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Phytocompounds in the management of COVID-19: A review

K.P. Shamna, Malarvizhi Arthanari* and Muhammad Musthafa Poyil,◆**

Deseeya Ayurvedic Pharmaceuticals Ltd., Calicut-673 574, Kerala, India

** Department of Microbiology, Vivekanandha College of Arts and Sciences for Women, Tiruchengode-637205, India*

*** Department of Basic Medical Sciences, College of Medicine, Prince Sattam bin Abdulaziz University, Al-Kharj, 11942, Saudi Arabia*

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Abstract

The rapid spread of coronavirus disease 19 (COVID-19) has forced the need for the discovery of new antiviral agent or the development of new vaccine to fight against the pandemic disease, COVID-19 or SARS-CoV-2 (severe acute respiratory syndrome corona virus-2), owing to its high mortality rate worldwide. Therefore, medicinal plants are gaining much attention for human health for the period of pandemic situation because of the efficient activity, cost effectiveness and limited side effects. These plants or phytochemicals have been used for several decades to treat various emerging virus infections through the inhibiting the various drug targets. Consequently, the current evidence indicating those medicinal plants or herbs and their component have the potent antiviral activity against SARS-CoV-2. Therefore, this review summarises the important Indian as well as Chinese medicinal plants and their phytochemicals or extracts which have the potency to battle with SARS-CoV-2 along with deciphered mechanism of action. These medicinal plants served as alternative treatment choice for the treatment of COVID-19 disease during this overwhelming pandemic situation.

1. Introduction

The history was created not only by the humans but also by the microbes which causes pandemic diseases, resulting millions of deaths in the entire world. To this credit, since December 2019, the entire world has looking the new coronavirus which is the first virus causes pandemic disease, resulting serious socioeconomic interruption (Boukhatem and Setzer, 2020). ICTV (International Virus Taxonomy Committee) has classified the coronavirus belongs to the family of coronaviridae (Gorbalenya *et al*., 2020) which has a huge single stranded RNA in their structure (Zhang *et al*., 2020; Jo *et al*., 2020). In fact, SARS-CoV-2 was shared 96% genome similarity with bat related coronavirus (Zhou *et al*., 2020). This novel virus was primarily recognized in patients who are admitted with severe respiratory condition in Wuhan city, China (Huang *et al*., 2020). In 2020, the WHO (world health organization) announced this disease as COVID-19 (coronavirus disease 19) or SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) (WHO, 2020). Within short time, the virus has caused serious incidence owing to quick spreading nature along with high level of morbidity and mortality, this becomes pandemic worldwide (Xu *et al*., 2020; WHO, 2020b). The initial stage of COVID-19 developed fever, followed by other complications like headache, diarrhea, cough, muscle pain, *etc*., in some cases these complications leads to lethality (Chen *et al*., 2020). Still, the deaths occurred by COVID-19 was remains unclear because the difficulty in treating patients as well as varied procedure, followed by each and every country. This rapid spread and disastrous condition emphasized the importance of successful as well as reasonable antiviral agents against the alarming COVID-19 treatment. Consequently, many researchers have constantly struggled for searching the successful vaccines or drug candidates against SARS-CoV-2, resulting twelve coronavirus vaccines have been approved by various health authoritarian (WHO, 2021b; CDC, 2021). Initially, COVID-19 was treated using some important medicinal plants extracts to save human lives from the adverse effect caused by the virus. Keeping this point as priority in this review, we mainly focused on the phytochemicals or compounds for the treatment of coronavirus infection.

Since, several decades, the herbal medicines as well as some of the dietary material have been used to treat a variety of viral infection (Vellingiri *et al*., 2020; Khanna *et al*., 2020; Dudani and Saraogi, 2020) and believed that this concept may work and become an important treatment procedure for coronavirus infection (Ling, 2020; Kumar *et al*., 2020; Di Matteo *et al*., 2020). For this reason, in this review, we have collected the earlier information regarding the herbs, medicinal plants and phytochemicals which were used for the treatment of coronavirus infection and also, highlighted the possible use of medicinal plants and food dietary supplements in treating the corona viral infection.

2. Drug targets of SARS-CoV-2

The coronavirus RNA has the genes which code for its structural protein (spike glycoprotein) responsible for virus entry to the host cell and non structural proteins like 3-chymotrypsin-like protease, papain-like protease, RNA-dependent RNA polymerase and helicase are essential in viral reproduction (Romano *et al*., 2020). Therefore, these proteins are predicted as drug targets against SARS-CoV-2.

2.1 Inhibition of virus attachment and penetration

In general, the inhibitions of virus adherence to the host cell, followed by the penetration are the efficient method to control the viral infection. At this point, the coronavirus entry to the host cell was

Corresponding author: Dr. Muhammad Musthafa Poyil

Department of Basic Medical Sciences, College of Medicine, Prince Sattam Bin Abdulaziz University, Al-Kharj, 11942, Saudi Arabia

E-mail: pmusthu@gmail.com

Tel.: +96-6565634412

mediated through spike gycoprotein (S protein) by adherent to the host cell receptors like ACE2 (angiotensin-converting enzyme 2) and CD14, then the fusion occurred to membrane of the host ((Wan *et al*., 2020; Luan *et al*., 2020). The multifunctional molecule S protein is the main protein, primarily attached to the host cell receptors present on the cell surface of the host using the S1 subunit, followed by viral fusion with host cell membrane by the S2 subunit ((Wang *et al*., 2020). The S protein symbolizes the target for drug or vaccine development due to its crucial functions (Shang *et al*., 2020).

2.2 Inhibition of virus proteases

The catalytic function of proteases is to hydrolyse the peptide bond present in protein. The coronavirus proteases such as 3CLpro and PLpro are cysteine protease class which are responsible for virus replication (Zhang *et al*., 2020). These proteins are involved in the virus polyproteins synthesis as well as maturation and thus, become the drug target against SARS-CoV-2.

2.3 Inhibition of RNA-dependent RNA polymerase and RNA helicases

A non-structural protein, RNA-dependent RNA polymerase (main Mpro) represents as target for wide spectrum anti SARS-CoV-2 drug development. Similarly, helicases are involved in each and every aspects of nucleic acid metabolism and thus, becomes the drug target against SARS-CoV-2.

3. Phytochemicals for the management of COVID-19 infection

Natural bioactive compounds played a major role in drug discovery particularly medicinal plants have considered as probable source for new antimicrobial agents including anti-COVID-19 drugs (Zandi *et al*., 2021). In the developing countries, around 80% of population were relied on herbal medicines for their treatment purpose owing to cost effect and minimal side effects (Jain *et al*., 2019; Shaito *et al*., 2020). For example, the Indian herbs were used as treatment option as well as preventive measures in various respiratory viral illnesses and also traditional Chinese medicines have been used for several decades to treat various epidemic diseases in china (Vellingiri *et al*., 2020). Considering this, the innovation of successful preventing measures is urgent for the current pandemic situations which will able stop the prevalence of coronavirus infection. Keeping this in mind, initial step has to boost the immune system by following certain food supplement in sequence to protect the infection by themselves (Giménez *et al*., 2020; Food Agriculture Organization, 2020; Calder, 2020). Many Indian medicinal plants have been reported for their medicinal effect against SARS-CoV-2 (Divya *et al*., 2020).

Anyone can consume herbs in variety of forms like leaves of *Ocimum tenuiflorum* (tulsi), seeds of *Foeniculum vulgare* (fennel), *Phyllanthus emblica* (Indian gooseberry), leaves of *Azadirachta indica* (neem) are used as tea and some herbs were used in cooking like *Piper nigrum* (black pepper), *Zingiber officinale* (ginger), *Allium sativum* (garlic), *Coriandrum sativum* (coriander), *Curcuma longa* (turmeric), *Murraya koenigi* (curry leaves), *Cuminum cyminum* (cumin), *Syzygium aromaticum* (clove) as well as some of them were consumed with warm water such as *Cinnamomum verum* (cinnamon), *Cinnamomum verum* (lemon), *Mentha piperita* (peppermint) to boost the immune system to fight against various viral infection (Vellingiri *et al*., 2020). Similarly, Rukaiya *et al*. (2022) studied the trikadu formulation for immune booster against COVID-19. Few of the medicines from Indian herbal origin were demonstrated for their anti-COVID-19 activity using docking analysis (Umesh *et al*., 2020). Twenty different compounds from Glycyrrhiza were investigated for their antiviral activity against spike glycoprotein using molecular docking analysis. Among them, Glyasperin A had a high affinity towards the protein, thereby virus entry was inhibited (Gupta *et al*., 2020; Sinha *et al*., 2020). One of the drug targets of SARS-COV-2 is papain like protease breaks the polyproteins which are needed for replication and survival. Library of Indian herbal medicines which were present in the root of the ginger, curcumin tested against SARS -CoV-2 using *in silico* molecular analysis and found that eight compounds from ginger showed the binding affinity towards the SARS-CoV-2 (Goswami *et al*., 2020). Fortunately, curcumin also inhibit the omicron which is variant (Anish *et al*., 2022).

Anamul *et al*. (2022) studied antiviral activity of various compounds present in *Artemisia herba-alba Asso* were investigated against SARS-CoV-2 using *in silico* analysis. The compounds 4,5-di-O-caffeoylquinic acid, schaftoside and rutin were found to have highest binding affinity to Mpro of SARS-CoV-2. Ethanolic extract of some important medicinal plants such as *Trichosanthes cucumerina* L., *Polygonum multiflorum* Thunb, *Glycyrrhiza radix, Psoralea corylifolia, Mollugo cerviana, Salvia miltiorrhiza* and *Rheum officinale* Baill were showed the anti-SARS-CoV-2 activity (Boukhatem and Setzer, 2020; Alagu Lakshmi *et al*., 2020). The herbal medicinal compounds, namely; allicin and allin isolated from garlic showed the inhibiting ability of COVID-19 through down regulating the protease which is responsible for viral replication. Every day garlic intake reduces the side effect of the daily used drug (Sucheta *et al*., 2020). Similar findings were obtained from Rathinavel *et al*. (2020) group stated that organosulfur compounds found in *Allium cepa* (onions) and *Allium sativum* (garlic) were showed the potent activity against COVID-19 by binding to drug target ACE2. Consequently, 6- gingerol from ginger (*Zingiber officinale)* was screened against SARS-CoV-2 and found that highest binding was obtained with the main protease 5R7Y, thereby replication was inhibited (Rathinavel *et al*. 2020).

3-chymotrypsinlike protease is the drug target for fighting against COVID-19. A series of terpenoids and alkaloids obtained from African plants were screened against SARS-COV-2 using bioinformatics tools and showed the drug likeliness towards the COVID-19 (Gyebi *et al*., 2020). The polyphenolic compound isolated from green tea as well as withanolides recognized from *W. somnifera* were exhibited the Mpro inhibition in SARS-CoV-2 infection using the docking analysis (Ghosh *et al*., 2020; Tripathi *et al*., 2020). Similarly, *A. paniculata* suppressed the caspase molecules and NOD like receptor which is associated with SARS-CoV-2 pathogenisis (Liu *et al*., 2020a). The flavonoids isolated from various natural products like *Curcuma xanthoriza, Curcuma xanthoriza, Caesalpinia sappan* and *Alpinia galangal* were investigated for their ability to inhibit the SARS-CoV-2 and found that it was effectively inhibit the ACE2 (Utomo *et al*., 2020).

The important phytocannabinoid, namely; cannabidiol was identified from *Canabis sativa* from Asian countries tested against SARS-CoV-2. The compound was able to down regulate the angiotensin converting enzyme ACE2 expression resulting reduction in the COVID-19 severity (da Silva *et al*., 2020). Another team from Canada extracted the more than 800 *C. sativa* extract with more content of cannabidiol

which was down regulated the important protein, serine protease required for viral entry into the host cell (Mabou *et al*., 2020). Similarly, two alkaloids, namely, cryptoquindoline and hydroxyusambarensine were identified in African medicinal plant exhibited the inhibitory activity against SARS-CoV-2 by inhibiting the Mpro (Gyebi *et al*., 2020). In the same way, another alkaloid compound was found to be active against the SARS-CoV-2 (Colson *et al*., 2020). Moreover, some researchers investigated the antiviral activity of flavonoids identified from medicinal plants such as quercetin, epigallocatechin-gallate, kaempferol, luteolin-7-glucoside, luteolin-7-glucoside, demethoxycurcumin, oleuropein, catechin, naringenin, zingerol, allicin and gingerol agains SARS-CoV-2 and exhibited the potent activity by inhibiting the Mpro (Khaerunnisa *et al*., 2020)

Likewise, Acharya *et al*. (2021) studied the anti-SARS-CoV-2 effect of coronil which containing triple herbal formulation (*Ocimum sanctum*, *Withania somnifera* and *Tinospora cordifolia*) using Zebra fish animal model and it was effectively protect the fish from viral pathogenesis by inhibiting the ACE2 spike protein. The same group have investigated the withaferin A and withanone compounds were identified in *Withania somnifera* evaluated for its antiviral activity against COVID-19 using zebra fish animal model. The compounds were able to protect the fish from the adverse effect of SARS-CoV-2 infection by binding to ACE2 receptor thereby inhibition in virus entry to the host cell (Acharya *et al*., 2021). Rhea *et al*. (2020) studied antiviral activity of four Indian herbal compounds were isolated from *Curcuma xanthorrhiza*, *Cinchona*, *Echinacea purpurea* and *Curcuma longa* against SARS-CoV-2 and found to be active against the pandemic virus by down regulating the ACE2 receptor spike protein leads to inhibition of virus entry to host cell. Similarly, fifteen herbal compounds were active against COVID-19 viral disease at concentrations between 0.1 nM to 50 nM using enzymatic assays. The compounds have the ability to bind the drug targets of 3CL protease and RNA polymerase of the virus. Based on this evidence, compounds nelfinavir, mefloquine and the plant extracts from *Mentha haplocalyx*, *Ganoderma lucidum* and *Perilla frutescens* were tested as anti-SARS-CoV-2 agent using hamster disease model and it showed the potent activity (Jia *et al*., 2021).

Attallah *et al*. (2021) studied the antiviral activity of ethanolic extract of *Agrimonia pilosa* against COVID-19 revealed the potent virucidal as well as immunomodulatory activity between 1.1 to 0.03 g/ml concentration. The compounds were identified as flavonoids along with coumarin groups and these compounds exhibited potent activity in animal model.

Table 1: List of plant derived phytochemicals and their mode of action against SARS-CoV-2

Name of the plant	Name of the phytochemicals	Mode of action	References
Zingiber officinale	6-gingerol	Binding affinity towards 5R7Y	Rathinavel *et al*. (2020)
Psorothamnus arborescens	Isoflavone	3CLpro inhibition	Qamar *et al*. (2020)
Piper longum	Piperine, Eugenol	Binds to spike protein	Kiran *et al*. (2020)
Carica papaya, Andrographis paniculata Burm	Quercetin, Ursolic acid	Binds to spike protein	Kiran *et al*. (2020)
Allium sativum	Organosulfur	ACE2 inhibition	Rathinavel *et al*. (2020)
Thymus vulgaris	Ursolic acid	Binds to 6LU7 and 6Y2E proteases	Sampangi *et al*. (2020)
Coriandrum sativum	Coriandrin	Binds to 6LU7 and 6Y2E proteases	Sampangi *et al*. (2020)
Rosmarinus officinalis	Rosmarinic acid	Binds to 6LU7 and 6Y2E proteases	Sampangi *et al*. (2020)
Brassica juncea	Glucobrassicin	Binds to 6LU7 and 6Y2E proteases	Sampangi *et al*. (2020)
Leucas zeylanica	Azetidin-2-one 3, 3-dimethyl-4-(1-aminoethyl, lorazepam and 11-oxa- dispiroundecan-1-ol	Binding to Mpro	Dutta *et al*. (2021)
Agrimonia pilosa	Glycyrrhizin	Binds to Mpro	Rehman *et al*. (2021)
Mentha haplocalyx, *Ganoderma lucidum* and *Perilla frutescens*	Nelfinavir, mefloquine	Bind to drug targets of 3CL protease and RNA polymerase	Jia *et al*. (2021)
Curcuma longa	Curcumin	Binds to ACE2 receptor	Rhea *et al*. (2020)
Ocimum sanctum, *Withania somnifera* and *Tinospora cordifolia*	Coronil	Inhibiting the ACE2 spike protein	Acharya *et al*. (2021)
African medicinal plant	Cryptoquindoline and Hydroxyusambarensine	Inhibiting Mpro	Gyebi *et al*. (2020)
Canabis sativa	Cannabidiol	Inhibiting ACE2 receptor	da Silva *et al*. (2020)
Green tea	Polyphenolic compound	Mpro inhibition	Ghosh *et al*. (2020)
Artemisia herba-alba Asso	4,5-di-O-caffeoylquinic acid, schaftoside and rutin	Binding affinity to Mpro	Anamul *et al*. (2022)

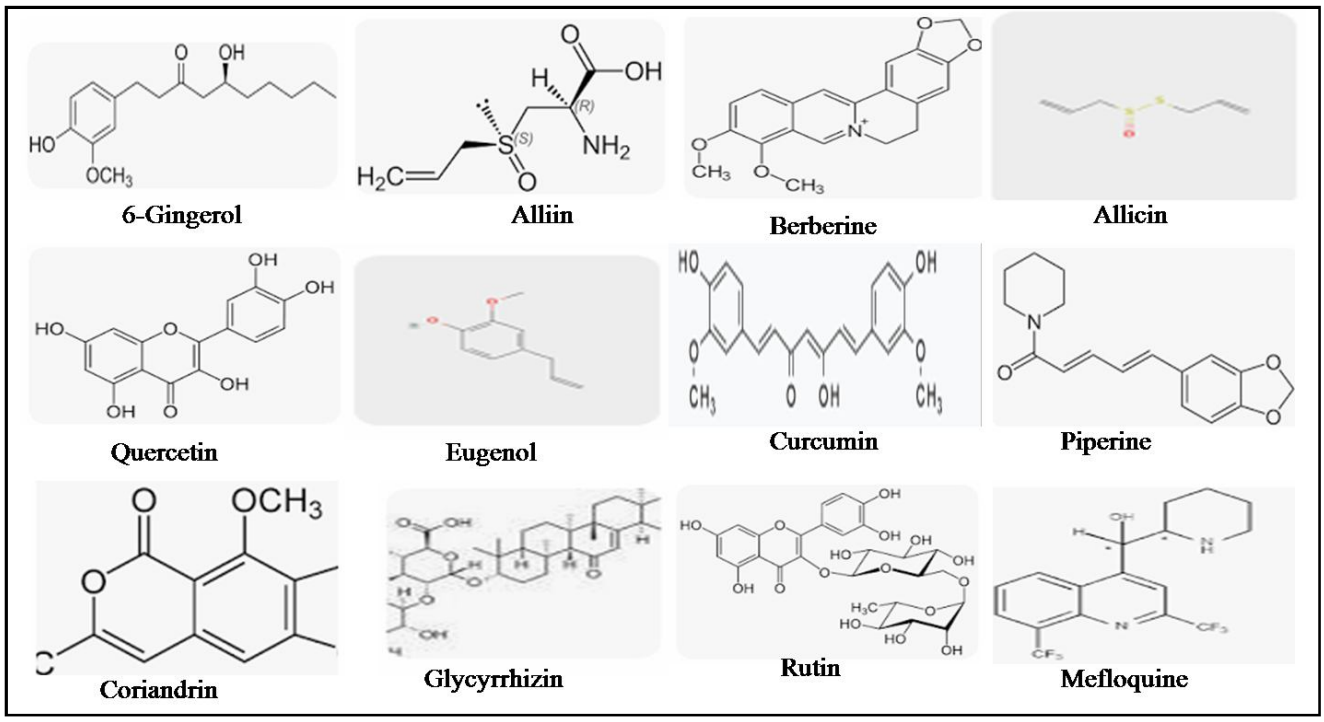

Figure 1: Chemical structure of some important plant derived phytochemicals.

Likewise, secondary metabolites like flavonoids, alkaloids, steroids and coumarins identified from medicinal plants were screened against SARS-CoV-2 using docking analysis to find the drug targets. The compound like glycyrrhizin and their metabolites were effectively binds to Mpro where as baicalin, a flavonoid was also effectively binds to RdRp (Rehman *et al*., 2021). Dutta *et al*. (2021) studied the antiviral potency of azetidin-2-one 3,3-dimethyl-4-(1-aminoethyl, lorazepam and 11-oxa-dispiroundecan-1-ol recognized in *Leucas zeylanica* were tested against SARS-CoV-2 and these compounds were able to show the binding affinity towards the Mpro. Similarly, the compounds isoquercetin, 7-hydroxyaloin B, MS 3 and 10-hydroxyaloin A were tested against the drug targets of SARS-CoV-2 using molecular docking analysis. The 10-hydroxyaloin A and isoquercetin were efficiently bound to spike protein and Mpro (Kushwaha *et al*., 2021). The plant derived secondary metabolites play a vital role in the development of antiviral agent against COVID 13 (Yashika *et al*., 2022).

The inhibitory as well as anti-inflammatory effects of Chinese herbal mixture named lianhuaqingwen which contains cluster of eleven important medicinal spices along with two minor compound was studied COVID-19 using Vero E6 cell line. The antiviral activity of the Chinese herbal mixture showed the activity in dose dependent manner and it also exhibited the anti-inflammatory activity (Runfeng *et al*., 2020). Fortunately, this herbal combination was approved by the Chinese national health commission for the coronavirus infection (Yang *et al*., 2020). Another group studied the activity of phytochemicals from Chinese plants against COVID-19 virus and the compound isoflavone (5, 7, 32, 42-tetrahydroxy-22-(3,3-dimethylallyl) from *Psorothamnus arborescens* exhibited the highest binding affinity to 3CL protein of SARS-CoV-2 (Qamar *et al*. 2020). Figure 1 and Table 1 summarizes some important plant derived phytochemicals used for the treatment of COVID-19.

4. Conclusion

The extensive quantity of research indicating that the phytochemical isolated from the medicinal plants and also their extracts that are believed as therapeutic agent for the treatment of dangerous pandemic disease COVID-19. Several compounds like flavonoids (zingerol, allicin and gingerol), alkaloids, *etc*., have the ability to down regulating the drug targets such as spike protein, Mpro, *etc*., resulting inhibition of virus entry, adsorption, penetration and pathogenesis of SARS-CoV-2. These result suggested that, these studies have to implement more preclinical as well as clinical trials to clarify the efficacy of the potential phytochemicals against SARS-CoV-2. Moreover, this review gives the information to the researchers and clinicians to understand the potential of medicinal plants for the efficient treatment against dangerous pandemic disease SARS-CoV-2.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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