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Role of underground stems as immunomodulators and may assist in the management and treatment of COVID-19

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Abstract

Plants have always been a great source for human being by unveiling invaluable therapeutic activities due to the presence of various secondary metabolites and other chemicals present in them. The various parts of the plant are beneficial in offering pharmacological and other biological properties. The utility of these plants in - particular underground stems are proved to possess beneficial immunomodulatory effects and on altering the immune system by diverse mechanisms. In present scenario, COVID-19 has gone into danger stage, which poses a threat to every single person which is caused due to enhance globalization and ability of the coronavirus to get acclimatize at all conditions all over the globe. The unabated transmission of this deadly coronavirus is due to lacks of drugs to fight against this outbreak. But, attempts were made to formulate the vaccines and few countries have developed the vaccines mainly Russia, India and other countries. Through, vaccines and other modalities may help scientific communities to bring out a solution and are continuously striving to unravel the pharmacologically active compounds in all directions that might prove a new insight for curbing viral infections and pandemics. Hence, the COVID-19 scenario highlights an essential need for effective therapeutics against SARS-CoV-2. The present review discusses the role of underground stems as immunomodulators and vital concepts related to COVID-19 which tends to boost the immunity through immunomodulators from medicinal plants.

1. Introduction

In this paper, an attempt has been made to explore the role of certain underground stems as immunomodulators which may help to suppress the symptoms in the management of COVID-19. The coronavirus disease has been the sudden outburst and WHO on 11th March 2019 declared COVID-19 as a Pandemic COVID-19 is caused by virulent severe acute respiratory syndrome coronavirus-2 (Sars-Cov-2) virus. SARS-CoV-2, provisionally called as 2019-novel coronavirus, an enveloped positive sense single stranded RNA virus which belongs to subfamily-Orthocoronavirinae, and family-Coronaviridae (Huang *et al.*, 2020; Gorbalenya *et al.*, 2020). Its morphology is like crown shaped over the surface (Figure 1) and broadly distributed among different mammalian species including the human being. The name resembles coronavirus-2 due to 70% resemblance to SARS coronavirus.

The host cell, namely; ACE2 in humans got encapsulated by SARs coronavirus-2 with the spikes proteins projected out. The ACE2 enzyme bound to cell membrane of the tissues present in the lungs, artery, kidney and intestine. WHO declared COVID-19 as a six public health emergencies of the international concern. In history, few more pandemic had occurred where herbs have used as a natural

treatments for various illness, including viral infections. The plants contain several chemical compounds which are having potency to fight against viruses and other illness caused within the body. Natural antimicrobials are extracted and became popular for use as alternative antivirals. Most antivirals are considered relatively harmless to the host, and therefore can be used to treat infections.

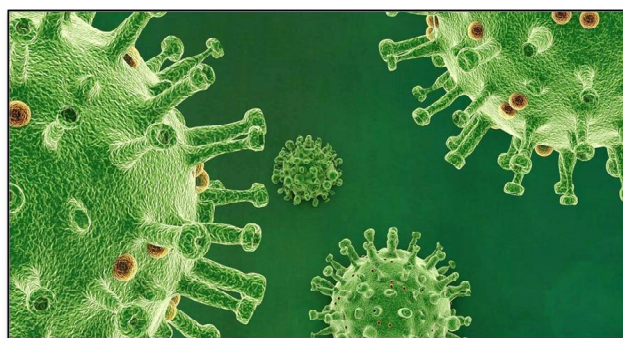


Figure 1: The predictive morphology of coronavirus.

2. Immune system stimulation

Medicinal plants constitute effective source of natural products, consumed as phytomedicines and the products obtained from medicinal plants have been playing significant role in drug discovery efforts for the treatment of various diseases. Phytochemicals present in the medicinal plants instead of attacking viruses directly they fight viruses involves encouraging the body immune system to attack them. Some antivirals stimulate the immune system to attack a specific or wide range of pathogens.

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Immunity defined as ability of body to neutralize and eliminate the pathogenic micro-organisms and their toxic products, thus protecting the individual. Autoimmune disease arises when body mounts an immune response against itself due to failure of distinguishing self tissues and cells from foreign antigens. Such diseases are rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and diabetes (type 1).

3. COVID-19 and traditional medicine

Globally, there are many healthcare systems recognized such as Herbal medicine, Oriental medicine, Chinese medicine, Korean medicine, etc. The novel COVID-19 is affected to human by virus, i.e., RNA virus (Coronaviridae family) susceptible to all age people to make them severely ill with various symptoms. The symptoms are mainly similar to that of influenza such as cough, sore throat, fever, pain, chills, shortness of breath, loss of taste and smell. Medicinal plants can play a major role as potential healing agents that can help to curb the symptoms and act against the virus by boosting the immunity, enhancing the power by posing as virucidal action and to suppress the mortality rate.

There are so many commercially available antiviral medicines which may serve as potent against the virus such as interferon- α , lopinavir/ritonavir, ribavirin, etc. (Dong *et al.*, 2020). Over all, the immunity plays an important role to fight against the coronavirus, unhealthy surrounding, microbes, bacteria, fungus and other virus, etc. Several modern medicines are available over the counter which can help to improve the immunity and acts against the virus but they are costly.

The potential medicinal plants can produce antiviral and immune-stimulant drugs to treat or act against the coronavirus. Such as *Withania somnifera*, *Rubia cordifolia*, *Curcuma longa*, *Azadiracta indica*, etc. (Srivastava *et al.*, 2020). Traditional medicine has a rich literature regarding infection invasion, source and cause of disease, measures to cure for the epidemics, pandemics for example cataract influenza, etc. (Khan and Al-Balushi, 2021). Combination of potent medicinal plant drugs can be used in controlling the symptoms of COVID-19. These combinations which may produce effects on boosting immunity, improve vital organ or tissues, muscle relaxant, prevent respiratory stress, congestion, breathless ness, prevent pneumonia and other associate condition.

In Unani System of medicine, there are potential single drugs like amla, zanjabeel, halelajat, chobezard, aqarqarha, amba haldi, etc., and a few compound formulations which has very good antiallergic as well as possess good immunity boosting properties, for e.g., tiryaq-e-wabai, arq-e-ajeab, Khameera marwareed, khameera abresham sheera unnab wala, habbe nazla, khameera marwareed khaas, habbe zahar mohra, khameera abresham hakeem arshad wala, etc. Many herbal formulations are effective to utilize in this pandemic for enhancing the immunity and increase the ability to fight against various diseases. Herbal formulations possess several biochemical compounds such as alkaloids, phenol, flavonoids, saponins, etc., which exhibits various pharmacological activities ranging from anti-oxidant, antibacterial, anti-inflammatory, antiviral to immune-stimulatory activities. Hence, they can enhance or boost the immunity of an individual which ultimately provide some cure or help in the symptomatic management of COVID-19.

4. Immunomodulation

Immunomodulations means that one can modulate immunity using various substances either of natural or synthetic origin. Certain medicinal plants promote positive health and maintain organic resistance against infection by re-establishing body equilibrium and conditioning the body tissues.

5. Combat COVID-19 viral infection

Novel coronavirus COVID-19 pandemic become an enormous catastrophe presenting devastating effects on entire world. It created havoc on population and killed several human beings worldwide; still the situation is not getting under control. Consequently, it makes to impose complete lockdown in different countries around the globe. Since decades, vaccination has been the only means to treat the viral infections. Though, the vaccination for COVID-19 has been developed, and reaching each and every individual is a difficult task, owing to which the scenario is worsening. Central drugs standard control organization (CDSCO) has granted two vaccines for emergency use authorization in India, i.e., Covishield® (Astra Zeneca's vaccine manufactured by Serum Institute of India) and Covaxin® (manufactured by Bharat Biotech Limited). Covishield® vaccine is a viral vector-based technology which was also used to manufacture Ebola vaccine. Covaxin® vaccine whole-virion inactivated coronavirus vaccine which was earlier used to manufacture vaccines like influenza, rabies and hepatitis-A. (Internet source, accessed on 19.04.2021). As of April 2021 vaccination doses in India are given in 123 million people and fully vaccinated 16.2 million and % of population fully vaccinated are 1.2 %. (Website source, accessed on 19.04.2021). The present health crises to the people at large and their responsibility on scientific community to look for the alternatives or techniques to develop successful viral vaccination against COVID-19 infection are strongly needed. The current situation prompts us to have healthy lifestyle, natural food products which can boost the immune functions of the body to combat the severity of viral infections. While enhancing the immune responses, they also provide resistance against various pathogenic organisms (Sarfraaz *et al.*, 2020).

6. Medicinal plants therapeutic approaches against COVID-19

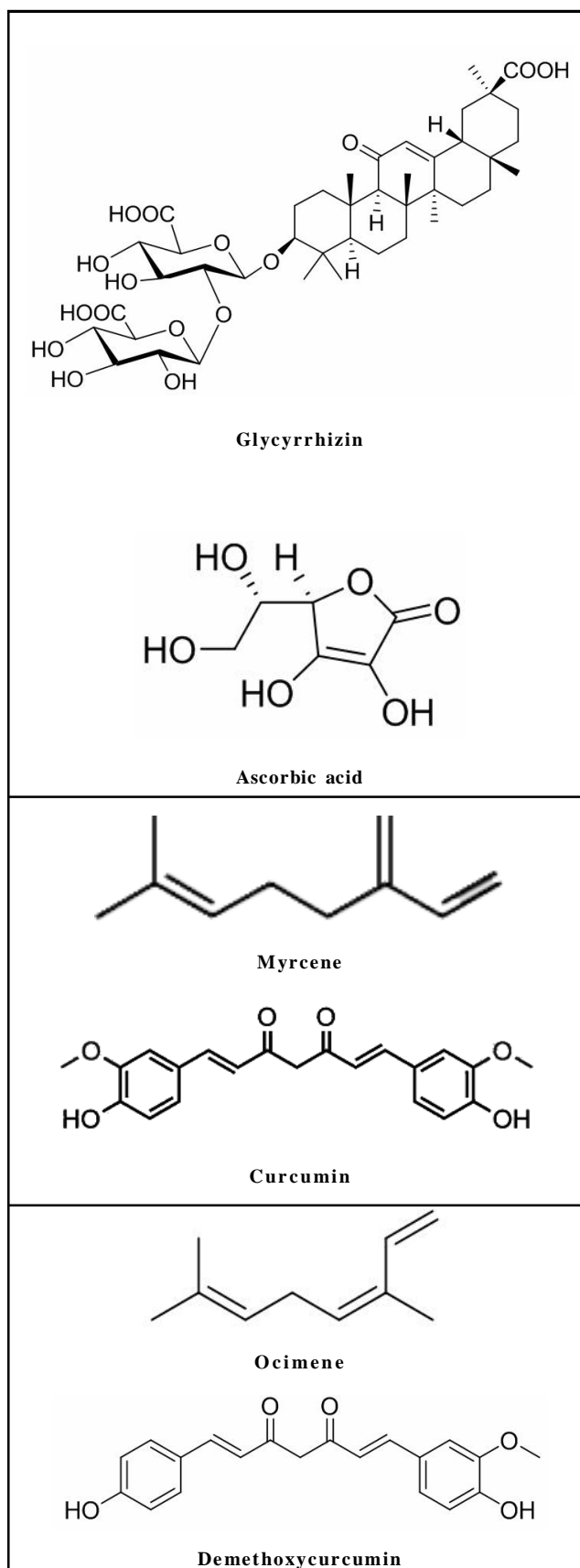
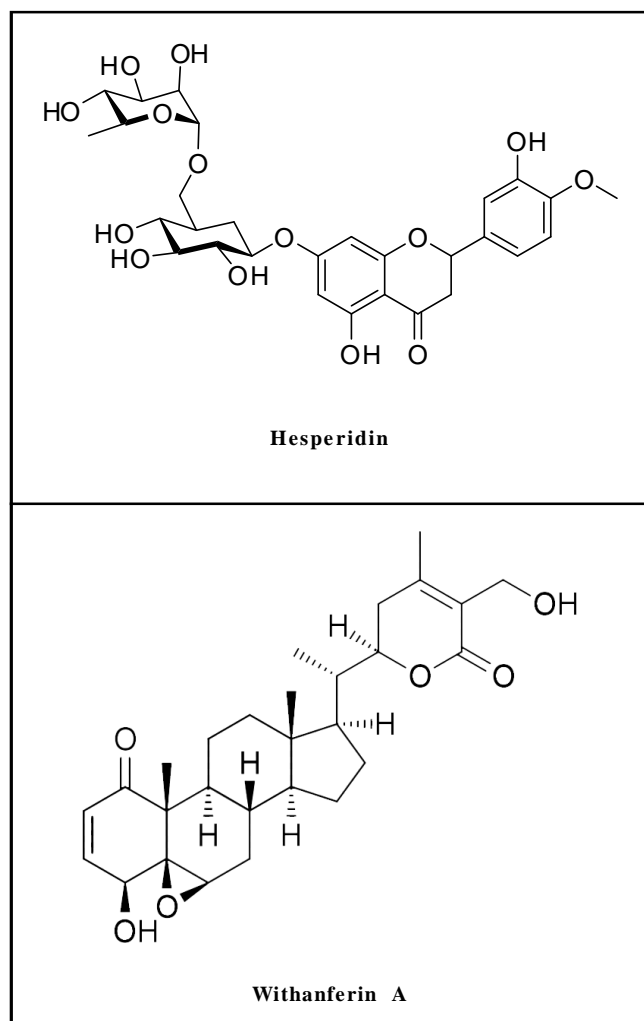
The traditional medicines are generally a great source of novel research and their usage are known since many centuries. Many plants contain phytochemical components extracted from herb or combination of herbs that may function to yield preferred pharmacological effects (Parasuraman *et al.*, 2014).

The traditional medicine which are effective and suitable to treat various infectious disorders, viz., Ayurveda, Siddha, Yoga, Unani, Homeopathy and Naturopathy. The traditional system of medicines use plants, animals, and mineral origin products for the treatment of wide range of diseases. Many formulations have been reported in classical text of the traditional system of medicine and still being used today. Total medicinal plants being used are more than 3000, whereas traditional system uses around 1500 species. The Ministry of AYUSH has recently introduced the Kadha as an immunity booster and lower the tenderness caused during COVID-19 catastrophe (AYUSH Advisory 2020). Few medicinal herbs are mix together and its decoction was consume to get relieve symptoms in COVID-19 and it also build one's own immune system to cope up with the

pandemic. The holistic approach of AYUSH systems of medicine gives focus on prevention through lifestyle modification, dietary management, prophylactic interventions for improving the immunity and simple remedies based on presentations of the symptoms.

7. Abilities of medicinal plants against coronaviruses in human

People all over the world in particular Asian countries like India, China and Middle Africa have been using medicinal herbs since prehistoric times (Hoareau and Dasilva, 1999). Utilizing medicinal plants for healthcare are very prevalent due to its scalability, cheap and affordable than modern medicine. These medicinal plants contain a wide range of phytochemicals, including alkaloids, terpenoids, phenolic compounds, tannins, glycosides, lignins, coumarins, flavonoids, steroids, and many have been shown to be effective against a variety of infections and pathogenic microorganisms. Medicinal plants are emerged with diverse phytochemicals (Table 1), such as alkaloids, terpenoids, flavonoids, phenolic acids, tannins, lignins, coumarins, stilbenes, *etc.* Some vital phytoconstituents structure are shown in Figure 2 which have been reported to potential against infections caused by pathogenic microorganisms (McCutcheon *et al.*, 1995; Semple *et al.*, 1998).



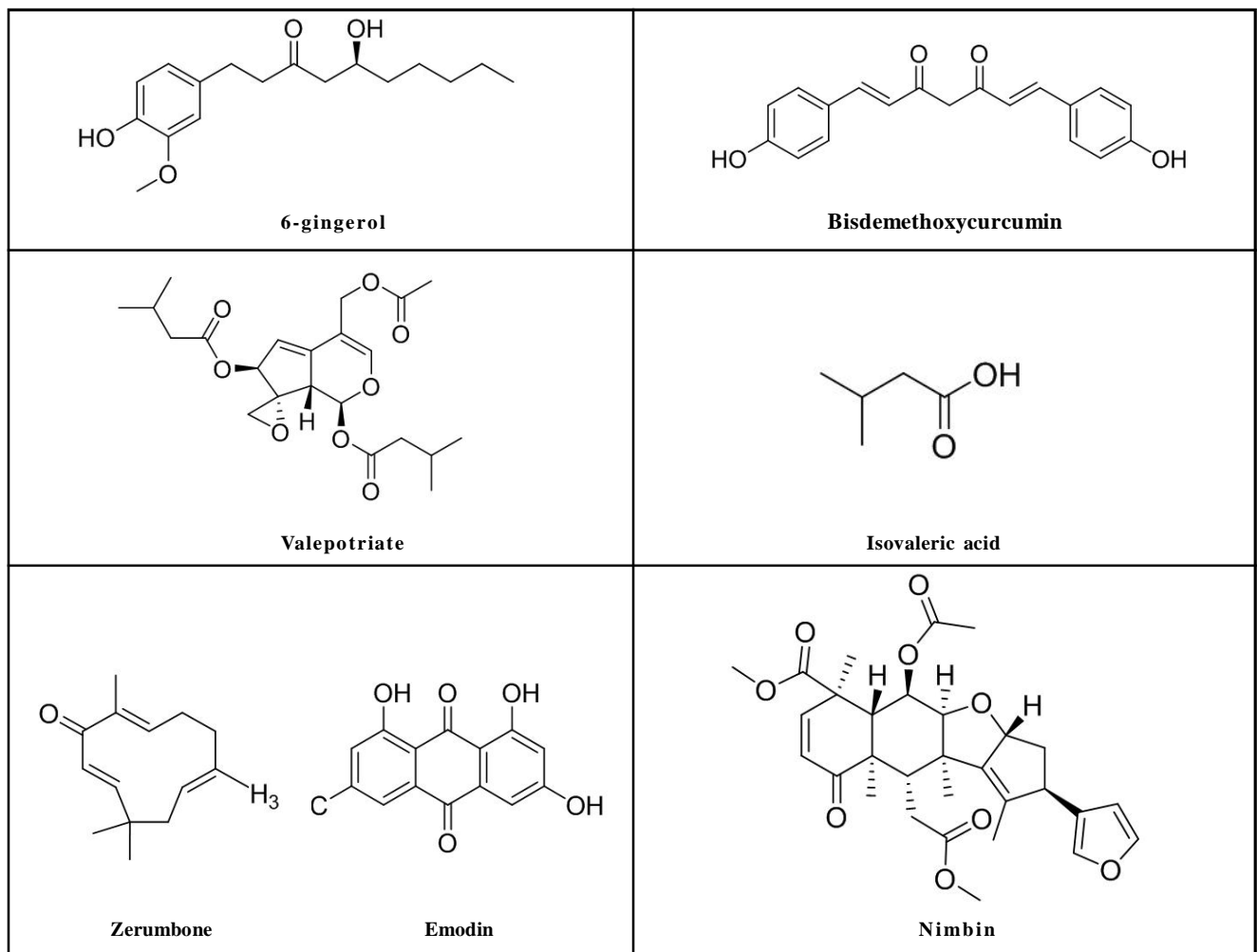


Figure 2: Structures of phytochemical compounds present in few roots and rhizomes.

Table 1: Roots and rhizomes with immunomodulatory effects

Botanical name	Common or regional names	Phytoconstituents	Therapeutic actions	Properties	References
<i>Curcuma amada</i> Roxb. (rhizome)	Unani name: Aambahaldi, English: Mango ginger	Phenolic acids, volatile oils, curcuminoids and terpenoids like difurocumenol, amadannulen, myrcene, ocimene	Alcoholic extract showed significant immune-modulatory effect in <i>in vitro</i> phagocytosis activity, delayed type hypersensitivity test and hem agglutination test	Immunomodulatory effect	(Karchuli and Pradhan, 2019)
<i>Anacyclus pyrethrum</i> DC (root)	Unani name: Aqarqarha; English:pellitory pyrethrum	Pellitorine, anacyclin, phenylethylamine, inulin, polyacetylenic amides and sesamin, pyrethrin pyrethrin A and B	Immunostimulant activity increased two -fold upon doubling the dosage of petroleum ether extract of roots administered. While a significant ($p<0.05$) improvement was observed in the humoral component, a highly significant ($p<0.01$) effect was observed in the cellular components of the immunity evaluated. The result forms a basis for <i>A. pyrethrum</i> as an adaptogen and immunomodulator in Ayurvedic system of medicine.	Immunomodulatory properties, antinociceptive, antiinflammatory and antioxidant activities	(Sharma <i>et al.</i> , 2010)

<i>Zingiber officinale</i> (Rhizome)	Unani name: Zanjabeel; English: Ginger	6-gingerol	Ginger essential oil recovered the humoral immune response in immunosuppressed mice. It has high binding affinity at R7Y COVID-19 activated sites, the main protease essential for replication and reproduction of SARS Cov-2. Possesses excellent druglikeness parameters with zero violations. The rhizome aqueous extract showed remarkably decline in the number of CD14 monocyte count with exposure of HBsAg and NDV as compared to control group. It showed anti-inflammatory as well as antiviral activity.	Anti-inflammatory as well as antiviral activity	(Carrasco <i>et al.</i> , 2009; Rathinavel <i>et al.</i> , 2020; Gupta and Chaphalkar, 2015)
<i>Valeriana wallichii</i> DC (root)	Unani name: -Tagar; English - Indian valerian	Valepotriates, isovaleric acid and hesperidin, <i>etc.</i>	The animals supplemented with the aqueous root extract of <i>V. wallichii</i> were found to adapt much faster as indicated by the improved malondialdehyde (MDA) and lactate dehydrogenase (LDH) levels as well as reduced superoxide dismutase (SOD) and catalase (CAT) levels in comparison to control. The study indicated that aqueous root extract of <i>V. wallichii</i> had adaptogenic activity as assessed by C-H-R animal model. Its extract was also found to be more safe and effective than alprazolam drug in alleviating the immunosuppression induced in restraint stress exposed rats.	Adaptogenic activity, immunomodulatory effect.	(Sharma <i>et al.</i> , 2012; Ibrahim <i>et al.</i> , 2016)
<i>Withania somnifera</i> Dunal (Root)	Unani name - Asgand; English- Asarbacca	Withaferin A	The immunomodulatory, anti-inflammatory, antistress, cognition facilitating and anti-aging effects produced by active principles of <i>W. somnifera</i> in experimental animals, and in clinical situations. A protective effect in cyclophosphamide-induced myelosuppression was observed in animals treated with WST and WS2, a significant increase in white blood cell counts and platelet counts was revealed. Cyclophosphamide-induced immunosuppression was counteracted by treatment with WS2, revealing significant increase in hemolytic antibody responses and hemagglutinating antibody responses towards sheep red blood cells. The <i>W. Somnifera</i> extract inhibited delayed type hypersensitivity reaction in mice model (Mantoux test). Administration of <i>W. somnifera</i> extract also showed an enhancement in phagocytic activity of peritoneal macrophages (76.5 pigmented cells/200) upon compared to control	Antistress, immunomodulatory, cognition-facilitating, anti-inflammatory and antiageing effects	(Bhattacharya <i>et al.</i> , 1997 ; Agarwal <i>et al.</i> , 1999; Davis and Kuttan, 2000)

			(31.5/200 cells) in mice. The results yield the immunomodulatory activity of <i>W. somnifera</i> extract, which is a known immunomodulator in the indigenous system of medicine.		
<i>Glycyrrhiza glabra</i> Linn (root)	Unani name: Aslus-soos; English Licourice root	Glycyrrhizin, liquiritigenin, glabridin, liquiritin and isoliquiringlycyrrhetic acid,	<i>In vivo</i> phagocytosis (carbon clearance method -CCM), determination of cellular immune response, plaque forming cell and haemagglutination antibody titre assay using sheep red blood cells. In cellular immune response study, an enhancement in foot pad thickness was recorded when compared to control group. The study showed the immunomodulatory activity of aqueous root extract of <i>G. glabra</i> L. at the dose 1.5 g/kg BW. <i>G. glabra</i> in combination with zinc has shown potentiation of immunomodulatory activity in all aspects of the study. <i>Glycyrrhiza glabra</i> extracts showed effective against HIV, herpes viruses, RSV, and severe acute respiratory syndrome-related coronavirus. Possess powerful antiviral properties and counter balance the activeness of COVID-19 and may use as an antiviral drug. Antiviral potential application as wound dressing materials, musk, gloves and against skin infection by electrospinning. licorice processed with PVA solution to form antiviral nano-membrane.	Immune response and antiviral	(Mazumder <i>et al.</i> , 2012; Chowdhury <i>et al.</i> , 2020)
<i>Chlorophytum borivilianum</i>	Unani name: Musli safed; English- Raddish	Ethanollic extract of the roots	The root ethanollic extract and its sapogenin were evaluated for immunomodulatory activity. Effect of azathioprine-induced myelosuppression and administration of extracts on hematological and serological parameters was assayed. Administration of extracts greatly improved survival against <i>Candida albicans</i> infection. There had been an increase in delayed-type hypersensitivity response, % neutrophil adhesion and <i>in vivo</i> phagocytosis by carbon clearance method (CCM) was observed after treatment with extracts. Root ethanollic extract shown immunostimulant activity was more pronounced as compared to sapogenins.	Immune-modulatory activity	(Thakur <i>et al.</i> , 2007)
<i>Curcuma longa</i> (Rhizome)	Unani name: Chobzard; English-Turmeric	Curcumin, Demethoxycurcumin,	<i>C. longa</i> was analysed for immune-modulatory activity in Balb/c mice. Curcumin increased the circulating antibody titre (512) against sheep red blood cells (SRBC). Curcumin administration increased the plaque forming cells in the spleen and the maximum number	Best potential to act as COVID-19 Mpro inhibitors. Treatment and prophylaxis	(Antony <i>et al.</i> , 1999; Sengupta <i>et al.</i> , 2011)

			<p>of PFC was observed on the 6th day (1, 130 PFC/106 spleen cells) after immunization with SRBC. The bone marrow cellularity (16.9×10^6 cells/femur) and γ-esterase positive cells (1, 622/4000 cells) are also enhanced with curcumin administration. A significant increase in macrophage phagocytic activity was observed into the curcumin treated animals ($p < 0.001$). The results indicated immunostimulatory activity of curcumin. The aqueous extract of <i>C. longa</i> offered significant protection from these damaging actions of CCl₄ on the non-specific host response in the peritoneal macrophages of CCl₄ intoxicated mice. <i>C. longa</i> shown to have immunotherapeutic properties along with its ability to ameliorate hepatotoxicity.</p>		
<i>Zingiber-zerumbet</i> (L.) (rhizhome)	(Unani name: zarnabad/narkachoor)	Zerumbone	<p>The aqueous extract of <i>Z.zerumbet</i> (CC-ZWE) in protecting the lungs by inhibiting the release of inflammatory mediators during short-term treatment, and modulating cytokine gene expressions during long-term treatment. The ZZ-CWE have beneficial effects for the treatment of asthmatic patients through its capabilities to inhibit the synthesis of LTC₄ and through the immunomodulation of Th1/Th2 cytokine production. The immune-modulatory effects of zerumbone isolated from <i>Z.zerumbet</i> investigated by evaluating the effects towards the lymphocytes proliferation (mice thymocytes, mice splenocytes and human peripheral blood mononuclear cells, PBMC), cell cycle progression and cytokine (interleukin 2 and 12) induction. Zerumbone produces as immunomodulatory agent which can react toward the immune cell cytokine production in dosage dependent pattern.</p>	Immuno-modulatory effects	(Chaung <i>et al.</i> , 2008; Keong <i>et al.</i> , 2010)
<i>Allium sativum</i> Linn. (Bulb)	Unani name: Seer, English, Garlic)	Essential oil, Allyldisulfide, Allyltrisulfide	<p>The changes in garlic during ageing examined by protein quantitation and gel electrophoresis. Purification and identification of the immune-modulatory proteins have been achieved by Q-sepharose chromatography and mitogenic activity. Only two major proteins (12–14 kDa range by SDS-PAGE) were observed in AGE. The purified protein components QA-1, QA-2, and QA-3 display Immunomodulatory and mannose-binding activity; QA-2 shows the highest mitogenic activity. The identity of</p>	Immuno-modulatory effect and Immunostimulant	(Chandrashekar and Venkatesh, 2009; Thuyet <i>et al.</i> , 2020)

			QA-2 and QA-1 proteins with the garlic lectins ASA I and ASA II, respectively, had confirmed by hemagglutination analysis. QA-3 exhibits mitogenic activity, but no hemagglutination activity. The immune-modulatory activity of AGE contributed by immune-modulatory proteins. The major immune-modulatory proteins identified as the well-known garlic lectins. A remedy for various diseases and viral infections. Possesses antiviral activity against influenza A and B, HIV, HSV-1, viral pneumonia, and common cold. Essential or volatile oil as crucial natural antiviral source to combat with coronavirus infection.		
<i>Rheum emodi</i>	Unani name: Revand	Emodin	Emodin compound reported to block the binding of SARS-Cov protein to ACE2. A potential lead therapeutic against the management or treatment of COVID-19.	Antiviral properties	(Ho <i>et al.</i> , 2007)
<i>Azadirachta indica</i>	Unani name: Neem	Neem leaf extract contains nimbin, nimbanene, 6-desacetylnimbinene, nimbandiol, nimbolide, ascorbic acid	Boost the immune system by triggering your cell-mediated immune system into overdrive. Boosts the body macrophage response, which also stimulates the lymphocytic system and boosts the production of white blood cells (WBC).	Potent antiviral agent, immune stimulant	(Kwawukume <i>et al.</i> , 2013)

8. Conclusion

Phytochemical evidence suggests that the active constituents present in medicinal plants have pharmacological properties against some bacteria and viruses, as well as immune-stimulatory effects, implying that they could be used to treat COVID-19 disease. Phytochemicals benefit and helps in rejuvenate the lost health and build up the immune system of human body to fight against the viruses and other foreign bodies. Over the past one year, the sudden outbreak of COVID-19 urge to identify the root cause of infection and explain the major global concern. Through, the use of potent medicinal plants and various herbal formulations, it is necessary to identify and conduct extensive research in order to develop a specific drug that can combat the novel coronavirus and, thus help humanity live a peaceful life.

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Conflict of interest

The authors declare that there are no conflicts of interest relevant to this article.

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