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Exploiting the promising therapeutic potential of plant phytoconstituents to combat COVID-19: A review

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Abstract

COVID-19, a word that became one of the commonest in the recent couple of years, rooted from the COVID-19 pandemic. The world faced and is still facing one of the biggest threats to mankind. Several attempts have been undertaken to combat this pandemic and one promising attempts among them are the use of phytochemicals against the SARS-CoV-2. Phytochemicals with limited or no side effects are recently gaining more importance as an alternative therapeutic and pharmacological agent in drug discovery and development.The diversely available bioactive compounds from a variety of plants and herbs are being extensively studied to bring an effective solution to overcome this unending occurrence of the COVID-19 virus. In that regard, this review aims to present the information about various phytoconstituents from a wide range of plants being studied for its potential antiviral properties against SARS-COV-2, so as to find an effective and promising therapeutic strategy to fight the pandemic.

1. Introduction

An unforgettable pandemic, the COVID-19 pandemic which commenced in the year of December 2019 and exploded all over the world in a very short course of time was caused by the zoonotic virus SARS-COV-2 (severe acute respiratory syndrome coronavirus-2). The virus which was originally named 2019-nCoV, was later named “Severe Acute Respiratory Syndrome Coronavirus 2” (Gorbalenya *et al*., 2020), the new novel coronavirus on the 11th of February 2020 by the International Committee on Taxonomy of viruses. It is believed to have originated and rapidly spread from Wuhan, China but it’s origin is still a mystery (Boni *et al.,* 2020; Pooladanda *et al*., 2020). As per the recent records of April 15, 2022, globally more than 503 million cases and 6.2 million deaths were reported due to this infection. Along with the healthcare system, there seemed to be a lot of changes in the normal lifestyle and habits of almost every individual around the world. The pandemic had a drastic impact on the social status of the world’s population and has also hampered economic growth of the all the countries (Ratten, 2020; Barau, 2020). COVID-19, is recognized as a communicable disease leading to mild to deadly respiratory illness. Individuals at almost all ages are at risk but pollution, hypertension, diabetes mellitus and cardiovascular diseases, are some of the factors that increase the risk of infection. The beginning of the infection has milder symptoms as in normal common cold, but in a course of time it leads to adverse conditions associated with fever, dry cough, fatigue and shortness of breath (Wu *et al*., 2020; Wang *et al*., 2020; Ogen *et al*., 2020; Onder *et al*., 2020). Several variants were identified throughout the pandemic since the first case of infection due to the rapid mutations taken up by the virus and each variant was designated with Greek letters like alpha, beta, gamma, delta, omicron, lambda, mu by the World Health Organization (WHO). The SARS-CoV-2 of the genus beta coronavirus is an enveloped virus with a positive-sense, single stranded RNA genome within it and has 79.5% sequence matching with SARS-CoV, both belonging to the Coronaviridae family of Nidovirales order. Among all the viruses in coronaviridae, SARS-CoV-2 seem to be the most severe one. The transmission rate of SARS-CoV-2 is much greater than that of SARS-CoV. The virus consists of three structural proteins in the envelope, the envelope protein (€) involved in packaging of virus, the membrane protein (M) which is a transmembrane glycoprotein that help in capsid development and the spike protein (S) that help in the viral entry into host. The other structural protein is the nucleocapsid protein present in the nucleocapsid (N) that surround the viral genome which in turn is shelled by the envelope outside (Naqvi *et al*., 2020). Some specific human proteins that are majorly present in the inner lining of the nose and the lung cells are recognised by the surface spike glycoproteins, and hence considered the most important part of SARS-CoV-2 which gives the crown like appearance to the virus (Hendaus and Jomha, 2020). Thus, these interactions lead to the configuration in the shape of spike glycoprotein resulting in the engulfment of virus by the human receptor cells. Once it enters the human cell, it undergoes reverse transcription and finally replicating itself with the cells. It then gains the ability to infect the neighbouring cells and tissues majorly damaging the cells of brain, heart, lungs and many other organs (Chowdhury, 2020).

Except for quarantine and symptomatic treatment protocol, there had been no clue to specifically treat this deadly infectious disease.

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Some therapeutic options that were followed later to combat Covid-19 globally included the monoclonal antibodies, drugs that had antimalarial, anthelmintic, antiviral and antibacterial properties, mesenchymal stem cells (MSCs), antiviral interferons, amniotic fluid cells and the convalescent plasma therapy (Pooladanda *et al*., 2020 ; Gupta *et al*., 2021), but still a definitive treatment for COVID-19 does not exist. As only limited clinically/FDA approved drugs, and a very few number of significantly effective vaccines are available recently against COVID-19, the highly virulent SARS-CoV-2, made it a must to come up with other effective therapeutic agents to overcome the pandemic, and thus every possible solution was explored. In that regard, researchers found various bioactive phytochemicals from plants to be more relevant long-term solution since it was more safer for the population with relatively lesser side effects compared to the other available drugs, and hence were studied extensively and proven to be promising therapeutic antiviral agents. It efficiently either has an inhibitory action on the viral replication or viral entry mechanism, also treat the infections that are underlying, caused by SARS-CoV-2 and thereby exploitation of these functions can be implemented in management of COVID-19 pandemic (Gyawali *et al*., 2020; Gurung *et al*., 2020; Parida *et al*., 2020). This review is hence focused on the potential phytochemicals against SARS-COV-2 playing a role at molecular levels, thus leading to a more safer and innovative treatment to combat COVID-19.

2. Mechanism of entry of virus

Since the external environment is directly in contact with the respiratory tract, the host cells present there are the primary and prominent entry portal for the engulfment of the virus within the cells (Matrosovich *et al.,* 2004). Once it gains entry through the mucus membranes, the receptor ACE2 protein, type 2 transmembrane serine protease (TMPRSS2) Z, and lysosomes protease (cathepsins) present in the host cells facilitate the entry of virus into the cells (Zhang *et al*., 2021). On entering the cell, the viral particle gets into the endosomes after which it results in the fusion of the viral membrane and the lysosomal membrane. The spike protein of the virus consists of two subunits, namely; S1 and S2 subunits. The S2 unit is a trimeric membrane fusion stalk and holds S1 unit which three receptor-binding heads. The receptor-binding domain (RBD) of the S1 subunit is recognized by it's receptor, the human angiotensin-converting enzyme-2 (hACE-2). This receptor is membrane-bound protein expressed in various human cells such as the renal tissue, vascular endothelium, intestinal epithelium, cardiovascular tissue and are found to be abundantly present in the lower portion of the respiratory tract (Zheng, 2020; Wang *et al*., 2020; Zou *et al.,* 2020). Once hACE-2 is recognised by S1, TMPRS S2 and lysosomal proteases (cathepsins) triggers the activation of SARS-CoV-2 spike protein where proteolysis occur at S1/S2 boundary making S1 dissociate from S2, thus leading to dramatic conformational changes in the segregated S2. Then, the ingression of virus is caused by the activation of the glycoprotein responsible for the viral entry into host cell. The viral proteins are synthesized by translating the uncoated RNA and new RNAs and the new virions are produced in the presence of RNA dependant RNA polymerase. Then, cell lysis take place and a load of new virions are released into the patient's body affecting all the neighbouring cells in vicinity (Walls *et al.,* 2020; Wang *et al.,* 2020).

3. Phytoconstituents-attractive alternatives against SARS-COV-2

Traditionally, a variety of medicinal plants and herbs are being used in the prevention, treatment and cure of several human health issues. The diversity in their bioactive components make them effective against different pathogens serving as potential therapeutic agents and also implemented in various other health applications. One among these important properties of the phytochemicals is their promising antiviral property where these constituents of plants fight against different stages of viral infections from its entry into the cell to the spread of infection. In that way, exploring the potentials of medicinal plants and their phytoconstituents, would bring in phytotherapy as an efficient lead to design and develop new novel alternatives against the threatening coronavirus. Several research studies reported a variety of phytochemicals medicinal plants extracts and herbs as potential anti-CoV agents. They are said to be effective against SARS-CoV-2 infection, and thus the future development of drugs from medicinal plant formulations, can efficiently help in control, prevention and cure of COVID-19 disease. A wide variety of phytoconstituents that fall under the following categories are being explored and studied for the treatment of COVID-19.

3.1 Flavonoids

Various flavonoids, the plant polyphenolic compounds are seen to have effective antiviral roles at the molecular levels such as preventing cell entry of virus by blocking the cell receptors and interfering the process of viral replication and translation, thus inhibiting the growth of virus. The metabolites, herbacetin, rhoifolin and pectolinarian were found to be against 3CL pro (Jo *et al*., 2019). The potential targets for flavonoids are the Mpro enzyme an important one helping in viral replication and translation and the ACE2 receptor that aid viral entry into the host cell. Studies reported that Mpro enzyme was inhibited by several flavonoids like azithromycin, mangiferin, elsamitrucin and procyanidin-β-2,7-dimethoxy flava N-42-O-β-D-glucopyranoside. Also, amentoflavone, hidrosmin, galloca the chingallate, diosmin, pectolinaren, quercetin and isoquercetin were against the Mproenzyme. Similarly, flavonoids including hesperetin, myricetin, linebacker and caflanone were seen to be effective against ACE-2 receptor (Ngwa *et al*., 2020; Chauhan and Karla, 2020). Another docking study showed that the flavonoids kaempferol, fisetin, quercetin, would serve as potential leads against the spike protein of SARS-CoV-2 (Pandey *et al*., 2020). Thus, various flavonoids can effectively act against SARS-COV 2.

3.2 Essential oils

Essential oils which are the volatile hydrophobic liquids extracted from plants are said to possess and exhibit their activity against a wide range of bacterial, fungal, and viral pathogens. It also has antioxidant and anti-inflammatory properties. Essential oil disrupts the viral envelope by readily interacting with the lipid bilayer of cell membrane made, thus being antiviral prior to the attachment of virus to host cells (Nadjib, 2020). There was a significant inhibitory activity against the ACE2 receptor shown by the essential oil component extracted from garlic (Thuy *et al*., 2020). The terpenes from cannabis were tested against COVID-19 where it inhibits viral replication and also prevents the entry of virus into host cell (Jahan and Onay,

2020). The highest number of compounds effective against Spro target were shown to be in essential oils from *V. zizanoides* (Torres Neto *et al*., 2021). Another study reported significant inhibition of spike glycoprotein-ACE2 interface by dithymoquinone from *Nigella sativa* and seemed to be effective than chloroquine.(Kulkarni *et al*., 2020). Thus, essential oils are one major group of phytochemicals that should to be well investigated to bring in new effective drugs against COVID-19 .

3.3 Alkaloids

Alkaloids, the basic nitrogen containing are organic compounds were found to be effective against viral replication. Some effective alkaloids with DNA interfering activity are resoquines anguinarine, quinine, chelidonine, cinchonine, isoquinoline, hartmine, coptisine, berberine, palmatin, tetradine and emetine, all of which could serve to be potential drug molecules (Jahan and Onay, 2020 ; Srivastava *et al*., 2020 ; Bleasel and Peterson, 2020). Around seventy-one compounds have been tested for their antiviral activity and among which , twenty-three were selected for molecular docking in relation to their pharmacokinetic and toxicity profiles. A number of potential inhibitors were the outcome of the tests. Out of seventy-one tested compounds 3 of them, namely; norquinadoline A, deoxytryptoquivaline and deoxynortryptoquivaline were reported to have effective binding towards ACE 2, the spike glycoprotein and SARS-CoV-2 main protease (Ismail *et al* , 2021).

3.4 Phenolic acids

Phenolics, the natural phenolic compounds that contain five or more hydroxyl groups are said to possess antiviral properties. Since most of the polyphenols are polar compounds that cannot cross the cell membrane, they are said to be effectively preventing the viral entry into host cells by binding to the viral protein on the viral envelope (Wink , 2020 ; Annunziata *et al*., 2020). Some polyphenols isolated from *Broussonetia papyrifera* such as broussochalcone A, papyriflavonol A, 32-(3-methylbut-2-enyl)-32,42,7-trihydroxy flavane, brousso flavan A, kazinol F, and kazinol J showed significant effects against the active site residues His 41 and Cys145 of the Mpro of SARS-CoV-2 (Park *et al*., 2017).

3.5 Stilbenes

Stilbenes are compounds that fall under the class of phytoalexins since their synthesis depends on the UV radiations. They are defensive naturally occurring phenolic components seen in grapes, berries and bark waste. Stilbenes are reported to disrupt the interface of S-ACE-2 receptor complex and hence inhibit the viral entry mechanism. Stilbenes which show antiviral properties are resveratrol, trans-resveratrol, piceatannol, pinosylvin and pterostilbene (Pandey *et al*., 2020 ; Wahedi *et al*., 2020). Among this, resveratrol is seen to be one of the important leads to design drug for COVID-19.

3.6 Anthraquinones

Anthraquinones, the natural aromatic compounds were seen to be effective against SARS-COV-2. Docking studies revealed that emodin, aloin A and B, rubiadin, aloe-emodin, pseudohypericin, damnacanthal, and chryosphanic inhibited the target Mpro of SARS-CoV-2 (Das *et al*., 2022; Khanal *et al*., 2020). Rhein and aloe-emodin from *Cassia fistula* were found to be effective against the main protease (7BZ5) of SARS-COV-2 (Dawood *et al*., 2021). In a study that screened nine anthraquinones, valrubicin and hyperic in were shown to be effective against spike protein while idarubicin and doxorubicin were the most effective against Mpro. Alsochrysophanol, aloesaponarin II, emodine, aloe-emodine, physcion and danthron were shown to be simultaneously effective against active sites of SARS-CoV-2 Mpro, spike and RdRp (elMazouri *et al*., 2021).

3.7 Saponins

The non-ionic detergents, saponins which are known for their cytotoxic properties against bacterial, fungal and viral pathogens (Kregiel *et al*., 2014). It can be one of the potential antivirals since it inhibits the viral particles by disrupting the viral envelope and capsid protein and also affect the viral particle binding to the host cells by interacting with host cell membrane, preventing the fusion, thus minimising the spread of infections. The efficient binding ability of glycyrrhizic acid at the interface of spike protein RBD and human ACE2 receptor make it an effective inhibitor of the virus (Bailly and Vergoten, 2020). GinsenosideRg12 from *Panax ginseng* and acankoreoside A from *Acanthopanax gracilistylus* was shown to be effective and better than hydroxy chloroquine, chloroquine and nelfinavir against COVID-19 Mpro (Rehan and Shafiullah, 2021). Saikosaponins, the triterpene saponin glycosides was reported to be effective against coronavirus HCoV-229E where the initial step of replication along with penetration and adsorption is interfered (Bahbah *et al*., 2020). Thus, more investigations in saponins can be made to develop another potential therapeutic agent against COVID-19.

3.8 Glycosides

Glycosides, the plant drived compounds are simple sugar molecules projecting different functional groups. Among them, the cardiac glycosides were reported to be effective against both DNA containing viruses and RNA containing viruses. Some of them include the cytomegalo virus, the herpes simplex virus, influenza virus and the coronavirus (Emamzadeh-Yazdi , 2013) where the host cell protein is targeted, and thus can be an efficient strategy to combat human viral infections (Wong *et al*., 2018). The GinsenosideRb1 that come under the class of steroid glycosides was shown to be effectively acting against SARS-CoV-2 (Islam *et al*., 2020).

3.9 Tannins

Tannins that are present in plants, wood, bark, fruits and seeds is believed to have an effective role in the antiviral therapy. Tannins being antioxidants are very effective against oxidative stress caused by the overproduction of free radicals in viral infections. (Sen *et al*., 2010). Persimmon-derived tannin is showed to both inactivate SARS-CoV-2 and also reduce its transmission (Furukawa *et al*., 2021). Another study showed that ellagic acid, arjunic acid, the asapogenol B, and euscaphic would be possible inhibitors of the Mpro enzyme. (Falade *et al*., 2021). Pedunculagin, tercatain, and castalinwere reported to interact with Cys145 and His 41 of 3CL pro where pedunculagin binding with the target was more effective (Khalifa *et al*., 2020). The gallotannin found in tea is shown to interfere with the activity of 3CLPro protease of coronavirus (Pandit and Singh, 2020).

Table 1: Phytoconstituents and their targets

S.No.	Compound	Source	Phytoconstituent	Target	Reference
1.	Alkaloids	*Strobilanthes cusia*	Tryptanthrin	Against CoV-NL63, alters structure of viral spike proteins.	Tsai *et al*., 2020
2.	Alkaloids	*Amaranthus tricolor*	Amaranthin	3CLpro inhibition	TahirUlQamar *et al*., 2020
3.	Alkaloids	*Piper nigru*	Moupinamide	Inhibition of PLpro	Mani *et al*., 2020
4.	Alkaloids	*Tinospora cordifolia*	Berberine	Interaction with protease	Srivastava *et al*., 2020
5.	Alkaloids	*Withania somnifera*	Anaferine	Targets NSP10, NSP16	Parida *et al*., 2020
6.	Alkaloids	*Withania somnifera*	Somniferine	Targets NSP15	Parida *et al*., 2020
7.	Flavaglines	*Algaria* sp.	Silvestrol	Against RNA helicase	Muller *et al*., 2018
8.	Flavonoids		Afzelin	3CLpro inhibition and also against ACE2	Antonio *et al*., 2020
9.	Flavonoids	*Citrus sinensis*	Naringenin	Mpro inhibition	Khaerunnisa *et al*., 2020
10.	Flavonoids	*Glycyrrhiza uralensis*	Licoleafol	3CLpro inhibition	TahirUlQamar *et al*., 2020
11.	Flavonoids	*Myrica cerifera*	Myricitrin	Inhibition of 3CLpro	TahirUlQamar *et al*., 2020
12.	Flavonoids	*Securigera securidaca*	Kaempferol	Inhibition of PLpro & 3CLpro	Khaerunnisa *et al*., 2020
13.	Flavonoids	*Silybum marianum*	Silybin	Agaisnt spike protein (TMPRSS2)	Pandit and Singh, 2020
14.	Flavonoids	*Withania somnifera*	Quercetin	Against PLpro and 3CLpro	Parida *et al*., 2020 Khaerunnisa *et al*., 2020
15.	Isoflavonoids	*Cicer arietinum*	Genistein	Blocks HSPA5	Elfiky, 2020
16.	Lactones	*Nigella sativa*	Limonin	Targets NSP16	Parida *et al*., 2020;
17.	Phenolic compounds	*Ecklonia cava*	Dieckol	Against 3CLpro	Park *et al*., 2013
18.	Phenolic compounds	*Punica granatum*	Punicalagin	Inhibition of ATP-induced IL-1β release	Tapia *et al*., 2019
19.	Phenolic compounds	*Camellia sinensis*	Theaflavin	Targets RdRp	Mani *et al*., 2020
20.	Phenolic compounds	*Zingiber officinale*	Gingerol	Targets main protease	Srivastava *et al*., 2020
21.	Phthalates	*Solanum nigrum*	Solvanol	Interaction with NSP16	Parida *et al*., 2020
22.	Steroidal compounds	*Withania somnifera*	Witha-stramonolide	Targets NSP12 D2	Parida *et al*., 2020
23.	Stilbenoids	*Vitis vinifera*	Resveratrol	Controlled expression of Toll-like receptor 3 (TLR3)	Zang *et al*., 2011
24.	Terpenoids	*Salvia miltiorrhiza*	Cryptotanshinone	Against 3CLpro and PLpro	Orhan and Senol Deniz, 2020
25.	Terpenoids	*Catharanthus roseus*	Vindolinine	Against NSP15	Parida *et al*., 2020
26.	Terpenoids	*Tinospora cordifolia*	Cordioside	Inhibition of main protease	Pandit and Singh, 2020

4. Conclusion

The adversely threatening conditions of COVID-19 seen all over the world and the unavailability of effective drugs, specific treatments and curative measures for COVID-19 till date are the major provoking factors for the researchers to search and explore possible alternatives to overcome the disease. In that regard, the bioactive components of the herbs and plants would definitely serve as potential leads in the development of a wide range of efficient therapeutic drugs against COVID-19 infection. Apart from its fast and wide usage, they are more advantageous and reliable due to their less toxic nature and are comparitively easy to develop. Further detailed *in vitro* and *in vivo*

evaluation should be done to assess the bioactivity of these phytoconstituents agaisnt SARS-CoV-2 activities. Several significant mechanisms and modes of action of these diversely available phytochemicals can definitely be exploited in developing promising and effective drugs to efficiently combat the prevailing threat.

Conflict of interest

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

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