, anti-histaminic, anti-inflammatory, anti-microbial, anticancer, and cardio-protective activities with low or no side effects [28]. TQ promotes autophagy in the human body. TQ prevents the activation of interferon regulatory factor 3 (IRF-3) by suppressing the activity of TANK-binding kinase 1 (TBK1). IRF-3 is crucial in the innate immune responses against viral and bacterial infections since it controls the generation of Type I interferons [29]. People who have rheumatoid arthritis (RA) are more susceptible to infection compared to healthy people. According to some studies, there is a possible link between RA and respiratory viral infections like parainfluenza or coronavirus [30]. Arthritis scores and pro-inflammatory cytokines levels (interleukin 1 beta,  $IL-1\beta$  and tumor necrosis factor alpha,  $TNF\alpha$ ) were significantly controlled by TQ, as found in a study on adjuvant-induced arthritic rats [31]. Therefore, this capability of TQ could decrease the severity of arthritis. The use of black cumin oil enhances insulin levels, reduces hyperlipidemia, promotes the growth of pancreatic islet cells, and increases the activity of hepatic

antioxidant enzymes while also boosting glycogen levels [32]. Viral infections can cause apoptosis that may lead to lymphocyte depletion in the host cell. Apoptosis caused due to viruses can be inhibited by antioxidants, along with the inhibition of viral replication. Thus, a linkage can be built between antiviral and antioxidant effects. TQ performs by activating the enzymes that protect cells from destruction caused by oxidative stress. Multiple studies have demonstrated that TQ enhances mRNA expression and activates several cytoprotective antioxidant enzymes, such as catalases, superoxide dismutase, glutathione reductase, and glutathione-S-transferase [33]. The powerful antioxidant effects of this substance have been assessed using in-vivo and in-vitro experiments [34]. Severe lung injury and upper respiratory tract infection was observed in patients suffering from COVID-19. And almost all patients of COVID-19 are suffering from pneumonia [5]. A couple of *in vivo* studies showed the protective effects of *N. sativa* and its oil on lung tissue damage [35,36]. TQ is an effective inhibitor of the majority of coronaviruses, including SARS-CoV-1, and the current coronavirus strain shares approximately 80% of its nucleotide identity with SARS-CoV-1 [37]. TQ has the potential to hinder the activity of SARS CoV2 proteases, which can decrease the replication of the virus. Additionally, TQ has demonstrated significant antagonism towards ACE 2 receptors, enabling it to disrupt the virus's entry into the host cells [33].

#### *Nigellidine, $\alpha$ -hederin*

These two naturally occurring compounds discovered in *N. sativa* has the capability to operate as active agents that can hinder the activity of the coronavirus [38]. Nigellidine and  $\alpha$ -hederin had the highest affinity for many molecular targets associated with SARS-CoV-2 and inflammation, including the primary protease (6LU7) and main peptidase (2GTB). These two compounds were more effective than hydroxychloroquine (HCQ) and favipiravir which were among the early treatment options of COVID-19 [39]. Based on a molecular docking analysis, nigellidine and  $\alpha$ -hederin demonstrated comparable or superior inhibition of both COVID-19 and SARS viruses compared to medications administered to patients in intensive care units [40]. Figure 2 presents a visual representation of the mechanism by which numerous compounds from *N. sativa* exert their pharmacological effects. Moreover, the documented outcomes of *N. sativa* in various *in-vivo* and *in-vitro* studies are presented in Table 2.



**Figure 2.** Mechanisms involved in pharmacological effects of *N. sativa* on COVID-19. Exploring the impact of seed nutrients on COVID-19 management. A multiphase therapeutic is clearly seen on oxidative stress reduction, inflammation control, and enhancement of immune function.

**Table 2.** General details and experimental studies conducted with Black cumin, Licorice, and Echinacea.

Names and parts	Scientific name	Types	Location	Active ingredients	Traditional uses	Observed effects	Ref.
Black cumin (Seeds)	<i>Nigella sativa L.</i>	Unani, ayurvedik	Indian subcontinent, Middle East, North Africa	Thymoquinone, nigellidine, $\alpha$ -hederin, thymol, 4-terpineol, carvacrol, carvone, tanethol, $\alpha$ -pinene, steroids, terpenes coumarins, etc	Hypertension, fever, flu, dyspepsia, rheumatism, diabetes, asthma, cough, bronchitis, headache, paralyzes, influenza, skin eruptions, vomiting, etc.	-Showed immunotherapeutic effects against Newcastle disease virus	[41]
						-Reduced virus shedding and enhanced immune responses against the effect of avian influenza in turkeys	[42]
						-Significant decrease in serum level concentration of malondialdehyde (MDA) and nitric oxide (NO)	[43]
						-Significantly improved hepatitis C virus(HCV) viral load in human subjects	[44]
						-Significantly reduced the systolic blood pressure, diastolic blood pressure, means arterial pressure, and heart rate in human subjects.	[45]
						-Human volunteers witnessed a decrease in clinical symptoms, including nasal itching, rhinorrhea, sneezing attacks, nasal congestion, turbinate hypertrophy, and mucosal pallor.	[46]
						-Significant enhancements were observed in forced expiratory volume in one second (FEV1), peak expiratory flow (PEF), serum interferon- $\gamma$ , and asthma control test (ACT) score in human subjects.	[47]
						-Considerably reduced the risk of lung damage in rats	[35]
						-Antimalarial activity in Swiss albino mice	[48]
						-Protective effects against rheumatoid arthritis. Significantly reduced the serum levels of HNE, IL-1 $\beta$ , TNF $\alpha$ and bone turnover markers.	[31]
						-Combined effect with $\alpha$ -lipoic acid( $\alpha$ -LA), L-carnitine reduced elevated blood glucose level in diabetic rat model	[49]
						-Boiled extract of caused significant increases in pulmonary function tests (PFTs), showed potent antiasthmatic effect on asthmatic airways in human patients	[50]
						-Reductions in fasting blood sugar (FBS) and HbA1c, increased the $\beta$ -cell functions.	[51]
						-Markedly decreased the function of inducible nitric oxide synthase (iNOS) and an increase in surfactant protein D in lung tissue	[36]
						-Increased the suppressor function of M $\phi$ in spleen and antiviral showed activity against murine cytomegalovirus in mice	[52]
						-Boiled aqueous extracts improve all asthmatic symptoms, asthma symptom/week, chest wheeze in patients	[53]
						Licorice (Roots, flowers, leaves)	<i>Glycyrrhiza glabra</i>
-Reduced HMGB1 binding to DNA and inhibited the influenza virus polymerase activity ( <i>in-vitro</i> )	[55]						
- Hospitalization case reduced, lower body temperature 24 to 48 h after admission in influenza and upper respiratory tract infection (in human subjects)	[56]						
-Inhibit HIV ( <i>in-vitro</i> )	[57]						
-Inhibits H5N1 influenza ( <i>in-vitro</i> )	[58]						
-Effective against rotavirus ( <i>in-vitro</i> )	[59]						
-Effective against duck hepatitis virus ( <i>in-vivo</i> )	[60]						
-Anti-diabetic effects in rats	[61]						
-Inhibits the replication of SARS-coronavirus (SARS-CoV) <i>in-vitro</i>	[62]						
-Virus penetration and proliferation reduced <i>in vitro</i> MARC 145 cells	[63]						
-Inhibiting virus replication in yellow fever, dengue, and west Nile virus ( <i>in vitro</i> Vero cells)	[64]						
-Inhibiting entry of herpes simplex virus (HSV1) ( <i>in vitro</i> Vero cells)	[65]						
-Cured diarrhea, improved small intestinal lesions and fecal virus shedding, reduced intestinal inflammation ( <i>in vivo</i> ; 3 days aged colostrum-deprived piglets) against porcine virus	[66]						
-Inhibited the SARS viral growth ( <i>in vitro</i> Vero cells)	[67]						

Echinacea (Leaves, roots, whole plants rhizome)	<i>Echinacea spp.</i>	Ayurvedik , Chinese medicine	North America, Canada, China	Different alkaloids, phenolic, propanoids, acids, and volatile oils	Snakebites, septic wounds, sore throats, blood purifiers, flu and colds, skin ulcers and burns, toothaches, etc.	-Echinaforce ( <i>E. purpurea</i> based hotdrink) improves influenza in patients [68] -Prevention of common cold episodes in human subjects [69] -Inhibits the dissemination and replication of influenza virus ( <i>in vitro</i> ) [70] -Immuno-pharmacological activity ( <i>in vitro</i> ) [71] -Antiviral activity against HSV-1 ( <i>in vitro</i> ) [72] -Increased life span in leukemic mice [73] -Induce CD34+ stem cell mobilization and homing to myocardial tissue in rats. [74] -Showed positive outcome in the management of ulcerative colitis in rats [75] -New Echinacea formulations at greater doses cleared viruses faster in individuals with acute RTI than preventive formulations. [76]
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### Licorice (*Glycyrrhiza glabra*)

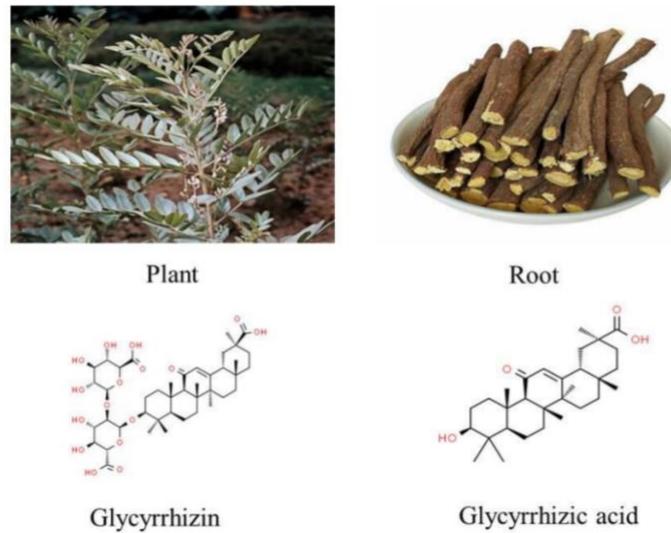
Licorice (Figure 3) has been a traditional remedy in Arabian, Chinese, Iranian, Greek, and Indian cultures for centuries [77]. Diseases like influenza, cough, liver damage, lung problems, and asthma are usually treated by licorice in oriental and folk medicine. With the ability to inhibit or slow the action of a variety of viruses, Licorice establishes itself as a broadly used antiviral containing more than 20 triterpenoids and 300 flavonoids [78]. After the emergence of COVID-19 in China, medical professionals from the State Administration of Traditional Chinese Medicine administered herbal combinations to individuals who were affected by the disease. The herbal formulation contained 6 grams of licorice which had a success rate of 90% [21,79].

#### *Glycyrrhizin*

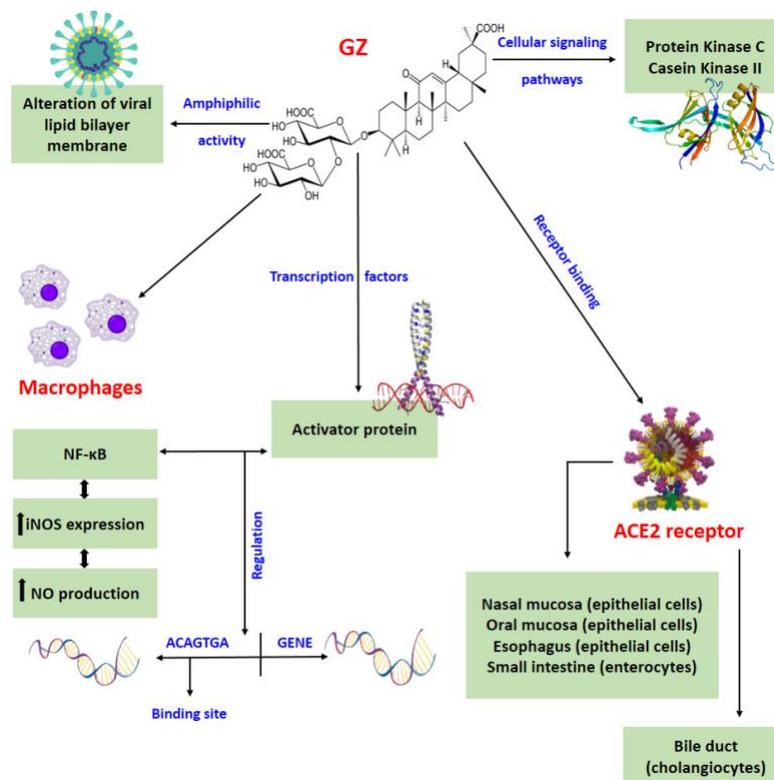
Glycyrrhizin (GZ) is usually effective against the envelope viruses like SARS related coronavirus, hepatitis D, flaviviruses, retroviruses, influenza A, herpesviruses, togaviruses, etc. as well as eleven types of flavivirus (dengue, yellow fever, Japanese encephalitis) [80]. GZ was found to be promising for the treatment of SARS [62] (Table 2). Moreover, two triterpenoids (GC and 18 $\beta$ -glycyrrhetic acid, 18 $\beta$ -GA) of Licorice possess antiviral potential [78]. Glycyrrhizin inhibits the SARS virus in invading a target cell and reproduction of virus. Glycyrrhizin was found to be the most effective antiviral against SARS among glycyrrhizin, 6-azauridine, pyrazofurin, ribavirin, and mycophenolic acid [81]. After a molecular docking, it can be seen that glycyrrhizin possesses the potential binding to *angiotensin-converting enzyme 2* gene (ACE2) (estimated Gibbs free energy 9 kcal/mo; binding sites: ARG-559, GLN-388, ARG-393, ASP-30, GLN-388 and ARG-393) [82]. The researchers concluded that the binding site would be around the hydrophobic region of ACE2 based on the hydrophobic nature of GZ. The infectivity of SARS-CoV-2 is greatly influenced by ACE2. Therefore, through its interaction with ACE2, GZ has the potential to inhibit the cellular entrance of SARS-CoV-2. Chrzanowski et al. [83] stated that topical use of GZ in the nasal and oral cavities could be the upper respiratory tract cells' first line of defense against SARS-CoV-2 infection. Several indicators indicate that GZ may be beneficial in treating respiratory infections and ARDS. For decades, many medicinal plant formulations containing GZ have been utilized to treat upper respiratory infections [84]. Research have proposed the utilization of GZ as a treatment for respiratory distress syndrome due to its capacity to decrease the buildup of platelets in the lungs and hinder the release of pro-inflammatory cytokines by activated inflammatory cells at the onset of the disease [85]. Figure 4 shows the action mechanisms of glycyrrhizin on SARS-CoV-2.

*Glycyrrhizic acid*

Glycyrrhizic acid (GA) has demonstrated efficacy in eradicating the SARS virus. GA has the ability to selectively focus on the protein structures of the SARS-CoV-2 virus and hinder its replication [86]. GA can inhibit nuclear factor- $\kappa$ B (NF- $\kappa$ B) and TNF activity which is surprisingly helpful for metabolic syndrome (MetS), ARDS, and inflammatory bowel disease (IBD). MetS is a risk factor for severe COVID-19 infection, and the recovery rate for IBS patients infected with COVID-19 is typically poor [87,88].



**Figure 3.** Licorice and its active constituents for COVID-19 and respiratory treatment options.



**Figure 4.** Comprehensive pathways of glycyrrhizin's antiviral activity against SARS-COV-2: viral membrane alteration, immune response modulation via macrophage activation and nitric oxide production, inhibition of cellular signaling pathways, and blockage of ACE2 receptor mediated entry.

### **Echinacea (*Echinacea spp.*)**

Echinacea (Figure 5) is considered as one of the most vital immune stimulants and used for centuries in Western herbal medicines [89]. Having the potential of increasing the number of macrophages inside the body, Echinacea has been one of the supportive herbs for the immune system with an effective antiviral, antibacterial, and antiseptic action. Usually, three species of Echinacea (*E. purpurea*, *E. angustifolia*, and *E. pallid*) are used to prepare various herbal preparations [89]. Echinacea medicinal formulations are commonly utilized for the prevention and management of upper respiratory tract infections [90].

#### *Different alkamides, phenolic, propanoids, acids, and volatile oils*

Caffeic acid, chicoric acid, and echinacin are three Echinacea compounds with significant antiviral activity [72]. Viruses, like coronavirus, influenza A and B, parainfluenza, some adenoviruses, respiratory syncytial viruses, neumoviruses, as well as bocaviruses are mainly responsible for human respiratory infections [91]. Echinacea interferes with the cytokine release from these viruses and helps to relieve respiratory problems. Moreover, the polysaccharides present in Echinacea possess anti-hyaluronidase action, which inhibits the viruses from taking over the body cells [89]. Echinacea exhibits immunomodulatory properties via regulating the activity of PRRs, pathogen-associated molecular patterns (PAMPs), and DAMPs, thereby inducing an antiviral response. Upon entering the host cell, the virus triggers PAMP signals that activate innate immunity cells containing PRRs [such as TLRs, retinoic acid-inducible gene-I RIG-I-like receptors (RLRs), and nucleotide-binding proteins], hence stimulating an effective immune response against the pathogen [92]. As previously stated, increased levels of IL-6 can exacerbate the acute lung injury or even damage the organ in the COVID-19 patient. *E. purpurea* extracts can lower IL-6 levels and protect against lung injury. In an experimental model, *E. purpurea* and the alkamide dodeca-2E,4E,8Z,10Z(E)-tetraenoic acid isobutylamide restored liver enzymes, attenuated inflammation, inhibited inflammatory cytokines, and activated the c-reactive protein [93]. The presence of phenolic components and chicoric acid in Echinacea extracts is responsible for their antioxidant and free radical scavenging properties [94]. Nevertheless, the extracts contain alkamides that exhibit reduced efficacy in scavenging free radicals [94]. The redox condition of a cell directly affects its vulnerability to oxidative stress, leading to potential consequences such as cell death and the release of viruses. SARS-CoV-2 infection can disturb redox balance by affecting NAD production, poly (ADP-ribose) polymerase (PARP) function, and proteasome and mitochondrial function, resulting to enhanced cell stress responses that aggravate inflammation [92]. COVID-19 patients may experience cardiovascular, pulmonary, renal, and neurological symptoms due to inflammation and oxidative stress generated by the virus. *E. purpurea* has demonstrated its ability to enhance endogenous antioxidants and radical-scavenging activity through several *in vitro* and *in vivo* experiments and models, leading to a reduction in oxidative stress (Table 2). Echinacea inhibits proinflammatory cytokines as well as the Nrf2/HO-1 and NF-B/Nrf2 signaling pathways, thereby suppressing ROS generation and controlling cell proliferation and inflammation [95]. ROS production can lead to an increase in IL-6 production and lipid peroxidation, which can lead to cell damage [96]. Echinaforce, a hot beverage made from extracts of *E. purpurea*, has been proposed as a preventive treatment for all coronaviruses, including the recently emerged SARS-CoV-2 [97]. Figure 6 depicts how Echinacea is

expected to reduce inflammatory cytokines and activate CB2/PPAR in the setting of the interplay between infection, immunity, and inflammation in COVID-19.

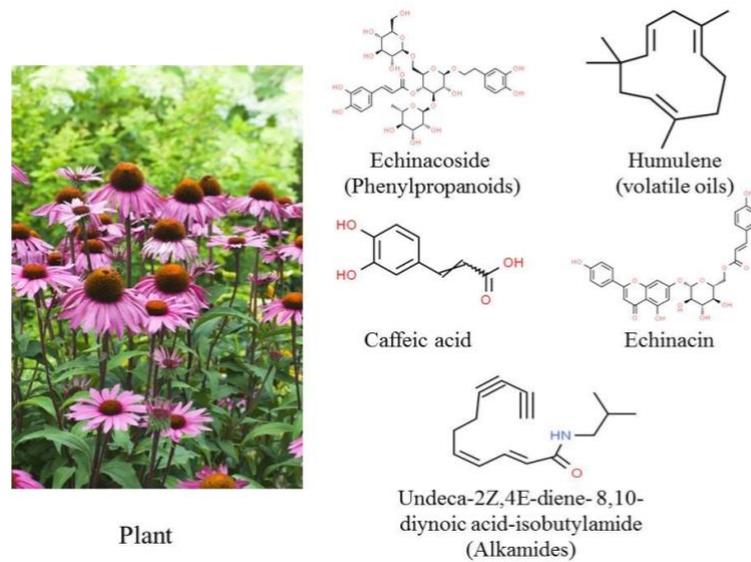


Figure 5. Echinacea and its active constituents for COVID-19 and respiratory treatment options.

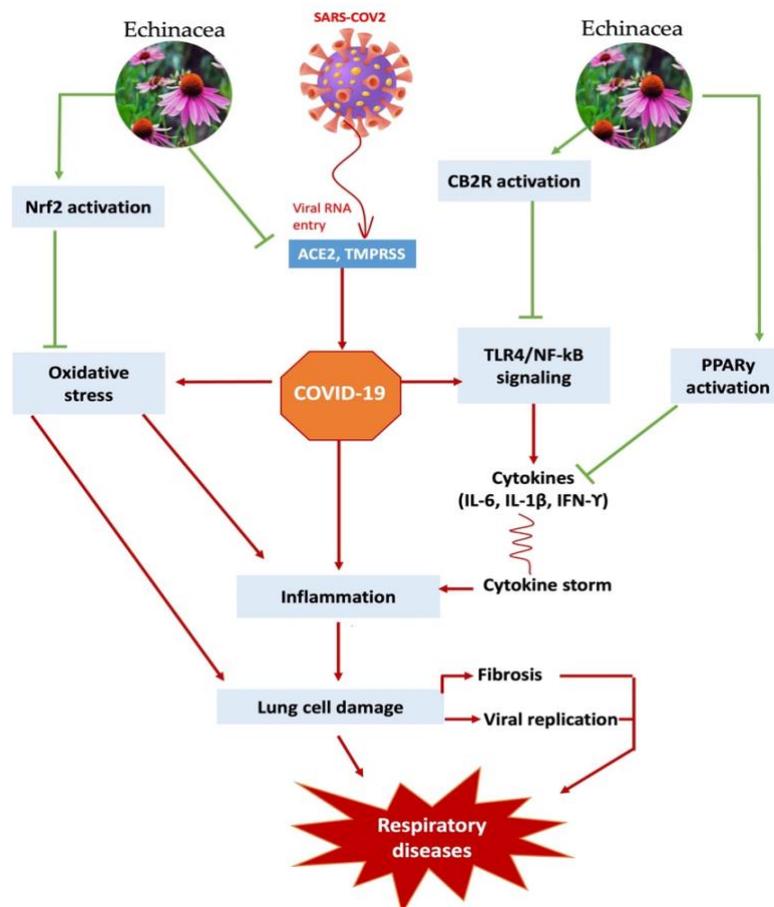


Figure 6. An illustration of possible mechanisms and effects of Echinacea on inflammatory cytokine inhibition and CB2/PPAR activation in the context of COVID-19 and respiratory diseases. Cannabinoid receptor 2, CB2R; Nuclear factor erythroid 2-related factor 2, Nrf2; Angiotensin-converting enzyme 2, ACE2; Transmembrane protease, serine 2, TMPRSS; Toll-like receptor 4, TLR4; Nuclear factor kappa B, NF-κB; Peroxisome proliferators-activated receptor  $\gamma$ , PPAR $\gamma$ .

## CONCLUSION AND PERSPECTIVES

Nowadays, phytotherapy provides viable options for treating respiratory infections, conditions with a high incidence in both infants and adults. The potential integration of herbal remedies into the healthcare realm in the future cannot be definitively dismissed. The utilization of this particular entity is extensive and has demonstrated effectiveness across a diverse array of contexts. Following the emergence of highly contagious SARS-CoV and middle east respiratory syndrome coronavirus (MERS-CoV), the world is now experiencing pandemic outbreak called COVID-19. This new virus belongs to the same beta-coronavirus group as its predecessors. Because of the high transmission rate and unpredictable nature to trace, the COVID-19 has posed a severe public health threat all over the world. Although some antiviral drugs are thought to be effective because of their previous efficacy in the treatment of SARS-CoV and MERS-CoV, and a number of vaccines are being developed as an emergency need, they may not be declared certain until long-term clinical trial results are available. Therefore, it is imperative to investigate potential alternatives that utilize non-traditional resources. In this review, we highlighted three potential medicinal plants which have a wide gamut of antimicrobial properties as well as pharmacological potentials, for the treatment and management of respiratory problems and COVID-19. These plants and their derivatives can play a vital role by enhancing the host immune responses and preventing virus replication, thus inhibiting further infection. Utilizing medicinal plants in lieu of conventional medications offers several benefits. Firstly, these plants exhibit fewer adverse effects when compared to synthetic drugs. Additionally, they can be cultivated domestically or found easily in natural surroundings. Moreover, there is a reduced likelihood of developing resistance to these plants as opposed to conventional antibiotics. Plants possess many bioactive chemicals that can provide a broad spectrum of medicinal benefits. Certain chemicals may not be accessible in synthetic drugs. However, adequate research and thorough clinical trials are necessary to find out accuracy in the fight against pathogenic viruses. These medicinal plants can create the new window for drug development against the COVID-19 in virtue of their natural origin, less or no side effects compared to synthetic drugs, and availability with low cost. Additionally, the current challenges will be to standardize pharmaceutical preparations and determine the pharmacokinetic properties for powdered seeds, oil, extracts, and other active constituents of these plants in order to ensure component stability. Additionally, it is crucial to consider the maximum permissible dosage and the safety of particular medical treatments for human use.

## AUTHOR CONTRIBUTIONS

MFJ and MMR: conceptualization, methodology, supervision, writing – original draft; writing - reviewing and editing; MAM, MSK, TI, MB, and MSA: literature search, writing – original draft; writing - reviewing and editing; MTIL, PCD, MARM, MA, and MJU: writing - reviewing and editing, and literature search. All authors have approved the final version of the manuscript.

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## CONFLICTS OF INTEREST

There is no conflict of interest among the authors.

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