Review Article

Novel SARS-CoV-2 and COVID-2019 Outbreak: Current Perspectives on Plant-Based Antiviral Agents and Complementary Therapy

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ABSTRACT

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) caused the novel Corona Virus Disease 2019 (COVID-19), which has been defined as a pandemic by the World Health Organization (WHO) in 2020. The rapid global spread of SARS-CoV-2 virus as a global health emergency has emphasized to findeffective treatment strategies in clinical trials. The several drug trials including Lopinavir (LPV) and Ritonavir, Chloroquine (CLQ), Hydroxychloroquine, Favipiravir (FPV), Remdevisir (RDV), Nitazoxanide, Ivermectin and Interferon, have been explored in COVID-19 patients and some of the drugs have been waiting clinical approval for their anti-SARS-CoV-2 activities. Clinical trials are still ongoing to discover promising new multidrug combination treatment for COVID-19 patients. Considering the difficulties to ascertain efficient drug candidates and the lack of specific anti-viral therapies against COVID-19 outbreak, the current management of SARS-CoV-2 should mainly be supportive. From this point of view, enhancing the immune system through medicinal plants with wide range of bioactive compounds, which exhibit antiviral activities, can play significant roles to increase defense barrier in COVID-19 patients. On the other hand, plant-based agents as complementary and alternative therapies have potential advantages to reduce symptoms of this life-threatening disease and could promote the public health. Recently, there has been a remarkable progress in the field of antiviral herbal therapy owing to increasing concerns about the development of drug resistance and limited advances in the field of antiviral drug discovery. This review provides an overview of published information onbiology, genomic structure, replication cycle and pathogenesis of SARS-CoV-2. It also aims to assemble the fact and a scientific intellectual groundwork on development of antiviral herbal therapy on the bases of extensive literature collection.

Key words: SARS-CoV-2, COVID-19, Outbreak, Medicinal plants, Antiviral.

INTRODUCTION

Viral infections have emerged throughout the human history and they caused dramatically outbreakssuch as Cholera, Ebola, Bubonic Plague, AIDS (Acquired Immunodeficiency Syndrome), Influenza, SARS (Severe Acute Respiratory Syndrome), MERS (Middle East Respiratory Syndrome) and currently COVID-19 (causative agent SARS-CoV-2 or 2019-nCoV). The emergence of the viral infections has often been multifactorial and the results of them can altered human civilization.[1-4] Coronaviruses (CoVs) belong to family of Coronaviridae, Arteriviridae, Roniviridae and Mesoniviridae families. Of which, Coronaviridae is the largest family and includes subfamily of Coronavirinae, that is now classified into four main genera including alpha (α)-coronavirus, beta (β)-coronavirus, gamma (γ)-coronavirus and delta (δ)-coronavirus. Alphacoronaviruses and β-coronaviruses infect variety of host

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cells and can cause life-threatening pneumonia in humans and some animals such as feline, porcine, canine, mice, bovine, bat and rodent, while γ-coronavirus and δ-coronavirus are specific of birds, but some of them can also infect other organisms.[5-8]

According to the International Committee for Taxonomy of Viruses, FECV (Feline Enteric Coronavirus) and FIPV (Feline Infectious Peritonitis Virus), the porcine TGEV (Transmissible Gastro-Enteritis Virus), Porcine PEDV (Epidemic Diarrhea Virus), PRCoV (Porcine Respiratory Coronavirus), CCoV (Canina Coronavirus) and human coronaviruses (HCoV-229E and HCoVNL63) are of α-coronaviruses. Betacoronaviruses also compromise Murine coronavirus (MHV) and Bovine Coronavirus (BCoV) and human coronaviruses (HCoV-OC43, HCoV-HKU1, SARS-CoV, MERS-CoV and SARS-CoV-2).[9,10]

Although, the history of CoVs began in the 1940's, the first human CoVs subsequently, named as (i) human CoV-229E (HCoV-229E) and (ii) HCoV-OC43, were reported in the 1960's.[1,2,7] After that, the virologist tried to identify general structure of CoVs, as well as replication and pathogenesis of them. The studies among the scientist provided to discovery of other new human coronaviruses such as (iii) HCoV- Hong Kong University 1 (HKU1), (iv) HCoV-NL63, (v) Severe Acute Respiratory Syndrome (SARS)-CoV and (vi) Middle East Respiratory Syndrome (MERS)-CoV.[5,11,12] Among these coronaviruses, SARS-CoV was identified as a global outbreak in 2003 and it had affected 8422 people in 32 countries, with the mortality of rate of 10-15%. SARS-CoV initially infected the bats and caused the disease by transmitting from bats to the palm musk cat and from there to humans.[12-14] Then, approximately after ten years, another highly pathogenic coronavirus MERS-CoV epidemic emerged in Saudi Arabia and spread to other Middle Eastern countries in 2013. Although, the major MERS-CoV pandemic was happened in the Republic of Korea, it was observed worldwide at any age of people with the fatality rate of 39%.[11,15,16]

Following this outbreak, the novel coronavirus namely 2019-nCoV or SARS-COV-2 has been caused COVID-19 outbreak emerged in Wuhan State, Hubei Province, China in December 2019. It has spread to more than 180 countries and territories US, Spain, Italy, France, Germany, United Kingdom, China and Iran continue to be the countries hardest-hit. Since, it has been infected many people and caused a high mortality rate in a short period, the World Health Organization (WHO) has declared the new coronavirus outbreak called COVID-19 a pandemic.[17,18] As of 15 May 2020, more than 4,426,937 confirmed cases of COVID-19 have been reported in many countries and territories, resulting in approximately 301,937 deaths all around the world. Moreover, the number of infected patients with COVID-19 and death from this virus are alarmingly increasing day by day.[19,20] Since its rapid infection ability from person to person and high mortality rate, finding efficient and accurate therapy strategies are urgently necessary to combat this disaster. Hence, scientists have been racing to understand novel coronavirus disease to reveal possible therapy strategies including drug discovery, therapeutic antibodies, cytokines, nucleic acid-based therapy, vaccines with the potential for treating and preventing coronavirus infections. Among the given strategies, to discover effective drugs, which may be applicable to COVID-19, have been seem to be the most certain option for immediate treatment. Although, no specific drug has been investigated or currently available for COVID-19 cases, clinical trials and evaluations of potential antiviral drug candidates are ongoing at different laboratories.[12,21]

Current researches on developing drugs against many viral diseases undertaken that medicinal plants used in traditional folk medicine have significant importance for the ongoing development of therapeutic agents and broad-spectrum drugs.[22-25] The information included in this review reveals that possible efforts to search for efficient complementary and alternative medicines from different herbal formulations against emerging coronavirus outbreak that is urgently necessary to reduce overwhelming impacts on worldwide healthcare systems. Moreover, biological properties of coronaviruses and their mechanisms of infection in the host cells, which are necessary to discover useful therapeutic routes for this outbreak, have been summarized in the presented review.

Genomic Structure of Human Coronaviruses

Coronaviruses are single stranded positive sense RNA viruses encapsulated within a membrane envelopeand their genome comprises approximately 26-32 kilobases nucleotides. In all CoVs encode five structural proteins: (i) spike protein (S), (ii) hemagglutinin esterase (HE) protein, (iii) membran protein (M), (iv) envelope protein (E), (v) nucleocapsid protein (N), respectively, from outside to inner membrane.[26-28] These proteins play critical roles for virion assembly, viral replication and transcriptionas well as suppression the host immune response (Figure 1).

(i) S protein, located outside of the virus, are a glycoprotein that gives the typical shape for the virion. These proteins act as cell surface receptor

proteins for introduce the host cell and interact with membrane proteins.[29]

(ii) Additionally, hemagglutinin esterase (HE) proteins can be found in some beta-coronaviruses in order to strengthen invading mechanism. They help in the attachment and destruction of certain sialic acid receptors that exist on the host cell surface.[28,29]

(iii) M proteins are glycosylated glycoproteins that are essential for regeneration in the virus cell. They are also necessary to fuse into the host celland bind to N proteins.[12]

(iv) E proteins are hydrophobic small proteins, covering completely the membrane. They allow attachment to the membrane of viruses and play a key role in the combining of the viral particules in the host cell.[12,30]

(v) N proteins are phosphoproteins that are able to bind viral genomic RNA. These proteins are important for structure, replication andtranscription mechanisms of coronaviruses through interactions with the RNA viral genome. It is also determined that these proteins give information about the pathogenesis in the host cell and virulence of CoVs.[29-31]

Besides structural proteins, most of the non-structural and accessary proteins are essential for coronaviral replication. Even though, specific roles of each non-structural proteins (NSPs) and accessory proteins have not been clarified scientifically, most of the NSPs from NSP1 to NSP16 and some of the accessory proteins have been reported to possess specific functions for CoVs replication.[16,17] Their known functions are summarized in Table 1.

Replication and Infection Mechanisms of Human Coronaviruses

Coronaviruses are viruses whose genomic material comprises single stranded-positive sense (+ss) RNA that acts as a messenger RNA (mRNA) in the infection cycle. Among all known CoVs, two-thirds of the genome encodes a viral RNA-dependent polymerase materials (RdRp), including two overlapping open reading frames (ORF1a and ORF1b) in the 5'untranslated region (UTR). In this region of the CoVs have been shown to consist of a replicase complex (ORF1a and ORF1b) encoding non-structural proteins (NSPs), when 3' terminus of the CoVs consist of structural proteins including nucleocapsid protein (N) gene, membrane protein (M) gene, envelope protein (E) gene and spike protein (S) gene.These structural canonical proteins, located at the 3' terminus of the genome, are not only involved in replication and transcription of the viral genome, but also help to make easier for the virus to enter and multiply into the host cell by suppressing the host's immune system.[16,17,32,33] Phylogenetic tree and genomic structure of CoVs including COVID-19 (SARS-CoV-2) are given in the Figure 2.

Researchers have released the first full genome sequence of 2019-nCoV by reverse transcription polymerase chain reaction (RT-PCR) methods on 10 January 2020.[17,18] Ongoing researches have revealed that SARS-CoV-2 has ancestral genomic similarities to SARS-coronaviruses. As of January 31, SARS-CoV-2 whole genome sequences from different laboratories and regions have identified and the data has presented to GISAID (Global Initiative on Sharing All Influenza Data) (https://www.gisaid.org/). As shown in the Figure 2 (a), the genome sequence alignment of different coronaviruses exhibits 54% identity at whole genome level. NSP coding region shows 58% identity, suggesting NSPs are more conserved among the CoVs, while structural proteins are less conserved with 43% identity at the whole genome level of different CoVs. As for SARS-CoV-2 (2019-nCoV), it has a genome structure same as the other β-CoVs including Bat-(SL) ZC45, Bat-(SL) ZXC21, SARS-CoV and MERS-CoV.[16]

S proteins of the CoVs include receptors on the cell surface and these receptors make recognition on the host cells, then the virus can entry into the cells and replication of the CoVs begin with the binding of the host cell surface. Aminopeptidase N, O-acetylated sialic acid, angiotensin-converting enzyme 2 (ACE2), dipeptidyl peptidase 4 (DPP4), transmembrane protease serine 2 (TMPRSS2) and airway trypsin-like protease TMPRSS11D are of the receptors used by human CoVs to entry the cell membrane of host cells.[28-31] Human CoVs and their cellular receptor proteins are summarized in the Table 2.

The replication of CoVs begins, after entering the host cell cytoplasm. The viral particules release the RNA genome and the replicase gene products ORF1a and ORF1b that are ready for translation into two polyproteins (pp1a and pp1ab), shown in the Figure 1. After that, pp1a and pp1ab are cleaved into almost 16 non-structural proteins (NSPs), which are responsible for assembling replication and transcription complex (RTC) in a double-membran vesicle (DMVs). Subsequently, the full-length positive strand of genomic RNA is converted into a full-length negative-strand template for the synthesis of new genomic RNAs, with the activities of replicase enzymes. 3' end of the genome encodes structural and accessory proteins (S, E, M, N and others such as HE protein, 3a/b protein, 7a/b protein, 9b/c protein etc.), necessary for viral replication and transcription, are produced by these

Table 1: Non-Structural and Accessory Proteins of CoVs and Their Functions.

Proteins of CoVs		Specific Functions	
Non-structural proteins (NSPs)	NSP-1	Cellular Saboteur	Forces the cell to make more virus proteins and cellular mRNA degradation
	NSP-2	Mystery Protein	Unknown
	NSP-3	Untagging and Cutting	Cuts loose other viral proteins and alters many of the infected cell's proteins
	NSP-4	Bubble Maker	Constructs double-membrane vesicles and parts for new copies of the virus
	NSP-5	Protein Scissors	Makes most of the cuts and inhibits IFN signaling
	NSP-6	Bubble Factory	Works together with NSP-3 and NSP-4 to make virus bubbles
	NSP-7	Copy Assistants	Make new copies of the RNA genome
	NSP-8	Copy Assistants	Make new copies of the RNA genome
	NSP-9	At the Heart of the Cell	Infiltrates tiny channels in the infected cell's nucleus and organizes dimerization
	NSP-10	Genetic Camouflage	Camouflages the virus's genes
	NSP-11	Unknown	Unknown
	NSP-12	Copy Machine	Assembles genetic letters into new virus genomes
	NSP-13	Unwinding RNA	Unwinds virus RNA (RNA helicase) and makes new copies
	NSP-14	Viral Proofreader	Corrects and edits the virus genome (exoribonuclease)
	NSP-15	Cleaning Up	Hides the virus RNA from the host cell's immune defenses
	NSP-16	More Camouflage	Works with NSP-10 and camouflages the virus's genes by negatively regulating immunity
Accessory proteins	ORF3a	Escape Artist	Pokes a hole in the membrane of the host cell, making it easier for new viruses to escapeand also triggers inflammation
	ORF3b	Unknown	Overlaps theRNA but it is not clear
	ORF6	Signal Blocker	Blocks both signals in the infected cells and some of the cell's own virus-fighting protein
	ORF7a	Virus Liberator	Triggers infected cells to commit suicide and allows more of the viruses to escape
	ORF7b	Unknown	Overlaps theRNA but it is not clear
	ORF-8	Mystery Protein	Its function is not clear
	ORF9b	Immune System Blocker	Overlaps theRNA and blocks interferon
	ORF9c	Unknown	Its function is not clear
	ORF10	Mystery Protein	Unknown

new genomic RNAs and they are distributed among the structural genes.[34,35] (Figure 1 and 2).

The novel coronavirus (SARS-CoV-2), originated from bats is a zoonotic virus that infects human. The virus primarily infects upper respiratory system in human beings. Transmission of COVID-19 infections occurs through respiratory droplet from human to human and touching of contaminated surfaces, as reported in the studies. Even though the common symptoms of the CoVs infections are similar, each CoVs infection includes unique symptoms.[35-38] General symptoms of human coronaviruses are summarized in the Table 2. As given in the Table 2, fever, cough, muscle pain, weakness, respiratory symptoms and shortness of breath are of some common symptoms observed in COVID-19. Of which fever and cough have been reported as common-symptoms in the patients. These common-symptoms can be changed depending on the patient immune response and asymptomatic people do not develop any symptom.[10,18,38,39]

Potential Treatment and Prevention Strategies for Coronaviruses

Currently, no efficient antiviral therapy is available for emerging COVID-19, but recommended treatment strategies are available. Although, scientists have been devoted to find new antiviral targets that can be CoVs proteases inhibitors (e.g. lopinavir/ritonavir), polymerases, methyltransferases, replicase inhibitors (e.g. 1,2,4-triazolederivative, remdesivir, disaproxil and lamivudine), kinase signaling pathway inhibitors

(e.g. trametinib, selumetinib, everolimus, rapamycin, dasatinib and imatinib mesylate), nucleic acid synthesis inhibitors (e.g. gemcitabine, hydrochlorideribavirin and mycophenolic acid), as well as entry inhibitors clinical trials have been ongoing with some of them.[12,40] Nowadays, plasma and antibodies obtained from the COVID-19 patients have been proposed for one of another potential strategy in treatment. Additionally, numerous researchers in some laboratories and institutes have mainly been focused on development various vaccine strategies, such as using inactivated viruses, live-attenuated viruses, viral vector-based vaccines and recombinant proteins.[29,37,41,42]

In generally, two potential treatment strategies have been employed for coronaviruses-related diseases: (1) Broad spectrum antiviral drugs and (2) anti-CoV drug discovery involves the de novo development. The first strategy possesses possible benefits, if pharmacokinetic and pharmacodynamic properties of the drugs are known in details. As for the second one, it is aimed to develop specific agents based on the genomic and biologic understanding of the individual CoVs.[12,37]

Ribavirin, lopinavir, ritonavir and combination therapy using interferon α-1 and corticosteroid, used for SARS-CoV patients have not been found so effective therapeutics that have been clearly revealed by previous reports. In another study, the combination of ritonavir and interferon β-1a had no significant effect on clinical outcome in the MERS patients, further, the combination of ribavirin, ritonavir; interferon α-2a resolved viremia within 2 days after commencement of treatment in a patient with severe MERS had no favorable response. However, the combination therapy of interferon and ribavirin showed the best result for MERS-CoV infection.[17,43,44]

Moreover, broad-spectrum inhibitors such as lycorine, emetine, monensin sodium, mycophenolate mofetil, mycophenolic acid, phenazopyridineand pyrvinium pamoate have showed strong inhibition in replication of human CoVs in a dose and time dependently. In one of the drug research has been revealed that four drugs including chloroquine, chlorpromazine, loperamide and lopinavir from the screening of FDA approved drugs library were able to suppress the replication of MERS-CoV, SARS-CoV and HCoV-229E.[44,45]

To identify potential antiviral agents against novel COVID-19, current researches have been primarily tried previous drugs used for the SARS- and MERS-CoV infections. Since SARS-CoV-2 is a newly discovered pathogen, drug trials in the management of patients with SARS-CoV-2 infection are still ongoing. Increasing understanding of the basic information about novel CoVs will provide opportunities for design specific and efficient therapeutics in the near future.[25,37,38]

Antiviral Effects of Medicinal Plants and Phytochemicals

Currently, approved remedy for management of many types of viruses is limited and often costly and ineffective because of viral multidrug resistance and toxic side effects. In that case, plant-based therapy could offer an alternative treatment for virus-related infections. Hence, it is necessary to examine natural

Table 2: Human Coronaviruses, Cell Surface Receptors and Symptoms of CoVs.

Human CoVs	Classification	Natural Host	Symptoms	Receptor Proteins
HCoV-229E	α-coronavirus	Bats	Mild respiratory tract infections	Human aminopeptidase N (CD13)
HCoV-OC43	β-coronavirus	Cattle	Mild respiratory tract infections	9-O-acetylated sialic acid
SARS-CoV	β-coronavirus	Palm civets	Severe acute respiratory infections, 10% mortality rate	Angiotensin-converting enzyme 2 (ACE2)
HCoV-NL63	α-coronavirus	Bats, palm civets	Mild respiratory tract infections	Angiotensin-converting enzyme 2
HCoV-HKU1	β-coronavirus	Mice	Pneumonia, lung inflammation	9-O-acetylated sialic acid (ACE2)
MERS-CoV	β-coronavirus	Bats, camels	Severe acute respiratory infections, 37% mortality rate	Dipeptidyl peptidase 4 (DPP4)
SARS-CoV-2	β-coronavirus	Bats	Fever, cough, muscle pain, weakness, respiratory symptoms, shortness of breath and death,	Angiotensin-converting enzyme 2 (ACE2) and transmembrane proteaseserine 2 (TMPRSS2)

antiviral phytochemicals used for successfully drug delivery applications in overcoming the multiple biological barriers.[33,46]

A number of medicinal plants, possessing diverse pharmacological properties including antiviral activites, havebeen used in traditional medicinefor thousand of years. In recent years, medicinal plants, which are good sources for drug discovery and pharmaceutical industry, have been preferred by the people for their primary healthcare. The beneficial therapeutic effects of plant-based products typically result from the phytochemicals found in the plants. Various phytochemicals derived from medicinal plants including alkaloids, steroids, lignans, diterpenoid lactones, aliphatics, glycosides etc. have showed to induce antiviral effects and prevent several viral diseases. As synthetic drugs are not available towards most of the viruses, so reserachers have been focused on to search for drugs obtained from different herbal formulations. Almost all around the world, people have been recently tend to use medicinal plants as complementary and alternative medicines in order to enhance immune system for fighting COVID-19.[17,47,48] Accordingly, hundreds of medicinal plants and secondary metabolites have been displayed, identifiedand analyzed in both preclinical and clinical trials for their medicinal activities; however, some have demonstrated significant antiviral activity in prevention of various viral diseases. Many medicinal plants individually or in combination with different formulations including decoctions, leaf powder, infusions, pastes and pills have been recommended in the eradication and management of various viral infections.[18,49] Antiviral herbal medicines have been used in many historic viral diseases, the findings related to antiviral medicinal plants and phytochemicals are collected in Table 3.

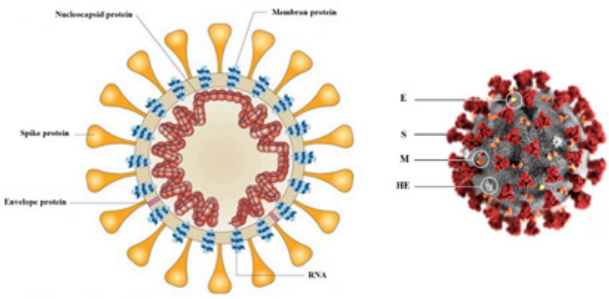

Figure 1: Structure of Coronaviruses (modified from https://www.id-hub.com/).

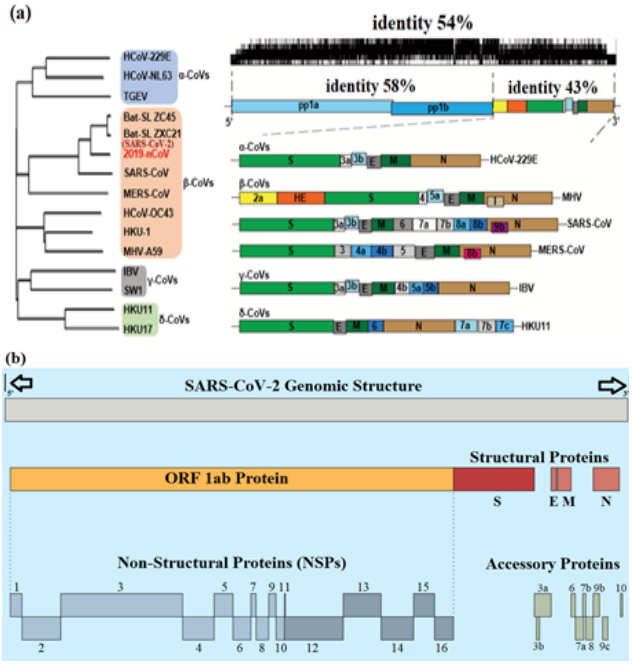

Figure 2: (a) Phylogenetic Tree and Genomic Organization of the Human Coronaviruses16 (b) SARS-CoV-2 Genomic Structure (modified from https://www.nytimes.com/interactive/science/coronavirus).

Table 3: Antiviral Medicinal Plants and Phytochemicals for Complementary and Alternative Therapy.

Medicinal Plant	Extract/Phytochemicals	Antiviral Activity	References
Aloe vera L.	Glycerine extract	Herpes simplex virus type 2 (HSV-2)	46,50
	Anthraquinones	Hepatitis B virus	51
Eucalyptus globulus Labill.	EOs	Herpes simplex virus (HSV-1) and Influenzavirus A (H1N1)	52
Baccharis gaudichaudiana, *B. spicata* and *B. anomala*	Extracts	Bovine herpes virus 1 and herpes simplex virus (HSV-1)	53
Melissa officinalis L.	Extracts	Avian infectious bronchitis virus (IBV)	54
		Herpes simplex virus type 1 (HSV-1), type 2 (HSV-2) and an acyclovir-resistant strain of HSV-1 (ACVres)	55
		Herpes simplex virus (HSV-1)	56,57
		Herpes simplex virus (HSV)	58,59

	EOs (lemon balm oil)	Avian influenza virus (AIV) subtype H9N2	60
		Herpes simplex virus (HSV-1 and HSV-2)	61,62
		Zika virus (ZIKV)	63
	Extracts and EOs	Herpes simplex virus (HSV), vaccinia virus, Semliki Forest and Newcastle virus	64
	Extracts and rosmarinic acid	Enterovirus 71 (EV71)	65
Alpinia galanga L.	Extracts and bioactive compounds	Novel coronavirus (SARS-CoV-2)	66
Chamomilla recutita L. *(syn. Matricaria recutita* L.*)*	Extracts and EOs	Herpes simplex virus (HSV), poliovirus	67,68
Sambucus nigra L.	Extracts and bioactive compounds	Human immunodeficiency virus (HIV), feline immunodeficiency virus (FIV), influenza virus, parainfluenza virus, human rhinovirus B, coxsackievirus, adenovirus Cand respiratory syncytial virus.	68-72
Citrus sp.	Extracts and bioactive compounds (hesperidin, hesperetin, naringenin, tangeretin, nobiletin)	Influenza A virus, hepatitis (B and C) virus,human respiratory syncytial virus (RSV), Vesicular stomatitis virus (VSV), Arenavirus Lassa virus (LASV) and novel coronavirus (SARS-CoV-2)	22,66,73-75
Rosmarinus officinalis L.	oleanolic acid, rosmarinic acid and eucalyptol	Herpes simplex virus (HSV-1) and hepatitis B virus (HBV)	76
	Extracts	Herpes simplex virus (HSV-1) and an acyclovir-resistant strain of HSV-1 (ACVres)	55
		Herpes simplex virus type 1 (HSV-1), type 2 (HSV-2) Newcastle disease virus (NDV), herpes simplex, vaccinia, Semliki Forestand West Nile viruses	77
		Measles, Mumps, Vesicular Stomatitis Virus (VSV) and Herpes simplex virus type-2 (HSV-2).	78
		Herpes simplex virus type 1 (HSV-1), type 2 (HSV-2)	79
	EOs (rosemary) and 1.8 cineole	Hepatitis A virus (HAV)	80
	EOs (rosemary) and rosemarinic acid	Zika virus (ZIKV)	63
	EOs (rosemary)	Herpes simplex virus type 1 (HSV-1)	81
		Avian infectious bronchitis (IBV),	82
	Extracts and cineol	Influenza A H1N1 and oral herpes simplex HSV-1	52
Cinnamomum zeylanicum Blume	EOs	Herpes simplex virus (HSV-1) and Influenza virus A (H1N1)	52

Glycyrrhiza glabra L.	Extracts and bioactive contituents (glycyrrhizin glycocoumarin, lycopranocoumarin and lycocarbon A)	Herpes simplex, Epstein-Barr, human cytomegalovirus, hepatitis A, B and C, influenza, HIV, varicella zoster virus (VZV) and SARS coronaviruses	83
	Extracts and kanzonol V	Zika virus (ZIKV)	63
	Extracts, glycyrrhizin and glycyrrhizic acid	Hepatitis (B and C), Human immmunodeficiency virus (HIV-1), herpes simplex virus (HSV) and SARS coronavirus	84-88
	Extracts	Herpes simplex virus (HSV-1) and influenza A virus	89,90
	Extracts and glycyrrhizin	Swine epidemic diarrhea virus	91
		Hepatitis A, B and C	92
		Influenza A virus (FLUAV), Rift Valley fever virus (RVFV), Human metapneumotic virus (HMPV), echovirus 1 (EV1), chikungunya virus (CHIKV), Ross River virus (RRV), Zika virus (ZIKV), hepatitis C virus (HCV), Sindbis virus (SINV), HIV-1, cytomegalovirus (CMV), hepatitis B virus (HBV) and herpes simplex virus type 1 (HSV-1),	93
		influenza virus, SARS coronavirus and Human immmunodeficiency virus (HIV)	83,92
	glycyrrhizic acid	Kaposi's sarcoma herpes virus (KSHV) and hepatitis B virus	94,95
Taraxacum officinale L.	Extracts	Hepatitis C virus (HCV), Influenza virus type A (H1N1)	96
Vitis spp.	Methanol extract from *V. labrusca*	Simian (SA-11) and human (HCR3) rotaviruses	97
	Methanol extract from *V. macrocarpon*		
Cistus spp.	Extracts from *C. laurifolius*	Parainfluenza – 3 (PI – 3)	98
	Extracts from *C. incanus* subsp. *tauricus*	Influenza virus (H1N1, H5N1 and H7N7), Pathogenic avian influenza virus (HPAIV)	99
	Extracts from *C. incanus* subsp. *tauricus*	Influanza A and B virus and other viruses	100
Tamarix nilotica	Hydro alcoholic extract	Herpes simplex-1 virus (HSV) and poliomyelitis-1 virus (POLIO)	101
Olea europea L.	Olea leaf and compounds (oleanolic acid and calcium elenolate)	Herpes simplex, polio viruses, rhinoviruses, mycoviruses, coxsackie virus, Varicella zoster, encephalo myocarditis	102
	Olea leaf and extracts	Herpes simplex virus (HSV-1), infectious laryngotracheitis viruses, Newcastle disease virus (NDV) and rhesus rotavirus	103-107
	oleuropein glycosides and their enzyme hydrolysates [2-(4-hydroxyphenyl) ethyl and 2-(3,4-dihydroxyphenyl)]	Rotavirus, rhinovirus, parvovirus, hepatitis, Epstein-Barr, herpes simplex, influenza, varicella zoster, cat leukemia viruses and viral hemorrhagic septicemia virus (VHSV)	108,109
Salvia officinalis L.	Extracts	Avian infectious bronchitis virus (IBV), Herpes simplex virus (HSV-1 and HSV-2), Measles, Mumps and Vesicular Stomatitis Virus (VSV)	54,57,78
	EOs, 1,8-cineol and α-thujone	SARS-CoV and HSV-1	110
	Extracts and EOs	Zika virus (ZIKV)	63

Mentha piperita L.	Extracts	Avian infectious bronchitis virus (IBV), respiratory syncytial virus (RSV), Herpes simplex virus type 1 (HSV-1), type 2 (HSV-2) and an acyclovir-resistant strain of HSV-1 (ACVres)	54,55,57,111
	Aqueous extract, hydroalcoholic extract and EOs	Herpes-simplex virus (HSV-1 and HSV-2)	112
Origanum vulgare L.	Extracts	Avian infectious bronchitis virus (IBV), equine arteritis virus (EAV), feline calicivirus (FCV), canine distemper virus (CDV), canine adenovirus (CAV) and canine cororavirus (CCoV)	54,113
	Extracts and bioactive compounds	Respiratory syncytial virus (RSV), Coxsackievirus B3 (CVB3), herpes simplex virus type 1 (HSV-1) and nonenveloped murine norovirus (NMN)	114,115
Thymus vulgaris L.	Extracts	Avian infectious bronchitis virus (IBV), Measles, Mumps, Vesicular Stomatitis Virus (VSV)and Herpes-simplex virus (HSV-1 and HSV-2)	54,78,112
	EOs	Herpes-simplex virus (HSV-1)	116
Thymus capitatus (L.) Hoffmans. and Link	EOs	Herpes simplex virus (HSV-1 and HSV-2), Echovirus 11 (ECV11) and Adenovirus (ADV)	117,118
Iresine herbstii Hook.	Acetone, dichloromethane, ethanol and petroleum ether extracts	Avian Newcastle disease virus	119
Ocimum bacilium L.	Aqueous extract	Herpes-simplex virus (HSV-1)	112
	Extracts and monoterpenes (camphor, thymol, linalool and 1,8-cineole)	Bovine viral diarrhoea virus (BVDV)	120
	Extracts and purified compounds (apigenin, linalool and ursolic acid)	Herpes viruses (HSV), adenoviruses (ADV), hepatitis B virus), coxsackievirus B1 (CVB1) and enterovirus 71 (EV71)	121
Solanum paniculatum L.	Extracts and compounds	Herpes-simplex virus (HSV-1), murine encephalomyocarditis virus, Equine herpesvirus-1 (EHV-1)	122-124
Tinospora cordifolia	Extracts	Hepatitis A virus, human influenza virus (HIV)	48,125
Curcuma longa L.	Extracts and curcumin	Dengue virus (serotype 2), herpes simplex virus, human immunodeficiency virus type 1 (HIV-1), Zika and Chikungunya viruses	68,126,127
Rhus coriaria L.	Extracts	Acyclovir resistant HSV-1 and hepatitis B virus (HBV)	128,129
Allium sativum L.	EOs	Novel coronavirus (SARS-CoV-2)	130

CONCLUSION

Coronaviruses (CoVs) are one of the largest families of viruses that interact with components of host cells at many levels, suggesting this causes the pathogenesis. After SARS and MERS epidemic, many genetic and molecular mechanisms of the human CoVs have been explored, but there are some challenges about the new highly pathogenic SARS-CoV-2 coronavirus and COVID-19 outbreak. One of the main reason for that RNA viruses can quickly modified theirgenomes, therefore the identified agents, drugs or vaccines are not properly evaluated for *in vitro* and *in vivo* studies.

Complementary therapy with medicinal plants are gaining popularity in the worldwide due to numerous advantages such as less expensive, more accessible, less toxicity and resistance, better patient tolerance and fewer or no side effects. Taken together, a revival of interest in medicinal plants for management of viral diseases that resulting in using medicinal plants in complementary and alternative medicine. Besides, they could serve as a source of antiviral drugs for pharmaceutical industry, due to their rich source of bioactive compounds and

benefits. The literature survey presented in this review has clearly proved that medicinal plants and their bioactive compounds have promising therapeutic potential towards virus infections. Since the lack of experimental and scientific evidence about effective compounds, efficacy, effectiveness, pharmacokinetics, quality and safety of herbal medicine, further clinical and standardization studies should be examined using the plants and phytochemicals to ensure their effective dosage and safety formulations and also explore their mechanism of action.

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CONFLICT OF INTEREST

Authors solely declare no conflict of interest regarding authorship and/or publication of this review.

ABBREVIATIONS

ACE2: Angiotensin-converting enzyme 2; **AIV:** Avian influenza virus; **CLQ:** Chloroquine; **CMV:** Cytomegalovirus; **COVID-19:** Corona Virus Disease 2019; **DMV:** Double-membran vesicle; **DPP4:** Dipeptidyl peptidase 4; **E:** Envelope protein; **EHV-1:** Equine herpesvirus-1; **FDA:** Food and Drug Administration; **FPV:** Favipiravir; **HBV:** Hepatitis B virus; HE: Hemagglutinin esterase; **HIV:** Human immunodeficiency virus; **HKU1:** HCoV- Hong Kong University 1; **HMPV:** Human metapneumotic virus; **HSV:** Herpes simplex virus; **IBV:** Avian infectious bronchitis virus; **KSHV:** Kaposi's sarcoma herpes virus; **LASV:** Arenavirus Lassa virus; **LPV:** Lopinavir; **M:** Membran protein; **MERS:** Middle East Respiratory Syndrome; **N:** Nucleocapsid protein; **NDV:** Newcastle disease virus; **NMN:** Non-enveloped murine norovirus; **NSPs:** Non-Structural Proteins; **ORF:** Open reading frame; **PI-3:** Parainfluenza − 3; **POLIO:** Poliomyelitis-1 virus; **RDV:** Remdevisir; **RSV:** Respiratory syncytial virus; **RTC:** Replication and transcription complex; **RVFV:** Rift Valley fever virus; **S:** Sspike protein; **SARS**: Severe Acute Respiratory Syndrome; **SARS-CoV-2 (2019-nCoV):** The Severe Acute Respiratory Syndrome Coronavirus 2; **SINV:** Sindbis virus; **TMPRSS2:** Transmembrane protease serine 2; **VSV:** Vesicular stomatitis virus; **VZV:** Varicella zoster virus; **WHO:** World Health Organization; **ZIKV:** Zika virus.

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PICTORIAL ABSTRACT

SUMMARY

- SARS-CoV-2 caused by COVID-19 pandemic has spread rapidly worldwide.
- Owing to the lack of experimental and scientific evidence about SARS-CoV-2, no effective therapy has been explored for COVID-19 yet.
- Because of the growing incidences of COVID-19, the available therapeutic approaches investigated for previous CoVs infections need to be improved and complemented with the plants-based anti-viral agents.
- Since ancient times, medicinal plants and phytochemicals have offered promising therapeutic potential to combat various viral infections as antiviral agents.
- Complementary and alternative treatment are gaining popularity around the world.
- Medicinal plants and phytochemicals are well-known natural immune-enhancers and may significantly contribute to manage COVID-19.
- This original review consolidates the scientific literature on biological and genomic properties of SARS-CoV-2 and highlights potential of antiviral medicinal plants to cope with COVID-19 outbreak.

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