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Dietary therapy and herbal medicine for COVID-19 prevention: A review and perspective

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A B S T R A C T

A novel coronavirus disease (COVID-19), transmitted from humans to humans, has rapidly become the pandemic responsible for the current global health crisis. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is said to be of zoonotic origin. This review describes the etiology and signs and symptoms as well as the current allopathic therapy for COVID-19. Additionally, findings of previous studies on the immunomodulatory effects and antiviral activities of particular foods and herbs on influenza virus and coronaviruses have been collated, with the aim of promoting the use of dietary therapy and herbal medicine as COVID-19 preventive therapies, while specific drugs and vaccines are yet to be discovered or are still under development. The volume of existing reports is irrefutable evidence that foods and herbs possess a potential antiviral ability against SARS-CoV-2 and can prevent COVID-19. Foods and herbs could be used as dietary or complementary therapy to prevent infection and strengthen immunity, as antiviral agents for masks, as disinfectants to curb aerosol transmission, or as sanitizing agents to disinfect surfaces. However, these hypotheses need to be experimentally verified for SARS-CoV-2 and COVID-19 patients.

1. Introduction

At the end of December 2019, the coronavirus outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occurred in Wuhan, Hubei, China,[1] leading to the rapid spread of 2019 novel coronavirus (COVID-19) into a pandemic responsible for the current global health crisis.[2,3] In May 2020, there have been approximately 5 million confirmed cases of COVID-19 and more than 30 thousand deaths worldwide, as reported by the WHO.[4] In this review, we aim to report historical records on the antiviral activity of a particular diet and herbal medicine on influenza virus, SARS-CoV-1, and SARS-CoV-2. This will promote the use of dietary therapy and herbal medicine as complementary COVID-19 prevention therapies, given the current absence of an effective drug and/or vaccine against COVID-19/SARS-COV-2. Several doctors and researchers have already attempted to use herbal medicines on clinical trials against SARS-CoV-2.[5] The longstanding use of dietary therapy and herbal medicine to prevent and treat diseases cannot be overemphasized, as several herbs exhibit antiviral activity.[6] Using dietary therapy and herbal medicine to prevent SARS-CoV-2 infections could be a complementary COVID-19 therapy, while drugs remain under development.

2. Methods

In this review and perspective, the authors searched and collected data related to COVID-19, herbal medicine, and dietary therapy. Google Scholar, PubMed, SciFinder, and ScienceDirect were the main search engines used. The search terms used included: coronavirus; etiology; signs; symptoms; allopathic therapy against COVID-19; immunomodulatory and antiviral activities of herbs

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against influenza, SARS-CoV-1, and SARS-CoV-2. The chosen articles were reviewed and interpreted by the authors. The perspective is an opinion of the authors regarding the use of foods and herbs as a prevention and complementary therapy against COVID-19.

3. Results and discussion

3.1. Etiology, signs, and symptoms of COVID-19

Early discoveries of COVID-19 pneumonia patients were suspected to be associated with the Huanan seafood market in Wuhan, where wild-animal trading occurred.[7] SARS-CoV-2 is postulated to have originated from a bat, because its full-length genomes are similar to the bat-derived SARS-CoV genome: 88% identical (Fig. 1). Phylogenetic analyses indicate that SARS-CoV-2 belongs to the subgenus *Sarbecovirus* of the genus *Betacoronavirus*. More so, homology modeling studies reveal that the receptor-binding domain structure of SARS-CoV-1 is similar to that of SARS-CoV-2.[8] SARS-CoV-2 might amplify in the intermediate mammalian host, probably pangolin, since the whole-genome of pangolin-CoV is 91.02% identical to SARS-CoV-2.[9] In a previous study, molecular and phylogenetic data showed that SARS-CoV-2 did not emerge directly from the pangolin-CoV.[10] However, the origin of the transmission from pangolin-to-human is still in debate. Trading pangolin in wet

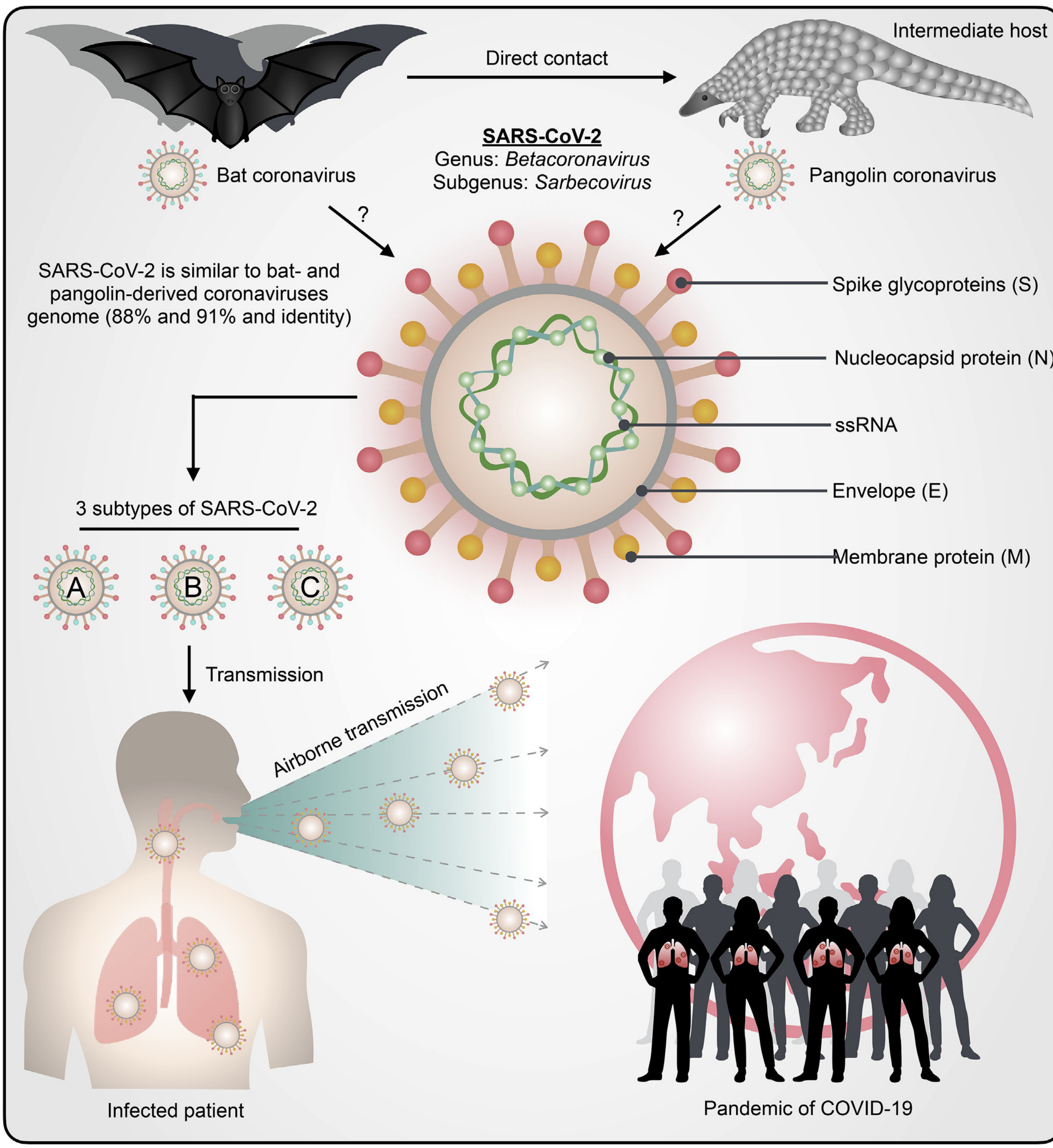

Fig. 1. SARS-CoV-2 etiology, transmission cycle, and structure. SARS-CoV-2 reportedly originates from bats, zoonotically transmitted to the intermediate mammalian host pangolin,[8,9] however, its origin is still under debating. SARS-CoV-2 belongs to the subgenus *Sarbecovirus* of the genus *Betacoronavirus*. Its genome mutates to form 3 types: A, B, and C.[12] It is an airborne disease transmitted from human-to-human. COVID-19 is currently a pandemic and global health crisis.[2]

markets should therefore be strictly prohibited to reduce the risk of future zoonotic transmission.[11] SARS-CoV-2 genomes have now mutated into 3 types; A, B, and C. Type A is closest to the ancestral bat-derived coronavirus. Great proportions of types A and C have been observed in Europeans and Americans, while type B is mainly found in East Asia.[12]

SARS-CoV-2 is a human-to-human aerosol transmission,[13] making the fear of contracting COVID-19 a major panic-trigger amongst numerous individuals. Based on data collected from 99 COVID-19 patients admitted in Jinyintan Hospital, Wuhan, the typical signs and symptoms include fever (83%), cough (82%), and shortness of breath (31%), which are often accompanied by muscle ache (10%), confusion (9%), headache (8%), and sore throat (5%) (Fig. 2).[14] Approximately 75% of these patients also presented with bilateral pneumonia (75%), 17% of them had acute respiratory distress syndrome, and 11% died over a short time span, owing to multi-organ failure.[14] Another study observed that the time from illness onset to dyspnea is approximately 8 days. In this study, 63% of patients had lymphopenia, and all the patients presented with pneumonia.[15] Other reliable indicators include the loss of taste and smell.[16]

3.2. Allopathic therapy against COVID-19

During the SARS-CoV-2 spread in Wuhan, allopathic therapy was used for COVID-19 treatment in the Wuhan Jinyintan Hospital (based on 99 patients), including antiviral treatment (76%), antibiotic treatment (71%), oxygen therapy (75%), and intravenous immunoglobulin therapy (27%),[14] although no COVID-19 drug has been approved by the US Food and Drug Administration. There is also no effective pharmacologic treatment against COVID-19.[17] Determining the drug target requires an understanding of the viral lifecycle. SARS-CoV-2 is a single-stranded RNA-enveloped virus.[18] SARS-CoV-2 and SARS-CoV-1 share similar host-entry mechanisms. It targets the cells by using the viral structural spike (S) protein bind with angiotensin-converting enzymes 2 (ACE2) receptor forming endosomes which enter the cells. TMPRSS2 is a host type 2 transmembrane serine protease helping virus enter through S protein. After the virus enters the cell, it synthesizes viral polyprotein, and RNA subsequently assembles and releases the new virus particles. Inhibiting viral cell entry and replication and modulating the immune system could be a potential target for drug therapy.[19] Current clinical tries on COVID-19 pharmacological treatments include hydroxychloroquine and remdesivir. Hydroxychloroquine, which reduces the viral load in COVID-19 patients, appears to be more effective when used in combination with azithromycin.[20] Remdesivir proved its potential against COVID-19 by displaying clinical improvement.[21] While many clinical trials aimed at discovering a potential effective COVID-19 drug are ongoing, using herbal medicines with well-known antiviral activity might be a complementary SARS-CoV-2 preventive therapy.

3.3. Immunomodulatory effect of foods and herbs and their antiviral activities against influenza, SARS-CoV-1, and SARS-CoV-2

Coronavirus can be treated using nutrition; for instance, treating influenza with very large amounts of vitamin C has been practiced for decades. The common cold, SARS-CoV-1, and SARS-CoV-2 fall under the same coronavirus family; hence, are regarded as the same viral type.[22] Therefore, vitamin C may be effective against

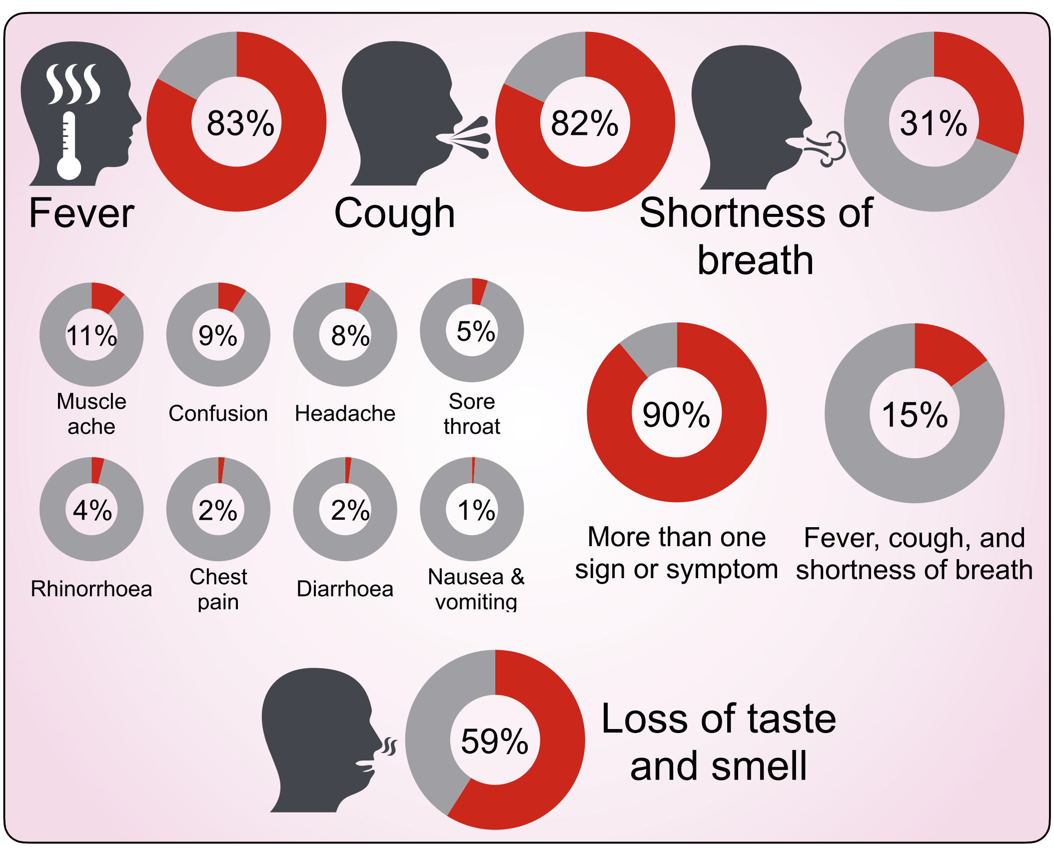

Fig. 2. Data from 99 patients admitted at Jinyintan Hospital, Wuhan, suggest the principal signs and symptoms of COVID-19 include fever, cough, shortness of breath, muscle ache, confusion, headache, and sore throat.[14] Loss of taste and smell is another strong indicator of SARS-CoV-2 infection.[16]

COVID-19; clinical studies are required. An evidence showed that vitamin D decreased the risk of COVID-19 outbreak in winter, which is a time when 25-hydroxyvitamin D (25(OH)D) level is low. Thus, vitamin D intake may reduce the risk of influenza and COVID-19 infections and related deaths.[23] Many foods and herbs are known to display antiviral and immunomodulatory activities. *Aloe vera*, *Angelica gigas* (Korean angelica), *Astragalus membranaceus* (Mongolian milkvetch), *Ganoderma lucidum* (lingzhi mushroom), *Panax ginseng* (ginseng), and *Scutellaria baicalensis* (Chinese skullcap) have been reported to exhibit immunomodulatory properties.[24] Their activities are based on selectively stimulating cytokines, activating lymphocytes, increasing natural killer cell counts, and enhancing macrophage actions. Rice bran, wheat bran, *Lawsonia alba* (hina), *Echinacea purpurea* (eastern purple coneflower), *Plumbago zeylanica* (Ceylon leadwort), and *Cissampelos pareira* Linn (velvetleaf) also exhibit immunomodulatory properties by stimulating phagocytosis. Eucalyptus essential oil is reported to improve the innate cell-mediated immune response that can be used as an immunoregulatory agent against infectious diseases.[25,26] Collectively, using these immunomodulatory foods and herbs could enhance the immune system and protect the body against COVID-19. However, these observations must be verified through scientific or clinical studies.

Numerous studies, although limited to *in vitro*, *in vivo*, and *in ovo* studies, have reported the bioactive components of foods and herbs against the influenza virus and SAR-CoV-1. Only a few clinical studies have been carried on the effects of specific foods and herbs against the influenza virus and SAR-CoV-1, as most clinical studies have been done on food and herb combinations, or the traditional Chinese formulas.[27] The antiviral activities reported for foods and herbs against the influenza virus are shown in Table 1. The antiviral influenza study models have mainly been Madin-Darby Canine Kidney cells (MDCK) and murine models, with the influenza strains being the influenza A virus subtype H1N1, H9N2, and H11N9. The extracts or bioactive compounds of garlic, ginger, Korean red ginseng, eucalyptus, tea tree, Tianmingjing, Machixian, fish mint, Chinese mahogany, cape jasmine, zhebeimu have been shown to exhibit antiviral activity against the influenza virus.[28–39]

The mode of action for influenza virus A inhibition is via inhibition of proliferation or penetration into MDCK cells. Garlic and

Table 1
Antiviral activity of foods and herbs against influenza virus.

Herbs	Bioactive compound and extract	Experimental model	Mode of action	References
Allium sativum (Garlic; 大蒜; Dà suàn)	Garlic aqueous extract	H9N2 virus infection in MDCK cells and chicken embryo	Anti-avian influenza virus H9N2 activity in both chick embryos and cell models	Rasool et al. (2017)[28]
	Garlic extract	H1N1 virus infection in MDCK cells	Inhibits H1N1 virus penetration and proliferation in cell culture	Mehrbod et al. (2008)[29]
Zingiber officinalis (Ginger; 薑; Jiāng)	Ginger aqueous extract	H9N2 virus infection in MDCK cells and chicken embryo	Anti-avian influenza virus H9N2 activity in both chick embryos and cell models	Rasool et al. (2017)[28]
Panax ginseng C.A. Meyer (Korean red ginseng; 紅參; Hóng cān)	Korean red ginseng powder capsule	H1N1 virus-induced respiratory tract infection in mice and MDCK cells	Ginseng enhances immunity by increasing the levels of influenza A virus-specific antibodies and their neutralizing activities. It modulates CD69-expressing immune cells and exhibits significant enhancement of influenza virus-specific IgA antibody in mice lungs.	Quan et al. (2006)[30]
Eucalyptus polybractea (Eucalyptus; **尤加利; Yóu jiā lì**)	Aerosol and vapor of eucalyptus oil	H11N9 virus infection in MDCK cells	Inhibits avian influenza virus H11N9 in aerosol and vapor form	Usachev et al. (2013)[31]
	Eucalyptus oil	H11N9 virus infection in MDCK cells	Pre-coated eucalyptus oil inactivates captured H11N9 virus in fiber material	Pyankov et al. (2012)[32]
Melaleuca alternifolia (Tea tree; 茶樹; Chá shù)	Aerosol and vapor of tea tree oil	H11N9 virus infection in MDCK cells	Inhibits avian influenza virus H11N9 in aerosol and vapor form	Usachev et al. (2013)[31]
	Tea tree oil	H11N9 virus infection in MDCK cells	Pre-coated tea tree oil inactivates captured H11N9 fiber material	Pyankov et al. (2012)[32]
Carpesium abrotanoides L. (Tianmingjing; 天名精; Tiān míng jīng)	4α,5α-dihydroxy-guaia-11(13)-en-12,8α-lactone	H11N9 virus infection in MDCK cells	Inhibits H1N1 virus activity	He et al. (2020)[33]
Portulaca oleracea L. (Machixian; 馬齒莧; Mǎ chǐ xiàn)	Water extract of *P. oleracea* L.	H11N9 virus infection in MDCK cells	Inhibits H1N1 and H3N2 in the early stages of influenza A virus infection, inhibits the binding of virus to cells, and exhibits good virucidal activity.	Li et al. (2019)[34]
Houttuynia cordata (Fish mint; 魚腥草; Yú xīng cǎo)	*H. cordata* ethanolic extract	H1N1 virus-induced acute lung injury in mice and RAW 264.7 cell model	Alleviates H1N1-induced acute lung injury in mice through antiviral and anti-inflammatory effects. Inhibition of viral neuraminidase activity and toll like receptor signaling	Ling et al. (2020)[35]
	H. cordata polysaccharide	H1N1 virus-induced acute lung injury mouse model	Alleviates lung injury and intestinal dysfunction	Chen et al. (2019)[36]
Toona sinensis (Chinese mahogany; 香椿; Xiāng chūn)	Catechin and gallic acid	H1N1 virus infection in MDCK cells	Inhibits H1N1 mRNA replication and MDCK plaque formation, neuraminidase activity, and viral glycoprotein	You et al. (2018)[37]
Gardenia jasminoides Ellis (Cape jasmine; 梔子; Zhī zi)	Geniposide	H1N1 virus-induced respiratory tract infection in mice and MDCK cells	Protects MDCK from H1N1 virus-induced cell injury and inhibits virus-induced alveolar wall changes, alveolar hemorrhage, neutrophil-infiltration, and inflammation in mice lungs	Zhang et al. (2017)[38]
Fritillaria thunbergii (Zhebeimu; 浙貝母; Zhè bèi mǔ)	*F. thunbergii* aqueous extract	H1N1 virus-induced respiratory tract infection in mice, virus infection in MDCK cells and in ovo studies	Inhibits H1N1 replication in embryonated eggs. Protects MDCK cells from H1N1 virus-induced cell injury. Increases mice survival rate from viral infection.	Kim et al. (2020)[39]

Table 2
Antiviral activity of foods and herbs against severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1).

Herbs	Bioactive compound and extract	Experimental model	Mode of action	References
Toona sinensis Roem (Chinese mahogany; 香椿; Xiāng chūn)	Tender leaf of *Toona sinensis* Roem crude extract fraction	Vero cell with SARS-CoV-1 strain FFM 1 infection model	Inhibits SARS-CoV-1 replication	Chen et al. (2008)[42]
Glycyrrhiza radix (Liquorice; 甘草; Gān cǎo)	Glycyrrhizic Acid Derivatives	Vero cell with SARS-CoV-1 strain FFM 1 infection model	Inhibits SARS-CoV-1 and increase cytotoxicity	Hoever et al. (2005)[43]
Lycoris radiata (Red spider lily; 石蒜; Shí suàn)	Lycorine	Vero cell with SARS-CoV-1 strain BJ001 and BJ006 infection model	Inhibits SARS-CoV-1 replication	Li et al. (2005)[44]
Rhizoma Cibotii (Rhizome of Scythian Lamb; 狗脊; gou ji)	*Rhizoma Cibotii* extract	Vero cell with SARS-CoV-1 infection model	Inhibits SARS-CoV-1 replication	Wen et al. (2011)[45]

ginger were found to inactivate avian influenza virus H9N2 activity in both MDCK cells and chick embryos.[28,29] The ethanolic extract and polysaccharides of fish mint have been shown to alleviate H1N1-induced acute lung injury in mice, hence simultaneously improving the immune system.[35] The aqueous extract of zhebeimu can inhibit H1N1 replication in embryonated eggs and increase the survival rate of virus-infected mice.[39] Some essential oils have been shown to exhibit anti-influenza activities. These include *Cinnamomum zeylanicum* leaf oil (cinnamon), *Citrus bergamia* (bergamot), *Cymbopogon flexuosus* (lemongrass) and *Thymus vulgaris* (Red Thyme).[40] A blend of essential oils also inhibits the infectivity of influenza virus via inactivating viral binding ability and viral protein translation in MDCK cells.[41] Tea tree oil and eucalyptus oil capturing on the fiber coating materials are capable of inactivating influenza virus A.[32]

Chinese mahogany, Chinese liquorice, red spider lily, the rhizome of *Scythian lamb*, and its extract or compound, have reported anti-SARS-CoV-1 activity in Vero cells with the SARS-CoV-1 infection model (Table 2).[42–45] Although some natural products as baicalein and baicalin were proved as the inhibitors of SARS-CoV-2,[46] there has been no published study on a single herb, its extract, and bioactive compound against SARS-CoV-2. Ding et al. (2017) investigated Lianhuaqingwen, a Traditional Chinese Medicine formula composed of a combination of 13 herbs (Table 3).[47] Lianhuaqingwen suppressed SARS-CoV-2 replication, reduced pro-inflammatory cytokine production, and changed the morphology of SARS-CoV-2 cells.[48] SARS-CoV-2 can cause dangerous and potentially lethal diseases through the respiratory route. Hence, studying the effect of a particular bioactive compound against SAR-CoV-2 requires a highly contained laboratory with inward directional airflow (Biosafety level 3; BSL-3),[49] posing a challenges for most researchers.

3.4. Perspective for using foods and herbs against COVID-19

Current literature carries strong evidence in support of dietary therapy and herbal medicine as potential effective antivirals against SARS-CoV-2 and preventive agents against COVID-19. For future studies, the authors believe there are 4 potential approaches for the application of dietary therapy and herbal medicine against COVID-19: (1) using foods and herbs as diet or supplement to prevent infection and strengthen immunity; (2) use as an antiviral agent by coating on masks; (3) use as an air-disinfectant (essential oil) to stop aerosol transmission; and (4) use as a surface sanitizing agent to provide a disinfected environment (Fig. 3).

Surgical masks are good at preventing virus spread into the air and transmission to humans.[50,51] However, after mask removal, the virus remains on the mask and is probably re-aerosolized, increasing the risk of human infection. Mask coating with an antiviral compound could be advantageous, but disinfectant toxicity to humans must be considered.

Table 3
Antiviral activity of herbs against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Herbs	Bioactive compound and extract	Experimental model	Mode of action	References
Lianhuaqingwen (連花清瘟; Lián huā qīng wēn)	Lianhua-Qingwen formula (13 herbs) (Ding et al.,2017) • *Forsythia suspensa* (Thunb.) Vahl (Weeping forsythia; 連翹; Lián qiáo) • *Ephedra sinica* Stapf (Chinese ephedra; 草麻黃; Cǎo má huáng) • *Lonicera japonica* Thunb. (Japanese honeysuckle; 忍冬; Rěndōng) • *Isatis indigotica* Fortune (Woad; 菘藍; Sōng lán) • *Mentha haplocalyx* Briq. (Mint; 薄荷; Bò hé) • *Dryopteris crassirhizoma* Nakai (Thick-stemmed wood fern; 粗莖鱗毛蕨; Cū jīng lín máo jué) • *Rhodiola rosea* L. (Golden root,; 紅景天; Hóng jǐng tiān) • *Gypsum Fibrosum* (Gypsum; 石膏; Shí gāo) • *Pogostemon cablin* (Blanco) Benth. (Patchouli; 廣藿香; Guǎng huò xiāng) • *Rheum palmatum* L. (Chinese rhubarb; 掌葉大黃; Zhǎng yè dà huáng) • *Houttuynia cordata* Thunb. (魚腥草; Yú xīng cǎo; Fish mint) • *Glycyrrhiza uralensis* Fisch. (Liquorice; 甘草; Gāncǎo) • *Armeniaca sibirica* (L.) Lam. (Siberian apricot; 山杏; Shān xìng)[47]	Vero E6 cells with SARS-CoV-2 infection model	Inactivate SARS-CoV-2 replication, reduce pro-inflammatory cytokines production and affect particle morphology of virus cell.	Li et al. (2020)[48]

Aromatherapy has been used for thousands of years in Egypt and India to treat various diseases,[52] and the antimicrobial and antiviral activity of essential oils have been confirmed by numerous studies.[53] However, most of these studies only investigated the effect of their liquid formula, limiting their administration to only via the oral route. Using essential oils vapors could increase their application against airborne bacteria and viruses. The anti-influenza virus activity of some essential oil vapors, such as that of *Citrus bergamia* (bergamot), *Eucalyptus globulus* (eucalyptus), *Pelargonium graveolens* (geranium), *Cinnamomum zeylanicum* leaf oil (cinnamon), and *Cymbopogon flexuosus* (lemongrass), has been reported. Their inhibitory mechanism is based on the inactivation of the principal external proteins of the influenza virus. The hemagglutinin protein of the virus appeared to be a major target of most of these oil vapors, and this may provide therapeutic benefits for people suffering from influenza or other respiratory viral infections.[40] Aerosolized tea tree oil reportedly inhibits airborne viral particles of H11N9 subtype avian influenza virus.[32] There are currently very few studies on the potential of the vapor form of essential oils. Air sterilization without human health damage using essential oils could be a good way to prevent COVID-19. However, the minimum essential oil concentration needed for SARS-CoV-2 inhibition should be investigated.

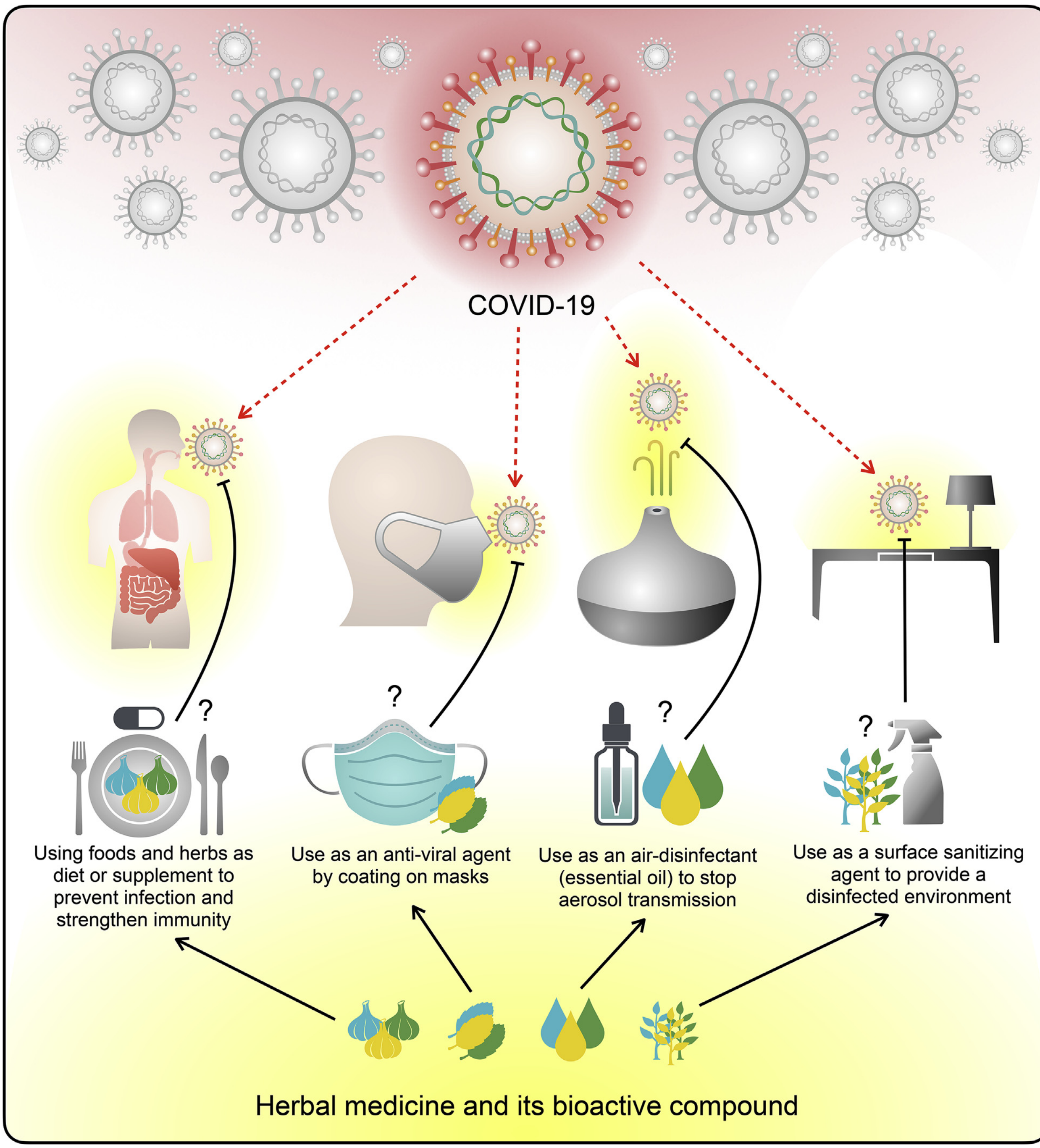

Fig. 3. The prospects of dietary therapy and herbal medicine for COVID-19 prevention. Dietary therapy and herbal medicine could be used against COVID-19 in the following four ways: (1) diet or supplement for infection prevention and immunity strengthening; (2) application as antiviral agent on masks; (3) air disinfection agent to stop aerosol transmission of the virus; and (4) surface sanitizing agent to afford a disinfected environment.

Many restaurants use cleaning detergents for surface sanitization; however, their safety and disinfection efficiency need further consideration. Natural antiviral extracts from herbs could be added to cleaning detergents to increase their anti-SARS-CoV-2 activity.

4. Conclusions

Currently, there are limited number of allopathic medicines considered effective against COVID-19. The design and development of drugs and vaccines require elucidation of the mechanism of SARS-CoV-2. Current literature provides obvious evidence supporting dietary therapy and herbal medicine as potential effective antivirals against SARS-CoV-2 and as preventive agents against COVID-19. Thus, dietary therapy and herbal medicine could be a complementary preventive therapy for COVID-19. However, these hypotheses require experimental validation in SARS-Cov-2 infection models and COVID-19 patients.

Declaration of competing interest

None of the authors has any conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtcme.2020.05.004.

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