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Review

Plant Derived Antiviral Products for Potential Treatment of COVID-19: A Review

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Abstract: COVID-19 caused by SARS-CoV-2 is declared global pandemic. The virus owing high resemblance with SARS-CoV and MERS-CoV has been placed in family of beta-coronavirus. However, transmission and infectivity rate of COVID-19 is quite higher as compared to other members of family. Effective management strategy with potential drug availability will break the virus transmission chain subsequently reduce the pressure on the healthcare system. Extensive research trials are underway to develop novel efficient therapeutics against SARS-CoV-2. In this review, we have discussed the origin and family of coronavirus, structure, genome and pathogenesis of virus SARS-CoV-2 inside human host cell; comparison among SARS, MERS, SARS-CoV-2 and common flu; effective management practices; treatment with immunity boosters; available medication with ongoing clinical trials. We suggest medicinal plants could serve as potential candidates for drug development against COVID-19 infection.

Keywords: Virus; human health; bat; SARS-CoV-2; fever; Wuhan

1 Introduction

COVID-19 appeared in Late December in Chinese city, Wuhan (Hubei province) [1]. This rapidly spread worldwide and has infected 3.78 million peoples globally causing 265 K deaths (as per 07-05-2020). Following the severity of pandemic, WHO declares public health emergency around the globe on 30 January 2020 [2] and has estimated a 4% case fatality rate (CFR) for COVID-19. CFR for COVID-19 is significantly higher as compared to seasonal influenza but much lower in comparison to (9.6%) of SARS-CoV outbreak of 2002/2003 and (34.3%) in MERS-CoV of 2015 [3,4].

In order to combat current worsen conditions, WHO has recommended to maintain social distancing, detect and isolate affected personnels, minimize human-animals interaction to avoid viral transmission, accelerate research and diagnosis, disseminate correct figure and statistics among public to avoid social and economic unrest. For developing effective prophylaxis of COVID-19, exploring the basic viral mechanism is a pre-requisite. Recent studies have exhibited high similarity between genome sequence of SARS-CoV-2, SARS-CoV and bat derived coronavirus [5]. However, transmission, pathogenesis and diagnostic technique are quite variant particularly could be due to receptor binding ability of spike (S) protein in COVID-19 [6,7]. Current prophylaxis involves ingestion of Lopinavir/Ritonavir, life support systems majorly depending upon patient condition. Researchers all around the world are exploring new pathways along with formulation of new drugs on daily basis to ameliorate the COVID-19 infection [8]. Medicinal plants serve as potential candidates for drug development of various illnesses [9]. A lot of research has been done previously on medicinal plants and have explored presence of various bioactives and phytochemicals that could help to alleviate the infection.

Developing long term strategies for preventing further outbreaks of such pandemic is the need of hour. Understanding impact of COVID-19 on environment is also of major concern. Although reduced transportation and industrial shutdown have improved air quality index with reduced water pollution in some parts of world [10] but how far this goes no one knows. Therefore, a combine effort is required from all aspects of society to fight against COVID-19 illness by practicing self-hygiene, quarantine and self-isolation measures [9]. In this review, origin and family, structure, genome and pathogenesis of the SARS-CoV-2 infection, management strategies, current prophylaxis, underway clinical trials, brief overview and the potential impacts of several medicinal plants for efficient cure of COVID-19 has been highlighted. Under this review, we suggest that the plant derived drugs could serve as an alternative to cope with SARS-CoV-2.

2 Origin and Family of Coronovirus

Coronaviruses are member of *Coronaviridae* family which mostly reside in birds and mammals [11]. This family includes two subfamilies: *Letovirinae* and *Orthocoronavirinae* (Fig. 1). Subfamily *Orthocoronavirinae* is most influential in humans and cause respiratory related disorders. Currently seven CoVs that infect humans has been revealed. Particularly, these CoVs are called as Human CoVs (HCoVs) and includes HCoV-NL63, and HCoV-229E from alpha-coronavirus genus; HCoV-OC43, HCoV-HKU1, SARS-CoV, MERS-CoV and SARS-CoV-2 from beta-coronavirus genus. Except the latter three mentioned rest of these seven HCoVs cause mild respiratory diseases in humans.

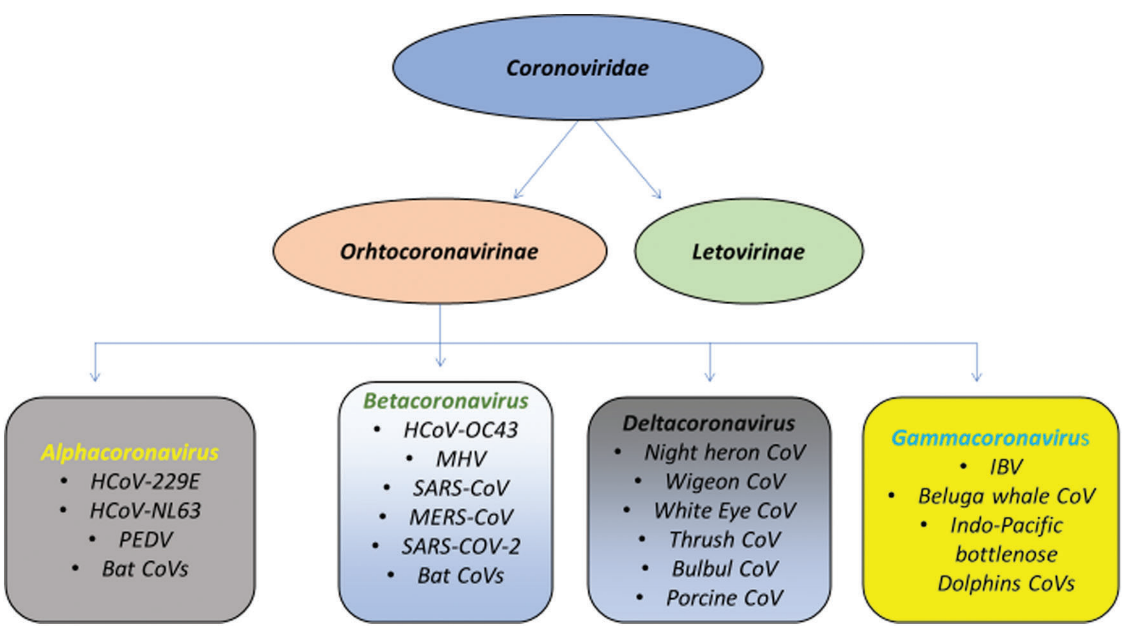

Figure 1: Categories of *Coronaviridae* family exhibiting particularly important genera of subfamily *Orthocoronavirinae*. COVID-19 causal agent SARS-CoV-2 lies in betacoronavirus

Among three of most infectious HCoVs, SARS-CoV and MERS-CoV are animal derived viruses that have prompted infectious outbreaks in 2002 and 2015 respectively [6] that led to significant losses in economy [12] and transmitted to humans via intermediate host (Fig. 2) following rapid transmission via human-human interaction [13]. Similar pattern was observed regarding SARS-CoV-2 that is sharing 96.2% genome sequence with bat derived coronavirus [14].

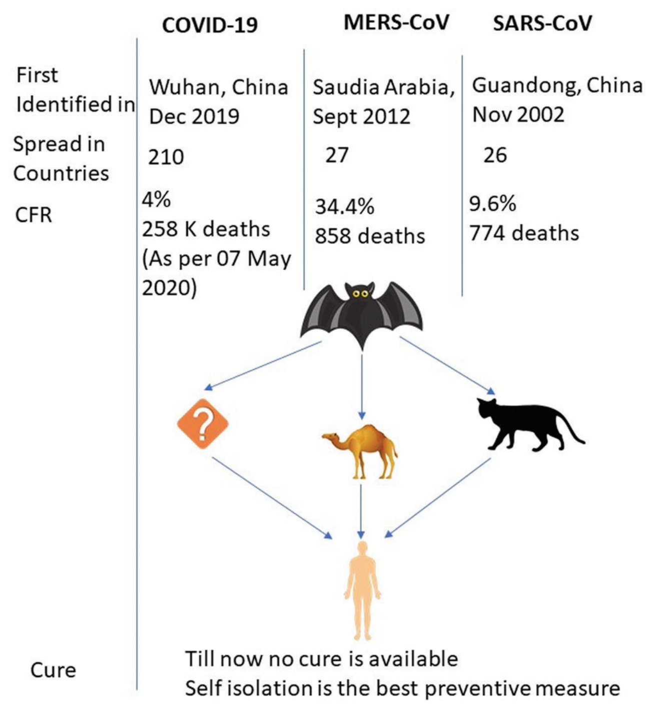

Figure 2: Overview of origin, spread and CFR of COVID-19, MERS-CoV and SARS-CoV

HCoVs are usually associated with infection in upper respiratory tract leading to mild and moderate illness. Humans get infected with any of these viruses during their life [15]. Previously, SARS-CoV and MERS-CoV were regarded as main causal agents of severe pneumonia in humans [16]. A comparison between common flu, SARS, COVID-19 and MERS has been exhibited in Tab. 1. SARS-CoV during 2002 to 2003 caused 774 deaths from 8000+ infections in 37 countries [17]. This pandemic was succeeded by the outbreak of MERS-CoV at Saudi Arabia in 2012, causing 858 casualties from a total of 2494 infected cases [18]. SARS-CoV-2 having zoonotic origin emerge in December 2019 preferably from bat and transmitted to humans. This virus exhibits symptoms of dry cough, fever, tiredness and difficulties in breathing after 14 days of incubation. In this incubation period, virus releases RNA which translates and replicates itself [19]. Under the severe conditions, SARS-CoV-2 results in pneumonia with ARDS thus require the life-support to keep the patient alive [20].

3 Structure, Genome and Pathogenesis of SARS-CoV-2

SARS-CoV-2 is single-stranded RNA virus, 50–200 mm in diameter [21], spherical in shape with spiking proteins (Fig. 3) protruding from the surface of virion [22]. It's 30 Kb genomic RNA contains structural proteins i.e., membrane proteins (M), spike proteins (S), nucleocapsid (N) proteins and envelope (E) proteins along with hemagglutinin-esterase (HE) [23]. Each of these proteins is having own functions as the N proteins form nucleocapsid. S proteins are most important ones, they generate homotrimeric spikes (S_1 and S_2) which facilitates pathogenesis [24] by binding with ACE2 receptor on

Table 1: Comparison of SARS-CoV-2, SARS-CoV, MERS-CoV and common flu

Disease	Symptoms	Period of Incubation	Days to Recover	Disease Transmission	Severe Complications	Available Cure
COVID-19	Dry Cough, Fatigue, Breathing issues & Fever	2–14 days	3–7 weeks	Human Interaction	Respiratory failure, High fever, Multiple organs failure	No available medication, Preventive measure could help
SARS-CoV	Headache, Dry Cough, Fever, Breathing issues with no upper respiratory tract	2–10 days	4–6 weeks	Human Interaction	Respiratory failure, Heart attack	Use of ventilator to facilitate O^2 supply. Antibiotics & Antiviral medicines
MERS-CoV	Fever, Cough Breathing difficulty	4–6 days	6–8 weeks	Human Interaction	Kidney failure Severe Pneumonia	Antiviral & Antibiotics
Common Flu	Runny nose, Low fever with headache, Sneezing	1–3 days	7–10 days	Human Interaction	None	Antibiotics

type II pneumocyte [25]. M and E protein together imparts shape of viral structure along with organizing viral assembly [26]. The hemagglutinin-esterase protein is in resemblance with influenza virus hemagglutinin thus retains acetyl-esterase activity [27]. This protein may facilitate the entry and pathogenesis of CoVs (Fig. 3). Moreover, genomic analysis depicts that these proteins are coded at 3' end of SARS-CoV-2 RNA. After pathogen intrusion into the host cell cytoplasm RdRP produces as a result of 5' end translation of viral RNA which ultimately produces virus-specific mRNAs from subgenomic negative strands [28].

Virus receptor binding affinity is crucial step because of spike (S) glycoprotein and ACE2 receptor. Research work has exhibited that SARS-CoV-2 possess greater affinity to ACE2 as compared to SARS-CoV [29]. Spike (S) glycoprotein divides itself into two sub-units S_1 & S_2 which utilizes ACE2 for viral fusion through cell membrane. Following pathogenesis in host cell, RNA is released and translated into polymerase proteins. Subsequently, negative sense RNA is produced and serve as a template for formation of subgenomic positive sense RNA. RNA and nucleocapsid (N) proteins replicate and translate in the cytoplasm, whereas other structural proteins, i.e., S, M and E are translated in the endoplasmic reticulum (ER) followed by translation and transportation to Golgi apparatus. These S, M and E proteins are further congregated in the er-Golgi intermediate region (ERGIC) to produce mature virions, which are then released from the host cell (Fig. 3).

4 Management

Following the pandemic situation exaggerated with the absence of efficient antiviral drug, effective management is the best possible solution. Main symptoms of COVID-19 are high fever and dry cough, therefore the Paracetamol and Guaifenesin known to relive fever and loosen cough are used as first line antipyretics drugs [30]. Patients dealing with severe respiratory issues should be supplemented with oxygen @ 5 L/min [25]. Recent studies have reported high renal malfunctioning from COVID-19 infection [31]. Sepsis protocol and continuous renal replacement therapy (RRT) may serve as best suited options to cope with these complications [19]. COVID-19 infected individuals may also develop bacterial or fungal infections, thus suitable antimicrobial drugs should be administrated. NHC, China has suggested the intake of lopinavir and ritonavir for protease inhibition.

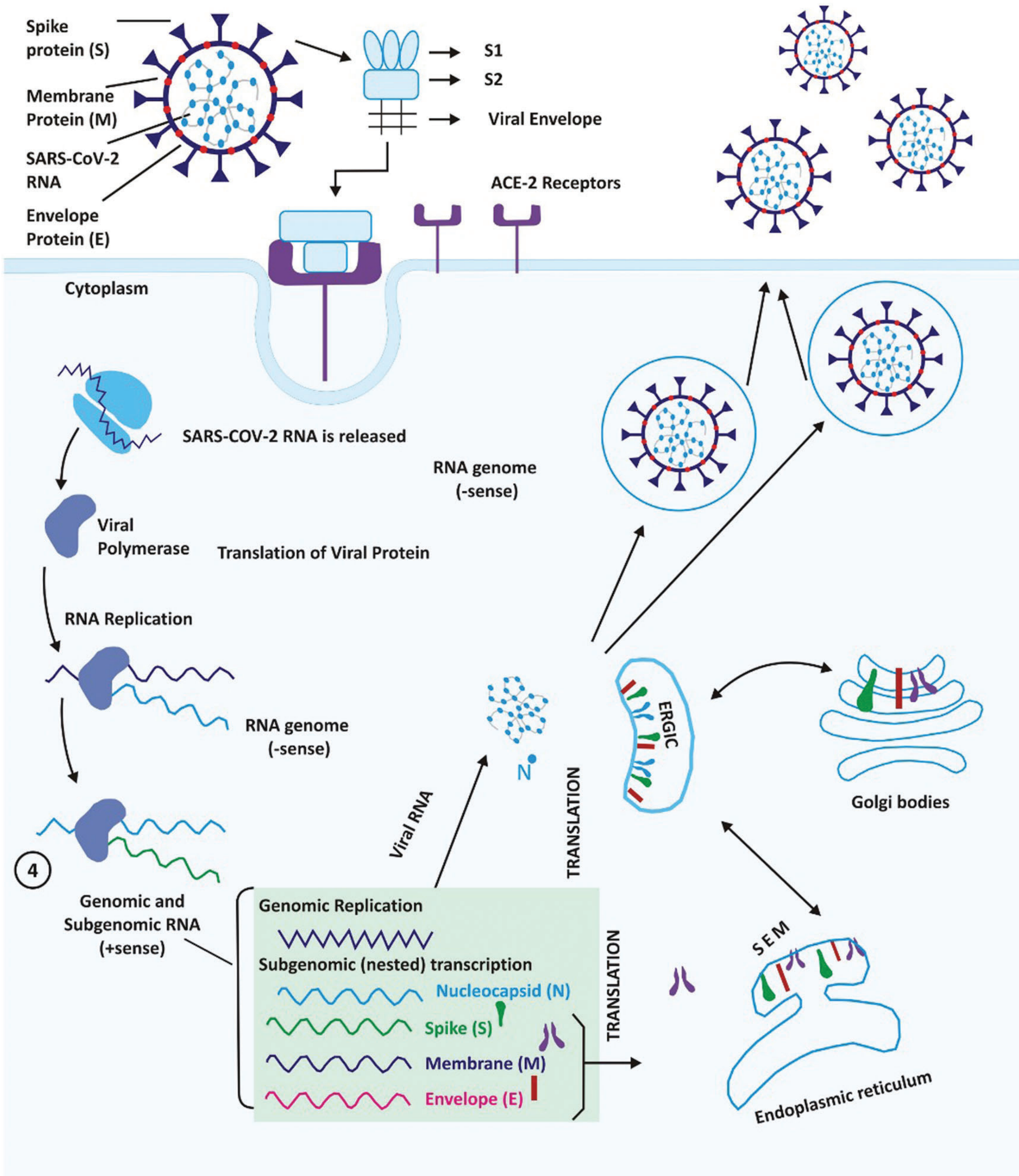

Figure 3: Entry and pathogenesis of SARS-CoV-2 inside host

In most cases, public health measures are key principal to control the spread of SARS-CoV-2. If these measures fail to control virus transmission, resultant scenario will turn into chaos as exhibited in crisis conditions of Italy. Therefore, social distancing is declared as best preventive measure to reduce virus outflow in a short period of time. On the contrary, health services should enhance rapid diagnostic capabilities, quarantine the individuals getting positive for COVID-19, track their contacts and isolate those who have symptoms.

5 Treatment

Treatment of COVID-19 can be distributed into two categories based on the target, one that act on strengthening the human immune system while the second which directly attack coronavirus itself. Regarding the first option, the inherent immune system is known to respond against pathogenesis by inhibiting the replication and contamination of coronavirus [32]. This is majorly ascribed to function of "interferon" namely protein which enhances the immunity by altering or blocking the signal pathways of cells essential for viral replication thus exhibits anti-viral effect.

5.1 Immunity Booster

5.1.1 Vitamin C

Vitamin C (L-ascorbic acid) one of highly consumed antioxidant also serves as enzyme cofactor for certain biochemical and physiological processes i.e., synthesis and regulation of hormones and collagen. Humans cannot synthesize vitamin C; therefore, they must obtain vitamin C from their diet [33]. Its high dose intravenous application has yielded protective effect on septic ARDS. Moreover, it enhances the alveolar epithelial barrier with up-regulated protein channels thus regulate alveolar fluid clearance [34]. As of February 14, 2020, Central South Hospital (NCT04264533) has launched a randomized controlled trial (RCT) to evaluate the efficiency of vitamin C for COVID-19 treatment. They hypothesized that intravenous vitamin C application could ameliorate severe acute respiratory infections. Prophylaxis include 7-day infusion of 12 grams of vitamin C (q12h) with the aim to measure the ventilation-free days. The outcomes are expected to come by September 2020 [35].

5.1.2 Vitamin D

It is well known that vitamin D can reduce the range of adaptive immunity and stimulate endothelial cells production [36]. This could be due to induced cathelicidins and defensins that reduce rate of viral replication and thereby lowering levels of pro-inflammatory cytokines causing inflammation in lungs. Various research studies and clinical trials have suggested the role of vitamin D in reducing influenza outbreak [37–39]. It has been observed that COVID-19 outbreak occurred in winter at times when vitamin D levels are lowest in body particularly to most of peoples living in northern latitudes who lack vitamin D due to long-term lack of sunlight. However, treatment with vitamin D could involve use of high vitamin D doses (10,000 IU/d) for few weeks. Whereas COVID-19 infected peoples should be administrated with higher vitamin D_3 doses.

6 Vaccination/Drug Development

At present, a variety of prophylaxis approaches are being investigated. The following given includes some highly effective options.

6.1 Remdesivir

Remdesivir directly inhibits the RNA dependent polymerase of SARS-CoV-2 thus declared as most proficient drug available for cure of COVID-19. It is a monophosphate amide-based drug that could inhibit SARS-CoV-2 RNA replication at very early stages. This drug has proved also efficient results for SARS-CoV, Ebola virus and MERS-CoV [40]. A lab study conducted on human cell line (Huh-7 cells) have exhibited its strong impact on SARS-CoV-2 NSP12 [30]. The recommended prophylaxis is a 10 days medication course, with 200 mg IV application followed by 100 mg IV for the next 9 days.

6.2 Ritonavir and Lopinavir

The combination of protease inhibitors ritonavir and lopinavir is usually applied for the treatment of HIV. Their formulations have also proved significance results against SARS infection [41]. China's current COVID-19 treatment guidelines involves intake 50 mg–200 mg for 10 days [42]. Clinical trials in

Wuhan, China (ChiCTR: 2000029308) having 199 patients depicts the safety and efficacy of the PO 50 mg–200 combination in severe COVID-19 patients. This combination (n = 99) was compared with standard care (n = 100). Results expressed significant variations in clinical improvement time on the 14th day between the two groups but this difference wasn't significant after 28th days. However, the CFR reduced by 5.8% and also the reduction in ICU stay time by 5 days [43]. Currently, there are 12 clinical trials evaluating ritonavir and lopinavir combination.

6.3 Umifenovir

Umifenovir is also an antiviral drug approved for the cure and prevention of influenza [44]. Till now, it is under clinical trial and not approved by the FDA. It is a membrane fusion inhibitor and suggested for an oral dose of 200 mg TDS for 10 days [42]. Currently, two RCT (GDCT0379047 and NCT04246242) are evaluating efficacy of Uminovir formulation in addition with recombinant cytokines and single application of Uminovir respectively.

6.4 Chloroquine

Chloroquine is an antimalarial drug known for inhibiting the pH-dependent replication stage of virus [45]. In addition, the immunomodulation of chloroquine is reliant on the inhibition and production of cytokines. Trials on the monkey cells (Vero E6) have shown that chloroquine hinders with receptor glycosylation, thus affecting the pathogenesis of COVID-19. This application has yielded positive outcomes from SARS-CoV-2 infected human cell lines (Huh-7 cells) under lab environment [30]. China's current COVID-19 treatment guidelines suggests usage of 300–500 mg oral intake of chloroquine phosphate for a period of 10 days.

Hydroxychloroquine also possess ameliorated efficacy as compared to alone chloroquine application for reducing SARS-CoV-2 infection. It is considered as an appropriate chemopreventive drug for mitigating COVID-19 outbreak. Preliminary data from China's first study (NCT04261517) showed positive results. While 400 mg of PO-hydroxychloroquine on the first day repeated by 200 mg application with an interval of 4 days is recommended [46].

7 Plant Derived Compounds Exhibit Antiviral Activity

Plants ascertaining multifaceted secondary metabolism serve as ample source of medicinal compounds thus assists in drug development [47]. Plant material has been used for treatment and prevention of various diseases and disorders involving viral respiratory infections [48]. The purpose of using such plant materials is stimulation and strengthening of immune system against virus caused inflammation. Several medicinal plants have been reported for exhibiting anti-coronaviral activity (a surrogate of SARSCoV). These includes *Clitoria ternatea, Leucas aspera, Indigofera tinctoria* (AO), *Vitex trifolia, Gymnema sylvestre*, *Cassia alata, Abutilon indicum, Sphaeranthus indicus, Gymnema sylvestre* and *Evolvulus alsinoides* [49]. *Vitex trifolia* and *Sphaeranthus indicus* has decreased inflammation of cytokines via modulating NF-kB pathway which is often involved in respiratory disorders in SARS-CoV [50,51]. Similarly, *Clitoria ternatea* is known to inhibit metalloproteinase (ADAM17) which is involved in ACE shredding. This could be achieved by utilizing *Clitoria ternatea* as ACE-2 shredding is linked with virus production [52]. Plants with ability to inhibit virus replication are often preferred as promising options to be adopted against viral outbreaks. Thus, *Glycyrrhiza glabra* and *Allium sativum* [53,54] could serve as alternate options for COVID-19 cure. *Clerodendrum inerme Gaertn*, a potential herb in cure of SARS-CoV-2 inactivates the viral ribosome and protein translation [55]. Moreover, *Strobilanthes Cusia* inhibits RNA genome formation thus targets the HCoVs [56].

Several medicinal plants i.e., *Hyoscyamus niger*, *Justicia adhatoda* and *Verbascum thapsus* exhibiting antiviral characteristics have alleviated disease infections arising from influenza viruses [57]. *Hyoscyamus* *niger* is a bronchodilator and possess inhibitory mechanism on Ca^{2+} channels [58] thus making it effective against downstream movement of virus. A lot of research trials has been conducted regarding ACE inhibition thus blocking virus entry. In this regard certain plant species i.e., *Coriandrum sativum*, *Coscinium fenestratum, Cynara scolymus, Punica granatum* and *Cassia occidentalis* have expressed significant outcomes [59]. While *Punica granatum* marked a specific mode of inhibition in comparison to others [60,61]. *Andrographis paniculate*, an annual herbaceous plant possesses strong anti-viral properties [62]. All of these proteins and molecules have active roles in SARS-COV pathogenesis and likely to have too in SARS-CoV-2 [63,64].

Several other plants have also exhibited inhibitory role against HIV infections, they could also serve as promising candidates for COVID-19 drug development. These plants involve *Eugenia jambolana* [65], *Acacia nilotica* and *Euphorbia granulate* [66]. Some plants like *Ocimum sanctum* [67], *Solanum nigrum* [68] and *Vitex negundo* [69] owing capability of targeting reverse transcriptase activity of HIV could also be used for potential development of COVID-19 drug.

During pandemics, timeliness is basic prerequisite for any drug development thus natural products could serve as suitable and effective option due to the fact that their safety is well-known so it can be instantly evaluated for combating patients. Therefore, we build a list of plant species (Tab. 2) with their active molecule known for possessing anti-viral activities and these could be suitable choices for combating the situations from COVID-19 pandemic.

Table 2: Overview of Plant material with their active molecules exhibiting anti-viral properties that could inhibit HCoVs

Species Name	Active Compound	Mode of Action	Virus Assessed	Reference
Platycodon grandiflorum	Platycodin D	Inhibit viral replication and pro-inflammatory cytokine expression	PRRSV	[70]
Reseda luteola	Luteolin	Inhibit entry of SARS-CoV, hve great affinity for S2 protein thus interfere virus-cell fusion process	SARS-CoV	[71]
Glycyrrhiza glabra	Glycyrrhizin	Induces *Glycyrrhiza glabra* nitrous oxide synthase which in turn blocks viral replication	SARS-CoV	[72]
Peganum harmala L	Harmine	Inhibit viral replication	Influenza A virus	[73]
Mentha piperita	Menthol & essential oils	Virucidal impact by incrementing virion density	IBV	[74]
Anthemis hyaline	Not known	Decreased transient receptor potential proteins (TRP's) gene expression	Coronavirus	[75]
Camellia japonica	Oleanane triterpenes	Blocking viral replication via affecting key structural protein synthesis	PEDV-Coronavirus	[76]
Zingiber officinalis	6-gingerol	Anti-viral potential	Avian influenza virus H9N2	[77]
Isatis indigotica	Sinigrin and Hesperetin	Inhibited viral cleavage activity	SARS-CoV $3CL^{pro}$	[78]

Table 2 (continued).

Species Name	Active Compound	Mode of Action	Virus Assessed	Reference
Vitis vinifera	Resveratrol	Reduced expression of nucleocapsid (N) protein, also lowers the apoptosis induced by virus	MERS-CoV	[79]
Rosmarinus officinalis	Carnosic acid	Blocks viral replication	Human respiratory syncytial virus (hRSV)	[80]
Houttuynia cordata	Quercetin	Virucidal activity, inhibits ATPase of multidrug resistance- protein	MHV, DENV-2	[81]
Moringa oleifera	Quercetin and kaempferol	Blocks initial stages of viral replication	FMDV	[82]
Cedrela sinensis	Phytochemicals	Inhibits viral replication	SARS-CoV	[83]
Rheum palmatum L.	Polyphenols	Significant inhibition of protease activity	SARS-3CL	[84]
Azadirachta indica	Azadirachtin	Virucidal activity	FMDV	[85]
Acacia nilotica	Phenolics	Inhibition	HIV-PR	[86]
Allium sativum		Inhibit viral proliferation	Influenza Virus	[87]
Clerodendrum inerme Gaertn	–	Inactivation of virus	SARS-CoV-2	[88]
Clitoria ternatea	Flavonol glycosides	Inhibition of metalloproteinase	-do-	[89]
Coriandrum sativum	–	Inhibition of ACE-2	-do-	[90]
Embelia ribes	–	-do-	-do-	[91]
Eugenia jambolana	Ellagic acid, Isoquercetin, Kaemferol	Inhibition of protease activity	Avian Influenza	[92]
Hyoscyamus niger	Flavonoids and Alkaloids	Inhibition of Ca^{2+} channels and Bronchodilator	SARS-CoV-2	[93]
Punica granatum	Punicalagins and Ellagitannin	Inhibition of ACE	-do-	[94]
Strobilanthes callosa	Phytosterols and Phenolic Compounds	Blocking of virus entry	HCoV-NL63	[56]

(Continued)

Table 2 (continued).

Species Name	Active Compound	Mode of Action	Virus Assessed	Reference
Vitex negundo	Viridiflorol and linalool	Inhibition of virus	HIV-1	[69]
Vitex trifolia	1, 8-cineole	-do-	SARS-CoV-2	[95]
Strobilanthes cusia	Quinazolinone alkaloids and monoterpenes	Blocking of virus replication	HCoV-NL63	[56]

8 Conclusion

Ongoing pandemic of COVID-19 has become the most severe and gruesome viral infection faced by human so far. Most of countries around the globe has taken preventive measures mainly countrywide lockdowns in addition with social distancing and self-quarantine that could help to break transmission string and lowers the inflow of new COVID-19 positive cases. This virus has infected 3.78 million peoples (As per 07 May 2020) causing 265 K casualties [2] in more than 210 countries/states worldwide. Extraordinary versatility of SARS-CoV-2 to transcript, translate, block immune system and infect host from numerous species has made this virus a horrifying nightmare for researchers. Several steps like determining gene pool of SARS-CoV-2, role of accessory and non-accessory proteins, elaborated RNA structure and replication will facilitate the process of drugs and vaccine production. This review highlights the crucial value of plants with antiviral capacity and known to treat various respiratory diseases from decades. Thus, significant pathological role of plant species could help in quest for COVID-19 drug development.

9 Future Outlook & Recommendations

The COVID-19 pandemic is posing serious risk for world in several aspects of life. Increasing casualties, social disruption with huge collapse of economy has incremented paranoid. Countries have grown isolationist, sealed their borders and urges home supply chains to combat invisible enemy. Remarkable sequestration in global economy have been observed with significant requisite of bail-out packages from governments to keep businesses and major industries afloat. Issues regarding socio-economic inequality has exaggerated as wealthy peoples are in a better condition to withstand the shifting scenario.

Despite prevailing uncertainties, social unrest, incrementing health and economic pressure several positive things have occurred throughout the world. Following the lockdown and quarantine, peoples shifts to become more purpose driven and social cohesion has incremented. Technological revolution has accelerated like concepts of online education, work from home was highly appreciated and adopted. Telemedicine stood as forefront of medical field. Emphasis on climate change is mixed and will be led by decline of investment in climate change sectors and agreements. Countries will be more focused on short time economic recoveries as compared to long term environmental impacts. Economic activities are predicted to rebound by end of 2020 with low economic recovery in first half of 2021. Interestingly, East-Asian countries have better handled the pandemic as compared to western world. Therefore, a quick economic recovery is expected in this region of world.

Administrating treatment guidelines and prevention strategies of WHO will help to reduce the influx of viral infection, thereby reducing the pressure on hospital and health system. Moreover, it will also allow researchers to gain more time for efficient drug development against COVID-19.

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