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6. Surviving The World Through The Ultimate Panacea: Plants

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Introduction:

The novel coronavirus 2019 (COVID-19), the unexpected pandemic, has caused severe panic among people worldwide. The advent of COVID-19 has kept the whole world on their toes. Countries are maximizing their efforts to combat the virus and minimize infection. However, most of the countries are unprepared for a disease at this magnitude and may not be able to prevent transmission or treat the condition efficiently. But the potential problem will continue to persist until the development of an effective viral vaccine. According to the World Health Organization (WHO), COVID-19 is the infectious disease caused by the coronavirus SARS-CoV-2. This new virus and disease were unknown before the outbreak began in Wuhan in December 2019. COVID-19 is now a pandemic disease, with nearly eight million confirmed cases and 434,367 deaths (WHO, 16 June 2020). Medicinal plants are considered as rich resources of biofunctional compounds which can be used in drug development or synthetic drugs. Ayurveda and Siddha practices originated in India and are still widely used among the Indian population. By identifying certain phyto-compounds, it is possible to effectively characterize medicinal herbs that could help to alleviate the infection. Hence, by repurposing the Indian medicinal plants, more innovative treatment options can be penned down for their role in defeating this viral transmission. At a time of worldwide anxiety, it is imperative to find long term solutions to prevent the transmission of such pandemics. So, it's time for all the citizens to join hands together to fight against corona-virus by practicing self-hygiene and social distancing. These plants play a critical role in the development of human cultures around the whole world. There are many benefits of herbal medicine as they are easier to obtain than prescription medicine, stabilizes hormones and metabolism, natural healing, strengthens immune system, fewer side effects. Application of modern technologies and methodologies in herbal medicine research can have a significant impact on the scientific validity, quality improvement, and standardization of herbal medicines.

Over View Of The Disease:

Coronaviruses (CoV) (Family: Coronaviridae) are enveloped viruses containing non-segmented, positive-stranded genomic RNA (Li, 2016) (Fig-1). Coronaviruses are named for the crown-like spikes on their surface (Fig 2). There are four main sub-groupings of coronaviruses, known as alpha, beta, gamma, and delta. People around the world commonly get infected with human coronaviruses 229E, NL63, OC43, and HKU1. It is found in 2 strains, which is named L and S strains. The S type is older, but the L type was more common in early stages of the outbreak. Coronaviruses having an impact on human health in past. SARS-CO V (Severe Acute Respiratory Syndrome Coronavirus) emerged in 2003, with a mortality rate of 10 % and more than 8000 cases were reported. MERS-CoV (Middle East Respiratory Syndrome Coronavirus) emerged in 2012, with a mortality rate of 35% and more than 2500 cases were reported. SARS-CoV-2 (COVID-19) emerged in 2019 and now declared as Pandemic. This Novel coronavirus (nCoV-19) has caused more than 8 lacks of deaths during January to August 2020 (Table 1.)

These viruses are pleomorphic particles with sizes ranging from 80 to 120 nm in diameter (Neuman et al., 2011). Their entire replication cycle takes place in the cytoplasm. Research findings indicated that the CoV envelope is involved in critical aspects of the viral life cycle, and that CoVs lacking CoV envelope make promising vaccine candidates (Schoeman & Fielding, 2019). CoVs are able to cause a number of diseases, including bronchitis, gastroenteritis, hepatitis, systemic diseases, and even death in birds, humans, and other animals. Coronavirus could possibly infect animals as well as humans causing severe gastroenteritis and respiratory complications. Serologically, three identified strains of the virus have been reported to date. They are classified as per their genome sequence and the host range. Two strains HCoV-229E and HCoV-OC43 have been recognized in 1960 causing the well-controlled common cold symptoms. The third life-threating corona virus named SARS-CoV can lead to lethal pneumonia. SARS-CoV has been identified as the most lethal coronavirus till then as has been mentioned in an article published in February 2004 (van der Hoek et al., 2004). This novel strain of corona virus managed to spread over a wide geographic location within a very short period of time.

Table 1: Growth Of The Virus At World Level

Journey of SARS-CoV-2 Towards Pandemic
December 2019: Unusual cases of Pneumonia reported in Wuhan, China
December 31, 2019: Coronavirus cases reported to WHO office China
January 1,2020: Seafood and meat market in Wuhan recognized as origin of the coronavirus and was closed
January 7, 2020: Chinese scientist identified the virus as a novel strain of coronavirus
January 12, 2020: Scientist shared the first entire sequence of the novel virus and diagnostic kit was designed
January 13, 2020: Thailand reported the first case of virus outside China
January 20, 2020: First case reported in US.
Journey of SARS-CoV-2 Towards Pandemic
January 24, 2020: First 3 cases reported in Europe
January 30, 2020: First confirmed case in India
End of January 2020: Novel virus was named SARS-CoV-2
January 30, 2020: WHO reported the disease as Global Public Health Emergency
February 11, 2020: WHO named the disease caused by SARS-CoV-2 as COVID-19
March 11, 2020: WHO declared COVID-19, a global pandemic.
July 2020: Total number of cases crossed 10 million globally with a death toll of over 5 lacs
August 25, 2020: Total mortality in the world over 8 lacs.

Transmission Of Disease:

SARS-Cov-2 appears to need to bind to the ACE 2 receptor to enable it to infect host cells. ACE2 receptors are found in ciliated epithelial cells in the upper and lower airway and in type II pneumocytes in the alveoli in the lower airway (Fig-3). Type II pneumocytes produce lung-lubricating proteins important for lung function. Four proteins, (Envelope, Spike, Membrane, Nucleocapsid) the spike, 3CLpro, PLpro, and RdRp are essential for the virus.

Therefore, therapeutics targeting one of these proteins is currently being tested as a possible treatment for SARS-CoV-2.

The penetration of the SARS-CoV-2 genome into the host cells occurs as a result of the SARS-CoV-2 spike protein binding to host receptors (Sigrist et al., 2020). By using phylogenetic analysis and critical site of ACE2 structure, different animals such as cat, pigeon, and sheep were predicted to be important intermediate hosts for SARS-CoV-2. Hoffmann *et al.* (2020) demonstrated that the ACE2 receptor is used by SARS-CoV-2 to enter human cells. Moreover, they reported that the use of TMPRSS2 inhibitors may be a promising therapeutic approach against SARS-CoV-2. TMPRSS2 is a transmembrane serine protease that cleaves both ACE2 and the S protein. Recently, Ortega et al. (2020) used *in silico* approaches to understanding the relationship between changes in SARS-CoV-2 Spike protein and ACE2 receptor. They demonstrated superior affinity of SARS-CoV-2 spike protein towards human ACE2 as compared to that of the Bat-CoV spike and ACE2. This study supported the idea that the ACE2 receptor may be the key "bridge" used by SARS-CoV-2 to transmit among humans. Chen et al. (2020) confirmed that although SARS-CoV and SARS-CoV-2 RBD of spike glycoprotein had 72% of structural similarities, SARS-CoV-2 RBD exhibited higher interaction with ACE2. ACE2 inhibitors are thought to indirectly alter the RBD binding site and therefore block SARS-CoV-2 infection. Likewise, Wrapp et al. (2020) found that the SARS-CoV-2 spike exhibited a higher affinity to ACE2 than SARS-CoV. Adedeji et al. (2013) demonstrated that early blocking of SARS-CoV with ACE2 inhibitors was one of the mechanisms used by novel efficient anti-SARS drugs. It is also notable that hypertension and diabetes mellitus significantly enhanced the risk of COVID-19 infection, in spite of using ACE2 inhibitors (Guan et al., 2019). Commercially available antiviral drugs mostly target the four major groups of viruses: human immunodeficiency virus (HIV), herpes, hepatitis and influenza (Razonable, 2011). Earlier outbreak episodes of viral infections like SARS-CoV and MERS-CoV as well as hemorrhagic fever viruses like Ebola were treated with this category of drugs (De Clercq, 2007). The major drugs undergoing clinical trials that have the potential to treat this viral infection (Table 2.) are listed, but due to side effects or developing drug resistance, more research may be required in traditional medicine to utilize them in the treatment of COVID-19.

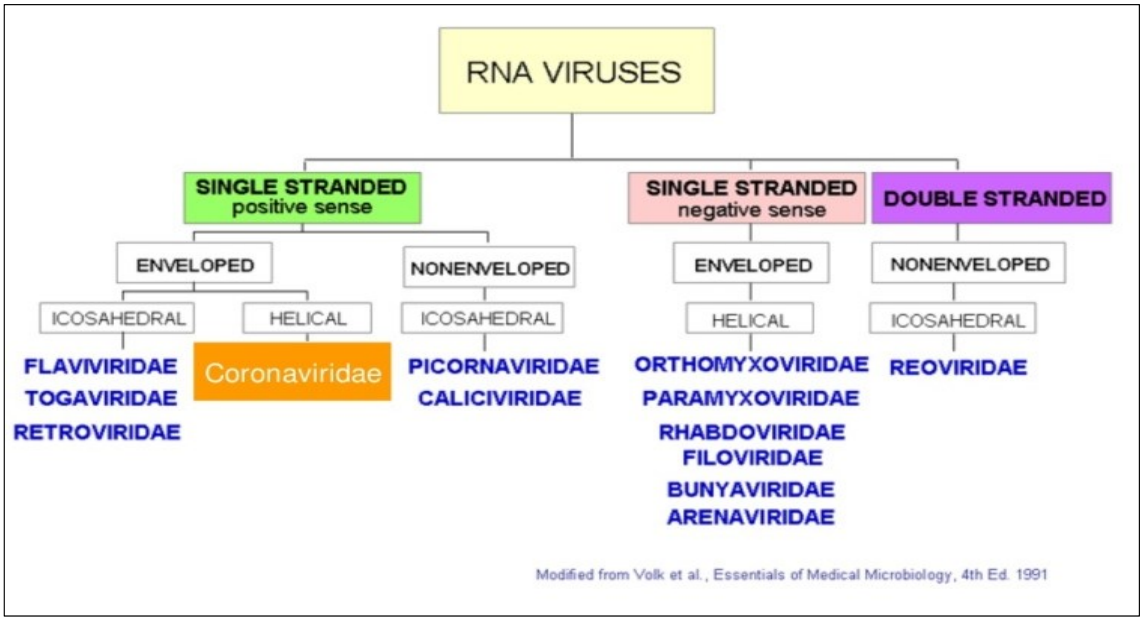


Fig-1 Classification of RNA Viruses

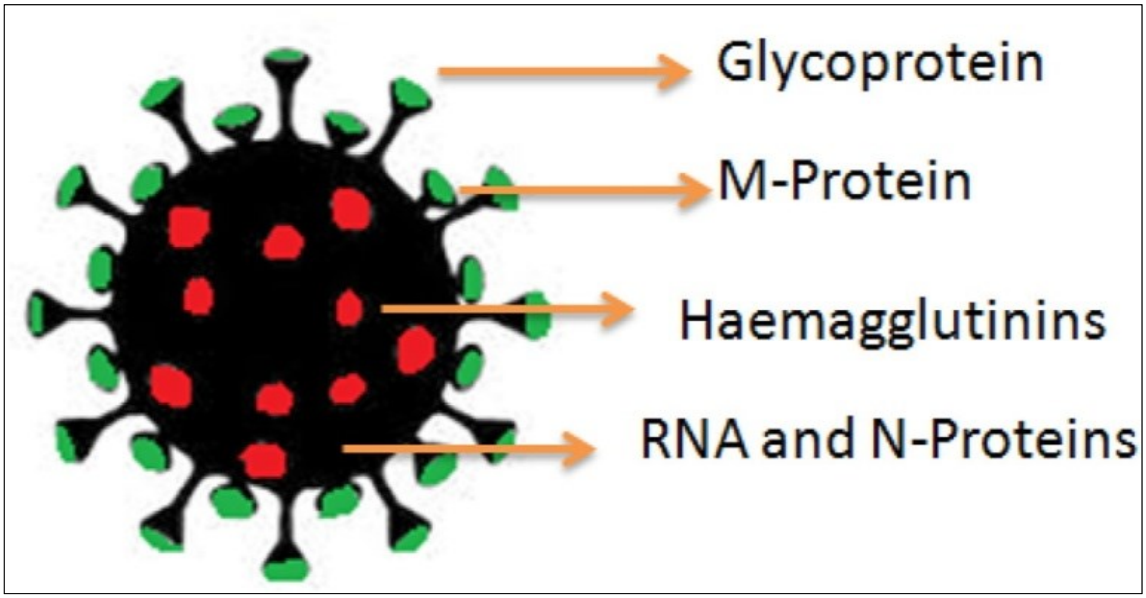


Fig-2 Model of Corona virus

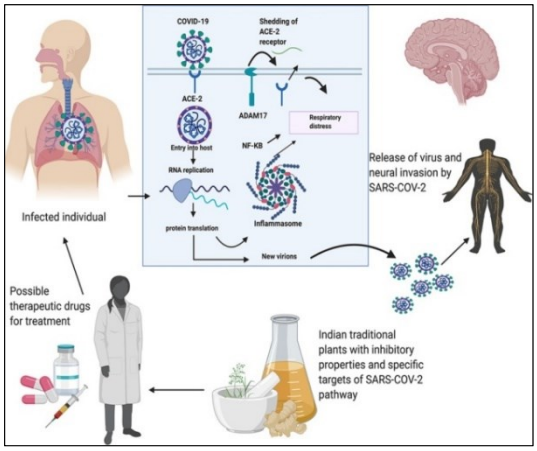
Natural Products A Cure For Control Of The Disease:

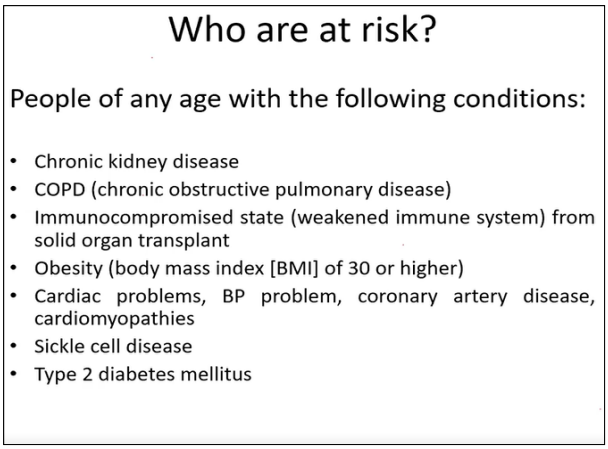
Natural products and their derivatives are used in folk medicine to treat numerous ailments including viral infections (Ganjhu et al., 2015). Nature provides a vast library of chemicals to explore and develop drugs for treatment of various ailments including viral diseases. To date, a good number of herbal medicines or their constituents have shown potential antiviral activity. However, there is a lack of adequate research on the development of anti-CoV

agents from such natural products. Such agents are not only important to combat CoV, but also play an important role to prevent viral attack.

To combat this deadly COVID-19, a number of conventional drugs like chloroquine, hydroxychloroquine, remdesivir, etc. have been tried and found with certain curative effect *in vitro*. However, the clinical drug response is not very encouraging and toxicity remains an inevitable issue causing serious adverse effects. This prompted us to study the inhibition of COVID-19 protease by Indian herbal plants. Because of the inherent side effects of the synthetic chemicals used in allopathic drugs, a sizeable population has switched over to the traditional system of medicine (herbal medicine) for their primary health care. Ayurveda, the age-old Indian system of medicine, is increasingly becoming a sought after system to bank on. The ayurvedic treatment has become an alternative to conventional medicines due to several reasons including easy availability, less or no side effects and less cost. India has always been a rich reservoir of medicinal plants because of several agro-climatic zones.

Fig-3. Natural Products as ACE2-Blockers.





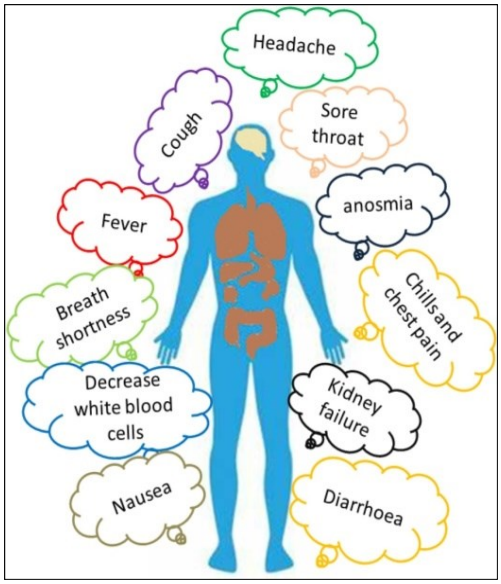


Fig 4- Symptoms of Covid-19.

Remdesivir	**Cortecosteroids**
Toxilizumab/Sarilumab	**Lopinavir/Ritonavir**
Nafamostat/Umifenovir	**Chloroquine/ hydroxychloroquine**
Ivermecetin	

Table 2- Drugs used in treatment of Covid-19

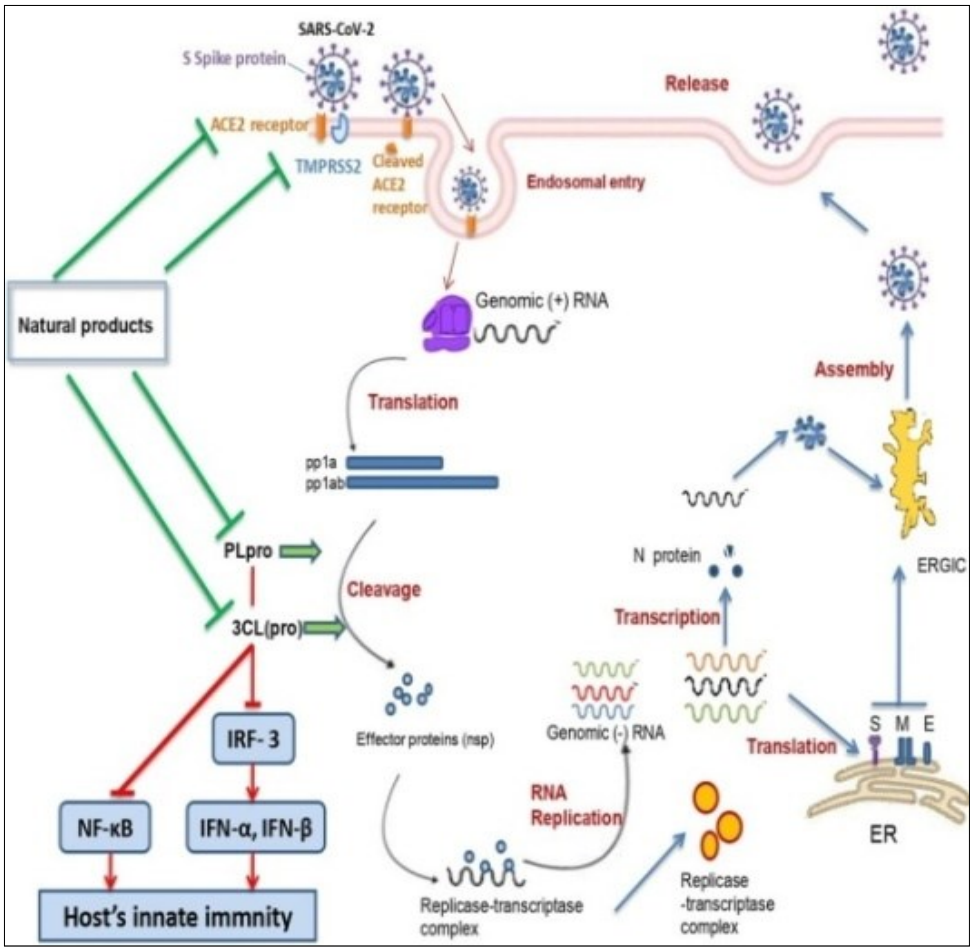


Fig- 5 Summary of Possible ant SARS-CoV 2

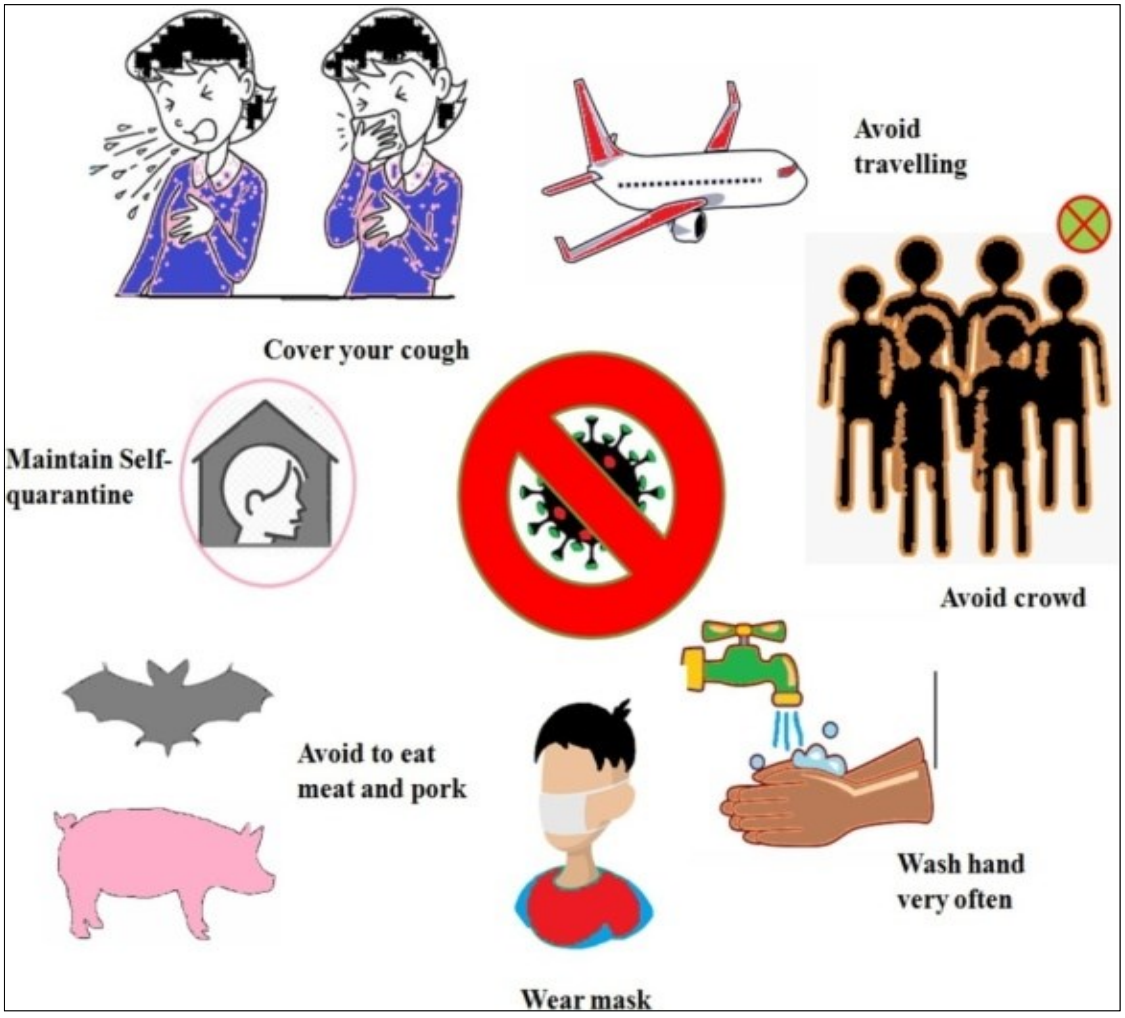


Fig-6 Precautions in Covid-era action of Natural products

India has varies species of medicinal plants that have secondary metabolites like steroids, saponins, flavonids, terpenes, phenols, alkaloids etc which have been found to possess anti-malarial, anti-viral or other similar activities. Traditional herbs from diverse geographical locations and various habitats are considered as potential sources of new drugs for treatment of viral infections, including those caused by SARS-CoV. Some natural products have been found to exhibit their antiviral activity through the inhibition of viral replication (Moghadamtousi, et.al, 2015; Oliveira et al., 2017). Other studies on coronavirus using medicinal plants are rather minimal in India, a study has shown anti-mouse coronaviral activity (a surrogate of SARS- CoV) by the plants. Some plants have been found to reduce inflammatory cytokines using the NF-kB pathway, a pathway that has been implicated in respiratory distress in SARS-CoV. *Allium sativum* (Keyaerts et al., 2007) have been known to target the viral replication of SARS-CoV, arising as promising candidates against SARS-CoV-2. *Adhatoda vasica* reduced infections caused by influenza viruses. The

molecular mechanism by which these plants target influenza virus can be studied to understand if they attack any molecules overlapping between SARS-CoV-2 and the Influenza viruses. Most importantly, various medicinal plants have shown inhibitory effects against ACE, those include *Cynara scolymus*, *Coscinium fenestratum*, *Punicagranatum Cassia occidentalis* and *Embeliaribes* (Hussain et al., 2018). The type II transmembrane serine-proteinase serine type 2 (TMPRSS2) cleaves the S spike proteins of SARS-CoV and MERS and ACE2 (Iwata-Yoshikawa et al., 2019). Since SARS-CoV-2 viral entry is conditioned by its binding to the ACE2 receptor, and the latter should be cleaved by the TMPRSS, finding agents able to suppress or down regulate the TMPRSS2 expression in human cells could represent a promising therapeutic or preventive approach. Several studies have demonstrated that natural products could down regulate or suppress TMPRSS2. Meyer and Jaspers, (2015); Mamouni et al., (2018) found that a standardized flavonoids formulation including luteolin, quercetin, and kaempferol significantly suppressed TMPRSS2 expression. 3CL(pro) belongs to the 16 nonstructural proteins of the SARS-CoV-2. Since it plays an important role in the SARS-CoV-2 replication process polyproteins, 3CL(pro) is considered a potential therapeutic target for anti-COVID-19 drugs (Zhang L. et al., 2020) Hence, medicinal plants-derived products or natural products able to selectively block the ACE2 receptor without inhibiting the enzyme activity may be useful to prevent and/or treat SARS-CoV-2 spread in humans without increasing ACE2 expression in patients and therefore increased risk for COVID-19. In table-3 a list of plants mentioned which have potential role in treating this deadly virus.

Harsingar (night jasmine or parijat) is distributed widely in sub-Himalayan regions, southwards to Godavari and also found in Indian gardens as ornamental plant. Giloy (Amrita or guduchi) is a large deciduous, extensively spreading climbing shrub found throughout India. Aloevera (ghrit kumari) is a well known medicinal plant with sharp pointed, lanced shaped and edged leaves having its origin in African content. Turmeric (circumin or haldi), is commonly used species in Indian subcontinent, not only for health but also for the preservation of food. Ashwagandha is known as adaptogenic herb with great immunity boosting properties. *Azadirachta* (Neem) with its centre of origin in southern and southeastern Asia is regarded as “village dispensary” in India and also a religious gift from nature. Red onion is a versatile vegetable, consumed fresh as well as in the form of processed products. Tulsi is the one of the most religious and medicinal plant in India and grown throughout the country from Andaman and Nicobar island to the Himalayas. *Cannabis* is a

plant of psychoactive drug and black pepper is a kind of household species used in India. *Gloriosa* is the native to Africa and South-East Asia. It is a national flower of Zimbabwe and the state flower of TamilNadu possess Colchicine alkaloid which has antimicrobial, antibacterial and antioxidant properties. *Vitex negundo* is a well-known herb in the ayurvedic and Unani pharmacopoeia also called Nirgundi, it is said to have originated in India and the Philippines and has antibacterial and anti-viral actions. Tea another common drink served throughout India has presence of polyphenols that are known to have antioxidant, antiviral and anti-inflammatory activities. *Zingiber* (Adarak) a well known spice possess antiviral activity against human respiratory syncytial virus (HRSV) and very potent in lung infections.

Today the need of the hour is to investigate these potential medicinal plants against this COVID-19 virus for preparing life saving drugs and also to identify and grow these medicinal plants in our country. Some of these plants belong to rare or endangered category. National Medicinal Plant Board and Ministry of Ayush and department of Rural, Govt. of India, have launched a flagship program to grow medicinal plants on a big scale in India. Government aims to promote R&D in all aspects of medicinal plants, development of agrotechniques, post-harvest management, storage and processing, developing molecular characterization tools etc. and promotion of IT in this sector to save mankind in this era.

Considerations:

Despite the promising possible anti-SARS-CoV-2 effects exhibited by both plant extracts and natural molecules, several limitations should be considered. Overall, due to the recent outbreak, the clinical usefulness of these products needs to be demonstrated since the current data are still immature, and no final conclusions have been validated. In spite of that, these plants are currently used to treat or manage symptoms reported in SARS-CoV-2 disease such as fever, inflammations, or cardiovascular and circulatory disorders. Moreover, efficacy and safety of the active natural products should be further studied *in vivo* and clinically validated in COVID-19 patients. Importantly, bioavailability, modes of administration, safe doses, time of exposure, pharmacokinetic profile, the health of the patients' digestive system, and disease stage are to be considered in the evaluation of the beneficial effects of natural products against SARS-CoV-2. Assessing the effects of combinations of active natural products with validated antiviral drugs could be a promising alternative to explore.

Conclusion:

Medicinal plants and natural products are still considered promising alternatives to prevent or treat several diseases. Since the outbreak of the COVID-19 pandemic in December 2019, various traditional herbal medicines have been used and resulted in positive health effects among COVID-19 patients. Although the studies evaluating the anti-SARS-CoV-2 effects of medicinal plants are still insufficient and relatively immature, some natural products with IC_{50} below 10 μM could be considered as promising anti-SARS-CoV-2 agents since they were able to block its life-cycle related proteins such as the cellular receptor ACE2, papain-like or chymotrypsin-like proteinases. Nevertheless, several limitations have been detected in relation to the specificity of the action exerted by such products, sustainable sourcing of the species, doses range used, or the use of appropriate controls. Furthermore, the bioavailability of natural products with possible anti-SARS-CoV-2 effects such as tannins should be considered besides the need for clinical validation of their usefulness and safety. The herbal mixtures, medicinal plants or natural products with possible anti-SARS-CoV-2 effects must be evaluated through prospective and interventional studies. A combination of natural products or herbal mixtures with validated anti-COVID-19 drugs may constitute a promising preventive and therapeutic alternative to be assessed. Thus natural products hold a great promise for drug development against CoV and require greater attention to the agents that have already been shown to exhibit potent activity against various strains of CoV.

Test	Mechanism of Detection	Testing material	Availability for POC	Positive Test Indicates	Use of tests
Nuclieic acid amplification tests (NAAT)	RT-PCR and NGS detection of genetic sequence of conserved region for regions of the virus. E.g. N, E, S and RdRP genes. Two independent sequences need to be detected	Ambulatory: nasopharyngeal swabs, sputum. In hospital: sputum, endotracheal aspirate, BAL, blood, feces	No: Needs to be performed in the lab	Confirms current SARS-CoV2 infection	Individual testing
Antibody based immunoassay	ELISA detecting IgM or IgG ani-SARS-CoV-2 antibodies	Serum	Yes (depending on test design)	IgM+: 3-5 days post onset IgG: past infection	Overall infection/immu nity rates in a community
Antigen based immunoassay	ELISA detecting viral proteins. E.g. S (spike protein) or N protein (nucleocapsid)	Nasopharyngeal swabs, sputum and other lower respiratory tract secretions, BAL blood, feces.	Yes (depending on test design)	Confirms current SARS-CoV2 infection	Individual testing
Clinical tests	Clinical symptoms (fever/cough) Epidemiological history Imaging (CT)	CT – detection of radiological features	Yes	Infection Possible	Triage to identify candidates for further testing

*Lateral flow assay based on CRISPR-cas technology in under development for diagnosis of COVID-19 and is expected to be highly sensitive and cost-effective

Source: The European Society of Cardiology

Table-3 List Of Plants having Anti-Viral Properties

S. No	Botanical name	Common name	Family	Active compund	Action on Virus
1.	*Adhatoda vasica*	Adoos, Adulsa	Acanthaceae	Vasicine, Quinazoline	Inhibitor of Covid-19 protease, lung and bronchiole disorders
2.	*Allium cepa*	Red onion	Amaryllidaceae	Quercetin	Checks virus multiplication, HIV-PR
3.	*Aloevera*	Ghritkumari	Asphodelaceae	Aloenin, Aloesin	3 CL protease inhibition
4	*Andrographis paniculata*	Kalmegh	Acanthaceae	Andrographolide	Chronic fever, anti-viral, ACE inhibitor
5	*Artemisia annua*	Agnidamini, Majtari	Asteraceae	Artemisinin	Inhibition of Vira-protease
6	*Azadirachta indica*	Neem	Meliaceae	Nimbin	Inhibits viral entry
7	*Camellia sinensis*	Black Tea	Theaceae	Theaflavin digallate	SARS-CoV
8	*Cannabis sativa*	Bhang	Cannabeaceae	Cannabidiol	Blocks viral entry
9	*Curcuma longa*	Haldi	Zingib eraceae	Curcumin	SARS-CoV
10.	*Cynara scolymus*	Hathichuk	Asteraceae	Lupeol, Sabinene	Inhibitory action towards HCOV-NL63, HIV-1
11.	*Dioscorea batatus*	Potato Yam	Dioscoreaceae	Diosgenin	Protease inhibition
12.	*Gloriosa superba*	Kalihari	Colchicaceae	Colchicine, Gloriocine	Anti-viral
13.	*Nyctanthes arbotristis*	Harsingar	Oleaceae	Nictoflorin, Astragalin	Blocking viral entry
14.	*Ocimum sanctum*	Tulsi	Lamiaceae	Ursolic acid, Apigenin	SARS-CoV, anti-viral properties
15.	*Piper longa*	Black Pepper	Piperaceae	Piperine	3CL protease inhibition.

S. No	Botanical name	Common name	Family	Active compund	Action on Virus
16.	*Tinospora cordifoila*	Giloy, Amrita	Menispermaceae	Berberine, Sitosterol	Inhibitory to viral protein
17	*Tylophora indica*	Antmool	Asclepiadaceae	Tylophorine	Inhibition of viral replication
18.	*Vitex negundo*	Nirgundi	Lamiaceae	Hyoscyamine, Benoquinone	Inhibition of ACE
19.	*Withania somnifera*	Ashwagandha	Solanaceae	Withanolide, Withaferin A	Immunity boosting,Inhibitory to viral entry
20.	*Zingiber officinale*	Ginger, Adarak	Zingiberaceae	Gingerol, Shogaol	Respiratory infections

1. Adhatoda 	**2. Allium** 	**3. Aloevera** 	**4. Andrographis** 
5. Artemisia 	**6. Azadiracta** 	**7. Camellia** 	**8. Cannabis** 
9. Curcuma 	**10. Cynara** 	**11. Dioscorea** 	**12. Gloriosa** 
13. Nyctanthes 	**14 Ocimum** 	**15. Piper** 	**16. Tinospora** 
17.Tylophora 	**18.Vitex** 	**19. Withania** 	**20. Zingiber** 

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