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Review

Positive Therapeutic Role of Selected Foods and Plant on Ailments with a Trend Towards COVID-19: A Review

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ABSTRACT: Each day since December 2019, increasing numbers of cases of the novel coronavirus 2019 (COVID-19) infection are being detected as it spreads throughout all continents of the world except Antarctica. The virus is transmitted through contact with an infected environment or person, and the symptoms include fever, cough, and difficulty breathing. The healthcare systems of many countries are overwhelmed due to limited therapeutic options and the absence of an approved vaccine. Due to its poor healthcare systems, Africa may be the worst hit continent if other therapeutic alternatives are not explored. This review explores the source and origin of the COVID-19 infection, and alternative therapeutic options derived from available and cheap medicinal foods and plants that have been shown to alleviate similar infections. The results demonstrate the inhibitory activities of selected food crops and plants against human viruses similar to the novel COVID-19.

Keywords: antiviral activity, COVID-19, foods, plants, therapeutics

INTRODUCTION

Viruses are of great danger to human health. They are constantly evolving and are the causes of many global infections. Viruses are highly infectious and are the cause of most pandemics/epidemics in recent history. For example, in 1918 Spanish influenza, described as the deadliest pandemic in recorded history, was caused by the deadly strain of the influenza virus H1N1. H1N1 infected about 500 million people and caused approximately 17∼50 million deaths worldwide (Taubenberger and Morens, 2006). Viruses are obligate intracellular parasites with a genome composed of either RNA or DNA, and a protein envelope known as a ‘capsid’. Viruses do not possess metabolism and therefore cannot replicate or biosynthesize proteins on their own (Ramawat and Mérillon, 2013). However, upon entering a living system, viruses penetrate host cells, release their genetic material, then reprogram host cells to directs their metabolic pathway to aid viral replication (Ramawat and Mérillon, 2013). Thus, viruses have been aptly described as “a piece of bad news wrapped in a protein coat” (Sohail et al., 2011).

Recently, several viral diseases have emerged such as the human immunodeficiency virus [HIV/acquired immune deficiency syndrome], hepatitis B and C, and dengue haemorrhagic fever, all of which have caused numerous death worldwide (Babar et al., 2013). Moreover, viruses have been responsible for several localized epidemics. For example, Ebola haemorrhagic fever in the tropical region of Sub-Saharan Africa was caused by the Ebola virus, Lassa haemorrhagic fever in West Africa was caused by Lassa virus (Nuwagira and Muzoora, 2020), a severe acute respiratory syndrome was caused by severe acute respiratory syndrome (SARS)-associated coronavirus (SARS-CoV; China in 2003), and the middle east respiratory syndrome was caused by another strain of coronavirus (Saudi Arabia in 2012) (Oppenheim et al., 2019). The unique characteristics of viruses make them difficult to control despite considerable development in medical sciences and relatively few drugs are available to treat vi-

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ral diseases (Obi and Shenge, 2018).

Several antiviral drugs have been approved for use, however these drugs have a narrow range of activity against many viral infections (Babar et al., 2013). This is because viruses can rapidly mutate, causing new strains to emerge that may exhibit resistance to drugs that target a particular viral component (Ahmad et al., 2020). Several food crops and plants have shown antiviral effects, therefore there is an urgent need to explore these crops/plants as traditional/alternative medicines for therapeutic options in the absence of or alongside insufficient orthodox medications (Mousa, 2015). For example, *Nigella sativa* may inhibit the hepatitis C virus (Oyero et al., 2016), essential oil of star anise may inhibit the herpes simplex virus type 1 (Astani et al., 2011), and *Allium sativum* (garlic) may inhibit infectious bronchitis virus and influenza virus (Mehrbod et al., 2009). Furthermore, *Glycyrrhiza glabra* (liquorice/licorice) has shown antiviral activity against hepatitis A, hepatitis B, influenza, and HIV-1, and the ability to inhibit replication of SARS-associated coronavirus *in vivo* (Babar et al., 2013).

Currently, the world is battling a COVID-19 pandemic caused by a novel coronavirus SARS-CoV2. This virus is responsible for at least 23,254 confirmed cases and 903 deaths in the Africa Region (Livingston et al., 2020). At the time of writing this manuscript, there are no treatments or vaccines for COVID-19, but over 100 COVID-19 vaccines are under development for human trials (WHO, 2020a). This pandemic has had an overwhelming effect on healthcare system worldwide, and Africa (especially Sub-Saharan Africa) may not be able to survive it. Therefore, there is a need for researchers in Africa stop this pandemic before the effects are devastating by using other research on treating viral infections with natural plants.

Some drugs have been reported to be effective for treating COVID-19. Nucleoside inhibitor produced by Gilead Sciences Inc. was found to be efficacious in treating a patient with nCoV-2019 in the United States (Nguyen et al., 2020). Also, Remdesivir (an adenosine analogue), which was effective against Ebola and some other RNA viruses, was approved by the US Food and Drug Administration on 1st May 2020 for emergency treatment of hospitalized COVID-19 patients. Furthermore, Gautret et al. (2020) showed that patients treated with hydroxychloroquine and azithromycin for 8 days had a 93% recovery rate. However, the rapid spread COVID-19 and the limited available therapeutic options make this virus a serious health challenge. Therefore, there is a need to explore the therapeutic use of alternative medicines that have proven effectiveness against other viral infections. This report explores common foods and plants with reported antiviral effect, and their potential efficacy against different virus infections that may be applicable to COVID-19.

CORONAVIRUSES AND COVID-19: AN OVERVIEW

Coronaviruses, named for their crown-like spikes on their outer surfaces (Fig. 1), are of the family Coronaviridae in the Nidovirales order. Coronaviruses are enveloped, RNA viruses. Their nucleic material comprises of non-segmented single-strand RNA, sub-grouped into alpha (α), beta (β), gamma (γ), and delta (δ) (Islam et al., 2020) ranging from 26∼32 kb in length and 80∼160 nm^9 in size. Coronaviruses cause several diseases, including bronchitis, hepatitis, and gastroenteritis, all of which may lead to death in humans, birds, and other animals (Chafekar and Fielding, 2018).

Former outbreaks of coronaviruses include the SARS-CoV, which broke out in Guangdong, China in 2002 (Zhong et al., 2003) and was thought to only infect animals. This was followed by the Middle East respiratory syndrome virus (MERS-CoV) that broke out in Saudi-Arabia in 2012 (Wang et al., 2013) and was shown to infect humans. The recent strains of human coronaviruses (HCoV) have been identified as HCoV-NL63 and HCoV-HKU1 after intensive screenings (de Wilde et al., 2018), which cause acute lung injury and acute respiratory distress syndrome and lead to pulmonary failure and fatality in humans.

The β-coronavirus (SARS-CoV2) broke out from Wuhan, China in 2019. The infection was initially traced to human seafood (Shereen et al., 2020), however human-to-human transmission was later ascertained. Human-to-human transmission of the virus arises from physical contact with an infected person's cough, sneeze, respiratory droplets, and aerosol, inhaled via the nose or mouth (Shereen et al., 2020; WHO, 2020b). The incubation period of SARS-CoV2 is 1∼14 days (WHO, 2020b). Initial

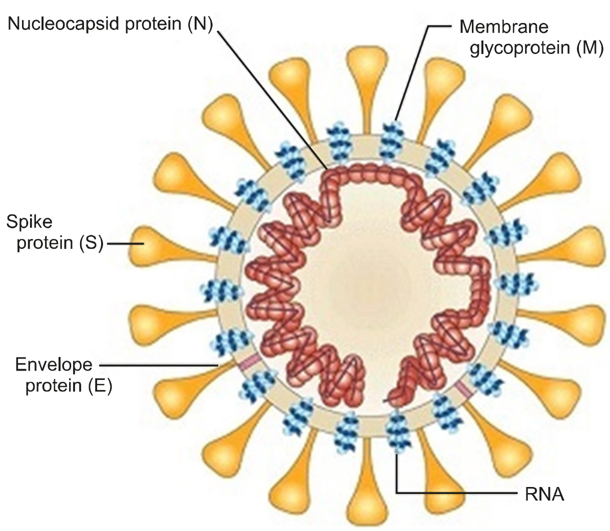

Fig. 1. A schematic diagram of the coronavirus structure (Peiris and Poon, 2008).

symptoms include cough, fever, fatigue, and myalgia, which may develop into pneumonia and/or severe acute respiratory syndrome requiring intensive care (30% of cases) (Huang et al., 2020).

The virus spread rapidly, traversing countries and continents, and was declared a pandemic by the World Health Organization on 11th March 2020 following infection of over 3 million people and after causing 200,000 deaths (Livingston et al., 2020). SARS-CoV2 infects all groups of people, with higher fatality rates reported for people with comorbidities such as diabetes, hypertension, Parkinson's disease, chronic obstructive pulmonary disease, cardiovascular disease and cancer (Zhang et al., 2004; Peiris and Poon, 2008; Zhang, 2020). SARS-CoV2 (nCoV-19) is very similar in structure and feature to other β-coronaviruses, containing crown-like proteins referred to as spike proteins (S-proteins). S-proteins, envelope proteins (E-proteins), and membrane proteins (M-proteins) are the three structural proteins that make up the lipid envelope cloaking the entire viral structure, while the helix-like structural protein nucleocapsid contains the viral genome (Yesudhas et al., 2020). S-proteins comprise of 2 functional units: S1 and S2. S1 is responsible for binding of the virus to host cell receptors, whereas S2 is responsible for fusion of viral membranes to host receptor membranes. These two processes are referred to as viral attachment, which is the first phase of viral infection. SARS-CoV2 binds to angiotensin-converting enzyme 2 (ACE2) on host cells (Yuki et al., 2020), the same receptors identified for SARS-CoV; however, SARS-CoV2 binds with a higher affinity than SARS-CoV due to a single N501T mutation in SARS-CoV2 (Wan et al., 2020). SARS-CoV2 also contains a furin cleavage site at the S1/S2 site, which has been implicated in its high pathogenicity (Yuki et al., 2020).

After entering into host cells, SARS-CoV2 releases its contents into host cells (known as uncoating of the genome). The viral RNA enters the host cell nucleus, and the virus uses the host cells' established metabolic mechanisms for replication. After replicating, the mRNA of the virus is translated into viral proteins (biosynthesis phase), then the viral particles are assembled (maturation phase) and released (Yuki et al., 2020).

ACE2 is highly expressed in lung epithelial cells, therefore there is a high probability that those cells will be the area of first attack upon infection. Three main components of innate immunity in the airways (dendritic cells, alveolar space epithelial cells, and alveolar macrophages) help to combat the virus before adaptive immunity can kick-off. Furthermore, during infection many cytokines are produced to help fight off the virus. T-cells help to mediate responses as antigen presentation by dendritic cells and macrophages help initiate responses. Immunological assays have shown that infection with SARS-CoV2 produces corresponding increases in pro-inflammatory cytokines, such as interleukin (IL)-6, IL-10, granulocyte-colony stimulating factor, and tumour necrosis factor (TNF)-α (Yuki et al., 2020).

COMBATING VIRUSES WITH NATURAL THERAPIES

Some extracts from green plants have been reported to fight against viral infections. Due to its rapid spread worldwide and the limited therapeutic options available to combat nCoV-19, the need to explore natural therapies cannot be over-emphasized. During the outbreak of SARS in 2002, China used a combination of traditional Chinese herbal medicine and western medicine, which proved effective in alleviating the symptoms of SARS (Zhang et al., 2004). Herbal traditional medicine has been employed in the management and treatment of nCoV-19 infection. One report showed that 50 COVID-19 patients treated with the Chinese herbal drug Taijie Quwen granules significantly improved without any symptoms after 7 days (Zhang, 2020). The study suggested Taijie Quwen granules reduced the occurrence of severe pneumonia in patients. In addition, a herbal concoction *Qingfei paidu* used to treat 214 COVID-19 patients in China yielded over 90% efficiency (Zhang, 2020).

Artemisia annua, *Pyrrosia lingua*, and *Lindera aggregata* have been reported to possess antiviral effect against SARS-CoV (Lau et al., 2008). Emodin from *Polygonum multiflonum* also inhibits the interaction between S-proteins of SARS-CoV and ACE2 receptors (the receptor the virus employs to infect host cells). Phenolic compounds from black tea (tannic acid, 3-isotheaflavin-3-gallate, and theaflavin-3,3^1-digallate) have also been reported to inhibit the chymotrypsin-like protease ($3CL^{pro}$) of SARS-CoV (Lau et al., 2008).

Since SARS-CoV is similar to the novel nCoV-19, food crops and plants possessing antiviral activity may be explored as potential therapeutics. Table 1 summarizes the notable foods/plants with bioactive components, viruses that they have been used to treat and their mechanisms of action. Many of these plants/foods possess antiviral activities against multiple viruses; the majority inhibit viruses at the point of viral replication, whereas others inhibit adsorption of viral particles into host cells, thereby preventing viral entry. These antiviral foods/plants possess active components that attack viruses at different points or stages. For example, turmeric contains the active component curcumin which exhibits antiviral activity against viruses including herpes simplex virus, HIV, hepatitis virus, and respiratory syncytial virus. The positive effect of curcumin in turmeric arises from its ability to inhibit the viral growth and replication, making it a con-

Table 1. Foods/plants and their bioactive components in the treatment viral infections

Food/plant	Bioactive component	Virus	Mechanism of action	Reference
Allium sativum (garlic root and essential oil)	Allicin, ajoene, diallyl disulphides, kaempferol, and quercetin	Influenza virus and Newcastle disease virus SARS-CoV	Inhibits viral multiplication Inhibits ACE2 protein Inhibits M^{pro}	Chavan et al. (2016) Thuy et al. (2020)
Zingiber officinales (fresh ginger)	Gingerols, zingerol, kaempferol, and zingiberone	Human respiratory syncytial virus	Inhibits viral replication via secretion of IFN-β	Chang et al. (2013)
Ocimum basilicum (basil leaf extract and essential oil)	Ursolic acid, apigenin, and linalool	Herpes simplex virus, adenovirus, hepatitis B virus, and enterovirus HIV type 1 and 2	Inhibits viral multiplication and replication, and inhibits secretion of viral antigen Inhibits viral replication	Chiang et al. (2005) Kpadonou Kpoviessi et al. (2014)
Curcuma longa (turmeric)	Curcumin	HIV Hepatitis viruses Influenza virus and respiratory syncytial virus	Inhibits of viral proteases Inhibits viral replication Inhibits viral entry, replication, and budding	Kim et al. (2010) Ou et al. (2013) Yang et al. (2017)
Moringa oleifera (leaf extract)	Niaziminin, quercetin, and kaempferol	Influenza virus and HIV Equine herpes virus Type 1 and type 2 herpes simplex virus	Inhibits viral cytotoxicity and possess immunomodulatory effect Inhibits viral replication	Saleem et al. (2020) Nworu et al. (2013) Imran et al. (2016)
Glycyrrhiza glabra (liquorice/licorice extract)	Glycyrrhizin, glycyrrhetinic acid, and 18β-glycyrrhetinic acid	SARS-CoV Hepatitis C Herpes simplex virus 1 Influenza A	Inhibits viral adsorption, penetration, and replication Inhibits virus core gene expression Inhibits viral replication Reduces endocytosis and viral uptake	Cinatl et al. (2003) Anagha et al. (2014) Wang et al. (2015) Wolkerstorfer et al. (2009)
Cocos nucifera (coconut oil)	Lauric acid and monolaurin	SARS-CoV Vesicular stomatitis virus and avian Influenza virus	Disintegrates viral membrane Inhibits virus maturation Prevents binding of viral proteins to host cell membranes	Abd El-Aziz and Stockand (2020) Arora et al. (2011)
Bryophyllum pinnatun (life plant) and *Viscum album* (mistletoe)	Flavones, anthocyanidins, and polyphenols	Rhinovirus, picornavirus, measles, polio, herpes simplex virus, rhinovirus, measles, polio, herpes simplex virus, and picornavirus	Inhibits viral adsorption	Obi and Shenge (2018)
Echinacea purpurea	Cichoric acid, caffeic acid, and akylamides	Influenza virus (H5N1 and H7N7)	Inhibits binding of virus to receptors and viral replication	Pleschka et al. (2009)
Scrophularia scorodona	Saikosaponnins	HCoV-22E9	Inhibits viral attachment and penetration	Cheng et al. (2006)

SARS-CoV, severe acute respiratory syndrome-associated coronavirus; ACE2, angiotensin-converting enzyme 2; M^{pro}, main protease; IFN-β, interferon beta; HIV, human immunodeficiency virus; HCoV, human coronavirus.

tender for antiviral drugs (Mathew and Hsu, 2018). These foods/plants work in a cycle for effective antiviral action, unlike orthodox antivirals which are specific against a specific antiviral component. Several plants/foods show antiviral effects, including oregano, fennel, lemon balm, and peppermint. We discuss the effects of common and cheap plants/foods with antiviral activity that are found in homes around the world, including *Allium sativum* (garlic), *Zingiber officinales* (ginger), *Moringa oleifera* (drumstick), and *Glycyrrhiza glabra* (liquorice/licorice).

Garlic

Garlic (*Allium sativum*) of the family Liliaceae has been utilized worldwide for culinary and therapeutic purposes (Rose et al., 2018). Garlic contains components that aid its utilization as a medication for heart and blood sicknesses and conditions including hypertension, elevated cholesterol (Mikaili et al., 2013), and cardiovascular infections. Garlic has also been used for its antiviral, antibacterial, and antifungal characteristics. Kaefer and Milner (2008) reported that garlic is an ideal therapeutic option for constant bronchitis infection because it induces expectoration, thereby making garlic syrup an important medication for asthma and other lung conditions.

The anti-viral action of garlic is credited to its flavonoids (quercetin) and organosulphur compounds (allicin, diallyl, trisulfide, and ajoene) (Sharma, 2019). Allicin is the main chemical present in garlic, is responsible for its flavour, and possess broad antimicrobial activity both *in* *vitro* and *in vivo* (Mehrbod et al., 2009). The significant anti-microbial activity of allicin is a consequence of a chemical reaction between allicin and thiol groups of various enzymes necessary for microorganism surveillance (Mehrbod et al., 2009). Allicin-containing supplements have been shown to prevent assaults of basic cold infection (Sharma, 2019). The mechanism of action of allicin has not been properly elucidated; however, allicin may pass through phospholipid membranes of cells to inhibit viral multiplication. An *in vitro* study showed that garlic extracts can inhibit replication of influenza viruses due to the presence of allicin, which inhibits viral RNA polymerase via interacting with thiol groups of RNA polymerases (Chavan et al., 2016). Allicin can modulate the immune system in response to viral infections (Sharma, 2019). For example, allicin may inhibit release of pro-inflammatory cytokines like IL-6 and TNF-α in cells infected with reticuloendotheliosis virus (Wang et al., 2017) by downregulating expression of nuclear factor (NF)-κB and inhibiting expression of NF-κB-mediated inflammatory genes (Sharma, 2019).

Ajoene, one of the organosulphur compounds in garlic, may inhibit HIV via inhibiting integrin-dependent processes, thereby blocking viral adhesion to host cells (Rouf et al., 2020). Furthermore, lectin, a non-sulphur containing compound in garlic, has been reported to inhibit viral attachment in SARS-CoV (Keyaerts et al, 2007). In addition, flavonoids in garlic have a strong inhibitory effect on virus multiplication, as they have been reported to block formation of viral proteins and genetic material (Zandi et al., 2011). Moreover, quercetin prevents viral entry and inhibits replication (Mousa, 2017), thereby minimizing viral infectivity. Quercetin interacts with haemagglutinin proteins, glycoproteins which helps viruses attach and fuse with host cells, thereby inhibiting entry of viruses into host cells. Quercetin is also able to increase zinc (Zn) uptake, a mineral which inhibits the activity of RNA polymerase, thereby preventing viral replication (Sreenivasulu et al., 2020). In addition, quercetin inhibits translation of hepatitis C (Gonzalez et al., 2009) and the main protease of SARS-CoV (Sharma, 2019).

Inhalation of essential oil from garlic prevents inflammation and constriction of airways since the compounds easily pass through the air-blood barrier in patients with mild symptoms (Lissiman et al., 2014). In this study, allicin/ajoene showed efficacy in treating the common cold caused by rhinoviruses and HCoV. Garlic acts as an immunomodulatory agent against viral pathogens as it possesses mitogenic activity towards human lymphocytes, splenocytes, and thymocytes (Babar et al., 2013). Furthermore, a randomised clinical control trial showed that some organosulphurs in garlic such as nallicin, diallyl sulphide (DAS), and diallyl disulphide are able to upregulate genes responsible for immune responses, and activate apoptosis of infected cells (Charron et al., 2015). DAS has been reported to exert its antiviral activity via activating nuclear factor erythroid 2p-45 related factor (Nrf2), which controls expression of genes involved in antiviral activity. Nrf2 activation may downregulate ACE2, thereby inhibiting viral attachment and penetration (Asif et al., 2020).

The main proteases of both SARS-CoV and nCov-19 (M^{pro}; key in proteolytic maturation of the viruses) have 96% similar active sites. Therefore, the bioactive compounds in garlic may be effective against both viruses (Khaerunnisa et al., 2020).

Ginger

Ginger (*Zingiber officinales* Roscoe) belongs to the family Zingiberaceae, and is a perennial plant with a thick rhizome. Ginger is consumed raw, or used for culinary (Zadeh and Kor, 2014) and medicinal (cold, nausea, asthma, respiratory disease, and rheumatism) purposes (Mao et al., 2019). The compounds in ginger are responsible for its distinct aroma, taste (sesquiterpene and monoterpenoid hydrocarbons), and flavour (gingerols, shogoals, paradols, and zingerone) (Mao et al., 2019). These latter are also responsible for its various anti-inflammatory, antiviral, antimicrobial and antioxidant activities (Mao et al., 2019).

Fresh ginger possesses antiviral activity against the human respiratory syncytial virus (HRSV) in both upper and lower respiratory tract cell lines (Chang et al., 2013). It inhibits viral attachment and internalisation, causing about 70% decrease in infection. (6)-, (8)-, and (10)-gingerols are the major constituents of fresh ginger that inhibit HRSV, acting by interacting with G and F proteins that the virus utilizes to attach to and penetrate host cells (Chang et al., 2013). Therefore, ginger is more effective when administered before viral inoculation.

Ginger may also increase the activities of antioxidant enzymes, such as glutathione peroxidase and superoxide dismutase, which may be helpful in inflammatory reactions triggered by viral infections (Mashhadi et al., 2013). Ginger inhibits the influenza virus H5N1 by preventing formation of plaques (Dorra et al., 2019). A recent study reported antiviral activity of gingerenone A, an active component in ginger. Gingerenone A inhibits Janus kinase 2 and p70S6 kinase, which are crucial in influenza virus replication. Gingerenone A may also prevent H5N1 replication in lungs by inhibiting expression of Janus kinase 2 (Wang et al., 2020). An *in vitro* study showed that ginger extract exhibits anti-viral effect against H9N2 avian influenza in chick embryos by inhibiting viral attachment and replication (Rasool et al., 2017). Another study reported that the combination of honey, ginger and garlic is efficacious in inhibiting replication of influenza in mammalian cell lines (Madin-Darby canine kidney cell monolayers) and human lymphocytes, and stimulates proliferation of uninfected T-lymphocytes (Vahed et al., 2016).

Basil

Basil (*Ocimum basilicum*), also known as scent leaf or fever leaf, is a shrub of the Lamicaea group of plants common to Africa, Asia, and Southern American (Gupta et al., 2011). It is one of the basic herbs with therapeutic properties for treatment of colds, and lower and upper respiratory tract infections in some African nations (Prabhu et al., 2009). Basil leaves show calming, antiparasitic, cyctoxic, and pain-relieving activities (Nweze and Eze, 2009). The characteristic smell of basil is credited to its volatile essential oil, known to be rich in aldehydes, terpenes, and phenols. The aqueous and alcoholic extracts of the leaves may possess antimicrobial activity against different enteric pathogens such as *Salmonella* Typhimurium and *Shigella dysenteriae* (Tiwari et al., 2011) due to its significant constituents such as eugenol, methyl eugenol, and caryophyllene.

The essential oil of basil leaves contains the powerful anti-viral compound eugenol (Raja et al., 2015), which may be effective against herpes, hepatitis B, and influenza A viruses. Eugenol can hinder expression of autophagic genes by inhibiting activation of Janus kinase 1, extracellular-signal-regulated kinase 1/2, and IκB kinase (IKK)/NF-κB pathways. It is also able to prevent the release of pro-inflammatory cytokines (IL-1, TNF-α, IL-6, and IL-8), which are induced by influenza through inhibiting the IKK/NF-κB pathway (Dai et al., 2013). An *in vitro* study showed that crude ethanol extracts of dried basil leaves can inhibit the growth of Zika viruses at the point of attachment and entry into host cells (Singh et al., 2019).

The extracted parts of basil, such as linalool, apigenin, and ursolic acid, show an expansive range of anti-viral action against DNA virus (adenoviruses) and RNA viruses (Sood et al., 2013). Some components of its essential oils (e.g., linalool, thymol, and carvacrol) may inhibit replication of influenza, HIV, and herpes simplex viruses. Linalool and thymol may inhibit haemagglutinin and neuraminidase, proteins important for attachment of influenza to host cells (Schnitzler et al., 2011). These purified extracts have been utilized in traditional Chinese medications against adenoviruses and enteroviruses (Chiang et al., 2005), and for treating measles in children (Raja et al., 2015). In this manner, the potential use of basil in crude and/or purified forms for treatment of viral infections justifies further study of it as a therapeutic agent in the treatment of coronavirus.

Drumstick

Drumstick (*Moringa oleifera*) is a plant belonging to the family Moringaceae, a single genus family with 13 known species (Gopalakrishnan et al., 2016). *M. oleifera* is considered a miracle tree, with its leaves, fruits and seeds having been used for years for traditional, medicinal, and industrial purposes to combat several health issues and malnutrition (Gopalakrishnan et al., 2016). For a very long period, *M. oleifera* has been used to treat ailments including bronchitis, catarrh, chest congestion, asthma, and anaemia (Razis et al., 2014). *M. oleifera* leaves and seed flour are good sources of natural antioxidants and phenolic compounds (Adeoti and Osundahunsi, 2017). *M. oleifera* exhibits antiviral, diuretic, antipyretic, anti-inflammatory, anticancer, and antibacterial activities (Imran et al., 2016), and possesses antiviral activity against equine herpesvirus 1, herpes simplex virus 1, and foot and mouth disease viruses (Younus et al., 2017).

M. oleifera has been exploited as a major antiretroviral molecule due to its immunomodulatory activity (Nworu et al., 2013), and antiviral activities against HIV, human cytomegalovirus, and polioviruses. A recent molecular docking study reported that some flavonoids and anthraquinones in *M. oleifera* may inhibit some proteins in SARS-CoV2, thus preventing its replication (Hamza et al., 2020). In a study of COVID-19 patients, capsules of *M. oleifera* leaf extracts and other plants demonstrated promising therapeutic results that require further investigations (Ather and Costigliola, 2020). Hypokalemia (potassium deficiency) has been reported in COVID-19 patients, resulting from an irregularity or disorder of the renin-angiotensin system due to decreased ACE2 activity. The high potassium content of *M. oleifera* could be important for COVID-19 treatment, in addition to its other immunomodulatory and antiviral constituents (Ignatov, 2020).

M. oleifera is a rich source of mineral Zn, making the plant an effective local and inexpensive solution for fighting Zn deficiencies (Gopalakrishnan et al., 2016). The Zn content of *M. oleifera* leaves ranges from 31.03 mg/kg to 32.90±0.85 mg/kg. These values are similar to the range reported by Barminas et al. (1998) to be the daily requirement of dietary Zn (25.5～31.03 mg of Zn/kg). Sufficient dietary Zn intake may be necessary for the synthesis of DNA and RNA, insulin, and function and/or structure of several enzymes (Brisibe et al., 2009). Zn mediates enzymes that run and renew cells, helping to maintain immune functions including cellular and humoral immunity. A previous study reported that Zn homeostasis is critical to protect against invading pathogens and overreactive immune systems causing autoimmune diseases (Gammoh and Rink, 2017). Furthermore, Zn is recognized as a potential therapeutic for people suffering from immune and inflammatory diseases (Gammoh and Rink, 2017).

Zn has anti-viral, antibacterial, anti-fungal and anticancer properties (Brisibe et al., 2009). Zn ions inhibit viral entry, local replication, and spread to organ during viral pathogenesis (Gammoh and Rink, 2017). The most common metal that binds viral proteins is Zn. Zn ions (Zn^{2+}) function as an important cofactor of some viral proteins and plays important roles in their survival and pathogenesis. Therefore, accessibility of Zn^{2+} in infected cells may be a limiting factor for viral life cycles. Zn^{2+} has been reported to play significant functions in the neuropathogenesis of HIV-1 infection, and HIV-induced central nervous system inflammation and neurodegeneration (Ishida, 2019).

Zn lozenges or syrup help individuals recover quickly from the common cold and reduce its symptoms within 24 h. Indeed, Zn supplements has been shown to decreases the morbidity of low respiratory tract infection in paediatrics in the developing world. In this study, a strong relationship was established between Zn deficiency and several infections, including HIV, tuberculosis, and pneumonia. In addition, Ishida (2019) reported that abnormalities observed in HIV-infected patients can be prevented by consumption of Zn since low levels of plasma Zn are associated with a 3-fold increase in HIV-related mortality. Therapeutic use of *M. oleifera* for its high Zn content could exhibit antiviral function, although this needs to be established, especially against COVID-19.

Liquorice/licorice

Liquorice/licorice (*Glycyrrhiza glabra*) is an herbaceous perennial plant belonging to the family Fabaceae. *G. glabra* roots have been used to treat coughs, colds, and influenza since ancient times (Pastorino et al., 2018), and to its ability to alleviate symptoms of throat and bronchial infections. Pastorino et al. (2018) indicated that the rhizomes and roots of *G. glabra* have been used to treat lung infections, gastric ulcers, and Addison's disease.

The bioactive components in *G. glabra* include glycyrrhizin, glyccyrrhetic acid, flavonoids, isoflavonoids, and chalcones (Michaelis et al., 2010). Glycyrrhizin, the major active component of *G. glabra* is responsible for antiviral activity against several viruses, including herpes simplex virus, hepatitis A, B, and C, Epstein-Barr, HIV, influenza, and SARS-associated coronavirus (Cinatl et al., 2003). Glycyrrhizin may inhibit SARS-associated coronavirus replication, adsorption and penetration (Anagha et al., 2014), which are early steps in cycles of viral replication, with better efficiency observed when administered during and after the adsorption period. Glycyrrhizin inhibits SARS-associated coronavirus replication *in vivo*, while its aglycone metabolite glycyrrhetinic acid inhibits inflammatory responses that occur as a consequence of viral infection (Michaelis et al., 2010).

The mechanism of glycyrrhizin's anti-viral activity is unclear. An *in vitro* study showed that glycyrrhizin is able to inhibit viral adsorption, penetration and replication by inducing nitrous oxide synthase in Vero cells (Cinatl et al., 2003). Studies have shown high expression of ACE2 and type 2 transmembrane serine protease (TMPRSS2) in upper and lower respiratory tracts, which support viral spread in human hosts and between individuals. As SARS-CoV primarily targets nasal goblet secretory cells, type II pneumocytes, and ileal absorptive enterocytes, and uses ACE2 as an entry point, reducing expressing of ACE2 in these cells may help combat the virus (Ziegler et al., 2020). Glycyrrhizin can act by reducing the expression TMPRSS2, which is needed in viral adsorption and penetration, thus inhibiting virus uptake. Glycyrrhizin can also activate plasma aldosterone mineralocorticoid receptors, which protect organs from binding to SARS-CoV and SARS-CoV2 via reducing ACE2 expression (Murck, 2020).

The active metabolite glycyrrhetinic acid present in *G. glabra* inhibits H-β-hydroxysteroid dehydrogenase, allowing cortisol to access mineralocorticoid receptors in aldosterone-specific peripheral tissues to result in high levels of aldosterone in these organs. High levels of aldosterone downregulates ACE2, decreasing the number of entry points for SARS-CoV2 (Murck, 2020). Glycyrrhizin and its metabolite glycyrrhetinic acid also affects anti-viral activity by its immunomodulatory properties. Although downregulation of ACE2 could negatively impact the cells as ACE2 protects some tissues (e.g., lungs), glycyrrhetinic acid exhibits immunomodulatory activity to help reduce inflammation in tissues including the lungs and heart. Glycyrrhetinic acid antagonises toll-like receptor 4 (TLR4) dependent mechanisms, thus reducing TLR4 expression in lungs and hearts of endotoxin receptor models of inflammation. This reduces release of pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1β (Murck, 2020). An *in vivo* study demonstrated protective effects of glycyrrhetinic acid in acute respiratory syndrome induced by TLR4 activation in mice (Seo et al., 2017). Another *in vivo* study also showed that administration of glycyrrhizin can reduce expression of the proinflammatory cytokine IL-33 in the serum, bronchoalveolar fluid, and lung tissues of mice with lipopolysaccharide-induced lung injury (Bailly and Vergoten, 2020).

Fig. 2 summaries the mode of infection of SARS-CoV2 and therapeutic approaches. This pandemic has imposed huge burdens on economies, religions, education systems, and all social activities worldwide. There is a need to revisit free, cheap, and available plants and foods that may aid the discovery of drugs, vaccines, nutraceuticals and functional foods for prevention and treatment of COVID-19. Most of the plants and foods described in this review are cheap, accessible, and available in most parts of the world and can be easily administered.

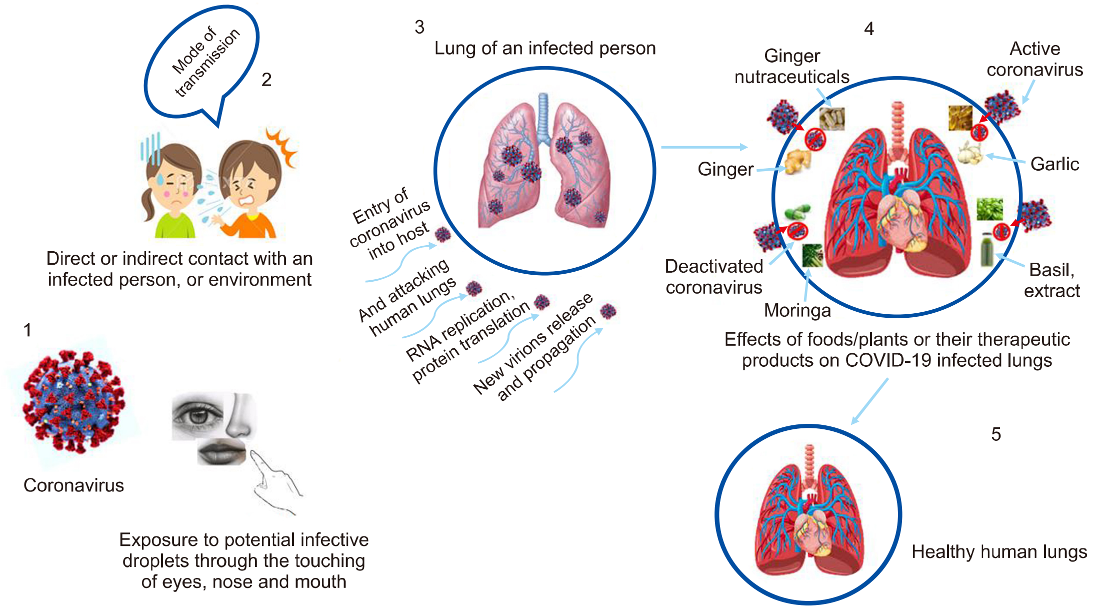

Fig. 2. Schematic diagram showing the effects of foods/plants and their products as a therapeutic approach on the treatment of virus infection related to nCoV-19 (Nikhat and Fazil, 2020).

CONCLUSIONS

With only a limited number of antiviral drugs and vaccines available, and rapid mutation rates of viruses resulting in emergence of new strains, identifying natural remedies for combating viral infections is an urgent unmet need. Since nCoV-19 is a novel virus, it is important to identify herbal therapies with proven effectiveness over time since orthodox therapies have limited success against certain infections. Also, the combined synergistic effects of the active ingredients in plants could be beneficial in treating these viral infections as each component could attack the virus at different stages of infective. The immune-modulatory effects of some of these foods and plants could help protect against future infections.

Although there is no conclusive evidence on the efficacy of these plants against COVID-19, their activity against similar infections *in vitro* and *in vivo* can be explored as a therapeutic option for COVID-19 and other viral ailments. Molecular techniques and agriculture may increase the usefulness of the key components for treatment of COVID-19 and/or related disease(s).

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AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

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