Potentials of plant-based substance to inhabit and probable cure for the COVID-19

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Abstract: COVID-19 has been the most devastating pandemic in human history. Despite the highest scientific efforts and investments, a reliable and certified medication has yet to be developed regarding to immune or cure this virus. However, while synthetic medications are gaining the focus of attentions, it appears from a significant number of recent studies that plant-based substances could also be potential candidates for developing effective and secure remedies against this novel disease. Citing such recent works, this review primarily demonstrates the antiviral potentials of medicinal plants for inhibiting human coronaviruses. It also shows the importance of antiviral plants substances, particularly in the development of a broad spectrum medication for coronaviruses including SARS-CoV-2 responsible for COVID-19.

Keywords: COVID 19, coronaviruses, MERS-CoV, SARS-CoV, antiviral plants, emodin, HCoV-229E, lycorine

1. Introduction

Viral diseases have always been a distressing threat for main kind, and many novel viral infections are reported constantly throughout the word with severe health issues (Zhang et al., 2020a). COVID-19 is an infectious viral disease caused by a new type of contagious and pathogenic human severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (Lai et al., 2020). This viral infection has turned into a pandemic, which are affecting world's population severely. Until 1:31 pm of 29 May 2020, the World Health Organization (WHO) reported that the total number of confirmed COVID-19 cases all over the world except Antarctica is 5,701,337, including 357,688 deaths; while in Turkey, total number of positive cases of COVID-19 reached to 160,979 with 4,461 deaths[1].

This ongoing pandemic is getting worse day by day, and no approved medication or vaccine has been established so far to treat COVID-19 patients (Suryanarayana and Banavath, 2020). Hence, an extensive research is being carried out to develop the effective treatment for virus-infected patients as well as determine the source, structure, infection mechanism of many coronaviruses (CoV) of zoonotic origin including SARS-CoV-2 (Ul Qamar et al., 2020). However, it is really difficult to develop a

broad spectrum antiviral medications since viruses can mutate their genetic materials easily which helps them to become resistant to any available drugs (Oyston and Robinson, 2012). Albeit an effective vaccine is the certain version of the viral treatment, development of a fully potential safe to use vaccine as well as reaching it to the market level is time consuming as it must meet several steps before getting approval (Oyston and Robinson, 2012). In addition, synthetically developed antiviral medications sometimes possess inauspicious side effects, which could cause significant health problem (Ghildiyal et al., 2020). Therefore, plant-based herbal medicine with effective antiviral potential can open new opportunities by minimizing these side effects (Ghildiyal et al., 2020).

Since the prehistoric times, people from different parts of the world have been utilizing plant for manufacturing herbal medicine to control infectious diseases, which might also possess anti-HCoV active extracts or compounds (Andrighetti-Fröhner et al., 2005; Yang et al., 2020). Medicinal plants are boosted with diverse secondary metabolites; some of them can interrupt viral protein and enzyme activities by binding with them, and prevent viral penetration, replication into the host cells (Li and Peng, 2013; Arbab et al., 2017; Akram et al., 2018; Dhama et al., 2018). Numerous studies have been confirmed the bioactive natural compounds which could be potential

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[1]WHO (2020). Coronavirus Disease (COVID-19) Dashboard [online]. Website https://covid19.who.int/ [accessed 29 May 2020] .

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candidates treating the novel SARS-CoV-2 due to their significant antiviral activity (ul Qamar et al., 2020; Zhang et al., 2020a). Moreover, traditional Chinese medicines (TCM) have been very popular as supplementary therapeutic medication, and might be able to demonstrate significant positive response in preventing SARS-CoV-2.

Presenting the origin, structure, transmission and infection mechanisms, this review primarily attempts to present a glimpse of the antiviral potentials of medicinal plants for inhibiting human coronaviruses. It also emphasizes the applications of plant-based TCM regarding to SARS coronaviruses. Besides, it shows the importance of antiviral phytochemicals of different plants, could be considerable for developing of a broad spectrum medication against the virulence effects of any types of coronaviruses including SARS-CoV-2.

2. Methodology

A literature search was conducted in the PubMed, Google Scholar and Web of Science in order to find the most recent published articles related to the keywords such as "coronavirus", "novel coronavirus", "CoV", "COVID-19", "SARS-CoV-2", "antiviral plants", "antiviral compounds", "phytochemicals", "herbal drugs", and "Traditional Chinese Medicine" until 27 May 2020. No language restriction was imposed in this article. Some of required information was searched using following websites: National Health Commission of the People's Republic of China (http://www.nhc.gov.cn/) and the WHO (https://www.who.int/). A brief description about coronaviruses, their origin, transmission and infection mechanism in host cell were given in the review. Significantly important phytochemicals, especially secondary metabolites with antiviral potential were classified and discussed properly by providing relevant figure. A partial list of significant phytochemicals with antiviral properties for preventing human coronaviruses was presented by a table. Moreover, this study represented an overall review about the in vitro or in vivo applications of plant-based substances on SARS-CoV-2, SARS-CoV and other human coronaviruses.

3. Findings and discussion

3.1. Coronavirus: origin, transmission and infection mechanism in humans

Coronaviruses are considered as highly pathogenic and capable of causing diseases among birds and mammals (Woo et al., 2010). They are assembled into the family Coronaviridae which belongs to the order Nidovirales. This virus group is further divided into 4 genera, i.e. alphacoronaviruses (α-CoV), betacoronaviruses (β-CoV), gammacoronaviruses (γ-CoV), and deltacoronaviruses (δ-CoV) (Woo et al., 2010). Alphacoronaviruses and betacoronaviruses have the tendency to infect mammals, whereas gammacoronaviruses and deltacoronaviruses are capable of infecting birds. Two betacoronaviruses (HCoV-HKU1 and HCoV-OC43) and 2 alphacoronaviruses (HCoV-229E and HCoV-NL63) are well-known and recognized as low pathogenic virus for human, and responsible for mild respiratory symptoms, which is identical to seasonal flue (Woo et al., 2007). However, the betacoronaviruses (β-CoV) have earned the greatest concern among all due to their clinical importance regarding the capability of causing serious illness in human race. Middle East respiratory syndrome-related coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV, SARS-CoV-2) are the most discussed betacoronaviruses of zoonotic origin because of their extreme capacity of developing fatal respiratory tract infections in human (Lu et al., 2020).

Coronaviruses are large, sphere-shaped, single-stranded RNA virus of approximately 125 nm in diameter (Fan et al., 2019). Their genomic RNA is the largest genome among all RNA viruses (size range between 26.2 and 31.7 kb, positive sense) (Fan et al., 2019). This single strand RNA (+ sense) is enclosed by an enveloped structured protein shell/ capsid protein of helical symmetry (Figure 1). This enclosed helical structure of genomic material and protein is known as nucleocapsid, which is further enfolded by an icosahedral protein shell (De Groot et al., 2011). Single-strand RNA and enfolded protein shells are again surrounded by a bulbous surface lipid bilayer, in which different structural protein i.e. spike (S), envelope (E), and membrane (M) are anchored at the ratio of 20:1:300 (Figure 1) (Lai and Cavanagh, 1997). A coronavirus particle can have about 74 surface spikes on average. The nature of the tissue tropism of a host cell as well as the binding pattern of viral spike protein and its suitable host cell receptor determine the species range of a virus and its infectivity (Neuman et al., 2011). In together, nucleocapsid, lipid bilayer and membrane proteins can provide protection when the virus is outside without its carrier or a suitable host (Neuman et al., 2011).

Considering the findings of evolutionary investigations and virus genome sequencing, it has found that warm-blooded flying vertebrates are the most suitable and impeccable natural host and reservoir for alphacoronaviruses and betacoronaviruses (Yin and Wunderink, 2018). For instance, in case of SARS-CoV-2, bat is believed to be the highly probable primary source of this virus which may jumped to unknown intermediate hosts, and then transmitted and infected human, and consequently caused the novel COVID-19. This is due to the fact that bat CoV RaTG13 virus and SARS-CoV-2 share 96.2% of identical genomic sequence which suggested that
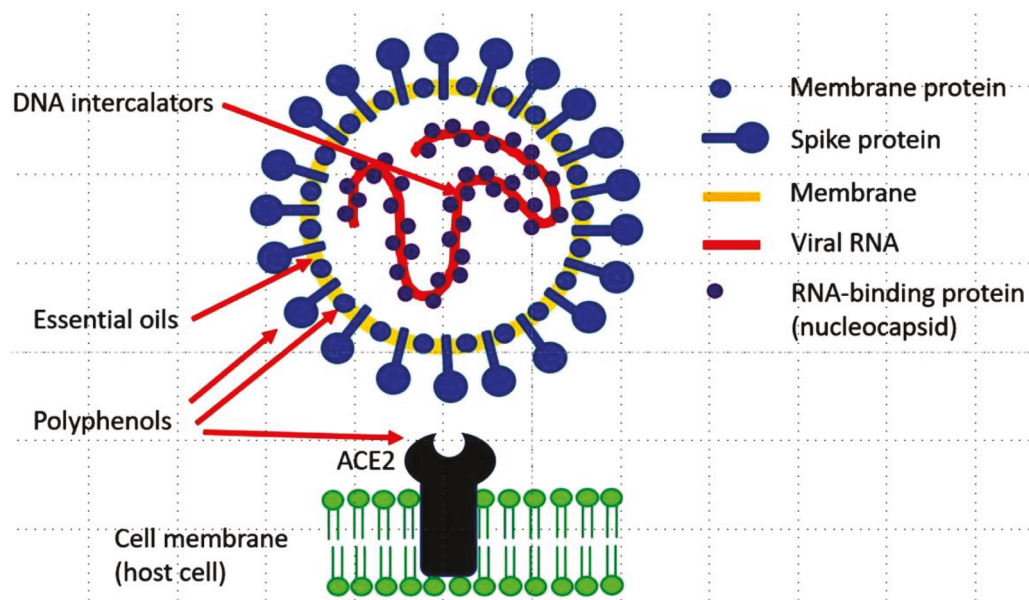
Figure 1. Illustration of the minimal composition of a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Wink, 2020).

both viruses might came from the same ancestor (Zhou et al., 2020).

Like any other coronaviruses, the main course of the transmission of SARS coronaviruses from human to human is by direct or indirect contact with infected carriers. Besides in a short range transmission, these viruses can spread by respiratory droplets (Moriyama et al., 2020). It is also evidenced that for long-range transmission, coronaviruses are able to transmit through aerosol (Moriyama et al., 2020). After shedding into the environment from infected host, SARS-CoV-2 and other coronaviruses can float to the ground and any other suitable surface through droplets, which help them to stay alive for a certain period of time, and infect again once come to the contact with new host (Lai et al., 2020).

Virus-host interactions are the most significant factors that influence viral entry and replication in host cells. Human epithelial cells are mostly targeted region by coronaviruses at the time of infection. SARS-related coronavirus enter into the human body through an aerosol route and attached with the epithelial cells of the respiratory tract (Ge et al., 2013). The S-proteins of the virus and their receptor of SARS-CoV-2 and other human coronaviruses play the main role to penetrate into the epithelial cells of human lung (Letko et al., 2020). For the attachment, spike protein receptor binding domain (RBD) of human SARS coronaviruses binds with angiotensin-converting enzyme 2 (hACE2) available in the outer cell membrane of human lung (Figure 1) (Letko et al., 2020). On the other hand,

binding domain (RBD) of MERS-CoV interacts with an extracellular type-II transmembrane glycoprotein called dipeptidyl peptidase-4 (DPP-4) (Mubarak et al., 2019).

Following the attachment, the cleaving of the receptor-attached spike protein and the fusion of virus into host cell are influenced by host protease. SARS coronaviruses follow 2 different paths to penetrate into the host cell based on the protease type. According to the fast path, a SARS virus enters into the cell through endocytosis at the presence of host's pH-dependent cysteine protease cathepsin L., which leads to form a membrane bounded endosome (Figure 2A) (Simmons et al., 2013). And then, this protease induces the attached spike protein to be activated that changes the shape of endosome and helps viral envelope to fuse with the endosomal wall (Simmons et al., 2013).

On the other hand, presence of type II transmembrane serine protease (TMPRSS2) at the outer membrane of the respiratory, urogenital and gastrointestinal epithelial cells induces proteolytic cleavage of viral spike protein. The S2' site of the S protein comprises single lysine or arginine residues (R/K↓) which can be targeted by TMPRSS2 for cleaving, and thus, SARS and other respiratory viruses can penetrate into the host cell directly by a fusion of viral envelope and host cell membrane (Figure 2B) (Heurich et al., 2014).

After the completion of the fusion, virus releases its nucleocapsid into the cytoplasm where the viral genome mimics the messenger RNA, and takes part in the translation process by cell ribosome (Figure 2A),

and thereby, generates various replicated proteins and a replication-transcription complex (RTC) (Guo et al., 2020). By using the genomic RNA as the template, RT-complex initiates the replication of RNA and subgenomic mRNAs (Fehr and Perlmanm, 2015). The mRNAs further translates accessory proteins and structural proteins. The structural proteins (envelope glycoproteins), nucleocapsid proteins and newly synthesized genomic RNA reorganize to form progeny viruses by attributing endoplasmic reticulum and Golgi (Perrier et al., 2019). Finally, with

the help of exocytose process (Figure 2A), the virion-containing viral particles discharge from the infected cell through secretory vesicles (Zhang et al., 2020b).

3.2. Potentials of medicinal plants against human coronaviruses

Without doubt, it is evident that people from different parts of the world, especially Asian countries, like India, China, Japan, Pakistan, and some parts of Africa have been utilizing plant as the herbal medicine since the prehistoric times (Hoareau and DaSilva, 1999). Medicinal plants for
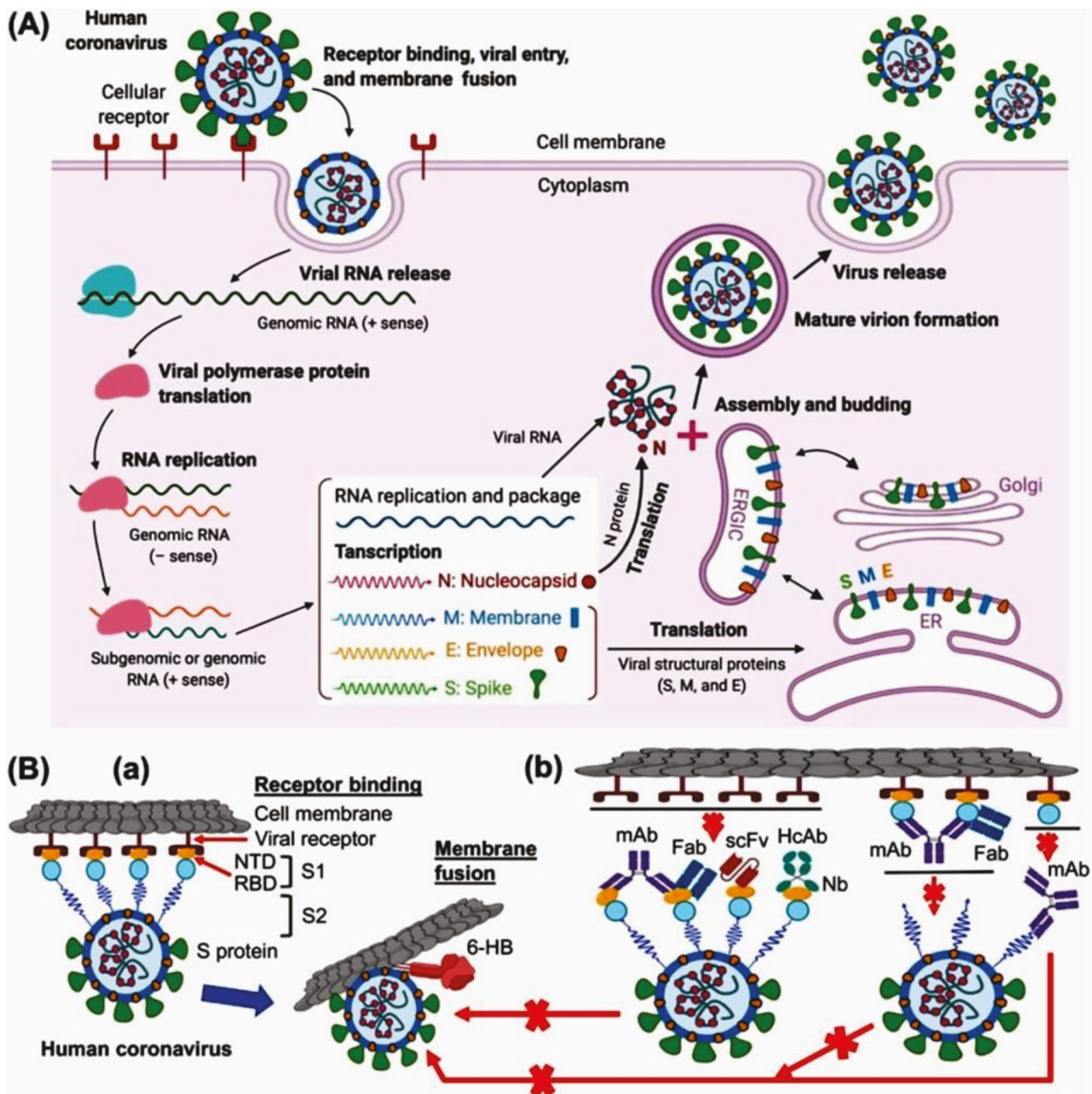
Figure 2. (A) Replication cycle of human coronavirus; (B) host cell receptor and viral protein (S-protein) binding and membrane fusion mechanism (Jiang et al., 2020).

herbal treatment are extremely popular in rural and tribal societies, mostly due to their high scalability, which make them cheaper and affordable than modern medicine. Medicinal plants are boosted with diverse phytochemicals, such as alkaloids, terpenoids, flavonoids, phenolic acids, tannins, lignins, coumarins, stilbenes etc., which have been reported to show their potentiality against infections caused by pathogenic microorganisms (McCutcheon et al., 1995; Semple et al., 1998).

Previous evidences have suggested that these phytochemicals may exhibit significant potential for treating viral infections; therefore, the Boots Drug Company (Nottingham, UK) showed their huge interest for the first time for developing large scale production of herbal medicine as antiviral agent, and seeking this purpose they screened at least 288 plants for estimating antiinfluenza activity (Chantrill et al., 1952).

Moreover, different investigation on antiviral potential of medicinal plants showed that plant extracts with highly active secondary metabolites can interrupt the replication of several highly pathogenic viruses (Figure 3). Plant-based biomolecules demonstrated significant inhibitory effects on hepatitis B virus (Huang et al, 2006), the human immunodeficiency viruses (HIV) (Asres and Bucar, 2005; Lubbe et al., 2012), herpes simplex virus type 2 (Debiaggi et al., 1988) and SARS coronaviruses (Ho et al., 2007; Sassi et al., 2008; Vieira et al., 2010).

However, this study only focuses on the antiviral potential of medicinal plants against human SARS coronaviruses since the COVID-19 pandemic by SARS-CoV-2 has become the greatest catastrophe event in the 21th century, and until now, there is no specific medication discovered to treat patients infected by this virus. Moreover, various important phytochemical groups, and their potentials for exhibiting human coronaviruses are discussed in details.

3.2.1. Essential oils

Essential oils from many medical plants such as *Citrus* spp., *Hyssopus officinalis*, *Illicium* spp., mayweeds, tea trees, *Mentha* spp., *Santalum* spp., *Pinus* spp., thymes, ginger, and other aromatic plants with antiviral activities were well documented by several researches (Li and Peng, 2013; Akram et al., 2018; Dhama et al., 2018; Ben-Shabat et al., 2020; Wink, 2020). Essential oils are able to insert nonspecifically into the lipid double layer of the viral envelope, which alter the fluidity of membrane (Ben-Shabat et al., 2020).

Monoterpenes, oxygenated sesquiterpenes and phenylpropanoids of essential oils are capable of disrupting the phospholipid bilayer membrane of human coronaviruses because of their lipophilic nature, which interfere the structure of viral envelope proteins during the infection (Schnitzler et al., 2003). Eucalyptol, a vital essential oil from gum trees (*Eucaliptus* spp.) was identified as an effective antiviral compound against coronavirus, especially SARS-CoV-2. This is due to the fact that this major component of eucalyptus oil consists of ether (-O), ketone (=O) and hydroxyl (-OH) groups which play the main inhibitory role against SARS-CoV-2 (Sharma, 2020).

Resveratrol (terpenoids) can prevent the entry and post entry of MERS-CoV by suppressing viral nucleocapsid and RNA expression, which eventually inhabit viral replication. At the concentration of 125–250 μM, resveratrol were able to diminish the Vero E6 cell death (Lin et al., 2017). Moreover, jensenone, a compound obtained from
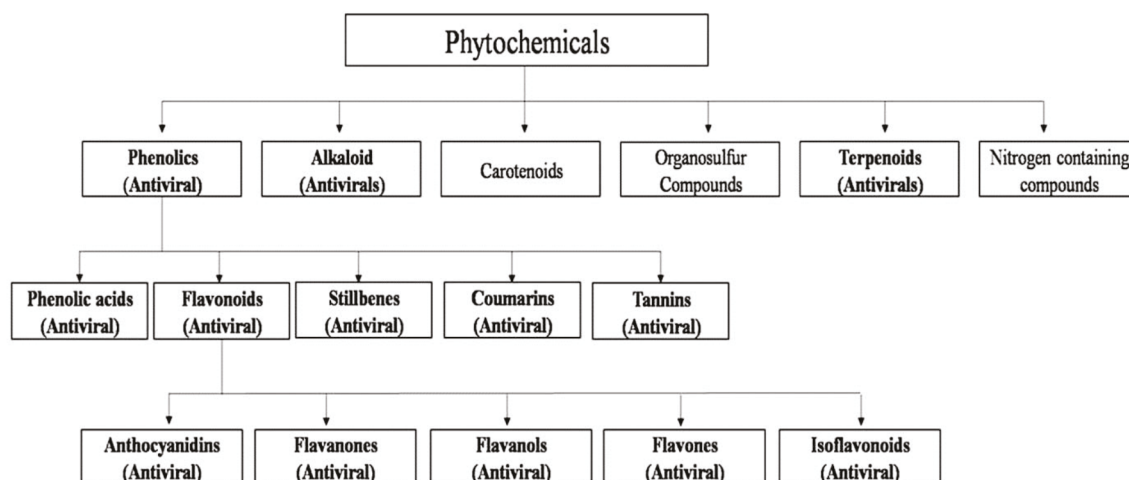
Figure 3. Classification of phytochemicals used as antiviral agents (Ghildiyal et al., 2020).

eucalyptus essential oil exhibited its antiviral potential to inhibit Mpro of SARS-CoV-2 responsible for COVID-19 (Sharma and Kaur, 2020). However, further research is necessary to find the suitability of this compound as medicine for human.

3.2.2. Alkaloids

Chloroquine is a synthetic derivative of quinine, a bitter alkaloid that comes from the bark of the cinchona tree (Quina). Chloroquine is a good candidate for the development of an effective drug to treat SARS-CoV-2 because of its DNA-intercalating properties (Devaux et al., 2020). Resochin (chloroquine) is another intercalating alkaloid that was developed as a medicine, particularly for fighting malaria, which is suggested to be a potential antiviral compounds. It is believed that this compound may interrupt the replication, transcription, and translation of viral genomic material (Wink, 2020). In addition, isoquinoline alkaloids such as palmatine and chelidonine were also reported as intercalating alkaloids, suggested to be the appealing drug candidates to battle SARS-CoV-2 (Ho et al., 2019; Wing, 2020).

In a recent study, human coronavirus (HCoV-OC43) infected MRC-5 human lung cells were utilized to estimate the antiviral activities of three pharmaceutically important bis-benzylisoquinoline alkaloids i.e. cepharanthine (CEP), fangchinoline (FAN), and tetrandrine (TET), isolated from *Stephania tetrandra* and other related species of Menispermaceae (Kim et al., 2019). These compounds also possess antiinflammatory and anticancer activities (Kim et al., 2019). However, the result showed that the replication of HCoV-OC43 inside host cells was dramatically decreased at IC_{50} values of 0.83, 1.01, and 0.33 µM for CEP, FAN and TET, respectively (Kim et al., 2019). Besides, expression of viral spike (S) and nucleocapsid (N) protein were also inhabited by these 3 alkaloids. In addition, a large number of alkaloids such as emetine, tylophorine and mycophenolate mofetil were reported to be very significant antiviral compounds (Shen et al., 2019; Suryanarayana and Banavath, 2020; Yang et al., 2020).

3.2.3. Phenolics, flavonoids, polyphenols, and others

Phenolic compounds, flavonoids, polyphenols, steroid, terpenoid, other active phytochemicals and their derivatives are common plant secondary metabolites that contain aromatic rings with 1 or several hydroxyl groups. The -OH groups of these compounds can form hydrogen ion bonds with positively charged amino groups of proteins, which inhibit the activity of a viral protein (Figure 1, Wink, 2020). According to Wink (2020), polyphenols are capable of binding easily with the lipoproteins of virus envelope, which can prevent the viral invasion in host cells. For a wide range of viruses, several studies confirmed the abovementioned activity of several phenolic antiviral

compounds such as curcumin, luteolin-7glucoside, epicatechin gallate, catechin, demethoxycurcumin, apigenin-7 glucoside, hypericin, bavachinin, psoralidin, corylifol, mycophenolate mofetil, silvestrol and tomentin are mentioned in the Table (Ryu et al., 2010; Yu et al., 2012; Cho et al., 2013; Kim et al., 2014; Park et al., 2017; Khaerunnisa et al., 2020; Yang et al. 2020).

Virally encoded 3C-like protease (SARS-CoV 3CLpro) is very significant viral enzyme that regulates the behaviors of coronavirus replication complexes (RTC) during viral replication (Lin et al., 2005). Therefore, this enzyme is assumed to be very crucial for the replication of SARS coronaviruses in infected host cells. Various plant-based phenolic compounds and isolated 5 major secondary metabolites from root extract of *Isatis indigotica* were used to study the antiviral potential against human corona viruses; in which, β-sitosterol, hesperetin, aloe emodin, indigo, and sinigrin were the significant phytochemicals that inhibited the cleavage activity of SARS 3CLpro enzyme with IC_{50} values of 1210, 365, 8.3, 752, and 217 µM, respectively (Lin et al., 2005).

Using HPLC assay, 720 naturally occurring compounds were also applied to screen the inhibitory activity of these compounds against this enzyme (Chen et al., 2005). Among these phytochemicals, 3 naturally occurring polyphenols from Pu'er (traditional Chinese fermented tea) and black tea, i.e. theaflavin-3, 30-digallate, 3-isotheaflavin-3-gallate, and tannic acid were able to inhibit SARS-CoV 3CLpro effectively at the IC_{50} values of 9.5, 7, and 3 µM, respectively (Chen et al., 2005).

Along with phenolic compounds and polyphenols, flavonoids were also found to be very effective against SARS 3CLpro enzyme of human coronaviruses. In a study, the activity of a replication protein i.e. SARS 3CLpro was prohibited by different flavor compounds available in *Litchi chinensis* seeds such as gallocatechin gallate, epigallocatechin gallate, quercetin, pectolinarin, rhoifolin, and herbacetin etc. (Gong et al., 2008). Moreover, several studies on the antiviral activity of flavonoids, especially on SARS-CoV and HCoV strains, were listed in the Table.

Like HCoV-NL63 and SARS-CoV, SARS-CoV-2 interacts with host cell using host receptor i.e. angiotensin-converting enzyme 2 (hACE2) (Letko et al., 2020). Hence, plant-based biomolecules that are capable of preventing the interaction with this receptor could increase and strengthen the security to fight against the infection of SARS-CoV-2. Previous studies have found that several phytochemicals, such as luteolin (flavonoid) extracted from *Veronica linariifolia*, scutellarin and tetra-*O*-galloyl-β-D-glucose (TGG), polyphenolic compounds extracted from *Gallachinensis* (Yi et al., 2004; Wang et al., 2016), nicotianamine (iron chelator in plants) from soybean seeds

Table. A partial list of antiviral plants inhibiting coronaviruses (CoV).

Medical plants	Antiviral compound (s)	Virus	Antiviral effects	References
Capsicum annuum, Curcuma longa, Mentha longifolia L.*, Olea europaea* L.*, Curcuma longa, Phoenix hanceana* and *Camellia sinensis*	Glucoside, Curcumin, Oleuropein, Luteolin-7, Epicatechin-gallate, Catechin, Demethoxycurcumin, glucoside, and Apigenin-7	Coronavirus (CoV)	COVID-19 Mpro protein was inhabited by all these antiviral compounds. However, further investigations are required to confirm their forthcoming applications.	Khaerunnisa et al., 2020
Hypericum perforatum L.	Hypericin	2019-nCoV NSP 14	C-terminal and N-terminal domains of 2019-nCoV NSP 14 were found to be bound by Hypericin.	Yang et al., 2020
Tylophora indica	Tylophorine	Coronaviruses	Tylophorine-based biomolecules exhibit broad spectrum potential for inhabiting coronaviruses.	Yang et al., 2020
Tylophora indica	Tylophorine	Enteropathogenic coronavirus transmissible gastroenteritis virus (TGEV)	Tylophorine blocked TGEV-induced apoptosis, and consequent cytopathic effect in ST cells.	Yang et al., 2010
Lycoris radiata	Lycorine	Severe acute respiratory syndrome (SARS)-CoV	Lycorine could be a potential reagent for antiviral drug development.	Suryanarayana and Banavath, 2020
Cannabis sativa	THC and CBD	Many diseases	Very limited evidences have demonstrated a possible role of cannabinoids as therapeutics for preventing viral illnesses.	Hill, 2020
Psoralea corylifolia	Bavachinin, Psoralidin Corylifol	SARS-CoV	The ethanol extract of these secondary metabolites demonstrated their high activity against SARS-CoVPLpro.	Kim et al., 2014
Clivia miniata	Lycorine and mycophenolate mofetil	HCoV-OC43, MERS-CoV, HCoV-NL63 and MHV-A59	Lycorine inhabited RNA, DNA, and protein synthesis, which effects on cell division. Mycophenolate mofetil exhibited immune suppressing effect on coronaviruses.	Shen et al., 2019
Carapichea ipecacuanha	Emetine		Emetine displayed strong anti-CoV activity by blocking MERS-CoV entry consistent with pseudo-virus entry assays.	
Aglaia foveolata Pannell	Silvestrol	HCoV-229E	Silvestrol exhibited in vitro potential of inhibition of cap-dependent viral mRNA translation.	Müller et al., 2018
Cannabis sativa	Cannabidiol	Any viral infection	Though cannabidiol is a vital factor of host responses to viral infectivity, it can induce apoptosis in mammalian cells.	Orzalli and Kagan, 2017
Broussonetia papyrifera	Kazinol A, Kazinol B, Kazinol F, and Kazinol J	Papain-like and 3-chymotrypsin-like coronavirus cysteine proteases	Both PL and 3CL CoV proteases were distinctly inhibited by these polyphenols.	Park et al., 2017

Table. Continued.

Medical plants	Antiviral compound (s)	Virus	Antiviral effects	References
Broussonetia papyrifera	Polyphenols such as biphenyl propanoid, Broussochalcone A, and Broussochalcone B	CoV cysteine proteases	Different polyphenols from *B. papyrifera* could be promising candidates for developing anticoronaviral medications.	Park et al., 2017
Peel extracts *of Citrus sinensis* (Cs), *Nigella sativa* (Ns), and *Anthemis hyalina* (Ah)	Essential oils	Coronavirus infected HeLa-epithelial carcinoembryonic antigen	Down-regulated the tryptophan operon (TRP gene) of CoV, and consequently, decreased the virus loads.	Ulasli et al., 2014
Ecklonia cava	Dieckol	Porcine epidemic diarrhea CoV	Dieckol can inhabit viral replication.	Kwon et al., 2013
Paulownia tomentosa	Tomentin (Flavonoid)	SARS-CoV	SARS-CoV papain-like proteas was inhabited by granulated flavonoids.	Cho et al., 2013
Camellia sinensis	Catechins	SARS-CoV	Throughout a screening of different teas, catechins from black tea were found to be the inhibitors of SARS-CoV N protein.	Roh, 2012
Aglaia perviridis	Myricetin and Scutellarein	SARS-CoV	In vitro study; affects ATPase activity that leads to inhibit the SARS-CoV helicase protein.	Yu et al., 2012
Pelargonium sidoides	Extract EPs® 7630	Human coronavirus (HCoV)	EPs® 7630 interferes with replication of different respiratory viruses such as HCoV.	Michaelis et al., 2011
Cibotium barometz	The extracts of *Cibotium barometz* (CBM)	SARS-CoV	SARS-CoV 3CL protease activity was significantly inhabited by CBM.	Wen et al., 2011
Curcuma longa L.	Curcumin	SARS-CoV	Curcumin exhibits wide-ranging and distinctive anti-SARS CoV activity.	Wen et al., 2007
Cibotium barometz, Taxillus chinensis, Cassia tora, Dioscorea batatas, and *Gentiana scabra*	Abietane-type diterpenoids, Lignoids	SARS-CoV	Demonstrated strong anti-SARS-CoV effects.	Wen et al., 2007
Torreya nucifera	Amentoflavone and Apigenin	SARS-CoV	The biflavone and amentoflavone showed most potent 3CL(pro) inhibitory effect.	Ryu et al., 2010
Cinnamomi cortex (CC) and *Caryophylli* (CF)	Cinnamtannin B1 (The extracts of CC such as Fr2)	Wild-type (wt) coronavirus (wtSARS-CoV) and HIV/SARS-CoV S pseudovirus	The evidence showed that Cinnamtannin B1 are able to improve the symptoms of a number of viral diseases, including SARS-CoV diseases.	Zhuang et al., 2009
Houttuynia cordata Thunb (HC)	The aqueous extract of HC	SARS-CoV	Activities of RNA-dependent RNA polymerase (RdRp) and SARS-CoV 3C-like protease (3CLpro) were hampered by the aqueous extract of HC.	Lau et al., 2008
Rheum officinale Baill., and *Polygonum multiflorum* Thunb.	Emodin	SARS-CoV	In a dose-dependent manner, emodin drastically blocked the interaction of the ACE2 enzyme of host cell and viral S protein. Besides, it can also inhabit the contagion of S-protein-pseudo typed retrovirus to Vero E6 cells.	Ho et al., 2007

and other food stuffs (Takahashi et al., 2015), a flavone glycoside named baicalin from *Scutellaria baicalensis* (Deng et al., 2012), emodin (quinone derivative) from genus *Polygonum* and *Rheum* (Ho et al., 2007) have striking capacity to hamper the interaction of host ACE2 and S-protein of SARS-CoV.

In an another study, molecular docking analysis was applied on different active phytochemicals including cannabinoids to determine the binding positions of these compounds with viral spike glycoprotein (S-protein) (Tallei et al., 2020). The results indicated that cannabinoids along with epigallocatechin gallate, hesperidine and pectolinarin hold remarkable binding sites, which could support them to be excellent S protein inhibitors by preventing viral attachment with host cells (Tallei et al., 2020).

Furthermore, TSL-1 and quercetin (flavonoids) from the leaf extract of *Toona sinensis* Roem (Chen et al., 2008) as well as glycyrrhizin (saponin) from liquorice roots (Cinatlet al., 2003) and saikosaponins (triterpene saponin) (Cheng et al., 2006) evidently demonstrated strong antihuman SARS coronavirus potential by preventing the mechanism of cellular attachment, entrance, adsorption, and penetration of a virion into the host cell.

For recognizing effective anti-SARS-CoV agents, an extensive screening through a cell-based assay was conducted on more than 10000 accessible synthetic and natural compounds and drugs (Wu et al., 2004). At nontoxic concentrations, isolated reserpine (indole alkaloids) from the extracts of *Lonicera japonica*, eucalyptus and genus *Rauwolfia*; aescin (saponins) from horse chestnut tree, and ginsenoside-Rb1 (steroids) from *Panax ginseng* exhibited excellent inhibition on the replication of SARS coronaviruses (Wu et al., 2004).

During the viral replication, RNA-dependent RNA polymerase (RdRp) enzyme is responsible for the synthesis of both positive- and negative-strand RNA. Using swine testicular (ST) cells, plant-derived toxic substances, like cardenolides (steroid) were applied to observe the activity of antitransmissible gastroenteritis coronavirus (TGEV) activity (Yang et al., 2018). The result showed that ouabain, an important cardenolide, reduced the quantity of TGEV in a given volume of fluid at 0–3000 nM. At the inhibitory concentrations of ouabain (37 nM and 23 nM), the number of viral RNA copies was also reduced to 50% due to the suppression of viral replication and TGEV activity, which finally diminished viral yield (Yang et al., 2018).

Lectins, the carbohydrate-binding proteins from *Nicotiana tabacum*, *Allium porrum*, and *Utrica dioica* were found to be significantly potential for slowing down the viral invasion and propagation to 50% (EC50) after applying the inhibitory concentrations (less than 1.3 µg/mL) of pure extract of lectins (Yonesi and Rezazadeh,

2020). These compounds are the defense proteins in plants that can perform like immunologic receptors, and therefore could be marked for treating COVID-19 patients.

Moreover, a partial list of plants with potential antiviral phytochemicals that may possibly play a vital role to cure the COVID-19 disease used worldwide is given in the Table. Moreover, this table focused on the antiviral compounds which could be a possible drug candidate for preventing SARS-CoV or SARS-CoV-2.

3.3. Clinical trials of traditional Chinese medicine (TCM) against human coronavirus

Since there are no approved antiviral medications, drugs or vaccines, currently the main treatment strategies for treating COVID-19 patients infected by the novel SARS-CoV-2 are supportive care, a combination of wide-ranging antiviral medicines, corticosteroids, healing plasma and some antibiotics (Yang et al., 2020). Lopinavir and ritonavir are commercially available effective HIV protease inhibitors which were also utilized to treat patients with the COVID-19 in combination with IFNα-2b or with suitable antibiotics (Yang et al., 2020). This is due to the fact that ribavirin was applied widely throughout the MERS and SARS epidemic as this protease inhibitor was permitted as efficient drug for respiratory syncytial virus (RSV) infected patients (Zumla et al., 2016). On the other hand, inhibitory activity of favipiravir was observed on RNA polymerase of RNA viruses like influenza (De Clercq, 2019). Although in vitro observation established the anti-SARS-CoV-2 activity of these medications (De Clercq, 2019), a vast range of in vivo trials are required confirming their potential for battlingthe COVID-19.

However, it has been reported that several plant species that have been used for thousands of years as TCM in controlling infectious diseases might possess anti-HCoV active compounds (Yang et al., 2020). It is very convincing that plant-based TCM showed significant positive response in preventing SARS-CoV. For instance, in a dose dependent manner, the extracts of *Ganoderma lucidum* (IC_{50}:41.9 µg/mL), *Coriolus versicolor* (IC_{50}:108.4 µg/mL) and *Sinomenium acutum* (IC_{50}:198.6 µg/mL) confirmed their inhibition against SARS-CoV RNA polymerase enzyme; which interrupted viral replication (Fung et al., 2011). Using a cell proliferation assay (MTS assay), extracts from more than 200 Chinese medicinal plants were used in a study to evaluate the potential of antiviral compounds against SARS coronavirus (Li et al., 2005). Among all plants, the virus were strongly inhibited by 4 herbs namely, *Lindera aggregate*, *Pyrrosia lingua*, *Lycoris radiate,* and *Artemisia annua*, which suggested the significance of medicinal plants for the treatment of SARS associated infectious diseases. Moreover, the results of this study also confirmed that a toxic alkaloid named lycorine

could be a potential agent for antiviral drug development (Li et al., 2005).

In 2003 at the time of SARS coronavirus' outbreak, the fatality rate until the 5th of May was more than 52% in Beijing; while about 18% in Singapore and Hong Kong. However in Beijing, death rate reduced dramatically to 1%–4% just after 10 days, which was believed to be the result of using plant-based TCM as a supplement medication with conventional therapy (Chen and Nakamura, 2004). Therefore in China, after gathering knowledge from the treatment strategies of MERS and SARS patients as well as following the existing Chinese clinical guideline, TCM have been incorporated with conventional medicine to treat the patients infected by SARS-CoV-2 (Yang et al., 2020).

Two traditional Chinese herbal medicines 'Sang Ju Yin' and 'Yu Ping Feng San' were utilized to observe the changes of defense system in host cell, and the result showed that it may possibly alter T cells which help to boost up the host defense capability (Poon et al. 2006). In an another independent study, the supplementary treatment with traditional Chinese herbal medicines confirmed remarkable effects in symptom development, which eventually help to shorten disease course caused by viral infection (Hsu et al., 2006). Moreover, these positive outcomes of traditional Chinese medicines in this controlled clinical trial were also supported by laboratory based in vitro studies.

A comparative study was performed to measure the application rate of different experimental drugs registered in China, based on the current treatment strategies as well as considering recent published literatures on COVID-19 pandemic (Figure 4). Among all these experimental drugs, such as western medicine like antimalarial drugs, antiviral drugs and biotherapy, traditional Chinese medicines, application of glucocorticoids and plasma; TCM has the highest rate with 32% (Zhang et al., 2020a). Therefore, considering the homology of SARS-CoV-2 and SARS-CoV, all of the abovementioned studies on TCM may shed light on the production of natural compound escapable of inhibiting SARS-CoV-2.

4. Concluding remarks

Less toxic natural products from traditional medicinal plants with antioxidant and antimicrobial properties have been frequently utilized for thousands of years for treating various infections due to their minimal side effects. As a result of irrepressible outbreak of COVID-19 and unavailability of approved medications, complementary and substitute treatments using plant-based phytochemicals could be incredibly promising for managing this pandemic by reducing the severity of infection caused by SARS-CoV-2. This is due to the fact that various phytochemicals such as lycorine, hypericin, emodin, tylophorine, ouabain, mycophenolate mofetil, silvestrol, myricetin, scutellarein etc. exhibited strong
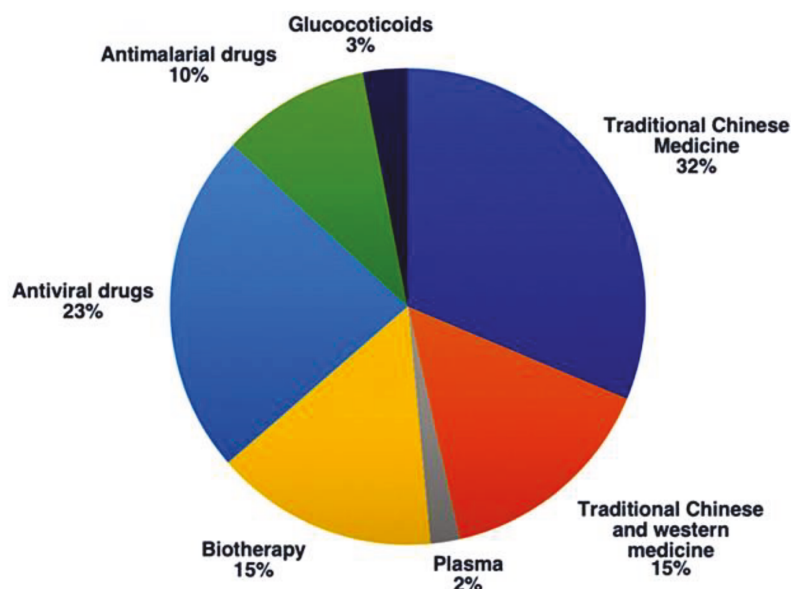
Figure 4. Percentage of the tested experimental drugs registered in China for 2019-nCoV therapy (Zhang et al., 2020a).

inhibitory effects against SARS-CoV-2 and other human coronaviruses. Besides, plant-based traditional Chinese medicines as supplementary medication showed their potential for reducing the fatality rate during the outbreak of SARS-CoV. However, vast range of double-blinded clinical studies with strict protocols is required to estimate the accurate potential of antiviral phytochemicals against COVID-19 with the aim of ensuring the fulfillment of international acceptable standards.

References

Akram M, Tahir IM, Shah SMA, Mahmood Z, Altaf A et al. (2018). Antiviral potential of medicinal plants against HIV, HSV, influenza, hepatitis, and coxsackievirus: a systematic review. Phytotherapy Research 32 (5): 811-822. doi:10.1002/ptr.6024

Andrighetti-Fröhner C, Sincero TCM, Da Silva AC, Savi LA, Gaido CM et al. (2005). Antiviral evaluation of plants from Brazilian Atlantic tropical forest. Fitoterapia 76 (3-4): 374-378. doi: 10.1016/j.fitote.2005.03.010

Arbab AH, Parvez MK, Al-Dosari MS, Al-Rehaily AJ (2017). In vitro evaluation of novel antiviral activities of 60 medicinal plants extracts against hepatitis B virus. Experimental and Therapeutic Medicine 14 (1): 626-634. doi: 10.3892/etm.2017.4530

Asres K, Bucar F (2005). Anti-HIV activity against immunodeficiency virus type 1 (HIV-I) and type II (HIV-II) of compounds isolated from the stem bark of *Combretum molle*. Ethiopian Medical Journal 43 (1): 15-20.

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

Chantrill BH, Coulthard CE, Dickinson L, Inkley GW, Morris W et al. (1952). The action of plant extracts on a bacteriophage of *Pseudomonas pyocyanea* and on influenza A virus. The Journal of General Microbiology 6(1-2): 74-84. doi: 10.1099/00221287-6-1-2-74

Chen CJ, Michaelis M, Hsu HK, Tsai CC, Yang KD et al. (2008). *Toona sinensis* Roem tender leaf extract inhibits SARS coronavirus replication. Journal of Ethnopharmacology 120 (1): 108-11. doi: 10.1016/j.jep.2008.07.048

Chen CN, Lin CPC, Huang KK, Chen WC, Hsieh HP et al. (2005). Inhibition of SARS-CoV 3C-like protease activity by Theaflavin-3, 30-digallate (TF3). Evidence-Based Complementary and Alternative Medicine 2 (2): 209-215. doi: 10.1093/ecam/neh081

Chen Z, Nakamura T (2004). Statistical evidence for the usefulness of Chinese medicine in the treatment of SARS. Phytotherapy Research 18 (7): 592-594. doi: 10.1002/ptr.1485

Cheng PW, Ng LT, Chiang LC, Lin CC (2006). Antiviral effects of saikosaponins on human coronavirus 229E *in vitro*. Clinical and Experimental Pharmacology & Physiology 33 (7): 612-616. doi: 10.1111/j.1440-1681.2006.04415.x

Cho JK, Curtis-Long MJ, Lee KH, Kim DW, Ryu HW et al. (2013). Geranylated flavonoids displaying SARS-CoV papain-like protease inhibition from the fruits of *Paulownia tomentosa*. Bioorganic & Medicinal Chemistry 21 (11): 3051-3057. doi: 10.1016/j.bmc.2013.03.027

Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H et al. (2003). Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. Lancet 361 (9374): 2045-2046. doi: 10.1016/S0140-6736(03)13615-X

De Clercq E (2019). New nucleoside analogues for the treatment of hemorrhagic fever virus infections. Chemistry–An Asian Journal 14 (22): 3962-3968. doi: 10.1002/asia.201900841

De Groot RJ, Baker SC, Baric R, Enjuanes L, Gorbalenya AE et al. (2011). Family Coronaviridae. In: King AM, Lefkowitz E, Adams MJ, Carstens EB (editors). Ninth Report of the International Committee on Taxonomy of Viruses. Oxford, UK: Elsevier, pp. 806-828. doi: 10.1016/B978-0-12-384684-6.00068

Debiaggi M, Pagani L, Cereda PM, Landini P, Romero E (1988). Antiviral activity of *Chamaecyparis lawsoniana* extract: study with herpes simplex virus type 2. Microbiologica 11 (1): 55-61.

Deng YF, Aluko RE, Jin Q, Zhang Y, Yuan LJ (2012). Inhibitory activities of baicalin against renin and angiotensin-converting enzyme. Pharmaceutical Biology 50 (4): 401-406. doi: 10.3109/13880209.2011.608076

Devaux CA, Rolain J-M, Colson P, Raoult D (2020). New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? International Society of Chemotherapy 12: 105938. doi: 10.1016/j.ijantimicag.2020.105938

Dhama K, Karthik K, Khandia R, Munjal A, Tiwari R et al. (2018). Medicinal and therapeutic potential of herbs and plant metabolites/extracts countering viral pathogens-current knowledge and future prospects. Current Drug Metabolism 19 (3): 236-263. doi: 10.2174/1389200219666180129145252

Fan Y, Zhao K, Shi ZL, Zhou P (2019). Bat coronaviruses in China. Viruses 11 (3): 210. doi: 10.3390/v11030210

Fehr AR, Perlman S (2015). Coronaviruses: an overview of their replication and pathogenesis. In: Maier HJ, Bickerton E, Britton P (editors). Coronaviruses. Methods in Molecular Biology, Vol. 1282. New York, NY, USA: Springer, pp. 1-23. doi: 10.1007/978-1-4939-2438-7_1

Fung KP, Leung PC, Tsui KW, Wan CC, Wong KB et al. (2011). Immunomodulatory activities of the herbal formula Kwan Du Bu Fei Dang in healthy subjects: a randomised, double-blind, placebo-controlled study. Hong Kong Medical Journal 17 (Supplement 2): 41-43.

Ge XY, Li JL, Yang XL, Chmura AA, Zhu G et al. (2013). Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. Nature 503 (7477): 535-538. doi: 10.1038/nature12711

Ghildiyal R, Prakash V, Chaudhary VK, Gupta V, Gabrani R (2020). Phytochemicals as antiviral agents: recent updates. Plant-derived Bioactives 12: 279-295. doi: 10.1007/978-981-15-1761-7_12

Gong SJ, Su XJ, Yu HP, Li J, Qin YJ et al. (2008). A study on anti-SARS-CoV 3CL protein of flavonoids from *Litchi chinensis* sonn core. Chinese Pharmacological Bulletin 24: 699-700.

Guo Y-R, Cao Q-D, Hong Z-S, Tan Y-Y, Chen, S-D (2020). The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak –an update on the status. Military Medical Research 7 (1): 11. doi: 10.1186/s40779-020-00240-0

Heurich A, Hofmann-Winkler H, Gierer S, Liepold T, Jahn O (2014). TMPRSS2 and ADAM17 cleave ACE2 differentially and only proteolysis by TMPRSS2 augments entry driven by the severe acute respiratory syndrome coronavirus spike protein. Journal of Virology 88 (2): 1293-1307. doi: 10.1128/JVI.02202-13

Hill KP (2020). Cannabinoids and the coronavirus. Cannabis and Cannabinoid Research 2020 April 28 [online ahead of print]. doi: 10.1089/can.2020.0035

Ho TY, Wu SL, Chen JC, Li CC, Hsiang CY (2007). Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction. Antiviral Research 74 (2): 92-101. doi: 10.1016/j.antiviral.2006.04.014

Ho YJ, Lu JW, Huang JL, Lai ZZ (2019). Palmatine inhibits Zika virus infection by disrupting virus binding, entry, and stability. Biochemical and Biophysical Research Communications 518 (4): 732-738. doi: 10.1016/j.bbrc.2019.08.120

Hoareau L, DaSilva EJ (1999). Medicinal plants: a re-emerging health aid. Electronic Journal of Biotechnology 2 (2): 56-70. doi: 10.2225/vol2-issue2-fulltext-2

Hsu CH, Hwang KC, Chao CL, Chang SG, Ho MS et al. (2006). Can herbal medicine assist against avian flu? Learning from the experience of using supplementary treatment with Chinese medicine on SARS or SARS-like infectious disease in 2003. Journal of Alternative and Complementary Medicine 12 (6): 505-506. doi: 10.1089/acm.2006.12.505

Huang KL, Lai YK, Lin CC, Chang JM (2006). Inhibition of hepatitis B virus production by *Boehmeria nivea* root extract in HepG2 2.2.15 cells. World Journal of Gastroenterology 12 (35): 5721-5725. doi: 10.3748/wjg.v12.i35.5721

Jiang S, Hillyer C, Du L (2020). Neutralizing antibodies against SARS-CoV-2 and other human coronaviruses. Trends in Immunology 41 (5): 355-359. doi: 10.1016/j.it.2020.04.008

Khaerunnisa S, Kurniawan H, Awaluddin R, Suhartati S, Soetjipto S (2020). Potential inhibitor of COVID-19 main protease (Mpro) from several medicinal plant compounds by molecular docking study. Preprints 2020: 2020030226. doi: 10.20944/preprints202003.0226.v1

Kim DE, Min JS, Jang MS, Lee JY, Shin YS et al. (2019). Natural Bis-benzylisoquinoline alkaloids-tetrandrine, fangchinoline, and cepharanthine, inhibit human coronavirus OC43 infection of MRC-5 human lung cells. Biomolecules 9 (11): 696. doi: 10.3390/biom9110696

Kim DW, Seo KH, Curtis-Long MJ, Oh KY, Oh JW et al. (2014). Phenolic phytochemical displaying SARS-CoV papain-like protease inhibition from the seeds of *Psoralea corylifolia*. Journal of Enzyme Inhibition and Medicinal Chemistry 29 (1): 59-63. doi: 10.3109/14756366.2012.753591

Kwon HJ, Ryu YB, Kim YM, Song N, Kim CY et al. (2013). *In vitro* antiviral activity of phlorotannins isolated from *Ecklonia cava* against porcine epidemic diarrhea coronavirus infection and hemagglutination. Bioorganic & Medicinal Chemistry 21 (15): 4706-4713. doi: 10.1016/j.bmc.2013.04.085

Lai C-C, Shih T-P, Ko W-C, Tang H-J, Hsueh P-R (2020). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. International Journal of Antimicrobial Agents 55 (3): 105924. doi: 10.1016/j.ijantimicag.2020.105924

Lai MM, Cavanagh D (1997). The molecular biology of coronaviruses. Advances in Virus Research 48: 1-100. doi: 10.1016/S0065-3527(08)60286-9

Lau KM, Lee KM, Koon CM, Cheung CS, Lau CP et al. (2008). Immunomodulatory and anti-SARS activities of *Houttuynia cordata*. Journal of Ethnopharmacology 118 (1): 79-85. doi: 10.1016/j.jep.2008.03.018

Letko M, Marzi A, Munster V (2020). Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nature Microbiology 5: 562-569. doi: 10.1038/s41564-020-0688-y

Li SY, Chen C, Zhang HQ, Guo HY, Wang H et al. (2005). Identification of natural compounds with antiviral activities against SARS-associated coronavirus. Antiviral Research 67 (1): 18-23. doi: 10.1016/j.antiviral.2005.02.007

Li T, Peng T (2013). Traditional Chinese herbal medicine as a source of molecules with antiviral activity. Antiviral Research 97 (1): 1-9. doi: 10.1016/j.antiviral.2012.10.006

Lin CW, Tsai FJ, Tsai CH, Lai CC, Wan L et al. (2005). Anti-SARS coronavirus 3C-like protease effects of *Isatis indigotica* root and plant-derived phenolic compounds. Antiviral Research 68 (1): 36-42. doi: 10.1016/j.antiviral.2005.07.002

Lin SC, Ho CT, Chuo WH, Li S, Wang TT et al. (2017). Effective inhibition of MERS-CoV infection by resveratrol. BMC Infectious Diseases 17 (1): 144. doi: 10.1186/s12879-017-2253-8

Lu R, Zhao X, Li J, Niu P, Yang B, Wu H et al. (2020). Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 395 (10224): 565-574. doi: 10.1016/S0140-6736(20)30251-8

Lubbe A, Seibert I, Klimkait T, Van Der Kooy F (2012). Ethnopharmacology in overdrive: the remarkable anti-HIV activity of *Artemisia annua*. Journal of Ethnopharmacology 141 (3): 854-859. doi: 10.1016/j.jep.2012.03.024

McCutcheon AR, Roberts TE, Gibbons E, Ellis SM, Babiuk LA et al. (1995). Antiviral screening of British Columbian medicinal plants. Journal of Ethnopharmacology 49 (2): 101-110. doi: 10.1016/0378-8741(95)90037-3

Michaelis M, Doerr HW, Cinatl-Jr J (2011). Investigation of the influence of EPs® 7630, a herbal drug preparation from *Pelargonium sidoides*, on replication of a broad panel of respiratory viruses. Phytomedicine 18 (5): 384-386. doi: 10.1016/j.phymed.2010.09.008

Moriyama M, Hugentobler WJ, Iwasaki A (2020). Seasonality of respiratory viral infections. Annual Review of Virology Vol. 7. doi: 10.1146/annurev-virology-012420-022445

Mubarak A, Alturaiki W, Hemida MG (2019). Middle East respiratory syndrome coronavirus (MERS-CoV): infection, immunological response, and vaccine development. Journal of Immunology Research 2019: 1-11. doi: 10.1155/2019/6491738

Müller C, Schulte FW, Lange-Grünweller K, Obermann W, Madhugiri R et al. (2018). Broad-spectrum antiviral activity of the eIF4A inhibitor silvestrol against corona- and picornaviruses. Antiviral Research 150: 123-129. doi: 10.1016/j.antiviral.2017.12.010

Neuman BW, Kiss G, Kunding AH, Bhella D, Baksh MF et al. (2011). A structural analysis of M protein in coronavirus assembly and morphology. Journal of Structural Biology 174 (1): 11-22. doi: 10.1016/j.jsb.2010.11.021

Orzalli MH, Kagan JC (2017). Apoptosis and necroptosis as host defense strategies to prevent viral infection. Trends in Cell Biology 27 (11): 800-809. doi: 10.1016/j.tcb.2017.05.007

Oyston P, Robinson K (2012). The current challenges for vaccine development. Journal of Medical Microbiology 61 (7): 889-894. doi: 10.1099/jmm.0.039180-0

Park JY, Yuk HJ, Ryu HW, Lim SH, Kim KS et al. (2017). Evaluation of polyphenols from *Broussonetia papyrifera* as coronavirus protease inhibitors. Journal of Enzyme Inhibition and Medicinal Chemistry 32 (1): 504-512. doi: 10.1080/14756366.2016.1265519

Perrier A, Bonnin A, Desmarets L, Danneels A, Goffard A et al. (2019). The C-terminal domain of the MERS coronavirus M protein contains a trans-Golgi network localization signal. The Journal of Biological Chemistry 294 (39): 14406-14421. doi: 10.1074/jbc.RA119.008964

Poon PM, Wong CK, Fung KP, Fong CY, Wong EL et al. (2006). Immunomodulatory effects of a traditional Chinese medicine with potential antiviral activity: a self-control study. The American Journal of Chinese Medicine 34 (1): 13-21. doi: 10.1142/S0192415X0600359X

Roh C (2012). A facile inhibitor screening of SARS coronavirus N protein using nanoparticle-based RNA oligonucleotide. International Journal of Nanomedicine 7: 2173-2179. doi: 10.2147/IJN.S31379

Ryu YB, Jeong HJ, Kim JH, Kim YM, Park JY et al. (2010). Biflavonoids from *Torreya nucifera* displaying SARS-CoV 3CL(pro) inhibition. Bioorganic & Medicinal Chemistry 18 (22): 7940-7947. doi: 10.1016/j.bmc.2010.09.035

Sassi BA, Harzallah-Skhiri F, Bourgougnon N, Aouni M (2008). Antiviral activity of some Tunisian medicinal plants against Herpes simplex virus type 1. Natural Product Research 22 (1): 53-65. doi: 10.1080/14786410701589790

Schnitzler P, Schuhmacher A, Astani A, Reichling J (2008). *Melissa officinalis* oil affects infectivity of enveloped herpesviruses. Phytomedicine 15 (9): 734-740. doi: 10.1016/j.phymed.2008.04.018

Semple SJ, Reynolds GD, O'leary MC, Flower RLP (1998). Screening of Australian medicinal plants for antiviral activity. Journal of Ethnopharmacology 60 (2): 163-172. doi: 10.1016/s0378-8741(97)00152-9

Sharma AD (2020). Eucalyptol (1, 8 cineole) from eucalyptus essential oil a potential inhibitor of COVID 19 corona virus infection by molecular docking studies. Preprints 2020: 2020030455. doi: 10.20944/preprints202003.0455.v1

Sharma AD, Kaur I (2020). Jensenone from eucalyptus essential oil as a potential inhibitor of COVID 19 corona virus infection. Research & Reviews in Biotechnology & Biosciences 7 (1): 59-66. doi: 10.20944/preprints202003.0455.v1

Shen L, Niu J, Wang C, Huang B, Wang W et al. (2019). High-throughput screening and identification of potent broad spectrum inhibitors of coronaviruses. Journal of Virology 93 (12): e00023-e00019. doi: 10.1128/JVI.00023-19

Simmons G, Zmora P, Gierer S, Heurich A, Pöhlmann S (2013). Proteolytic activation of the SARS-coronavirus spike protein: cutting enzymes at the cutting edge of antiviral research. Antiviral Research 100 (3): 605-614. doi: 10.1016/j.antiviral.2013.09.028

Suryanarayana L, Banavath D (2020). A Review on identification of antiviral potential medicinal plant compounds against with COVID-19. International Journal of Research in Engineering, Science and Management 3 (3): 675-679.

Takahashi S, Yoshiya T, Yoshizawa-Kumagaye K, Sugiyama T (2015). Nicotianamine is a novel angiotensin-converting enzyme 2 inhibitor in soybean. Biomedical Research 36 (3): 219-224. doi: 10.2220/biomedres.36.219

Tallei TE, Tumilaar SG, Niode NJ, Fatimawali F, Kepel BJ et al. (2020). Potential of plant bioactive compounds as SARS-CoV-2 main protease (Mpro) and spike (S) glycoprotein inhibitors: a molecular docking study. Preprints 2020: 2020040102. doi: 10.20944/preprints202004.0102.v2

Ul Qamar MT, Alqahtani SM, Alamri MA, Chen LL (2020). Structural basis of SARS-CoV-2 3CLpro and anti-COVID-19 drug discovery from medicinal plants. Journal of Pharmaceutical Analysis 2020 March 26 [available online] (in press). doi: 10.1016/j.jpha.2020.03.009

Ulasli M, Gurses SA., Bayraktar R, Yumrutas O, Oztuzcu S et al. (2014). The effects of *Nigella sativa* (Ns), *Anthemis hyalina* (Ah) and *Citrus sinensis* (Cs) extracts on the replication of coronavirus and the expression of TRP genes family. Molecular Biology Reports 41 (3): 1703-1711. doi: 10.1007/s11033-014-3019-7

Vieira RF, Bizzo HR, Deschamp, C (2010). Genetic resources of aromatic plants from Brazil. Israel Journal of Plant Sciences 58 (3-4): 263-271. doi: 10.1560/IJPS.58.2.263

Wang W, Ma X, Han J, Zhou M, Ren H et al. (2016). Neuroprotective effect of scutellarin on ischemic cerebral injury by down-regulating the expression of angiotensin-converting enzyme and AT1 Receptor. Public Library of Science One 11 (1): e0146197. doi: 10.1371/journal.pone.0146197

Wen CC, Kuo YH, Jan JT, Liang PH, Wang SY et al. (2007). Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus. Journal of Medicinal Chemistry 50 (17): 4087-4095. doi: 10.1021/jm070295s

Wen CC, Shyur LF, Jan JT, Liang PH, Kuo CJ et al. (2011). Traditional Chinese medicine herbal extracts of *Cibotium barometz*, *Gentiana scabra*, *Dioscorea batatas*, *Cassia tora*, and *Taxillus chinensis* inhibit SARS-CoV replication. Journal of Traditional and Complementary Medicine 1 (1): 41-50. doi: 10.1016/s2225-4110(16)30055-4

Wink M (2020). Potential of DNA intercalating alkaloids and other plant secondary metabolites against SARS-CoV-2 Causing COVID-19. Diversity 12 (5): 175. doi: 10.3390/d12050175

Woo PC, Huang Y, Lau SK, Yuen KY (2010). Coronavirus genomics and bioinformatics analysis. Viruses 2 (8): 1804-1820. doi: 10.3390/v2081803

Woo PC, Wang M, Lau SK, Xu H, Poon RW et al. (2007). Comparative analysis of twelve genomes of three novel group 2c and group 2d coronaviruses reveals unique group and subgroup features. Journal of Virology 81 (4): 15741585. doi: 10.1128/JVI.02182-06

Wu CY, Jan JT, Ma SH, Kuo CJ, Juan HF et al. (2004). Small molecules targeting severe acute respiratory syndrome human coronavirus. Proceedings of the National Academy of Sciences of the United States of America 101 (27): 10012-10017. doi: 10.1073/pnas.0403596101

Yang CW, Chang HY, Lee YZ, Hsu HY, Lee SJ (2018). The cardenolide ouabain suppresses coronaviral replication via augmenting a Na+/K+-ATPase-dependent PI3K_PDK1 axis signaling. Toxicology and Applied Pharmacology 356: 90-97. doi: 10.1016/j.taap.2018.07.028

Yang CW, Lee YZ, Kang IJ, Barnard DL, Jan JT et al. (2010). Identification of phenanthroindolizines and phenanthroquinolizidines as novel potent anti-coronaviral agents for porcine enteropathogenic coronavirus transmissible gastroenteritis virus and human severe acute respiratory syndrome coronavirus. Antiviral Research 88 (2): 160-168. doi: 10.1016/j.antiviral.2010.08.009

Yang Y, Islam M S, Wang J, Li Y, Chen X (2020). Traditional Chinese medicine in the treatment of patients infected with 2019-new coronavirus (SARS-CoV-2): a review and perspective. International Journal of Biological Sciences 16 (10): 1708-1717. doi: 10.7150/ijbs.45538

Yi L, Li Z, Yuan K, Qu X, Chen J et al. (2004). Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells. Journal of Virology 78 (20): 11334-11339. doi: 10.1128/JVI.78.20.11334-11339.2004

Yin Y, Wunderink RG (2018). MERS, SARS and other coronaviruses as causes of pneumonia. Respirology 23 (2): 130-137. doi: 10.1111/resp.13196

Yonesi M, Rezazadeh A (2020). Plants as a prospective source of natural anti-viral compounds and oral vaccines against COVID-19 coronavirus. Preprints 2020: 2020040321. doi: 10.20944/preprints202004.0321.v1

Yu MS, Lee J, Lee JM, Kim Y, Chin YW et al. (2012). Identification of myricetin and scutellarein as novel chemical inhibitors of the SARS coronavirus helicase, nsP13. Bioorganic & Medicinal Chemistry Letters 22 (12): 4049-4054. doi: 10.1016/j.bmcl.2012.04.081

Zhang Q, Wang Y, Qi C, Shen L, Li J (2020a). Clinical trial analysis of 2019-nCoV therapy registered in China. Journal of Medical Virology 92 (6): 540-545. doi: 10.1002/jmv.25733

Zhang W, Du RH, Li B, Zheng XS, Yang XL et al. (2020b). Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. Emerging Microbes & Infections 9 (1): 386-389. doi: 10.1080/22221751.2020.1729071

Zhou P, Yang XL, Wang XG, Hu B, Zhang L et al. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 579: 270-273 doi: 10.1038/s41586-020-2012-7

Zhuang M, Jiang H, Suzuki Y, Li X, Xiao P et al. (2009). Procyanidins and butanol extract of *Cinnamomi cortex* inhibit SARS-CoV infection. Antiviral Research 82 (1): 73-81. doi: 10.1016/j.antiviral.2009.02.001

Zumla A, Chan JF, Azhar EI, Hui DS, Yuen KY (2016). Coronaviruses –drug discovery and therapeutic options. Nature Reviews Drug discovery 15 (5): 327-347. doi: 10.1038/nrd.2015.37