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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