



COVID- 19: The role of medicinal plants and research institutions

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Abstract

Coronavirus disease 2019 (COVID-19) is a novel life-threatening infectious respiratory disease and a pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that belongs to the coronavirus family. COVID 19 was declared a Public Health Emergency of International Concern by the World Health Organization on 30 January 2020. The virus first reported in Wuhan, China, in December 2019. An impaired immune response is one of the factors that play a role in its pathogenesis and results in poor outcomes of COVID-19 patients. Currently, there is no effective antiviral medication to prevent or treat COVID-19. There have been many studies on potential conventional medicines used as antivirals. However, the outcomes of these studies showed that the drug candidates were not significantly effective against the disease. Natural products from medicinal plants with known safety profiles are a promising source for the discovery of potential treatment. Currently, people believe that taking herbal immune boosters and related products can prevent and even successfully treat COVID-19. Such tropical plants with antiviral properties and immunomodulatory activities can be great sources of treatment for COVID-19 as well as being utilized as complementary to allopathic treatment to improve recovery and the quality of life of patients. This review discusses some medicinal plants, including *Allium sativum*, *Allium cepa*, *Adansonia digitata*, *Azadirachta indica*, *Momordica charantia*, *Psidium guajava* and *Moringa oleifera* which are considered for the treatment of COVID-19, coupled with the need for research institutions to collaborate to search for preventive and or cure for COVID-19.

Keywords: COVID-19, coronaviruses, medicinal plant, immune booster, antiviral and natural products

Introduction

COVID-19 is a viral infectious disease which causes serious life-threatening respiratory diseases and it is a public health emergency challenge. It is known to spread from animal to person and among people through respiratory droplets produced during coughing or sneezing ^[1]. COVID-19 virus is a novel strain that has not been previously identified in humans ^[2] and belongs to a large family of viruses called coronaviruses. The disease is caused by the virus SARS-CoV-2, first identified in Wuhan, Hubei Province, China, in December 2019. The most likely ecological reservoirs for SARS-CoV-2 are bats ^[1]. Common signs and symptoms of infection may include respiratory symptoms, fever, cough, shortness of breath and breathing difficulties. In more severe cases, the infection can cause pneumonia, severe acute respiratory syndrome, kidney failure and even death ^[2]. The time between exposure and symptom onset is usually five days but may range from two to fourteen days ^[2].

Globally, COVID-19 as of 27th November 2020, more than 60, 074, 174 million cases have been reported across 220 countries and territories, results in more than 1, 416, 292 deaths. More than 39, 1000,000 people have recovered ^[3]. COVID-19 has been added to the list of infectious diseases and given very highest attention, and the World Health Organization (WHO), has declared COVID-19 as a pandemic ^[1].

Globally, there is no effective treatment or vaccine for Covid-

19, however, healthcare providers mostly treat symptoms associated with the virus by the use of hydroxychloroquine, chloroquine, lopinavir, ritonavir, remdesivir and azithromycin depending on the severity of the illness coupled with the provision of supportive care (e.g. oxygen therapy, fluid management) for infected persons. While vaccines and antiviral agents are the most effective tools to prevent and treat viral infections, there is no vaccine or specific antiviral therapy to prevent or treat COVID-19 ^[4]. According to the website of the National Institute of Health Clinical Trials, there are 3,265 clinical trials in search of COVID-19 treatment as of 4th January 2020 ^[1]. Moreover, the development of these remedies may require a longer period of time ^[5], which indicates that more immediate and appropriate preventive and treatment options should be found as soon as possible because of the rapid spread of the infection.

COVID-19 has become a challenging pandemic because it cannot be contained within the health systems available globally. Health infrastructures, healthcare funding, social structures and impact of COVID-19 on societies are damming to the existence of humanity. All resources must be mobilized including traditional medicine. Globally, the use of traditional medicines has continued to expand rapidly with many people depending on natural products for their primary health care needs ^[6]. Eighty-eight (88%) of WHO 194 membership admits to the use of Traditional and Complementary Medicine in their countries. This past decade has seen a tremendous surge in

acceptance and public interest in natural products in both developing and developed countries, where natural products are sold not only in pharmacy shops but also in food stores and supermarkets. The WHO estimates that about 80 per cent of the world's population living in the developing countries rely on natural products as a primary source of healthcare [7, 8, 9].

Natural products specifically herbal preparations were used in the prevention and treatment of Severe Acute Respiratory Syndrome (SARS) virus epidemic in the year 2003. A finished herbal product was able to prevent over 1,000 study participants from contracting SARS among some healthcare workers [10]. Two other cohort studies resulted in the participants taking herbal products not getting the SARS virus even though the participants were all front-line health workers treating SARS patients in two separate hospitals in China [11].

Herbal medications were further employed during the H1N1 pandemic in the year 2009 in the prevention of the H1N1 virus [12]. Multiple human studies using randomized and non-randomized controlled clinical human studies in more than over 25,000 highly exposed participants in hospitals and schools protected the participants from contracting the H1N1 virus when the outbreak was great in China. The rate of infectivity was also lower among the group that took herbal medicines than the control group that took no intervention [13].

Natural products are a promising and potential source of treatment of various illnesses including infectious diseases and COVID-19 [14]. Natural products are widely used among the majority of the world's population. By identifying certain phytochemicals, it is possible to effectively use some tried natural products that could help to alleviate the infection. Hence, by repurposing natural products, more innovative and alternative treatment options can be penned down for their role in defeating this viral transmission [15]. Harnessing the potential of natural products as alternative and complementary to conventional drugs in the management of COVID-19 present a valuable resource to this end. It has been reported that China used Traditional Chinese Medicine to treat patients with Covid-19, and Hubei Province Health Commission head Wang Hesheng said that treatment at Wuhan hospitals involved a combination of Traditional Chinese Medicine (TCM) and allopathic medicines yielding good outcomes [16, 17].

Although several reports are available on the use of natural products to manage some diseases, knowledge of natural products used to treat COVID-19 is limited, and not well documented. It has been well reported that natural products contain various types of phytochemicals including alkaloids, flavonoids, phenolic compounds, glycosides and tannins, and so could be potential sources of boosting immune responses, as well as halting the replication of the virus [18]. A literature survey and the utilization of natural products with anecdotal and empirical evidence is an important prerequisite to search for novel antiviral agents for the prevention and treatment of COVID-19 worldwide.

According to the WHO, about 80% of the population of the developing countries depend on traditional medicines for their primary healthcare needs. Also, globally, the advent of the COVID-19 virus pandemic has triggered the emergency

preparedness of the allopathic healthcare system of every country that, it can no longer contain the situation anymore. What then, can traditional, complementary and alternative medicines practitioners who are the first point of call for the majority of the population do to the potential patients who troop to their facilities? Should they leave the patients to their faith and be left on the hook to spread the disease?

Ghana currently relies on clinical guidelines prescribed by the WHO for the management of Covid-19 which are based on allopathic medicine, without recourse to traditional medicine even though, it has been integrated into the healthcare delivery system since the year 2011. It is anticipated that in the wake of Covid-19 pandemic, state institutions, such as the Ministry of Health, Ghana Health Service, Food and Drugs Authority (FDA), Department of Herbal Medicine, Kwame Nkrumah University of Science and Technology, KNUST, Centre for Plant Medicine Research (CPMR), Institute of Traditional and Alternative Medicine (ITAM), Ghana Federation of Traditional Medicine (GHAFTRAM) and medicinal plants and natural product experts in research institutions across Ghana would collaborate to develop suitable natural product therapies as both an alternative and complementary into both present and future therapeutic options for the management/treatment of COVID-19 [19].

This, therefore, calls for a collaborative effort in harnessing the diverse expertise, scientific knowledge and anecdotal reports and human resources to provide the required synergies to make strides in the discovery and development of plant medicine against COVID-19 [19].

Ethnobotanical and pharmacological studies on some Ghanaian indigenous medicinal plants such as; *Paullinia pinnata*, *Solanum torvum*, *Alstonia boonei*, *Acacia kamerunensis* among others have successfully been used to treat a plethora of viral infections such as common cold, pneumonia, measles, smallpox, hepatitis and human immunodeficiency virus (HIV) in Ghana [20, 21]. Studies have demonstrated that these medicinal plants have the ability to successfully prevent and destroy viral replication. There are enough scientific data to show that antiviral medicinal plants possess activity which can be unearthed to combat COVID-19, and medicinal plants might prove to be one of the ways forward.

Traditionally also in Ghana, inhalation of steam from boiled leaves of *neem* tree, *Ocimum viride*, and *Cymbopogon citratus* have been used for decades against infectious diseases and proven to help soothe flu's and heal coughs and fevers, key symptoms of COVID-19 virus and some respiratory illnesses. This was confirmed by Mr Kwadwo Odoom Eduful, the president of the Ghana Federation of Traditional Medicine Healers Association (GHAFTRAM) [22]. Also, Mr Eduful mentioned that some herbal products with immune boosting activities have already been registered by the Food and Drugs Authority (FDA), Ghana [23]. Recently, a Ghanaian nurse based in the USA, who tested positive to Covid-19 claimed she used; *Xylopi aethiopica* fruits, *Piper guineense*, *Alium sativum* (Garlic), lemon and *Zingiber officinale* (ginger) as a recipe to successfully treat COVID-19 [24].

Therefore, the aim and objective of this paper were to review some Ghanaian Traditional Medicines and plants used by

Traditional Medicine Practitioners, and the role it can play in the prevention and management of COVID-19 pandemic.

Medicinal Plants with Potential COVID-19 Preventive Activity

Since preventive measures have not been effective and curative agents have not been found yet, medicinal plants and herbal medicines with immunomodulatory activities are being used by a lot of people in most communities globally. A review of literature highlighted about fifteen medicinal plants that could prevent or be used as an alternative treatment for COVID-19 patients. Medicinal plants and herbal products have been reported to interrupt the replication of viral particles, and they also act as immunomodulators and immune stimulants due to the presence of antioxidants coupled with other phytochemicals.

Those medicinal plants with anti-viral activities and could have potential anti-COVID 19 activities are; *Zingiber officinale*, *Allium sativum*, *Allium cepa*, *Adansonia digitata* (stem bark), *Azadirachta indica* (leaves and seeds), *Momordica balsamina* (Fruit pulp and leaves), *Psidium guajava* (leaves), *Moringa oleifera* [25, 26, 27].

Zingiber officinale Roscoe

Ginger is traditionally used in the preparation of food and as a medicine. Phytoconstituents found in ginger are monoterpenes [8-phellandrene, (+)-camphene, cineole, citral, borneol]; Volatile oil (oleo-resin): sesquiterpenes (zingiberene, bisabolene); gingerols; vitamin B group (niacin, riboflavin, thiamine, folic acid); Vitamin C; reducing sugars; lecithins; phosphatidic acids; mucilage [28]. Studies conducted on *Zingiber officinale* on H₉N₂ Avian influenza virus proved it had potent activity at 10% concentration. Cytotoxicity and embryotoxicity tests on ginger using MTT assay and egg inoculation respectively showed it had a less toxic effect on vero cells with a cell survival rate at 50%. Ginger is having potent activity against other viruses like HEp2 Human Respiratory Syncytial (HRS), human rhinovirus (type 2), vesicular stomatitis virus, human cytomegaloviruses, vaccinia virus, parainfluenza virus (type 3), and herpes simplex virus (type 1 and 2) [29, 30].

Allium sativum Linn.

Allium sativum (Garlic) is commonly used as traditional medicine and in the diet of many people globally. It has been established that garlic contains many phytoconstituents including volatile organosulphur compounds (allicin, diallyl sulfide, diallyl disulfide, diallyl trisulfide, cysteine sulfoxides, etc.), ajoenes (E-ajoene, Z-ajoene), amino acids; oleo-resins; vitamins A, B, C and D; minerals (germanium, calcium, copper, iron, potassium, magnesium, selenium, zinc); saponins; cyanogenic glycosides; thioglycosides; flavonoids (quercetin, Myricetin, Kaempferol) [31].

Garlic has antiviral activity from both in-vitro and *in vivo* studies. There are dose-dependent antiviral activities of garlic against human rhinovirus (type 2), herpes simplex (type 1 and 2), cytomegalovirus, vesicular stomatitis virus, dengue virus, influenza virus (A, B), parainfluenza virus (type 3) and vaccinia virus [32]. *Allium sativum* extract at a concentration

15% had activity against H₉N₂ Avian influenza virus. However, at 25% garlic had a cytotoxic effect on the chick embryos [32].

Garlic possesses immunomodulatory activity and has prophylactic activity against viruses due to the presence of organosulphur compounds. This effect of garlic enhances human immunity thereby reducing the transmission of viruses among humans [33]. There is evidence from preclinical studies providing evidence that organosulphur compounds in *Allium sativum* have potential activity against many viruses found in humans, animals and plants. Some of the mechanisms through which garlic exert antiviral activity are; blocking of viruses from entering host cells, reverse transcriptase, immediate-early gene 1 (IEG1) transcription and synthesis of DNA, inhibition of viral RNA polymerase, downregulation of the signal pathway for extracellular-signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK). Garlic has a prophylactic effect against contracting influenza viruses [32, 33, 34]. Ajoene, allicin and diallyl trisulfide are some phytoconstituents present in *Allium sativum* that have antiviral activities. Allicin is to permeate phospholipid cell membranes to access and exert its intracellular antiviral replication effect.

Allium cepa L.

Allium cepa (onion) has been part of the human diet for many years. Hippocrates and Charak, founding fathers of medicine and Ayurveda respectively, all acknowledged the healing powers of *Allium* genus. Some phytochemicals identified in onion include; essential oils and volatile, monosulphides (allyl methyl sulphide, dimethyl sulphide), disulphides (methyl propyl disulphide, dimethyl disulphide), oxygen compounds (dimethyl furan, propanal, 2-methylpentanal), thiophene derivatives (2,4-dimethylthiophene, 2,5-dimethylthiophene), trisulphides (methyl propyl trisulphide, dimethyl trisulphide), thiols (allyl thiol, hydrogen sulphide), tetrasulphide (dimethyl tetrasulphide), carbohydrates (saccharose, fructosans), flavonoids (quercetin, Myricetin, Kaempferol), amino acids, minerals (Selenium, Potassium), vitamins (B₁, B₂, C) peptides [35, 36].

Allicin, ribavirin, zalcitabine and quercetin found in onion and garlic have been associated with inhibition of viral infections. These phytochemicals have the capability to modify translation and transcription of viral genetic codes in host cell cells; interrupt viral assembly through blocking of protein and genetic material production within the virus; prevent viruses from attaching to its cells [31]. Quercetin and kaempferol, flavonoids in onion are able to inhibit influenza and enteroviruses from attaching to its host cell. Quercetin hinders RNA polymerase which is key in the replication of viruses and also influences the signalling pathway of viruses with their host cells [37].

Paullinia pinnata Linn.

Cyanogenic glycosides; saponins; tannins; paullinoside (1a, 2a), 13β,17β -dihydroxy-28-norolean-12-ene, β -amyirin, β -sitosterol glucopyranoside and β -sitosterol [38]. *Paullinia pinnata* demonstrated antiviral activity when tested against herpes simplex [39].

***Adansonia digitata* Linn.**

Adansonia digitata (Baobab) is a commonly used traditional plant for its medicinal and nutritional value in Africa. Various fractions from the fruit, seed and leaves baobab (aqueous, methanol, DMSO) has activity against herpes simplex virus, influenza virus, respiratory syncytial virus ^[40].

***Solanum torvum* Swartz**

Many compounds have been isolated from *S. torvum* and these account for its biological effects. Some of its phytoconstituents are saponins (glycosides of torvogenin, chlorogenin, sisalagenone), apigenin, flavonoids (quercetin, kaempferol), coumarins (scopoletin, scopolin, aesculin), alkaloids (solasodine, solasonine), vitamins (B group, C), fixed oil, β -sitosterol ^[41]. The root and stem of *Solanum torvum* have activity against Herpes simplex virus ^[42].

***Ocimum viride* Willd**

Terpenes (mono, sesqui, diterpenes), viridone, ursolic acid, crismaritin are some identified compounds from *O. viride* ^[43]. This plant has ethnobotanical use as antiviral ^[44].

***Azadirachta indica* A. Juss**

Compounds isolated from the neem plant include alkaloids, triterpenes (azadirachtin, nimbolide, gedunin, salanin, meliacins), diterpenes, tannins, fixed oils, reducing sugars, coumarin; vitamin C, stigmasterol and carotenoids. Neem possesses immunostimulatory activity by improving humoral immunity. It enhances human antibody levels by increasing T-lymphocytes count and also total lymphocyte count ^[45].

***Momordica charantia* Linn.**

Momordica charantia usually called bitter melon contains: charantin; momordicine (1,2,3); Alkaloids (momordicine); carotenoids (cryptoxanthin, β -carotene); 5-hydroxytryptamine; vitamin (B, C); amino acids (asparagine, arginine, tyrosine, leucine); fatty acid; rosmarinic acid; γ -aminobutyric acid; volatile oil; saponins; cucurbitacins; carbohydrates; alpha-amino butyric acid. *M. charantia* possess activity against HIV replication and herpes simplex (type 1). *M. charantia* has broad-spectrum against influenza viruses (H1N1, H5N1 and H3N2). It has the ability to increase gamma interferon production which is a natural antiviral agent in the body and this effect can be utilized in COVID-19 management ^[46].

***Psidium guajava* Linn.**

Some compounds isolated from *Psidium guajava* are tannins (hydrolysable); saponins and sapogenins; volatile oils (sesquiterpenes); reducing sugars; flavonoids (quercetin); calcium oxalate crystals; starch; vitamin A, vitamin B group (niacin; nicotinic acid, thiamine) and vitamin C; fatty acids; carotenoids; fibres ^[28]. *Psidium guajava* have demonstrated immunostimulatory activities but compounds responsible have not been identified ^[47]. Guava has antiviral activity against influenza virus ^[49].

***Moringa oleifera* Lam.**

Some phytoconstituents identified in *Moringa* are estrogenic substances (including β -sitosterol); pectinesterase;

pterygospermin; alkaloids (moringine and moringinine); acetylated glycosides (e.g. niaziminin A, niaziminin B niazirin, niazirinin); glycosides containing isothiocyanates; (4-[(4'-Oacetyl- α -L-rhamnosyloxy)benzyl] isothiocyanate), β -carotene, ascorbic acid, octadecamethyl-cyclononasiloxane, 1, 2-benzene dicarboxylic acid, 9-octadecenoic acid, methyl ester-hexadecanoic acid oleic acid, reducing sugars; tannins, flavonoids and cardiac glycosides ^[50]. *Moringa* has been associated with activity against influenza A (H1N1), HIV, hepatitis B virus, herpes simplex virus, Epstein Barr virus, Newcastle disease virus, ^[50]. *Moringa oleifera* extract inhibits viral haemagglutination and sialidase actions through multi-target sites ^[48].

***Cymbopogon citratus* (D.C.) Stapf**

Cymbopogon citratus commonly called lemon grass is used traditionally as tea and have proven to contain terpenes (mono, sesqui, triterpenes), volatile oils (citral, geraniol, citronellal, camphene), alkaloids, flavonoids, tannins. *C. citratus* demonstrated antiviral activity against herpes simplex, dengue fever, herpes simplex (1 and 2). *C. citratus* is more potent in preventing the entry of viruses and interrupt with viral replication ^[51, 52].

***Xylopia aethiopica* (Dunal) A. Rich**

Compounds identified from *X. aethiopica* are diterpenoids (xylopic acid, kaurane, trachylobane and kolavane diterpenes), volatile oils (monoterpenoids: cineole, cuminic aldehyde, terpinone, β -pinene), oleoresins, acetogenins, minerals (copper, manganese, and zinc). *X. aethiopica* had activity against measles ^[53].

***Piper guineense* Schum and Thonn.**

Many compounds have been isolated from *Piper guineense* including piperine, wisanine, dihydrowisanine, dihydropiperine, resin, piperylin, lignans-dihydrocubebin, sesamin, aschantin and volatile oils. *P. guineense* possesses antiviral action and has been used in the management of some viral diseases ^[54].

***Zingiber officinale* Roscoe**

Some groups of phytoconstituents isolated from ginger are monoterpenes (8-phellandrene, camphene, cineole, citral, borneol), Volatile oil (oleo-resin), sesquiterpenes (zingiberene, bisabolene), Vitamins (thiamine, niacin, riboflavin, folic acid and vitamin C), gingerols, reducing sugars, lecithins, phosphatidic acids, mucilage ^[55]. It has been established that fresh ginger extract blocks the attachment and internalization of human respiratory syncytial virus (HRSV) and Newcastle disease virus (NDV) ^[56].

Role of Natural Products and Research Institutions in COVID-19

Metabolites of natural products have the potential to be used as treatment as was in the case of SARS-CoV-1 ^[57]. Medicinal plants have been used as an option since they are the basis for the discovery of natural compounds for the development of therapeutic agents. Flavonoids of medicinal plants have powerful immunomodulatory potentials ^[58]. There has been a

report on the successful utilization of medicinal plant to prevent COVID-19 in Morocco ^[60]. Research institutions should collaborate to search for potential secondary metabolites from natural products and other sources to find a preventive or cure for COVID-19. The preparation and the modes of use of these medicinal plants are almost the same for most medicinal plant in different part of Ghana. This is an indication that knowledge and utilization of medicinal plants have been streamlined through experimentation and exchange of information. The biological effects and secondary metabolites in the plants used for the prevention and curative purposes for Covid-19 have been established. These medicinal plants play vital role in nutrition and human health. They contain sugars, vitamins, minerals, fatty acids, amino acids, enzymes among others. These plants contain a wide range of secondary bioactive metabolites such as flavonoids, organosulfur compounds, glycosides, alkaloids, among others. This variety of bioactive metabolites are responsible for the many biological effects such as immune boosting, antiviral, antibacterial, and antioxidant activities.

Conclusion

There should be more organized and conscious effort to maximize the potentials of natural products in the wake of COVID-19 pandemic. Natural products can be explored and used as anti-COVID-19 agents as it is the only alternative in the midst of unavailable and ineffective orthodox medicine. Natural products can be of help in the current global pandemic of COVID-19 invasion. Some of the natural products are good sources of immune boosters to improve recovery and prevent infections. All countries should have a registry of potential medicinal plants with antiviral activities. Adequate resources should be allocated and personnel empowered to research and discover an alternative treatment to COVID-19. This and other such related works can be exploited in scientific researches with collaboration in the field of pharmacognosy, pharmacology and biochemistry to harness the potentials of medicinal plant to discover preventive, curative and or an alternative therapy to combat COVID-19.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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