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Pooja Reddy M
Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), Hyderabad, Telangana, India

Priyanka Makhal
Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), Hyderabad, Telangana, India

Venkata Rao K
Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), Hyderabad, Telangana, India

Corresponding Author:
Venkata Rao K
Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), Hyderabad, Telangana, India

Potential herbal drugs and phytochemicals to minimize the risk of COVID-19: A review

Pooja Reddy M, Priyanka Makhal and Venkata Rao K

Abstract
Coronavirus COVID-19 is presently spreading very aggressively across the world and is extremely difficult to control as no appropriate medications or vaccines are found in the market. Natural/ Herbal medicine provides a broad range of therapeutic ingredients that serve as a peripheral guide for solving the myriad mystery of the current pandemic. Several studies are in progress with an objective to identify potential Indian herbal drugs and phytochemicals to minimize the risk of COVID-19. Therefore, the repositories of rapidly evolving reports have been retrieved from PubMed, Google Scholar, Science Direct, and Embase, and the results of which are summarized. To conclude, certain herbal drugs and phytopharmaceuticals could be a possible therapeutic approach to minimize the risks of SARS-COV-2.

Keywords: Corona virus disease 2019 (COVID-19), traditional Indian medicine, phytochemicals, herbal remedies, immunomodulators, anti-viral herbal drugs

Introduction
Viral diseases tend to arise and pose a significant problem for public health. Over the last twenty years, there have been many viral epidemics such as the Cholera (2001), Plague (2002), Severe Acute Respiratory Syndrome SARS – (2002 to 2003), Dengue fever (2003), Chikungunya, and Zika virus (2006), Nipah virus (2018). [1] In a timeframe that goes to the present day, 2019-novel coronavirus (nCoV) has become a major source of disaster in the 21st century.

COVID-19 Overview
Coronaviruses (CoVs) are part of the family Coronaviridae (order Nidovirales) and the subfamily Orthocoronaviridae. There are four coronavirus genera Alpha, Beta, Gamma and Delta [2, 3]. CoVs are enveloped, non-segmented, single-stranded positive-sense RNA (ssRNA) viruses typically found with spike-like projections on its oval surface visible under an electron microscope (coronam is the Latin term for crown), hence the name coronaviruses (CoV) [4]. Its positive polarity is 27-32 kb, the ssRNA is 29,903 bp long and the size range is 80-160 nm.
In late December 2019, many people from Wuhan City, Hubei Province of China began visiting hospitals complaining about severe pneumonia of unknown etiology. On 30 January 2020, the new viral pneumonia was declared as Public Health Emergency of International Concern by the World Health Organization (WHO). In February 2020, the WHO announced "COVID-19" as the official name of coronaviras disease. The International Committee of Virus Taxonomy's (ICTV) experts subsequently named it as SARS CoV 2 virus because it was found to be very close to the one that caused the outbreak of SARS (SARS-CoVs). Owing to a growing amount of infected people across continents and a massive loss of human existence, the WHO has declared the novel epidemic of COVID-19 a pandemic. The "worldwide spread" of a new illness is known as a pandemic. WHO recorded 20,280,518 documented cases with 739,761 fatalities and 13,205,119 recovered cases as of August 10, 2020, and were distributed to 213 countries [5].
The most common source of COVID-19 transmission is symptomatic people. There appears to be a slight possibility of transmission before symptoms develop, though this cannot be ruled out. According to current evidence, the virus is primarily transmitted between people through respiratory droplets (coughing and sneezing) and contact routes (G. O. of N. H. Committee & Office of the Government of the Chinese Traditional Medicine, 2020). Therefore Physical distancing and isolation is the only approach to combat this outbreak. The COVID-19 incubation period is reported to be 1–14 days. Fever, cough and shortness of breath are the common symptoms of COVID-19 [6].
Currently, the United States Food and Drug Administration (USFDA) not approved any specific drug for the treatment of COVID-19. The present therapies such as oxygen therapy,

antiviral therapy and corticosteroid therapy are primarily for supportive care and to ease the symptoms. More than 90 vaccines are being developed against SARS-CoV-2 by research teams across the world however there is much more work to be done to develop safe and effective vaccines.[7] In the wake of the pandemic, work and production of novel molecules become labor-intensive and the production of such drugs can take months and years. Therefore the crucial demand of the hour is therapy for the SARS-CoV-2 virus. Herbal medicines/herbal formulations are known to be effective in reducing infectious conditions. In various viral diseases, conventional medications are substituted by herbal drugs as life-saving medicines. The phytoconstituents of herbal drugs can act as an ancillary guide in solving the mysteries of the present pandemic. Identifying the antiviral mechanism of phytoconstituents can lead to effective anti-coronavirus therapies. Based on the target, the expected therapies can be classified into two categories: one is a human cell or immune system; the other is coronavirus itself. Literature shows that Indian medicinal herbs and phytochemicals regulate the immune response and useful in viral infection management. Therefore, this review is mainly focused on analysis of Indian and Chinese herbal drugs for targeting SARS-CoV-2. It is expected that the review helps the scientific community to accelerate the development of SARS-CoV-2 therapies.

Methodology

A systematic literature search has been carried in data repositories by using combination key words including "(COVID19, SARS CoV-2) and (Indian herbal drugs, Herbal medicines, Antiviral herbal drugs, Phytochemicals, Chinese herbal medicines)". Similarly, literature search was performed in Google and WHO COVID 19 database and the results of the review/research articles have been summarized.

Immunomodulatory herbal drugs and pjytochemicals to minimize the risk of COVID-19

Natural products are involved in the regulation of immune functions. They regulate the immune response in a pleiotropic way and engage in different adaptive/innate immune processes. Therefore active immune modulators from natural resources could be a prophylactic remedy to prevent SARS CoV-2 infection. Indian medicinal system collectively known as AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha and Sowa-Rigpa and Homeopathy) [8]. Ayurveda established in India around 2500 and 500 BC and considered as world's oldest holistic ("whole-body") healing systems in human history. Charak Samhita, a foundational Sanskrit text on Ayurveda described a rasayana formulation "Chywanprash Awaleha" has been in use from the past 4000 years for enhancement of non-specific immunity. Emblica officinalis is the principal constituent of the rasayana formulation along with several other herbal powders and extracts. "The Ministry of AYUSH" now recommending Chywanprash Awaleha as an immune modulator to reduce the risk of COVID-19 [9].

The plants with a significant proportion of glycosides, terpenoids, flavonoids, coumarins, lectins, sapogenins, alkaloids, thiosulfinates and volatile oils have a substantial immunomodulatory effect. Tillu G *et al.* [10] and Nair A *et al.* [11] documented certain essential medicinal plants which are commonly used in clinical practice to strengthen insusceptibility and immunomodulatory function. The herbs include Acacia catechu, Acoruscalamus, Allium sativum, Andrographis paniculate, Azadirachta indica, Boerhavia diffusa, Curcuma longa, Cynodondactylon, Ficus benghalensis, Murraya koenigii, Ocimum sanctum, Panax ginseng, Picrorhiza scrophulariiflora, Terminalia arjuna, Tinospora cordifolia (Guduchi). In another study by Das S *et al.* [12] suggest Glycyrrhiza glabra (Yashtimadhu), Zingiber officinale, Withania somnifera (Ashwagandha), Astragalus membranaceus as immune-modulatory medicinal herbs. Alternatively, some medicinal plants like Panax ginseng, Ocimum sanctum, Tinospora cordifolia, Terminalia arjuna are reported to posses immune stimulant activity [13]. Andrographis paniculata known as "Indian echinacea" is said to act as a natural immune-booster [14, 15]. The images of few commonly used immunomodulatory /immunostimulant medicinal herbs are depicted in Figure-1 [2, 16].

Fig 1: Potential immunomodulatory medicinal herbs for COVID-19, a. Chywanprash Awaleha, b. Withania somnifera, c. Glycyrrhiza glabra, d. Nigella sativa, e. Psorothamnus-arborescens, f. Strobilanthus cusia, g. Senna alexandrina, h. Salvia officinalis, i. Emblica Officinalis, j. Curcuma longa, k. Terminalia arjuna, l. Acacia catechu (seed).

Herbal drugs and Phytochemicals for targeting COVID-19

The identified drug targets for COVID-19 are primarily from the life cycle or from its replication process. Figure-2 depicts the life cycle of SARS COV-2. To discuss briefly, the virus viral structural spike (S) glycoprotein are key factor for virus attachment and enty into cells. The S protein binds to the receptor Angiotensin-Converting Enzyme-2 (ACE-2). The Trans Membrane Serine Protease Type-2 (TMPRSS2) facilitates fusion of viral and host cell membranes via the S protein. After the virus entry, RNA is released in the cytoplasm and the replication-transcription complex (RTC) guides the synthesis of polyproteins 1a/1ab [17, 22]. These polyproteins are processed by virally encoded proteases into non-structural proteins that produce viral RNA synthesis and modification functions nonstrctural proteins. Therefore, the key targets for therapeutic designs are ACE-2 [23], TMPRSS2 [24], S protein [23], and virally encoded proteases (includes main proteases (M^{pro}) [25], 3-Chymotrypsin-like protease (CL^{pro}) [26, 27], Papain like proteases [28], RNA-dependent RNA polymerase [29], and Helicase [30]).

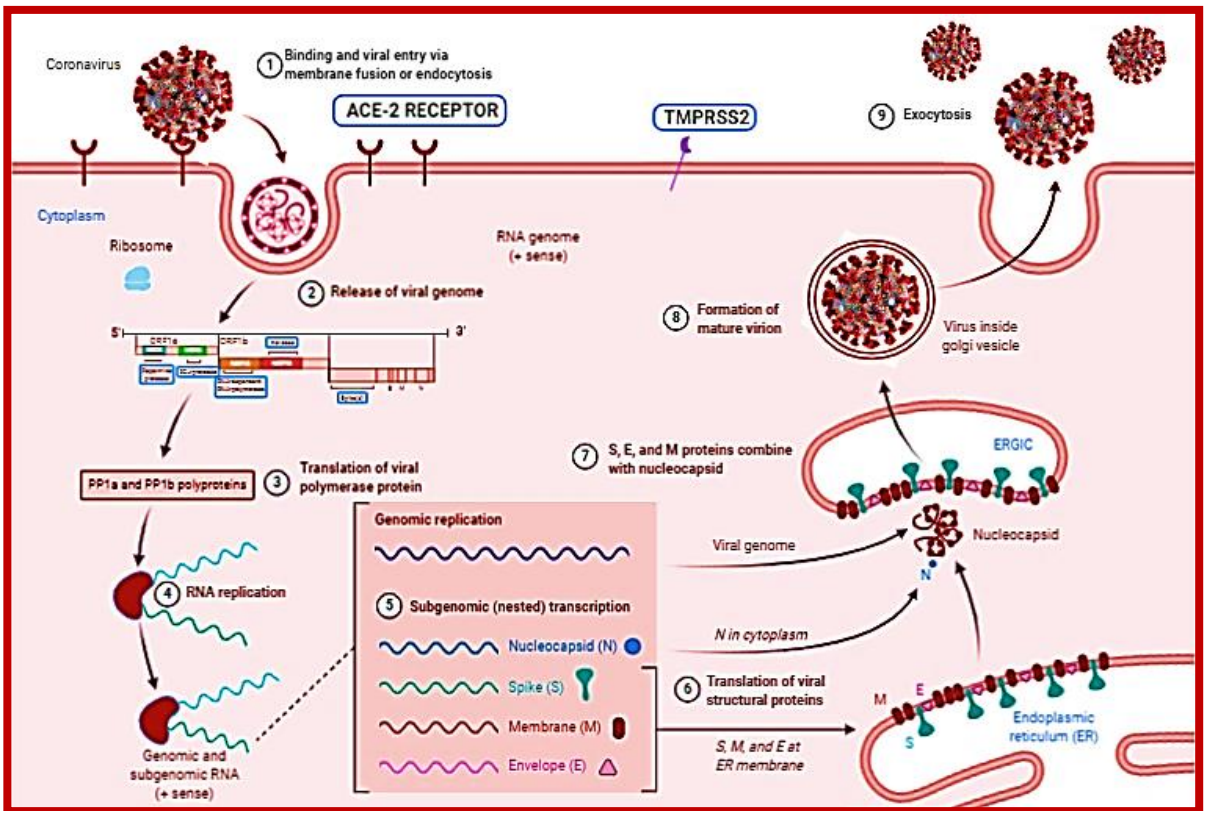

Fig 2: Life cycle of SARS-CoV-2

The main protease (M^{pro}) is one of the best-characterized drug targets among coronaviruses. M_{pro} is pivotal for proteolytic processing of the polyproteins (pp1a/pp1ab) that are required for viral replication and transcription. Inhibition of M^{pro} prevents maturation of the protein and spread of the infection. The crystal structure of M^{pro} from SARS COV-2 is reported by Zhenming Jin *et al.* (PDB ID: 6LU7) [31]. Khaerunnisa *et al.* [32] performed a molecular docking study using 6LU7 to identify the phytochemicals with potential M^{pro} inhibitory activity. The binding energy the compounds were compared with antiretroviral drugs nelfinavir and lopinavir. The results shows that kaempferol, quercetin, luteolin-7-glucoside, demethoxycurcumin, naringenin, apigenin-7-glucoside, oleuropein, curcumin, catechin, epicatechin-gallate binding energies are comparable to the refence standards and have the potential to acts as COVID 19 M^{pro} inhibitors. Similarly, Enmozhi SK *et al.* [15] carried computational studies with andrographolide, the active constituent of Andrographis paniculata. In the docking analysis all the binding conformations of andrographolide involved in both H-bond and salt bridge interactions with high affinity at the M^{pro} binding pocket. Aanouz *et al.* [33] studied binding energy and molecular interactions of 67 phytochemicals with M^{pro}. By comparing the molecules with chloroquine the study proposes digitoxigenin, crocin and β-eudesmol as potential M^{pro} inhibitors. Tahir ul Qamar M *et al.* [34] predicted the 3D structure of 3-chymotrypsin-like cysteine protease ($3CL^{pro}$), also called as M^{pro} enzyme essential for virus replication and life cycle. The study screened a huge plant inventory with 32,297 medicinal plants containing potent antiviral phytochemicals. The proposed top nine plants that may inhibit 3CLpro activity are Psorothamnus arborescens, Myricacerifera, Hyptisatrorubens Poit, Amaranthus tricolor, Glycyrrhiza uralensis, Camellia sinensis, Fraxinussie boldiana, Phyllanthus Emblica, Phaseolus vulgaris. As many of the herbal drugs or phytochemicals of the above studies alredy known for antiviral activity, *in vitro* and *in vivo* activity against SARS-Cov-2 main protease could be interesting.

The host Angiotensin-Converting Enzyme-2 (ACE-2) was found to be an important receptor for the attachment of viral S protein. The S protein comprises two functional subunits i.e, the S1 subunit responsible for binding to the host ACE-2 and the S2 subunit responsible for fusion of the viral and cellular membranes and internalization of the virus. The herbal drugs or phytochemicals that neutralize virus entry and bind with the hACE2-S complex or perturb the binding complex might be potential remedy for SARS-CoV-2 infection. Joshi T *et al.*

[35] virtually screened a library of 318 phytochemicals from 11 herbal plants which have been known for their antiviral, antibacterial, and antifungal activities. The top 10 phytochemicals that bind to Human ACE-2 receptor (PDB ID 1R4L) with significantly lower binding energy are present in Piper longum, Phaseolus vulgaris, Curcuma longa, Ocimum gratissimum, Syzygium aromaticum, Artemisia absinthium, Inula helenium. The phytochemicals were also screened on M^{pro} (6LU7) and found that Phaseolus vulgaris has maximum phytochemicals binding to both M^{pro} and ACE-2 targets. Patanjali Research Institute claims that 1000 phytochemicals from more than 100 medicinal plants were virtually screened against COVID-19 essential proteins[36]. The phytochemicals, Withanone from Withania somnifera, Tinocordiside from Giloy (Tinospora cardifolia) and Scutellarein from Ocimum sanctum showed good binding affinity with ACE2-receptor binding domain complex. The study proposed that Ashwagandha herb may be the first choice of herb with potential to combat COVID-19. Garlic essential oils have been rich source of organosulfur compounds. A docking analysis by Thuy *et al.* [37] showed 17 organosulfur compounds that can inhibit both the ACE2 and M^{pro}.

Similarly, targeting the spike glycoprotein with herbal drugs and phytochemicals inhibits viral entry and reduce the risk of COVID19. Ubani A *et al.* [38] virtually screened 22 antiviral phytochemicals consisting of flavonoids and terpenes using prefusion confirmation of COVID19 trimeric spike protein (PDB ID: 6VSB). The docking study demonstrated scopodulcic acid, baicalin, silybinin, solaninidine, naringenin with best binding energies. Silybinin, an FDA approved drug for the management of hepatitis disease, is reported for wide range of anti-viral activities will make a good candidate of repurposing. Similarly, Pandey P *et al.* [39] performed molecular docking and ADME studies on spike ectodomain structure (6VYB). The binding energy of the compounds are compared with hydroxylchloroquine, the study presented the flavonoids fisetin, quercetin and kamferol as potential spike protein inhibitors. Using molecular dynamics simulation binding of the compound to hACE2- S-protein complex, near the interface of hACE2 and S-protein binding is demonstrated.

Thymoquinone (TQ), the most studied active component of Nigella sativa has been reported for antiviral, antibacterial, anti-inflammatory, and immunomodulatory properties. Administration of an extract containing TQ before the infection of the cells with the MHV-A59 (mouse hepatitis virus-A59) coronavirus resulted decrease in the replication of the virus *in vitro* [40]. Based on the anecdotal case report combined with anti-viral and immunomodulatory effects of TQ, Sommer P A *et al.* [41] propose use of TQ may help to treat people infected with SARS COV-2.

Traditional Chinese Medicine (TCM) for COVID-19

Chinese medicines (CM) as a source of potential novel drugs for COVID 19 have been reviewed by earlier reports. As we intend to cover both Indian and Chinese herbal drugs the summary of previous reviews has been briefly discussed along with recent updates. Mani JS *et al.* [42] in their thorough analysis reviewed all papers up to 25th March 2020 focusing primarily on the antiviral action of prepared conventional CMs, which usually contain numerous plant species. The analysis suggested tryptanthrin, scutellarein, silvestrol, saikosaponin B2, and polyphenols–including quercetin, myricetin, caffeic acid, psoralidin, isobavachalcone, and lectins such as griffithsin, lycorine as some of the major compounds that gave promising outcomes in human coronavirus therapy. Luo *et al.* [43] analysis of the TCM levels used in 23 provinces found Radix astragali (Huangqi), Radix glycyrrhizae (Gancao), Radix saposhnikoviae (Fangfeng), Rhizoma atractylodis Macrocephalae (Baizhu), Lonicerae japonicae Flos (Jinyinhua), and Fructus forsythia (Lianqiao) as the 10 Chinese herbs most widely used in the treatment of COVID-19. Ang L *et al.* [44] in their review thoroughly analyzed all the herbal formulations given by the Chinese guidelines, which has identified Glycyrrhizae radix et Rhizoma, Armeniacae semen Amarum, Ephedrae herba and Gypsum fibrosum as high-frequency herbs of use.

Chen Cheng *et al.* [45] reviewed the effects of cytokine storm responsible for acute respiratory distress syndrome (ARDS) in COVID-19 and stated that it has been a key therapeutic target for reversing the condition of critically ill patients. He proposed that Shenfu Sini Decoction (TCM) containing astragalus, ginseng, yam, betel nut and other Chinese herbal ingredients could even be used in COVID-19 severe patients. The treatment is related to the suppression of cytokine storms by the regulation of the renin-angiotensin-aldosterone system.

Tsai *et al.* [46] investigated the potential anti-Human coronavirus NL63 (HCoV-NL63) activity of Strobilanthes cusia leaf methanol extract and its major components. The phytochemical tryptanthrin, an indoloquinazoline alkaloid was found to have strong virucidal activity against HCoV-NL63 infection. Wu C *et al.* [47] virtually screened a huge database of 2924 compounds from the zinc database and 1066 natural compounds from in-house inventory. The flavonoids hesperidin, neo-hesperidin, baicalin, rutin, kaempferol 3-O-rutinoside, andrographolide, neoandrographolide and 14-deoxy-11,12-didehydroandrographolide, and a sequence of xanthones from the plants of Swertia genus were found to interact effectively with the targets of SARS-CoV-2. In another virtual screen study by Ren X *et al.* [48] on 66 phytochemicals, frequently distributed in 26 types of CMs showed that Gancao (Glycyrrhizae Radix Et Rhizoma) and Huang Qin (Scutellariae Radix) CMs – are the highest frequency pair found to exhibit potent anti-SARS-COV-2 behavior with ACE-2 and $3CL^{pro}$ hydrolase binding affinity.

Phytopharmaceuticals under clinical development for COVID-19

AQCH, an herbal formulation derived from Cissampelos pareira (Cipa) plant variety is currently under clinical trial as a phytopharmaceutical medication for the COVID-19. As per the Ayurvedic medicine in India, the cipa extract finds its use in the treatment of various human ailments [49]. Cipa extract tends to possess an intrinsic antipyretic activity and strong antiviral activity against all four prevalent Dengue Virus serotypes [50]. Drug Controller General of India (DCGI) has permitted to commence clinical studies on 'AQCH' to Sun Pharmaceuticals, India on June 5, 2020. The drug has shown anti-SARS-CoV-2 effects in *in vitro* studies conducted in collaboration with the International Center for Genetic Engineering and Biotechnology (ICGEB), Italy. A Phase II clinical trial has launched in 210 COVID-19 patients at 12 centers across India [51].

Conclusions

Coronavirus is still a huge threat to all nations. The virus is spreading and causing several deaths throughout the world. As there is no medicine readily available for prevention of the disease, the use of certain herbal drugs or formulations could be an alternative approach to deter the spread of the virus

while enhancing immunity. Recent studies showed that herbal drugs and phytochemicals bind to different targets of SARS COV-2. Though majority of the reported data is limited to computational studies, further *in vitro* and *in vivo* investigations may lead to development of COVID19 therapies. In this direction, the phytopharmaceutical formulation AQCH has been studied in a small group of animals and progressed to clinical trials.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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