Revista Brasileira de Farmacognosia (2021) 31:142–161
https://doi.org/10.1007/s43450-021-00132-x

REVIEW

Coronavirus Disease 2019 and Herbal Therapy: Pertinent Issues Relating to Toxicity and Standardization of Phytopharmaceuticals

Kayode Komolafe[1] · Titilope Ruth Komolafe[1,2] · Toluwase Hezekiah Fatoki[2] · Afolabi Clement Akinmoladun[2] · Bartholomew I. C. Brai[1] · Mary Tolulope Olaleye[2] · Afolabi Akintunde Akindahunsi[2]

Received: 2 December 2020 / Accepted: 19 January 2021 / Published online: 11 March 2021

Abstract
Coronavirus disease 2019 (COVID-19) is a virulent viral disease that has now become a public health emergency of global significance and still without an approved treatment regimen or cure. In the absence of curative drugs and with vaccines development still in progress, alternative approaches to stem the tide of the pandemic are being considered. The potential of a phytotherapeutic approach in the management of the dreaded disease has gained attention, especially in developing countries, with several claims of the development of anti-COVID-19 herbal formulations. This is a plausible approach especially with the increasing acceptance of herbal medicine in both alternative and orthodox medical practices worldwide. Also, the established efficacy of herbal remedies in the treatment of numerous viral diseases including those caused by coronaviruses, as well as diseases with symptoms associated with COVID-19, presents a valid case for serious consideration of herbal medicine in the treatment of COVID-19. However, there are legitimate concerns and daunting challenges with the use of herbs and herbal products. These include issues of quality control, unethical production practice, inadequate information on the composition, use and mechanisms, weak regulatory policies, herb-drug interactions and adverse reactions, and the tendency for abuse. This review discusses the feasibility of intervention with herbal medicine in the COVID-19 pandemic and the need to take proactive measures to protect public health by improving the quality and safety of herbal medicine deployed to combat the disease.

Keywords Herbal medicine · Traditional medicine · Herb-drug interaction · Standardization · Drug control · Phytochemicals

Introduction

Coronavirus disease 2019 (COVID-19) is a virulent viral disease that was first reported in Wuhan, a city in the Hubei province of China where it was believed to have originated in December 2019. The virus causing the disease which mainly targets the human respiratory system was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses in February 2020 (Xie et al. 2020). COVID-19 is now a public health emergency of global significance, and as of 30th June 2020, the World Health Organization (WHO), which has since upgraded its threat status to the "highest" level, reported over 10 million confirmed global cases with 503,862 deaths and an overall mortality rate of 4.8%. A large chunk of the confirmed cases and deaths were recorded in the Americas (5,136,705 cases and 247,129 deaths) and Europe (2,692,086 cases and 197,254 deaths). Unfortunately, the continent of Africa which had previously recorded far fewer incidences and deaths has now witnessed an alarming surge in the total number of cases (297,290) and deaths (6010) (WHO 2020 June 30). An underestimation of infections and deaths, especially in Africa countries, is almost certainly due to the limitations of testing and monitoring.

"Coronaviruses," from the Latin word "corona" or crown to depict their crown-like morphology when viewed under an electron microscope, are enveloped positive sense, single-stranded RNA viruses belonging to the family of coronaviridae and with diameter sizes ranging between 60 and 140 nm (Singhal 2020; Stanley et al. 2020). The Coronavirinae, being a sub-family of the

✉ Kayode Komolafe
kayode.komolafe@fuoye.edu.ng

1 Department of Biochemistry, Faculty of Science, Federal University Oye-Ekiti, PMB 373, Oye-Ekiti, Nigeria

2 Department of Biochemistry, School of Sciences, The Federal University of Technology, PMB 704, Akure, Nigeria

coronavidae family, is subdivided into four genera, namely the alpha, beta, gamma, and delta coronaviruses (Fehr and Perlman 2015). The COVID-19-causing virus, SARS-CoV-2, belongs to the beta genera. Coronaviruses contain a genome approximately 30 kb in size with a 5′ cap structure along with a 3′ poly (A) tail which allows for its role as mRNA necessary for the translation of the replicase gene to proteins. The gene encodes the nonstructural proteins and occupies almost 70% of the genome, unlike the structural and accessory proteins which make up just a little above 30% of the viral genome. A leader sequence and untranslated region that contains multiple stem-loop structures required for RNA replication and transcription are contained at the 5′ end of the viral genome (Fehr and Perlman 2015). Cryo-electron tomography and cryo-electron microscopy revealed that the coronavirus virions are spherical. About four main structural proteins that are encoded within the 3′ end of the viral genome and have been identified in coronavirus particles. These include the spike (S) proteins needed to gain access to the endoplasmic reticulum of the host cells and which give the distinctive spike structure on the viral surface and the appearance of a solar corona (Beniac et al. 2006) and the membrane (M) proteins thought to give the virion its shape (Armstrong et al. 1984). Others are the envelope (E) protein that could be involved in the pathogenesis and lethality of the virus as well as the nucleocapsid (N) proteins involved in RNA binding (Chang et al. 2006; Nieto-Torres et al. 2014; Fehr and Perlman 2015).

The β genera coronaviruses, to which SARS-COV-2 belongs, are notorious for causing human infections and outbreaks around the world (Singhal 2020). In 2002, a group 2b β-coronavirus, SARS-CoV was identified as the culprit behind the severe acute respiratory syndrome (SARS) outbreak that originated in the Guangdong Province of China. The disease affected over 8000 people with over 700 deaths and a mortality rate of 7% over 1 year before it was contained. In 2012, another group 2c β-coronavirus, named Middle East respiratory syndrome-CoV (MERS-CoV) was responsible for a series of highly pathogenic respiratory tract infections in Saudi Arabia and other parts of the Middle East with a fatality rate of approximately 50% (Zaki et al. 2012; Fehr and Perlman 2015). Although the disease did not become a major outbreak as envisaged or projected, sporadic cases continued throughout 2013 and by 2014 a total of 855 cases, with 333 deaths documented by the European Center for Disease Prevention and Control (Fehr and Perlman 2015). Of course, the coronavirus disease 2019 caused by SARS-CoV-2, another β-coronavirus, now remains by far the deadliest and most significant β-coronavirus outbreak in the last decades. SARS-CoV-2 is both humidity and heat sensitive and they could be inactivated when subjected to a temperature above 50 °C for 30 min (ECDPC 2020) or stored for a long period at a temperature below −80 °C. Apart from heat, they can be effectively inactivated by solutions containing 75% ethanol or chlorine like those present in frequently recommended hand sanitizers (Zumla et al. 2016; Stanley et al. 2020; Zhou et al. 2020). In terms of the survival of SARS-CoV-2 on different surfaces, the virus is capable of being viable up to 3 h in the air post aerosolization, up to 24 h on paper and clothing, and up to 2–3 days on plastic and stainless steel (ECDPC 2020). Coronavirus orchestrates deleterious inflammatory changes mainly in the respiratory system as well as in the enteric and central nervous systems of animals and humans (Fehr and Perlman 2015; Stanley et al. 2020). Apart from the lung which is the major target organ of COVID-19, the disease also affects and damages the kidneys, heart, genitals, and liver (Ma et al. 2020; Xie et al. 2020). The hallmarks of COVID-19 that make it more dangerous and dicey than previous forms of coronavirus diseases, i.e., MERS and SARS, are related to its long incubation period and the relatively low pathogenicity (Lippi and Plebani 2020). These two factors contribute immensely to the sustained incidences and the amplification of the disease outbreak in China and all over the world.

COVID-19 has come with a huge economic toll and social burden having forced almost all the countries of the world at one point or the other to partial or total lockdown ranging from weeks to months. The disease also poses a great challenge to medical personnel saddled with the responsibility of managing COVID-19 patients since it requires immense expertise, self-control, and commitment to assuage the risk of infection as well as the constant need for increased manpower and materials. The deleterious effects of the pandemic on economic, social, and medical statuses of countries in the world will surely remain with mankind for a while.

Discussion

Epidemiology

COVID-19 can affect anyone irrespective of age. Children, however, are relatively less susceptible to COVID-19 infections and are also likely to present with milder symptoms than adults when infected (Zimmermann and Curtis 2020). Even though a few cases of the severe symptoms of the disease have been reported, the predominant clinical condition in children is febrile upper respiratory tract disease and the course of the disease is usually milder and shorter. Also, in pregnant women, the clinical manifestations are mostly mild although few incidences of severe disease and fatal outcomes have been registered (Zaigham and Andersson 2020). Underlying health conditions that predispose to negative prognosis include chronic respiratory disease, diabetes, hypertension, cardiovascular disease, obesity, and compromised immune system (Petrilli et al. 2020; Singhal 2020). People with these underlying health conditions and the elderly ones with reduced immunity are more likely to be at higher risk for severe COVID-19 illness (Singhal 2020). Data obtained from the study of

4203 mostly Asian patients underpinned hypertension, cardiovascular disease, and diabetes as the most common comorbidities (ECDPC 2020; Zhang and Liu 2020).

Pathology and Pathogenesis

Covid-19 is a disease of the lung and the histological architecture of a diseased patient presents diffuse alveolar damage like other respiratory illnesses caused by viruses like SARS-CoV and MERS-CoV. However, SARS-CoV-2 infection could be distinguished by the presence of endothelial injury of wide severity, blood clot or thrombosis, microangiopathy, and angiogenesis. The pathogenesis of COVID-19 is believed to involve the invasion of the alveolar epithelial cells by the SARS-CoV-2 virus via binding to the angiotensin-converting enzyme-2 (ACE2) receptor through the coronavirus spike (S) protein. The invasion of the epithelial cells is thought to promote direct toxicity and exacerbate immune response which could lead to massive cytokines activation and mobilization capable of inflicting lung injury that could lead to respiratory failure and death in severe cases (Chang et al. 2006; Jiang et al. 2020; Ren et al. 2020; Xie et al. 2020). SARS-CoV-2 could invade other organs with the presence of ACE2 including the heart, kidney, and intestines causing lethal damages and a pathological condition called multiple organ dysfunction syndrome (MODS) (Xie et al. 2020). Levels of inflammatory mediators and cytokines including the interleukins (IL-6, IL-7, IL-10), interferon gamma-induced protein 10, monocyte chemoattractant protein-1, macrophage inflammatory protein 1a, and tumor necrosis factor-α (TNF-α) are known to be elevated in severe COVID-19 cases and the excessive activation of these factors might be linked with poor prognosis as it could be an indication of the progression from the mild form to the severe form of the disease (Gong et al. 2020; Singhal 2020; Xie et al. 2020). Another potentially useful indicator of severity and prognosis is the viral load which could be 60 times higher in severe patients compared with mild cases (ECDPC 2020; Liu et al. 2020).

Symptoms and Clinical Presentation

The clinical presentations of COVID-19 are known to be varied as they range from an asymptomatic state to acute respiratory distress syndrome and multi-organ dysfunction (Singhal 2020). Observational study and documentation across various health facilities have indicated that the most common symptoms of COVID-19, in mild or moderate cases, are also common to other respiratory infections. These include, in the order of frequency, headache, anosmia, nasal airway obstruction, cough, fatigue, muscular pain or myalgia, rhinorrhea or runny nose, loss of taste, sore throat, fever (ECDPC 2020; Lechien et al. 2020) and gastrointestinal symptoms like abdominal pain, vomiting, and diarrhea in some cases (Docherty et al. 2020; ECDPC 2020). The disease could progress in some patients, after a week, to more severe forms like pneumonia and respiratory failure which is the major causative agent of fatality in severe COVID-19 cases (Xie et al. 2020; Zhang et al. 2020).

Transmission

SARS-COV-2 is contained in fluids and droplets in cough or sneeze of infected persons and the disease could be contracted when in contact with infected droplets in the air or when contaminated surfaces are touched. The RNA of the virus could be detected in respiratory tract specimens 24–48 h before clinical symptoms and up to 8 days in mild cases or longer in severe cases. SARS-COV-2 RNA is also detectable in feces, blood, saliva, urine, tears, and breast milk (ECDPC 2020). The infectivity of the detectable RNA in the substances of human origin remains to be proven. There are cases of asymptomatic individuals that have been confirmed through laboratory testing to have the virus. These individuals could proceed to develop some symptoms at a later stage of infection or remain asymptomatic throughout (Luo et al. 2020). Transmission of the disease from asymptomatic carriers is possible even though the risk of being infected by asymptomatic or even pre-symptomatic patients is considerably higher (ECDPC 2020). Symptomatic patients can be infectious as long as symptoms persist even when undergoing clinical recovery.

Testing for COVID-19

Diagnostic test samples obtained from the upper (nasopharyngeal/oropharyngeal swabs, nasal aspirates, nasal wash, or saliva) or lower (sputum or bronchoalveolar lavage) respiratory tracts have all been used for the detection of SARS-CoV-2. Different types of detection assays could be used for COVID-19 diagnostic testing and screening depending on the expected outcome. These include nucleic acid test to detect the presence of SARS-CoV-2 RNA using RT-PCR techniques, antigen tests to detect the presence of viral antigen, and the antibody test to detect the presence of antibodies generated against the virus using techniques including enzyme-linked immunosorbent assays, chemiluminescence assays, and lateral flow assays. Also, whole genome sequences can be performed to determine the sequence of the virus in a sample to detect variants. Sensitivity for nasopharyngeal swab tests in patients was found to be about 98% compared with 91% for saliva tests (ECDPC 2020; Gorbalenya et al. 2020).

Orthodox Treatment for COVID-19

As of now, there is no specific, clinically approved treatment regimen for COVID-19; hence, all interventions are basically supportive and symptomatic. Patients are made to undergo isolation to prevent infecting others and those present with mild symptoms are made to remain hydrated while placing them on diet and drugs to control fever and cough (Singhal 2020). Plasma from recovered patients has been used to treat patients with severe cases while various antiviral drugs such as lopinavir-ritonavir, favipiravir, ribavirin, molnupiravir, and azithromycin have also been used with varying degrees of success (Xie et al. 2020). Molnupiravir (MK-4482/EIDD-2801) is a prodrug of the synthetic nucleotide derivative *N*(4)-hydroxycytidine originally developed for the treatment of the influenza virus. It is an orally active antiviral drug which mechanism of action involves the introduction of copying errors during viral RNA replication (Cox et al. 2020). Safety issues related to the use of some of the drugs are documented. Favipiravir limitations include its teratogenicity (Delang et al. 2018), and ability to cause corrected QTc interval prolongation (Chinello et al. 2017), transient thrombocytopenia and lipaemia (Trivedi et al. 2020). Remdesivir could elevate liver enzymes and contains sulfobutylether-β-cyclodextrin, an agent capable of worsened renal impairment; hence, the drug is not recommended for use by those with severe liver disease or renal impairment (Trivedi et al. 2020). Although molnupiravir affords promising potential in the reduction of upper respiratory tract SARS-CoV-2 load and suppressed animal-to-animal transmission in ferrets population, the possible side effects are yet to be deduced (Cox et al. 2020).

Use of Herbs in Disease Management

In the last few decades, the patronage of herbal medicine has surged and now boasts of a huge market having been embraced by many developed countries in Europe and North America under the umbrella of complementary and alternative medicine (CAM). It is now widely believed that CAM has the potential of affording healthier living in the world (Nissen 2010; Ekor 2014). This is unlike in the past when the bias against traditional medicine was strong due to the wide acceptance of allopathic medicine, out-of-context criticism by those with little knowledge of herbal medicine who tend to focus on reported toxicities, institutionally driven media propaganda, and influence of western beliefs.

Approximately 80% of the world population, many of whom live in developing countries, rely on herbal medicine as the primary source of healthcare due to several reasons ranging from ready accessibility, affordability, and cultural acceptance (Bandaranayake 2006; Ekor 2014). The rich repertoire of bioactive phytochemicals in plants makes them very essential to drug discovery and a source of viable alternative medicines. Reports have emerged about people, especially in the developing African and Asian countries, employing herbal medicine to treat COVID-19 (Chinsembu 2020). Recently, the World Health Organization (WHO) and Africa Centre for Disease Control (CDC) constituted a committee to assist and guide African countries on the use of herbal medicine against the novel coronavirus (Forku 2020). The WHO, however, has cautioned against adopting products that have not undergone rigorous clinical trials to ascertain their safety and effectiveness against COVID-19 following its meeting with 70 African traditional medicine experts to discuss the role of traditional medicine during the pandemic (Gikandi 2020). Reports have emerged about people, especially in the developing African and Asian countries, employing herbal medicine to treat COVID-19. A review of natural compounds that could be useful to the management of SARS-COV2 and their probable mechanisms of actions was recently reported (Chinsembu 2020). Recently, the World Health Organization (WHO) and Africa Centre for Disease Control (CDC) constituted a committee to assist and guide African countries on the use of herbal medicine against the novel coronavirus (Forku 2020). The WHO, however, has cautioned against adopting products that have not undergone rigorous clinical trials to ascertain their safety and effectiveness against COVID-19 following its meeting with 70 African traditional medicine experts to discuss the role of traditional medicine during the pandemic (Gikandi 2020).

Efficacy of Phytopharmaceuticals in Viral Diseases

Viral infections have formed part of human civilization with an increasing number of new cases, morbidity, and mortality in modern times. Influenza virus, AIDS (acquired immunodeficiency syndrome), dengue, Ebola, and SARS (severe acute respiratory syndrome) are among the aggressive viral diseases with tens of millions of new infections with associated mortality yearly. Many types of viruses have no approved drugs and vaccines are available for only a few like hepatitis A and B, mumps, and varicella (Nováková et al. 2018; Ben-Shabat et al. 2020). The efficacy of medicinal plants in the management of viral diseases has been demonstrated in studies performed *in vitro*, *ex vivo*, and *in vivo*. Antiviral properties could be due to their chemical constituent including polyphenols (such as phenolic acids, flavonoids, proanthocyanidins, and tannins), saponins, quinones, terpenes, lignins, alkaloids, polysaccharides, steroids, and thiosulfonates (Tang et al. 2012; Anu and Thomas 2019; El-Saber Batiha et al. 2020). The antiviral effects of some plants are attributable to the synergistic or additive effects of their constituents whereas the effects of others have been narrowed down to specific chemical markers present in such plants.

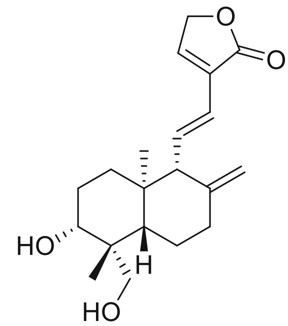
Antiviral Medicinal Plants

Moringa oleifera Lam.

The antiviral property of *Moringa oleifera* Lam., Moringaceae, has been attributed to the flavonoid kaempeferol (Singh et al. 2020). The aqueous extract of the plant inhibited the growth of Newcastle disease virus in chicken eggs (Monera and Maponga 2012; Popoola and Obembe 2013). In mice, the ethanol extract delayed the development of skin lesions and mortality caused by the herpes simplex virus type 1 (HSV-1). Treatment with the leaf powder has also been correlated with improved immunity and ability to fight infections among HIV/AIDS patients in some parts of Africa while also slowing down the antiretroviral drug-induced apoptosis of helper T cells in patients on active antiretroviral therapy (HAART) (Ogbuagu et al. 2016; Singh et al. 2020). According to Ogbuagu et al. (2016), the HIV/AIDS patients received 20 g daily of *M. oleifera* leaf powder mixed with normal meal for 60 days and the pre- and post-CD4 counts were analyzed. Findings revealed markedly increased post CD4 counts compared with pre-CD4 counts in male (496.1 ± 61.52 cells/mm^3 vs 362.7 ± 49.68 cells/mm^3) and female patients (547.6 ± 57.9 cells/mm^3 vs 459.7 ± 40.65 cells/mm^3).

Andrographis paniculata (Burm. f.) Wall.

Dengue, a mosquito-borne viral disease caused by dengue virus (DENV), is assuming an alarming dimension with currently no vaccine or antiviral drugs for its control. Ali-Seyed and Vijayaraghavan (2020) reviewed the anti-dengue virus activities of *Andrographis paniculata* (Burm.f.) Wall, Acanthaceae, a medicinal plant common to tropical Asian countries. Treatment of dengue virus patients with herbal mixtures containing *A. paniculata* for a week caused considerable symptomatic relief and improvement of the dengue fever (Tang et al. 2012). The plant possesses antimicrobial and anti-inflammatory properties as well as anti-larval activity for the disease-causing mosquito and insects. Bicyclic diterpenoid lactones and diterpenoids components including andrographolide, neoandrographolide (NAND), and 14-deoxy-11,12-didehydroandrographolide (**1**) (DDAND) have been identified as the active phytochemicals responsible for the activities (Ali-Seyed and Vijayaraghavan 2020). According to the report, one of the active phytoconstituents of the plant, 14-deoxy-11,12-didehydroandrographolide, exerts a time-dependent inhibitory action on thrombin-induced platelet aggregation (Thisoda et al. 2006) which is one major mechanism of dengue viral infections. Active constituents in the plant exert antiplatelet effect by modulating platelet-activating factor through various signaling pathways including eNOS-NO/cyclic-GMP PLC 2-PKC and PI3 kinase/Akt-MAPKs (Ali-Seyed and Vijayaraghavan 2020; Lu et al. 2011).



1

Carica papaya L.

In addition, studies have shown that treatment with papaya leaf extract significantly increased the platelet count and reversed the hallmark thrombocytopenia associated with dengue fever (Dharmarathna et al. 2013; Singh et al. 2020) within 24 h in five patients (Kala 2012). The bleeding in dengue patients is associated with a decreased platelet count accompanied by increased vascular permeability and plasma leakage. Hence, a study conducted to evaluate whether papaya leaf extract could protect blood cells against stress-induced gave a positive result (Ranasinghe et al. 2012). Also, the leaf extract of *C. papaya* could decrease the production of inflammatory cytokines in the dengue virus-infected AG129 mice (Norahmad et al. 2019), downregulate DENV NS1 envelop protein and stimulate IFN-α expressions in THP-1 cells (Sharma et al. 2019; Singh et al. 2020).

Allium sativum L.

Garlic (*Allium sativum* L., Liliaceae), an aromatic herbaceous annual spice, has a long history of use in herbal medicine for the treatment of viral infections like cold and influenza (Stuart 2014). Folkloric herbal mixtures prepared from mature garlic cloves have been established to enhance the immune system (El-Saber Batiha et al. 2020). Garlic extracts have been documented to exhibit antiviral activities against herpes simplex type 1 and 2, human rhinovirus type 2, human cytomegalovirus (HCMV), parainfluenza virus type 3, and influenza B, via the production of neutralizing antibodies. This has been ascribed to the presence of several phytochemicals like allicin, allyl methyl thiosulfinate, and methyl allyl thiosulfinate (Sawai et al. 2008; Gruhlke et al. 2016; El-Saber Batiha et al. 2020). Some of these active garlic constituents exhibit their actions via mechanisms ranging from the prevention of critical thiol enzymes and adhesive interaction and fusion of leukocytes to enhancing natural killer-cell (NK-cell) activity that destroys virus-infected cells (El-Saber Batiha et al. 2020).

Lannea schweinfurthii Engl.

Methanol extract of *Lannea schweinfurthii* Engl., Anacardiaceae, stem bark shows strong antiviral activities against herpes simplex virus type 1, vesicular stomatitis virus T2, Coxsackie B2, and Semliki Forest A7 in a research carried out by Maregesi et al. (2008). *In vitro* study conducted by Maregesi et al. (2010), using the microdilution assay, also demonstrated the anti-HIV activities of aqueous and methanol extracts of *L. schweinfurthii* stem bark against human immunodeficiency virus type 1 (HIV-1, IIIB strain) and type 2 (HIV-2, ROD strain) and established the superior efficacy of the 80% methanol extract (Maroyi 2019).

Pterocaulon spp.

Furthermore, the use of several species of the genus *Pterocaulon*, Asteraceae, as decoctions or infusions in ethnomedicine is widespread. Apart from coumarins that are abundant across the genus, flavonoids, terpenes, and polyacetylenes have also been identified as active constituents (Medeiros-Neves et al. 2018). Extracts and compounds isolated from these species have been tested for antiviral activities against DNA (human cytomegalovirus) and RNA viruses (Ross River virus and poliovirus type 1) with positive outcomes against poliovirus. In a crystal violet assay conducted at a non-cytotoxic concentration of 6–52 μg/ml, the extract of *Pterocaulon* spp. inhibited poliovirus-induced CPE by more than 75% (Semple et al. 1998). Similarly, a flavonoid, chrysosplenol C, isolated from the extract demonstrated activity against poliovirus with an EC50 of 0.27 μg/ml (0.75 μM) (Semple et al. 1999; Medeiros-Neves et al. 2018).

Illicium verum Hook. f.

Star anise (*Illicium verum* Hook. f., Schisandraceae), an evergreen, shrub-like tree with star-shaped fruit, is widespread and popularly sought for its culinary and ethnomedicinal values in southwestern Asia. Many active secondary metabolites belonging to the polyphenolic, flavonoid, tannin, alkaloid, triterpenoid, saponin, and anthraquinone classes of phytochemicals were found to be present in star anise (SA) and many of these are potent antiviral agents. A popular and widely studied metabolite that is abundant in SA, shikimic acid (3,4,5-trihydroxy-1-cyclohexene-1-carboxylic acid), is a key intermediate of the shikimic acid pathway and is used in the industrial synthesis of the antiviral drug oseltamivir phosphate (OSP) (Candeias et al. 2018). This drug effectively inhibits surface protein neuraminidase (NA) enzyme of the seasonal influenza virus types A and B, avian influenza virus H5N1, and human influenza virus H1N1 (Bradley 2005). Apart from shikimic acid, several other molecules with prominent antiviral effects have also been identified in SA. These include the novel illiverin A and tashironin A as well as other aromatic compounds with considerable anti-HIV activity (Song et al. 2007). The inhibitory efficacy of essential oils from star anise against HSV-1 and HSV-2 has also been demonstrated *in vitro* (Patra et al. 2020). Extracts of star anise not contaminated with the Japanese variant of the plant could be well tolerated in animals to a large extent. However, oral use of up to 500 mg/kg of the ethylacetate extract has been linked with convulsion and lethal toxicity in mice as a result of the veranisatins phytoconstituents which, at lower dosages, are also responsible for the analgesic and sedative properties of the plant (Wang et al. 2011).

Lysiphyllum strychnifolium (W. G. Craib) A. Schmitz

A recent study has suggested that *Lysiphyllum strychnifolium* (W. G. Craib) A. Schmitz, Fabaceae, could be a promising source of novel neuraminidase inhibitors active against the influenza virus since the ethanolic extracts of the leaves and stems of the plant demonstrated considerable inhibitory activities against avian influenza virus subtype H5N1 (Sukprasert et al. 2020).

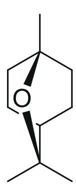
Antiviral Phytochemicals

Polyphenolics and Flavonoids

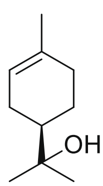
The antiviral effects of some common flavonoids and phenolic acids widely present in dietary and medicinal plants against life-threatening viral infections have been established (Anu and Thomas 2019). Flavonoids are a ubiquitous group of bioactive phytochemicals in plants and plant-based food. The inhibitory efficacy of flavonoids such as baicalin, myricetin, quercetin, pinocembrin, and kaempferol-7-*O*-glucoside against HIV1/HIV 2 via various mechanisms has been demonstrated (Cushnie and Lamb 2005; Anu and Thomas 2019). (-)-Epigallocatechin gallate (EGCG) could prevent HIV attachment and infection by binding to CD4 expressed on T-cell and destroying the phospholipids in the viral envelope (Anu and Thomas 2019). Similarly, EGCG and other flavonoids like myricetin, epicatechin gallate, gallocatechin gallate, and luteolin proved to be potent against the dreaded Zika virus responsible for microcephaly and Guillain-Barre syndrome in the infants (Carneiro et al. 2016; Lim et al. 2017; Anu and Thomas 2019). For instance, rutin is effective against HSV 2/HSV 1, avian influenza virus, and parainfluenza virus while its aglycone, quercetin, is toxic to a host of viruses including poliovirus, dengue virus, rhinovirus, respiratory syncytial virus, Epstein-Barr virus, adenovirus, and HCV (Ben-Shabat et al. 2020). The antiviral mechanisms of quercetin could involve direct inhibition of replication, as in the case of dengue virus type-2 (Zandi et al. 2011), viral genome transcription, and protein synthesis, as in the case of rhinoviruses (Ganesan et al. 2012), or by affecting the processes of viral attachment and entry (Ben-Shabat et al. 2020). The antiviral properties of other flavonoids are well documented and could proceed by mechanisms including inhibiting nucleoprotein production in viruses like the avian influenza H5N1 virus (Sithisarn et al. 2013; Ben-Shabat et al. 2020). Another flavone glycoside, baicalin, has demonstrated activity against many viruses, including dengue virus (Moghaddam et al. 2014), respiratory syncytial virus (Shi et al. 2016), enterovirus (Li et al. 2015), human immunodeficiency virus (Li et al. 2000), and hepatitis B virus (Huang et al. 2017) through various mechanisms (Ben-Shabat et al. 2020).

Terpenoids

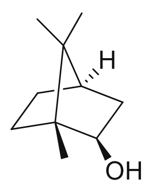
Apart from flavonoids, terpenoids hold promising antiviral properties. Over 80% HSV-1 inhibition was reported for monoterpenoids including 1,8-cineole (**2**), thymol, α-terpineol (**3**), α-terpinene, and γ-terpinene (Astani et al. 2010; Yang et al. 2020). Isoborneol (**4**) present in many volatile oils could totally inhibit HSV-1 replication at a concentration of 0.06%. Similarly, tereticornate A (**5**) isolated from *Eucalyptus globulus* Labill., Myrtaceae, showed higher anti-HSV-1 potency (IC_{50} 0.96 μg/ml) than the standard antiviral drug, acyclovir (IC_{50} 1.92 μg/ml) (Yang et al. 2020). Putranjivain-A (**6**), a diterpene from the plant *Euphorbia jolkinii* Boiss., Euphorbiaceae, reportedly showed considerable anti-HSV-2 potency (IC_{50}: 6.3 μM), and similar effects against HSV-1 were shown by triterpenes like moronic acid (**7**) (EC_{50} 3.9 μg/ml) and betulonic acid (**8**) (EC_{50} 2.6 μg/ml) (Cheng et al. 2004; Kurokawa et al. 1999; Yang et al. 2020). Significant inhibition of hepatitis B virus (HBV) and hepatitis C virus (HCV) was demonstrated by artemisinin and its derivatives (Wohlfarth and Efferth 2009). A semisynthetic derivative of artesiminin, artesunate, is a more effective inhibitor of hepatitis B surface antigen (HBsAg) and it is capable of a synergistic interaction with lamivudine (an orthodox anti-HBV drug). Also, a pentacyclic triterpenoid, betulinic acid, that could be found in *Syzygium claviflorum* (Roxb.) Wall.ex Steud., Myrtaceae, and its derivatives possess anti-HIV activity. These compounds are capable of disrupting fusion between the HIV virus and cells as well as inhibiting reverse transcriptase activity and assembly of the virus (Yang et al. 2020). Common triterpenoids of plant origin like oleanolic acid and ursolic acid could both reduce HCV NS5B RdRp virulence (Kong et al. 2013) and inhibit enterovirus replication (Ben-Shabat et al. 2020; Zhao et al. 2014).



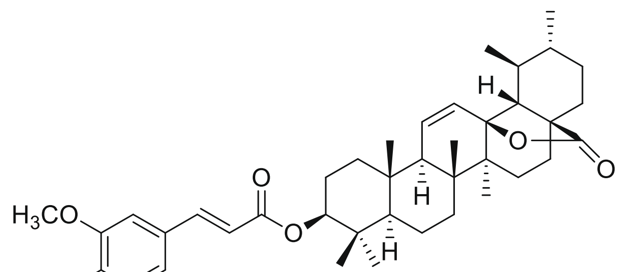
2



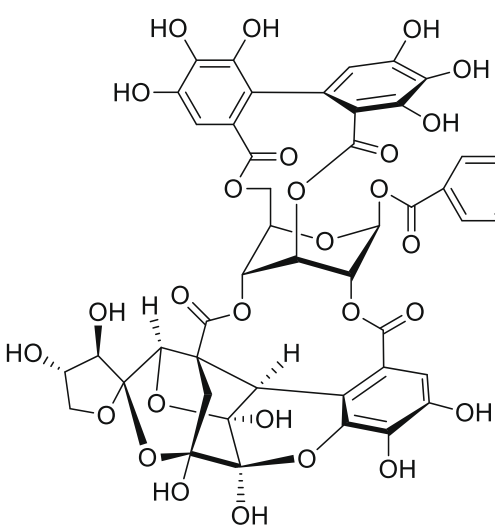
3



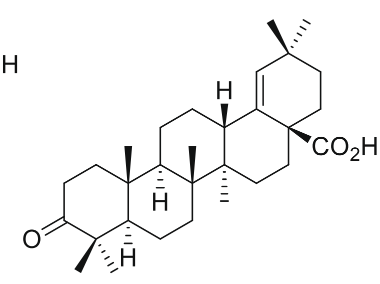
4



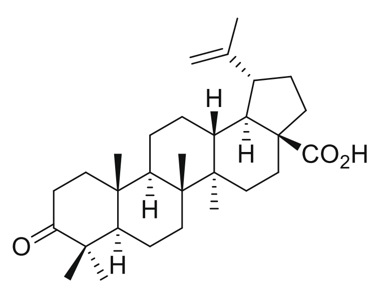
5



6



7



8

Herbs for the Treatment of Coronavirus-Dependent Diseases

Plants and plant products could be useful sources of drug-like molecules for combating coronaviruses-dependent diseases. The 2002 SARS episode witnessed the effective combination of traditional Chinese herbal medicine with western medicine in the treatment of infections with clinically improved symptoms typified by relief/improvement in elevated body temperature, cough and breathing difficulties, and general quality of life (Liu et al. 2012; Li et al. 2020). Yang et al. (2016) demonstrated the toxicity of three medicinal plants, *Camellia japonica* L., Theaceae, *Saposhnikovia divaricata* (Turcz.) Schischk., Apiaceae, and *Dryopteris crassirhizoma* Nakai, Dryopteridaceae, against porcine epidemic diarrhea virus (PEDV) via inhibition of PEDV replication. PEDV is a coronavirus responsible for serious infections and high mortality in pigs. Four structurally representative oleanane-triterpenes characterized from *C. japonica* were found to reduce the RNA levels of GP6 nucleocapsid, GP2 spike, and GP5 membrane protein which are key genes and proteins required for PEDV replication in a comparable or even superior manner to the positive control, azauridin. Coumarins extracted from *S. divaricata* exhibited dose-dependent anti-PEDV activity and a novel coumarin from the plant was shown to exhibit stronger activity than the positive control, azauridine. The authors established the role of functionalization and the importance of structure-function relationship in the antiviral properties of the phytochemicals. Further, the inhibitory activity of *D. crassirhizoma* against PEDV was attributed to the constituent phloroglucinol phytochemicals.

Baicalin, characterized from *Scutellaria baicalensis* Georgi, Lamiaceae, a popular plant in Chinese herbal medicine, was shown alongside established antiviral drugs like lopinavir, ribavirin, and rimantadine, to exhibit detectable *in vitro* antiviral activities in clinical isolates of SARS coronavirus using the fetal rhesus monkey kidney (fRhK-4) cell line (Chen et al. 2004). The use of intravenous baicalin for alternative treatment where available and affordable was suggested. Apart from SARS viruses, baicalin could inhibit HIV-1 at the level of cellular entry, by conjugating with selected chemokines thus interfering with their capacity to activate critical cellular receptors, and at the level of HIV-1 reverse transcriptase by the inhibition of the enzyme possibly via interfering with the binding of viral RNA to the transcriptase near the active site of the enzyme (Chen et al. 2004). A study conducted by Wen et al. (2007) to evaluate several phytocompounds including terpenoids, lignoids, and curcumin for anti-SARS-CoV activities using a cell-based assay measuring SARS-CoV-induced cytopathogenic effect on Vero E6 cells showed promising effects of some of the compounds. The authors submitted that specific abietane-type diterpenoids and lignoids exhibit strong anti-SARS-CoV effects.

The antiviral activity of the ethanol extract of *Sambucus formosana* Nakai, Viburnaceae, a Chinese medicinal herb with ethnomedicinal applications against inflammation and viral infections, and the constituent phenolics, against human coronavirus NL63 was investigated (Weng et al. 2019). The extract exhibited relatively weak cytotoxic but concentration-dependent anti-HCoV-NL63 activity typified by a significant reduction of virus yield, plaque formation, and virus attachment. Phenolic acids from the plant, caffeic acid, chlorogenic acid, and gallic acid, were suggested to be responsible, at least in part, for the antiviral capacity having demonstrated the capacity to reduce the production of progeny HCoV-NL63 particles *in vitro*. The authors pointed out that caffeic acid could play an important antiviral role by influencing the binding of HCoVNL63 to the ACE 2 receptor and co-receptors.

In a study by Li and colleagues (2005) using 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium inner salt (MTS) assay for virus-induced cytopathic effect (CPE), four Chinese medicinal herb extracts with potential antiviral activity were identified. The most potent of the extracts, *Lycoris radiata* (L'Her.) Herb., Amaryllidaceae, was further subjected to an in-depth characterization that led to the discovery of the active SARS-CoV agent, lycorine with an EC_{50} value of 15.7 ± 1.2 nM, a CC_{50} value of 14,980.0 ± 912.0 nM (in cytotoxicity assay), and a selective index (SI) > 900.

Potential Herbs Against Coronavirus Disease 2019

It is established that a healthy immune system is advantageous and protective against the clinical and mortal effect of SARS-CoV2 infection. Certain phytocompounds predominant in fruits and leafy vegetables are capable of promoting healthy immune responses by providing antioxidants polyphenols and bioactive agents able to modulate immune functions (Calder et al. 2020; Zhang and Liu 2020). The genome of SARS-COV2 shares close similarity with those of previously pandemic SARS coronaviruses like SARS-CoV and MERS-CoV fuelling the possibility that herbs and medications found to be effective in previous incidences of coronavirus diseases could also be beneficial in the treatment of COVID-19 (Gasmi et al. 2020). The therapeutic efficacy of some medicinal plants is traceable to their antioxidant phytochemicals notably the polyphenols and flavonoids (Komolafe et al. 2017) and some of these possess inhibitory effects on 3 chymotrypsin-like protease (3CLpro) essential for the replication of coronaviruses like

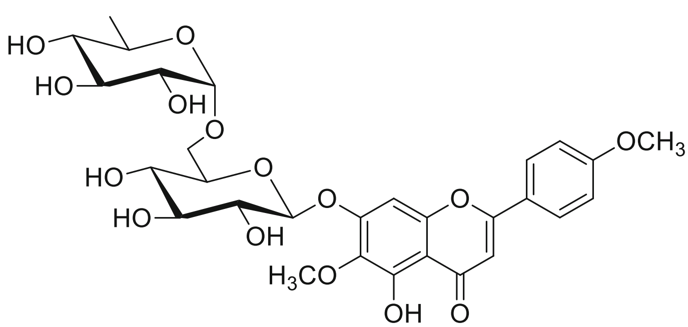
MERS-CoV and SARS-COV (Gasmi et al. 2020). A comprehensive molecular docking analysis by Murugan et al. (2020) revealed a highly promising therapeutic potential of *A. paniculata* diterpenoid, neoandrographolide, against the SARS-COV-2 virus. The compound showed strong interactions with key proteins responsible for viral replication, namely 3-chymotrypsin-like protease, 3CLpro (31.4 kcal/mol), and papain-like proteinase, PLpro (28.5 kcal/mol), as well as RNA-directed RNA polymerase, RdRp (24.1 kcal/mol), involved in RNA synthesis and spike protein responsible for host cell recognition.

The suppressive effect that some flavonoids like quercetin, helichrysetin, rhoifolin, pectolinarin (**9**), and isobavachalcone (**10**) have on MERS-CoV, SARS-CoV, and even hepatitis C virus has been demonstrated to be through 3CLpro inhibition (Ryu et al. 2010; Gasmi et al. 2020; Jo et al. 2020). Ryu et al. (2010), while establishing some basic structure-activity relationships of flavonoids, demonstrated the inhibitory effects (IC_{50}) of apigenin (280.8 μM), quercetin (23.8 μM), luteolin (**11**) (20.2 μM), and a biflavone amentoflavone (**12**) (8.3 μM) which exhibited the highest potency, against coronavirus 3C-like proteases. This suggests that herbs and herbal products with 3CLpro inhibitory activity might help combat SARS-COV2 particularly since the virus causes the upregulation of 3CLpro expression (Prajapat et al. 2020).

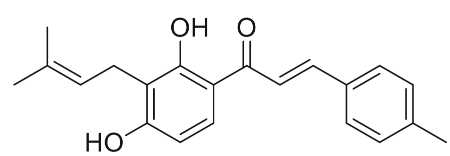
Traditional Chinese Medicine and COVID-19

Many COVID-19 patients in China have at one time or the other been treated with herbal formulations that modulate the T-cells and enhance host defense mechanisms (Patel et al. 2020; Yang et al. 2020). A review of the herbal treatment recommended for the management of pediatric COVID-19 by the Chinese provincial guidelines showed that the medicinal herbs *Scutellariae radix*, *Artemisiae annuae herba*, *Belamcandae rhizoma*, *Armeniacae semen*, *Coicis semen*, *Ephedrae herba*, *and Gypsum fibrosum* individually or collectively form vital components of the approved herbal formulations. Some of the herbs including *Artemisiae annuae herba*, *Scutellariae radix* (through its component, baicalin), *Ephedrae herba*, and *Gypsum fibrosum* possess established antiviral properties against influenza or pneumonia. Others like *Armeniacae semen* and *Coicis semen* are useful for the treatment of upper respiratory tract infection (Ang et al. 2020).

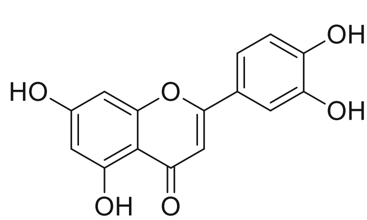
Liu et al. (2020) highlighted the advantages of Chinese herbal formulations with potential usefulness in the management of COVID-19 infection and its hallmark pneumonia and respiratory symptoms. *Qingfei Paidu* decoction is a combination of classical TCM prescriptions for treating cold pathogens and its chemical substances showed an inhibitory effect on 3CL protein of coronavirus (Liu 2020; Zhao et al. 2020). Another herbal formula *Pneumonia no. 1*, compounded from five Chinese herbal medi-



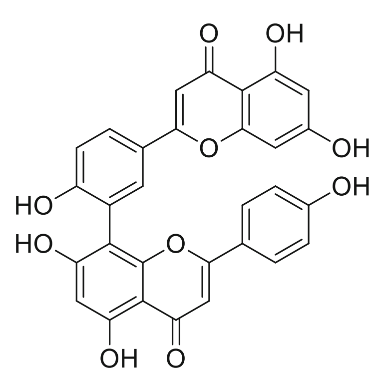
9



10



11



12

cines, has been clinically tested on COVID-19 patients with the mild form of the disease with over 50% reversal of symptoms and no patient progressing to the severe form of the disease (Liu 2020). Shufeng Jiedu Capsule (SFJDC), another herbal formula, was shown to act additively with arbidol (a broad-spectrum antiviral compound) in improving respiratory system symptoms such as fever, cough, chest tightness, and shortness of breath in COVID-19 mild disease patients (Liu 2020).

A multi-herbal formulation, Pudilan (PDL), used in traditional Chinese medicine (TCM) for heat-clearing and detoxification and clinically employed recently with appreciable success as an anti-SARS-CoV-2 infective agent, was evaluated for therapeutic potential against COVID-19 using network pharmacology tools (Kong et al. 2020). The findings show that the anti-COVID-19 mechanism of PDL proceeds via inhibition of angiotensin-converting enzyme 2 (ACE2) and prevention of SARS-CoV-2 entry into cells. The herbal extract might also prevent the cytokine storm thorough negative interactions with pro-inflammatory cytokines and factors (Kong et al. 2020).

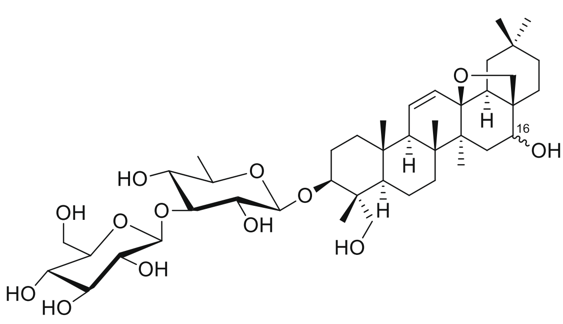
Saikosaponins A (**13**) and D (**14**) are capable of preventing coronaviruses viral penetration and early-stage CoVs infection, while luteolin from *Veronica linariifolia* Pall. Ex Link, Plantaginaceae, and tetra-*O*-galloyl-β-D-glucose (**15**) from *Rhus chinensis* Mill., Anacardiaceae, could suppress the coronaviruses by binding to the virus surface spike proteins (Patel et al. 2020; Yang et al. 2020). In a study involving virtual screening of antiviral compounds from plants to identify promising lead molecules for SARS-CoV-2 main protease (Mpro) enzyme, an essential target involved in viral polyprotein processing, the binding affinity of selected small drug-like molecules to the main proteases of SARS-CoV-2, SARS-CoV, and MERS-CoV was determined using molecular docking. Bonducellpin D (**16**), which showed higher binding affinity (−9.28 kcal/mol) as compared to the control (−8.24 kcal/mol), was identified as the best lead molecule. The authors suggested that Bonducellpin D could be a promising drug candidate since it also exhibited broad-spectrum inhibition potential against SARS-CoV Mpro and MERS-CoV Mpro and the high similarity of SARS-CoV-2 Mpro to SARS-CoV Mpro (96.08%) and MERS-CoV Mpro (50.65%) (Gurung et al. 2020).

Furthermore, a clinical trial was conducted to assess the safety and efficacy of Lianhuaqingwen capsule, a Chinese herbal product, in 284 COVID-19 patients randomized to receive usual treatment alone or in combination with the herbal formulations (Hu et al. 2021). The rate of recovery from symptoms (coughing, fatigue, fever) was taken as the primary indicator of effectiveness. It was shown that herbs had no adverse effects at the evaluated doses while treatment shortened the overall recovery time (median: 7 vs. 10 days, $p < 0.001$). Also, patients on formulations had better chest computed tomographic manifestations and were relieved of symptoms including coughing (7 vs. 10 days), fatigue (3 vs. 6 days), and fever (2 vs. 3 days) faster than those not on the herbal formulations.

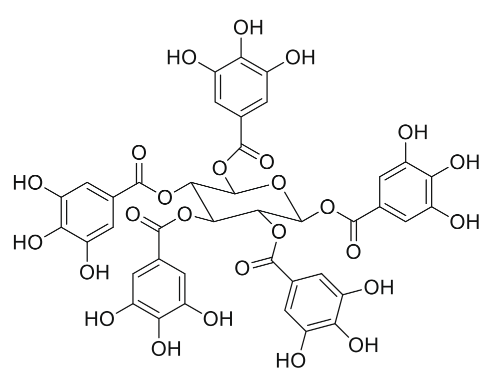
Indian Ayurvedic Medicine and COVID-19

The Indian Ayurveda traditional system of medicine has relatively limited literature documentation on the treatment of coronavirus disease 2019 unlike the Chinese traditional medicine. A case report reputed to be the first of his kind by Girija and Sivan (2020) demonstrated the successful treatment of a COVID-19-positive patient entirely with Ayurveda Indian medicine. According to the authors, the patient who presented with severe symptoms of high fever, body pain,, and cough along with other COVID-19 symptoms relied on Ayurvedic medicines comprising of *Sudarshan Churna* and *Dhanwantara Gutika* tablets, *Talisadi Churna* with honey, and a regulated diet. Almost all symptoms were arrested, and smell was partially restored after 16 days of treatment while blood samples taken after 31 days of treatment came out negative for the SARS-COV2 IgM antibody.

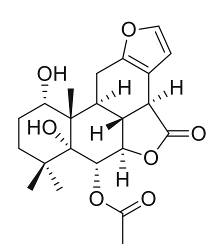
A magazine publication mentioned that COVID-19 patients were successfully treated at the All India Institute of Ayurveda (AIIA) Health Centre in Delhi with Ayurvedic treatment protocol, including diet and yoga. The positive



13 = 16β
14 = 16α



15



16

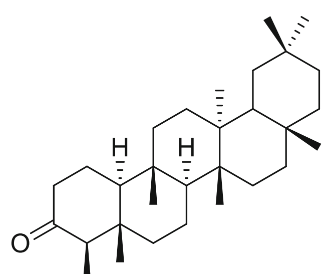
development prompted the AYUSH ministry to submit that the traditional system of medicine could be exploited as it holds a huge potential in preventive and curative healthcare of the pandemic (PTI 2020).

A discussion on a joint Indian and US trials of Ayurveda formulations for COVID-19 recently took place. Indian researchers on Ayurvedic medicine proposed Ashwagandha, an Ayurvedic medicine, for COVID-19 treatment. It was suggested that the withanone phytoconstituent of the plant could work with caffeic acid phenethyl ester (CAPE), the active ingredient in propolis, to influence the replicative enzyme(s) in the SARS-COV-2 (TrialSiteNews 2020). The preliminary report by the NIH suggests there is no evidence yet that the treatment works but that there is evidence of contamination by metals (*e.g.*, mercury and lead) in many of the Ayurvedic medicinal products under investigation (TrialSiteNews 2020).

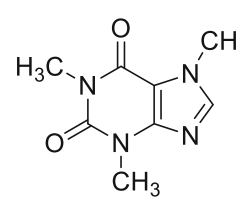
African Traditional Medicine and COVID-19

Many African countries are encouraging or taking active measures aimed at developing indigenous herbal medicine to combat the COVID-19 pandemic. A herbal remedy, "Covid-Organics," formulated from artemisia (used in malaria treatment) and other Malagasy plants and claimed to prevent or cure COVID-19 was launched in Madagascar with several other African countries showing interest in obtaining it. The government of South Africa indicated its willingness to assist authorities in Madagascar to test and analyze the Covid-Organics (Finnan 2020). In Nigeria, the National Agency for Food and Drug Administration and Control (NAFDAC) saddled with the responsibility of ensuring adequate control and minimum standards for both conventional and herbal drugs in the nation was directed by the Ministry of Health to assess the efficacy and safety of a plant-based cough mixture as treatment for COVID-19 (Adebowale 2020). This followed series of calls by natural health practitioners and experts on the need for developing indigenous solutions to the pandemic. According to the Health Authority, constituent herbs of the herbal mixture which include *Allium sativa* (garlic); *Allium cepa* (onion); *Zingiber officinale* (ginger): *Piper guineense* (West African black pepper); and *Adansonia digitata* (baobab fruit) have scientific evidence of use in the management of respiratory infections and possess anti-inflammatory and antiviral effects (Adebowale 2020). Many important personalities in the socio-cultural spheres also lent their voices to the calls for the development of scientifically validated indigenous herbal alternatives to combat COVID-19. A paramount traditional ruler with historical reputation of being the guardian of the socio-cultural affair of the Yoruba people of Southwestern Nigeria proposed a partnership with traditional medicine practitioners to create an herbal formula from different botanicals including *Newbouldia laevis* (boundary tree), *Azadirachta indica* (neem), *Allium cepa* (onion), *Anchomanes difformis* (forest anchomanes, Blume), *Tetrapleura tetraptera* (Aidan fruit), *Xylopia aethiopica* (African pepper), and *Vernonia amygdalina* (bitter leaf) as well as sulfur for the treatment of the dreaded viral infection (Oluremi 2020). There are recent reports on the potential relevance of Jobelyn, a *Sorghum bicolor* extract, for the management of COVID-19. The herbal medicinal product, often marketed as dietary supplement, was subjected to clinical trials for safety and effectiveness in the management of widespread anemic conditions, including sickle cell disease. Jobelyn is reputed to be capable of boosting the antioxidant profile and the immune system by increasing CD4 T-lymphocyte count with potential positive outcomes in COVID-19 treatment (SickleCellNews 2020).

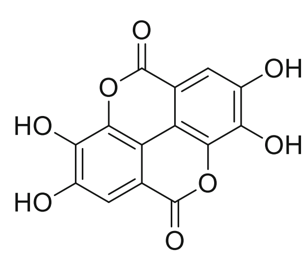
Fatoki et al. (2020) employed gene network analysis, molecular docking, and sequence and structure dynamics simulations to identify therapeutic compounds and phytochemicals with potential to modulate the expression network of genes involved in SARS-CoV-2 pathology in the human host and to understand the dynamics of key proteins involved in the virus-host interactions. Their findings revealed that ellagitannins and friedelanone (**17**) showed high binding energies against 3-chymotrypsin-like protease (3CLpro), papain-like protease (PLpro), helicase (nsp13), RNA-dependent RNA polymerase (nsp12), 2′-*O*-ribose methyltransferase (nsp16) of SARS-CoV-2 and DNA-PK and CK2alpha in human. They also revealed that medicinal plants containing phytochemicals such as caffeine (**18**), ellagic acid (**19**), and quercetin could be beneficial in COVID-19 therapy (Fatoki et al. 2020).



17



18



19

Herbal Medicine and Salient Issues

Medicinal Plants and Herbal Formulation Uses: Myths and Facts

There is a recent resurgence of interest in herbal medicine even where there were no historically rooted cultural practices or acceptance. This is probably as a result of (i) better public awareness following improved packaging and market strategies with claims of effectiveness of herbal products on multiple diseases; (ii) the popular, market-driven belief that herbal medicines, because they are from a natural source, are more effective and safer than orthodox drugs, and (iii) the relatively high cost of orthodox medicines and the ease in obtaining herbs without necessarily going for interview-style consultations by those drifting towards self-medications. Also, those with a cultural history of the use of herbs in the management of diseases often believe that the diagnosis and prognosis of some endemic diseases can only be fully comprehended by traditionalists and practitioners of herbal medicine but not by orthodox physicians. The increasing popularity and availability of herbal medicine have brought issues of their safety and herb-drug interactions to the fore of global concern especially in the light of the recent pandemic. One positive side of the traditional system of medicine is the long history of application in the treatment of diseases based on empirical knowledge spanning several centuries or millenniums. This enhances safety in many cultural settings as a systematic selection of medicinal plants for use would have made toxic fatalities uncommon. Compelling results from experimental investigations have validated the safety, particularly in animal models, of some herbs and herbal medicine. However, there is a widespread belief that herbal medicines are generally safe and this could make consumers fail to take cognizance of adverse reactions and thus underreporting such cases (Neergheen-Bhujun 2013). Also, a sizeable number of those who use herbal medicine as the primary source of healthcare are illiterates or semi-illiterates from rural areas of developing countries where documentation ethics and access to facilities may be elusive. This may also contribute to the dearth of information on the toxicity of herbs and issues of herb-drug interactions. This is because in such instances, the efficacy of such drugs is rated by the judgment and testimonies of previous users which are solely based on the therapeutic effects on the intended pathological condition with very little information on the side effects or toxicity. Tactical marketing strategies, aimed at highlighting the strengths but not the limitations, are also employed by herbal sales representatives to project products into greater limelight. Among those with a cultural history of herbal use in disease management, there is historic oral information on the efficacy of specific herbal drugs against clearly identified pathological conditions. This is sufficient to advertise the products to potential buyers and users.

The efficacy of herbs used in traditional systems of medicines cannot be downplayed but there is a call to exercise caution when using herbal products. There is a common misconception that herbal medicines are completely safe and without adverse effects. Herbs could produce undesirable or toxic effects that could be serious or even fatal and the literature is replete with numerous examples of such cases (Ekor 2014; Mensah et al. 2019). These notwithstanding, traditional/herbal medicine could be safe when used appropriately as dietary/food supplements or medicines. In a few reported cases of herbal toxicity too, only weak or no causal association between the use of herb and toxic responses could be substantiated (Neergheen-Bhujun 2013).

Pertinent Issues of Herbal Medicinal Uses

Major uncertainties with the use of herbal products are quality assurance issues, non-compliance with standard production practice (WHO 2004; Palombo 2006), and little information relating to effective use and approaches (Mensah et al. 2019).

Issues Relating to Standardization and Regulation

Ordinarily, herbal medicines are supposed to be licensed and have a product license validating their safety, quality, and efficacy just like their orthodox counterparts. They should contain information on indications, contraindications, treatment regimen, and side effects spelt out on a leaflet accompanying the medicine. Since the major determinants of toxicity of drugs or herbal products are actually dosage and time of exposure, lack of well-elucidated or validated information on dosages and treatment regimen of herbal medicines would constitute a major challenge. Licensing protocols for the production and marketing of herbal medicines are usually relaxed such that little or no evidence of the efficacy and safety is required before marketing (Ekor 2014) thus lowering the quality of production. The failure of regulatory agencies in some countries, for example, the US FDA, to include herbal products and phytopharmaceuticals within their purview expose consumers to further risks. Based on the peculiarities of herbal products, meeting the required stringent conditions for drug approval could be difficult, hence the creation of alternative and simplified herbal registration scheme like the Traditional Herbal Medicines Registration Scheme introduced in the UK which ensures that minimum safety and quality standard are met while other relevant information is spelt out to promote the safe use of medicines (Raynor et al. 2011; Ekor 2014). The NAFDAC performs a similar role in Nigeria and many herbal drugs have been subjected to NAFDAC scrutiny with operational and marketing licenses granted to the companies responsible for their production. However, as common in many developing countries, there are many unregistered and poorly regulated herbal products being sold without restraint in the market and by trado-medical practitioners. In fact, some herbs in Southwestern Nigeria are termed “200-diseases remedy” whereby one herb or herbal mixture is claimed to exhibit scientifically unproven therapeutic effects against many unrelated pathological conditions. There are claims by some herbal medicine practitioners on the availability of drugs for COVID-19 managements just as there are reports of indiscriminate uses of antimalarial herbal preparations to combat COVID-19 (Team AUC-R et al. 2020). Obviously perturbed by the spate of increasing herbal formulations on sale for COVID-19 management in the region, the WHO-established Regional Expert Committee on Traditional Medicine for COVID-19, the Africa Centre for Disease Control and Prevention, and the African Union Commission for Social Affairs recently approved a protocol for phase III clinical trials of herbal medicine for COVID-19. Terms of reference for the establishment of a data and safety monitoring board for herbal medicine clinical trials were also given (Africa 2020).

Issues Relating to Quality Control of Products

Despite the preponderance of phytomedicines in the markets in many countries, there are poor quality control measures for these products and the stringent regulations that are in place for orthodox medicines are absent. Quality irregularities of herbal products of different production batch and production timeframe are not uncommon, and this has a direct consequence on the efficacy and safety of such products. A review of laboratory and clinical evidence on the effects of multi-component herbal products in the management of chemotherapy-associated toxicity and side effects established the ameliorative effects of herbs on most side effects of chemotherapy including neurotoxicity, hematotoxicity, cardiotoxicity, and nephrotoxicity (Fu et al. 2018). However, the authors pointed out the inconsistency in product quality as well as lack of mechanistic and pharmacokinetic studies as troubling limitations. Existing regulatory bodies for herbal products vary from country to country and there is often a lack of standardized analytical methods (Raclariu et al. 2018). Currently, this scenario is very much applicable to most COVID-19 herbal formulations. Actually, quality control of herbal products is a complex process involving physical, chemical, and biological procedures as well as the deployment of various analytical methods and tools (Kunle et al. 2012). Herbs at the point of collection are subjected to physical screening including macro- and microscopic examination to remove adulterants like foreign organic matter. Analyses of the ash contents, crude fiber contents, and moisture contents could give valuable information on the identity, purity, and stability of the crude drugs. Qualitative (using infrared and ultraviolet techniques) and quantitative chemical evaluations are employed to identify, characterize, and quantify the phytochemical constituents in the crude drug. The quantitative aspects involve the use of various techniques including supercritical fluid chromatograph (SFC), high-performance thin-layer chromatography (HPTLC), high-performance liquid chromatography (HPLC), gas chromatography-mass spectroscopy (GC-MS) (Balekundri and Mannur 2020) and the HPLC-electrospray ionization-mass spectrometry (HPLC-ESI-MS). The versatility of HPLC to efficiently profile compounds in herbal extracts and the rapid structural characterization by MS afford a new practicable approach to identifying unknown herbal constituents (Yang et al. 2009; Kumar 2017). DNA barcoding is a genomics-based tool for taxonomic identification. Based on molecular and computational information, it uses standardized DNA regions, named DNA barcodes, to identify a species or taxon, providing the authentication of raw plant material. When combined with high-resolution analytical chromatographic instrumentation, DNA barcoding could afford marked impact in the quality control of herbal drugs and phytopharmaceuticals, as well as in the safety and regulation of herbal products and the discovery and development of herbal drugs (Gesto-Borroto et al. 2021). For example, three ginseng species (*Panax*, Araliaceae) are commercially cultivated: *P. ginseng* C. A. Meyer (ginseng), *P. quinquefolius* L. (American ginseng), and *P. notoginseng* (Burkill) F.H. Chen ex C. Y. Wu et K M. Feng (Sanqi). *Panax ginseng* and *P. quinquefolius* are widely used in the treatment and healthcare for respiratory diseases (Zhang et al. 2020). Ginseng can exert direct antiviral effects by inhibiting viral attachment, membrane penetration, and replication; the foremost antiviral activities of ginseng are attributed to the enhancement of host immunity (Im et al. 2016). Several candidate DNA regions or markers were evaluated to establish a more accurate and effective identification for these ginseng species, and the combination of *psbA-trnH* and ITS was found to be the most successful ones for their identification (Zuo et al. 2011). In addition, toxicological studies establish potentially toxic components and ascertain safety in animals just as microbial analyses are conducted to establish the presence or absence of harmful microbial contaminations (Kunle et al. 2012).

Issues Relating to Production Practices/Ethics

Particularly widespread among ethnic groups in many developing nations, herbal drugs are not produced under the most hygienic and standard conditions and there is no specification of appropriate doses for treatments. Against this, backdrop, the safety of traditional and herbal medicines is a major concern to health authorities and individuals (Ekor 2014). There are instances when herbal preparations are deliberately or inadvertently adulterated with undeclared active components or pharmaceutical substances during production thereby changing the course of pharmacology or toxicology of such products. Reports of alleged contamination of some Ayurvedic medicinal products under investigation for COVID-19 management by metals like mercury and lead readily come to mind (TrialSiteNews 2020). With the numerous cases of herbal preparations for the management of COVID-19 by in non-standard settings and without appropriate regulation of production setups, the possibilities of harmful adulterations cannot be ruled out.

Issues Relating to Interactions of Herbs with Metabolizing Enzymes and Allopathic Drugs

The bioactive compounds in plants are vast and vary in terms of structure and chemical properties within and among species. The various bioactive components in herbal medicine are most times largely uncharacterized and they could induce or suppress drug-metabolizing enzymes and xenobiotic transporters with varying consequences when co-administered with conventional drugs (Oga et al. 2016). It has been observed that some of the adverse effects ascribed to herbs could be due to interactions with exogenously introduced agents like drugs (allopathic medicines). Herbs could interact with orthodox medicines to cause increased or decreased pharmacological or toxicological effects of both types of medicine. Such herb-drug interactions could result in a synergistic or additive effect with potentially lethal implications. For instance, reports have shown that bleeding is drastically increased when Gingko biloba extract is used concomitantly with conventional drugs like aspirin or warfarin (Pezzani et al. 2019). The dried rhizome and roots of *Glycyrrhiza glabra* L., Fabaceae, known as liquorice, are used extensively in TCM as one of the components of herbal formulations for the treatment of respiratory infections and management of COVID-19 (Liu 2020). The herbal product was reported to be capable of interfering with the pharmacokinetics of orthodox medicines (De Smet and D'Arcy 1996).

In some cases, co-administration of herbs with conventional drugs could result in adverse effects that are distinct from the pharmacological effects of either the drug or the herb. For example, garlic and Ginko react with aspirin with the potential side effects of increasing the risk of bleeding whereas hawthorn interacts with digoxin to cause arrhythmias (Naveed et al. 2020).

Issues Relating to the Intrinsic Toxicity of Herbs

A few phytoconstituents are documented in traditional medicine to be intrinsically toxic or poisonous (Fennell et al. 2004; Ekor 2014; Kuete 2014; Mensah et al. 2019). The issue of the possible toxicity and mutagenicity of plants used in traditional medicine has been reviewed (Ekor 2014; Mensah et al. 2019). Some examples of toxic herbal remedies for the treatment of respiratory conditions are the following:

***Ephedra sinica* Stapf** Ephedra (*Ephedra sinica* Stapf, Ephedraceae) is one of the herbs used for making potent herbal preparations and with a long history of application, especially in traditional Chinese medicine, for the treatment of respiratory maladies including asthma, allergies, bronchitis, and flu. The herb is also marketed in the USA as a weight loss dietary supplement. However, the use has been associated with several serious adverse effects on the cardiovascular and central nervous systems (Chen et al. 2010; Hackman et al. 2006; Verduin and Labbate 2002). According to a review of the *Ephedra* species by González-Juárez et al. (2020), the adverse effects of the plants, including the severe forms of cardiovascular disorders, myocardial infarction, and cardiac arrest, are caused by (−)-ephedrine and (+)-pseudoephedrine active constituents.

***Glycyrrhiza glabra* L.** Licorice (*G. glabra*) is a common herb used for the treatment of upper respiratory tract inflammation and for suppressing ulcers in the gastric gland and the duodenum. The prolong usage, however, is accompanied by severe side effects. The herbs could suppress the renin-aldosterone-angiotensin system (RAAS) with the accompanying physiological consequences including sodium and water retention, hypokalemia, hypertension, and cardiomyopathy (Neergheen-Bhujun 2013).

***Lantana camara* L.** *Lantana camara* L., Verbenaceae, is one of the plants used in traditional system of medicine in the management of respiratory disorders including tuberculosis, asthma, and catarrhal infections (Kirimuhuzya et al. 2009). In a review work on the use of herbs and the associated challenges, Mensah et al. (2019) highlighted hepatotoxicity of *L. camara* in animal models following chronic usage.

Pertinent Suggestions

The validation of adverse reactions to herbal medicines and herbal products is important but could be complicated by various factors. Although *in vitro* cellular studies are popularly used and considerably valuable in evaluating the cytotoxicity of herbs and herbal products, they are best carried out under *in vivo* conditions since the complicated toxic responses under *in vivo* settings cannot be elucidated by toxic responses in cells. Under *in vivo* conditions, exposure to certain hepatic enzymes could influence the toxicity of herbs by producing toxic metabolites (increasing toxicity) or promoting detoxification (decreasing toxicity) of toxic metabolites. Also, cellular models might not be able to account for tissue penetration, clearance, and excretion of herbal products (McGaw et al. 2014).

Co-administration of herbs and drugs, particularly in developing countries, could be more than is reported or imagined among patients undergoing treatment for various pathological conditions and this raises particular safety concerns. It is important for relevant health institutions and practitioners to carry out adequate monitoring of patients for such developments. The high incidences of concurrent use of herbal medicines with orthodox medicines in some climes have prompted healthcare practitioners to request for frequent probing of health behavior and choices of patients (Amaeze et al. 2018). Actually, herbal medicines are not designed, in the traditional context, to be used with other types of medicines as now being commonly done (WHO 2004; Mensah et al. 2019). The tendency to abuse herbs and herbal medicine in rural areas of developing countries is very high due to some factors that include poverty, ready accessibility to herbs, and inaccurate information on the preparation or composition of herbal formulations. Also, insufficient knowledge about dosing could lead to abuse, whether directly or indirectly, since all drugs are poison except when used within the safe limit. Herbs with induced contractive effect on smooth muscles and traditionally used for relieving constipation have been employed at high dosages for abortifacient purposes by the youth due to the effect on endometrial muscles (Mensah et al. 2019). Most importantly, herbs are not to be used without recourse to dosing instead, just like orthodox drugs, guidelines and direction of use in line with the available indigenous/traditional best practices should be followed since each herb or herbal mixture has its unique therapeutic margin and safety threshold. In other words, the use of herbal products, like other types of drugs, should be accompanied by the consciousness of the potential benefits and risks.

Future Perspectives and Conclusion

Approximately 80% of the world population relies on herbal medicine and products as a source of healthcare due to the surge in global patronage of alternative and complementary medicine in the last few decades. The rich repertoire of bioactive phytochemicals in plants makes them a potential source of viable therapeutics. The efficacy of herbs against numerous viral diseases and some of the clinical presentations of COVID-19 are well established. COVID-19 affects the respiratory system where it orchestrates deleterious inflammatory changes and presents some level of similarities in terms of symptoms to other respiratory illnesses caused by viruses. SARS-COV2, the causative virus of COVID-19, shares high genome similarity with those of previously pandemic SARS coronaviruses like SARS-CoV and MERS-CoV, both of which were considerably managed by herbal intervention. This coupled with past and emerging experimental findings indicates that herbs could be successfully deployed for the management of COVID-19 symptoms. This is buttressed by the fact that many formulations are already in place or the pipeline in many parts of the world in this regard. Herbal medicine will continue to gain prominence in the healthcare systems of many countries. It is therefore important for governments and regulatory agencies to address the major challenges facing this sector which are the issues of quality assurance, standardization, and regulation. Relevant bodies including the WHO should provide global best practices for the production, administration, and use of herbal medicine with reasonable but stringent measures being put in place as obtained for orthodox drugs. There should also be adequate enlightenment of end-users of herbal medicines. With adequate standardization and regulatory processes, together with proper enlightenment of users, the facts will be separated from fiction and the benefits of herbal medicines could be better deployed to benefit the world.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s43450-021-00132-x.

Authors' Contribution KK, HTF, and ACA conceived the idea presented in this work. KK, RTK, ACA, and BICB were involved in the literature search and preparation of the manuscript. ACA, BICB, MTO, and AAA revised the final draft of the manuscript.

Declarations

Competing Interests The authors declare no competing interests.

References

Adebowale N (2020) Nigerian govt directs NAFDAC to assess herbal mixture as possible COVID-19 treatment. Premium Times, May 8, Abuja, Nigeria. Available from https://www.premiumtimesng.com/coronavirus/391945-nigerian-govt-directs-nafdac-to-assess-herbal-mixture-as-possible-covid-19-treatment.html, Accessed 12 Aug 2020.

Africa W (2020) Expert panel endorses protocol for COVID-19 herbal medicine clinical trials. Brazzavile. Available from https://www.afro.who.int/news/expert-panel-endorses-protocol-covid-19-herbal-medicine-clinical-trials. Accessed 20 Sep 2020.

Ali-Seyed M, Vijayaraghavan K (2020) Dengue virus infections and anti-dengue virus activities of *Andrographis paniculata*. Asian Pac J Trop Med 13:49–55. https://doi.org/10.4103/1995-7645.275412

Amaeze OU, Aderemi-Williams RI, Ayo-Vaughan MA, Ogundemuren DA, Ogunmola DS, Anyika EN (2018) Herbal medicine use among type 2 diabetes mellitus patients in Nigeria: understanding the magnitude and predictors of use. Int J Clin Pharm 40:580–588. https://doi.org/10.1007/s11096-018-0648-2

Ang L, Lee HW, Kim A, Lee JA, Zhang J, Lee MS (2020) Herbal medicine for treatment of children diagnosed with COVID-19: a review of guidelines. Complement Ther Clin 39:101174. https://doi.org/10.1016/j.ctcp.2020.101174

Anu JJ, Thomas (2019) Therapeutic potential of dietary flavonoids against viral-borne infections: a review. Drug Invention Today 11:469–479

Armstrong J, Niemann H, Smeekens S, Rottier P, Warren G (1984) Sequence and topology of a model intracellular membrane protein, E1 glycoprotein, from a coronavirus. Nature 308:751–752. https://doi.org/10.1038/308751a0

Astani A, Reichling J, Schnitzler P (2010) Comparative study on the antiviral activity of selected monoterpenes derived from essential oils. Phytother Res 24:673–679. https://doi.org/10.1002/ptr.2955

Balekundri A, Mannur V (2020) Quality control of the traditional herbs and herbal products: a review. Future J Pharm Sci 6:67. https://doi.org/10.1186/s43094-020-00091-5

Bandaranayake WM (2006) Quality control, screening, toxicity, and regulation of herbal drugs. In: Ahmad IAF, Owais M (Ed.). Modern Phytomedicine, https://doi.org/10.1002/9783527609987.ch2

Beniac D, Andonov A, Grudeski E, Booth T (2006) Architecture of the SARS coronavirus prefusion spike. Nat Struct Mol Biol 13:751–752. https://doi.org/10.1038/nsmb1123

Ben-Shabat S, Yarmolinsky L, Porat D, Dahan A (2020) Antiviral effect of phytochemicals from medicinal plants: applications and drug delivery strategies. Drug Deliv Transl Re 10:354–367. https://doi.org/10.1007/s13346-019-00691-6

Bradley D (2005) Star role for bacteria in controlling flu pandemic? Nat Rev Drug Discov 4:945–946. https://doi.org/10.1038/nrd1917

Calder PC, Carr AC, Gombart AF, Eggersdorfer M (2020) Optimal nutritional status for a well-functioning immune system is an important factor to protect against viral infections. Nutrients 12:1181. https://doi.org/10.3390/nu12041181

Candeias NR, Assoah B, Simeonov SP (2018) Production and synthetic modifications of shikimic acid. Chem Rev 118:10458–10550. https://doi.org/10.1021/acs.chemrev.8b00350

Carneiro BM, Batista MN, Braga ACS, Nogueira ML, Rahal P (2016) The green tea molecule EGCG inhibits Zika virus entry. Virology 496:215–218. https://doi.org/10.1016/j.virol.2016.06.012

Chang C-k, Sue S-C, Yu T-h, Hsieh C-M, Tsai C-K, Chiang Y-C, Lee S-j, Hsiao H-h, Wu W-J, Chang W-L, Lin C-H, Huang T-h (2006) Modular organization of SARS coronavirus nucleocapsid protein. J Biomed Sci 13:59–72. https://doi.org/10.1007/s11373-005-9035-9

Chen F, Chan KH, Jiang Y, Kao RYT, Lu HT, Fan KW, Cheng VCC, Tsui WHW, Hung IFN, Lee TSW, Guan Y, Peiris JSM, Yuen KY (2004) *In vitro* susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J Clin Virol 31:69–75. https://doi.org/10.1016/j.jcv.2004.03.003

Chen WL, Tsai TH, Yang CC, Kuo TB (2010) Acute effects of *Ephedra* on autonomic nervous modulation in healthy young adults. Clin Pharmacol Ther 88:39–44. https://doi.org/10.1038/clpt.2010.66

Cheng HY, Lin TC, Yang CM, Wang KC, Lin LT, Lin CC (2004) Putranjivain A from *Euphorbia jolkini* inhibits both virus entry and late stage replication of herpes simplex virus type 2 *in vitro*. J Antimicrob Chemoth 53:577–583. https://doi.org/10.1093/jac/dkh136

Chinello P, Petrosillo N, Pittalis S, Biava G, Ippolito G, Nicastri E, Team IE (2017) QTc interval prolongation during favipiravir therapy in an Ebolavirus-infected patient. PLoS Neglec Trop D 11:e0006034. https://doi.org/10.1371/journal.pntd.0006034

Chinsembu KC (2020) Coronaviruses and nature's pharmacy for the relief of coronavirus disease 2019. Rev Bras Farmacogn 30:603–621. https://doi.org/10.1007/s43450-020-00104-7

Cox RM, Wolf JD, Plemper RK (2020) Therapeutic MK-4482/EIDD-2801 blocks SARS-CoV-2 transmission in ferrets. Res Sq. https://doi.org/10.21203/rs.3.rs-89433/v1

Cushnie TP, Lamb AJ (2005) Antimicrobial activity of flavonoids. Int J Antimicrob Agents 26:343–356. https://doi.org/10.1016/j.ijantimicag.2005.09.002

De Smet P, D'Arcy P (1996) Drug interactions with herbal and other non-orthodox remedies. In: D'Arcy PF, McElnay JC, Welling PG (eds) Mechanisms of drug interactions. Handbook of experimental pharmacology, vol 122. Springer, Berlin, pp 327–352. https://doi.org/10.1007/978-3-642-61015-8_12

Delang L, Abdelnabi R, Neyts J (2018) Favipiravir as a potential countermeasure against neglected and emerging RNA viruses. Antivir Res 153:85–94. https://doi.org/10.1016/j.antiviral.2018.03.003

Dharmarathna SLCA, Wickramasinghe S, Waduge RN, Rajapakse RPVJ, Kularatne SAM (2013) Does *Carica papaya* leaf-extract increase the platelet count? An experimental study in a murine model. Asian Pac J Trop Biomed 3:720–724. https://doi.org/10.1016/S2221-1691(13)60145-8

Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, Holden KA, Read JM, Dondelinger F, Carson G, Merson L, Lee J, Plotkin D, Sigfrid L, Halpin S, Jackson C, Gamble C, Horby PW, Nguyen-Van-Tam JS, Ho A, Russell CD, Dunning J, Openshaw PJ, Baillie JK, Semple MG (2020) Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ 369:m1985. https://doi.org/10.1136/bmj.m1985

ECDPC (2020) Coroaviruses: general backgroud. European Centre for Disease Prevention and Control

Ekor M (2014) The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. Front Pharmacol 4:177. https://doi.org/10.3389/fphar.2013.00177

El-Saber Batiha G, Magdy Beshbishy A, Wasef LG, Elewa YHA, Al-Sagan AA, Abd El-Hack ME, Taha AE, MA-E Y, Prasad Devkota H (2020) Chemical constituents and pharmacological activities of garlic (*Allium sativum* L.): a review. Nutrients 12. https://doi.org/10.3390/nu12030872

Fatoki TH, Ibraheem O, Ogunyemi IO, Akinmoladun AC, Ugboko HU, Adeseko CJ, Awofisayo OA, Olusegun SJ, Enibukun JM (2020) Network analysis, sequence and structure dynamics of key proteins of coronavirus and human host, and molecular docking of selected phytochemicals of nine medicinal plants. J Biomol Struct Dyn:1–23. https://doi.org/10.1080/07391102.2020.1794971

Fehr AR, Perlman S (2015) Coronaviruses: an overview of their replication and pathogenesis. In: Maier H, Bickerton E, Britton P (eds) Coronaviruses. Methods in molecular biology, vol 1282. Humana Press, New York. https://doi.org/10.1007/978-1-4939-2438-7_1

Fennell CW, Light ME, Sparg SG, Stafford GI, van Staden J (2004) Assessing African medicinal plants for efficacy and safety: agricultural and storage practices. J Ethnopharmacol 95:113–121. https://doi.org/10.1016/j.jep.2004.05.025

Finnan D (2020) South Africa steps up to help Madagascar test herbal cure for Covid-19. France 24, May 8. Available from https://www.rfi.fr/en/africa/20200508-south-africa-steps-up-to-help-madagascar-test-herbal-cure-for-covid-19. Accessed 12 Aug 2020.

Forku R (2020) WHO, Africa CDC form COVID-19 traditional remedy panel. Anadolu Agency, July 22. Available from https://www.aa.com.tr/en/africa/who-africa-cdc-form-covid-19-traditional-remedy-panel/1918964. Accessed 12 Aug 2020.

Fu B, Wang N, Tan HY, Li S, Cheung F, Feng Y (2018) Multi-component herbal oroducts in the prevention and treatment of chemotherapy-associated toxicity and side effects: a review on experimental and clinical evidences. Front Pharmacol 9:1394. https://doi.org/10.3389/fphar.2018.01394

Ganesan S, Faris AN, Comstock AT, Wang Q, Nanua S, Hershenson MB, Sajjan US (2012) Quercetin inhibits rhinovirus replication *in vitro* and *in vivo*. Antivir Res 94:258–271. https://doi.org/10.1016/j.antiviral.2012.03.005

Gasmi A, Noor S, Tippairote T, Dadar M, Menzel A, Bjørklund G (2020) Individual risk management strategy and potential therapeutic options for the COVID-19 pandemic. Clin Immunol 215:108409. https://doi.org/10.1016/j.clim.2020.108409

Gesto-Borroto R, Medina-Jiménez K, Lorence A, Ma V (2021) Application of DNA barcoding for quality control of herbal drugs and their phytopharmaceuticals. Rev Bras Farmacogn. In Press

Gikandi H (2020) Madagascar defends coronavirus herbal remedy. The World, May 13, Addis Ababa. Available from https://www.pri.org/stories/2020-05-13/madagascar-defends-coronavirus-herbal-remedy. Accessed 12 Aug 2020.

Girija P, Sivan N (2020) Ayurvedic treatment of COVID-19/SARS-CoV-2: a case report. J Ayurveda Integrat Med. https://doi.org/10.1016/j.jaim.2020.06.001

Gong J, Dong H, Xia SQ, Huang YZ, Wang D, Zhao Y, Liu W, Tu S, Zhang M, Wang Q, Lu F (2020) Correlation analysis between disease severity and inflammation-related parameters in patients with COVID-19 pneumonia. MedRxiv. https://doi.org/10.1101/2020.02.25.20025643

González-Juárez DE, Escobedo-Moratilla A, Flores J, Hidalgo-Figueroa S, Martínez-Tagüeña N, Morales-Jiménez J, Muñiz-Ramírez A, Pastor-Palacios G, Pérez-Miranda S, Ramírez-Hernández A, Trujillo J, Bautista E (2020) A review of the *Ephedra* genus: distribution, ecology, ethnobotany, phytochemistry and pharmacological properties. Molecules 25:3283. https://doi.org/10.3390/molecules25143283

Gorbalenya AE, Baker SC, Baric RS, de Groot RJ, Drosten C, Gulyaeva AA, Haagmans BL, Lauber C, Leontovich AM, Neuman BW, Penzar D, Perlman S, Poon LLM, Samborskiy DV, Sidorov IA, Sola I, Ziebuhr J, Coronaviridae Study Group of the International Committee on Taxonomy of V (2020) The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol 5:536–544. https://doi.org/10.1038/s41564-020-0695-z

Gruhlke MCH, Nicco C, Batteux F, Slusarenko AJ (2016) The effects of allicin, a eeactive sulfur species from garlic, on a selection of mammalian cell lines. Antioxidants 6:1. https://doi.org/10.3390/antiox6010001

Gurung AB, Ali MA, Lee J, Farah MA, Al-Anazi KM (2020) Unravelling lead antiviral phytochemicals for the inhibition of SARS-CoV-2 Mpro enzyme through *in silico* approach. Life Sci 255:117831. https://doi.org/10.1016/j.lfs.2020.117831

Hackman RM, Havel PJ, Schwartz HJ, Rutledge JC, Watnik MR, Noceti EM, Stohs SJ, Stern JS, Keen CL (2006) Multinutrient supplement containing ephedra and caffeine causes weight loss and improves metabolic risk factors in obese women: a randomized controlled trial. Int J Obes 30:1545–1556. https://doi.org/10.1038/sj.ijo.0803283

Hu K, Guan W-J, Bi Y, Zhang W, Li L, Zhang B, Liu Q, Song Y, Li X, Duan Z, Zheng Q, Yang Z, Liang J, Han M, Ruan L, Wu C, Zhang Y, Jia Z-H, Zhong N-S (2021) Efficacy and safety of Lianhuaqingwen capsules, a repurposed Chinese herb, in patients with coronavirus disease 2019: a multicenter, prospective, randomized controlled trial. Phytomedicine.:153242. https://doi.org/10.1016/j.phymed.2020.153242

Huang H, Zhou W, Zhu H, Zhou P, Shi X (2017) Baicalin benefits the anti-HBV therapy via inhibiting HBV viral RNAs. Toxicol Appl Pharmacol 323:36–43. https://doi.org/10.1016/j.taap.2017.03.016

Im K, Kim J, Min H (2016) Ginseng, the natural effectual antiviral: protective effects of Korean Red Ginseng against viral infection. J Ginseng Res 40:309–314. https://doi.org/10.1016/j.jgr.2015.09.002

Jiang S, Du L, Shi Z (2020) An emerging coronavirus causing pneumonia outbreak in Wuhan, China: calling for developing therapeutic and prophylactic strategies. Emerg Microbes Infect 9:275–277. https://doi.org/10.1080/22221751.2020.1723441

Jo S, Kim S, Shin DH, Kim MS (2020) Inhibition of SARS-CoV 3CL protease by flavonoids. J Enzyme Inhib Med Chem 35:145–151. https://doi.org/10.1080/14756366.2019.1690480

Kala CP (2012) Leaf juice of *Carica papaya* L.: a remedy of dengue fever. Med Aromat Plants 1. https://doi.org/10.4172/2167-0412.1000109

Kirimuhuzya C, Waako P, Joloba M, Odyek O (2009) The anti-mycobacterial activity of *Lantana camara* a plant traditionally used to treat symptoms of tuberculosis in South-western Uganda. Afr Health Sci 9:40–45

Komolafe K, Akinmoladun AC, Komolafe TR, Olaleye MT, Akindahunsi AA, Rocha JBT (2017) African locust bean (*Parkia biglobosa* Jacq Benth) leaf extract affects mitochondrial redox chemistry and inhibits angiotensin-converting enzyme *in vitro*. Clin Phytosci 3:19. https://doi.org/10.1186/s40816-017-0057-4

Kong L, Li S, Liao Q, Zhang Y, Sun R, Zhu X, Zhang Q, Wang J, Wu X, Fang X, Zhu Y (2013) Oleanolic acid and ursolic acid: novel hepatitis C virus antivirals that inhibit NS5B activity. Antivir Res 98:44–53. https://doi.org/10.1016/j.antiviral.2013.02.003

Kong Q, Wu Y, Gu Y, Lv Q, Qi F, Gong S, Chen X (2020) Analysis of the molecular mechanism of Pudilan (PDL) treatment for COVID-19 by network pharmacology tools. Biomed Pharmacother 128:110316. https://doi.org/10.1016/j.biopha.2020.110316

Kuete V (2014) Toxicological survey of African medicinal plants, 1st edn. Elsevier, London

Kumar B (2017) Application of HPLC and ESI-MS techniques in the analysis of phenolic acids and flavonoids from green leafy vegetables (GLVs). J Pharm Anal 7:349–364. https://doi.org/10.1016/j.jpha.2017.06.005

Kunle OF, Egharevba HO, Ahmadu PO (2012) Standardization of herbal medicines - a review. Int J Biodivers Conserv 4:101–112. https://doi.org/10.5897/IJBC11.163

Kurokawa M, Basnet P, Ohsugi M, Hozumi T, Kadota S, Namba T, Kawana T, Shiraki K (1999) Anti-herpes simplex virus activity of moronic acid purified from *Rhus javanica in vitro* and *in vivo*. J Pharmacol Exp Ther 289:72–78

Lechien JR, Chiesa-Estomba CM, Place S, Van Laethem Y, Cabaraux P, Mat Q, Huet K, Plzak J, Horoi M, Hans S, Rosaria Barillari M, Cammaroto G, Fakhry N, Martiny D, Ayad T, Jouffe L, Hopkins C, Saussez S (2020) Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. J Intern Med 288:335–344. https://doi.org/10.1111/joim.13089

Li BQ, Fu T, Dongyan Y, Mikovits JA, Ruscetti FW, Wang JM (2000) Flavonoid baicalin inhibits HIV-1 infection at the level of viral entry. Biochem Biophys Res Commun 276:534–538. https://doi.org/10.1006/bbrc.2000.3485

Li X, Liu Y, Wu T, Jin Y, Cheng J, Wan C, Qian W, Xing F, Shi W (2015) The antiviral effect of baicalin on enterovirus 71 *in vitro*. Viruses 7:4756–4771. https://doi.org/10.3390/v7082841

Li Y, Liu X, Guo L, Li J, Zhong D, Zhang Y, Clarke M, Jin R (2020) Traditional Chinese herbal medicine for treating novel coronavirus (COVID-19) pneumonia: protocol for a systematic review and meta-analysis. Syst Rev 9:75. https://doi.org/10.1186/s13643-020-01343-4

Lim HJ, Nguyen TT, Kim NM, Park JS, Jang TS, Kim D (2017) Inhibitory effect of flavonoids against NS2B-NS3 protease of ZIKA virus and their structure activity relationship. Biotechnol Lett 39:415–421. https://doi.org/10.1007/s10529-016-2261-6

Lippi G, Plebani M (2020) A modern and pragmatic definition of laboratory medicine. Clin Chem Lab Med 58:1171. https://doi.org/10.1515/cclm-2020-0114

Liu C-X (2020) Pay attention to situation of SARS-CoV-2 and TCM advantages in treatment of novel coronavirus infection. Chinese Herbal Medicines 12:97–103. https://doi.org/10.1016/j.chmed.2020.03.004

Liu X, Zhang M, He L, Li Y (2012) Chinese herbs combined with Western medicine for severe acute respiratory syndrome (SARS). Cochrane Database Syst Rev 10:Cd004882. https://doi.org/10.1002/14651858.CD004882.pub3

Liu Y, Yan LM, Wan L, Xiang TX, Le A, Liu JM, Peiris M, Poon LLM, Zhang W (2020) Viral dynamics in mild and severe cases of COVID-19. Lancet Infect Dis 20:656–657. https://doi.org/10.1016/s1473-3099(20)30232-2

Lu WJ, Lee JJ, Chou DS, Jayakumar T, Fong TH, Hsiao G, Sheu JR (2011) A novel role of andrographolide, an NF-kappa B inhibitor, on inhibition of platelet activation: the pivotal mechanisms of endothelial nitric oxide synthase/cyclic GMP. J Mol Med 89:1261–1273. https://doi.org/10.1007/s00109-011-0800-0

Luo S-H, Liu W, Liu Z-J, Zheng X-Y, Hong C-X, Liu Z-R, Liu J, Weng J-P (2020) A confirmed asymptomatic carrier of 2019 novel coronavirus. Chin Med J 133:1123–1125. https://doi.org/10.1097/CM9.0000000000000798

Ma L, Xie W, Li D, Shi L, Mao Y, Xiong Y, Zhang Y, Zhang M (2020) Effect of SARS-CoV-2 infection upon male gonadal function: a single center-based study. MedRxiv. https://doi.org/10.1101/2020.03.21.20037267

Maregesi SM, Pieters L, Ngassapa OD, Apers S, Vingerhoets R, Cos P, Berghe DAV, Vlietinck AJ (2008) Screening of some Tanzanian medicinal plants from Bunda district for antibacterial, antifungal and antiviral activities. J Ethnopharmacol 119:58–66. https://doi.org/10.1016/j.jep.2008.05.033

Maregesi S, Van Miert S, Pannecouque C, Feiz Haddad MH, Hermans N, Wright CW, Vlietinck AJ, Apers S, Pieters L (2010) Screening of Tanzanian medicinal plants against *Plasmodium falciparum* and human immunodeficiency virus. Planta Med 76:195–201. https://doi.org/10.1055/s-0029-1186024

Maroyi A (2019) Review of ethnomedicinal, phytochemical and pharmacological properties of *Lannea schweinfurthii* (Engl.) Engl. Molecules 24:732. https://doi.org/10.3390/molecules24040732

McGaw LJ, Elgorashi EE, Eloff JN (2014) 8-Cytotoxicity of African medicinal plants against normal animal and human cells. In: Kuete V (Ed.) Toxicological survey of African medicinal plants. Elsevier, pp. 181-233. https://doi.org/10.1016/B978-0-12-800018-2.00008-X

Medeiros-Neves B, Teixeira HF, von Poser GL (2018) The genus *Pterocaulon* (Asteraceae) - a review on traditional medicinal uses, chemical constituents and biological properties. J Ethnopharmacol 224:451–464. https://doi.org/10.1016/j.jep.2018.06.012

Mensah MLK, Komlaga G, Forkuo AD, Caleb Firempong, Anning AK, Dickson RA (2019) Toxicity and safety implications of herbal medicines used in Africa. In: Builders PF, Herbal Medicine, IntechOpen, Available from https://www.intechopen.com/books/herbal-medicine/toxicity-and-safety-implications-of-herbal-medicines-used-in-africa. https://doi.org/10.5772/intechopen.72437

Moghaddam E, Teoh BT, Sam SS, Lani R, Hassandarvish P, Chik Z, Yueh A, Abubakar S, Zandi K (2014) Baicalin, a metabolite of baicalein with antiviral activity against dengue virus. Sci Rep 4:5452. https://doi.org/10.1038/srep05452

Monera TG, Maponga CC (2012) Prevalence and patterns of *Moringa oleifera* use among HIV positive patients in Zimbabwe: a cross-sectional survey. J Public Health Afr 3:6. https://doi.org/10.4081/jphia.2012.e6

Murugan NA, Pandian CJ, Jeyakanthan J (2020) Computational investigation on *Andrographis paniculata* phytochemicals to evaluate their potency against SARS-CoV-2 in comparison to known antiviral compounds in drug trials. J Biomol Struct Dyn. https://doi.org/10.1080/07391102.2020.1777901

Naveed M, Majeed F, Taleb A, Zubair HM, Shumzaid M, Farooq MA, Baig M, Abbas M, Saeed M, Changxing L (2020) A review of medicinal plants in cardiovascular disorders: benefits and risks. Am J Chin Med 48:259–286. https://doi.org/10.1142/s0192415x20500147

Neergheen-Bhujun VS (2013) Underestimating the toxicological challenges associated with the use of herbal medicinal products in developing countries. Biomed Res Int 2013:804086–804089. https://doi.org/10.1155/2013/804086

Nieto-Torres JL, DeDiego ML, Verdiá-Báguena C, Jimenez-Guardeño JM, Regla-Nava JA, Fernandez-Delgado R, Castaño-Rodriguez C, Alcaraz A, Torres J, Aguilella VM, Enjuanes L (2014) Severe acute respiratory syndrome coronavirus envelope protein ion channel activity promotes virus fitness and pathogenesis. PLoS Pathog 10:e1004077. https://doi.org/10.1371/journal.ppat.1004077

Nissen N (2010) Practitioners of Western herbal medicine and their practice in the UK: beginning to sketch the profession. Complement Ther Clin Pract 16:181–186. https://doi.org/10.1016/j.ctcp.2010.06.001

Norahmad NA, Mohd Abd Razak MR, Mohmad Misnan N, Md Jelas NH, Sastu UR, Muhammad A, Ho TCD, Jusoh B, Zolkifli NA, Thayan R, Mat Ripen A, Zainol M, Syed Mohamed AF (2019) Effect of freeze-dried *Carica papaya* leaf juice on inflammatory cytokines production during dengue virus infection in AG129 mice. BMC Complem Altern Med 19:44. https://doi.org/10.1186/s12906-019-2438-3

Nováková L, Pavlík J, Chrenková L, Martinec O, Červený L (2018) Current antiviral drugs and their analysis in biological materials - part II: antivirals against hepatitis and HIV viruses. J Pharm Biomed Anal 147:378–399. https://doi.org/10.1016/j.jpba.2017.07.003

Oga EF, Sekine S, Shitara Y, Horie T (2016) Pharmacokinetic herb-drug interactions: insight into mechanisms and consequences. Eur J Drug Metab Pharmacokinet 41:93–108. https://doi.org/10.1007/s13318-015-0296-z

Ogbuagu EN, Ufearo SC, Ogbuagu C, Okonkwo RD (2016) CD4 pattern in HIV positive patients on HAART exposed to *Moringa oleifera* leaf powder in south east Nigeria. Int J Infect Dis 45:267. https://doi.org/10.1016/j.ijid.2016.02.595

Oluremi A (2020) Ooni of Ife claims he has 'tested' cure for coronavirus. Premium Times, March 30, Abuja, Nigeria. Available from https://www.premiumtimesng.com/news/top-news/384977-ooni-of-ife-claims-he-has-tested-cure-for-coronavirus.html. Accessed 12 Aug 2020.

Palombo EA (2006) Phytochemicals from traditional medicinal plants used in the treatment of diarrhoea: modes of action and effects on intestinal function. Phytother Res 20:717–724. https://doi.org/10.1002/ptr.1907

Patel SKS, Lee J-K, Kalia VC (2020) Deploying biomolecules as anti-COVID-19 agents. Indian J Microbiol 60:263–268. https://doi.org/10.1007/s12088-020-00893-4

Patra JK, Das G, Bose S, Banerjee S, Vishnuprasad CN, del Pilar Rodriguez-Torres M, Shin H-S (2020) Star anise (*Illicium verum*): chemical compounds, antiviral properties, and clinical relevance. Phytother Res 34:1248–1267. https://doi.org/10.1002/ptr.6614

Petrilli CM, Jones SA, Yang J, Rajagopalan H, Donnell LF, Chernyak Y, Tobin K, Cerfolio RJ, Francois F, Horwitz LI (2020) Factors associated with hospitalization and critical illness among 4,103 patients with COVID-19 disease in New York City. MedRxiv. https://doi.org/10.1101/2020.04.08.20057794

Pezzani R, Salehi B, Vitalini S, Iriti M, Zuñiga FA, Sharifi-Rad J, Martorell M, Martins N (2019) Synergistic effects of plant derivatives and conventional chemotherapeutic agents: an update on the cancer perspective. Medicina 55:110. https://doi.org/10.3390/medicina55040110

Popoola JO, Obembe OO (2013) Local knowledge, use pattern and geographical distribution of *Moringa oleifera* Lam. (Moringaceae) in Nigeria. J Ethnopharmacol 150:682–691. https://doi.org/10.1016/j.jep.2013.09.043

Prajapat M, Sarma P, Shekhar N, Avti P, Sinha S, Kaur H, Kumar S, Bhattacharyya A, Kumar H, Bansal S, Medhi B (2020) Drug targets for corona virus: a systematic review. Indian J Pharmacol 52:56–65. https://doi.org/10.4103/ijp.IJP_115_20

PTI (2020) Delhi institute cures COVID-19 patients with Ayurvedic treatment protocol, records zero deaths, Financial Express, July 28. Delhi, India. Available from https://www.financialexpress.com/lifestyle/health/delhi-institute-cures-covid-19-patients-with-ayurvedic-treatment-protocol-records-zero-deaths/2038007/. Accessed 12 Aug 2020

Raclariu AC, Heinrich M, Ichim MC, de Boer H (2018) Benefits and limitations of DNA barcoding and metabarcoding in herbal product

authentication. Phytochem Analysis 29:123–128. https://doi.org/10.1002/pca.2732
Ranasinghe P, Ranasinghe P, Abeysekera WP, Premakumara GA, Perera YS, Gurugama P, Gunatilake SB (2012) *In vitro* erythrocyte membrane stabilization properties of *Carica papaya* L. leaf extracts. Pharm Res 4:196–202. https://doi.org/10.4103/0974-8490.102261
Raynor DK, Dickinson R, Knapp P, Long AF, Nicolson DJ (2011) Buyer beware? Does the information provided with herbal products available over the counter enable safe use? BMC Med 9:94. https://doi.org/10.1186/1741-7015-9-94
Ren L-L, Wang Y-M, Wu Z-Q, Xiang Z-C, Guo L, Xu T, Jiang Y-Z, Xiong Y, Li Y-J, Li X-W, Li H, Fan G-H, Gu X-Y, Xiao Y, Gao H, Xu J-Y, Yang F, Wang X-M, Wu C, Chen L, Liu Y-W, Liu B, Yang J, Wang X-R, Dong J, Li L, Huang C-L, Zhao J-P, Hu Y, Cheng Z-S, Liu L-L, Qian Z-H, Qin C, Jin Q, Cao B, Wang J-W (2020) Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. Chin Med J 133:1015–1024. https://doi.org/10.1097/CM9.0000000000000722
Ryu YB, Jeong HJ, Kim JH, Kim YM, Park JY, Kim D, Nguyen TT, Park SJ, Chang JS, Park KH, Rho MC, Lee WS (2010) Biflavonoids from *Torreya nucifera* displaying SARS-CoV 3CL(pro) inhibition. Bioorg Med Chem 18:7940–7947. https://doi.org/10.1016/j.bmc.2010.09.035
Sawai T, Itoh Y, Ozaki H, Isoda N, Okamoto K, Kashima Y, Kawaoka Y, Takeuchi Y, Kida H, Ogasawara K (2008) Induction of cytotoxic T-lymphocyte and antibody responses against highly pathogenic avian influenza virus infection in mice by inoculation of apathogenic H5N1 influenza virus particles inactivated with formalin. Immunology 124:155–165. https://doi.org/10.1111/j.1365-2567.2007.02745.x
Semple S, Reynolds G, O'Leary M, Flower R (1998) Screening of Australian medicinal plants for antiviral activity. J Ethnopharmacol 60:163–172. https://doi.org/10.1016/s0378-8741(97)00152-9
Semple SJ, Nobbs SF, Pyke SM, Reynolds GD, Flower RL (1999) Antiviral flavonoid from *Pterocaulon sphacelatum*, an Australian Aboriginal medicine. J Ethnopharmacol 68:283–288. https://doi.org/10.1016/s0378-8741(99)00050-1
Sharma N, Mishra KP, Chanda S, Bhardwaj V, Tanwar H, Ganju L, Kumar B, Singh SB (2019) Evaluation of anti-dengue activity of *Carica papaya* aqueous leaf extract and its role in platelet augmentation. Arch Virol 164:1095–1110. https://doi.org/10.1007/s00705-019-04179-z
Shi H, Ren K, Lv B, Zhang W, Zhao Y, Tan RX, Li E (2016) Baicalin from *Scutellaria baicalensis* blocks respiratory syncytial virus (RSV) infection and reduces inflammatory cell infiltration and lung injury in mice. Sci Rep-UK 6:35851–35851. https://doi.org/10.1038/srep35851
SickleCellNews, 2020. Sickle Cell News (2020) Coronavirus & SCD: Jobelyn should form part of your defence strategy. Sickle Cell News. Available from https://sicklecellnews.com/coronavirus-scd-jobelyn-should-form-part-of-your-defence-strategy/. Accessed 12 Aug 2020
Singh AK, Rana HK, Tshabalala T, Kumar R, Gupta A, Ndhlala AR, Pandey AK (2020) Phytochemical, nutraceutical and pharmacological attributes of a functional crop *Moringa oleifera* Lam: an overview. S Afr J Bot 129:209–220. https://doi.org/10.1016/j.sajb.2019.06.017
Singh SP, Kumar S, Mathan SV, Tomar MS, Singh RK, Verma PK, Kumar A, Kumar S, Singh RP, Acharya A (2020) Therapeutic application of *Carica papaya* leaf extract in the management of human diseases. Daru J Pharm Sci 28:735–744. https://doi.org/10.1007/s40199-020-00348-7
Singhal T (2020) A review of coronavirus disease-2019 (COVID-19). Indian J Pediatr 87:281–286. https://doi.org/10.1007/s12098-020-03263-6
Sithisarn P, Michaelis M, Schubert-Zsilavecz M, Cinatl J Jr (2013) Differential antiviral and anti-inflammatory mechanisms of the flavonoids biochanin A and baicalein in H5N1 influenza A virus-infected cells. Antivir Res 97:41–48. https://doi.org/10.1016/j.antiviral.2012.10.004
Song WY, Ma YB, Bai X, Zhang XM, Gu Q, Zheng YT, Zhou J, Chen JJ (2007) Two new compounds and anti-HIV active constituents from *Illicium verum*. Planta Med 73:372–375. https://doi.org/10.1055/s-2007-967162
Stanley CN, Ayodeji OA, Stanley PC (2020) Review of pathogenesis of COVID-19: considerations. JAMMR 32:30–34. https://doi.org/10.9734/jammr/2020/v32i730446
Stuart J (2014) Herbal medicines. 4th ed. JJMLA 102:222–223. https://doi.org/10.3163/1536-5050.102.3.019
Sukprasert S, Pansuksan K, Sriyakul K (2020) *Lysiphyllum strychnifolium* (Craib) A. Schmitz extract, a novel neuraminidase inhibitor of avian influenza virus subtype H5N1. J Herbal Med 20:100330. https://doi.org/10.1016/j.hermed.2020.100330
Tang LI, Ling AP, Koh RY, Chye SM, Voon KG (2012) Screening of anti-dengue activity in methanolic extracts of medicinal plants. BMC Complem Altern Med 12:3. https://doi.org/10.1186/1472-6882-12-3
Team AUC-R, Akindele AJ, Agunbiade FO, Sofidiya MO, Awodele O, Sowemimo A, Ade-Ademilua O, Akinleye MO, Ishola IO, Orabueze I, Salu OB, Oreagba IA, Asekun OT, Odukoya O (2020) COVID-19 Pandemic: a case for phytomedicines. Nat Prod Comm 15:1934578X2094508. https://doi.org/10.1177/1934578X20945086
Thisoda P, Rangkadilok N, Pholphana N, Worasuttayangkurn L, Ruchirawat S, Satayavivad J (2006) Inhibitory effect of *Andrographis paniculata* extract and its active diterpenoids on platelet aggregation. Eur J Pharmacol 553:39–45. https://doi.org/10.1016/j.ejphar.2006.09.052
TrialSiteNews (2020) Ayurvedic medicine as COVID-19 treatment: research begins, Evidence Thin. Trial Site News, July 11, Delhi India. Available from https://trialsitenews.com/ayurvedic-medicine-as-covid-19-treatment-research-begins-evidence-thin/. Accessed 12 Aug 2020.
Trivedi AS, Sadhna, Ashtey B (2020) Investigational treatments for COVID-19. Pharm J 304:7938. https://doi.org/10.1211/PJ.2020.20208051
Verduin ML, Labbate LA (2002) Psychosis and delirium following metabolife use. Psychopharmacol Bull 36:42–45
Wang G-W, Hu W-T, Huang B-K, Qin L-P (2011) *Illicium verum*: a review on its botany, traditional use, chemistry and pharmacology. J Ethnopharmacol 136:10–20. https://doi.org/10.1016/j.jep.2011.04.051
Wen C-C, Kuo Y-H, Jan J-T, Liang P-H, Wang S-Y, Liu H-G, Lee C-K, Chang S-T, Kuo C-J, Lee S-S, Hou C-C, Hsiao P-W, Chien S-C, Shyur L-F, Yang N-S (2007) Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus. J Med Chem 50:4087–4095. https://doi.org/10.1021/jm070295s
Weng JR, Lin CS, Lai HC, Lin YP, Wang CY, Tsai YC, Wu KC, Huang SH, Lin CW (2019) Antiviral activity of *Sambucus formosana* Nakai ethanol extract and related phenolic acid constituents against human coronavirus NL63. Virus Res 273:197767. https://doi.org/10.1016/j.virusres.2019.197767
WHO (2004) WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems. World Health Organization, Geneva, p 82
Wohlfarth C, Efferth T (2009) Natural products as promising drug candidates for the treatment of hepatitis B and C. Acta Pharmacol Sin 30:25–30. https://doi.org/10.1038/aps.2008.5

Xie P, Ma W, Tang H, Liu D (2020) Severe COVID-19: a review of recent progress with a look toward the future. Front Public Health 8:189. https://doi.org/10.3389/fpubh.2020.00189

Yang M, Sun J, Lu Z, Chen G, Guan S, Liu X, Jiang B, Ye M, Guo DA (2009) Phytochemical analysis of traditional Chinese medicine using liquid chromatography coupled with mass spectrometry. J Chromatogr A 1216:2045–2062. https://doi.org/10.1016/j.chroma.2008.08.097

Yang J-LH, Ha TKQ, Oh WK (2016) Discovery of inhibitory materials against PEDV corona virus from medicinal plants. Japanese J Vet Res 64:S53–S63. https://doi.org/10.14943/jjvr.64.suppl.s53

Yang W, Chen X, Li Y, Guo S, Wang Z, Yu X (2020) Advances in pharmacological activities of terpenoids. Nat Prod Comm 15: 1934578X2090355. https://doi.org/10.1177/1934578X20903555

Yang Y, Islam MS, Wang J, Li Y, Chen X (2020) Traditional Chinese medicine in the treatment of patients infected with 2019-new coronavirus (SARS-CoV-2): a review and perspective. Int J Biol Sci 16: 1708–1717. https://doi.org/10.7150/ijbs.45538

Zaigham M, Andersson O (2020) Maternal and perinatal outcomes with COVID-19: a systematic review of 108 pregnancies. Acta Obstet Gynecol Scand 99:823–829. https://doi.org/10.1111/aogs.13867

Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA (2012) Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med 367:1814–1820. https://doi.org/10.1056/NEJMoa1211721

Zandi K, Teoh BT, Sam SS, Wong PF, Mustafa MR, Abubakar S (2011) Antiviral activity of four types of bioflavonoid against dengue virus type-2. Virol J 8:560. https://doi.org/10.1186/1743-422x-8-560

Zhang L, Liu Y (2020) Potential interventions for novel coronavirus in China: a systematic review. J Med Virol 92:479–490. https://doi.org/10.1002/jmv.25707

Zhang B, Zhou X, Qiu Y, Feng F, Feng J, Jia Y, Zhu H, Hu K, Liu J, Liu Z, Wang S, Gong Y, Zhou C, Zhu T, Cheng Y, Liu Z, Deng H, Tao F, Ren Y, Cheng B, Gao L, Wu X, Yu L, Huang Z, Mao Z, Song Q, Zhu B, Wang J (2020) Clinical characteristics of 82 death cases with COVID-19. MedRxiv. https://doi.org/10.1101/2020.02.26.20028191

Zhang Z, Xu P, Wang Z, Zhao D, Huang Q, Lu J, Sun L, Wang J, Li X (2020) Effect of Panax ginseng on preventing acute respiratory tract infection: a protocol for systematic review and meta-analysis. Medicine 99:e20690. https://doi.org/10.1097/md.0000000000020690

Zhao CH, Xu J, Zhang YQ, Zhao LX, Feng B (2014) Inhibition of human enterovirus 71 replication by pentacyclic triterpenes and their novel synthetic derivatives. Chem Pharm Bull 62:764–771. https://doi.org/10.1248/cpb.c14-00088

Zhao S, Lin Q, Ran J, Musa SS, Yang G, Wang W, Lou Y, Gao D, Yang L, He D, Wang MH (2020) Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: a data-driven analysis in the early phase of the outbreak. Int J Infect Dis 92:214–217. https://doi.org/10.1016/j.ijid.2020.01.050

Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL (2020) A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 579:270–273. https://doi.org/10.1038/s41586-020-2012-7

Zimmermann P, Curtis N (2020) Coronavirus infections in children including COVID-19: an overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in children. Pediatr Infect Dis J 39:355–368. https://doi.org/10.1097/inf.0000000000002660

Zumla A, Chan JF, Azhar EI, Hui DS, Yuen K-Y (2016) Coronaviruses — drug discovery and therapeutic options. Nat Rev Drug Discov 15: 327–347. https://doi.org/10.1038/nrd.2015.37

Zuo Y, Chen Z, Kondo K, Funamoto T, Wen J, Zhou S (2011) DNA barcoding of Panax species. Planta Medica 77:182–187. https://doi.org/10.1055/s-0030-1250166