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Review

Medicinal plant-derived compounds as potential phytotherapy forCOVID-19: Future perspectives

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Currently, the human being faces a contagious virus called SARS-CoV-2 with a high transmission ability, infection, and a relatively high mortality rate, especially for the elderly. All research interest is directed to finding a drug or vaccine to save millions of people's lives; some have succeeded and applied now in some countries. Medicinal plants represent a green treasure that renders plentiful primary and secondary metabolites characterized by potent biological activities. Interestingly, the secondary metabolites, alkaloids, flavonoids, tannins, and terpenoids, own a broad antiviral history. The plant antiviral capabilities may be due to inhibition of viral attachment to/penetration of the host cell; inhibition of the virus replication; suppressing RNA replication; downregulation of viral proteins translation; interfering with virus non-structural/structural protein; downregulation of virus-induced pro-inflammatory/inflammatory signaling pathways in the host cell, and antioxidant activity thus abating the virus-induced oxidative stress effect. Presently, as we are trapped with a surly virus, there are attempts to exploit the power of nature. Therefore, this review's main objective is to refer to some medicinal plants or their derivatives that limit the virus's virulence or alleviate the symptoms associated with this virus.

Key words: SARS-CoV-2, medicinal plants, natural extracts, flavonoids, alkaloids, antiviral.

INTRODUCTION

At the end of 2019, a Coronavirus disease (COVID-19) caused by SARS-CoV-2 was reported in Wuhan, the

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sprawling capital of Hubei province, with approximately 11 million people in the central region of the People's Republic of China (Zhu et al., 2020). Afterward, it has expanded all over the world, affecting more than 26 countries (Aanouz et al., 2020). On January 30, 2020, the World Health Organization (WHO) had proclaimed the international concern for the public health emergency; By the 11th of 2020, the virus was confirmed to be pandemic (Rosales-Mendoza et al., 2020). WHO has reported on Apr 15, 2020, that there are 1,914,916 confirmed infected cases present in 213 countries, areas, or territories around the world, along with 123,010 deaths; on October 18, 2020, there are over 40 million confirmed infected cases around the world, along with 1.1 million deaths (WHO, 2020). It can be said that the COVID-19 pandemic spread rapidly by leaps and bounds and entered a new risky phase that threatens the human being and the economy worldwide. Researchers and the power of science are currently in a battle against that deadly virus, and they intend to seek a way to control its spreading and find a potent cure or vaccine as soon as possible. Thus, it is pivotal to discover other alternatives in order to overcome this virus.

SARS-CoV-2 belongs to genera *Beta coronavirus* and subgenus *Sarbecovirus* (Lu et al., 2020). Several hosts of coronaviruses have been reported, including some aves, bats, dogs, camels, mice, cats, and other novel mammalian hosts (Bande et al., 2015; Su et al., 2016). The size of SARS-CoV-2 ranges from 65 to 125 nm in diameter (Su et al., 2016). It possesses an envelope and a single positive-strand RNA genome, encapsulated with a helical capsid (Lu et al., 2020; Su et al., 2016). COVID-19 can be transmitted via respiratory droplets, sneezing, coughing, and aerosols that can penetrate the humans' cellular barriers through the mouth, nose, or eye (Li et al., 2020; Riou and Althaus, 2020; Xie et al., 2020). The viral entry to the host cell is mediated by the viral S protein, Angiotensin-Converting Enzyme 2 (ACE2) host receptor, and Transmembrane Serine Protease 2 enzyme (TMPRSS2) (Hoffmann et al., 2020). General symptoms of the disease involve fever, sore throat, pneumonia, cough, headache, diarrhea, muscle pain, shortness of breath, renal failure, and even death (Cascella et al., 2020).

Viral infection control can be done not only by using drug therapy but also by a prophylactic strategy, which is better in some way (Denaro et al., 2020). Unfortunately, just limited knowledge with many gaps exist about the virus, as it is an emerging disease. Till now, there are many efforts to relieve the disease symptoms or to suppress the virus. Unluckily, no treatment specific for COVID-19 is available until now, so the best ways at the current moment to reduce the infection spreading and protect the public are the use of some pre-existing chemical drugs and supportive care (Rosales-Mendoza et al., 2020) along with keeping the global use of these chemical drugs, they did not give the expected outcomes or demolish the severe symptoms. Moreover, drug development is a long process that takes years to be validated and accomplished besides their undesirable side effects, including minor headaches, gastrointestinal side effects, nephrotoxicity, and many others as well as patient compliance (Nisar et al., 2018). Therefore, it is must be oriented towards using natural substances from plants, algae, and animals to treat COVID-19 (Aanouz et al., 2020).

The next stages will be critical to find and validate the best clinical management and present the possible effective treatments for humanity (Rosales-Mendoza et al., 2020). Natural products from medicinal plants have been used to treat human diseases in many countries and societies. They are the backbone of folk medicine, and they have gathered attention owing to their potent therapeutic potentiality (Ben-Shabat et al., 2020). WHO reported approximately 20,000 plant species are utilized for medicinal purposes (Cho et al., 2015). Herbalism is the oldest therapeutic system used to cure patients, and the choice of the substance depends on the patient's symptoms (Wyganowska-Swiatkowska and Kurhanska-Flisykowska, 2012). Additionally to the therapeutic potentialities of the natural or herbal treatment they are inexpensive, available, and safe, with minimal side effects comparing to chemical drugs (Akram et al., 2020).The curative potential of medicinal plants is mainly due to a broad range of secondary metabolites such as glycosides, alkaloids, flavonoids, terpenes, and tannins (Akram et al., 2020; Ben-Shabat et al., 2020). For the pros mentioned earlier, many researchers directed their interest towards medicinal plants (Ang et al., 2020; Capell et al., 2020; Hassan, 2020) as an exciting and significant approach that should be considered because of their bioactive compounds that have potent antiviral activity. Galanakis et al. (2020) and Xian et al. (2020) reviewed the roles of many plant bioactive compounds and food ingredients against human coronaviruses and COVID-19. Yang et al. (2020) identified traditional Chinese medicine for the treatment of novel coronavirus. Ang et al. (2020) signified the herbal medicine for treating COVID-19. However, none of them correlate the potential mechanism of some medicinal plants' extracts with their prophylactic/inhibitory effects against COVID-19.

PLANT SECONDARY METABOLITES AS PROPHYLACTIC FOR COVID-19

Plants' secondary metabolites play important roles in plant physiology and possess many therapeutic potentialities, such as antiviral, antifungal, antibacterial, antioxidant, anti-inflammatory, and anticancer. Flavonoids are the most important secondary social distance (Balachandar et al., 2020). Despite the metabolites; they have numerous classes according to the structure, such as isoflavonoids, flavones, biflavonoids, and others

(Croft, 1998); they have been proven to exhibit antiviral activities which encourage the exploration of their antiviral potential against SARS-CoV-2. It was reported that they could inhibit the infectivity of some of the single-stranded RNA viruses in the Reoviridae, Flaviviridae, Coronaviridae, and Retroviridae (Andres et al., 2009). Flavones are known for their antiviral activity since the 1990s; Mucsi et al. (1992) demonstrated that a flavone that is called apigenin and acyclovir simultaneously enhanced the antiviral effect against herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) in cell culture with a fractional inhibitory concentration values of 0.6-0.8. Apigenin, a member of the flavone family, is a non-toxic and non-mutagenic dietary flavonoid isolated from parsley, artichoke, basil, celery, Ecballium, and other plants (Ross and Kasum, 2002). It showed potent antiviral activity *in vitro* against the hepatitis B virus and adenoviruses (ADV). Apigenin possesses various pharmacological effects, such as anti-inflammatory, anticancer, antioxidative, and antiviral functions (Wang et al., 2014). It was also revealed that it is active against RNA viruses (Lv et al., 2014).

Outstandingly, molecular docking is a perfect method to screen compounds and reach a possible potent substance against the desired target before experimental studies because it is easy, fast, and low-cost (Joshi et al., 2020). Potential natural anti-SARS-CoV-2 compounds were discovered based on COVID-19 $3CL^{pro}$ inactivation, as the 3-chymotrypsin-like protease ($3CL^{pro}$ or M^{pro}) has an essential role in the replication of the virus, so it can be considered a probable target for inhibition of coronaviruses. Therefore, a group of scientists in a recent study screened 32,297 possible antiviral phytocompounds to discover novel antiviral compounds. Nine non-toxic natural compounds were concluded as potential drugs (Ul Qamar et al., 2020). They achieved their conclusion via demonstrating the interaction of those nine phytochemicals via hydrogen bonding and other interactions with His 41, Cys 145 of COVID-19 $3CL^{pro}$ to clarify the blocking mechanism of this protein; the most important were 5,7,3',4'-Tetrahydroxy-2'-(3,3 dimethylallyl) isoflavone from *Psorothamnus arborescens* with the highest binding affinity about -29.57 kcal/mol, and myricitrin from *Myrica cerifera* (-22.13 kcal/mol). Hussain and Green (2017) mentioned in their review that isoflavones have been reported to exert antiviral activity against numerous viruses, including SARS-CoV. Andres et al. (2009) also indicated that isoflavones had antiviral potential that affected the viral binding to the host cell and consequently inhibited its entry and replication. It can also inhibit the viral glycoprotein formation, which constitutes the virus envelop (Andres et al., 2009).

Myricetin is produced principally by the family Myricaceae members and some other families. It is a flavonoid widely available in vegetables, fruits, and some other plants such as terebinth (*Terebinthina chica*), nettle (*Urtica dioica*), purslane (*Portulaca oleracea*), and rose hip (*Rosa canina*) (Özcan et al., 2012). It has been proved that myricetin has potent activities against some viral enzymes, including kinases, helicases, many DNA polymerases, RNA polymerases, and also reverse transcriptases (Semwal et al., 2016). Ono et al. (1990) disclosed that the myricetin has notable inhibition for the reverse transcriptase enzyme by just using a small concentration of 1 and 2 µg/mL that completely inhibited the reverse transcriptase enzyme of both of Rauscher murine leukemia virus (RLV) and human immunodeficiency virus (HIV). Many previous studies proved that myricetin displayed activity against SARS-CoV, it was also reported that it showed inhibition ability for the coronavirus helicase via disturbing the ATPase activity *in vitro* by a half-maximal inhibitory concentration (IC_{50}) value of 2.71 µM (Keum and Jeong, 2012; Yu et al., 2012).

Interestingly, myricetin's effect is not just antiviral, but it was also reported to exert anti-inflammatory activity in both *in vitro* assays and *in vivo* animal models (Wang et al., 2010). Takano-Ishikawa et al. (2006) demonstrated that the concentration 62.5-125 µg/mL of myricetin (IC_{50}: <1000 mM) exerted anti-inflammatory capability via preventing Nuclear factor-kappa B (NF-κB) activation. It also displayed anti-inflammatory activity by inhibiting LPS-induced prostaglandins production (Takano-Ishikawa et al., 2006). Moreover, the LPS-induced Tumor necrosis factor-α (TNF-α) and Interleukin 1 beta (IL-1β) secretion (Bai and Zhu, 2010) were decreased by myricetin (Ko, 2012) in RAW264.7 cells. It seems that myricetin would be a potential remedy for SARS-CoV-2 due to its antiviral and anti-inflammatory effects by inhibiting many viral enzymes and suppressing cytokine production.

Additionally, flavonoids from other herbs were screened, including scutellarein, quercetagetin, and dihydromyricetin, and they showed effective repression of $3CL^{pro}$ activity (Liu et al., 2020). Likely, twelve phytochemicals, including eight di-terpenoids and four bi-flavonoids of *Torreya nucifera,* were investigated by Ryu et al. (2010) when they exhibited a potent anti-SARS-CoV $3CL^{pro}$ ability. The presence of a polyphenolic compound named amentoflavone that possesses antioxidative and anti-inflammatory effects (Lee et al., 2012) would be the main reason. Besides, it significantly expressed an inhibitory effect against Herpes simplex virus 1 (HSV-1) (Li et al., 2019a), Coxsackievirus B3 (CVB3) (Wilsky et al., 2012), and respiratory syncytial virus (RSV) (Ma et al., 2001).

Furthermore, Ryu et al. (2010) molecular docking revealed that the C5 hydroxyl group of amentoflavone could form 2 hydrogen bonds with the nitrogen atom of the imidazole ring of His163 (3.154 Å) and OH of Leu141 (2.966 Å), which belong to the S1 site of $3CL^{pro}$. Another indication is that the hydroxyl group in the B ring of amentoflavone forms hydrogen bonds with Gln189 (3.033 Å), which belongs to the S2 site of $3CL^{pro}$. Accordingly,

biflavonoids could be used as COVID-19 inhibitors because the genome sequence of SARS-CoV-2 $3CL^{pro}$ is similar to that of SARS-CoV $3CL^{pro}$ (Ul Qamar et al., 2020).

Peele et al. (2020) performed a virtual screening for 24 natural plant-based compounds with previously proved to have antiviral properties, and this was done using the Glide program of Schrödinger. They demonstrated that the aflavin digallate (plant-based phenol derivative) docked with the best docking score showing H-bond interactions with THR 26, HIS 41, ASB 142, GLU166, HIS 163, and GLN 189. Azhagiya Singam et al. (2020) proposed two possible candidates that could also interact with the main protease M^{pro} of SARS-CoV-2; carlinoside, which has free binding energy -74.32±4.77 Kcal/mol and quercetin 3-o-sophoroside with a free binding energy of -72.03±7.51 Kcal/mol. These compounds can be found in bell pepper, tomato, and broccoli, which could be possible drugs since they are readily absorbed. Previously, carlinoside showed a therapeutic value in hyperbilirubinemia, in addition to topical anti-inflammatory properties (Costa et al., 2016).

Another computational experiment mentioned the inhibitory potential of catechin and curcumin polyphenols derived from green tea and turmeric, respectively, against SARS-CoV-2. Both compounds possessed a dual binding affinity since they could interact with both ACE2 and spike (S) viral protein. Although catechin's binding affinity was greater than that of curcumin, the latter showed a direct interaction with the receptor-binding domain (Jena et al., 2021). Polyphenolic compound catechins, such as epicatechin gallate (ECG), epigallocatechin gallate (EGCG), and epigallocatechin (EGC) with EC50 values of 22-40, 22-28, and 309-318 µM, respectively, showed antiviral activity against influenza by inhibiting hemagglutination activity; consequently, suppressing the viral replication (Song et al., 2005). Catechins also inhibit HIV-1 replication in various life cycle's steps of the virus by interfering with protease activity and RT, blocking gp120-CD4 interaction through binding to CD4 and destroying virions (Fassina et al., 2002) and Epstein-Barr virus by inhibiting the transcription of immediate-early genes; and thus, blocking its lytic cycle (Chang et al., 2003).

Curcumin is a polyphenolic compound extracted from roots of rhizome plant *Curcuma longa* (family Zingiberaceae, common name: turmeric) and it is known for its extensive therapeutic properties, including anti-inflammatory by inhibiting the pro-inflammatory NF-κB (Edwards et al., 2017), antioxidant (Mošovská et al., 2016), and antitumor activity; curcumin-light caused cell cycle arrest (G0/G1, G2/M- and S-phase) in the bladder cancer cells by different molecular action modes in the different cell lines (Roos et al., 2019). For many decades, curcumin is extensively used in India to cure infectious and inflammatory diseases (Pang et al., 2015). This can be attributed to its ability to regulate the expression of many inflammatory enzymes and some TFs; its anti-inflammatory effect is mainly via the up-regulation of peroxisome proliferator-activated receptors (PPAR-γ), transcription factors (TFs) that critically regulate the inflammatory cytokines, leading to the inactivation of NF-κB, the primary regulator of immune response and a pro-inflammatory mediator which induces the inflammatory cascade (Ciavarella et al., 2020). Additionally, it has been investigated as one of the natural compounds that exert antiviral ability (Manoharan et al., 2020; Praditya et al., 2019). This ability was reported against a broad spectrum of viruses, including Influenza virus, Hepatitis virus, HIV, HSV-2, HPV viruses, and Adenovirus (Das et al., 2020). It can block viral binding to the cell surface of chikungunya virus and zika arthropod-borne viruses (Mounce et al., 2017) and membrane modulation through non-linear membrane thinning and thus, weakens the elasticity of the membrane (Hung et al., 2008). Capsaicin extracted from hot pepper (Family: Solanaceae) also has anti-inflammatory properties via activating PPAR-γ, which consequently inhibits TNF- α, a pro-inflammatory cytokine. It can also inhibit the accumulation of inflammatory dendritic cells (DCs) and other inflammatory cells around small pulmonary vessels after exposure to inhaled antigens (Hua et al., 2018).

Sanna et al. (2021) showed the effectiveness of hot and cold extract (breastin) of the ornamental plant; *Nerium oleander* (NO), common oleander, against Poliovirus types 1 Sabin strain (Sb-1). *Nerium oleander* belongs to the family Apocynaceae, widely distributed in both tropical and subtropical regions, and it is considered a poisonous plant. Their results proved both extracts' antiviral capability by half maximal effective concentration (EC_{50}) values 1 and 0.6 mg/ml, respectively. They demonstrated that the *N. oleander* antiviral activity was mainly during the first 2 h after infection (Sanna et al., 2021). Singh et al. (2013) demonstrated that the oleandrin, a glycoside extracted from *N. oleander*, had an antiviral ability via reducing the levels of an envelope glycoprotein (gp120) of human immunodeficiency virus type-1 (HIV-1) particles and also showed *in vitro* inhibition activity for HIV-1 infectivity (Singh et al., 2013). Avci and Dik (2014) performed an antiviral assay of *N. oleander* distillate (NOD) against the parainfluenza-3 virus (PI-3); they found that the NOD, along with Acyclovir, exerted notable antiviral activity ($P<0.05$) against PI-3 (Oguzhan Avci, 2014). Aanouz et al. (2020) also demonstrated the binding affinity and the interaction type between 67 compounds extracted from different aromatic medicinal plants and SARS-COV-2 M^{pro} using molecular docking. Three compounds had high binding energy, where the crocin, a carotenoid ingredient of Saffron (Rameshrad et al., 2018), exhibited interaction energy equal to (-8.2 kcal/mol); meanwhile, the digitoxigenin (from *N. Oleander*), revealed -7.2 kcal/mol (Aanouz et al., 2020). Boff et al. (2019) screened the antiviral activity of semisynthetic 16 new derivatives based on the scaffold of

digitoxigenin against HSV-1 and HSV-2. They demonstrated that two derivatives exhibited the most antiviral capability, including 3β-[(N-(2- hydroxyethyl) aminoacetyl] amino-3-deoxydigitoxigenin) (C10) and (3β (hydroxyacetyl) amino-3-deoxydigitoxigenin) (C11). They selected these two compounds to investigate their exact mechanism of action against the HSV as per their results. They revealed that the IC_{50} values of C10 and C11 against HSV-1 (KOS strain) are 0.23 and 0.24 µM, against HSV-1 (29-R strain) are 0.18 and 0.19 µM; against HSV-2 (333 strain) are 0.27 and 0.30 µM, respectively (Boff et al., 2020).

Many alkaloids, essential secondary metabolites, are characterized by their biological activity and medical uses. Some extracted alkaloids are recently proved to have abilities against COVID-19 (Bleasel and Peterson, 2020). A group of Nigerian researchers conducted docking analysis for some terpenoids and alkaloids extracted from African medicinal plants; their results proved that some of these compounds have high binding energy towards the $3CL^{pro}$ of the COVID-19. Among all studied compounds, the 10-Hydroxyusambarensine, an Indole alkaloid extracted from *Strychnos usambarensis* (Loganiaceae), exhibited the highest binding affinity value -10.0, which is higher than those of ritonavir and lopinavir (used as reference). They also proved that these alkaloids interacted via conventional hydrogen bonds to the Gln189 residue and a carbon-hydrogen bond to Gln166 and Cys14 (Gyebi et al., 2020). Alkaloids have significant effects on the different phases of influenza virus replication *in vitro*. Quinolizidine and isoquinoline are two groups of alkaloids that have been demonstrated to exert activity on the synthesis of viral proteins.

Additionally, alkaloids can affect the different viral replication stages and inhibit pro-inflammatory cytokines (Moradi et al., 2017). Omacetaxine mepesuccinate, formerly known as homoharringtonine, is a natural alkaloid extracted from *Cephalotaxus fortunei* (Cephalotaxaceae). It contains trees and shrubs that are coniferous evergreen and indigenous to Asia. Previously, the bark has been used in China as a traditional medication for various indications (Dong et al., 2018). Homoharringtonine has been reported to exhibit potent antiviral activity against the varicella-zoster virus by down-regulating its lytic genes (Kim and Song, 2019), coronaviruses (porcine epidemic diarrhea virus and murine hepatitis virus), rhabdoviruses (vesicular stomatitis virus (VSV)) (Andersen et al., 2019; Dong et al., 2018), and echovirus 1 (EV1) (Andersen et al., 2019).

Gong et al. (2019) elucidated that Foot-and-Mouth Disease Virus (FMDV) infection was inhibited by homoharringtonine treatment at the early phases of viral replication. Their results indicated that it could become a promising candidate for further development as an FMDV inhibitor. Recently, Choy et al. (2020) proved its ability to inhibit the SARS-Cov-2 replication *in vitro* with an EC_{50} value of 2.55 µM. It was established that it could bind to the 80S ribosome in eukaryotic cells and suppress protein synthesis via interfering with chain elongation(Schneider-Poetsch et al., 2010). Further researches are needed to be done to know the exact mechanism of that promising compound.

More than 20 piperidine alkaloids have been identified in the Indian tobacco Lobelia (*Lobelia inflata*). This fabulous plant has been used for centuries as a herbal remedy for moderate and severe respiratory illnesses, including asthma, bronchitis, pneumonia, and cough. Several therapeutic potentialities have been demonstrated for the leaves and seed pods, such as anti-asthmatic, antispasmodic, emetic, expectorant, and respiratory stimulant effects (Robbers, 1996). Interestingly, α-Lobeline is regarded as the most therapeutically active alkaloid extracted from Lobelia. It is a nicotine agonist, a potent respiratory stimulant, activating the carotid and aortic body chemoreceptors, and it can relax lung tissue and aid in expectoration (Felpin, 2004; Leung, 1996).

Celastrol (a quinone methide triterpenoid-tripterine) is a chemical compound that is used in traditional Chinese medicine. It can be isolated from the root extracts of *Tripterygium wilfordii* (common name: Thunder god or duck vine, family: Celastraceae). Previous researches proved its ability to reduce the inflammatory mediators (Habtemariam et al., 2020; Jiang et al., 2020; Kim et al., 2009b, c) *in vitro* and *in vivo* experiments through the defeat of NF-κB signaling (Kim et al., 2009a). It has also been shown to reduce the pro-inflammatory cytokines such as interleukin-8 (IL-8), TNF-α (Wei and Wang, 2017). Hoffmann et al. (2020a) mentioned that the inhibition of TMPRSS2 could exert a dual effect on COVID-19, firstly by limiting viral entry by decreasing the cleavage of the viral S protein in the ACE2 receptor mediating the viral entry and secondly by inhibiting the NF-κB pathway. The celastrol is likely to perform both mechanisms.

Notably, ACE-2 plays a crucial role in viral pathogenicity by binding to viral particles aiding the host cell's breaching and the subsequent cascade of the virus life cycle. There is a broad range of anthraquinones, tannins, flavonoids, and stilbenes that exhibited multiple biological activities, including antioxidative, antitumor (Choi et al., 2007), anti-inflammatory (Dong and Jeon, 2009), antiviral (Lin et al., 2010; Ma et al., 2001), and antibacterial effects as indicated by clinical practice and modern pharmacological studies (Zuo et al., 2008). Emodin (1,3,8-trihydroxy-6-methylanthraquinone) is chiefly extracted from some plant species such as *Cassia*, *Polygonum*, and *Rhamnus* species, which belong to families Fabaceae, Polygonaceae, and Rhamnaceae, respectively (Dong et al., 2016). It showed antiviral properties through inactivation of enveloped viruses by disrupting the lipid bilayer (Sydiskis et al., 1991) and inhibition of casein kinase 2 (CK2) that is required and exploited by numerous viruses to phosphorylate essential

proteins needed to complete their life cycle (Battistutta et al., 2000). It was likely proven to display antiviral activity via the prevention of S protein binding to ACE 2 receptors (Dabaghian et al., 2020). Ho et al. (2007) mentioned that the structure of emodin has a high similarity to the structure of Promazine, which has demonstrated the anti-SARS-CoV effect, which is also a phenolic compound consisting of three cyclic rings. Furthermore, *Rheum palmatum* showed anti-Hepatitis B virus (HBV), anti-Japanese encephalitis virus (JEV) (Chang et al., 2014), and a potent inhibitory effect on the main protease (M^{pro}) of SARS-CoV with an IC_{50} value of 13.76 ± 0.03 µg/ml (Luo et al., 2009). As previously mentioned, the SARS-CoV-2 is similar to the SARS-CoV, so this bioactive compound may have a prominent effect on preventing COVID-19.

For many years, *Houttuynia cordata* has been used to alleviate lung symptoms such as cough, phlegm, and dyspnea and is known for its effectiveness in treating infectious diseases and pneumonia (Zhonghua, 2005). In a previous study, the efficacy of *Houttuynia cordata* to inhibit SARS was attributed to the extract's prominent effect against RNA-dependent RNA polymerase (RdRp) and SARS-CoV $3CL^{pro}$ in addition to immune-stimulation of CD4+ and CD8+ T cells (Lau et al., 2008). Furthermore, a study revealed the significant inhibition of SARS-CoV protease activity via several medicinal herb extracts, including *Gentiana scabra, Taxillus chinensis, Cibotium barometz, Dioscorea batatas,* and *Cassia tora* (Wen et al., 2011). *Cibotium barometz* is an antioxidant, antibacterial, and tyrosinase inhibitor, according to Lai et al. (2009), while *Cassia tora* has antibacterial and antifungal properties (Kim et al., 2004). Nevertheless, *D. batatas* extract exhibited anti-inflammatory properties due to its ability to inhibit NF-κB mediated iNOS and COX-2 expressions (Jin et al., 2010).

Besides, Cinatl et al. (2003) demonstrated that glycyrrhizin (or glycyrrhizic acid, GLR), which is a triterpenoid saponin isolated from the roots of Liquorice (*Glycyrrhiza glabra*), possesses antiviral activity (Bailly and Vergoten, 2020). Glycyrrhizin was the most effective inhibitor of SARS replication and viral adsorption and subsequent penetration (Cinatl et al., 2003). A possible interpretation for the glycyrrhizin antiviral activity would be due to its immune-stimulating properties, which might repress the massive production of cytokines that progress SARS-COV-2 patients' status more rapidly (Huang et al., 2020; Michaelis et al., 2011). Additionally, glycyrrhizin can inhibit reactive oxygen species (ROS), which affect viral replication through the reduction of NF-κB activation, p38, c-Jun N-terminal kinase (JNK), and redox-sensitive signaling events (Michaelis et al., 2011). Moreover, numerous medicinal plants containing GLR were used to treat upper respiratory infections and acute respiratory distress syndrome (ARDS) (Bailly and Vergoten, 2020). Considering the study of Cinatl et al. (2003), along with the Michaelis et al. (2011), glycyrrhizin could be a suitable candidate for inhibiting SARS-COV-2 by their dual effect; boosting the host immune system as well as repressing the viral entry.

This paragraph was modified and combined with the preceding paragraph which is talking about curcumin. Carvacrol is another compound derived from *Thymus* species (Family: Lamiaceae), a typical plant of the Mediterranean area, has anti-inflammatory properties via the inhibition of an inflammatory enzyme (COX-2). The plant's extracts were observed for an inhibitory effect against Bronchitis Virus (IBV). Furthermore, the extracts displayed the highest inhibition on viral replication and totally blocked viral production at 1 to 0.25 $\log_{10}$ CC_{50} (cytotoxic concentration) (Orhan and Senol Deniz, 2020). Another interesting study has been done by Nakano et al. (1997), which proved that the polysaccharide extracted from *Aspalathus linearis* almost wholly blocked HIV binding to the cells at a concentration of 250 µg/ml (Nakano et al., 1997). The anti-influenza activity of the alkaline extract of the green leaves of *A. linearis* was also evaluated and attributed to the existence of sialidase-inhibiting components that can affect the virus entry to the host cell because the sialidase enzyme is responsible for the desialylation of the haemagglutinin (HA) of the virus which partially unmasks the HA protein and facilitates its binding to the target cell surface (Rahmasaria et al., 2017).

GENERAL ANTIVIRAL ACTIVITIES OF SOME MEDICINAL PLANTS WITH A PROMISING ANTI-COVID-19 APPROACH

Medicinal plants are distributed worldwide. In particular, Egypt is a fertile land for them, with many previous studies that manifested Egyptian native medicinal plants' ability as antiviral therapeutic agents (Fahmy et al., 2020). Their various uses have also been demonstrated to remedy many illnesses, including infectious diseases (Soltan and Zaki, 2009). Much previous research revealed that medicinal plants' usage is promising in developing antiviral drugs (Ben-Shabat et al., 2020; Denaro et al., 2020; Kitazato et al., 2007). Several isolated bioactive compounds from plants have promising potential to be used against many viruses or as prophylactic natural products (Denaro et al., 2020). Akram et al. (2018) pointed to the antiviral effects of various medicinal plants that could exert a tremendous role in inhibiting viral growth. Vellingiri et al. (2020) supposed that these plants' therapeutic derivatives would contribute to viral infection control, and the lack of proper documentation is a significant reason for the little usage of these natural medications over time. Research on these herbs and medicinal plants may help promote their biotechnological and therapeutic applications to prevent and defeat various pathogens and diseases. The traditional Chinese medicinal plants also have been

proved to contain valuable bioactive substances that could be used as natural drugs against multiple diseases with or without minimal side-effects (Qamar et al., 2019). Dhama et al. (2018) attributed the antiviral mechanism of phytochemicals of medicinal plants to the inhibition of viral entry, protein expression, and viral genome replication, in addition to the interference with transcription and confusion of the assembly of the virus particles and their release from the infected cell. Therefore, a further configuration of these phytochemicals' interrelation with the possible inhibition of the COVID-19 is essential.

Soltan and Zaki (2009) performed an antiviral screening bioassay for 42 medicinal plants in Egypt. Their results confirmed that some plant species had high antiviral potential against the poliovirus. They attributed their antiviral potentialities to the presence of some phytochemicals such as a high quantity of essential oil and tannins in *Achillea fragrantissima*, methoxyflavones in *Jasonia montana*, and iridoid glucosides in *Globularia arabica*. Excitingly, out of 200 herbs screened for their antiviral effect, four possible potent herbal extracts (*Lycoris radiata*, *Pyrrosia lingua*, *Artemisia annua*, and *Lindera aggregate*) exhibited EC_{50} values between 2.4±0.2 and 88.2±7.7 μg/ml. Of the four plants, *Lycoris radiata* was the most potent herb (The EC_{50} values of inhibition are 2.4±0.2); also lycorine was identified as the active inhibitory constituent (Li et al., 2005). Lycorine expressed a viral replication inhibitory effect against the Zika virus (ZIKV) by acting as RdRp inhibitor (Chen et al., 2020) and Human enterovirus 71 (EV71) by blocking viral polyprotein elongation during the translation process (Liu et al., 2011). This indicates that lycorine could be a SARS-COV-2 inhibitor, but further investigations should be done to understand its mechanism of action and how it interacts with coronavirus.

Erythrina speciosa, a flowering tree that belongs to the family Fabaceae, is mainly disseminated in tropical and subtropical areas. The antiviral activities of *E. speciosa* and its constituents were investigated where vitexin showed *in vitro* inhibitory potentialities against HSV and Hepatitis A Virus (HAV). Besides, they applied the molecular docking approach to explore the mode of action of vitexin where it could settle in the binding pocket of HSV-1 thymidine kinase and HAV 3C proteinase with a binding energy of -7.83 and -7.55, respectively. They also detected the polar and nonpolar sites as well as the maximum number of hydrogen bonding in the case of HAV 3C proteinase (Fahmy et al., 2020).

Balanites aegyptiaca (common name: Desert date) is distributed in Africa and South Asia and belongs to the family Zygophyllaceae (Hall, 1992); its bark's aqueous extract was used in the treatment of both AIDS and HIV. It was proven that an oral administration of the aqueous extract had shown excellent results for the treatment of

HIV patients (Hamid, 2001). It also showed significant anti-hepatitis C virus (HCV) activity; this was attributed to the effect of the extract on the viral entry either by direct interaction with viral particles itself or blocking the viral receptors on the cell line (Chothani and Vaghasiya, 2011).

Allium sativum L. (common name: Garlic) is an aromatic herbaceous plant and extensively used as a spice for Egyptian cooking purposes. It is also used as a traditional medicine from ancient times. Bulbs of *A. sativum* are stated to encompass many valuable phytochemicals, including sulfur-containing compounds (El-Saber Batiha et al., 2020; Mathew and Biju, 2008) such as allicin (diallyl thiosulfinate) [S-(2-propenyl)-2-propene-1-sulfinothioate]. It is considered the most active compound of garlic, and is responsible for its smell and taste. It has been reported that garlic extracts had antiviral activity against many kinds of viruses, including influenza B, Parainfluenza virus type 3, human rhinovirus type 2, herpes simplex type 1&2, and human cytomegalovirus (HCMV) (Gruhlke et al., 2016). Sawai et al. confirmed that the garlic extract exhibited antiviral and protective activity against influenza viruses by improving the production of neutralizing antibodies *in vivo* experiments when given to mice; they attributed these gleaming abilities to the presence of many vital phytochemicals, the most notable are allicin and ajoene. The main reason for the ajoene's antiviral activity is the anticipation of adhesive interaction and leukocytes' fusion (Sawai et al., 2008). Meanwhile, allicin interaction with the thiol-containing proteins may be the reason for its antiviral potentiality (El-Saber Batiha et al., 2020; Zhen et al., 2006). As the ACE2 is the receptor for SARS-CoV-2 to enter the healthy cells, and the viral spike proteins have to interact with ACE2 to initiate its replication cycle; there are many cysteine residues in the binding domain of the viral S proteins and ACE2, which may offer active sites for the allicin to act, and this can reduce the attachment of the COVID-19 to the ACE 2. It may also act as a ligand for the SARS-CoV-2 $3CL^{pro}$, which is essential for viral replication (Lobo-Galo et al., 2020).

Syzygium (S.) aromaticum (common name: clove) belongs to the family Myrtaceae. It has many active compounds, such as phenolic compounds (mainly eugenol, the major bioactive molecule) and gallic acid derivatives (Batiha et al., 2019; Cortes-Rojas et al., 2014). The antiviral, anti-inflammatory, antioxidant, and anticancer activities of eugenol were evaluated by Han and Parker (2017). Previous studies proved the antiviral efficacy of the aqueous extracts of S*. aromaticum* against influenza A virus (IAV) and HSV-1 combined with the acyclovir (Batiha et al., 2020a). The primary mechanism of eugenol against HSV-1 and HSV-2 is by inhibiting viral replication and, consequently, reducing the viral infection (Reichling et al., 2009). Khalil et al. (2019) also evaluated the anti-influenza A virus potentiality of *Psidium guajava* (common name: Guava), a plant from Myrtaceae, which is widely distributed in tropical and subtropical regions of the world. They performed their experiments on the

plant's flowers and green leaves; their results proved that the Guava extracts exhibited a stimulatory effect of pro-apoptotic signaling, including P53, IL-1β, and IL-8 improve the cellular immune response. Consequently, this could cause inhibition of the IAV replication because IAV stimulates Akt/protein kinase (Protein kinase B) signaling and the inhibition of p53 signaling cascades at the early stage of infection to guarantee viral replication. This evidence could be helpful in the case of COVID-19. It has also been mentioned that the Akt was dephosphorylated 18 h after infection in SARS-CoV infected Vero E6 cells, attributing this to the M protein expression. It might be possible that M expression leads to Akt dephosphorylation, so stimulation of Akt/protein kinase signaling might control the viral infection (Mizutani et al., 2004); it would be the same for COVID-19.

Cistus incanus (Ci) (Pink Rockrose, family: Cistaceae, order: Malvales) is mainly distributed in Mediterranean regions of Southern Europe and North. It has a high amount of polyphenols (Riehle et al., 2014), and its extracts have been demonstrated to have antioxidant, anti-inflammatory, antiviral, and antibacterial activities (Wittpahl et al., 2015). Rebensburg et al. (2016) performed a comprehensive study that revealed the antiviral activities of Ci against HIV and Filoviruses. Their results proved that Ci extracts possessed a broad inhibitory activity against different HIV isolates and the Ebola virus. They also demonstrated that the mode-of-action mainly targets viral envelope proteins by preventing the virus's primary attachment to host cells (Rebensburg et al., 2016).

Cynaropicrin, a guaianolide, has biological activities mainly due to the presence of the g-butyrolactone (Elsebai et al., 2016b). This natural compound has anti-inflammatory properties by suppressing the transcription activity of NF-κB (Li et al., 2019b). Elsebai et al. (2016b) evaluated the antiviral efficacy of the aqueous leaf extracts of *Cynara scolymus* (the wild Egyptian artichoke) with a high content of sesquiterpene lactones, in particular cynaropicrin, which is responsible for its bitter taste of artichoke. Their results disclosed the effectiveness of cynaropicrin against HCV as it acts by preventing the viral entry into target cells but not affecting the viral replication (Elsebai et al., 2016a).

Quercetin (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4-Hchromen-4-one)), is the most extensively investigated flavonol. It can be found in some fruits and vegetables, such as *S. aromaticum* (Clove) (Batiha et al., 2020a), *Brassica oleracea* (Broccoli), *Piper nigrum* (Pepper), *Allium cepa* (Onions), *Malus domestica* (Apple), which are a prevalent food in Egypt (Batiha et al., 2020b). Quercetin has many pharmacological activities, including anticancer, antiviral, anti-inflammatory, and much more (Dabeek and Marra, 2019). Moreover, it has been reported that quercetin can suppress HCV and the dengue virus type-2 (DENV-2); this suppressive ability was attributed to the inhibition of the non-structural protein 3 protease activity (Batiha et al., 2020b; Zandi et al., 2011). *Epimedium koreanum* Nakai (Berberidaceae) is an evergreen flowering plant, and its aerial parts have been broadly used in folk Korean and Chinese medicine (Cho et al., 2012). Cho et al. (2015) revealed that the aqueous extract of this plant induced antiviral activities against Influenza A subtypes (H1N1, H5N2, H7N3, and H9N2) *in vivo*, and also HSV and VSV *in vitro*, via secretion of type I IFN. The possible mechanism of quercetin against the HSV was declared by Hung et al. (2015); they suggested that it is mainly by blocking viral binding and penetration to the host cell. They also reported that quercetin inhibits NF-κB activation, critical for HSV gene expression.

Another interesting study evaluated the anti-HSV-1 activity of the fruit chloroform extract of the flowering plant *Quercus brantii* Lindl. Their results verified that this extract had a high amount of condensed tannins, which exert a potent inhibitory effect (IC_{50} 2.9 µg/ml), they attributed that due to their ability to prevent the viral entry (Karimi et al., 2017). Arunkumar and Rajarajan (2018) performed a bioactivity-guided fractionation for the ethanolic extract of the fruit peel of *Punica granatum* L., where the main bioactive compound isolated was the punicalagin (PUG), which exerted a surprising result by 100% anti-HSV-2 activity at 31.25 µg/ml. Of course, this gleaming result requires more research to reach the exact mechanism of action.

Isatis indigotica (family: Cruciferae) extracts have anti-inflammatory (Ho and Chang, 2002), anti-influenza (Liang et al., 2020; Yang et al., 2013), and anti-Japanese encephalitis virus (JEV) (Chang et al., 2012) properties. In an *in vitro* assay by Hsuan et al. (2009), they proved its antiviral activity against swine pseudorabies virus (PrV), which causes a fatal disease called Aujeszky's disease in swine (Mettenleiter, 2008). Intriguingly, Lin et al. (2005) certified that this potent antiviral activity is attributed to the extract's bioactive compounds, including sinigrin, aloe-emodin, hesperetin, indigo, and β-sitosterol, which which could block SARS-$3CL^{pro}$. Also, they proved that indirubin, a bioactive compound of *I. indigotica,* exhibited the most significant inhibitory effect on PrV replication, where the IC_{50} values of leaves and root extracts on the virus replication were about 99 and 156 µg/ml, respectively (Hsuan et al., 2009). These studies suggest that these extracts are capable of boosting the immune response along with blocking $3CL^{pro}$ activity and thus could be a potent remedy against SARS-CoV-2.

Acacia nilotica is a tree from the family Fabaceae; it owns antiviral effects against many RNA viruses. The antiviral ability of aqueous extract of its leaves (concentrations from 3.125 to 100 g/ml) and pods (concentrations ranging from 12.5 to 100 g/ml) was demonstrated against Peste des petits ruminants virus, and this was attributed to the presence of some bioactive compounds such as polyphenols, saponins, alkaloids, terpenoids, flavonoids, and tannins (Raheel et al., 2013).

Notably, the family Fabaceae involves many plants (*E. speciose*, *A. nilotica*, and *A. linearis*) that possess various antiviral-related activities against several viral strains, so we do recommend the screening of other Fabaceae plants against COVID-19 and other coronaviruses. *Tanacetum vulgare,* an herbaceous plant, mainly grows in the temperate regions of Europe, Asia, and North Africa. Vilhelmova et al. evaluated this plant's antiviral effect against three types of viruses, which are coxsackievirus B1, HSV-1 (selective index of 7.07), and IAV. They disclosed that the crude aqueous ethanolic extract from aerial parts of this plant had an antiviral ability via interacting with the virus's capsid and supercapsid proteins, thus changing its structure and preventing its cellular entry. Moreover, their flavonoids might interact with the viral neuraminidase that has an essential role in the spread and release of the virus progeny (Vilhelmova et al., 2020).

Desert plants are a treasure of valuable phytochemicals, a cheap source of medicine for local communities. *Alhagi maurorum* (family Fabaceae) is used in folk medicine as a purgative, diaphoretic, expectorant, and diuretic *Calophyllum lanigerum* is a flowering plant that belongs to the family Calophyllaceae and is mainly distributed in Asia. It showed antiviral activity against HIV by inhibiting the viral reverse transcriptase enzyme by its interaction with the bioactive compound calanolide A. Similarly, *Scutellaria baicalensis* was proven to have a flavonoid (Baicalin), which exerted the inhibition effect on the viral reverse transcriptase enzyme and suppressed viral replication (Kitazato et al., 2007). A recent study was done on roots of *S. baicalensis* because of their efficacy to treat viral infection symptoms, their broad antiviral spectrum, in addition to their extensive usage for hemostasis, detoxification, and heat-clearing (Liu et al., 2020). Thus, the plant extract's ability, baicalein, a bioactive constituent, and analog flavonoids against SARS-CoV-2 $3CL^{pro}$ were assessed. This study demonstrated the powerful capability of baicalein to block SARS-CoV-2 $3CL^{pro}$ with higher activity than the plant crude extract, and both affected viral replication in vero cells.

In other studies, baicalein showed a virucidal activity against JEV (Johari et al., 2012) and DENV-2 (Zandi et al., 2012) replication with a significant anti-adsorption effect. Thereby, we suggest that baicalein and its analogs might be a promising treatment for this novel coronavirus. However, further studies are needed to illustrate molecular and cellular mechanism(s) of action and evaluate its effect *in vivo*. A wild plant that belongs to the family Fabaceae is called *Retama raetam* (Forssk). It is common to the North and East Mediterranean region. Edziri et al. (2008) screened the antiviral activities of flower extracts of *R. raetam* against HCMV and coxsackie B virus type 3 (CVB3). They demonstrated that all extracts contain polyphenols, flavonoids, and tannins. Upon these results, *R. raetam* flower extracts were recommended to be manifested as an antiviral agent for COVID-19.

CONCLUSION

Our world has many challenges and conflicts. During the past years, there were emerging problems regarding the microorganisms' ability to resist our medications, including bacteria and viruses. We are currently facing one of the most resistant viral species, namely SARS-CoV-2, with its high ability to spread and infect. This microorganism resistance pushes scientists and researchers to seek other alternatives as a primary intention. Natural medicines exhibit a crucial inevitable role in treating various diseases and alleviating symptoms. It was concluded that there are many mechanisms by which medicinal herbs can exert their antiviral activity ranging from viral entry to viral replication and host signaling pathways. Some plants might prevent SARS-CoV-2 attachment to/or penetrate the host cell by inhibiting their binding to ACE-2 or interfering with spike protein. Others might target the structural/non-structural viral protein by affecting their expression, processing, or synthesis, such as inhibition of SARS-CoV-2 protein synthesis ($3CL^{pro}$ and RdRp). Many plants possess anti-inflammatory and antioxidant bioactivity, which act as an immune stimulant, boosting the host immune system against any infection. Keeping a proper diet will keep the body healthy and be safe against any future illness.

FUTURE PERSPECTIVE AND RECOMMENDATIONS

Owing to the gleaming importance of the medicinal plants and their auspicious abilities for prophylaxis from/treatment of COVID-19, our perception is the exploitation of these plants to elucidate each valuable compound, achieving a full understanding of the exact mode of action for fulfilling clinical needs. Consumers' growing awareness of healthy products would open the field to broaden these natural drugs. Fortunately, the fortification of food products with these natural substances would gain their attention. More economic and business studies are also needed to lower the financial cost to convoy the market needs. The existence of many plant-derived products with their antiviral capabilities through different mechanisms of action would be a promising drug for COVID-19. Therefore, we do recommend maintaining fruits and vegetables in our daily diets such as garlic, onions, orange, lemon, mandarin, pepper, broccoli, black and green tea, apple, cherry, grapes, cabbage, clove, ginger, and berries because of their broad recorded antiviral activity against many viruses through different mechanisms. Testing numerous herbal extracts on SARS-CoV-2 from other countries, whether Africa or any other origin, along with the use of

drugs to fight this novel virus, which would eventually speed up the recovery process is also profoundly recommended.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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