Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

South African Journal of Botany 139 (2021) 386–398

Contents lists available at ScienceDirect

South African Journal of Botany

journal homepage: www.elsevier.com/locate/sajb

Review

Natural product remedies for COVID-19: A focus on safety

Aitebiremen Gift Omokhua-Uyi, Johannes Van Staden*

Research Centre for Plant Growth and Development, School of Life Sciences, University of KwaZulu-Natal Pietermaritzburg, Private Bag X01, Scottsville 3201, South Africa

ARTICLE INFO

Article History:
Received 26 November 2020
Revised 23 January 2021
Accepted 3 March 2021
Available online 18 March 2021

Edited by S Gupta

Keywords:
Coronavirus
COVID-19 treatment
Natural products
Safety
Self-medication
Toxicity

ABSTRACT

Infection by the novel coronavirus SARS-CoV-2 causing the coronavirus disease (COVID-19), is currently a global pandemic with more than two million deaths to date. Though a number of vaccines have recently been approved against the virus, availability remains a big challenge, and also acceptance by most people has become a big debate. This review discusses possible/proposed natural product remedies and some major conventional treatment options used to manage the infection and, safety concerns on the use of unproven or unapproved health products against COVID-19. An extensive literature review indicated that the influx of unproven and unapproved health products in the global market are on the rise, leading to various forms of self- medication. To this effect, there have been warnings by the United States Food and Drug Administration and the World Health Organisation against the use of such products. Conventional drugs such as remdesivir, chloroquine/hydroxychloroquine and dexamethasone are the major proposed drugs that are currently undergoing clinical trials for the management of this disease. Efforts are being made globally in the search for possible therapeutics which may be the best way to eradicating this disease. Some countries have approved the use of natural products in the management of COVID-19, despite little or no clinical evidence on their efficacy and safety. Natural products may hold a great potential in the fight against COVID-19 but without detailed clinical trials, their potency against the virus and their safe use cannot be established. To attain this goal, extensive research followed by clinical studies are needed. Collaborative efforts between researchers, clinicians, governments and traditional medicinal practitioners in the search and development of safe and effective therapeutics from natural products for the treatment of COVID-19 could be a potential option.

1. Introduction

Coronaviruses are a large group of viruses belonging to the family Coronaviridaea that cause upper-respiratory tract illnesses, ranging from common colds to more severe diseases (WHO, 2020a). Coronaviruses are zoonotic with many varieties common in animal species (WHO, 2020a). From these animal origins, they can undergo mutation, recombination and adaptation and be passed on to humans (Health24, 2020; Lau et al., 2020; WHO, 2020a). The first coronavirus was characterised and identified in humans in the mid-1960s (Kahn and McIntosh, 2005; Andersen et al., 2020; Jaiswal and Saxena, 2020). To date, seven coronaviruses have been recorded in humans and are classified as α-coronaviruses (NL63 and 229E) and β-coronaviruses (OC43 and HKU1) (Andersen et al., 2020; Jaiswal and Saxena, 2020). The β-coronavirus SARS-CoV, which causes severe acute respiratory syndrome (SARS) was first recorded in humans in 2002 (Lau et al., 2020). This was followed by the β-MERS-CoV, known as the Middle East respiratory syndrome (MERS) coronavirus, in 2012 (CDC, 2020a; Schröder, 2020). The SARS-CoV was transmitted from civet cats to humans with outbreaks traced to Chinese markets, while the MERS-CoV was believed to have been contracted by humans first in Saudi Arabi from dromedary camels who may have been infected by bats (Kan et al., 2005; Paden et al., 2018; WHO, 2019a, 2020a).

The recent outbreak is the SARS-CoV-2, a novel coronavirus which causes the disease COVID-19 (Lau et al., 2020). The first reported case was in China in December 2019. The virus was believed to have developed in bats and later in pangolins (Hassanin, 2020; Panyod et al., 2020; Zhang et al., 2020) and to have spread from a Chinese seafood marketplace (Shereen et al., 2020). However, recent studies show a virus with 99% genomic agreement to SARS-CoV-2, suggesting that the COVID-19 virus is the result of a recombination between two different viruses. Thus, the exact origin of the virus is still uncertain (Hassanin, 2020). The virus spreads through saliva droplets from talking and discharge from the nose and mouth of an infected person, through coughing or sneezing (CDC, 2020b). When these droplets are aerosolized, the virus can remain viable in the air for about 3 h, suggesting possible airborne transmission (van Doremalen et al., 2020). The presence of SARS-CoV-2 RNA have

* Corresponding author.
E-mail address: rcpgd@ukzn.ac.za (J. Van Staden).

https://doi.org/10.1016/j.sajb.2021.03.012
0254-6299/

also been detected in stools and urine of infected patients (Sun et al., 2020; Wang et al., 2020a). With more research, other possible SARS-CoV-2 routes of transmission may be discovered. Hence, alternative forms of transmission cannot be excluded when taking safety measures.

Most people exposed to the COVID-19 virus experience mild to moderate respiratory illness and recover without requiring special treatment (WHO, 2020b). However, the older population and those whose immune systems have been compromised due to medical conditions such as diabetes, obesity, chronic kidney disease, cardiovascular diseases, chronic respiratory diseases (CRDs), cancers, sickle cell disease and human immunodeficiency virus - acquired immunodeficiency syndrome (HIV-AIDS) are at higher risk (CDC, 2020c; Clark et al., 2020). People infected with COVID-19 usually start to show symptoms between 2-14 days after exposure to the virus (CDC, 2020d). Symptoms include cough, headache, muscle or body aches, fever or chills, fatigue, shortness of breath or difficulty with breathing, new loss of taste or smell, congestion or runny nose, sore throat, nausea or vomiting and diarrhoea (CDC, 2020d). Due to the novel nature of the virus, the list of possible symptoms is not exhaustive, and research is still ongoing.

The disease progression and mortality rates of MERS and SARS cannot be compared to that of COVID-19 which has resulted in unprecedented number of deaths more than two million and placed massive pressure on the world economy (Gazeta, 2020). The World Health Organisation (WHO) declared the COVID-19 outbreak a global pandemic (WHO, 2020c). Millions of people have been placed under quarantine all over the world as a measure to curb the COVID-19 outbreak. Only recently has the economy in certain countries started to open gradually even though the infection rate is still on the increase. A global situation report by the WHO as of 7:08pm Central European Summer Time (CEST) on 15 January 2021 showed 91,816,091 confirmed cases of COVID-19, including 1,986,871 deaths (WHO, 2020d). This review highlights: (1) proposed/repurposed therapeutics for the management of COVID-19 virus including natural products (2) the dangers of self-medication in using products with no clinical evidence of therapeutic activity, possible mechanisms of action and safety records against COVID-19 and (3) possible ways forward that may assist in the fight against the pandemic.

2. Methodology

The information presented in this review was obtained from scientific literature databases such as Google Scholar, Science-Direct, PubMed, Scifinder, Web of Science and Scopus. Key words used include; Coronavirus, COVID-19, natural products, traditional, herbal preparation, toxicity, safety, World Health Organisation, Centers for Disease Control and Food and Drug Administration. More than 400 units of literature were screened and those relevant to the aim of this review were considered.

3. Conventional drugs currently under investigation and used in the management of COVID-19

Though a number of vaccines have recently been approved against the SARS-CoV-2 virus, availability to the public remains a big challenge, and also acceptance by most people has become a big debate. In most cases, patients are given medical care or supportive therapy with oxygen and fluids to help relieve symptoms (Auwaerter, 2020; Eyvazzadeh, 2020). Sometimes antibiotics are used to treat secondary infections (Farooq, 2020; Hassanin, 2020). However, there are many ongoing clinical trials evaluating potential treatments. Drugs of target for the treatment of COVID-19 should be able to stop the replication of the virus SARS-CoV-2 that causes COVID-19, thereby reducing its disease-causing ability. Some of the established drugs currently under trials supported by the WHO are: remdesivir, chloroquine and hydroxychloroquine, and dexamethasone (Jean et al., 2020; Joseph, 2020; WHO, 2020e).

3.1. Remdesivir

Remdesivir is an intravenous antiviral drug which was developed during the Ebola crisis. The drug can block the replication of viruses (Jean et al., 2020; Wang et al., 2020b). In a current study, 36 (68%) COVID-19 patients out of 53 treated with remdesivir showed clinical improvement (Grein et al., 2020). In another study, 541 patients were treated with remdesivir while 521 received the placebo. Patients treated with remdesivir recovered faster than patients in similar conditions who received the placebo (Beigel et al., 2020). In a multicentre trial in ten hospitals in Hubei province, China, most patients administered remdesivir for 10 days recovered faster than those administered the placebo. However, no significant advantage was recorded. Adverse events of 66% (102 out of 155) were reported in patients administered remdesivir while 64% (50 out of 70) were reported in patients who received the placebo (Wang et al., 2020c). Currently, there is a randomized controlled clinical trial (Adaptive COVID-19 Treatment Trial 3 (ACTT 3)), evaluating the safety and efficacy of remdesivir plus the immunomodulator interferon β-1a (traded as Rebif) in COVID-19 patients. This trial is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID). The drug shows antiviral and anti-inflammatory properties, and the type 1 interferon can inhibit SARS-CoV-2, SARS-CoV and MERS-CoV (Medscape, 2020).

3.2. Chloroquine and hydroxychloroquine

Chloroquine and hydroxychloroquine are currently used to treat malaria, arthritis and lupus disease. In a study conducted by Self et al. (2020), hospitalized patients with respiratory illness from COVID-19 that were administered hydroxychloroquine compared with placebo, did not show significant improvement clinically after 14 days. Hence authors suggested that hydroxychloroquine is not effective against COVID-19. Some other clinical trials using hydroxychloroquine in COVID-19 patients also concluded that it did not in any way prevent infections better than a placebo (Herper, 2020). However, some clinical trials on the drug are still being conducted (Chen et al., 2020). In May 2020, chloroquine, hydroxychloroquine and remdesivir received emergency use authorization (EUA) from the Food and Drug Administration (FDA, 2020a) to manage severe cases of COVID-19 under hospital settings. However, on June 15, 2020, the FDA revoked the emergency use authorisation of chloroquine and hydroxychloroquine in cases where clinical trials were unavailable. The main concern with these drugs was their ability to cause cardiac problems (FDA, 2020b).

3.3. Dexamethasone

Current studies show dexamethasone as one of the most promising drugs for managing COVID-19. Dexamethasone is a glucocorticosteroid used in the treatment of different inflammatory conditions related to allergic disorders, skin conditions and lupus, psoriasis, ulcerative colitis, arthritis and respiratory disorders (Chemocare, 2020, WHO, 2020e). Dexamethasone is also used either alone or in combination with other drugs to treat some types of cancers or to prevent/treat cancer-related conditions (NCI, 2019). A preliminary clinical trial released by the University of Oxford, United Kingdom (UK) to the WHO on June 16, 2020, showed the effective use of dexamethasone in patients with COVID-19 under critical conditions. The treatment reduced mortality in patients on ventilators by about one-third. For patients requiring only oxygen, mortality was cut by about one-fifth (WHO, 2020e). The study, however, indicated that the positive effect was not as clear in patients with milder symptoms of the

disease. A recent recovery trial conducted on 1007 hospitalised COVID-19 patients with respiratory failure that were administered a moderate dose of dexamethasone for 10 days with supplemental oxygen or mechanical ventilation, showed a reduced mortality rate. However, the same recovery trial also indicated that there might be an increased mortality rate in patients administered dexamethasone in the absence of supplementary oxygen or mechanical ventilator (Matthay and Thompson, 2020). Following the outcome of the above studies, it can be deduced that it might not be advisable to administer dexamethasone to patients without oxygen support or ventilator.

Even though the adverse effects of this drug may be less severe, this may not be the case with COVID-19 patients with Strongyloidiasis comorbidity, a rare but fatal parasitic disease caused by nematodes mostly associated with *Strongyloides stercoralis* (Stauffer et al., 2020). Therefore, proper diagnosis is very important before administering corticosteroids such as dexamethasone to patients. There is a relationship between corticosteroid therapy and strongyloidiasis with a two- to three-fold increased risk of being infected by *S. stercoralis* (Fardet et al., 2006). With little knowledge available on the mechanism involved in susceptibility, it is hypothesized that this may be through its suppressive effects on some major mediators of the immune response such as eosinophils to the parasite (Fardet et al., 2006). Such hypothesis needs to be tested through clinical studies.

4. Natural products as possible management/treatment options for COVID-19

The use of natural products in the treatment and management of infections and diseases has a long history in human existence. Hence, it is possible that treatment for viral infections such as COVID-19 can be discovered from natural products such as plants and microorganisms (Sohail et al 2011; Abdalla and McGaw, 2018). For example, one of the proposed treatments (as explained above) for COVID-19 is chloroquine (Farooq, 2020). Chloroquine is an anti-malaria drug which is an analogue of quinine isolated from the plant extract of *Cinchona officinalis* L. belonging to the family Rubiaceae (Lowe, 2020). Exploration of microorganisms such as endophytes as possible treatment for COVID-19 may also be beneficial as they are sources of treatments for other human diseases (Abdalla and McGaw, 2018).

4.1. Endophytes

Endophytes are microorganisms, mainly bacteria and fungi, living in the intercellular and intracellular regions of healthy plant tissues without constituting any harm to the plant. These organisms have a symbiotic relationship with the host plant. Many plants host at least one endophytic microbe (Ryan et al., 2008). These endophytes act as biological defences for the host plants against plant pathogens through the release of metabolites against plant predators or lyse affected cells by either inducing cell defence mechanisms or promoting the growth of the plant (Alvin et al., 2014). Endophytes can release hydrolytic enzymes or active compounds which help prevent the colonization of plant by pathogens, nematodes or insects (Strobel, 2003; Hallmann et al., 2006). Endophytes produce biologically active compounds, similar to those present in the host and sometimes distinct compounds that are effective against diseases such as cancers, viral infections and other life-threatening ailments (Abdalla and McGaw, 2018). Several compounds have been isolated from endophytes that are useful for the treatment of various diseases caused by bacteria, fungi, and viruses. Zhang et al. (2011) evaluated the antiviral activity of isolated compounds Emerimidine A and Emerimidine B from the endophytic fungi *Emericella* sp. from the mangrove plant *Aegiceras corniculatum* (L.). These compounds exhibited moderate antiviral activity. An endophytic fungi *Pleospora tarda* isolated from *Ephedra aphylla* Forssk showed a 40.7% inhibition against herpes simplex virus (HSV) and 15.2% against Vesicular stomatitis virus (VSV) (Selim et al., 2018). Although not tested, authors hypothesised that two compounds; alternariol and alternariol-(9)-methyl ether isolated from the endophytic fungi may be responsible for the antiviral activity. Extracts of endophytic fungi such as *Alternaria alternata, Nigrospora sphaerica* and *Phialophora* sp. showed antiviral activity against the HSV (Manganyi and Ateba 2020). Compounds from endophytic fungi *Phomopsis* sp. isolated from *Achyranthes bidentate* Blume was reported to display promising antiviral activity against HIV-1 (Yang et al., 2020). Following the above reported antiviral activities, it is not unlikely that effective therapeutics may be discovered from endophytes. However, this may not be known if investigations are not carried out. For example, camphotothecin and podophyllotoxin are anticancer drugs isolated from endophytes (Puri et al., 2005, 2006).

4.2. Medicinal plants

A plethora of research exploring herbal formulations and plant-derived molecules as possible treatments against COVID-19 are ongoing in countries such as China, India, Switzerland, Spain, USA, Saudi Arabia, Senegal, Nigeria, South Africa, among others (Akindele et al., 2020; Benarba and Pandiella, 2020; Islam et al., 2020; Koe, 2020; Li et al. 2020; Orhan and Deniz, 2020; Stirgus, 2020). A natural product supplement of curcumin and artemisinin-based oral spray with the product name artemiC, developed by MCG in collaboration with a Swiss firm Micelle Technology is currently undergoing clinical trials as a possible treatment for COVID-19 (Koe, 2020). Another example is the collaboration between the Universities of Yale, Minnesota and Michigan in two randomized trials evaluating the efficacy of administering a dietary supplement containing resistant starch to non-hospitalized COVID-19 patients (Mansour, 2020). There is some scientific evidence supporting dietary therapy and herbal medicines as potential antiviral agents against COVID-19, as have been noticed with other viral diseases (Panyod et al., 2020).

A recent review screened 55 research articles to identify active phytochemicals against coronavirus infection. Compounds such as quercetin, tryptanthrin, scutellarein, saikosaponin B2, myricetin, caffeic acid, psoralidin, isobavachalcone and griffithsin were reported to inhibit human coronavirus, serving as leads for further studies (Mani et al., 2020). The most promising small molecules capable of inhibiting coronavirus contained a conjugated fused ring structure with the majority classified as polyphenols (Mani et al., 2020). Theaflavin (a polyphenol) from *Camellia sinensis* (L.) Kuntze suppressed SARS-CoV-2 via the inhibition of RNA-dependent RNA polymerase (RdRp) activity (Lung et al., 2020). A detailed mechanism of action and safety profile for this phytochemical will be necessary. Plant-derived alkaloids such as emetine, homoharringtonine and cepharanthine are other small molecules which display broad-spectrum antiviral activities and are currently being targeted as potential therapeutics for COVID-19 (Wang and Yang, 2020). Cepharanthine inhibits SARS-CoV-2 through the suppression of agiotensin-converting enzyme 2 (ACE2) activity (Fan et al., 2020). Other plant molecules such as 7-methoxycryptopleurine, ouabain, lycorine, silvestrol, homoharringtonine and tylophorine are also under investigation (Islam et al., 2020).

The potential of plant molecules with anti-inflammatory properties in the treatment of COVID-19 are also being considered. One example is celastrol (Nabavi et al., 2020), a plant-derived product mainly found in the Celastraceae family (Kutney et al., 1981). Extracts from the plant family have been used traditionally in the treatment of oedema, fever and joint pain, and they have low toxicity (Allison et al., 2001). The compound celastrol has been exploited as a source of neuroprotective agent. A collaborative screening of existing drugs against neurodegenerative diseases showed celastrol as one of the active components (Zhao et al., 2012). The anti-inflammatory activity of this compound both in *in vitro* and *in vivo* animal models

was evaluated and mechanisms of action established (Nabavi et al., 2020). Celastrol alleviated chronic obstructive pulmonary disease in the lungs of mice (Shi et al., 2018). It has an anti-inflammatory pathway through the suppression of nuclear factor kappa B (NF-κB) signalling (Zhang et al., 2019). In a study conducted on MERS-CoV and SARS-CoV infections, the inflammatory response mediated by NF-κB pathway was regulated by transmembrane serine protease 2 (TMPRSS2) levels within the airway in a TMPRSS2 knockout murine model (Iwata-Yoshikawa et al., 2019; Nabavi et al., 2020), suggesting that the inhibition of TMPRSS2 may exert a dual effect on COVID-19, limiting viral entry by reducing the cleavage of the spike protein in ACE2 receptor mediated viral entry (Hoffmann et al., 2020; Nabavi et al., 2020).

There is a high demand for herbal products in the treatment of COVID-19 in some countries in Africa, Asia and in the United States of America, with approval by governments in some countries (Timoshyna et al., 2020). Some scientists have suggested the repurposing of available drugs in the market for the management of COVID-19, as the fastest way to curb the spread of the disease, as many diseases share overlapping molecular pathways Hodos et al., (2016); Ahmad et al., (2020). The use of herbal remedies has been widely embraced in China with 91.5% of the total number of coronavirus cases nationwide using repurposed herbal products for treatment. Based on clinical observation, more than 90% efficacy was observed (Timoshyna et al., 2020). More than 125 plant species are reported to be used in the Chinese herbal formulations to treat COVID-19 patients. The most mentioned plants were *Schisandra chinensis* Turcz. (Baill.), *Glycyrrhiza uralensis* Fisch., *Atractylodes macrocephala* Koidz., *Astragalus membranaceus* fisch. ex bunge, *Lonicera japonica* Thunb., *Scutellaria baicalensis* Georgi., *Panax quinquenfolius* L. and *Angelica sinensis* (Oliv.) Diels. Twenty-eight traditional medicine guidelines that provide treatment measures for COVID-19 have been documented, of which 26 were issued by the Chinese government and two by the Korean medicine-professional associations (Ang et al., 2020). Following these guidelines, the most recommended herbal formulas were Shen Fu Tang with Angong Niuhuang Pill or Su He Xiang Pill for treatment of severe case of COVID-19 and a combined formula of Xiang Sha Liu Junzi Tang and Li Zhong Pill at the recovery stage (Ang et al., 2020). In the formulation of these herbal remedies for COVID-19, 12 common herbs include *Glycyrrhiza* Radix et Rhizoma, *Glycyrrhiza uralensis*, Armeniacae Semen Amarum, Ephedrae Herba, Gypsum Fibrosum, Scutellariae Radix, Atractylodis Rhizoma, Poria Sclerotium, Citri Reticulatae Pericarpium, Pinelliae Praeparatum Cum Zingiberis, Forsythiae Fructus, Magnoliae Officinalis Cortex and Agastachis Herba. These herbal formulae were used to treat patients with mild, moderate to severe cases and in recovery. Another Chinese herbal product, Lianhua Qingwen which has been clinically proven active against influenza virus, has also been screened against the SARS-CoVs (Lv et al., 2020). In a clinical trial, the herbal capsule reduced symptoms such as cough, fatigue, fever and shortness of breath in 63 COVID-19 patients (Lv et al., 2020). A 91.5% recovery rate was recorded in 142 COVID-19 patients after 14 days of administering Lianhua Qingwen in a multicenter open-label randomized controlled trial, and this herbal product was confirmed to be safe (Hu et al., 2020). As part of self-care measures, a recommendation was made by the Ministry of AYUSH, Government of India on the use of Ayurveda immune boosters against COVID-19 (Li et al., 2020; Timoshyna et al., 2020; Vellingiri et al., 2020). Honey has also gained some attention due to its antiviral properties with reports on its ability to prevent viral replication (da Cruz et al., 2019; ClinicaTrials.gov, 2020). With safety in focus, it is pertinent that most of these repurposed herbal formulations mentioned above with no available safety data, are properly evaluated for use in COVID-19 patients, especially those with co-morbidities. It is also very important that the mechanisms of action of these herbal formulations are known to avoid contraindications or interactions with unintended molecular targets.

4.3. In silico *screening of plant secondary phytochemicals against SARS-CoV-2*

In the search for effective therapeutics against COVID-19 from plant products, focus should be on plant molecules that are able to interact and bind with the SARS-CoV-2 virus proteins capable of promoting viral entry, replication and infection. Researchers have suggested that any therapeutic of interest should be able to show a high affinity to binding and inhibiting the SARS-CoV-2 spike protein, main protease enzyme (Mpro) and RdRp which are associated with host attachment and viral replication, resulting in infection in the individual. This has been demonstrated through *in silico* studies which is a quick way to identifying potential drugs (Table 1) (e.g Kar et al., 2020; Puttaswamy et al., 2020). The SARS-CoV-2 spike protein is known to attach itself to the human receptor ACE2 through the receptor binding domain (RBD), and this enables viral entry in host cells causing a breakdown in the system of the host Tai et al., (2020). In a molecular docking study conducted by Kar et al. (2020) at the active binding pocket of the RBD of SARS-CoV-2 spike protein, phytocompounds such as adhatodine and anisotine, from *Justicia adhatoda* L.; beta-amyrin and mangiferin from *Swertia chirata* C.B.Clarke; beta-carotene and eugenol from *Ocimum sanctum* L. were found to exhibit an inhibitory effect against the spike protein with anisotine showing the most promising inhibitory potential in terms of binding energy score of 7.8 kcal/mol. A comprehensive interaction profiling of the anisotine-RBD SARSCoV- 2 spike protein complex showed that anisotine interacted with the RDB residues Lys417, Tyr453, Tyr495, Phe497 and Tyr505 of SARS-CoV-2 spike protein. Same inhibitory effect was observed with anisotine against the SARS-CoV-2 Mpro at the active binding pocket where there was an interaction against its residues Gly143, His41, Gln189 and Met165. Considering the findings from this study it can be deduced that anisotine is a potential drug target against the SARS-CoV-2 virus. Hence extensive studies should be carried out on this phytocompound for the possible development of therapeutic against COVID-19. In another molecular docking study, Puttaswamy et al. (2020) evaluated 4,704 ligands against four target proteins: Spike, RdRp, Mpro and the Human TMPRSS2 priming the SARS-CoV-2 spike protein. Authors observed a unique pattern of structurally similar interaction of some phytochemicals with the target proteins. Among the phytochemicals evaluated, triterpenoids showed more than 50% strong interaction with the spike protein-RDB. Also, 32% of molecules that showed interesting interaction with the active site of human TMPRSS2 were flavonoids. Some of the plant molecules were seen to interact with more than one of the target proteins. For example, agathisflavone was seen to interact with RdRp and TMPRSS2, amentoflavone interacted with Mpro and spike protein, while isoginkgetin interacted with RdRp and Mpro. Through an *in silico* screening of the Traditional Chinese Medicine Systems Pharmacology Database (TCMSPD), compounds such as kaempferol, lignan, moupinamide, N-cisferuloyltyramine, quercetin, sugiol, tanshinone IIa, betulinic acid, dihydrotanshinone, coumaroyltyramine, cryptotanshinone, desmethoxyreserpine and dihomo-γ-linolenic acid were identified as potential leads for the development of COVID-19 treatment (Alamanou, 2020).

5. Safety concerns in the use of unproven natural products against COVID-19

The use of herbal remedies as complementary or alternative medicines has been widely embraced in different parts of the world such as Africa, Australia, UK and other countries in Europe, North America and Asia (Calapai, 2008; Braun et al., 2010; Anquez-Traxler, 2011; Nirmal et al., 2013). In Africa, an estimate of 80% of the population

Table 1
Molecular docking studies of some plant molecules as potential therapeutic targets against SARS-CoV-2.

Protein target	Plant molecule	Natural source	Plant family	Binding energy score	References
Spike protein	Bismahanine	Murraya koenigii (L.) Spreng	Rutaceae	−9.1	Puttaswamy et al. (2020)
	Coagulin N	NA	NA	−9.1	Puttaswamy et al. (2020)
	Arecatannin A3	NA	NA	− 8.9	Puttaswamy et al. (2020)
	Coagulin K	NA	NA	− 8.9	Puttaswamy et al. (2020)
	Tannic acid	NA	NA	− 8.9	Puttaswamy et al. (2020)
	Kamalachalcone C	*Mallotus philippensis* (Lam.) Müll. Arg.	Euphorbiaceae	− 8.8	Puttaswamy et al. (2020)
	Pseudojervine	*Veratrum album* L.	Melanthiaceae	− 8.7	Puttaswamy et al. (2020)
	Flavin adenine dinucleotide	NA		− 8.6	Puttaswamy et al. (2020)
	Graecunin E	*Trigonella foenum-graecum* L.	Fabaceae	− 8.6	Puttaswamy et al. (2020)
	Taraxerol	*Clerodendrum trichotomum* Thunb.	Lamiaceae	−7.5	Kar et al. (2020a)
	Friedelin	*Clerodendrum trichotomum* Thunb.		−7.3	Kar et al. (2020a)
	Stigmasterol	*Clerodendrum trichotomum* Thunb.		77.2	Kar et al. (2020a)
	Anisotine	*Justicia adhatoda* L.	Acanthaceae	−7.8	Kar et al. (2020)
	Adhatodine	*Justicia adhatoda* L.		−7.0	Kar et al. (2020)
	Beta-carotene	*Ocimum sanctum* L.	Lamiaceae	−7.2	Kar et al. (2020)
	Eugenol	*Ocimum sanctum* L		−7.3	Kar et al. (2020)
	Mangiferin	*Swertia chirata* (Wall.) C. B. Clarke	Gentianaceae	−7.5	Kar et al. (2020)
	Beta-amyrin	*Swertia chirata* (Wall.) C. B. Clarke		−7.1	Kar et al. (2020)
	Glycyrrhizic acid	*Glycyrrhiza glabra* L.	Fabaceae	− 9.5	Puttaswamy et al. (2020)
	cis-Miyabenol C	*Foeniculum vulgare* Mill. (fennel).	Apiacae	− 9.4	Puttaswamy et al. (2020)
	Proanthocyanidin A2	NA	NA	− 9.2	Puttaswamy et al. (2020)
	Granatin B	*Punica granatum* L.	Punicaceae	− 9.1	Puttaswamy et al. (2020)
	Hippophaenin B	NA	NA	− 9.1	Puttaswamy et al. (2020)
	3-Caffeoyl-5-Feruloylquinic Acid	NA	NA	−9.0	Puttaswamy et al. (2020)
TMPRSS2	3,3′-Biplumbagin	NA	NA	−8.9	Puttaswamy et al. (2020)
	Agathisflavone	NA	NA	−8.9	Puttaswamy et al. (2020)
	Aromoline	NA	NA	−8.9	Puttaswamy et al. (2020)
	Chrysophanein	NA	NA	−8.9	Puttaswamy et al. (2020)
RdRp	Eriodictyol-7-O-rutinoside	*Citrus limon* (L.) BURM.f.	Rutaceae	−9.9	Puttaswamy et al. (2020)
	Narirutin	NA	NA	−9.7	Puttaswamy et al. (2020)
	Hippomannin A	NA	NA	−9.6	Puttaswamy et al. (2020)
	Isoginkgetin	Ginkgo biloba L.	Ginkgoaceae	−9.5	Puttaswamy et al. (2020)
	Kaempferol 3-O-(6′′-galloyl)-beta-D-glucopyranoside	NA	NA	−9.5	Puttaswamy et al. (2020)
	Myricetin 3-rutinoside	*Chrysobalanus icaco* L.	Chrysobalanaceae	−9.5	Puttaswamy et al. (2020)
	Rotundioside B	*Bupleurum rotundifolium* L.	Apiaceae	−9.5	Puttaswamy et al. (2020)
	Tellimagradin I	NA	NA	−9.5	Puttaswamy et al. (2020)
	Agathisflavone	NA	NA	−9.4	Puttaswamy et al. (2020)
	Emblicanin A	NA		−9.4	Puttaswamy et al. (2020)
	Taiwanhomoflavone A	*Cephalotaxus wilsoniana* Hayata	Taxaceae	−9.8	Joshi et al. (2020)
	Beta-carotene	*Ocimum sanctum* L.		−7.1	Kar et al. (2020)
	Lactucopirin 15-oxolate	*Lactuca virosa* L.	Asteraceae	−7.6	Joshi et al. (2020)
	Taraxerol	*Clerodendrum trichotomum* Thunb.		−7.4	Kar et al. (2020a)
Mpro	Anisotine	*Justicia adhatoda* L.	Acanthaceae	−8.4	Kar et al. (2020)
	Adhatodine	*Justicia adhatoda* L.		−7.9	Kar et al. (2020)
	Vasicoline	*Justicia adhatoda* L.		−7.4	Kar et al. (2020)
	Vasicolinone	*Justicia adhatoda* L.		−7.3	Kar et al. (2020)
	Beta-carotene	*Ocimum sanctum* L.		−7.8	Kar et al. (2020)
	Eugenol	*Ocimum sanctum* L.		−7.6	Kar et al. (2020)
	Caryophyllene	*Ocimum sanctum* L.		−7.1	Kar et al. (2020)
	Amarogentin	*Swertia chirata* (Wall.) C. B. Clarke		−8.0	Kar et al. (2020)
	Mangiferin	*Swertia chirata* (Wall.) C. B. Clarke		−7.8	Kar et al. (2020)
Mpro	Taiwanhomoflavone A	*Cephalotaxus wilsoniana* Hayata	Taxaceae	−9.6	Joshi et al. (2020)
	Lactucopirin 15-oxolate	*Lactuca virosa* L.	Asteraceae	−8.2	Joshi et al. (2020)
	Glycyrrhizin	*Glycyrrhiza glabra* L.	Fabaceae	−8.1	Narkhede et al.(2020)
	Tryptanthrine	*Strobilanthes cusia* (Nees) O.Kuntze	Acanthaceae	−8.2	Narkhede et al.(2020)
	β-sitosterol	*Strobilanthes cusia* (Nees) O.Kuntze		−7.2	Narkhede et al.(2020)
	Indirubin	*Strobilanthes cusia* (Nees) O.Kuntze		−7.6	Narkhede et al.(2020)
	Indican	NA	NA	−7.5	Narkhede et al.(2020)
	Indigo	*Isatis indigotica* L.	Brassicaceae	−7.5	Narkhede et al.(2020)
	Hesperetin	*Citrus reticulata* Blanco	Rutaceae	−7.9	Narkhede et al.(2020)
	Crysophanic acid	*Rheum palmatum* L.	Polygonaceae	−7.3	Narkhede et al.(2020)
	Rhein	*Aloe barbadensis* Mill.	Asphodelaceae	−8.9	Narkhede et al.(2020)
	Berberine	*Berberis aristata* DC.	Berberidaceae	−8.1	Narkhede et al.(2020)
	β-caryophyllene	*Ocimum* spp.	Lamiaceae	−7.2	Narkhede et al.(2020)
	Taraxerol	*Clerodendrum trichotomum* Thunb.	Lamiaceae	−8.4	Kar et al. (2020a)
	Friedelin	*Clerodendrum trichotomum* Thunb.		−7.9	Kar et al. (2020a)
	Stigmasterol	*Clerodendrum trichotomum* Thunb.		−7.7	Kar et al. (2020a)
	Friedelin	*Clerodendrum trichotomum* Thunb.		−7.1	Kar et al. (2020a)
	Stigmasterol	*Clerodendrum trichotomum* Thunb.		−7.0	Kar et al. (2020a)
	Isoginkgetin	*Ginkgo biloba* L.		−9.5	Puttaswamy et al. (2020)
	Hypericin	*Hypericum perforatum* L.	Clusiaceae	−10.4	Puttaswamy et al. (2020)
	Amentoflavone	Ginkgo biloba L.		−9.7	Puttaswamy et al. (2020)
	Terflavin B		Combretaceae	−9.7	Puttaswamy et al. (2020)

(*continued*)

Table 1 (*Continued*)

Protein target	Plant molecule	Natural source	Plant family	Binding energy score	References
		Terminalia chebula Retz., *Terminalia catappa* L.			
	Mudanpioside J	*Paeonia delavayi* Franch	Paeoniaceae	−9.6	Puttaswamy et al. (2020)
	Quercetin 3,5-digalactoside	NA	NA	−9.6	Puttaswamy et al. (2020)
	Vescalagin	*Castanea sativa* Mill	Fagaceae	−9.6	Puttaswamy et al. (2020)
Mpro	Ginkgetin	*Ginkgo biloba* L.		−9.5	Puttaswamy et al. (2020)
	Cyanidin 3,5-diglucoside	NA	NA	−9.4	Puttaswamy et al. (2020)
	Delphinidin-3-O-(6-p-coumaroyl) glucoside	NA	NA	−9.4	Puttaswamy et al. (2020)
ACE2	Taiwanhomoflavone A	*Cephalotaxus wilsoniana* Hayata	Taxaceae	−7.6	Joshi et al. (2020)
	Epicatechin-(4b,8)-epicatechin-(4b,6)-catechin	NA	NA	−8.2	
	Epicatechin-4-epigallocatechin	NA	NA	−7.2	Joshi et al. (2020)
	Lactucopicrin 15-oxalate	*Lactuca virosa* L.	Asteraceae	−8.3	Joshi et al. (2020)
	Lactucopicrin	*Lactuca virosa* L.		−8.3	
	Vitetrifolin D	NA	NA	−7.3	Joshi et al. (2020)
	Myricitrin	*Myristica fragrans* Houtt.	Myristicaceae	−7.1	Joshi et al. (2020)
	Apigenin	NA	NA	−7.1	Antonio et al. (2020)
	Kaempferol	NA	NA	−7.2	Antonio et al. (2020)
	Cassameridin	*Litsea kawakamii* Hayata	Lauraceae	−8.1	Joshi et al. (2020)
	Afzelin	*Nymphaea odorata* Aiton	Nymphaeaceae	−7.1	Joshi et al. (2020)
	Isoquercitrin	NA	NA	−7.8	Antonio et al. (2020)
	Silybin	NA	NA	−8.0	Antonio et al. (2020)
	Tetrahydrocurcumin	NA	NA	−8.0	Antonio et al. (2020)
	Aloin	NA	NA	−8.4	Antonio et al. (2020)
	Isoaloresin	NA	NA	−7.8	Antonio et al. (2020)
	Quercetin	NA	NA	−8.7	Antonio et al. (2020)
	Withaferin A	NA	NA	−9.6	Antonio et al. (2020)
	Hinokinin	NA	NA	−7.1	Antonio et al. (2020)
	Phillygenin	NA	NA	−7.8	Antonio et al. (2020)
	Hupehemonside	NA	NA	−7.1	Antonio et al. (2020)
	Imperialine-3-b-D-glucoside	NA	NA	−7.1	Antonio et al. (2020)
TMPRSS2	Silybin	NA	NA	−11.9	Antonio et al. (2020)
	Tetrahydrocurcumin	NA	NA	−8.8	Antonio et al. (2020)
	Corydine	NA	NA	−7.9	Antonio et al. (2020)
	Aloin	NA	NA	−9.2	Antonio et al. (2020)
	Baicalin	NA	NA	−8.5	Antonio et al. (2020)
TMPRSS2	Geniposide	NA	NA	−14.7	Antonio et al. (2020)
	Dictyosphaeric acid A	NA	NA	−14.0	Antonio et al. (2020)
	Durumolide K	NA	NA	−13.9	Rahman et al. (2020)
	Microcarpin	NA	NA	−13.3	Antonio et al. (2020)
	Isogemichalcone B	NA	NA	−13.1	Antonio et al. (2020)

Only plant molecules with binding anergy score between -7 and -15 are reported.

use herbal remedies (Mahomoodally, 2013; WHO, 2019b). Herbal remedies have a global annual market of about US$60 billion (WHO, 2019b). The international trade in medicinal plants is expected to reach US$5 trillion by 2050 (Niraml et al., 2013). Thus, natural products have contributed immensely in the health care system globally. However, natural products may have adverse effects and must be used with caution. It is essential that the general public is aware of the risk associated with the use of unproven or uncertified products.

Since the beginning of the COVID-19 pandemic, people have resorted to self-medication. The internet has been flooded with numerous products acclaimed to fight the virus. This led the United States Food and Drug Administration (FDA) to issue warnings to more than 68 firms producing and marketing these products (FDA, 2020c). Some of these products are: cannabidiol, restorative botanicals, hemp products, colloidal silver, vitamins, minerals, grapefruit seed extract amongst many others (Table 2). The warnings were issued as urgent measures to protect consumers from the negative effects that might result, as these products have not been proven, approved or authorised for use against COVID-19 (FDA, 2020c). For example, colloidal silver can cause serious side effects such as permanent bluish-grey discoloration on the skin (argyria) and contra-indications with antibiotics and thyroxine (NCCIH, 2017). A previous warning on the use of colloidal silver was issued by the FDA in 1999 indicating that the product is not safe or effective for treating any disease or condition (FDA, 1999). Kratom from *Mitragyna speciosa* plant is another acclaimed treatment. It is used traditionally to treat diarrhoea and fatigue and as a possible treatment for pain and management of opioid withdrawal symptoms (NCCIH, 2018). The extract is sold as a treatment for muscle pain or to suppress appetite (Mayo Clinic, 2020). Two compounds,7-hydroxymitragynine and mitragynine, isolated from the leaves interacts with opioid receptors in the brain, producing sedation, pleasure, and decreased pain when administered in high doses (NCCIH, 2018). However, no scientific evidences of its health benefits exist (NCCIH, 2018). Side effects of kratom include increased aggression, hallucinations and delusion, nausea, constipation, irritability, anxiety, itching, difficulty in breathing, loss of appetite and weight, tremor, psychosis, seizures, liver damage and cases of fatalities (NCCIH, 2018; Mayo Clinic, 2020). Ginseng detoxication pills which probably originated from the genus *Panax,* is another example of an acclaimed product in the management of COVID-19 (FDA, 2020c). The genus *Panax* in Greek means “all healing.” It is so called because it is believed to cure any kind of human disease (Kim, 2018). Ginseng is one of the most popular herbal remedies in the global market and there are several pharmacological reports on its ginsenoside compounds (Kim, 2018). However, the product also causes mastalgia and vaginal bleeding even when used at the recommended doses (Baldwin et al, 1986; Dunnick and Nyska, 2013). Other side effects include lack of concentration, headaches, transient nervousness, excitation, epistaxis and allergies (Ekor, 2014). A case of Stevens–Johnson syndrome was

Table 2
A list of acclaimed new drug products related to the fight against Coronavirus Disease 2019 (COVID-19) with no scientific proof.

Product	Unproven/Unapproved claims	Product originally intended	Issued date of warning	References
Corecyte™ Healthy lung wellness injection and other CoreCyte products	Treat and/or prevent COVID-19 via intravenous administration; Improve and support lung health and protect against coronavirus.	–	17 Aug 2020	FDA 2020c
Salt inhaler products	Boost the immunity of your lungs and respiratory tracts with breathing salt therapy to effectively fight coronavirus.	–	11 Aug 2020	FDA 2020c
Chaga products	It may help fight against coronavirus.	–	6 Aug 2020	FDA 2020c
BERSIH antiseptic alcohol 70% hand sanitizer and hand sanitizer gel	Contains 70% alcohol	–	4 Aug 2020	FDA 2020c
Clearcare nogerm advanced hand sanitizer and lavar gel hand sanitizer	Products contain 70% and 75% ethanol	–	23 July 2020	FDA 2020c
MMS tablets, nasal and mouth spray	If you have any flu-like symptoms or confirmed to have COVID-19, take 125 mL of one tablet dissolved in 2 L of water every two hours for eight days; One tablet dissolved in 1.5 L of water to be used in nasal or mouth dispensers into the nose and deep into the throat with three squirts per application against COVID-19.	–	3 Aug 2020	FDA 2020c
E-Munity	The antiviral tincture boosts immune system and strengthen the body against COVID-19 and similar diseases.	–	10 July 2020	FDA 2020c
Traditional Chinese Medicines (TCM)	TCM Lianhua Qingwen plays an important role in fighting against COVID-19 and its capsule has been proven effective for the treatment of COVID-19; Research provides scientific evidence for Lianhua Qingwen; Combining Western medicine and TCM appear to be the best approach to treating COVID-19.	–	6 July 2020, 26 June 2020	FDA 2020c
COVID supplement protection pack, Thymosin-Alpha, and Methylene blue capsules	Improve immunity of the tissues most susceptible to COVID viral attack; Improve immune response once the virus has entered the body; Improve immune response after one experiences respiratory symptoms or fatigue; Improve immune response for those at high risk of moderate-to-severe COVID disease; Methylene blue works by producing a hydrogen peroxide burst within the blood to kill the coronavirus on contact.	–	30 June 2020, 19 June 2020	FDA 2020c
Iodine products	Taking iodine in the form of Lugol's iodine (the Coronavirus Terminator) internally kills COVID-19 or any other virus; Adding Lugol's iodine to 'Ciggy Juice' ramps up the application of antiviral iodine to sensitive lung tissue.	Dietary supplement	10 June 2020	FDA 2020c, NIH 2020
Essential oil	Potent antiviral properties and a powerful antibiotic, particularly for RNA viruses, like the coronavirus responsible for acute respiratory syndromes.	Aromatherapy	8 June 2020, 26 May 2020	FDA 2020c
Silver Biotics, Silver Lozenges with Vitamin C	Take three or four swigs of liquid silver product a day as prophylactic against COVID -19.	To enhance immune system	1 June 2020	FDA 2020c
Silver gel ultimate skin and body care	Dab the silver gel around your nostrils.	First aid for skin	1 June 2020	FDA 2020c
Non-alcohol-based hand sanitizer - Purifi™	The product is certified against coronavirus.	–	28 May 2020	FDA 2020c
StayWell copper	Prevent, treat, mitigate, or cure COVID-19.	Antimicrobial germ killer	28 May 2020	FDA 2020c
Colloidal silver	Boost immune system; Colloidal silver has been a very effective way to kill virus; It's a potent remedy for any infection; Drink the silver and even nebulize it to get it directly in the lungs and at the site of the virus; Atomized fumes through ultrasonic humidifier can be inhaled deep into the lungs which may inhibit the virus from replicating too quickly; Colloidal silver 1100 PPM Immune support protect your immune system.	–	14 Aug 2020, 26 May 2020, 11 May 2020, 1 April 2020, 6 March 2020	FDA 2020c
Nano silver 10 PPM (silver solution)	The Nano silver 10 PPM is your totally non-toxic key to halting COVID-19 attachment, penetration, and replication, with no reason to panic about COVID-19.	–	15 May 2020	FDA 2020c
Vitamins	New study reveals vitamin D may be the key to COVID-19; Severity of coronavirus patient outcomes is directly tied to the patient's vitamin D status.	Immune support	26 May 2020, 20 May 2020	FDA 2020c
	Vitamin D3-K2.	Immune support	11 May 2020	FDA 2020c
	Your Coronavirus Secret Weapon – Vitamin C.	–	13 July 2020, 26 May 2020, 20 May 2020, 6 April 2020	FDA 2020c
Herb oils and minerals	-	General wellbeing	26 May 2020	FDA 2020c
COVID-19 cough syrup and COVIDXIX syrup	Prevent, treat, mitigate, or cure COVID-19.	–	8 May 2020	FDA 2020c
Grapefruit seed extract	Gives a little extra daily protection.		26 May 2020	FDA 2020c

(*continued*)

Table 2 (*Continued*)

Product	Unproven/Unapproved claims	Product originally intended	Issued date of warning	References
		General health benefits		
Colostrum	Colostrum is nature's way of protection against any immune threat.	Immune boaster, growth maintenance	26 May 2020	FDA 2020c
Cod liver oil products	Can help clear off cellular debris after any viral infection.	Source of vitamin A and D for general health benefits	26 May 2020	FDA 2020c
Cannabidiol (CBD) oils and other CBD products	CBD may suppress the productions of cytokines in the setting of infection; CBD oil and related products help combat COVID-19.	Anxiety, insomnia, epilepsy and other health benefits	19 Aug 2020, 26 May 2020, 21 May 2020, 16 April 2020	FDA 2020c, Grinspoon 2020
nCoV19 spike protein vaccine (NCB)	Two shots get you a titer that binds the spike protein and the receptor binding domain and make you immune to nCoV-2019.	–	21 May 2020	FDA 2020c
Kratom	Contains compounds that can strengthen the immune system and keep the coronavirus at bay; May be type of master key against COVID-19.	–	15 May 2020	FDA 2020c
CBD Hemp extract and supplements	Helps build a higher functioning immune system that can aid with symptoms and help a person stay healthy, to fight off illness and can help with COVID-19.	–	15 May 2020	FDA 2020c
White Eagle native herbs	Yahweh: This formula works for almost every disease such as coronavirus.	–	14 May 2020	FDA 2020c
	Kolon Kleen: Works against coronavirus.	–	14 May 2020	FDA 2020c
	Maska Miakoda: Works with Yaweh formula for coronavirus.	–	14 May 2020	FDA 2020c
	Shar Mar formula	–	14 May 2020	FDA 2020c
	Socota and Henna herbal tea: Recommended for all respiratory viruses especially the coronaviruses.	–	14 May 2020	FDA 2020c
Dietary supplements	NAC (N-acetylcysteine): Recommended for coronavirus.	General wellbeing	14 May 2020	FDA 2020c
	Adaptogens: Reduce cortisol levels and improve immune response.	–	14 May 2020	FDA 2020c
	Zinc: Reduce the severity and duration of colds, flu, infections, wounds, and many other diseases.		14 May 2020	FDA 2020c
	Magnesium: Assist with immune response and reduce susceptibility to viral infections.	General wellbeing	14 May 2020	FDA 2020c
Immune shot	Contains vitamin D3 that may help to fight COVID-19 by reducing the incidence, severity, and risk of death from current COVID -19.	–	11 May 2020	FDA 2020c
Plum dragon herbs (Chinese herbs for cold-damp) Shanghan Lun phase of COVID-19	Boast immune system in the fight against COVID -19.	–	8 May 2020	FDA 2020c
Durisan hand sanitizer	The water-based and alcohol-free kills 99% of human coronavirus.	–	7 May 2020	FDA 2020c
Medicinal mushrooms	Mushrooms to be taken alongside each other in tincture form for both prevention and treatment and should be doubled if symptoms of COVID-19 begin.	General wellbeing	7 May 2020	FDA 2020c
Elderberry Syrup	–	–	7 May 2020	FDA 2020c
Liquorice root	Liquorice root act as a potential treatment for COVID-19.	–	7 May 2020	FDA 2020c
Stephen Buhner COVID herbal blends, COVID-19 core formula	–	–	7 May 2020	FDA 2020c
Glutagenic virus protection kit	Use for prevention and as treatment against COVID-19	–	6 May 2020	FDA 2020c
Liposomal sublingual gel supplement	The mixture gives a rapid and thorough reversal of COVID-19.	–	6 May 2020	FDA 2020c
Liposomal vitamin C with silver excelsior immunity boost bundle	Help keep the immune system at top performance.	–	4 May 2020	FDA 2020c
Transdermal patch (Santiste Labs LLC)	Offers possible resistance to the novel coronavirus; Boost your immune system and provide antiviral support all day.	–	27 April 2020	FDA 2020c
Hopewell products (Warrior essential oil, Cinnamon bark, lung support, respiratory relief)	–	–	27 April 2020	FDA 2020c
Prefense non-alcoholic hand and skin sanitizer	Prefense hand and skin sanitizer offers an alternative to alcohol-based gels; The only product on the market today that kills germs on contact and offers continuous protection for up to 24 hours or 10 hand washings with only one application.	–	23 April 2020	FDA 2020c
CopperTouch	Kills coronaviruses.	–	21 April 2020	FDA 2020c
Earth Angel oils	Rub on top of the feet, wrists, and chest to fight viruses.	General wellbeing	14 April 2020	FDA 2020c
ViralDefense tincture	–	–	13 April 2020	FDA 2020c
Alpha 11 and Alpha 21		–	13 April 2020	FDA 2020c

(*continued*)

Table 2 (*Continued*)

Product	Unproven/Unapproved claims	Product originally intended	Issued date of warning	References
	The use of Arogya's ayurvedic products like Alpha 21 and Alpha 11 prevent you from being infected with coronavirus.			
Herbs of Kedem	Contain compounds that may inhibit the attachment of the new coronavirus to cells in the body.	General wellbeing	10 April 2020	FDA 2020c
Super silver toothpaste, super blue toothpaste, super silver wound gel and superblue silver immune gargle	Boost your immune system against virus.	–	9 April 2020	FDA 2020c
Respiratory aid kit	The kit gives support to the immune system and the lungs and helps get through the respiratory illnesses more quickly and more easily.	–	9 April 2020	FDA 2020c
Miracle mineral solution (MMS) (chlorine dioxide)	Confirmed cases of COVID-19 patients recovered after treatment with MMS.	–	8 April 2020	FDA 2020c
Fortify humic beverage concentrate	Clinically proven antiviral that could help fight COVID-19; Can fight latent infections, because once the virus reactivates, it prevents the newly created viruses from entering your cells and reproducing, reducing your viral load over time.	–	8 April 2020	FDA 2020c
Electric fulvic beverage concentrate	Extremely effective as antiviral.	–	8 April 2020	FDA 2020c
China Corona Nosode	Boost immune system.	–	7 April 2020	FDA 2020c
CoronaDefender herbal sachet	Formulated for modifying your body surface so that the novel coronavirus stands less chance to survive on your body.	–	6 April 2020	FDA 2020c
Chinese herbal tea	Prevent COVID-19.	General wellbeing	6 April 2020	FDA 2020c
Chinese herbal solutions	Use for prevention and treatment of COVID -19.	–	6 April 2020	FDA 2020c
Herbal Agastachis pill	–	–	6 April 2020	FDA 2020c
CoronaDefender Herbal tea	Formulated for internal use to better prepare yourself for fighting with the novel coronavirus when necessary.	–	6 April 2020	FDA 2020c
Ginseng detoxication pill	Use it if infected with the novel coronavirus.	–	6 April 2020	FDA 2020c
Honeysuckle and forsythia formula	Use it if infected with coronavirus.	–	6 April 2020	FDA 2020c
Cannabis indica	It speeds up recovery from coronavirus.	–	6 April 2020	FDA 2020c
Saline therapy	It strengthens the lungs to fight against the novel coronavirus.	General wellbeing	30 March 2020	FDA 2020c
Corona-Cure antiseptic nasal defense	Kills COVID-19; Protect the vulnerable nasal passages from COVID-19 infection.	–	26 March 2020	FDA 2020c
Quinessence antivirus synergy	It can't hurt to use the essential oils to avoid infection until a cure has been developed.	–	6 March 2020	FDA 2020c
Vivify holistic clinic formula #1 and #3	Works against coronavirus.	–	6 March 2020	FDA 2020c
Vivify holistic clinic – Boneset (Loose leaf tea)	Effective against coronavirus.	–	6 March 2020	FDA 2020c
Baptized COVID organics	Relief symptoms of COVID-19.	–	4 May 2020	Mugabi 2020, WHO, 2020f

reported after the administration of ginseng to a patient for three days (Dega et al., 1996). The plant products may also have carcinogenic effects in the liver and thyroid and can induce tumorigenesis in the nasal cavity (Ekor, 2014).

While acknowledging the fact that traditional medicines have enormous health benefits that may be exploited as possible therapeutics for COVID-19, the WHO recently warned against the use of unproven traditional herbs in the treatment of COVID-19 (Mugabi, 2020; WHO, 2020f). This came after a herbal drink named Baptized COVID Organics was introduced in Madagascar and acclaimed as being helpful in the treatment of COVID-19. Some African countries such as Guinea, Equatorial Guinea, Guinea-Bissau, Liberia and Tanzania purchased large quantities of this herbal drink (Mugabi, 2020). The drink is derived from an anti-malaria plant *Artemisia* and mixed with other herbs. Although, the drink is acclaimed as helpful in relieving symptoms of COVID-19, there is currently no scientific proof or evidence. There is the fear of possible toxicity which may lead to adverse effects and no published safety evidence for this drink exists. A concern is that people who consume this drink may become susceptible to malaria as they may develop resistance to the drug artemisinin (Mugabi, 2020). Several herbal formulations have received approval from the Chinese Government and three patented herbal drugs are currently being used to treat COVID-19, with no strong scientific evidence of efficacies and safety (Ang et al., 2020; Cunningham et al., 2020; Yang, 2020). Finding an effective treatment for an ailment is important but safety is a major priority that must never be ignored. It cannot be disputed that all drugs, be it conventional, complementary or alternative, carry risks for the users (Juhn et al., 2007; Ghenadenik et al., 2012; Yang, 2020). However, with detailed clinical studies, safe dose ranges are attained, and possible adverse effects or contra-indications are known. Such important information assists in the prescription of such therapeutics to patients. Hence, it is of utmost importance that rigorous clinical studies with safety as a major focus are carried out on herbal remedies.

There is much misleading information available on the internet on the use of garlic (*Allium sativum* L.) against COVID-19, which has led to the increased demand of garlic (McClain, 2020; Wiesemeyer, 2020). Although garlic has some medicinal properties, there is no evidence of its efficacy against COVID-19 (WHO, 2020g). Adverse effects which include light headedness, nausea, alteration of platelet function and coagulation, burning sensation in the gastrointestinal tract, diaphoresis, hypotension and allergy have been associated to the use of garlic (Rose et al., 1990; Borrelli et al., 2007; WebMD, 2020a).

Another example of widely spread, misleading information is the use of ginger (*Zingiber officinale* Rosc.) to cure COVID-19. Ginger is often included in diets to treat nausea, vomiting, diabetes, migraine, menstrual cramps and osteoarthritis (Mashhadi et al., 2013; WebMD, 2020b). The plant possesses anticancer, anti-inflammatory, antidiabetic and antioxidant properties (Mashhadi et al., 2013). However, its cure against COVID-19 has not been established. The WHO warned in a message conveyed by the executive director of the WHO Health Emergencies Program, Michael Ryan on 3rd April 2020 that,

though, ginger can have some health benefits, no evidence on its ability to cure COVID-19 exist (Wintle, 2020). Some side effects of ginger include heartburn, mouth irritation and diarrhoea. Although there are no reports of its contra-indication, there are concerns that ginger may interact with anticoagulants NCCIH (2016). Hence, it is not wise to use unproven natural products with the notion that they are completely free of side effects.

One of the most used herbs in Chinese and Korean traditional medicine is the Semen Armeniacae Amarum, known as apricot seed (*Prunus armeniaca* L.). It has a long history in controlling acute lower respiratory infections (Jin et al., 2009). This is one of the common herbs included in the Chinese herbal formulations against COVID-19 (Ang et al., 2020). *In vivo* studies have shown its toxicity in rats, leading to fatalities (Suchard et al., 1998; Kim et al, 2012; Park et al., 2013). This toxicity has been linked to the presence of amygdalin and hydrogen cyanide which is more concentrated in the endocarp and can cause life-threatening respiratory disorders (Park et al., 2013). As a result, it is advised that the endocarp is removed when using it in herbal formulations (Park et al., 2013). Hence, a strong quality control needs to be set for this herb even after clinical studies on its potency against COVID-19 is established.

6. Collaboration between research scientists, government and medicinal practitioners as a possible way forward

The inclusion of traditional medicinal practitioners in the management of health crises is an important option that should not be overlooked. In many African countries, especially in the rural areas, and among the poor, traditional medicinal practitioners are often the closest resource when it comes to health issues with an estimated 80% of the African population using herbal remedies (WHO, 2019b). Most of these traditional healers have learned a wealth of knowledge from their ancestors with regards to plant medicinal use. It is regarded as a trade which helps to sustain their livelihoods (Karunamoorthi et al., 2013; Hamilton, 2014). These traditional healers may be aware of the negative effects that might result but do not have the capacity to follow the drug development process. Hence, a criticism of traditional healing is that, traditional healers lack a body of evidence to authenticate their practice through scientific knowledge (Mokgobi, 2014). Having the knowledge that a natural product can cure, manage or treat an infection is not enough. With the influx of herbal remedies and increase in self-medication especially in this COVID-19 era, safe use of drugs is an issue of great public health importance. The need for extensive toxicity assessment on herbal products for safe use and protection of public health cannot be overemphasized. However, there are many challenges when it comes to the regulation of herbal medicines in different parts of the world. Because of this, there is a need for a global standard and strong regulatory policies on herbal medicines (Ekor, 2014; WHO, 2019b).

It is risky to use a drug when important parameters such as how it is absorbed, distributed, metabolized and excreted, the mechanisms of action of that drug, the safe dosage range, side effects or adverse effects that may result due to possible toxicity, and its interaction with other drugs and treatments are not known. Five major processes are involved in drug development. These include discovery and development, preclinical research, clinical research, FDA review and FDA post-market safety monitoring (FDA-CDER, 2016; FDA, 2018). The WHO has set some basic criteria that need to be followed in herbal formulations. These processes include efficacy, safety, quality control, marketing and regulatory guidelines (Akerele, 1993; WHO Technical Report, 2018). Drug development processes may be rigorous but seems to be the only way to develop an effective and safe therapeutic (Yang, 2020). The safety assessment of effective therapeutics is critical for drug use. *In silico* methods for the assessment of drug safety has recently become a useful tool (Arvidson et al., 2008; Rahman et al., 2020). Such methods are relevant in identifying safe doses, drug interaction, among others, thereby giving a quick understanding of such a drug and a quick lead for further investigation. Though dose-response relationship is usually the main focus when it comes to safety assessment, some researchers have argued that this is not enough as other parameters need to be taken into consideration, before it can be concluded that a drug is safe. According to Li (2004), Five key parameters to be considered are; (1) Possible toxicity due to drug–target interactions, including interactions with unintended molecular targets, or with molecular targets in unintended organs; (2) Chemical scaffolding and side-chains with safety concerns; (3) Toxicity in animals *in vivo* and *in vitro*; (4) Safety concerns due to toxification or detoxification, organ distribution, clearance and pharmacokinetic drug–drug interactions and (5) Physiological, environmental and genetic factors that may enhance a patient's susceptibility. Most of these drug development stages need to be carried out by research scientists and clinicians. Therefore, collaborative efforts are needed. For instance, traditional medicine researchers in Togo are working in collaboration with scientists to find ways for traditional medicine to be integrated into the treatment of COVID-19 (Mugabi, 2020). Governments, especially in developing countries, have pivotal roles to play in these collaborations, such as capacity building for traditional healers and scientists alike. With the available wealth of knowledge on natural products with antiviral properties, possible safe and effective preventive agents or therapeutics against COVID-19 may be discovered through such global collaborative efforts and selfless dedication to practice.

7. Recommendation and conclusion

The COVID-19 pandemic has resulted in the influx of high volumes of unproven and unapproved products in the market globally and increased self-medication. A number of vaccines have recently been approved for use to curb the spread of the virus. However, availability and acceptance by some critics is a big challenge. Conventional drugs such as remdesivir, chloroquine/hydroxychloroquine and dexamethasone are the major proposed drugs that are currently under trials for the management of this disease. Repurposing of therapeutics including those of natural products already available in the market, have been advocated by researchers with some countries already approving such for treatment or management of COVID-19. Natural products are helpful in the treatment of infections, but the consumption of unproven and unapproved products is a great health risk. It is of utmost importance that proposed or repurposed natural products against the novel SARS-CoV-2 virus are well evaluated for efficacy, mechanisms of action and safety before use. Collaborative efforts between researchers, governments and traditional medicinal practitioners in the search and development of possible safe and effective therapeutics from natural products, that may be helpful in the treatment or management of COVID-19 is a good option to explore.

Declaration of Competing Interest

The authors of this review declare no conflict of interest whatsoever.

Acknowledgements

The authors are grateful to Dr Wendy Stirk (Research Center for Plant Growth and Development, University of KwaZulu-Natal, South Africa), May Okafor (University of KwaZulu-Natal, South Africa), Mrs Lee Warren (Research Center for Plant Growth and Development, University of KwaZulu-Natal, South Africa) and Dr. Osariyekemwen Uyi (Pennsylvania State University, United States of America) for their valuable technical support and copy-editing. AGO-U is grateful to the

Research Centre for Plant Growth and Development under the University of KwaZulu-Natal for Postdoctoral research funding.

References

Abdalla, M.A., McGaw, L.J., 2018. Bioprospecting of South African plants as a unique resource for bioactive endophytic microbes. Front. Pharmacol. 9, 1–10.

Ahmad, J., Ikram, S., Ahmad, F., Rehman, I.U., Mushtaq, M., 2020. SARS-CoV-2 RNA dependent RNA polymerase (RdRp) - A drug repurposing study. Heliyon 6, 4502.

Akerele, O., 1993. Nature's medicinal bounty: don't throw it away. World Health Forum 14, 390–395.

Akindele, A.J., Agunbiade, F.O., Sofidiya, M.O., Awodele, O., Sowemimo, A., Ade-Ademilua, O., Akinleye, M.O., Ishola1, I.O., Orabueze, I., Salu, O.B., Oreagba, I.A., Asekun, O.T., Odukoya, O., 2020. COVID-19 pandemic: a case for phytomedicines. Nat. Prod. Commun. 15, 1–9.

Alamanou, M.T., 2020. Anti-Coronavirus Natural Products and *In silico* Screening. . https://towardsdatascience.com/anti-coronavirus-natural-products-and-in-silico-screening-54d9f03b7daf. (Accessed 28 June 2020).

Allison, A.C., Cacabelos, R., Lombardi, V.R.M., Alvarez, X.A., Vigo, C., 2001. Celastrol, a potent antioxidant and anti-inflammatory drug, as a possible treatment for Alzheimer's disease. Prog. Neuropsychopharmacol. Biol. Psychiatry 25, 1341–1357.

Alvin, A., Miller, C.I., Neilan, B.A., 2014. Exploring the potential of endophytes from medicinal plants as sources of antimycobacterial compounds. Microbiol. Res. 169, 483–495.

Andersen, K.G., Rambaut, A., Lipkin, W.I., Holmes, E.C., Garry, R.F., 2020. The proximal origin of SARS-CoV-2. Nat. Med. 26, 450–455.

Ang, L., Lee, H.W., Choi, J.Y., Zhang, J., Lee, M.S., 2020. Herbal medicine and pattern identification for treating COVID-19: A rapid review of guidelines. Integr. Med. Res. 9, 100407.

Anquez-Traxler, C., 2011. The legal and regulatory framework of herbal medicinal products in the European Union: a focus on the traditional herbal medicines category. Drug Inf. J. 45, 15–23.

Antonio, A.D.S., Wiedemann, L.S.M., Veiga-Junior, V.F., 2020. Natural products' role against COVID-19. RSC Adv. 10, 23379–23393.

Arvidson, K.B., Valerio, L.G., Diaz, M., Chanderbhan, R.F., 2008. *In Silico* toxicological screening of natural products. Toxicol. Mech. Methods 18, 2–3.

Auwaerter, P.G., 2020. Coronavirus Treatment: What's in Development. John Hopkins Medicine. https://www.hopkinsmedicine.org/health/conditions-and-diseases/coronavirus/coronavirus-treatment-whats-in-development. (Accessed 16 July 2020).

Baldwin, C.A., Anderson, L.A., Phillipson, J.D., 1986. What pharmacists should know about Ginseng? Pharm. J. 237, 583–586.

Beigel, J.H., Tomashek, K.M., Dodd, L.E., Mehta, A.K., Zingman, B.S., Kalil, A.C., Hohmann, E., Chu, H.Y., Luetkemeyer, A., Kline, S., de Castilla, D.L., Finberg, R.W., Dierberg, K., Tapson, V., Hsieh, L., Patterson, T.F., Paredes, R., Sweeney, D.A., Short, W.R., Touloumi, G., Lye, D.C., Ohmagari, N., Oh, M., Ruiz-Palacios, G.M., Benfield, T., Fätkenheuer, G., Kortepeter, M.G., Atmar, R.L., Creech, C.B., Lundgren, J., Babiker, A.G., Pett, S., Neaton, J.D., Burgess, T.H., Bonnett, T., Green, M., Makowski, M., Osinusi, A., Nayak, S., Lane, H.C., 2020. Remdesivir for the treatment of Covid-19 – preliminary report. N. Engl. J. Med. 383, 1813–1826.

Benarba, B., Pandiella, A., 2020. Medicinal plants as sources of active molecules against COVID-19. Front. Pharmacol. 11, 1189.

Borrelli, F., Capasso, R., Izzo, A., 2007. Garlic (*Allium sativum* L.): Adverse effects and drug interactions in humans. Mol. Nutr. Food Res. 51, 1386–1397.

Braun, L.A., Tiralongo, E., Wilkinson, J.M., Poole, S., Spitzer, O., Bailey, M., Dooley, M., 2010. Adverse reactions to complementary medicines: the Australian pharmacy experience. Int. J. Pharm. Pract. 18, 242–244.

Calapai, G., 2008. European legislation on herbal medicines: a look into the future. Drug Saf. 31, 428–431.

CDC, 2020a. Middle East Respiratory Syndrome (MERS). Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/mers/about/symptoms.html. (Accessed 23 June 2020).

CDC, 2020b. What you Should Know About COVID-19 to Protect Yourself and Others. . https://www.cdc.gov/coronavirus/2019-ncov/downloads/2019-ncov-factsheet.pdf. (Accessed 15 July 2020).

CDC, 2020c. People of Any Age With Underlying Medical Conditions. Centeres for Diseases Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. (Accessed 27 June 2020).

CDC, 2020d. Coronavirus Disease 2019 (COVID-19) Symptoms of coronavirus. https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html. (Accessed 16 July 2020).

Chemocare, 2020. Dexamethasone. http://chemocare.com/chemotherapy/drug-info/dexamethasone.aspx. (Accessed 16 January 2021).

Chen, Y., Shen, T., Zhong, L., Liu, Z., Dong, X., Huang, T., Wang, Q., Xiao, H., 2020. Research progress of Chloroquine and Hydroxychloroquine on the COVID-19 and their potential risks in clinic use. Front. Pharmacol. 11, 1167.

Clark, A., Jit, M., Warren-Gash, C., Guthrie, B., Wang, H.H.X., Mercer, S.W., Sanderson, C., McKee, M., Troeger, C., Ong, K.L., Checchi, F., Perel, P., Joseph, S., Gibbs, H.P., Banerjee, A., Eggo, R.M., 2020. Global, regional, and national estimates of the population at increased risk of severe COVID-19 due to underlying health conditions in 2020: a modelling study. Lancet Glob. Health 8, 1003–1017.

ClinicaTrials.gov, 2020. Efficacy of Natural Honey Treatment in Patients With Novel Coronavirus. . https://clinicaltrials.gov/ct2/show/NCT04323345.

Cunningham, A.C., Goh, H.P., Koh, D., 2020. Treatment of COVID-19: old tricks for new challenges. Crit. Care 24, 91.

da Cruz, B.C.F., Ronqui, L., Scharnoski, P., Scharnoski, P., Peruzzolo, M., Santos, P.D.R., Halak, A., Wielewski, P., Magro, J.M., de Araujo, K.F., 2019. Health Benefits of Honey. https://www.intechopen.com/online-first/health-benefits-of-honey. (Accessed 14 July 2020).

Dega, H., Laporte, J.L., Francès, C., Herson, S., Chosidow, O., 1996. Ginseng as a cause for Stevens–Johnson syndrome? Lancet 347, 1344.

Dunnick, J.K., Nyska, A., 2013. The toxicity and pathology of selected dietary herbal medicines. Toxicol. Pathol. 41, 374–386.

Ekor, M., 2014. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. Front. Pharmacol. 4, 177.

Eyvazzadeh, A., 2020. Treatment for coronavirus disease (COVID-19). Healthline. https://www.healthline.com/health/coronavirus-treatment. (Accessed 27 March 2020).

Fan, H.H., Wang, L.Q., Liu, W.L., An, X.P., Liu, Z.D., He, X.Q., Song, L.H., Tong, Y.G., 2020. Repurposing of clinically approved drugs for treatment of corona-virus disease 2019 in a 2019-novel coronavirus-related coronavirus model. Chin. Med. J. 133, 1051–1056.

Fardet, L., Genereau, T., Cabane, J., Kettaneh, A., 2006. Severe strongyloidiasis in corticosteroid-treated patients. Clin. Microbiol. Infect. 12, 945–947.

Farooq, D., 2020. Effectiveness of Hydroxychloroquine in COVID-19 Patients (Covid). United States National Library of Medicine.. ClinicalTrials.gov https://clinicaltrials.gov/ct2/show/NCT04328272?type=Intr&cond=covid19&draw=2&rank2. (Accessed 7 April 2020).

FDA, 1999. United States Food and Drug Administration Rules and regulations: over-the-counter drug products containing colloidal silver ingredients or silver salts. Final rule. Fed. Regist. 64, 44653–44658.

FDA, 2018. The Drug Development Process. United States Food and Drug Administration. https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process. (Accessed 6 July 2020).

FDA, 2020a. Coronavirus (COVID-19) Update: FDA Issues Emergency use Authorization for Potential COVID-19 Treatment. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment. (Accessed 20 June 2020).

FDA, 2020b. FDA Cautions Against use of Hydroxychloroquine or Chloroquine for COVID-19 Outside of the Hospital Setting or a Clinical Trial Due to Risk of Heart Rhythm Problems. https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or. (Accessed 6 July 2020).

FDA, 2020c. Fraudulent Coronavirus Disease 2019 (COVID-19) Products. . https://www.fda.gov/consumers/health-fraud-scams/fraudulent-coronavirus-disease-2019-covid-19-products. (Accessed 29 August 2020).

FDA-CDER, 2016. Botanical Drug Development Guidance for Industry. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. . https://www.fda.gov/files/drugs/published/Botanical-Drug-Development–Guidance-for-Industry.pdf.

Gazeta, N., 2020. A Virology Expert Answers Key Questions on COVID-19. World Economic Forum. https://www.weforum.org/agenda/2020/03/covid-19-explained-virology-expert/. (Accessed 27 March 2020).

Ghenadenik, A., Rochais, É., Atkinson, S., Bussières, J.F., 2012. Potential risks associated with medication administration, as identified by simple tools and observations. Can. J. Hosp. Pharm. 65 (4).

Grein, J., Ohmagari, N., Shin, D., Diaz, G., Asperges, E., Castagna, A, Feldt, T., Green, G., Green, M.L., Lescure, F.X., Nicastri, E., Oda, R., Yo, K., Quiros-Roldan, E., Studemeister, A., Redinski, J., Ahmed, S., Bernett, J., Chelliah, D., Chen, D., Chihara, S., Cohen, S.H., Cunningham, J., Monforte, A.D, Ismail, S., Kato, H., Lapadula, G., L'Her, E., Maeno, T., Majumder, S., Massari, M., Mora-Rillo, M., Mutoh, Y., Nguyen, D., Verweij, E., Zoufaly, A., Osinusi, A.O., DeZure, A., Zhao, Y., Zhong, L., Chokkalingam, A., Elboudwarej, E., Telep, L., Timbs, L., Henne, I., Sellers, S., Cao, H., Tan, S.K., Winterbourne, L., Desai, P., Mera, R., Gaggar, A., Myers, R.P., Brainard, D.M., Childs, R., Flanigan, T., 2020. Compassionate use of Remdesivir for patients with severe Covid-19. N. Engl. J. Med. 382, 2327–2336.

Grinspoon, P., 2020. Cannabidiol (CBD) – What we Know and What we Don't. Harvard Health Publishing. https://www.health.harvard.edu/blog/cannabidiol-cbd-what-we-know-and-what-we-dont-2018082414476. (Accessed 14 July 2020).

Hallmann, J., Schulz, B., Berg, G., 2006. Isolation procedures for endophytic microorganisms. Microbial Root Endophytes. Springer, Berlin, Heidelberg, New York, pp. 299–314.

Hamilton, A.C., 2014. Medicinal plants, conservation and livelihoods. Biodivers. Conserv. 13, 1477–1517.

Hassanin, A., 2020. Coronavirus Origins: Genome Analysis Suggests two Viruses May Have Combined. World Economic Forum. https://www.weforum.org/agenda/2020/03/coronavirus-origins-genome-analysis-covid19-data-science-bats-pangolins/. (Accessed 16 January 2020).

Health24, 2020. Infectious Diseases. https://www.health24.com/Medical/Infectious-diseases/Coronavirus/a-brief-history-of-the-coronavirus-family-including-one-pandemic-we-might-have-missed-20200325. (Accessed 7 April 2020).

Herper, M., 2020. Hydroxychloroquine Does not Prevent Covid-19 Infection if Exposed, Study Says. https://www.statnews.com/2020/06/03/hydroxychloroquine-does-not-prevent-covid-19-infection-in-people-who-have-been-exposed-study-says/. (Accessed 18 June 2020).

Hodos, R.A., Kidd, B.A., Khader, S., Readhead, B.P., Dudley, J.T., 2016. Computational approaches to drug repurposing and pharmacology, Wiley Interdiscip. Rev. Syst. Biol. Med. 8, 186–210.

Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Nitsche, A., 2020. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181, 271–280.
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., Zhong, N., 2020. Efficacy and safety of Lianhuaqingwen capsules, a repurposed Chinese herb, in patients with Coronavirus disease 2019: a multicenter, prospective,randomized controlled trial. Phytomedicine 2020, 153242.
Islam, M.T., Sarkar, C., El-Kersh, D.M., Jamaddar, S., Uddin, S.J., Shilpi, J.A., Mubarak, M.S., 2020. Natural products and their derivatives against coronavirus: a review of the non-clinical and pre-clinical data. Phytother. Res. 2020, 1–22.
Iwata-Yoshikawa, N., Okamura, T., Shimizu, Y., Hasegawa, H., Takeda, M., Nagata, N., 2019. TMPRSS2 contributes to virus spread and immunopathology in the airways of murine models after coronavirus infection. J. Virol. 93, 1815–1818.
Chapter 12 Jaiswal, N.K., Saxena, S.K., 2020. Classical Coronaviruses. S.K. In: Saxena, S.K. (Ed.), Coronavirus Disease 2019 (COVID-19), Medical Virology: from Pathogenesis to Disease Control. Springer Nature, pp. 141–213.
Jean, S.S., Lee, P.I., Hsueh, P.R., 2020. Treatment options for COVID-19: the reality and challenges. J. Microbiol. Immunol. Infect. 53, 436–443.
Jin, J., Liu, B., Zhang, H., Tian, X., Cai, Y., Gao, P., 2009. Mutagenicity of Chinese traditional medicine Semen Armeniacae amarum by two modified Ames tests. BMC Complement. Altern. Med. 9, 43.
Joseph, A., 2020. New England Journal retract Covid-19 Studies, Including one that Raised Safety Concerns About Malaria Drugs. Lancet https://www.statnews.com/2020/06/04/lancet-retracts-major-covid-19-paper-that-raised-safety-concerns-about-malaria-drugs/. (Accessed 13 June 2020).
Joshi, R.S., Jagdale, S.S., Bansode, S.B., Shankar, S.S., Tellis, M.B., Pandya, V.K., Chugh, A., Giri, A.P., Kulkarni, M.J., 2020. Discovery of potential multi-target-directed ligands by targeting host-specific SARS-CoV-2 structurally conserved main protease. J. Biomol. Struct. Dyn. https://doi.org/10.1080/07391102.2020.1760137 1-4..
Juhn, P., Phillips, A., Buto, K., 2007. Balancing modern medical benefits and risks. Health Aff. 26, 647–652.
Kahn, J.S., McIntosh, K., 2005. History and recent advances in coronavirus discovery. Pediatr. Infect. Dis. J. 24, S223–S227.
Kan, B, Wang, M, Jing, H, Xu, H, Jiang, X, Yan, M, Liang, W, Zheng, H, Wan, K., Liu, O., Cui, B., Xu, Y., Zhang, E., Wang, H., Ye, J., Li, G., Li, M., Cui, Z., Qi, X., Chen, K., Du, L., Gao, K., Zhao, Y.T, Zou, X.Z., Feng, Y.J., Gao, Y.F., Hai, R., Yu, D., Guan, Y., Xu, J., 2005. Molecular evolution analysis and geographic investigation of severe acute respiratory syndrome coronavirus- like virus in palm civets at an animal market and on farms. J. Virol. 79, 11892–11900.
Kar, P., Kumar, V., Vellingiri, B., Sen, A., Jaishee, N., Anandraj, A., Malhotra, H., Bhattacharyya, S., Mukhopadhyay, S., Kinoshita, M., Govindasamy, V., Roy, A., Naidoo, D., Subramaniam, M.D., 2020. Anisotine and amarogentin as promising inhibitory candidates against SARSCoV- 2 proteins: a computational investigation. J. Biomol. Struct. Dyn. 2020, 1–12.
Karunamoorthi, K., Jegajeevanram, K., Vijayalakshmi, J., Mengistie, E., 2013. Traditional medicinal plants: a source of phytotherapeutic modality in Resource-Constrained Health care settings. Evid. Based Complement. Altern. Med. 18, 67–74.
Kim, J.H., 2018. Pharmacological and medical applications of Panax ginseng and ginsenosides: a review for use in cardiovascular diseases. J. Ginseng Res. 42, 264–269.
Kim, S.R., Lee, J.W., Lim, S.Y., Jung, Y.S., Choi, H.Y., Kim, J.D., 2012. Rat single oral dose toxicity test of Armeniacae Semen (including endocarp). Korean J. Intern. Med. 33, 145–159.
Koe, T., 2020. Covid-19 Natural Product Trial: New Curcumin, Artemisinin Supplement to be Tested on Patients. Nutra Ingredients-asia.com. https://www.nutraingredients-asia.com/Article/2020/04/23/COVID-19-natural-product-trial-New-curcumin-artemisinin-supplement-to-be-tested-on-patients. (Accessed 11 June 2020).
Kutney, J.P., Hewitt, G.M., Kurihara, T., Salisbury, P.J., Sindelar, R.D., Stuart, K.L., Townsley, P.M., Chalmers, W.T., Jacoli, G.G., 1981. Cyto-toxic diterpenes triptolide, tripdiolide, and cyto-toxic triterpenes from tissue cultures of Tripterygium wilfodii. Can. J. Chem. 59, 2677–2683.
Lau, S.K.P., Luk, H.K.H., Wong, A.C.P., Li, K.S.M., Zhu, L., He, Z., Fung, J., Chan, T.T.Y., Fung, K.S.C, Woo, P.C.Y., 2020. Possible bat origin of severe acute respiratory syndrome coronavirus 2. Emerg. Infect. Dis. 26, 1542–1547.
Li, A.P., 2004. A comprehensive approach for drug safety assessment. Chem. Biol. Interact. 150, 27–33.
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.
Lowe, D., 2020. Chloroquine, past and present. Sci. Transl. Med. https://blogs.sciencemag.org/pipeline/archives/2020/03/20/chloroquine-past-and-present. (Accessed 7 April 2020).
Lung, J., Lin, Y.S., Yang, Y.H., Chou, Y.L., Shu, L.H., Cheng, Y.C., Liu, H.T, Wu, Y., 2020. The potential chemical structure of anti-SARS-CoV-2 RNA-dependent RNA polymerase. J. Med. Virol. 92, 693–697.
Lv, R.B., Wang, W.J., Li, X., 2020. COVID-19 suspected cases treated with Lianhua Qingwen decoction: A clinical observation of 63 cases. J. Chin. Med. 2, 1–5.
Mahomoodally, M.F., 2013. Traditional medicines in Africa: an appraisal of ten potent African medicinal plants. Evid.-Based Complement. Altern. Med. 2013, 14.
Manganyi, M.C., Ateba, C.N., 2020. Untapped potentials of endophytic fungi: a review of novel bioactive compounds with biological applications. Microorganisms 8, 1934.
Mani, J.S., Johnson, J.B., Steel, J.C., Broszczak, D.A., Neilsen, P.M., Walsh, K.B., Naiker, M., 2020. Natural product-derived phytochemicals as potential agents against coronaviruses: a review. Virus Res. 284, 197989.
Mansour, S., 2020. The Role of Resistant Starch in COVID-19 Infection. NIH United States National Library of Medicine.. ClinicalTrials.gov https://clinicaltrials.gov/ct2/show/NCT04342689. (Accessed 16 July 2020).
Mashhadi, N.S., Ghiasvand, R., Askari, G., Hariri, M., Darvishi, L., Mofid, M.R., 2013. Anti-oxidative and anti-inflammatory effects of ginger in health and physical activity: review of current evidence. Int. J. Prevent. Med. 4 (Suppl 1), S36–S42.
Matthay, M.A., Thompson, B.T., 2020. Dexamethasone in hospitalised patients with COVID-19: addressing uncertainties. Lancet Respir. Med. S2213–S2600.
Mayo Clinic, 2020. Kratom: Unsafe and Ineffective. https://www.mayoclinic.org/healthy-lifestyle/consumer-health/in-depth/kratom/art-20402171. (Accessed 15 July 2020).
McClain, S.D., 2020. Shortages, High Prices Press Garlic Supply. Capital Press. https://www.capitalpress.com/nation_world/agriculture/shortages-high-prices-press-garlic-supply/article_84b280d4-88e5-11ea-8606-7b44e2297dec.html. (Accessed 17 June 2020).
Medscape, 2020. NIAID Testing remdesivir plus MS drug for COVID-19. Medscape Medical News. https://www.medscape.com/viewarticle/935606. (Accessed 16 January 2021).
Mokgobi, M., 2014. Western-trained health care practitioners' knowledge of and experiences with traditional healing. Afr. J. Phys. Health Educ. Recreat. Dance 2014 (Suppl 2), 1.
Mugabi, I., 2020. COVID-19: WHO Cautions Against the Use of Traditional Herbs in Africa. https://www.dw.com/en/covid-19-who-cautions-against-the-use-of-traditional-herbs-in-africa/a-53341901. (Accessed 24 June 2020).
Nabavi, S.F., Nabavi, S.M., Habtemariam, S., Berindan-Neagoe, I., Cismaru, A., Izadi, M., 2020. Should we try the anti-inflammatory natural product, celastrol, for COVID-19? Phytother. Res. 2020, 1–2.
Narkhede, R.R., Pise, A.V., Cheke, R.S., Shinde, S.D., 2020. Recognition of natural products as potential inhibitors of COVID-19 main protease (Mpro): In-silico evidences, Nat. prod. bioprospect. Nat. prod. bioprospect. 10, 297–306.
NCCIH, 2016. Ginger. National Center for Complementary of Integrative Health. https://www.nccih.nih.gov/health/ginger. (Accessed 2 September 2020).
NCCIH, 2017. Colloidal Silver. National Center for Complementary and Integrative Health. https://www.nccih.nih.gov/health/colloidal-silver. (Accessed 18 June 2020).
NCCIH, 2018. Kratom. National Center for Complementary and Integrative Health. https://www.nccih.nih.gov/health/kratom. (Accessed 15 July 2020).
NCI, 2019. Dexamethasone. National Cancer Institute, the National Institutes of Health. https://www.cancer.gov/about-cancer/treatment/drugs/dexamethasone#:~:text=Use%20in%20Cancer,Leukemia.
NIH, 2020. Iodine Fact Sheet for Health Professionals. National Institute of Health. https://ods.od.nih.gov/factsheets/Iodine-HealthProfessional/. (Accessed 16 July 2020).
Nirmal, S.A., Pal, S.C., Otimenyin, S.O, Aye, T., Elachouri, M., Kundu, S.K., Thandavarayan, R.A., Mandal, S.C., 2013. Contribution of herbal products in global market. Pharmacol. Rev. 2013, 95–104.
Orhan, I.E., Deniz, F.S.S., 2020. Natural products as potential leads against coronaviruses: could they be encouraging structural models against SARS-CoV-2? Nat. Prod. Bioprospect. 10, 171–186.
Paden, C.R., Yusof, M.F.B.M., Al Hammadi, Z.M., Queen, K., Tao, Y., Eltahir, Y.M., Elsayed, E.A., Marzoug, B.A., Bensalah, O.K.A., Khalafalla, A.I., Al Mulla, M., Khudhair, A., Elkheir, K.A., Issa, Z.B., Pradeep, K., Elsaleh, F.N., Imambaccus, H., Sasse, J., Weber, S., Shi, M., Zhang, J., Li, Y., Pham, H., Kim, L., Hall, A.J., Gerber, S.I., Al Hosani, F.I., Tong, S., Al Muhairi, S.S.M., 2018. Zoonotic origin and transmission of Middle East respiratory syndrome coronavirus in the UAE. Zoonoses Public Health 65, 322–333.
Panyod, S., Ho, C.T., Sheen, L.Y., 2020. Dietary therapy and herbal medicine for COVID-19 prevention: a review and perspective. J. Tradit. Complement. Med. 10, 420–427.
Park, J.H., Seo, B.I., Cho, S.Y., Park, K.R., Choi, S.H., Han, C.K., Song, C.H., Park, S.J., Ku, S.K., 2013. Single oral dose toxicity study of prebrewed Armeniacae Semen in Rats. Toxicol. Res. 29, 91–98.
Puri, S.C., Nazir, S., Chawla, R., Arora, R., Riyaz-ul-Hasan, S., Amna, T., Ahmed, B., Verma, V., Singh, S., Sagar, R., Sharma, S., Kumar, R., Sharma, R.K., Qaz, G.N., 2006. The endophytic fungus *Trametes hirsutaas* a novel alternative source of podophyllotoxin and related aryl tetralin lignans. J. Biotechnol. 122, 494–510.
Puri, S.C., Verma, V., Amna, T., Qazi, G.N., Spiteller, M., 2005. An endophytic fungus from *Nothapodytes foetida* that produces Camptothecin. J. Nat. Prod. 68, 1717–1719.
Puttaswamy, H., Gowtham, H.G., Ojha, M.D., Yadav, A., Choudhir, G., Raguraman, V., Kongkham, B., Selvaraju, K., Shareef, S., Gehlot, P., Ahamed, F., Chauhan, L., 2020. *In silico* studies evidenced the role of structurally diverse plant secondary metabolites in reducing SARS-CoV-2 pathogenesis. Sci. Rep. 10, 20584.
Rahman, N., Basharat, Z., Yousuf, M., Castaldo, G., Rastrelli, L., Khan, H., 2020. Virtual screening of natural products against Type II Transmembrane Serine Protease (TMPRSS2), the priming agent of Coronavirus 2 (SARS-CoV-2). Molecules 25, 2271.
Rose, K.D., Croissant, P.D., Parliament, C.F., Levin, M.B., 1990. Spontaneous spinal epidural hematoma with associated platelet dysfunction from excessive garlic ingestion: a case report. Neurosurgery 26, 880–882.
Ryan, R.P., Germaine, K., Franks, A., Ryan, D.J., Dowling, D.N., 2008. Bacterial endophytes: recent developments and applications. FEMS Microbiol. Lett. 278, 1–9.
Schröder, I., 2020. COVID-19: A risk assessment perspective. ACS Chem. Health Saf. 27, 160–169.
Self, W.H., Semler, M.W., Leither, L.M, Casey, J.D., Angus, D.C., Brower, R.G., Chang, S.Y., Collins, S.P., Eppensteiner, J.C., Filbin, M.R., Files, D.C, Gibbs, K.W., Ginde, A.A., Gong, M.N., Harrell, F.E., Hayden, D.L., Hough, C.L., Johnson, N.J., Khan, A., Lindsell, C.J., Matthay, M.A., Moss, M., Park, P.K., Rice, T.W., Robinson, B.R.H., Schoenfeld, D.A., Shapiro, N.I., Steingrub, J.S., Ulysse, C.A., Weissman, A.,

Yealy, D.M., Thompson, B.T., Brown, S.M., 2020. Effect of hydroxychloroquine on clinical status at 14 days in hospitalized patients with COVID-19: a randomized clinical trial. J. Am. Med. Assoc. 324, 2165–2176.
Selim, K.A., Elkhateeb, W.A., Tawila, A.M., El-Beih, A.A., Abdel-Rahman, T.M., El-Diwany, A.I., Ahmed, E.F., 2018. Antiviral and antioxidant potential of fungal endophytes of Egyptian medicinal plants. Fermentation 4, 49.
Shereen, M.A., Khan, S., Kazmi, A., Bashir, N., Siddique, R., 2020. COVID-19 infection: origin, transmission, and characteristics of human coronaviruses. J. Adv. Res. 24, 91–98.
Shi, K., Chen, X., Xie, B., Yang, S.S., Liu, D., Dai, G., Chen, Q., 2018. Celastrol alleviates chronic obstructive pulmonary disease by inhibiting cellular inflammation induced by cigarette smoke via the Ednrb/Kng1 Signaling Pathway. Front. Pharmacol. 9, 1276.
Sohail, M.N., Rasul, F., Karim, A., Kanwal, U., Attitalla, I.H., 2011. Plants as a source of natural antiviral agents. Asian J. Anim. Vet. Adv. 6, 1125–1152.
Stauffer, W.M., Alpern, J.D., Walker, P.F., 2020. COVID-19 and Dexamethasone a potential strategy to avoid steroid-related Strongyloides hyperinfection. J. Am. Med. Assoc. 324, 623–624.
Stirgus, E., 2020. Universities across Georgia research ways to prevent, treat COVID-19. Coronavirus pandemic: research. Atlanta J.-Const. https://www.ajc.com/news/state–regional/the-fight-for-cure/gGkf3FXK5OeP5QVYClLcCJ/.
Strobel, G.A., 2003. Endophytes as sources of bioactive products. Microbes Infect. 5, 535–544.
Suchard, J.R., Wallace, K.L., Gerkin, R.D., 1998. Acute cyanide toxicity caused by apricot kernel ingestion. Ann. Emerg. Med. 32, 742–744.
Sun, J., Zhu, A., Li, H., Zheng, K., Zhuang, Z., Chen, Z., Shi, Y., Zhang, Z., Chen, S.B., Liu, X., Dai, J., Li, X., Huang, S., Huang, X., Luo, L., Wen, L., Zhuo, J., Li, Y., Wang, Y., Zhang, L., Zhang, Y., Li, F., Feng, L., Chen, X., Zhong, N., Yang, Z., Huang, J., Zhao, J., Li, Y.M., 2020. Isolation of infectious SARS-CoV-2 from urine of a COVID-19 patient. Emerg. Microbes Infect. 9, 991–993.
Tai, W., He, L., Zhang, X., Pu, J., Voronin, D., Jiang, S., Zhou, Y., Du, L., 2020. Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: implication for development of RBD protein as a viral attachment inhibitor and vaccine. Cell. Mol. Immunol. 17, 613–620.
Timoshyna, A., Xu, L., Ke, Z., 2020. COVID-19—the Role of Wild Plants in Health Treatment and Why Sustainability of Their Trade Matters. Traffic. https://www.traffic.org/news/covid-19-the-role-of-wild-plants-in-health-treatment/. (Accessed 11 June 2020).
van Doremalen, N., Bushmaker, T., Morris, D.H., Holbrook, M.G., Gamble, A., Williamson, B.N., Tamin, A., Harcourt, J.L., Thornburg, N.J., Gerber, S.I., Lloyd-Smith, J.O., De Wit, E., Munster, V.J., 2020. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. N. Engl. J. Med. 382, 1564–1567.
Vellingiri, B., Jayaramayya, K., Iyer, M., Narayanasamy, A., Govindasamy, V., Giridharan, B., Ganesan, S., Venugopal, A., Venkatesan, D., Ganesana, H., Rajagopalan, K., Rahman, P.K.S.M., Cho, S.G., Kumar, N.S., Subramaniamk, M.D., 2020. COVID-19: a promising cure for the global panic. Sci. Total Environ. 725, 138277.
Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., Shi, Z., Hu, Z., Zhong, W., Xiao, G., 2020b. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in* vitro. Cell Res. 30, 269–271.
Wang, W., Xu, X., Gao, R., Lu, R., Han, K., Wu, G., Tan, W., 2020a. Detection of SARS-CoV-2 in different types of clinical specimens. J. Am. Med. Assoc. 323, 1843–1844.
Wang, Y., Zhang, D., Du, G., Du, R., Zhao, J., Jin, Y., Fu, S., Gao, L., Cheng, Z., Lu, O., Hu, Y., Luo, G., Wang, K., Lu, Y., Li, H., Wang, S., Ruan, S., Yang, C., Mei, C., Wang, Y., Ding, D., Wu, F., Tang, X., Ye, X., Ye, Y., Liu, B., Yang, J., Yin, W., Wang, A., Fan, G., Zhou, F., Liu, Z., Gu, X., Xu, J., Shang, L., Zhang, L., Cao, L., Guo, T., Wan, Y., Qin, H., Jiang, Y., Jaki, T., Hayden, F.G., Horby, P.W., Cao, B., Wang, C., 2020c. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 395, 1569–1578.
Wang, Z., Yang, L., 2020. Turning the tide: Natural products and natural-product-inspired chemicals as potential counters to SARS-CoV-2 infection. Front. Pharmacol. 11, 1013 |.
WebMD, 2020a. Garlic. https://www.webmd.com/vitamins/ai/ingredientmono-300/garlic#:~:text=Garlic%20has%20been%20used%20safely,increase%20-the%20risk%20of%20bleeding.
WebMD, 2020b. Ginger: Possible Health Benefits and Side Effects. https://www.webmd.com/vitamins-and-supplements/ginger-uses-and-risks#2. (Accessed 2 September 2020).
WHO Technical Report Series, 2018. World Health Organisation Guidelines on Good Herbal Processing Practices for Herbal Medicines. https://www.who.int/traditional-complementary-integrative-medicine/publications/trs1010_annex1.pdf?ua=1. (Accessed 14 July 2020).
WHO, 2019a. Middle East respiratory syndrome coronavirus (MERS-CoV). https://www.who.int/news-room/fact-sheets/detail/middle-east-respiratory-syndrome-coronavirus-(mers-cov. (Accessed 13 January 2021).
WHO, 2019b. WHO Global Report on Traditional and Complementary Medicine 2019. https://www.who.int/traditional-complementary-integrative-medicine/WhoGlobalReportOnTraditionalAndComplementaryMedicine2019.pdf?ua=1. (Accessed 16 January 2020).
WHO, 2020a. About COVID-19. . http://www.emro.who.int/health-topics/corona-virus/about-covid-19.html. (Accessed 14 July 2020).
WHO, 2020b. Coronavirus. https://www.who.int/health-topics/coronavirus#tab=tab_1. (Accessed 29 August 2020).
WHO, 2020c. World Health Organisation Announces COVID-19 outbreak a pandemic. http://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid19/news/news/2020/3/who-announces-covid-19-outbreak-a-pandemic. (Accessed 27 March 2020).
WHO, 2020d. WHO Coronavirus Disease (COVID-19) Dashboard. https://covid19.who.int/?gclid=EAIaIQobChMIosyV2brX6wIVDevtCh0vpw45EAAYASAAEgLKaPD_BwE. (Accessed 16 January 2021).
WHO, 2020e. WHO Welcomes Preliminary Results About Dexamethasone Use in Treating Critically Ill COVID-19 Patients. https://www.who.int/news-room/detail/16-06-2020-who-welcomes-preliminary-results-about-dexamethasone-use-in-treating-critically-ill-covid-19-patients. (Accessed 17 June 2020).
WHO, 2020f. WHO Supports Scientifically-Proven Traditional Medicine. https://www.afro.who.int/news/who-supports-scientifically-proven-traditional-medicine. (Accessed 18 June 2020).
WHO, 2020g. Coronavirus Disease (COVID-19) Advice for the Public: Myth Busters. Can Eating Garlic Help Prevent Infection With the New Coronavirus? https://www.who.int/images/default-source/health-topics/coronavirus/myth-busters/19.png. (Accessed 17 June 2020).
Wiesemeyer, J., 2020. USDA Officials, Forecasts are Murky Re: Factoring in phase 1 of U.S./China Accord. https://www.profarmer.com/markets/policy/usda-officials-forecasts-are-murky-re-factoring-phase-1-us/china-accord. (Accessed 14 July 2020).
Wintle, T., 2020. Enjoy Ginger, but it's not a 'Cure' for COVID-19, Says WHO. . https://newseu.cgtn.com/news/2020-04-03/Enjoy-ginger-but-it-s-not-a-cure-for-COVID-19-says-WHO–Pn0Wuje3UA/index.html.
Yang, Y., 2020. Use of herbal drugs to treat COVID-19 should be with caution. Lancet N. Am. Ed. 395, 1689–1690.
Yang, Z., Wu, K., Xu, Y., Xia, X., Wang, X., Ge, M., Shao, L., 2020. Three novel chromanones with biological activities from the endophytic fungus Phomopsis CGMCC No. 5416. J. Antibiot. (Tokyo) 73, 194–199.
Zhang, G., Sun, S., Zhu, T., Lin, Z., Gu, J., Li, D., Gu, Q., 2011. Antiviral isoindolone derivatives from an endophytic fungus *Emericella* sp. associated with *Aegiceras corniculatum*. Phytochemistry 72 (11–12), 1436–1442.
Zhang, R., Chen, Z., Wu, S.S., Xu, J., Kong, L.C., Wei, P., 2019. Celastrol enhances the anti-liver cancer activity of Sorafenib. Sci. Monit. 25, 4068–4075.
Zhang, T., Wu, Q., Zhang, Z., 2020. Probable pangolin origin of SARS-CoV-2 associated with the COVID-19 outbreak. Curr. Biol. 30, 1346–1351.
Zhao, H., Michaelis, M.L., Blagg, B.S.J., 2012. Hsp90 Modulation for the treatment of Alzheimer's disease. Adv. Pharmacol. 2012, 6.