DOI: http://doi.org/10.5281/zenodo.4250485
U.S. ISSN 2694 -4812

The Perspectives of Medicinal Plants for COVID-19 Treatment: A Review

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***Abstract*— The World Health Organization (WHO) declared the COVID–19 as a pandemic disease due to its rapid spreading worldwide, caused by a novel coronavirus (SARS-CoV-2) that has brought about many fatalities. Until now, no effective treatment in the form of anti-virus medication or vaccine has been available for the disease. Therefore, this review aimed to identify some important medicinal plants with herbal formulae and guidelines which are used to treat viral diseases especially pandemic COVID-19 disease. Based on this argument, an online search was performed, which assisted to identify a group of plant species harboring antiviral properties. In the recent past, some natural herbal compounds prepared from existing medicinal plants available surrounding us have demonstrated encouraging antiviral properties. This review can be used as guidance of traditional medicine for the alternative treatment of COVID-19 disease with the utilization of medicinal plants.**

Keywords*— COVID-19; Medicinal plants; Traditional Chinese medicine; Viral diseases

I. INTRODUCTION

The novel coronavirus disease 2019 (COVID-19) is pneumonia associated with the highly contagious disease first emerged in Wuhan, Hubei Province, China in December.[1] WHO identified a novel coronavirus (SARS-CoV-2) from the throat swab of a patient on January 7, 2020.[2] Consequently, on 30 January 2020 WHO declared COVID-19 a public health emergency as there is no specific treatment presently available to cure the disease.[3] Due to the lack of vaccine and proper treatment, this global pandemic COVID-19 is responsible for 1,204,355 deaths and more than 46,762,710 confirmed cases until November 1, 2020 and this virus affected189 countries and territories around the world (Figure 1).[4,5] Based on clinical common sense, COVID-19 disease can be divided into three major stages, which are: stage I, an asymptomatic incubation period with or without detectable virus; stage II, non-severe symptomatic period with the presence of virus; stage III, severe respiratory symptomatic stage with high viral load.[6,7] Simple approaches are widely being ignored whole time for the treatment, where two-phase division can be promising: the first immune defense-based protective phase and the second inflammation-driven damaging phase.[8] However, in order to overcome the pandemic crisis as quickly as possible, it requires the use of all resources. The extraction of medicinal plants provides a stimulating or boosting effect on the human immune system which can be beneficial for fighting against coronavirus. However, lack of knowledge of medicinal plants among researchers and medical practitioners allowing the progress of this disease.

Medicinal plants are the natural parts, which are used at least or without processing for curing diseases at different regional-scale.[9] The phytochemicals of medicinal plants have direct or indirect therapeutic effects to prevent and treat various infectious and non-infectious diseases.[10,11] More than 80% of the world populations including China, India with many developing and developed countries depend on traditional drugs as the main source of health care, where a major portion is occupied by medicinal plants.[12] Preventing this outbreak of COVID-19 discovery of the vaccine and the practice of effective therapeutic agents is essential. So, this review article tries to summarize the potential perspective use of medicinal plants against coronavirus disease.

II. METHODS

The present reviews are based on clinical trials, cohort or other population studies using medicinal plants for preventing contagious respiratory virus diseases. The information was collected from electronic databases including PubMed, Google Scholar, official media websites (WHO, Worldometer) as well as database using keywords related to COVID-19 and traditional Chinese herbal medicine etc. to get knowledge about the medicinal plants with their traditional use to treat COVID-19 affected patients. The search date was up to November 1, 2020 and found different medicinal guidelines that provide treatment measures for COVID-19.

III. DISCUSSION

Significance of medicinal plants from ancient to modern times

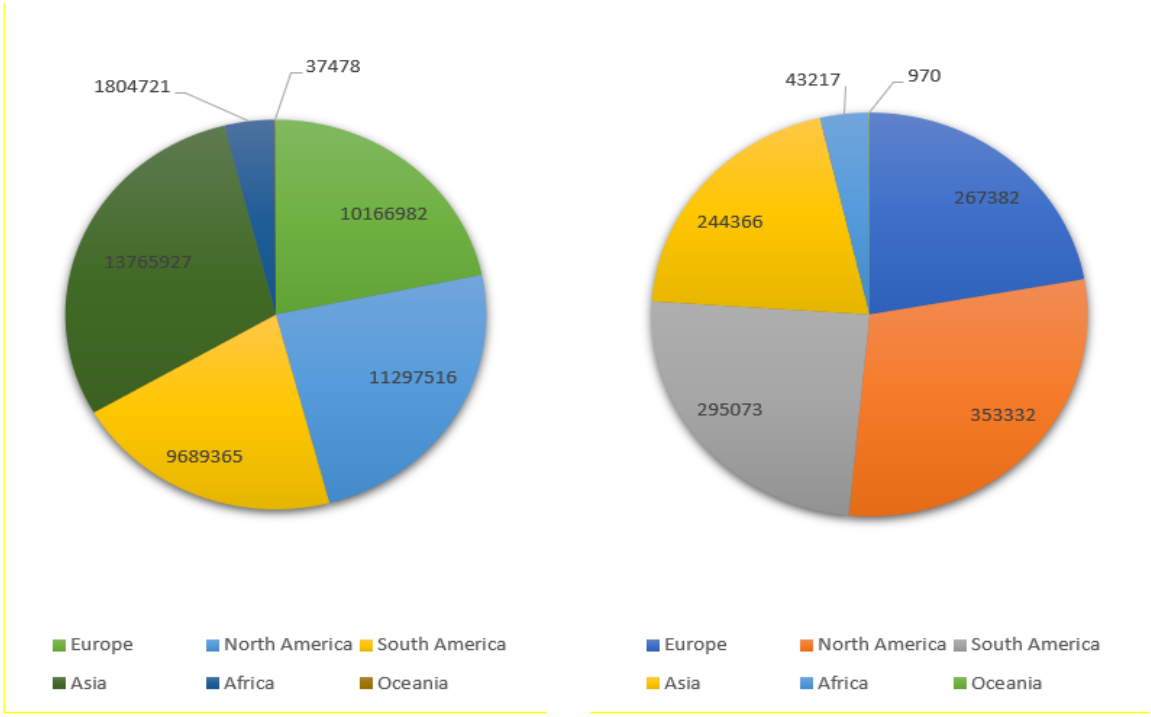
From ancient times, medicinal plants have been playing a vital role in curing critical diseases in different countries like China, India, Greece and Rome.[13] Products of medicinal plants are the basis for treating various human diseases and their demand and acceptance is rising progressively with time.[14] Despite the rapid growth of industrialization, traditional drugs are widely being used in Asia, Africa, and Latin America for a wide array of treatments. The National Institutes of Health (NIH) of the United States implement the complementary and

alternative medicine (CAM) to use in the health systems, practices, and products, which are not measured to be a part of conventional medicine. On the other hand, traditional Chinese medicine (TCM) is the most popular conventional medicinal system used in treatments after Indian medicine in the world.[15] More than 3.3 billion people in the less developed countries use medicinal plants daily.[16] Biological properties of medicinal plants play an important role in the production of active compounds during secondary metabolism in case of treatment of infectious diseases.[17] Today from curing colds and coughs to inflammation and parasitic infections traditional medicinal plants are still in use.[18] The use of medicinal plants and their products is significantly recognized worldwide and the reputation is increasing at an exponential rate. From a study in 2008, it was reported that 50% of our available drugs are directly or indirectly derived from medicinal plants and more or less 25% of medical prescriptions contain one or more active elements from plants.[19,20]

Medicinal plants are being used to treat infections and viruses like common cold, influenza, fever and herpes with the enhancement of the immune system of the human body as the active ingredients of these plants have significant therapeutic effects.[10] Moreover, pure chemicals such as aspirin (from Willow Bark), morphine (from Opium), digoxin (from foxglove), quinine (from Cinchona skin), atropine (from deadly nightshade, Jimson weed, and mandrake), reserpine (from Indian snakeroot), physostigmine (from Calabar bean and the Manchineel tree), pilocarpine (from Maranham jaborandi), vincristine (from Madagascar periwinkle), vinblastine (from Madagascar periwinkle), artemisinin (from sweet wormwood) and taxol (from Pacific yew tree) were isolated from medicinal plants and are being used in the preparation of different drugs. Diseases like diabetes mellitus, arthritis, high blood pressure, microbial infections, and cancer are treated by using medicinal plants.[21-23]

Antiviral effects of medicinal plants

With less or, no adverse effect of medicinal plants is being used for many communities to this day. Moreover, a wide array of medicinal plants shows a significant antiviral effect on epidemic diseases (Table 1). In the case of TCM, it is one of the most popular used therapeutic approaches to combat viral diseases in the world. TCM enhances the resistance of the body to epidemic disease with unique insights, control and prevention experience over thousands of years of experience.[24] In previous studies, TCM was showed promising results as an effective treatment for Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS).[25] Moreover, the treatment combination of western medicine with TCM significantly decreased the adverse effects of glucocorticoid, antibiotic, and antiviral treatments for SARS.[26] For treating asthma and other respiratory problems, a Chinese medicinal plant Ephedra is being used for more than 2000 years. The active compound of Ephedra is Ephedrine, which is



a. Total number of infected cases

b. Total number of deaths

Figure 1. Total number of infected and deaths cases

used in the pharmaceutical preparations to relieve asthma symptoms and other respiratory problems, helping in the breathing of patients more easily.[19] Furthermore, San Wu Huangqin Decoction, Lianhuaqingwen capsule, and Yinhuapinggan granule are the names of popular Chinese herbal formula effective in blocking of the proliferation and replication of the influenza viral particles.[27] Therefore, in developing proper treatments for COVID-19, medicinal plants can become an important tool to our arsenal.[28]

Prospective treatments of COVID-19 using medicinal plants

The COVID-19 disease spread rapidly and there is no cure at this time. Although scientists are working at their level best, it is better to avoid infection at any cost. Up to this time, there is no effective antiviral treatment for MERS-CoV, SARS-CoV, SARS-CoV-2 virus, however, 23 provinces of China are using TCM formulae to cure this illness.[29,30] In China, respiratory infections are treated with traditional herbal medicines as an alternative treatment. TCM has a successful history in the prevention and treatment of several epidemics. In 2003, TCM showed a remarkable therapeutic effect on SARS.[24,31] Assessment of SARS and MARS treatments in past investigations are being implemented in current drug research. Previous records on SARS and H1N1 influenza treatment exhibited that Chinese herbal formula could have the potential effect to cure COVID-19 in a high-risk population.[30] Currently, greater than 85% of COVID-19 patients in China are receiving TCM for finding potential treatments.[32] Every virus has a unique structure and behavior, which drastically differs from the infection methodology in different human bodies. Patients' health condition, age, sex and previous medical history significantly vary the effectiveness of herbal medicinal plants.

According to recent clinical results, TCM showed a significant result in the prevention and control of COVID-19.[24,33] The integration of Chinese and Western medicine had been practiced on patients since December 2019.[34] A combination of TCM containing Lopinavir/Ritonavir, Arbidol, and Shufeng Jiedu Capsule (SFJDC) exhibited beneficial result in a three out of four patients.[35] Furthermore, clinical trials on evaluating the safety and efficiency of lopinavir-ritonavir and interferon-α 2b are ongoing.[36] Chinese herbal plants like astragalus, liquorice, fangfeng, baizhu and honeysuckle are very popular in use; however, the best period of using this decoction is only one week.[37] Additionally, Mahuang *(Ephedrae herba)*, Xingren *(Armeniacae semen amarum)*, and Chaihu (*Bupleuri radix*) are being used in decoctions as the bitterness of these plants is caused by aromatic hydrophobic substances like ephedrine and amygdalin, which may constrain the communication of the S protein with ACE2 in virus.[28] In recent studies, TCM based treatments such as *qingfei paidu* decoction (QPD), *gancaoganjiang* decoction, *sheganmahuang* decoction, *qingfei touxiefuzheng* recipe, *etc.* performed well in COVID-19 patients with pneumonia symptoms. Among all these treatments, QPD has been suggested as a general prescription in China, which has a cure rate of over 90%.[24]

On the other hand, *in silico* screening of herbal plants resulted in the discovery of molecules having the direct potentiality to inhibit novel coronavirus.[70-72] Although there might be a lack of evidence on the safety issues of Chinese herbs, it is believed there are no major noticeable side effects on the human body.[37] Overall, TCM can show positive responses in the treatment of contagious disease, however, proper research is recommended before using it as a cure. Presently in China, it has been recommended to use routine treatment including antibiotic drugs with nutritional support and mechanical ventilation (if required) and TCM for COVID-19.[73]

Now, preventive measures and explore health remedies are the main focuses of our scientific community. Herbal experts emphasize on medicinal plants that can be effective in strengthening the immune system of our body to inhibit the spread of COVID-19. The traditional use of black cumin (*Nigella sativa* L.) as a panacea in Islamic and Christian communities of North Africa is practiced from centuries.[74] *Nigella sativa* is refered to by many researchers for its different advantages as antiviral, mitigating, hostile to malignancy, pain relieving and so forth.[75-77] Identification of favorable molecules in black cumin for COVID-19 treatment is being studied to compare with drugs like chloroquine, hydroxychloroquine, azithromycin, arbidol, remdisivir, lopinavir/ritonavir, ribavirin, chloroquine phosphate and favipiravir as it has a proven use in antiviral treatment in previous studies.[78-80] Results from molecular docking exhibited that Nigellidine and α- Hederin can be used in COVID-19 treatment and the discovery of M^{pro} protease structure in SARS CoV-2 opens new possibilities to come up with a more reliable solution to settle the medicinal use of black cumin.[78] In another experiment, Moroccan medicinal plants like *Crocus sativus*, *Nerium oleander* and *Lauris nobilis* that having Crocin, Digitoxigenin, and β-Eudesmol molecules have inhibition capacity from SARS CoV-2 in molecular docking, which is based on the energy of interaction between molecules and studied protein.[81]

IV. CONCLUSION

The highly infectious disease COVID-19 spreads through respiratory droplets and close contact with susceptible hosts. It is strongly recommended to eliminate the route of transmission and treat patients with available medications and treatments, as well as to improve the expected vaccine, because of the information gap about the mechanism of infection and no potential cure. Disease surveillance systems, active response teams and improve high tech laboratories are mandatory measures to control this pandemic. Previous research studies and clinical evidence on SARS and H1N1 influenza prevention may also help in creating COVID-19 prevention tactics, which is required to be evaluated in well design population studies. Herbal remedies may seem as harmless in most of the cases, clinical trials and research are required to examine the effect on

Table 1. List of medicinal plants with possible antiviral effect on viral diseases

Virus	Botanical name	Origin	Active constituents	Mode of action	References
Avian influenza virus (H9N2) 35 and murine cytomegalovirus	*Nigella sativa*	Western Asia	Thymoquinone	Enhancement of antioxidant properties	[38]
Dengue virus type-2 (DEN-2)	*Azadirachta indica* Juss.	India	Azadirachtin	Inhibition of DEN-2 both *in vitro* and *in vivo* by aqueous extract	[39]
Dengue virus, Herpes virus, Hepatitis B virus and HIV	*Momordica charantia*	Eastern India	Potent protein	Inhibition of replication by virus	[40]
Hepatitis B virus (HBV)	*Hedyotis diffusa*	China and Europe	Iridoid glycosides	Not obvious	[41]
HBV	*Polygonum cuspidatum* Sieb. & Zucc.	East Asia, Japan China Korea	Emodin	Prevents HBV replication	[42,43]
HBV	*Boehmeria nivea L.*	China	Tormentic acid	Root extracts reduce HBV replication both *in vitro* and *in vivo* cases	[44,45]
Hepatitis C virus (HCV)	*Silybum marianum*	Southern Europe and Asia	Flavonolignans	Possible intervention through antioxidant action mechanism	[46]
HCV	*Saxifraga melanocentra* Engl. & Irmsch.	Central Nepal to South western China	1,2,3,4,6-penta-*O*-galloyl-beta-d-glucoside	Anti HCV activity	[47]
Herpes simplex virus (HSV)	*Phyllanthus urinaria* L.	Asia	1346TOGDG and geraniin	Inhibition of HSV-1 and HSV-2	[48]
HSV	*Carissa edulis* Vahl.	Tropical Africa	Lupeol	Exhibits anti-HSV 1, and 2 activities both *in vitro* and *in vivo*	[49,50]
HSV	*Tanacetum vulgare*	United Kingdom	3,5-DCQA, Axillarin	Inhibition of later stage replication by virus	[51]
HSV-1 and -2	*Achyranthes aspera*	India	Triterpene oleanolic acid	Inhibition of early-stage replication of virus and modulation of immunological traits in the affected host cell	[52]
HSV-1 and HSV-2	*Ficus benjamina*	South and Southeast Asia and Australia	Quercetin 3-*O*-rutinoside, Kaempferol 3-*O*-rutinoside and Kaempferol 3-*O*-robinobioside	Effective inhibition of HSV infection	[53]
HSV-2	*Basella rubra*	Southeast Asia	Polysaccharide (BRN-3)	By constraining virus adsorption to host cells	[54]

Virus	Botanical name	Origin	Active constituents	Mode of action	References
HSV-2	*Cassia javanica*	Southeast Asia	ent-Epiafzelechin-(4α→8)-epiafzelechin	Inhibition of replication by virus	[55]
HSV-2	*Vaccinium vitis-idaea*	Eurasia to North America	Proanthocyanidin A-1	Inhibition of viral attachment and penetration	[56]
HSV and HIV	*Prunella vulgaris*	Europe	Anionic and polyanionic polysaccharide	Inhibition of both early and later stages of virus replication	[57]
Human Respiratory Syncytial Virus (HRSV)	*Gentianae macrophyllae*	China	Compound RG3-1	Inhibition of viral replications by RG3-1	[58]
HRSV	*Forsythia suspense*	China	2-(1,4-dihydroxy cyclohexanyl)-acetic acid	Not obvious	[59]
Influenza A, human coronavirus, HRSV and parainfluenza	*Pelargonium sidoides*	South Africa	Polymeric polyphenols and coumarins	Reduction of rhinovirus infection on human bronchial epithelial cells by modulating viral binding proteins	[60,61]
Influenza virus	*Sambucus spp.* L. (Elderberry extracts)	North America	Flavanols, Quercetin-3-glucoside, Quercetin-3-rutinoside, a number of anthocyanins	Plant extracts effective in treatment for influenza	[62,63]
Influenza-A (H3N2 subtype), Influenza-B	*Scutellaria baicalensis*	Japan	Isoscutellarein-8-methylether (5,7,4'-trihydroxy-8-methoxyflavone)	Inhibition of replication by influenza virus	[64]
Influenza-A and B	*Schizonepeta tenuifolia*	China	Volatile oil and extracts	Relieving pulmonary infection	[65]
Murine Leukemia Virus	*Angelia sinensis*	China	Synthetic sulfated angelica polysaccharides	Inhibition of replication by the virus and improve the immunity of the host	[66]
SARS-CoV	*Houttuynia cordata*	Japan	Flavonoids: (quercetin, isoquercitrin, afzelin, hyperin, reyoutrin, rutin)	To inhibit the viral 3CL protease and create a blockage in the action of viral RNA-dependent RNA polymerase	[67]
SARS-CoV	*Lycoris radiate*	China	Lycorine	Possession of anti SARS-CoV effect	[68]
Vaccinia virus HSV-1, HIV-1 &2 and Reovirus	*Quillaja saponaria*	Chile	Triterpenoid saponins	Disruption of viral envelopes and capsid proteins	[69]

affected patients. The current review includes some important investigations for the treatment of COVID-19 disease by using medicinal plants all over the world. As COVID-19 has no specific treatments or vaccines in our hands, we must continue our investigation to find the most suitable treatment for this pandemic.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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