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SARS-COV-2 Analytical Review: Its Biology, Immunology And Exploration Of Medicinal Plants As An Alternative Management Strategy

Samuel Mong'are[1]*, Eric O Omwenga[1], Musyoki Stanslaus[2], Maacah Apicha[3], and Atebe Rogers[4]

[1]*Department of Medical Microbiology and Parasitology, School of Medicine, Kisii University, P.O Box, 408-40200 Kisii, Kenya*
[2]*Department of Medical Laboratory Science, School of Health Science, Kisii University, P.O Box, 408-40200 Kisii, Kenya*
[3]*Department of Nursing, School of Health Science, Kisii University, P.O Box, 408-40200 Kisii, Kenya*
[4]*Department of Pharmacy, School of Health Science, Kisii University, P.O Box, 408-40200 Kisii, Kenya*
**Corresponding Author: Dr Samuel Mong'are, Kisii University, P.O Box, 408-40200 Kisii.*

Abstract
Background: *The coronavirus pandemic has shaken the world with countless lives being lost and others devastated, economies destroyed, healthcare protocols overhauled while patients and healthcare workers are experiencing unprecedented levels of stress. SARS-Co-2 causes a viral infection that is highly infectious and vast in its transmission making its containment practically impossible. The biology, life cycle and pathogenesis of SARS-Co-2 virus is not clearly understood. There is no specific drug for COVID-19. Therapeutic approaches have been suggested such as nucleoside analogs like Remdesivir, anti-inflammatory drugs or Lopinavir/Ritonavir to treat COVID-19 but their clinical usefulness against COVID-19 infection remains unclear. Therefore, this review was designed to document the nature of SARS-Cov-2 virus, its structure, life cycle and pathogenicity and also to identify major medicinal plants with anticovid properties.* ***Materials and methods:*** *We searched PUB MED, MEDLINE and Google Scholar with several key words namely medicinal plants, herbal plants, antiviral properties, SARS-Cov-2, immunomodulatory, phytochemicals, and combating COVID for recent articles related to COVID-19, life sciences and biomedical topics in the world. For us to cure COVID-19 infections and prevent epidemics; there is need to develop new therapeutic strategies. Several strategies have been devised by scientists and other innovators to address the issue of COVID-19 based on its different dynamics.* ***Results:*** *This paper has documented the nature of SARS-Cov-2 virus and reviewed major herbs and medicinal plants specifically Moringa oleifera, Allium cepa L., Allium sativum, Azadirachta indica,* Nigella sativa , *Ocimum sanctum, PiperNigrum L., Astragalus membranaceus, Cinchona and Sambucus nigra for their therapeutic potential against COVID-19 and associated infections.* ***Conclusion:*** *This review notes that medicinal plants have several active compounds that act differently on various viruses including SARS-CoV-2; hence they are potential source of therapeutic agents in combating COVID-19.*

***Key words**: Antiviral, COVID-19, immunomodulatory, Medicinal Plants, herbs*

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I. Introduction

In December 2019, a novel coronavirus, SARS-CoV-2, was identified among patients in Wuhan, China. The virus spread very first globally after the first case was identified hence causing one of the most devastating pandemics in the history of humankind. This necessitated for an urgent need of coming up with control strategies that were geared towards reducing the transmission hence reducing the deaths associated with it. The major control measures taken by then at Wuhan were lock down and strict quarantine[1]. Other countries adopted physical distancing measures and restricting movement of people. These measures were not sustainable due to the impact the virus had on the economy and social aspects especially in low- and middle-income countries[2].

Other measures employed included social and physical distancing measures like teleworking, distance learning, reducing and avoiding crowding, closure of non-essential facilities and services, shielding and protecting vulnerable groups, local or national movement restrictions and staying at home measures[2]. However, these measures are not protective enough but only serve to slow the spread of the disease by stopping chains of transmission of COVID-19 and preventing new ones from appearing. This shows that there is an urgent need for effective COVID-19 treatment.

Currently, the focus is on developing novel therapeutics against SARS-CoV-2 virus. At least 13 different vaccines have been approved by World Health Organization key among them being Pfizer/BioNtechComirnaty, SII/Covishield, AstraZeneca/AZD1222, Janssen/Ad26.COV2.S, Moderna COVID-19/mRNA 1273, Sinopharm COVID-19 and the Sinovac-CoronaVac vaccines[2]. These vaccines are being used by all except children hence there is need to focus on COVID-19 specific drugs that are safe for use by people of all ages. A few scientific professionals are currently exploring the potential of herbal remedies and medicinal plants in the treatment of COVID-19 disease. Medicinal plant products are the basis for treating various human diseases that have been in existence from the Precambrian period with their demand and acceptance rising progressively to date[3]. Globally, herbal treatments have been proven effective in controlling the 2003 severe acute respiratory syndrome (SARS) outbreak among other contagious diseases[4]. Therefore, medicinal plants have a promising future because there are more than one million plants globally in which the biological activities of most of them are yet to be evaluated and their pharmacological properties could be decisive in the treatment of present pandemics like COVID-19 virus or future disease outbreak[5]. Therefore, this review focuses on SARS-CoV-2 biology, immunology, and the role of medicinal plants as the alternative management strategy against COVID-19 disease.

Nature of SARS-CoV-2 virus

Corona virus is a member of the Coronaviridae family in the Nidovirales order that has been documented to be causing the ongoing coronavirus disease 2019 (COVID-19) pandemic. This pandemic is a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that has affected the world[6]. COVID-19 was declared a pandemic on February 20, 2020 and since then it has caused detrimental effects globally in all sectors among them health and general economies[7]. The infected and death numbers are ever increasing globally; as of 6th December 2021, this condition had resulted to 266,308,226 confirmed cases and 5,274,100 deaths globally[8].

Coronaviruses just like other common human viruses have repeatedly evolved during the past 1000 years[9]. The first recovery of coronaviruses involved the identification of illnesses in animals followed by the isolation of infectious bronchitis virus (IBV) from chickens in 1937[10] and murine hepatitis viruses (MHV) from mice in 1949[11]. Since then, several strains of this virus have been isolated and characterized. However, during the last two decades, 5 types of coronaviruses (CoV) have been found to infect humans, including SARS-CoV (2003), human coronavirus NL63 (HCoV-NL63, 2004), human coronavirus HKU1 (HCoV-HKU1, 2005), Middle East Respiratory Syndrome Coronavirus (MERS-CoV, 2012) and SARS-CoV-2 (2019)[12], among which SARS-CoV, MERS-CoV, and SARS-CoV-2 are highly pathogenic CoVs. Together with 2 human CoVs (HCoV-229E and HCoV-OC43) discovered in the 1960s, 7 types of CoVs have been found to infect humans to date[7]. The frequent global CoV pandemics in the new century have alarmed experts and indicated the great threat of pathogenic CoVs to public health worldwide.

Even though the current pandemic has been caused by SARS-CoV, there exists several non-pathogenic CoVs in various species of wild animals and they do possess a diverse genetic makeup. Among such wild animals are the wild birds, marine mammals, cats, bats, rodents amongst many more[7]. However, based on various phylogenetic and genetic sequencing done so far, it is now clear that most human CoVs have been shown to originate from wild animals at different time points and through different paths[13, 7]. This clearly gives a clear indication that COVID 19 virus could have had an origin from animals. This supports the documentation indicating that COVID 19 was first reported as a pneumonia-like condition of unknown cause in Wuhan city, Hubei Province, China in December 2019, and most of the patients involved were related to the Huanan Seafood Wholesale Market[14]. Later, the causative agent was confirmed as the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), previously named 2019 novel coronavirus (2019-nCoV), and the disease was termed coronavirus disease-2019 (Covid-19)[15, 7].

Based on phylogenetic analysis, SARS-CoV-2 was found to be in a distinct lineage with Bat-SARS-like coronaviruses that belong to the order *Nidovirales*, family *Coronaviridae*, genus *Betacoronavirus*, and subgenus *Sarbecovirus*[16]. SARS-CoV-2 shares 96.3%, 89%, and 82% nucleotide similarity with bat CoV RaTG13, SARS-like CoV ZXC21, and SARS-CoV, respectively, which confirms its zoonotic origin.[17, 18]

These narrative confused scientists as it was thought that this virus is only transmissible between animals and humans when the outbreak started, till data from Germany indicated the human-to-human transmission.[19; 17] This was compounded by the rapid community-based transmission that was observed thereafter in which most patients were not directly in contact with wild animals.[14] It is now clear that SARS-CoV-2 is transmitted between humans through direct contact, aerosol droplets, faecal–oral route, and intermediate fomites from both symptomatic and asymptomatic patients during the incubation period.[16, 14]

Biology and structure of SARS-CoV-2 virus

The newly discovered coronavirus belongs to the genus Betacoronavirus and family *Coronaviridae*that has a circular shape with a diameter of 60 – 100 nm. It has an envelope enclosing a positive – sense single – stranded RNA (+SSRNA)[20]. As a member of coronavirus family, the genome size of SARS-CoV-2 which was sequenced recently is approximately 29.9 kb [21]. Phylogenetic analysis has revealed that this genome sequence has an 89% similarity to two bat – derived SARS – like coronaviruses (bat – SL –CoVZC45 and bat – SL – CoVZXC21), approximately 79% similarity to SARS – CoV and approximately 50% similarity to MERS – CoV[22]. The envelope is lined with surface spikes that are 9 – 12 nm long and four other major structural proteins [spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins] as shown in the schematic figure 1 below. The membrane protein (M) plays a pre-dominant role in the intracellular formation of virus particles while the spike (S) protein enhances mediation between the envelope and the host cell membrane thus aiding the entry of the virus into the host cell[23]. However, it should be noted that the arrangement of nucleocapsid protein (N), envelope protein (E), and membrane protein (M) among beta coronaviruses are different from other corona viruses[24].

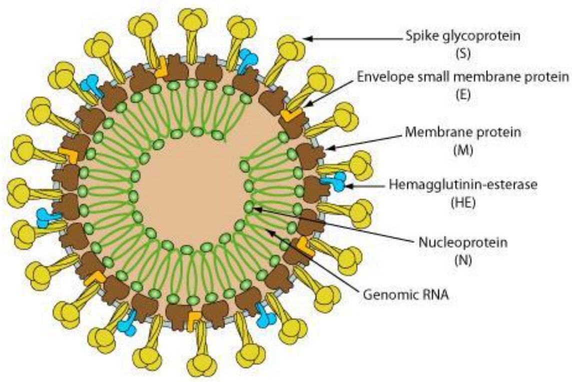

Figure 1.Schematic of a coronavirus. From Biowiki (http://ruleof6ix. fieldofscience.com/2012/09/a-new-coronavirus-should-youcare.html).

Other than the four structural proteins (S, E, M, and N) SARS-CoV-2 contains sixteen non-structural proteins (Nsp1−16) that perform various functions. For instance, RNA processing and replication is mediated by Nsp1 non- structural protein. While Nsp2 non- structural protein modulates the survival signalling pathway of host cell. Separation of the translated protein is believed to be the function of the Nsp3 non-structural proteins. Nsp4 non-structural proteins contains trans-membrane domain 2 (TM2) and modifies ER membranes. Also processing of polyprotein during replication is because of non-structural proteins Nsp5 while non-structural protein Nsp6 is a presumptive trans-membrane domain. The presence of Nsp7 and Nsp8 significantly increases the combination of Nsp12 and template-primer RNA. Nsp9 functions as assRNA-binding protein. Nsp10 is critical for the cap methylation of viral mRNAs[25]. Nsp12 contains the RNA-dependent RNA polymerase (RdRp), which is a critical composition of coronavirus replication/transcription. The non-structural protein Nsp13 binds with ATP and the zinc-binding domain in nsp13 participates in the process of replication and transcription. The proofreading exoribonuclease domain is a function of Nsp14 non-structural proteins. While non-structural proteins Nsp15 has Mn(2+)-dependent endoribonuclease activity. Nsp16 is a 2'-O-ribose methyltransferase[26, 25].

However, it was documented in one study that there are some NSP-mediated effects on splicing, translation, and protein trafficking to inhibit host defences[27]. Upon SARS-CoV-2 infection, non-structural protein NSP16 binds mRNA recognition domains of the U1 and U2 snRNAs hence suppressing mRNA splicing. At the same time non-structural protein NSP1 binds to 18S ribosomal RNA in the mRNA entry channel of the ribosome to interfere with the translation of mRNA. Non-structural proteins NSP8 and NSP9 binds to the 7SL RNA which locates at the Signal Recognition Particle to disrupt protein trafficking to the cell membrane[27, 25]. These, therefore, are some SARS-CoV-2 proteins which may potentially be antiviral drug targets based on their structures.

Lifecycle and Pathogenesis of SARS-CoV-2

The lifecycle of the SARS-CoV-2 (COVID-19) is not any different from other RNA viruses known more so the ones that belong to the coronaviridae family. The virus is mainly spread through the air especially if it is contaminated with the viral particles. Soon after inhalation of the SARS-CoV-2 virus, the virus binds to ACE2 (the angiotensin converting enzyme 2) by its spike and allows COVID-19 virus to enter and infect cells. Such receptors are common among the lung epithelial cells which have come out to be the primary target of the virus[28]. The protease TMPRSS2 enables completion of this initial process of attachment by priming the spike protein via its activation[29]. Upon entry to the host cell and the virus uncoats transcription and translation of its genome follows in the cytoplasmic membranes. This involves a well-coordinated process of both continuous and discontinuous RNA synthesis that is mediated by the viral replicate, a huge protein complex encoded by the 20-kb replicase gene[30]. In addition to common enzymes amongst the RNA viruses like RNA dependent RNA polymerase, RNA helicase, and protease activities, the coronavirus replicase has been reported recently to employ a variety of RNA processing enzymes that are not (or extremely rarely) found in other RNA viruses and include putative sequence-specific endoribonuclease, 30 -to-50 exoribonuclease, 20 -O-ribose methyltransferase, ADP ribose 10 -phosphatase and, in a subset of group 2 coronaviruses, cyclic phosphodiesterase activities[31, 29]. After replication viral proteins are then assembled at the cell membrane and genomic RNA is incorporated as the mature particle forms are released by budding from the internal cell membranes[32].

Even though more has been documented on the mode of transmission and mortality of the clinical disease (COVID 19), much less facts are known about its pathobiology. Based on the cells that are likely infected, COVID-19 can be divided into three phases that correspond to different clinical stages of the disease i.e., asymptomatic phase (stage 1), Upper airway and conducting airway response (stage 2) and hypoxia, ground glass infiltrates, and progression to acute respiratory distress syndrome - ARDS (stage 3)[33]. During stage 1, inhaled virus SARS-CoV-2 will most likely bind to epithelial cells in the nasal cavity and starts replicating[28, 34]. *In vitro* data has documented that SARS-CoV-2 infects the ciliated cells as the primary cells conducting airways[35]. Additionally, as the virus propagates, locally limited innate immune response is observed. At this stage the viral load is low though infected individuals are still infectious and the virus can be detected by nasal and throat swabs.

During the 2nd stage of the disease (Upper airway and conducting airway response), viral propagation could have happened, and the viruses start migrating down the respiratory tract along the conducting airways. At this point a more robust innate immune response is triggered and the COVID-19 condition is clinically manifested. Nasal swabs or sputum should yield the virus (SARS-CoV-2) as well as early markers of the innate immune response. The level of CXCL10 (or some other innate response cytokine) may be predictive of the subsequent clinical course[36]. Viral infected epithelial cells are a major source of beta and lambda interferons[37]. CXCL10 is an interferon responsive gene that has an excellent signal to noise ratio in the alveolar type II cell response to both SARS-CoV and influenza[38]. However, it should be noted that about 80% of the infected patients at this stage are usually having mild condition that is mostly restricted to the upper and conducting airways[39]. These individuals may be monitored at home with conservative symptomatic therapy.

Severity of COVID 19 disease is experienced at stage 3 and unfortunately, about 20% of the infected patients will progress to this stage. Such patients will develop pulmonary infiltrates and some of them will develop very severe disease. Initial estimates of the fatality rate are around 2%, but this varies markedly with age[39]. The fatality and morbidity rates may be revised once the prevalence of mild and asymptomatic cases is better defined. The virus now reaches the gas exchange units of the lung and infects alveolar type II cells as compared to type I cells[40, 41]. The infected alveolar units tend to be peripheral and subpleural[42] and with the continuous propagation of the SARS-CoV within type II cells, large number of viral particles are released, and the cells undergo apoptosis and die as the released viral particles attack new cells[38]. The pathological result of SARS and COVID-19 is diffuse alveolar damage with fibrin rich hyaline membranes and a few multinucleated giant cell[33]. The aberrant wound healing may lead to more severe scarring and fibrosis than other forms of ARDS. Recovery will require a vigorous innate and acquired immune response and epithelial regeneration. The immunocompromised and the elderly individuals are particularly at risk because of their diminished immune response and reduced ability to repair the damaged epithelium. The elderly also have reduced mucociliary clearance, and this may allow the virus to spread to the gas exchange units of the lung more readily[43].

The virus has also been documented to have severe effects on the immune system which in turn enhances the severity of the COVID 19 infection. For instance, it has been documented to significantly increase cytokine and chemokine levels (IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA) in patients. In some of the severe cases especially among those patients admitted to the intensive care unit, high levels of pro-inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα have been observed that are reasoned to promote disease severity[44].

Pathogenesis of COVID 19 infection has been enhanced by underlying conditions like cardiovascular, diabetes and cerebrovascular diseases which have been documented as co-morbidities. Several abnormalities also have been documented like cellular immune deficiency, coagulation activation, myocardia injury, hepatic and kidney injury, and secondary bacterial infection amongst patients suffering from this infection[45]. In most cases of severe disease and death, lymphopenia and sustained inflammation have been recorded. These observations in COVID-19 patients are like those that were noted amongst patients who had severe acute respiratory syndrome (SARS) during the 2003 epidemic. As such, there could be a biological mechanism behind this epidemiological anomaly[46, 29].

Mode of transmission and preventive measures for SARS-CoV-2

The mode of transmission of the SARS-COV2 amongst humans is mainly thought to be through respiratory droplets produced when an infected person coughs or sneezes. Such droplets if they happen to land in the mouths or noses of people who are nearby or possibly be inhaled into the lungs can end up causing this infection[47]. However, other routes like contact with contaminated fomites and inhalation of aerosols, produced during aerosol generating procedures have also been postulated to be involved in the transmission dynamics of this condition. This has even been worsened by the fact that transmission can also occur from asymptomatic individuals (or individuals within the incubation period). However, the extent to which this occurs remains unknown[48].

So far, no authenticated medication has been approved for management of this condition hence need for employment of proper preventive strategies that should be followed to the letter to limit the spread of cases[49]. This includes such strategies like early screening, diagnosis, isolation, and treatment/management are necessary to prevent further spread more as currently we only have limited treatment options. These strategies are focused on the isolation of patients and careful infection control, including appropriate measures to be adopted during the diagnosis and the provision of clinical care to an infected patient[47].

Various personal protective measures have been championed with the aim of reducing or preventing SARS-CoV-2 spread amongst populations. Social distancing and good hygiene practices are amongst the most common measures that have been adopted globally[49]. For instance, social distancing mainly reduces overcrowding, clustering and close interactions in each population set up hence preventing COVID-19 spread via respiratory droplets just in case infected individuals are present [50, 2]. This approach has been employed globally with good results being documented regarding reduction of the spread rate of the SARS-CoV-2. Such measures have been applied like staying indoors, school closures, working from home where possible, and avoiding social gatherings to enhance social distancing[51].

On the other hand, good hand hygiene practices have also been explored as another strategy that can reduce the spread of respiratory diseases such as SARS-CoV and influenzas causative viruses can survive on surfaces for extended periods. Such a method despite being used, it has not been proven beyond reasonable doubts to reduce SARS-CoV-2 transmission[52]. A systematic review on hand hygiene shows that the effectiveness of hand hygiene practices in preventing influenza and its transmission in the community is insufficient. However, due to its proven efficacy in general infectious disease prevention and control, it is still critical to adopt good hand hygiene practices as a general preventive measure[53]. This strategy includes such measures like hand washing using soaps and use of disinfectants more so ones that contain 70% ethanol. It is further recommended that high touch areas like door handles, tables and chairs should be disinfected regularly. Disposable gloves should also be used when cleaning or handling surfaces, clothing, or linen soiled with body fluids[47].

Due to lack of timely diagnosis of COVID-19 amongst most regions in the world, use of protective gear like masks have also greatly contributed to the reduction of the spread rate of COVID-19. This is because in any given population at a given time there must be infected people who are potentially asymptomatic or presymptomatic people and hence they are a danger to those without[2]. Therefore, the usage of masks is key in controlling the spread of this condition amongst any population[54]. This measure can be particularly relevant in epidemic situations when the number of asymptomatic but infectious persons in the community can be assumed to be high. Wearing a face mask could be considered, especially when visiting busy, closed spaces, such as grocery stores, shopping centres, political gatherings, when using public transport; and for certain workplaces and professions that involve physical proximity to many other people (such as members of the police force, cashiers – if not behind a glass partition, etc.) and when teleworking is not possible[55]. Individuals should be counselled to avoid touching the eyes, nose, and mouth when removing the covering, practice hand hygiene after handling it, and launder it routinely. Face covering with protective masks primarily helps in containing secretions of and preventing transmission from individuals who have asymptomatic or presymptomatic infection[47].

However, it should be noted that the efforts that are used in managing the pandemic have also experienced various drawbacks among them are non-adherence and non-willingness to employ the preventive strategies which in most cases has been found to be influenced by various global factors like news media, politics, or local factors such as infected family members or friends[56, 57]. Many studies and surveys are being carried out by countries to understand people's attitudes and perception of COVID-19 and their association with knowledge, protective behaviours, and practices[57, 49].

Besides the public health COVID-19 preventive measures, herbal remedies have been and continue to play an integral part of healthcare system in Kenya and the world at large [58]. For ages, human beings have made judicious use of natural products to manage their health issues effectively before the dawn of conventional medicine[59]. The usage still persists in a significant portion of the population as a remedy to ailments and management of the same in the modern society[60]. This is more evident especially with the emergency of new health challenges such as COVID-19 pandemic and other terminal ailments[43]. With no clear established understanding of emerging ailments, the population usually reverts to its indigenous body of knowledge for disease management. There is increasing evidence that herbal remedies can be beneficial in alleviating COVID 19 symptoms[61].

Potential of medicinal plants in the treatment and prevention of COVID-19 disease

Medicinal plants are the natural parts, which are used at least or without processing for curing diseases at different regional scale[62]. They have been widely used to treat a variety of infectious and non-infectious ailments since it has been proven that plant extracts and plant compounds are eco-friendly, target-specific, less expensive, and highly efficacious against a wide range of disease causing agents and vectors[63]. Research shows that 25% of the commonly used medicines contain compounds isolated from plants[64] and that several plants could offer a rich reserve for drug discovery of infectious diseases. Ethnomedicinal plants have different compounds like monoterpenoids, flavonoids, triterpenoids, iridoid glycosides, sesquiterpenes, benzoic and phenolic compounds which have been documented to be having strong antiviral potential[65].

Due to this, Chinese herbs and plants have been used for a long time as traditional medicine and immune system boosters[66]. To date, many guidelines related to the use of herbal medicine have been issued for the prevention and treatment of COVID-19 with recent clinical evidence showing that the therapeutic effectiveness of traditional medicine in treating different stages of COVID-19 is high[67]. Globally, traditional healers are using various medicinal plants for the treatment of COVID-19 related infections as follows:

One of the widely used medicinal plants is *Moringa oleifera, which is* a plant from the family Moringacea. The plant is used in many traditional medicines and pharmacopeias against an array of medical conditions that include malaria, diabetes, skin infection, tuberculosis, anaemia, headaches, epilepsy, and sexually transmitted diseases among others. In African traditional medicine, this plant is popularly used against acquired immunodeficiency syndrome (AIDS) and related secondary infections that are associated with HIV[68]. *Moringa oleifera* acts as antiviral, diuretic, antipyretic, anticancer, anti-inflammatory, and antibacterial plant[69]. The most used parts of the plant are the leaves, which are rich in vitamins, carotenoids, polyphenols, phenolic acids, flavonoids, alkaloids, glucosinolates, isothiocyanates, tannins and saponins[70].

Extracts from *Moringa oleifera* contain several active compounds that act differently on a few viruses. Moringa A, an isolate from *Moringa oleifera* seeds inhibits H1N1 virus replication in host cells, and further protects infected cells from cytopathic effect induced by Influenza A viruses[71]. Further research has shown that the extracts derived from seeds, leaves, roots, and fruits of medicinal plants exhibited antiviral activities against RNA and DNA viruses[72]. Moringa oil has been used on patients with chronic laryngitis, pharyngitis, and rhinitis where Moringa oil was used with drops in the throat and nose and the effects seen were permanent. Further, moringa oil has effects on various viruses, such as the proven reduction of potassium (K) in the presence of SARS-CoV-2 virus and COVID-19 disease, implying that the chemical composition of Moringa is applicable for prevention, treatment, and recovery of a number of infections[73]. Moringa leaves have medicinal properties that need further study, especially their antioxidants' ability because they contain polyphenols, flavonoids, and ascorbic acid[74].

Onion, (*Allium cepa* L.), is one of the most consumed and grown vegetable crops in the world whose characteristic flavour makes it the third most essential horticultural spice with a substantial commercial value. Onions contain generous amounts of the flavonoid quercetin that protects against cataracts, cardiovascular disease, and cancer. The bulb is anthelmintic, anti-inflammatory, antiseptic, antispasmodic, carminative, diuretic, expectorant, febrifuge, hypoglycaemic, hypotensive, lithontripic, stomachic and tonic[75]. A study investigating antiviral activity of *Azadirachta indica*, *Xylopia aethiopica* and *Allium cepa* isolates as potential anti-viral remedies for Covid-19 showed that Quercetin 3,7,4-triglucoside, Quercetin-7,4-diglucoside, Quercetin 3,4-diglucoside, Quercetin-4-glucoside among other isolates, could target all the viral proteins studied by exhibiting good binding affinity hence they may serve as ideal inhibitors for SARS-CoV-2[76]. This is supported by Chinese researchers who screened some potential Chinese herbal medicines and identified phytochemicals and medicinal plants that might directly inhibit the SARS-CoV-2 virus. Key among the identified phytochemicals is quercetin present in 13 natural products, which occur in traditional Chinese medicines and could exert anti-COVID-19 activity[77].

Allium sativum (Garlic) together with *Allium cepa* (Onion) are plants which are considered for therapeutic strategies that can be used for the inhibition of SARS-CoV-2 virus infection. Garlic has been seen to possess high anti-viral properties that have been proved to minimize influenza A and B viral infections[78]. Garlic is also effective against different viruses such as cytomegalovirus, rhinovirus, HIV, herpes simplex virus 1, herpes simplex virus 2, viral pneumonia, and rotavirus. The presence of sulfur-containing phytochemicals in garlic (*Allium sativum* L.) provides substantial immunomodulatory, anti-inflammatory, anticancer, antitumor, antidiabetic, anti-atherosclerotic, and cardioprotective features[79]. Research has identified 230 Cameroonian medicinal plant species that are promising sources of ingredients for the fight against the 2019 novel corona virus where *Allium sativum* is one of them[80]. Of these plants, 102 are already documented for their traditional use in managing at least 3 common symptoms of COVID-19. Molecular docking analysis of *Allium sativum*, has shown that alliin (one of the sulfur-containing phytochemicals in garlic) has higher anti-viral potential to prevent COVID-19[79]. This bioactive component alone or in combination with the main therapeutic drug would be an efficient therapy to eradicate SARS-CoV-2 with the lowest side effects and toxicity. Further research has shown that *Allium sativum* has the potential to decrease the expression of proinflammatory cytokines and to reverse the immunological abnormalities to more acceptable levels[81]. In addition, *Allium sativum* bulb has alkaloids as the main photochemical that targets cough, fever and myalgia, which are COVID 19 symptom[4]. Onion and garlic are important plants which could be used as an alternative treatment for viral infection and for the prevention of severe COVID 19 disease development because their phytochemicals have been observed to block the formation of protein and genetic material in the virus [78]. Therefore, *Allium sativum* may be used as a preventive measure against COVID-19 infection for the sole role of boosting immune system cells and in repressing the production and secretion of proinflammatory cytokines.

Azadirachta indica (neem) is a plant that has found varied use in ecological, medicinal, and agricultural sectors. It has been classified as a highly promising plant species that can treat COVID-19 symptoms because it is the source of the key phytochemicals that have relevant pharmacological activities like antiviral, anti-inflammatory, immunostimulant, or containing secondary metabolites with confirmed anti-SARS-CoV-2 activity[87]. Leaves of neem plant are traditionally boiled and consumed for treatment of fever, with reported anti-inflammatory effects in animal studies. Neem plays a satisfactory role in the treatment of infectious diseases due to its phyto-ingredients that include limonoids, nimbin and nimbolide[82]. Other phytochemicals with the potential of treating COVID 19 symptoms (cough, fever, and myalgia) include alkaloids, phenolics, tannins and terpenoids. More than 140 chemically active compounds have been isolated from different parts of this plant including flowers, leaves, seeds, roots, fruits, and bark and are being used traditionally as a cure for many diseases[83]. Therefore, its biological and pharmacological activities can be attributed to these active compounds which include antiplasmodial, antitrypanosomal, antioxidant, anticancer, antibacterial, antiviral, larvicidal and fungicidal activities[84].

In silico docking studies have demonstrated that neem leaf extracts and its phytochemicals such as flavonoids and polysaccharides have direct antiviral effects against various viruses including dengue[85]. Molecular docking has shown that nimbaflavone, rutin, and hyperoside compounds have perfect binding capabilities with reported conserved residues (ASP302, SER50) of influenza virus nucleoprotein that is involved in the binding of drugs[83]. Further, specific to SARS-CoV-2, molecular docking studies have demonstrated that the neem derived compounds nimbolinA, nimocin, and cycloartanols have the potential of binding to envelope (E) and membrane (M) glycoproteins of the SARS-CoV-2 and act as inhibitors[86].

Many studies on COVID-19 treatment are focused on substances that strengthen the immune response by enhancing phagocytic activity, increasing antibody response or by immune modification by immune cells[87]. Several studies have indicated that plant extracts' utility may provide these immune boosting, modulation, and preventive efficacy and specifically, the following plants have been used to purposely boost the immune system and serve as immunomodulators in relation to COVID-19 complications:

Nigella sativa is a plant that has been used for many years due to its good immune modulation with antioxidant and anti-inflammatory benefits in severe respiratory disorders [88]. Studies on molecular docking also provide evidences that *N. sativa* improves COVID-19 disease and may have better results than majority of approved drugs. Many bioactive molecules have been identified from *N. sativa* which include thymoquinone, vitamins (like Vitamin E, Folic acid, Pyridoxine, Niacin, Riboflavin, Thiamine), and minerals (like Magnesium, Potassium, Phosphorus, Iron, Copper, Sodium and Calcium)[89].

Some phytochemicals like thymoquinone have been documented to possess immunomodulation effects. Thymoquinone[90] as an immune modulator has been shown to provide much benefit as a gene regulator, anti-proliferative, an antioxidant, and provide antiviral activity in respiratory disorders[91]. Thymoquinone decreases the expression of mRNA of interferon genes (IFN-α, IFN-β) by suppressing IRF-3 through phosphorylation of TANK-binding kinase 1[92]. This plant is very effective in the management of inflammation in the lungs as studies indicate that *N. sativa* has also an ameliorating effect against leukocytes[93]. The thymoquinone also inhibits the release of histamine from mast cells through reduction of calcium influx by blocking protein kinase C and oxidation[94]. Thus, Thymoquinone has the potential to provide immune modulation and ability to inhibit immune inflammatory responses because of cytokine storm of IL-1, IL-10, IL-6, IL-18, NF-κB and TNF-α,[95]. Besides Thymoquinone, a molecular docking has shown that α- hederin and Nigellidine found in *N. sativa* seeds can inhibit COVID-19 since this compound may target papain-like protease (PLPro), spike protein (SP) and 3C-like protease (3PLPro) found in SARS virus[96].

Ocimum sanctum (Holy Basil, Tulsi) is also a well-known medicinal plant for its therapeutic potential as anti-viral, anti-inflammatory and an immune booster[97]. *Tulsi* is already being used in the management of COVID-19 and chest infections like pneumonia and cough[98]. Studies have assessed the immunomodulatory effect of *Tulsi* leaves, where significant increase of T helper and Natural Killer cells was reported[99]. These cells are critical in the fight against viral infections hence *Tulsi* is a potential candidate for immune modulation in the management of COVID-19. A docking study showed that the binding affinity of *Tulsi* extract compounds mainly 7 photophilic compounds and dihydrodieuginol B, with SARS CoV receptors is high[100] hence further studies may qualify *Tulsi* as a preventive and an immune modulator in the management of COVID-19.

PiperNigrum L. (Black Pepper) is another medicinal plant and is extensively used worldwide. It is highly enriched with over 600 phytochemicals which vary from *terpenes, lignans, and neolignan, alkaloids/amides* with several medicinal properties among them antiviral and anti-inflammatory/immune properties[101]. *Astragalus membranaceus (Astragalus)* roots have also been shown to be good immune modulators very powerful in strengthening the immune response against viral diseases and a good anti-inflammatory agent[102]. It was observed to increase LITAF, IL-12, IL-10, IL-4, IL-6, and antibody titres within the first week of treatment.

The *Cinchona* bark is a medicinal plant rich in quinine, an alkaloid that is very much known for its effective treatment of malaria. This plant also has antiviral properties and has been explored in the treatment of SARS-CoV-1[103] and has been shown to be a good anti-inflammatory[104]. *Sambucus nigra (Elderberry)*, a purple berry widely available in Europe and Western Asia is another potential candidate for COVID-19 treatment through immune modulation. This medicinal fruit is rich in flavonoids with benefits as an antioxidant and anti-inflammatory agent which may help in protecting health cells from harmful free radicals and boost immunity against respiratory infections[105]. A fresh *ginger* has also been shown to help in stimulating mucosal cells to secrete IFN-β which contributes much in the fight against viral infections[106]. Many other plants have also been shown to have anti-inflammatory activity however much has not been done to elucidate the immune modulation activities, therefore, need further research to give more insight.

Conclusion And Recommendations

The herbal and plant-based compounds are eco-friendly, target-specific, less expensive and highly efficacious against a wide range of disease causing agents including SARS-Cov-2. Therefore, botanicals have been found to be suitable alternatives for new and selective agents for the treatment of COVID-19 and associated infections.

Future prospects should focus on:

1. Usage of novel strategies like nanobiotechnological advancements in delivery of phytochemicals to the viruses as they have been found to enhance delivery and the slow release of the compounds of interest for longer periods will increase efficacy.
2. Synergistic effects of the most promising medicinal plants to explore their potential in inhibiting viral activity and stimulation of immune system activity.

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Declarations

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Author Contributions

SM and EO were involved in the design of the review work. Each of the five authors had a section of the manuscript to work on with a view to drafting the manuscript and manuscript review. SM further compiled all the sections to make the first draft of the manuscript. All the authors read the manuscript, made corrections on it, SM worked on the revisions and finally all the authors read and approved the final manuscript.

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