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Could nature be the solution- A review on selected folklore medicinal plants with antiviral activities repurposed for COVID-19 treatment

Arvind Kumar Goyal[a,*], Sushil Kumar Middha[b] & Talambedu Usha[c]

[a]Department of Biotechnology, Bodoland University, Kokrajhar 783 370, Bodoland Territorial Region, Assam, India

[b]Department of Biotechnology,

[c]Department of Biochemistry, Maharani Lakshmi Ammanni College for Women, Bengaluru 560 012, Karnataka, India

E-mail: arvindgoyal210883@gmail.com

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The outbreak and rapid spread of novel Coronavirus SARS-CoV-2 has resulted in global pandemic. The purpose of this work is to provide an ethnopharmacological overview of selected medicinal plants having antiviral activity along with their applications to treat COVID-19 related symptoms based on fragmented literature. Hundreds of published research articles were screened and reviewed using online search engines such as PubMed, PMC and Google Scholar with relevant keywords related to coronavirus, antiviral medicinal plants, phytochemical compounds, cough and fever. A total of 12 plants having antiviral activity against a number of viruses were documented with their probable mechanism of action. Most of the studied plants and their compounds were also reported to have other therapeutic potentials and were used to boost immunity, treat cough, fever, tiredness, difficulty in breathing and diarrhoea, which are common symptoms of COVID-19 infections as per World Health Organization. This review hopefully opens a new horizon in the development of antiviral drug against novel coronavirus COVID-19.

Keywords: Antiviral, COVID-19, Coronavirus; Herbal, Medicinal plants

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The COVID-19, 2019-nCoV or SARS-CoV-2 virus, all stand for a single virus nomenclature which was reported during December 2019 in Wuhan, China. Initial studies have revealed that COVID-19 is less pathogenic compared to the other coronaviruses (CoV), however, the transmission ability is much higher[1]. The same is evident from the escalating number of infections around the world since the day of inception. On 11th March, 2020, the World Health Organization confirmed COVID-19 as a pandemic, which cost an anticipated $30 to $100 billion in worldwide economy[2].

Within less than three months, it has affected as many as 213 countries and territories and two international conveyances (the Diamond Princess Cruise ship harboured in Yokohama, Japan and the Holland America's MS Zaandam cruise ship). As of 1st August, 2020, the number of confirmed cases registered worldwide account for above 18 million and a total of around 688,247 people were affected by this deadly virus having a fatality rate of 3.82%. China, from where the virus was first reported[1], topped the list in terms of registered cases followed by Italy and USA during March 2020. In contrast to this, by 15th April, USA had taken the first position based on the number of confirmed cases followed by Spain, Italy, France, Germany and others (www.worldometers.info/coronavirus/), whereas USA struggles to save the lives of its people and stands first in the tally of the death toll which is increasing with the passage of time followed by Italy and Spain.

India, the second largest populated country in the world, recorded its first case of infection on 30th January, 2020, in a patient having a travel history from Wuhan University, China, to Kerala state. During February, 2020, there were only two cases of COVID-19 in India, however, it increased at an exponential rate since March 2020 and by 1st August, 2020 it reached over 1.80 million, of which 38,165 were reported dead with mortality rate of 2.11% (www.covid19india.org). A total of nearly 1.19 million people recovered from the impact of the

*Corresponding author

deadly virus. The COVID-19 virus has affected the entire geographical territory of India. Of all the States and Union Territories, Maharashtra, Tamil Nadu, Andhra Pradesh, Karnataka and Delhi were severely affected.

With the passage of time, the number of confirmed cases, death toll, and the number of countries affected by COVID-19 are ever increasing and have become a matter of deep concern. People are fighting for their lives in hospitals to combat the virus and till date no successful antiviral oral drug exists to prevent the pandemic as it takes several months of research to develop an effective drug/vaccine against a novel infection[3]. In this period of struggle and race to combat COVID-19, the traditional herbal medicine emerges as a first line of defence for the people especially in India[4].

Herbal medicines have been an indispensable part of the healthcare system of the people inhabiting the developing countries since ancient times[5,6]. Innumerable plants are already established as drugs for various ailments including bacterial, fungal, viral etc., but their effectiveness towards COVID-19 is yet to be affirmed by clinical trials. This review focuses on 12 potential candidates majorly found in India that have been reported to possess antiviral activities against various viruses in addition to being effective in treating COVID-19 related symptoms such as fever, cough, tiredness, difficulty in breathing and diarrhoea.

Plants as a source of drug

Advantages and disadvantages

The following specific advantages help us to proceed for drug development from plant sources:

- The ethnomedicinal history of the candidate plants opens up a horizon for investigation since the long-term use by humans is presumed to be relatively safer compared to unexplored ones[7].
- Botanical resources exhibit incredible chemical and structural diversity. The structural diversity in turn helps the researchers to create novel chemical entities using the tools of *in-silico* drug designing[8].
- Drug development from botanical sources is also associated with certain disadvantages:
- Drug development from botanical sources may result in overexploitation of the candidate due to commercialization[7].
- Nowadays, there is an increasing trend of protecting the traditional formulation or drugs by the intellectual property rights. These in turn limit the drug discovery process at various stages[9].

Potentiality of the bioactive compounds to become a drug

The existing standards for drug discovery in pharmaceutical industries and scientific confinement in isolating novel compounds with desirable activity limit the development of new drugs. Koehn and Carter[10] listed a number of attributes for the bioactive compounds from plant origin to be an effective drug molecule such as increased chirality, steric complexity, oxygen atoms, hydrogen bond acceptors and donors, molecular rigidity, lower ratio of aromatic ring atoms to total heavy atoms and wider distribution of molecular property. The complexity of chemical entities of plant origin makes it a daunting task for medicinal chemists to initiate the drug discovery process[11].

Though an enormous number of phytochemicals are known to be biochemically active and have favorable absorption, distribution, metabolism, excretion and toxicity profiles but all cannot be considered to be effective drugs.

Complementary and alternative medicines and coronavirus

Coronavirus (Coronaviridae family; CoV), is a single-stranded RNA virus, found to be the root cause of respiratory tract infections in mammals as well as avians. The World Health Organization delegated three major pathogenic viruses rising from animal reservoirs such as severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and novel coronavirus (2019-nCoV/SARS-CoV2) popularly known as COVID-19, which is considered highly fatal. The use of saikosaponins (A, B2, C and D) from *Bupleurum* spp. was explored by Cheng *et al.*[12] for its antiviral activity against HCoV-22E9. They inhibit viral attachment and penetration stages of virus[12]. Lin *et al.*[13] identified plant derived inhibitors such as myricetin and scutellarein against SARS-CoV enzymes (nsP13 helicase and 3CL protease) from *Isatis indigotica*.

Methodology

Based on the rationale, an online search was performed during 15th March to 15th April, 2020 using

various bibliographical databases, PubMed, PMC and Google Scholar, using coronavirus and medicinal plants as key words along with anti-viral, anti-pyretic, anti-fatigue, anti-dyspnoea, anti-diarrhoeal, cough etc. To ensure the scientific names with respect to the accepted names, synonyms, families, author citations we searched plant database such as "International Plant Names Index" (www.ipni.org). Hundreds of articles were reviewed for this purpose, but only relevant papers were screened for extracting the related information (Fig. 1).

Probable potential candidate species that can inhibit Covid-19

A large number of plants and phytochemical compounds have been documented for control of viruses and future drug development. In this review we discuss 12 medicinal plants that emerged to have broad spectrum antiviral activity besides being used to treat cough, fever, diarrhoea and shortness of breath etc.

Azadirachta (*A.*) *indica* A. Juss.

A household name amongst Indians, *A. indica* (Family: Meliaceae) is popularly known as neem. It finds its application in all form of medicines like Ayurveda, Unani, and Homeopathy for treating various diseases since centuries[14]. Neem is laden with a number of bioactive molecules which are effective as anti-inflammatory, anti-ulcer, anti-diabetic, immune-modulator, anti-mutagenic, anti-carcinogenic, antioxidant and anti-viral drugs[15]. Sairam *et al.*[16] reported the antiviral activity of neem oil (NIM-76) against polio vaccine in Vero cell line by restraining the replication of the virus. Similar type of activity was also reported by Parida *et al.*[17] in their study on the impact of aqueous extract of neem leaves on dengue virus type-2 in $C_{6/36}$ cells. Though the exact mechanism of action is not clear, it is evident from the above studies that they interfere possibly with viral replication, their envelop structure and thus help control the viral infections[18]. A total of 173 patents were granted since 2000 as reported by Singh *et al.*[19].

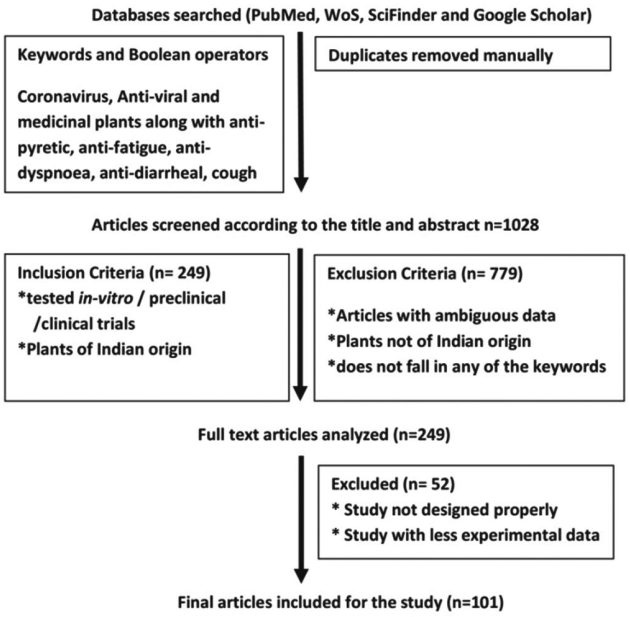

Fig. 1 — Flow chart of the research design

Camellia (*C.*) *sinensis* (L.) Kuntze

Beverage tree crop, *C. sinensis* (Family: Theaceae) is native to Southeast Asia and it is the most widely consumed drink globally next to water. It is rich in polyphenolic flavonoids, catechins. Four different forms of catechins are reported in tea leaves viz., e (-) -epicatechin (EC), (-) -epicatechin-3-gallate (ECG), (-) -epigallocatechin (EGC) and (-)-epigallocatechin-3-gallate (EGCG) [20]. EGCG and EGC are the most abundant and largely explored on medical grounds[21]. The efficacy of EGCG was studied to combat Hepatitis C virus (HCV) by Calland *et al.*[22] They found that EGCG had the potential to inhibit the entry either by altering the virion or by blocking interaction between the envelop glycoprotein (gB and gD) and the virus. This study is in consonance with earlier study on the effect of EGCG on HIV where it binds to the CD4 cells, restricting the binding of viral glycoproteins to CD4 cells and thus suppressing viral infection[23]. In 2012, Ling *et al.*[24] systematically tested the anti-influenza A activity of EGCG on Madin-Darby canine kidney cells and inferred that EGCG has the potential to inhibit the replication of influenza A. Liang *et al.*[25] evaluated the efficacy of (+) -catechin in swine testicle cell lines against transmissible gastroenteritis coronavirus infection and revealed that (+)–-catechin impaired the viral RNA replication and prevent infection.

Cinnamomum sp.

Cinnamon botanically known as *Cinnamomum* sp. (Family: Lauraceae), a spice known for its fragrance finds its utilization not only in cooking but also in medicine[26]. The resinous compounds present in cinnamon helps to inhibit the entry of HIV-1 into the host cells probably by binding itself with the HIV-1 virion[27]. Premanathan *et al.*[28] screened bark of *Cinnamomum cassia* against HIV-1 and HIV-2 in

MT-4 cells and found it to be effective against both the infections. In 2016, Connell *et al.*[29] assessed the anti-HIV-1 activity of cinnamon-derived compound (IND02) and opined that this compound not only obstructs viral replication but also binds to the viral envelop glycoprotein and prevent infection. In addition to this, IND02 restrains T cell exhaustion by restoring the population of CD4+ T cell[30]. In a separate study, Fauvella and his team[30] experimented the anti-HCV activity of IND02. They inferred that IND02 obstructs the HCV viral entry but does not have any role to play in its replication.

***Curcuma* (*C.*) *longa* L.**

Turmeric, scientifically know as *C. longa* (Family: Zingiberaceae), is largely explored on scientific grounds to validate its therapeutic effects[11,31,32]. Curcumin, the principal ingredient in *C. longa* has a plethora of pharmacological properties. The anti-viral activity of *C. longa* in general and curcumin in particular has been screened and validated against a number of viruses by different researchers. The anti-viral activity of curcumin is well established in case of HIV, different scientists have reported different mechanisms of action against HIV virus. Mazumder *et al.*[33] and Gupta *et al.*[34,35] hypothesized that curcumin and its derivatives inhibit the activity of HIV-1 integrase enzyme. Ali and Banerjea[36] studied the effect of curcumin on HIV-1 Tat protein which is associated with viral replication and revealed that curcumin inhibits HIV-1 by degrading the viral Tat protein. In an attempt to evaluate the anti-HCV activity of curcumin in hepatoma cell lines and primary human hepatocytes, Anggakusuma *et al.*[37] concluded that curcumin hinders the entry of HCV irrespective of its genotypes. Besides these, curcumin, the active component of *C. longa* has been effective against Coxsackievirus, Enterovirus 71(EV71) and Rift Valley fever virus by inhibiting viral replication[38-40], Chikungunya virus and Human Norovirus by obstructing the viral entry in the host[40,41]. In case of Influenza A virus, curcumin combats the virus by three mechanisms by attacking envelop (*i.e.*, virus inhibition) in addition to limiting viral replication and entry[42,43].

***Emblica* (*E.*) *officinalis* Gaertn. or *Phyllanthus* *(P.)* *emblica* L.**

E. officinalis, *P. emblica* or Indian gooseberry (Family: Phyllanthaceae), rejuvenating herb is known as Amla in India[44]. A number of studies have been carried out to assess the anti-HIV activity of amla over years. Bothiraja *et al.*[45] observed the anti-HIV activity of *E. officinalis* by detecting viral p24 antigen concentration. They inferred that *E. officinalis* can help treat HIV-1 by reducing viral load. In 2012, two studies reported the anti-HIV-1 activity of *P. emblica*[46,47]. Both experiments revealed the anti-HIV-1 reverse transcriptase activity of *P. emblica*. *P. emblica* was also subjected to determine anti-HSV-1 and anti-HSV-2 activity[48,49]. Qu *et al.*[48] opined that *P. emblica* can be a potential anti-HSV therapy based on their results. Xinag *et al.*[49] established that 1,2,4,6 tetra-O-galloyl β D glucose, isolate of *P. emblica* retarded the viral entry and pacified viral particles. Lv *et al.*[50] isolated sesquiterpenoid glycosides from *P. emblica* and checked for its anti-Hepatitis B virus activity. They surmised that the glycoside altered HBsAg and HBeAg secretions. Liu *et al.*[51] and Wang *et al.*[52] evaluated the efficacy of Norsesquiterpenoids and Phyllaemblicin B respectively in the management of Coxsackie virus B3 (CVB3). Liu *et al.*[51] employed HeLa cells to assess the virucidal activity of Noresesquiterpenoids and revealed that they possess strong anti-CVB3 activity. Wang *et al.*[52] also used HeLa cell line and elucidated that Phyllaemblicin B has potent anti-CVB3 activity. The compound not only inhibited the replication of CVB3 virus but also induced apoptosis. In an *in silico* approach, Amini and Mansouri[53] established that the ursolic acid from *P. emblica* has the potential to impede E1 and E2 proteins, which are the major component of Human Papilloma Virus DNA replication and thus have anti-HPV activity.

***Foeniculum* (*F.*) *vulgare* Mill.**

F. vulgare or Fennel (Family: Apiaceae), is an aromatic herb with culinary and medicinal uses. This plant is bestowed with a number of health benefits since antiquity[54] and a lot of work has been carried globally to ascertain the same. However, this virtually remains unexplored for probable antiviral activity. Orhan and his team[55] evaluated the virostatic efficacy of fennel against Herpes simplex type-1 (HSV-1) and parainfluenza type-3 on Vero cells and found it to be effective against both of the viruses but the mechanism was not known[54].

***Mentha* (*M.*) *spicata* L.**

Spearmint or *M. spicata* (Family: Lamiaceae) is a perennial aromatic herb used in various delicacies[55]. A number of reports are available which justify its

medicinal use in conditions such as common cold[56] and digestive disorders[57] but there are only a few reports on antiviral activity of *Mentha* sp.

***Ocimum* (*O.*) *sanctum* Linn.**

Tagged as "Extract of Life", *O. sanctum* (Family: Lamiaceae) is also popular as Tulsi. It is a holy herb with immense health benefits[58]. A boon for the treatment for cold and cough, tulsi has been reported to have antiviral activity against hepatitis and encephalitis based on clinical trials[59-61]. The anti-HSV activity of *O. sanctum* was studied using green monkey kidney cell lines. *O. sanctum* demonstrated multiple effects such as restricting viral entry, viral replication and thus established to possess antiviral activity against HSV[62]. Tulsi plant was subjected to test for antiviral activity against dengue virus-1 (DENV-1) on HepG2[63]. It showed cytopathic effect and thus inhibited DENV-1, besides it also hindered viral replication. Rege and Chowdhary[64] made an attempt to ascertain *O. sanctum* as a potential candidate against HIV. They reported triple mechanism of action of *O. sanctum* against HIV viz., obstructing the gp120 and CD4 interaction, hindering HIV-reverse transcriptase and HIV-protease enzyme.

***Picrorhiza* (*P.*) *kurroa* Royle ex Benth.**

P. kurroa (Family: Plantaginaceae) or Kutki, a herb is well recognized for its hepatoprotective activity in the traditional system of medicine[65]. Several experiments have been carried out to evaluate the antiviral activity of *P. kurroa* on hepatitis virus but their mechanism of action is not reported[66,67]. Win *et al.*[68] employed TREx-HeLa-Vpr cell lines to assess the anti-viral protein A (Vpr) of bis-iridoid glycosides isolated from *P. kurroa*. The glycosides suppressed the expression of Vpr and thus were established as natural inhibitor of Vpr.

***Tinospora* (*T.*) *cordifolia* (Willd.) Miers ex Hook. f. & Thomson**

T. cordifolia (Family: Menipsermaceae), commonly referred as Guduchi or Giloy is an immune boosting climber. It is a storehouse of many bioactive constituents thus has myriad applications in the field of pharmaceuticals[69]. Kalikar *et al.*[70] made an attempt to investigate the role of *T. cordifolia* in the management of HIV. They focused mainly on six parameters namely total leukocyte count, differential leukocyte count, erythrocyte sedimentation rate, platelet count, haemoglobin among the HIV patients and found that *T. cordifolia* was mainly effective in suppressing the HIV associated symptoms with decreased eosinophil count and haemoglobin[70,71]. The HIV-1 reverse transcriptase inhibition activity of Guduchi was studied by Estari *et al.*[72], they reported that the plant was effective in inhibiting the HIV-1RT and thus possesses anti-HIV activity. Recently in 2019, the protective effect of silver nanoparticles obtained from *T. cordifolia* was evaluated against Chikungunya virus in Vero cell lines[73]. The investigators reported that *T. cordifolia* has the potential to inhibit Chikungunya virus.

***Withania* (*W.*) *somnifera* (L.) Dunal**

Aswagandha or Indian ginseng, botanically known as *W. sominifera* (Family: Solanaceae) is an indigenous plant having a number of therapeutic uses[74]. Grover *et al.*[75] explored the antiviral potential of a steroidal lactone, Withaferin A obtained from *W. sominifera* against HSV *in silico* and validated it be effective in hindering the viral replication. The human neuronal cell line, SK-N-MC was employed to ascertain the anti-HIV activity of aswagandha and it was noted that aswagandha could inhibit HIV-1 related disorders[76].

***Zingiber* (*Z.*) *officinale* Rosc.**

Ginger, scientifically referred as *Z. officinale* Rosc. (Family: Zingiberaceae), a spice that has been shown to demonstrate innumerable therapeutic effects against various ailments in India and China[77]. A plethora of researches have been conducted on this medicinal plant. Imanishi *et al.*[78] used Madin-Darby canine kidney cells to investigate the anti-influenza A/Aichi/2/68 (Aichi) virus of *Z. officinale*. It was found that *Z. officinale* did not have any direct impact on the virus but was able to suppress the viral load by activating the macrophage and producing TNF-α. Same laboratory from Germany, carried out two experiments to ascertain the anti-HSV activity of ginger oil using African green monkey kidney cells (R-37 cells)[79,80]. Schnitzler *et al.*[79] concluded that ginger oil was able to inhibit HSV-1 virus prior to adsorption. Similar mode of action was reported by Koch *et al.*[80] while working on HSV-2 virus. A number of studies were carried out to screen the influence of *Z. officinale* on HCV[81-83]. Experimental studies revealed that ginger suppressed viral replication and thus inhibited HCV grown on hepatocellular carcinoma HepG2 cell line.[82] El-Wahab *et al.*[81] also reported similar mechanism against the virus. In another study, Abdel-Moneim *et*

al.[83] suggested that *Z. officinale* was potent in depleting hepatitis C viral load. Solvent based study was carried out by Sharma *et al.*[84,85] to establish the modulatory effect of *Z. officinale* (methanolic and aqueous) on matrix metalloproteinases and tissue inhibitors of metalloproteinases on dengue virus infected C6/36 cell lines. Both the methanolic and aqueous extracts of ginger prevent dengue-virus infections by down regulating and up regulating the expression of matrix metalloproteinases and tissue inhibitors of metalloproteinases, respectively.

The plants under study are rich source of pharmacologically active metabolites such as curcumin, phyllaemblicin B, azadiractin, eugenol, berberine, tinosporin and withaferin A. They exert the activity either singly or in synergy (Fig. 2A and 2B).

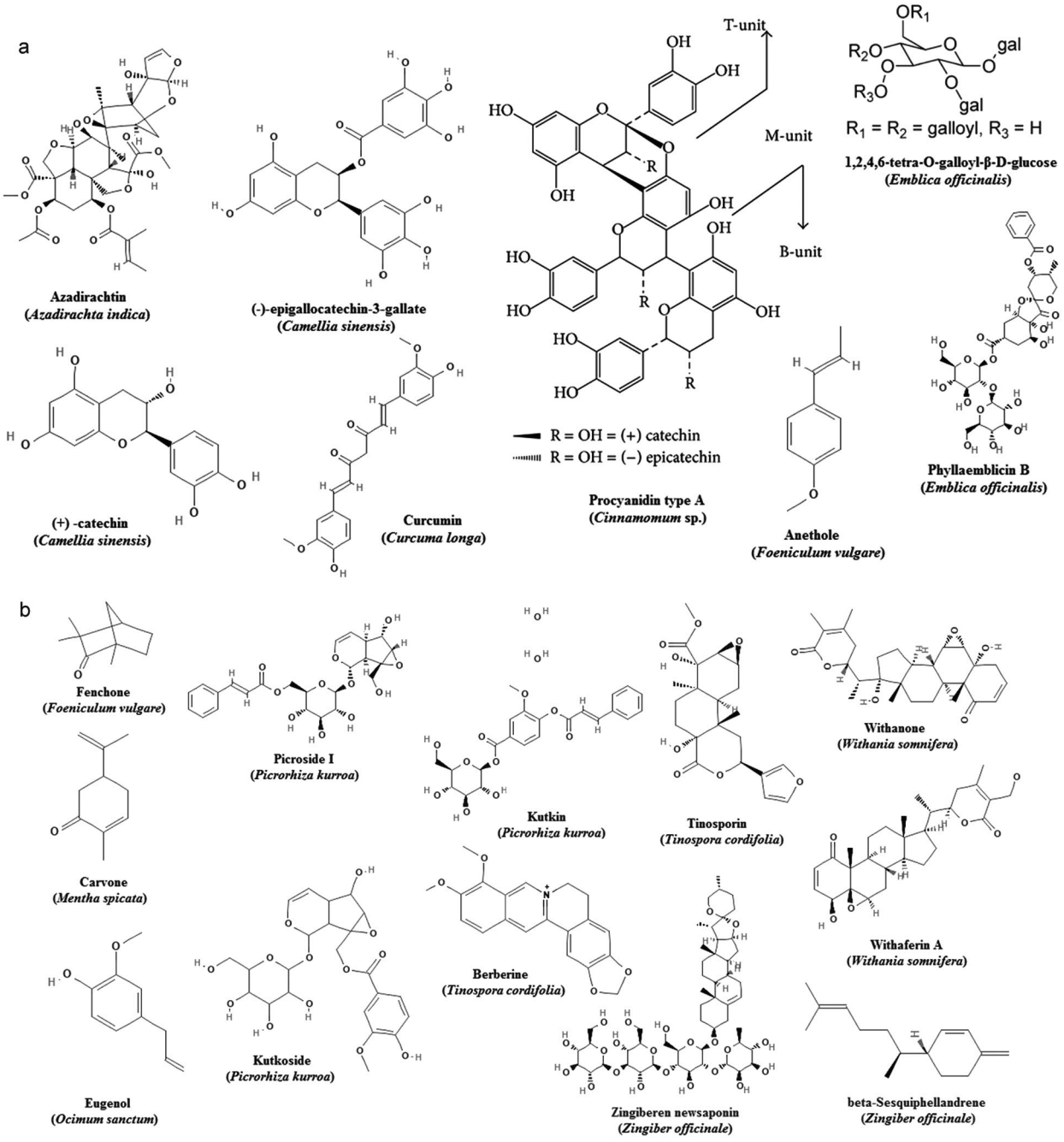

Fig. 2 — (A&B): Chemical structure of the major components having antiviral activity (*Courtesy:* https://pubchem.ncbi.nlm.nih.gov/ *accessed on 6th June, 2020*)

Table 1 — Plants and their natural compounds for clinical management of COVID-19

Plant name	Compound	Target
Azadirachta indica	Azadirachtin	IS-Spike protein inhibitor[92], PL-Pro protein inhibitor[91], SARS-CoV-2 M^{Pro} inhibitor[93]
Camellia sinensis	(-)-epigallocatechin-3-gallate	All the three sites of spike protein[94]
	(+) –catechin	Spike-protein near RBD site and ACE2[95]
Curcuma longa	Curcumin	RBD site of Spike-protein and ACE2[95], SARS-CoV-2 M^{Pro} and ACE2 inhibitor[96]
Emblica officinalis	Phyllaemblicin B	SARS-CoV-2 M^{Pro} inhibitor[97]
Mentha sp	Carvone	SARS-CoV-2 M^{Pro} inhibitor, SARS-CoV-2 S^{Pro} inhibitor[98]
Ocimum sanctum	Eugenol	SARS-CoV-2 M^{Pro} and ACE2 inhibitor[96]
	Tinosporin	Spike glycoprotein inhibitor, SARS-CoV-2 M^{Pro} inhibitor, RdRp inhibitor[99]
	Cordioside	Spike glycoprotein inhibitor, SARS-CoV-2 M^{Pro} inhibitor, RdRp inhibitor[99]
Withania somnifera	Withanone	SARS-CoV-2 M^{Pro} inhibitor[100]
	Withaferin A	Spike glycoprotein inhibitor[99], SARS-CoV-2 M^{Pro} inhibitor[99], RdRp inhibitor[99], SARS-CoV-2 M^{Pro} inhibitor[101]

The targets of herbal products against CoVs

Active compounds, found in herbal formulations of Indian origin, have shown antiviral activity by acting on several molecular targets as illustrated in Table 1. Authors reviewed the targets of natural products against coronavirus. These targets include the binding domain of the SARS-CoV-2 spike protein, coronavirus main 3-chymotrypsin-like cysteine protease, papain-like protease, SARS-CoV-2 RNA-dependent RNA polymerase, SARS-CoV-2 endoribonucleoase other kinase such as viral helicase and the host receptor human angiotensin−converting enzyme[86].

The prospective of natural compounds for clinical management of COVID-19

The spike protein(S) fundamentally known as entry protein is the primary determinant of tropism. Angiotensin−converting enzyme 2 is expressed in a wide variety of tissues and is also found in lower respiratory tract[101]. The S protein binds to the host receptor angiotensin−converting enzyme 2 and undergoes conformational changes leading to proteolytic cleavage of its protein by cathepsin or other proteases aiding in fusion of viral and cellular membrane. After fusion, the genomic material (RNA) binds directly to host ribosome and gets translated in two large proteases: 3-chymotrypsin-like cysteine protease and papain-like protease by proteolysis for packaging new virions[87]. To replicate RNA genome, virus encodes a specific replicase, named RdRp. Therefore, the virus needs four specific protein entities to exhibit its pathogenicity. Hence, targeting these proteins could be the possible cure for SARS-CoV-2. Previous genomic studies of COVID-19 indicated that catalytic sites of the four COVID-19 enzymes are highly conserved and showed similarity to SARS and MERS enzyme[88]. So it is wise to use drug repurposing approach using existing MERS and SARS inhibitors for COVID-19 treatment[89].

The coronavirus spike (S) *N*-glycoprotein is also the main target for vaccine development as it is antigen presented at viral surface and recognized by the host immune system of the infected host. This S-protein is responsible for host cell non-covalent attachment, which makes it special for the future drug designing approach and infection[90].

Conclusions and future perspectives

Viral infection especially COVID-19 is a major threat to mankind and public health. During the last two decades, the world has witnessed the emergence and resurgence of a number of novel and deadly viruses which pose a serious threat to human health such as Nipah virus (1999), SARS-CoV (2002-03), Swine H1N1 influenza A virus (2009), MERS-CoV (2012), Ebola virus (2014-16), Zika virus (2015). The sequence similarity and phylogenetic analysis of SARS-CoV2 against a collection of other known coronavirus sequences found that it can be classified as β-coronavirus[88]. The ongoing outbreak of the pandemic virus COVID-19, which has created havoc globally, spreads its wings over 213 countries and two international conveyances. Though the world cannot restrict such outbreaks, with the development in the field of science and technology, researchers are well equipped to identify the pathogens within a short span of time. Despite advancement in development of antiviral drugs, there are still special needs to find new antiviral agents to combat the multi-drug resistant viruses that are evolving.

At present, the entire world is grappling for the drugs to overcome the pandemic caused by COVID-

19 either synthetic or herbal. Therefore, drug repurposing using plant sources could be used as an alternative to heal the world. Plants have always been an indispensable part of drugs for various ailments since time immemorial and virus is no exception. The published literatures affirm the antiviral activity of a significant number of plants that have been or could be used as a potential drug either singly or in combination to overcome viral outbreak.

A total of 12 plants viz., *A. indica*, *C. sinensis*, *Cinnamomum* sp., *C. longa*, *E. officinalis*, *F. vulgare*, *M. spicata*, *O. sanctum*, *P. kurroa*, *T. cordifolia*, *W. somnifera*, *Z. officinale* which have been in news as effective against COVID-19 since the outbreak has been reviewed to examine their efficacy. The above mentioned plants have been found effective against a number of viruses such as Influenza A, HCV, HIV-1, HIV-2, Polio virus, T-gastroenteritis coronavirus, hepatitis B virus, Coxsackievirus, Enterovirus 71, Rift Valley fever virus, Chikungunya virus, human Norovirus, herpes simplex virus 1 and 2, human Papilloma virus, Parainfluenza virus-1, dengue virus, human respiratory synctial virus, human Rota virus, vesicular stomatitis virus etc.

Synthetic medicines might be able to manage symptoms quickly in infected patients, but may have severe side effects. These herbal medications have the benefits of low toxicity. These products could be a good immune-modulator and manage cytokines linked with immune responses and enhance resistance to viral infection by improving immune system.

It was evident from the literature that the plants were effective in reducing viral load by restricting viral entry into the host, inhibiting viral replication, obstructing the gp 120 and CD4 interaction, hindering viral-reverse transcriptase, viral-protease enzyme, degrade viral Tat protein etc. Therefore, based on the above review, we may infer that these plants may be effective in prevention and management of COVID-19 either individually or in conjunction with each other. It is the need of hour to explore these plants and try to formulate, standardize and evaluate a formulation against COVID-19 which play a major role in antiviral drug development.

Challenges and limitations

Some of the key issues connected with herbal formulations and compounds derived from natural sources include a lack of knowledge regarding the mechanism of action of herbal compounds in a particular disease and their influence on various targets. As indicated in this review, these products could help in the treatment of COVID-19 via a variety of mechanism. Bioavailability and solubility are the key hurdles in developing a natural product to drug therapeutics, as the major compounds covered in this research only have *in-silico* validations[91]. Hence, the success rate, amount of time consumed and high cost involved eventually challenge these compounds to enter in clinical trials.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Authors' Contributions

AKG conceptualized the study. AKG, SKM and TU performed the literature search, analysed the data, created tables and figures. All the authors approved the manuscript for final submission.

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