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SHORT REVIEW

Common Medicinal Plants and their Role against COVID-19 for Protection and Treatment

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Abstract

COVID-19 is a deadly serious infectious disease caused by SARS-CoV-2, spreading widely with a rise in number of deaths every day. Because of the rapid transmission, various research domains have much responsibility to find a suitable drug or vaccine as soon as possible within a short time to save lives. Plant based chemical constituents serve as potential therapeutics against COVID-19, which is evident by current reports of screening phytochemicals against potential targets by computational techniques. Medicinal plants are used since ancient times and are known highly for their effective treatment of several infectious diseases. This review summarizes the use of medicinal plants to treat COVID-19 infection and aims to draw more attention towards investigating potent chemical constituents from medicinal plants.

Keywords: Antiviral, Phytochemicals, Secondary Metabolites, SARS-CoV-2

1. Introduction

As of 3rd December 2020, with over 64.5 million confirmed cases and 1.49 million deaths worldwide, the outburst of highly transmissible virus known as Coronavirus (COVID-19) has spread tremendously. The first viral infection was identified in October 2019 at Wuhan city, China. The primary symptoms identified were dry cough, sore throat, fever and shortness of breath and it was confirmed as Corona virus-2 (SARS-CoV-2).

SARS-CoV-2 belongs to the beta genus of Coronaviridae family, close to SARS-CoV and MERS-CoV, which evolved globally with a death rate of 10% and 36% in 2002 and 2012 respectively[1]. Usually, virus mutation is very fast and it was confirmed within a month that corona virus-2 was able to mutate rapidly. The genome and mutation rate over time is similar to SARS-CoV. The treatment approach for coronavirus is based on either the disruption of coronavirus or increasing resistance in human cell[2]. It can be achieved by measuring the antiviral efficacy of a wide variety of anti-viral drugs, interferon, and inhibitors such as cyclophilin used in the treatment of virus-induced pneumonia[3], high-throughput screening of many therapeutic molecules[4], design and characterization of valid vaccine or drug are quite essential[5]. Interferon plays a prime role in preventing viral replication by blocking the viral binding and replicating pathways of signals[6]. The SARS-CoV-2 spike protein can recognize the entry receptor for human angiotensin-converting enzyme II (ACE2) and infect the lung epithelial cells[7,8]. The spike protein receptor-binding domain binds to the ACE2 receptor. The host protease TMPRSS2 breaks the spike protein to expose fusion peptides and they are capable of merging the viral membrane and cell membranes[9]. The susceptibility of host cells to being infected dictates the cellular tropism of the virus which is determined in

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SARS-CoV-2 by the presence of the receptor necessary for the entry of the ACE2 receptor. In many human tissues ACE2 is expressed, with different symptoms arising from infection[10,11]. When a human cell is infected by SARS-CoV-2, the virion releases its RNA in the cytoplasm. Translation and replication occur and by exocytosis, new virions are then released from the cell[12].

2. Medicinal Plants

India is bestowed with rich biodiversity of fauna and flora. Usage of plant materials for prevention, management and treatment of various illness is common in Indian system of medicines like *Ayurveda, Siddha,* and *Unani*. The medicinal uses of plants have been documented in ancient *Vedas* and other scriptures. Later, *Ayurveda* developed between 2500 and 500 BC[13]. In Indian continent, plant products play a key role as pioneer sources of drugs[14]. India is very unique for its practice of traditional medicine and ethnomedicine. The traditional Indian medicinal formulations are multi-component blends whose therapeutic application is purely based on the scientific clinical evidence[15]. Medicinal plants have always played a pivotal role to overcome viral transmission causing diseases[16]. COVID-19 has made us realize the importance of herbal products in disease prevention. Ministry of AYUSH, Government of India has recommended many herbal based formulations as prevention or as control measures for COVID-19. The role of commonly used medicinal plants in India and other countries in the management of COVID-19 disease are reviewed in this paper.

3. *Andrographis paniculata*

Andrographis paniculata belongs to the family Acanthaceae and native to India and Sri Lanka. Commonly it is used in the treatment of influenza, diabetes, high blood pressure and skin diseases. It was reported in a study that more than 10 flavonoids and 20 diterpenoids were derived from *A. paniculata* which proved to have potent medicinal properties[17]. The chemical constituents were found to be in higher quantities in the plant leaves in comparision to other plant parts. It was noted that andrographolide and its derivatives from *A. paniculata* have strong antiviral activity against different classes of viruses, such as influenza virus, hepatitis B virus, herpes simplex virus, human immunodeficiency virus, human papilloma virus, etc. The Biomolecular docking, dynamics molecular and quantum mechanics based free energy calculations with selective molecules of AGP1, AGP2, AGP3, AGP4 were characterized against target macromolecules of 3CLpro, PLpro, RdRp with spike protein of corona virus. Few commercial drugs were compared with the selected phytochemicals against the virus. It was found that AGP3 in future can be used as a promising drug for the COVID-19 treatment[18]. Many chemical constituents from *Curcuma longa* and *Andrographis paniculata* were studied to control the COVID-19 virus by *insilco* analysis against the main protease enzyme of SARS CoV-2. The chemical components such as andrographolide, cyclocurcumin, curcumin and dihydroxy dimethoxy flavone were active against the virus[19].

4. *Glycyrrhiza glabra*

Glycyrrhiza glabra belongs to Fabaceae family and is native to Mediterranean region, Southern Europe and Southwest Asian regions. It contains glycyrrhizic acid (GLR), which is mainly used to cure diseases of the liver, viral hepatitis and specific inflammation of the skin. GLR showed activities against viruses, including humans and animals infected with SARS. GLR is a non-hemolytic saponin that has both cytoplasmic and membrane effects; it is a potent immuno-active anti-inflammatory agent. GLR induces cholesterol-dependent disorganization of lipid rafts at the membrane level. GLR plays a major role in prevention of coronavirus to enter cells. The HMGB1 gene encodes the high mobility group protein 1 (HMG-1) and amphoterin, a protein found in humans. Intra cellular level GLR can trap the HMG-1 to block the warning functions of HMGB1. Both the cholesterol and HMG boxbinding functions of GLR were studied and the molecular docking approach was carried out. In addition to its use as a safe medication, the membrane and cytoplasmic effects of GLR make GLR a promising candidate to be tested against COVID-19 infection in combination with other medications[20]. In another *invitro* study SARS-related coronaviruses, respiratory syncytial viruses, arboviruses, vaccinia viruses, and vesicular stomatitis viruses were studied knowing the antiviral activity against HIV-1 virus. The mechanism for antiviral activity of *Glycyrrhiza spp.* include decreased transport to membrane and sialylation of the surface antigen of the hepatitis B virus, decreased membrane fluidity leading to inhibition of HIV-1 viral membrane fusion with the cell, interferon-gamma induction in T-cells, and phosphorylating enzyme inhibition in vesicular stomatitis virus infection and viral rate reduction[21].

5. *Panax ginseng*

Panax ginseng belongs to the Araliaceae family and native to Korea. It is used to treat diabetes, cardiovascular diseases, central nervous system, and also act as an antioxidant. It was reported that ginsenosides, polysaccharides, polyacetylenes, phytosterols, and essential oils are the

active substances found in ginseng, where ginsenosides were known to be the main bioactive ingredient[22]; it includes ginseng polysaccharides or ginseng saponin. The antiviral properties of ginseng polysaccharide and ginseng saponin have been studied and were found to be effective against influenza virus infection symptoms[23]. In addition to antiviral activity, ginseng also has a role in viral infection as a mucosal adjuvant against the influenza virus[24].

6. *Withania somnifera*

Withania somnifera (Indian ginseng) is an antiviral, anti-inflammatory, and potent antioxidant plant. Using docking experiments, the protein targets of SARS-CoV-2, namely NSP15 endoribonuclease and the spike protein receptor binding domain were targeted. The findings showed that at the binding site of selected proteins the glucoside compounds withanoside X and quercetin from *W. somnifera* has favorable interactions. Withanoside X was found to be the most promising inhibitor with the highest binding free energy (Gbind = -89.42 kcal/mol). The molecule optimizes its conformation during MD studies to better fit with the receptor active site, explaining the high binding affinity. Indian ginseng may also be used as one of the alternatives for the treatment of the COVID-19 virus based on proven therapeutic evidence[25].

7. *Azadirachta indica*

Azadirachta indica belongs to the Meliaceae family and is native to the Indian subcontinent. Its uses are multifarious and has been used as a medicinal herb since ancient times. Neem leaves exhibit anti-microbial, anti-inflammatory, and also anti-viral properties. To identify coronavirus membrane and envelope protein inhibitors, molecular docking and simulation methods were used. These proteins were virtually screened against a total of 70 neem plant compounds and further examined for the identification of some potential compounds. These compounds bound themselves to the proteins of the virus, proving their capability to suppress the functionality of these components. Identification of inhibitors can be further studied against COVID-19 infection using computational techniques[26].

8. *Carissa spinarum*

Carissa spinarum or bush plum is a shrub belonging to the Apocynaceae family and native to tropical regions of Africa, Southern Asia, and Australia. It is used for inflammation, arthritis, epilepsy, viral infection, and cancer treatment. *Carissa spinarum* is used for its anti-viral properties due to the presence of alkaloids, tannin, glycosides, saponins, terpenoids, flavonoids, and steroids. The chemical constituents include primary and secondary metabolites which play a key role in the defense mechanism against injury and viral diseases[27]. These are found in the leaves, fruits, stems, bark, seeds, and roots.

9. *Curcuma longa*

Curcuma longa is a herb rich in curcumin belonging to the family Zingiberaceae and native to tropical South Asia. It has antiviral, anti-inflammatory, antipyretic, antifatigue, and other properties that could be very effective against COVID-19. In a study, curcumin was found to interfere with SARS-CoV-2 viral replication mechanisms and to be effective in the therapeutic intervention of COVID-19 infection[28]. Curcumin has been proven to inhibit SARS-corona virus replication[29]. The genomic similarity of SARS-CoV-2 with SARS-coronavirus (>80%) and Middle East respiratory syndrome-coronavirus indicates the possibility of curcumin being used as a potent compound against COVID-19[30].

10. *Nigella sativa*

Nigella sativa belongs to the family Ranunculaceae and is native to Eastern Europe and Western Asia. The herb is used to treat various illnesses, including influenza, headache, high blood pressure, diabetes, inflammation, eczema, fever, and asthma. Computational analysis of molecular docking, ADMET and MM-PBSA has been used to characterize the *N. sativa* therapeutic potential against COVID-19. Dithymoquinone (DTQ) a compound in *N. sativa* along with ACE2 interface showed a high affinity for SARS-CoV-2 and interacts with several hotspot residues both by hydrophobic and hydrophilic bonding. This compound has high solubility, absorption rates, and is found to be a promising biomolecule against infection[31]. It was also noticed that *N. sativa* includes other bioactive components such as thymoquinone, nigellimine, dithymoquinone, and thymohydroquinone. *N. sativa* can be used along with a Zinc supplement[32]. In general, for any infection, Zn enhances the immunity. The added Zn salt supplement with *N. sativa* acts as an ionophore to allow Zn2+ to enter pneumocytes the target cell for SARS-CoV-2. Zn salts are known to inhibit the replication of viruses such as HIV, HSV, and SARS-CoV. In these viruses, Zn is known to impede the viral entry or inhibiting the viral RdRp activity[33–35].

11. Other Folk Herbal Medicines

It was reported that some essential oils, including *Cinnamomum zeylanicum* leaf oil, *Citrus bergamia, Cymbopogon flexuosus* and *Thymus vulgaris*[36], also exhibit anti-influenza properties. *Laurus nobilis* has been used as a folk medicine to treat diseases caused by SARS-CoV[37]. *Juniperus oxycedrus* plant are used in folk medicine for the treatment of various infectious diseases[38]. *Aloysia gratissima* and *Artemisia arborescens* exhibit antiviral activity against HSV-1 and HSV-2 virus[39,40]. *Leptospermum scoparium, Matricaria recutita, Melaleuca alternifolia,* and *Mentha piperita* exhibit antiviral properties against HSV-1/HSV-2 virus[41–44]. Antiviral compounds such as Curcumin, Oleuropein, Luteolin-7, and Catechin from plants like *Capsicum annuum, Curcuma longa, Mentha longifolia, Olea europaea, Phoenix hanceana,* and *Camellia sinensis* was found to inhibit Mpro coronavirus[45]. Tylophorine compounds from the *Tylophora indica* exhibit potentials inhibiting coronaviruses[46].

Psoralea corylifolia contains antiviral compounds such as Bavachinin, Psoralidin Corylifol; they were studied against SARS-CoV and ethanol extract of secondary metabolites recorded high activity against SARS-CoV PLpro[47]. *Paulownia tomentosa* containing tomentin compound was used for treating SARS-CoV infection[48]. *Camellia sinensis* containing catechins was also used as inhibitors of SARS-CoV N protein[49].

Myricetin and Scutellare in compounds present in *Aglaia perviridis* were used for the treatment of SARS-CoV. *Invitro* study affects the ATPase activity which inhibits the SARS-CoV helicase protein[50]. The use of *Kadha* (herbal tea/decoction) a mixture of *Ocimum tenuiforum, Cinnamomum verum, Piper nigrum, Zingiber officinale,* and *Vitis vinifera* was given to boost immunity against coronavirus[51]. *Zingiber officinale* also contains the quercetin flavonoid, which has shown *insilico* potential to bind to the main protease (3CLpro) of SARS-CoV and SARS-CoV-2[52]. Digitoxigenin in *Nerium oleander* was used in treatment as antiviral and anti-cancer inhibitors[53]. *W. somnifera, T. cordifolia,* and *O. sanctum* phytoconstituents not only impede the interaction of viral protein to the host cell but also serve safe against coronavirus without exhibiting any toxicity[54].

Various diseases like asthma, sinuses, fever, and chronic indigestion can be cured with the help of *Piper nigrum* fruit. Antiviral activity against vesicular stomatitis Indiana virus and Human parainfluenza virus has been exhibited by the chloroform seeds extract[55,56]. Antiviral activity against Coxsackievirus was demonstrated by piperamides found in the plant[57]. The leaf extract of *Vitex negundo* was found to inhibit the Chikungunya virus[58]. It was reported that *Phaseolus Vulgaris* plant was confirmed to have antiviral property against the human immunodeficiency virus-1 and Drosophila C virus[59–61].

Calendula flavonoid based chemical constitutes such as rutin, isorhamnetin-3-O-b-D, and calendoflaside were selected and found to be highly effective in inhibiting Mpro, the main protease for SARS-CoV-2 causing COVID-19. They have the ability to form a stable complex with Mpro, these three molecules from *Calendula officinals,* especially calendoflaside and rutin compounds, proved to be an anti-COVID-19 protease drug to fight against the novel protease drug but however it requires clinical trials for further analysis[62].

Asparagus racemosus was studied using molecular docking and dynamic approaches against SARS-CoV-2. Two proteins NSP15 endoribonuclease and spike receptor-binding domain of SARS-CoV-2 along with the plant compounds were examined. The compounds Asparoside-C, Asparoside-D, and Asparoside-F were found to be more effective molecules with NSP15 and complex molecule domain of receptor binding site of SARS-CoV-2 with the reference of molecular docking and dynamic studies. The molecular interaction has also theoretically proved that MM-GBSA has moderate molecular affinity and better interaction with Asparoside-C and Asparoside-F against virus spike protein binding domain along with Endoribonuclease respectively. *Asparagus racemosus* has antiviral potential and it showed that Asparoside-C and Asparoside-F have a good binding with target proteins and serve as an inhibitor[63].

Metabolites found in conifer angiosperm families are Abietane-type diterpenes, more than 200 compounds exhibited anti-inflammatory, anti-diabetic, antitumor, antimicrobial, and antimalarial properties. It was found that both betunolic acid and savinin compounds are present in Cupressaceae species. Lignoid groups with antiviral activity have been tested recently. In addition to their diversity of bioactive compounds, dibenzylbutyrolactones primarily exhibit antiviral activity. Savinin and hinokinin compounds are active against SARS-CoV-1 and HIV[64,65].

12. Discussion

The research implication on COVID-19 alone in 21st century contributed more than 60% to the publication history. New drug research against the virus is constantly being carried out to solve human problems using different biological and synthetic method. Most of the pharmaceutical companies in the world are designing inactivated or attenuated rapid vaccines for COVID-19,

however very few have been successful with different efficacy rates. Though the inactivated and attenuated vaccines may provide effective immune response, existing problem like reversion of virulence and other side effects associated with this vaccine developing strategy yet to be studied carefully. Indeed, the post immunization research on humans could result in either a positive or negative impact. Meanwhile these kinds of rapid vaccines are assumed to be having some genetic side effects. Because of these reasons few countries are hesitating to take the rapid vaccines. Hence, the responsibility of pharmaceutical companies is to design a suitable synthetic drug or natural derivative to eradicate the viral infection without side effects. During the initial period of COVID-19 viral infection, many South East Asian countries used several traditional antiviral herbal extracts to improve the health status of infected people and prevent the infection in healthy people. Indeed, these traditional plant extracts were shown to provide more than 90% recovery from the infection in many patients.

A variety of chemical constituents from plant origins including Myricitrin, Licoleafol, Curcumin, and Crocin, have been suggested as possible inhibitors for COVID-19 based on *insilico* approach. *Invitro* phytoconstituent evaluation studies have shown that diammonium glycyrrhizinate, chloroquine diphosphate, and hydroxychloroquine can be potential COVID-19 virus inhibitors, and few of them are in clinical trials. Plants like *Alnus japonica, Angelica keiskei, Cibotium barometz, Cullen corylifolium, Ecklonia cava, Paulownia tomentosa, Quercus infectoria, Rheum* sp., *Polygonum* sp., *Salvia miltiorrhiza, Sambucus javanica, Scutellaria baicalensis, Torreya nucifera* and *Tribulus terrestris* were also evaluated for *in-vitro* and shown effective inhibition of COVID-19.

Information obtained from literature studies show that the promising treatment for COVID-19 may be from the use of conventional medicinal extracts alone or in combination with synthetic drugs. Using the traditional medicine strategy, one has to determine their bioactivity, inhibition properties, biological evaluation, and further investigation about the potentials of many plant-based phytochemicals against the COVID-19 infection.

13. Conclusion

The recent global problem is the COVID-19 pandemic. There is a wide scope for medicinal plants which possess antiviral properties to be developed into anti-COVID-19 drugs. The best way of preventing COVID-19 infections would be to identify the right type of compound from the right type of medicinal plant, responsible for altering or disturbing any steps of the virus replication cycle. It is important to explore herbal products capable of inhibiting or altering the structural protein (spike glycoprotein) configuration, non-structural proteins (3-chymotrypsin-like protease, papain-like protease, helicase, and RdRp), and accessory proteins coded by the SARS-CoV-2 genome. It is always safe to use herbal products which are proved to be very secure, safe, and an efficient source for drug detection responsible for managing the current pandemic situation.

There is a dire need to investigate Protease and RNA polymerase inhibitors known to be active against SARS and MERS. Different phytochemicals (flavonoids, polyphenols, alkaloids, proanthocyanidins, and terpenoids) have already been proved to have antiviral properties; they need to be screened while treating SARS-CoV-2 infected patients. There is a wide scope for herbal extracts in Indian continent which may help relieve the symptoms and be effective against COVID-19 infection without any side effects but with more therapeutic efficacy.

14. Abbreviation

ACE2-Angiotensin-Converting Enzyme 2

ADMET-Absorption, Distribution, Metabolism, Excretion and Toxicology

ARDS-Acute Respiratory Distress Syndrome

COVID-19- Corona Virus Disease-19

DTQ- Dithymoquinone

GLR- Glycyrrhizic Acid

HIV-Human Immunodeficiency Virus

HMG-1 -High Mobility Group Protein-1

HSV-Herpes Simplex Virus

MD- Molecular Docking

MERS-Middle East Respiratory Syndrome

MM-PBSA-Molecular Mechanics Poisson-Boltzmann Surface Area

RdRp-RNA-directed RNA polymerase

RNA- Ribonucleic acid

SARS-Severe Acute Respiratory Syndrome

SARS-CoV-2-Severe Acute Respiratory Syndrome Coronavirus-2

TMPRSS2- Transmembrane serine protease 2

Zn-Zinc

15. References

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