



## PHYTOTHERAPEUTIC POTENTIAL OF HERBAL SUPPLEMENTS FOR COVID-19

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**Abstract :** The current Coronavirus Disease-19 (COVID-19) pandemic caused by Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) has reportedly posed a significant threat to the global public health institution systems. The treatment has been supportive and not effective. Coupled with the lack of vaccine interventions, the search for effective therapeutic alternatives is still on. Herbal supplements have been used in the treatment of viral diseases for years and could serve as an alternative for COVID-19 therapy if the combinations are known and tested. Recent studies have proved that certain herbal supplements have exhibited antiviral activity against similar coronaviruses. Besides, molecular docking studies further proved the efficacy of the antiviral activity of the herbal supplements against SARS-CoV-2. However, there is still a need for in-vitro and in-vivo studies of the antiviral activity of these herbal supplements against SARS-CoV-2. Nevertheless, these herbal supplements have a high therapeutic potential for COVID-19 therapy. This study reveals the chemical composition of herbal supplements to come up with findings that can redefine research and development, risk analysis, and containment of the novel coronavirus disease.

Keywords: Herbal, Therapy, Antiviral, COVID-19

### 1. Introduction

The current pandemic of the Coronavirus Disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) has affected almost all countries and regions in the world (WHO, 2020). This novel strain belongs to the coronavirus family which

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comprises viruses that caused the Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) in the past (Ang *et al.*, 2020). The disease presents as an acute respiratory illness that could result in death, particularly in individuals with co-morbidities or compromised immunity (Ang *et al.*, 2020). As there are no vaccines or effective antiviral treatments, current therapeutic options are only supportive, and survival owes primarily to the immune system of infected individuals (Ang *et al.*, 2020).

Herbal supplements have been in existence for thousands of years and have been considered safe based on anecdotal evidence, but many scientists express their doubts due to lack of scientific data and compositional analyses that would support the anecdotal shreds of evidence (Jeong *et al.*, 2012). Herbal supplements are natural products that could potentially play a significant role in the therapeutic development of antiviral drugs (Lin *et al.*, 2014). The antiviral activity of these natural products reportedly affects the viral life cycle as well as virus-host-specific interactions (Lin *et al.*, 2014). Nearly 80% of the populace in the developing countries rely on herbal medicine for protection and wellness from rhinovirus, coronavirus, influenza virus among others (Anlu *et al.*, 2019; Lin *et al.*, 2014).

Traditionally, plant extracts in the form of herbal supplements have been used to treat various conditions caused by viruses, and these plant extracts showed *in vitro* and *in vivo* activity against heterogeneous diseases conditions such as Hepatitis B and C, influenza, dengue, and polio (Chen *et al.*, 2014). So, the longstanding use of herbal supplements in the treatment of diseases cannot be over-emphasized as the exhibition of antiviral activity by herbal supplements has been continuously proven in recent years (Panyod *et al.*, 2020). Nevertheless, the search for potential effective therapeutic options and vaccines is still on for COVID-19 (Kwon *et al.*, 2020).

With the apparent state of uncertainty concerning the global pandemic of COVID-19, the need for a healthy immune system is imperative, as there are no current vaccines or treatments for the disease (Jayawardena *et al.*, 2020). Certain plant extracts can serve as herbal supplements that boost the immune system of individuals as well as protect the body against COVID-19. Even though these herbal supplements have been reportedly proven to be effective against viruses similar to SARS-CoV-2, there is no scientific evidence that it cures the disease (Singer *et al.*, 2020; Yang *et al.*, 2020). However, *in silico* studies of the activity of herbal supplements against SARS-COV-2 have shown promising results (Jena *et al.*, 2019; Salim & Nouredine, 2020). Therefore, the use of these herbal supplements could potentially play a significant role in the complementary therapy of COVID-19.

## 2. Receptor Interaction and Immunological Pathway of SARS-CoV-2

Angiotensin-converting enzyme 2 (ACE2) is the receptor that facilitates the entrance of SARS-CoV2 into the human cell for replication (Wan *et al.*, 2020). The epithelium of the upper respiratory tract is the first point of attack by the virus followed by the alveoli region of the lungs (Xu *et al.*, 2020). On the lower respiratory tract, binding of the virus to the ACE2 receptor located on the type II pneumocytes triggers a waterfall of inflammation (Tian *et al.*, 2020; Zhang *et al.*, 2020). Moreover, other organs that express ACE2 such as the heart, renal system, and small intestine are also point of targets for the virus attack (Bennardo *et al.*, 2020; Chen *et al.*, 2020). The spike protein on SARS-CoV2 binds the catalytic domain of ACE2 on the cell surface resulting in translocation of the enzyme-virus complex into the cell (Zhang *et al.*, 2020; Zhou *et al.*, 2020). The enzyme-virus complex generated hinders the normal catalytic function of the enzyme in regulating ANG II signaling. ANG II then accumulates and consequently leads to increased inflammation and necrosis in the alveoli region. The enzyme-virus complex is proteolytically cleaved by the host serine protease TMPRSS2 leading to the release of ACE2 and activation of the spike protein (Akbarshakh & Eduardo, 2020; Akram & Mannan, 2020).

Noteworthy, SARS-CoV2 produces an outburst of immune reaction in the host otherwise termed “cytokine storm”. Enhanced levels of leukocytes and pro-inflammatory plasma cytokines seen in infected individuals immensely contribute towards multiple organ dysfunction (Rothan & Byrareddy, 2020). Elevated amounts of pro-inflammatory cytokines which include; IL1B, IL6, IL7, IL8, IL9, IL10, IL12, IFN $\gamma$ , IP10, MCP1, MIP1 $\alpha$ , MIP1 $\beta$ , and TNF $\alpha$  were seen in the blood and sputum of SARS-CoV2 infected patients, all of which contribute towards lung damage (Huang *et al.*, 2020; Rothan & Byrareddy, 2020). While the respiratory system is the main entry point for the virus, other complications such as acute cardiac injury, multiple organ failure, or even death could arise in the absence of therapeutic intervention (Du *et al.*, 2020; Huang *et al.*, 2020).

## 3. Forms of Herbal Supplements

Since its inception, different parts of plants such as seeds, leaves roots and flowers have been used as herbal supplements to reap therapeutic benefits (NIH, 2013). These plant parts are prepared using a variety of procedures such as extraction, infusion, decoction, tinctures ashing, and so on, to produce a highly efficient finished product with low toxicity. These

finished products may then be available in the form of orals, nasals, topicals, or rectals (Okafor, 2013).

**Table 1: Forms of Herbal Supplements**

Forms	Applications
Orals	Tablets, Capsules, powders, drinks
Nasal	Snuff, Smoking, passive inhalation, steaming
Topical	Lotion
Rectal	Sitz baths

Source: Okafor (2013)

#### 4. Potential Herbal Supplements for Covid-19 Therapy

##### 4.1 Elderberries (*Sambucus nigra*)

Elderberry supplements have been advised to be considered at the preliminary phase of the COVID-19 pathogenesis (Kronbichler *et al.*, 2020). Elderberries are diaphoretic, antipyretic, and diuretic herbal supplements that are used in the treatment of fever, cough, nasal congestion, mucous discharge, sinusitis, cold, and flu while also strengthening the immune system (Karolina *et al.*, 2018; Zakay-Rones *et al.*, 2004). Elderberries possess high antioxidant properties which are majorly ascribed to the presence of a significant amount of phenolic compounds “anthocyanins” (Karolina *et al.*, 2018). In addition to phenolic compounds, they contain flavonoids, vitamins, lectins, etc. (Kronbichler *et al.*, 2020). Although there is a current paucity of research on the antiviral activity of elderberries against SARS-CoV-2, studies carried out on the activity of plant lectins against the MERS-CoV and the SARS-CoV, close relatives of the SARS-CoV-2, revealed inhibitive activity against the virus invitro (De Clercq, 2006; Keyaerts *et al.*, 2007). *Sambucus nigra* fruit specific agglutinin I (SNA-If), a lectin similar to Griffithsin, a potent inhibitor of the MERS-CoV, and an attractive anti-coronavirus candidate, was found in ripe elderberry fruits as a minor protein (Kronbichler *et al.*, 2020). This suggests that SNA-If could potentially inhibit the spike protein function of SARS-CoV-2 or have other effects (Kronbichler *et al.*, 2020). Moreover, preclinical evidence has reported inhibitory activity on replication and attachment of Human coronavirus NL63 (HCoV-NL63) and increases inflammatory cytokines (Alschuler *et al.*, 2020; Weng *et al.*, 2019). Although potential anti-coronavirus characteristics of elderberry supplements have not been investigated during the COVID-19 pandemic, they are easily

accessible as an over the counter herbal medicine which is seemingly safe. Also, the Evidence-Based Systematic Review of Elderberry and Elderflower carried out by the Natural Standard Research Collaboration revealed that elderberries could be applied during the early course of the COVID-19 infection, if the previous efficacy and potential adverse effects are understood (Kronbichler *et al.*, 2020; Ulbricht *et al.*, 2014).

#### 4.2 Purple Coneflower (*ECHINACEA*)

The genus of Echinacea contains nine species of which only three (*Echinacea angustifolia*, *Echinacea pallida*, and *Echinacea purpurea*) are essential for herbal medicine purposes (Kembuan *et al.*, 2020). Echinacea extracts possess antiviral and immunomodulating properties via innate immune system enhancement which is significant in the treatment of upper respiratory infections such as the common cold (Kembuan *et al.*, 2020; Young & Zampella, 2020). Recent studies have shown that Echinacea extracts exhibit significant virucidal activities against HSV -1, RSV, Influenza A and B virus (Pleschka *et al.*, 2009; Sharma *et al.*, 2009). Recent research on the antiviral activity of Echinacea extracts against MERS-CoV, SARS-CoV, and HCoV 229E showed that the viruses were irreversibly inactivated at comparable concentrations, which suggests that the extracts could potentially inhibit SARS-CoV-2 (Singer *et al.*, 2020). Besides, the findings of a model study carried out by Anandan *et al.* (2020) showed that *Echinacea purpurea* could be used as a possible inhibitor of COVID-19 pathogenesis, and in synergy, with other technologies, it could aid in addressing the current pandemic (Anandan *et al.*, 2020). However, currently, there is no data on the *in vivo* activity in COVID-19 infected individuals.

#### 4.3 Astragalus (*Astragalus membranaceus*)

*Astragalus* which can also be referred to as Huangqi is one of the ancestral herbs used by the Chinese in ancient times to prevent pestilence as well as COVID-19 in recent times (Luo *et al.*, 2020). *Astragalus* polysaccharides can be used as an immunomodulatory and antiviral agent (Orhar & Deniz, 2020). Extracts of *Astragalus* alone or in combination with other herbs significantly decrease the possibility of acute respiratory tract infections, fatigue, and anorexia. (Abdullahi *et al.*, 2016; Su *et al.*, 2016). Also, it can promote antibody production, stimulate cell proliferation, cytokine expression, and lymphocyte surface antigen expression (Abdullahi *et al.*, 2016). The antiviral potentials of *Astragalus* against infectious bronchitis virus were evaluated in a study using chick embryo kidney cells, the study revealed the

inhibitory and virucidal effects of the plant and its prospect as an adjuvant during vaccine production (Zhan *et al.*, 2017). Since SARS-CoV-2 and SARS-CoV share a striking similarity, *Astragalus membranaceus* in conjunction with some other herbs which was used in the previous SARS-CoV epidemic were employed by traditional Chinese medicine practitioners as a preventive measure for COVID-19 (Yang *et al.*, 2020). The complex inhibits lung inflammation through immunosuppression which reduces cytokine level during COVID-19 pathogenesis (Wu *et al.*, 2020). Consequently, reducing cytokine storm which one of the reasons for mortality (Wu *et al.*, 2020).

#### **4.4 Black Seeds (*Nigella sativa*)**

The seeds and oil of *Nigella sativa* have been vital in a wide range of medicinal applications over time due to its potential pharmacological activity which includes anticancer, antidiabetic, immunomodulatory, analgesic, antimicrobial, anti-inflammatory, bronchodilator, and antioxidant properties (Ahmad *et al.*, 2020; Rahman, 2020). Diseases such as rheumatoid arthritis, diabetes, asthma, inflammatory and digestive diseases can be treated using black seeds (Rahman, 2020). It also confers lung and tracheal protection via aiding tracheal contractions induced by leukotriene B<sub>4</sub>, induces tracheal relaxant effects, and exerts antispasmodic and mucociliary pulmonary clearance (El Sayed *et al.*, 2020). Black seeds contain several bioactive compounds such as thymoquinone, thymodroquinone, dithymoquinone; and phytochemical compounds such as saponins, alkaloids, and phenolic compounds (Salim & Nouredine, 2020; Yimer *et al.*, 2019). The antiviral activity of this herbal supplement has been extensively researched, and studies have revealed its activity against Human Immunodeficiency Virus, Hepatitis C, and cytomegalovirus (Barakat *et al.*, 2013; Forouzanfar *et al.*, 2014; Onifade *et al.*, 2013). Likewise, it was also recently revealed that extracts of black seed reduced the pathogenicity of avian influenza virus (H9N2) through DNA methylation/ demethylation (Haslberger *et al.*, 2020). This antiviral activity has been strongly correlated to the presence of thymoquinone in the black seeds (A. Ahmad *et al.*, 2020). However, in-vitro activity against coronaviruses have been reported for extracts of *Nigella sativa*, although the mechanism of actions was not known, the viral loads were reduced to an undetectable state (Ulasli *et al.*, 2014). Furthermore, molecular docking of compounds of *Nigella sativa* was carried out in a recent study, which revealed that *Nigella sativa* compounds give an energy score that is almost similar to chloroquine, this suggests the potential of *Nigella sativa* seeds to act as treatment against COVID-19, so preventive use of



this seeds against the coronavirus infection is encouraged (Salim & Nouredine, 2020). Besides, black seed oil extracts could be beneficial in adjuvant therapy due to their ability to reduce toxicity and adverse effects of the drug, this feature could potentiate the effect of hydroxychloroquine during the treatment of COVID-19 (Al-noaemi & Hammoodi, 2020).

#### **4.5 Turmeric (*Curcuma longa*)**

Turmeric extracts have a long history of treating diseases with minimal side effects (Liu & Ying, 2020). Curcumin, a medically important polyphenolic compound extracted from turmeric, has been reported to have antioxidant, anticancer, antidiabetic, and anti-inflammatory properties, has been extensively studied *in vivo* and *in vitro* (Samad & Yusuf, 2020; X. Xu *et al.*, 2018). Curcumin exhibits a pleiotropic antiviral activity against viruses such as herpes simplex virus, respiratory syncytial virus, influenza, and parainfluenza viruses; this owes to the extract potentiality to trigger cellular signaling pathway such as apoptosis via interaction with various molecular targets, modulate immune responses, and inhibit cytokine storm induced by the viral antigen during viral infection (Liu & Ying, 2020; Zahedipour *et al.*, 2020). The antiviral activity against SARS-CoV-2 was also investigated using molecular simulation, and the study revealed that curcumin has the potential ability to directly bind to the spike protein receptor-binding domain, predicting its therapeutic potential for COVID-19 (Jena *et al.*, 2019). Furthermore, curcumin substantially regulates the renin-angiotensin-aldosterone system components, which explains its significance in the upregulation and downregulation of ACE and ATIR receptors expression while mediating anti-inflammatory effects which attenuates the level of pro-inflammatory cytokines and reactive oxygen species (Manoharan *et al.*, 2020). This potential ability to downregulate the ACE2 receptor, a major pathway in the pathogenesis of COVID-19 infection, could be significant in ameliorating the condition of infected individuals as well as serving as preventive measures (Rocha & Assis, 2020).

#### **4.6 Oregano Oil (*Origanum vulgurae*)**

Oregano is a Mediterranean plant that is important as aromatic herbs used in treating diseases (Ciavarella *et al.*, 2020). Carvacrol, a monoterpenoid phenol found in oregano oil extract, possesses antioxidant, antibacterial, and anti-inflammatory properties (Ciavarella *et al.*, 2020). In-vivo and In-vitro studies revealed its antiviral potentials against Herpes virus, rotavirus as well as Respiratory syncytial virus (Ma & Yao, 2020; Pilau *et al.*, 2011; Sharifi-

Rad *et al.*, 2017). Computational studies evaluating the potential activity and drug targets of carvacrol against SARS-CoV-2 have been evaluated by various researchers using molecular docking approach in the absence of in-vitro and in-vivo studies, the SARS-CoV-2 main protease, an enzyme that processes translated polyproteins, was reportedly inhibited by carvacrol which showed a very good binding affinity to the target (Kumar *et al.*, 2020). A significantly high binding affinity to the ACE2 receptor interface on the SARS-CoV-2 Spike protein was reported and could be compared to chloroquine (S. Ahmad *et al.*, 2020; Kulkarni *et al.*, 2020). It is worthy of note that an in-vitro study of the antiviral activity of oregano against SARS-CoV, a close relation to SARS-CoV-2, showed oregano oil decreased viral titers from 5million particles per ml at baseline to 167 particles per ml within 15 minutes (Ijaz, 2003). So, oregano extracts could potentially serve as a preventive and therapeutic measure against COVID-19 can be considered.

## 5.0 Regulation of Herbal Supplements

The World Health Organization (WHO) defines herbal medicines as traditional drugs, remedies, or dietary supplements obtained from herbs, herbal materials, herbal preparation, or finished herbal products, which encompasses pharmacological properties similar to that of conventional drugs (Fisher, 2019; Griffith & Tengenah, 2010; Sahoo *et al.*, 2010). Several regulation models have been used to regulate traditional and complementary herbal medicines but challenge majorly owing to safety, and quality control has deterred the development and implementation of these regulation models in several countries (Aboushanab *et al.*, 2019; Awodele *et al.*, 2014; Sahoo *et al.*, 2010). Safety assessment, efficacy, and monitoring in addition to quality control and lack of background knowledge about the herbal medicines are challenging tasks for regulatory authorities have to overcome (Awodele *et al.*, 2014; Sahoo *et al.*, 2010). Additionally, the safety and efficacy of herbal medicines must be proven before the administration of herbal medicines, but then the procedure required to achieve this feat is a very complex one when compared to conventional medicine (Awodele *et al.*, 2014; Cecília *et al.*, 2014).

Notwithstanding, in the face of the challenges, countries belonging to the European Union, the United Kingdom, Australia and few Asian countries such as China, India, Korea, Japan, and Malaysia have all took giant steps through the development of national policies and regulations on herbal medicines which although varies for the country but overall ensures the safety of herbal medicine practice (Awodele *et al.*, 2014). Likewise, the Traditional Medicine



Strategy established by the WHO promotes the integration of herbal medicine practice into the health care system of countries while training the traditional medicine practitioners herbal medicine practice fused primary health care services using appropriate regulations recommended by the national health systems (Awodele *et al.*, 2014).

The United States Food and Drug Administration (FDA) regulates herbal medicines as foods in the form of dietary supplements under the U. S. Food and Drug Administration (FDA) (Brown, 2016). It regulates both the ingredients and the final product under the Dietary Supplement Health and Education Act of 1994 while the FDA's Food Safety and Applied Nutrition watch over the products from time to time (Brown, 2016). Furthermore, due to the high potential of contamination or defects of these products that could pose health hazards for humans, a guidance title Defect Levels Handbook was released by the FDA to enlighten the producers (Fisher, 2019). In Japan, where herbal medicines are classified into Kampo and non-Kampo crude drug products, Japanese Pharmacopoeia is majorly used as the official standard for assuring the quality of medicine (Maegawa *et al.*, 2014). Kampo extracts and crude drugs of Kampo products have been registered in the Japanese Pharmacopoeia to assure the quality of distributed products. However, Kampo medicines which are sold separately from herbal products, are regulated by the Ministry of Health and welfare. The Ministry of Health and Welfare is responsible for approving over-the-counter Kampo medicines as well as the approval standards of the medicines which are reviewed and published from time to time (Maegawa *et al.*, 2014). In Europe, Herbal products used for therapeutic purposes are by default, categorized as medicines under European Law (Mills, 2011). At the start, analytical pharmaco-toxicological tests and clinical trials for herbal medicines were required under the European Union (EU) regulations, However, the enforcement of traditional herbal medicinal products directive allowed the creation of a regulatory framework for the herbal medicinal products using traditional use marketing registrations (TURs) and well-established use marketing authorizations (WEU-MAs), those approved for TURs and WEU-MAs are then published in the EU Herbal monograph from time to time (Qu *et al.*, 2018). The National Competent Authorities at the national level and the Committee on Herbal Medicinal Products which assess the EU Herbal monographs constitute the European regulatory framework for herbal medicines (Qu *et al.*, 2018). In Saudi Arabia which uses a direct governmental legalization model, the National Center for Complementary and Alternative Medicine (NCCAM) is responsible for regulating, monitoring, and supervising herbal medicines (Aboushanab *et al.*, 2019). The Saudi Food and

Drug Authority complementarily acts by regulating herbs, food supplement products, and complementary medicine devices (Aboushanab *et al.*, 2019). In Africa, Herbal medicine is neither registered nor controlled by regulatory bodies. Countries like South Africa, Nigeria, Ghana, Kenya among others, have a unique licensing system that enables the health authorities of these countries to examine the constituents, safety, and quality of the herbal medicines before marketing (Sharad *et al.*, 2011).

Since the beginning of the COVID-19 pandemic, only a few herbal medicines have been regulated for treatment. Two countries, China and South Korea are the only countries to have issued treatment guidelines for herbal medicines, seven and two versions respectively, on the prevention and treatment of COVID-19 (Association of Korean Medicine News, 2020; National Health Commission of China, 2020). In China, using government-issued guidelines has reference, twenty-five traditional medicine related guidelines have been developed by the local authorities in accordance to their regional characteristics while clinical experts belonging to the Association of Korean Medicine and Korean Association of Traditional Medicine issued guidelines each (Ang *et al.*, 2020). No other herbal medicine guidelines have been issued to date despite promising reports in other geographical regions.

## 6. Conclusion

The use of herbal supplements remains the cornerstone of traditional medicine. The current state of the pandemic has given rise to the exploration of different alternatives for the search of potential therapeutic solutions for the disease. Although there are currently no experimental studies of antiviral activity against SARS-CoV-2, certain herbal supplements have shown high therapeutic potential through assessment of antiviral activity against the close relatives of SARS-CoV-2 *in vivo* and *in vitro* as well as SARS-CoV-2 *in silico*.

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