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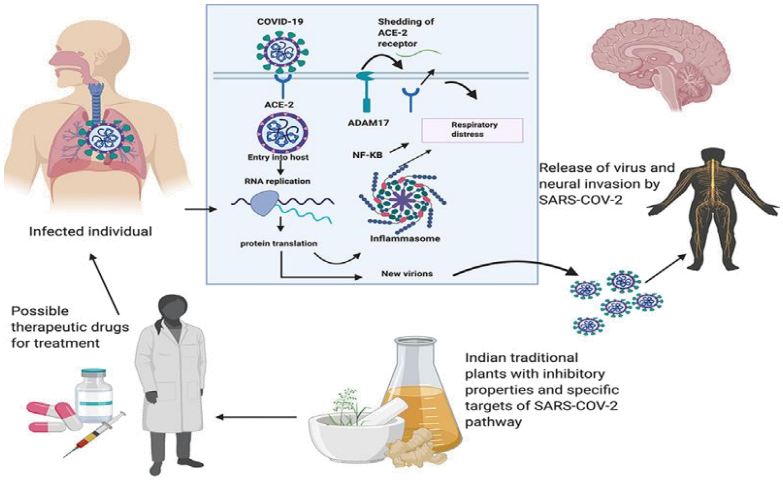
Traditional Indian Medicinal Plants in the Treatment of Patients Infected With Human Coronavirus 2019 (SARS-CoV- 2): A Review

Sujoy Pal[1], Anirban Banerjee[2], Alakesh Maity[3].
1)& 3) Nasa Remedies, Makkhanpur, Firozabad, Uttar Pradesh
2) Serdia Pharmaceuticals (India) Private Limited
Corresponding author:Sujoy Pal

Abstract: *The Novel Coronavirus Disease 2019 (COVID-19) is caused by SARS-CoV-2, which is the causative agent of a po-*
tentially fatal disease that has become a global pandemic as announced by WHO. The outbreak of COVID-19 has created panicworldwide due to inadequate risk assessment considering the urgency of the situation. The COVID-19 pandemichas entered a dangerous new phase. When compared with SARS and MERS, COVID-19 has spread more rapidly,due to increased globalization and adaptation of the virus in every environment. Slowing the spread of theCOVID-19cases will significantly reduce the strain on the healthcare system of the country by limiting the num-ber of people who are severely sick byCOVID-19 and need hospital care. Hence, the recent outburst of COVID-19highlights an urgent needfor therapeutic agents targeting SARS-CoV-2. Here, we have discussed the structure of virus;varying symptoms among COVID-19, SARS, MERS and common flu; the probable mechanism behind the infection and its immune response. Further, the current treatment options,synthetic drugs available, ongoing trials and recentdiagnostics for COVID-19 have been discussed. We suggest traditional Indian medicinal plants as possible noveltherapeutic approaches, exclusively targeting SARS-CoV-2 and its pathways.

Pictorial Representation of Abstract



Abbreviations: ACE2 – Angiotensin-convertingenzyme2; ACE2-Fc-AngiotensinConvertingEnzyme2Fc; ADAM17- ADAMmetallopeptidasedomain17; ARDS-,Acuterespiratorydistress syndrome; ASC- Apoptosis-associated speck-like protein containing a CARD; CNS- Central Nervous System; COVID-19- Coronavirus disease 2019; ER- Endoplasmic reticulum; Exon- Exoribonuclease; FDA- Food and Drug Administration; FP-Internal fusion protein; HCoV- Human coronavirus; HIV- Human immunodefi ciency virus;JAK-STAT- Janus kinase/signal trans- ducerandactivatoroftranscription; JNK- c-JunN-terminalkinase; MCP-1-Monocytechemoattractantprotein-1; MERS- MiddleEastrespiratorysyndrome;MERS-CoV- MiddleEast respiratory syndrome coronavirus; MHV- Mouse hepatitis virus; mRN- Messenger RNA; NF-Kb- Nuclear Factor kappa-light-chain-enhancer of activated B-cells; NIH- National Institutes of Health; NLRP3- Nod-like receptor protein 3; ORF- Open reading frame; PHEIC- Public Health Emergency of International Concern; PHEV- Porcine Hemagglutinating Encephalomyelitis Virus; RBD- receptor binding domain-; RBM- Receptor binding motif; RCT- Randomized controlled treatment; RdRp- RNA dependent RNA polymerase; RNA-

Ribonucleic acid; ROS- Reactiveoxygenspecies; RTC-Replicase-transcriptasecomplex;SARS-Severeacuterespiratorysyndrome;SARS-COV2-Severeacuterespiratorysyndromecoronavirus-2;TM-Transmembrane;TMPRSS11a-Transmembrane serine protease11a;TNF -Tumornecrosisfactor;TRAF3-TNF receptorassociatedfactor3;TRS-Transcriptionalregulatorysequence;WHO-World Health Organization.

Keywords – Coronavirus Disease 2019 (COVID 19), SARS-CoV-2, Mechanism of action, Therapeutic approach, Indian Traditional Medicinal Plants.

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I. Introduction:

The novelcoronavirus disease2019(COVID-19),caused by the Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is in the midst of worldwide panic and global health concern since December 2019.As of April 11th,2020,the World Health Organization(WHO) has reported 12,68,354 active cases and1,08,827death cases worldwide,and it has spread to 210 countries(WHO,2020a).

Withthis emerging battle against this deadly virus, the WHO has adviced to interrupt human-human contact, isolate patients at early stages, identify and reduce transmission from the animal source, address important mysteries about the virus and accelerate research, communicateinformation correctly to the public and minimize the social and economic impact. At this point, it is very vital to understand the basic mechanism of the virus to develop a specific medicine.Currently, it has been established that SARS-CoV-2 shares sequence homology with the SARS-CoV and a bat corona virus(Gorbalenya,2020).

Despite its similarity to SARS-CoV, its transmission, efficiency and diagnostic methods are different. The distinguishing factor is probably the nucleotide changes in the spike(S) protein and its receptor-binding do main(RBD)(Kannanetal.,2020;Coutardetal.,2020;Wanetal.,2020)

Current scenarios show us the use of Lopinavir & Ritonavir as well as supportive care based on the extremity of the illness. From the research point of view different drugs are being developed at an extremely quick pace and new targets are being identified on a daily basis across the globe. Similarly numerous drugs are also under clinical trials. Researchers are very curious about how to provide the best protection tothe public before a vaccine can be made available.(Balachander etal.,2020). Ayurveda & Siddha practicesoriginated in India millions of years ago are still widely used among the Indian population & hold its own legacy and importance among the common people of India. Certain phytoconstituents can be identified and different medicinal plants can be fragmented and characterized accordingly opening a way of moreinnovative treatment for the role in defeating this viral transmission.In this review the structure,immunological influence, mechanism of action of the SARS-CoV 2 infection in the human host cell, the availability of drugs based on the disease, ongoing clinical trials, recent diagnostics and the effective use of different Indian medicinal plants for the effective therapeutic treatment of COVID-19 has been discussed. Through this review we suggest that the Indian traditional medicinal plants may be a crucial step to fight viruses like the SARS-CoV 2.

1) A Brief overview of Corona virus:

Coronaviruses having a total of 39 species under the broad realm of Riboviria, belong to the family Coronaviridae, suborder Comidovirinae and order Nidovirales (Gorbalenyaetal.,2020). All the SARS CoV fall under the species *Severe acute espiratory syndrome – related coronavirus* and genus *Beta-coronavirus*. Most of the species under this head are enzootic and only a few of these species infect humans (Schoeman and Fielding, 2019). At present seven human CoVs (HCoVs) have been confirmed. They are Human coronavirus *NL63* (HCoV-NL63), Human coronavirus 229E (HCoV-229E) belonging to the *alpha-coronavirus genus*; Human coronavirus OC43(HCoV –OC43), Human coronavirus (HCoV-HKU1), SARS-CoV, SARS-CoV-2 and Middle East respitarory syndrome coronavirus (MERS-CoV) belonging to the *beta-coronavirus genus*. HCoV-229E, HCoV-NL63, HCoV- HKU1 and HCoV-OC43 strains are responsible for causing mild respiratoty diseases in humans. The SARS-CoV-2 is a zoonotic virus that belongs to the Coronaviridae family that can infect human and several animal species (Luet 2020). The SARS-CoV-2 belongs to the sub-genus *Sarbecovirus* and mostly resembles a bat coronavirus

withwhich it shares 96.2% sequence homology (Chan et al., 2020a). Presently it is being assumed that SARS-CoV-2 has been brought in to human host cell by an unidentified animal from where it has spread among humans.

Human coronaviruses mainly infect the upper respiratory tract resulting in illnesses like influenza and common cold. The SARS-CoV and MERS-CoV are the two majo rcauses of severe pneumonia in human (Song et al., 2019). Investigations needs to be performed to trace the exact source of infection as the exact origin of SARS-CoV-2 is still a mystery to researchers across the globe. The WHO, on February 11,2020, officially

named the viral disease COVID-19 (Jiang et al., 2020;Guamer,2020). The Coronavirus Study Group of the International Committee on Taxonomy of Viruses named the new pathogen as SARS-CoV-2 (Gorbalenya, 2020). The forerunner SARS-CoV-2 first came out in 2002 (Peiris et al.,2004). This was followed by the arrival of MERS-CoV in 2012 at Saudi Arabia. (Zaki et al.,2012). A correlative study of the symptoms amid COVID -19, SARS, MERS and common flu has been elucidated. (Table -1).

Table-1 Symptomatic correlation of COVID-19, SARS, MERS and Common flu.

Diseases	**Symptoms**	**Onset of disease**	**Incubation period**	**Recovery**	**Transmission of disease**	**Complications if any**	**Treatments if available**
Novel Coronavirus (COVID19)	Fever,Cough,Shortness of breath,Fatigue	Sudden	2-14 days after exposure	2-8 weeks	Human to Human	Acute pneumonia,septic shock,respiratory failures in adverse condition	No vaccines available,only symptoms can be treated
Severe Acute Respiratory Syndrome (SARS)	Fever, Dry Cough, Headache, Difficulty in breathing, Muscle aches, Loss of appetite, Diarrhoea	Sudden	2-7 days after exposure	5-6 weeks	Human to Human	Heart, Liver and respiratory failure in adverse condition.	Breathing ventilator to deliver oxygen.Pneumonia treating antibiotics.Antiviral medicines. Steroids to reduce lung swelling.
Middle East Respiratory Syndrome (MERS)	Fever, Chills, Diarrhoea, Nausea, Vomiting, Congestion, Sneezing, Sore throat	Sudden	5-6 days after exposure	6-7 weeks	Human to Human	Acute pneumonia, Kidney failure in adverse condition	Treatment only for symptoms such as Fluids replacement. Oxygen therapy.
Common flu	Runny or stuffy nose, Sneezing, Sore throat, Mild Headache, Low grade fever	Gradual	2-3 days after exposure	7-10 days	Human to Human	Extremely rare or none	Symptoms can be treated by medication.

2) Structural assembly of SARS-CoV-2 virus:

The SARS-CoV-2 comes from the largest family of RNA viruses and its genome varies from 27 -32 kilobases in size (125 nm or 0.125µm) .It is a single stranded enveloped RNA virus which possess a positive-sense RNA genome also known as (+ssRNA) with a 5' – cap structure and 3'-poly-A-tail.(Chen, 2020). The viruses which belong to this group have few familiar attributes associable to SARS-CoV-2 as well. The virus has four vital structural proteins which are (E) the envelope protein, (M) the membrane protein, (S) the spike protein and (N) the nucleocapsid protein which are required to regulate the function and viral structure (Shoeman and Fielding, 2019).Among these four proteins the most important ones are N and S, where the former helps the virus to develop the capsid and the entire viral structure appropriately and the later helps in the attachment of virus to the host cells.(Siu et al., 2008; Walls et al., 2020). The S protein has three important sections namely, the large ectodomain, a single- pass transmembrane anchor and a short intracellular tail. These are having a vital role in anchoring the host cells. Amidst theses sections the ectodomain has two subunits which are, the S1 receptor binding subunit and S2 the membrane fusion subunit.These subunits are in the clove-trimeric or crown structure which is the reason of the coronavirus (corona=crown) got its name. (Zumla et al., 2016). It has been reported that the SARS-CoV and SARS-CoV-2 have similar kind of receptors, especially the receptor binding domain(RBD) and the receptor binding motif (RBM) in the viral genome. (Yin and Wunderink 2018; Zhang et al., 2020; Tai et al., 2020).During the SARS infection, the RBM of the S protein gets directly attached to the Angiotensin Converting Enzyme 2 (ACE2) in the human or the host cells. (Phan, 2020). The ACE2 protein is expessed in various organs of the human body mainly in the lungs, kidney and intestine, the prime targets of the coronavirus. (Zhao et al., 2020).

It is interesting to note that SARS-CoV-2 mechanism of action in infection of humans is identical to the SARS.It has been reported that the RBM of the SARS-CoV-2 has a major amino acid residue (Gln493) that favours the attachment and fusion of the viral S protein with virus into the ACE2 protein of the human cell

especially the one present in the lungs resulting in respiratory infections in humans (Zhao et al., 2020; Yin and Wunderink, 2018). The findings from the structural assembly suggest that the knowledge in depth about the receptors, its targets and basis of viral replication would be a base for finding the remedy of the SARS-CoV-2 infection. An interpretation about the structure and binding of S protein to ACE2 has been portrayed. (Fig.1).

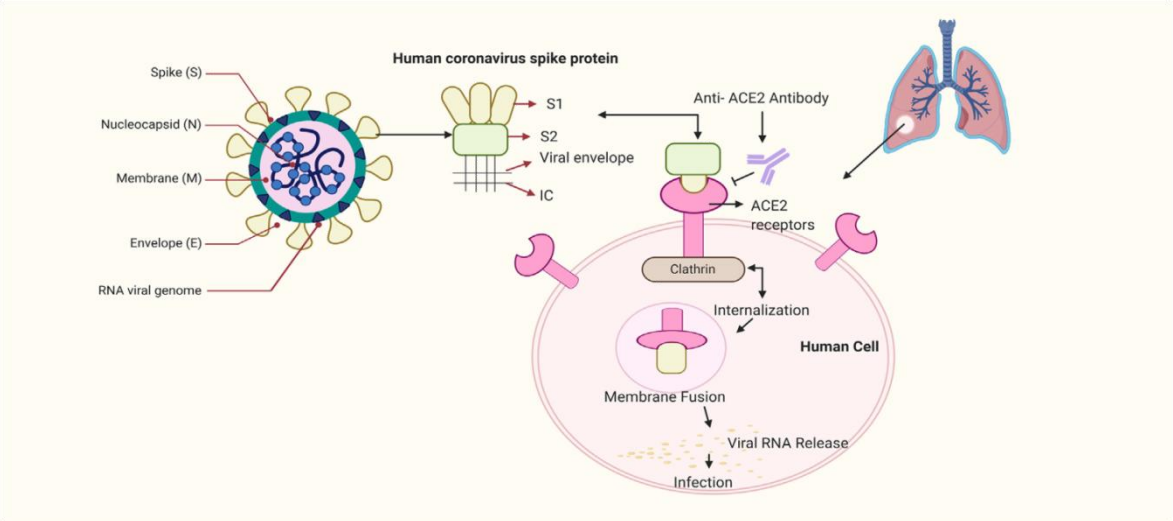


Fig 1. Structure and binding of SARS-CoV-2 to ACE2 protein of human host cell.

3) Replication of SARS-CoV-2:

The viral RNA replication is the most uncommon and exceptive step performed by the virus for its survival inside the host body. The tools needed for the process of replication are open reading frames (ORFs), two replicase genes (rep1a and rep 1 ab), a slippery sequence (5'-UUUAAAC-3') and two polyproteins (pp1a and pp1 ab). Both these polyproteins consists of the most vital proteins of the virus that are the Nsp proteins (Nsp1-11 and Nsp 1-16), these proteins commonly occur in these virus types. (Baranov et al., 2005). Further these Nsp proteins (Nsp ½, Nsp2/3 and Nsp ¾) gather to form the replicase-transcriptase complex (RTC) creating an environment inside the host body convenient for RNA synthesis and replication. These Nsps, also have different roles in RNA replication of the virus.Nsp12 encodes the RNA-dependent RNA polymerase(RdRP) domain, Nsp13 encrypts with RNA helicase domain and RNA 5'-triphosphase, Nsp14 encodes the exoribonuclease(ExoN) facilitating replication conformity and lastly Nsp16 encodes 2'-Omethyltransferase activity. These data proves that Nsp protein has an important function in keeping the virus alive inside the host body by aiding basic synthesis, replication and translation.

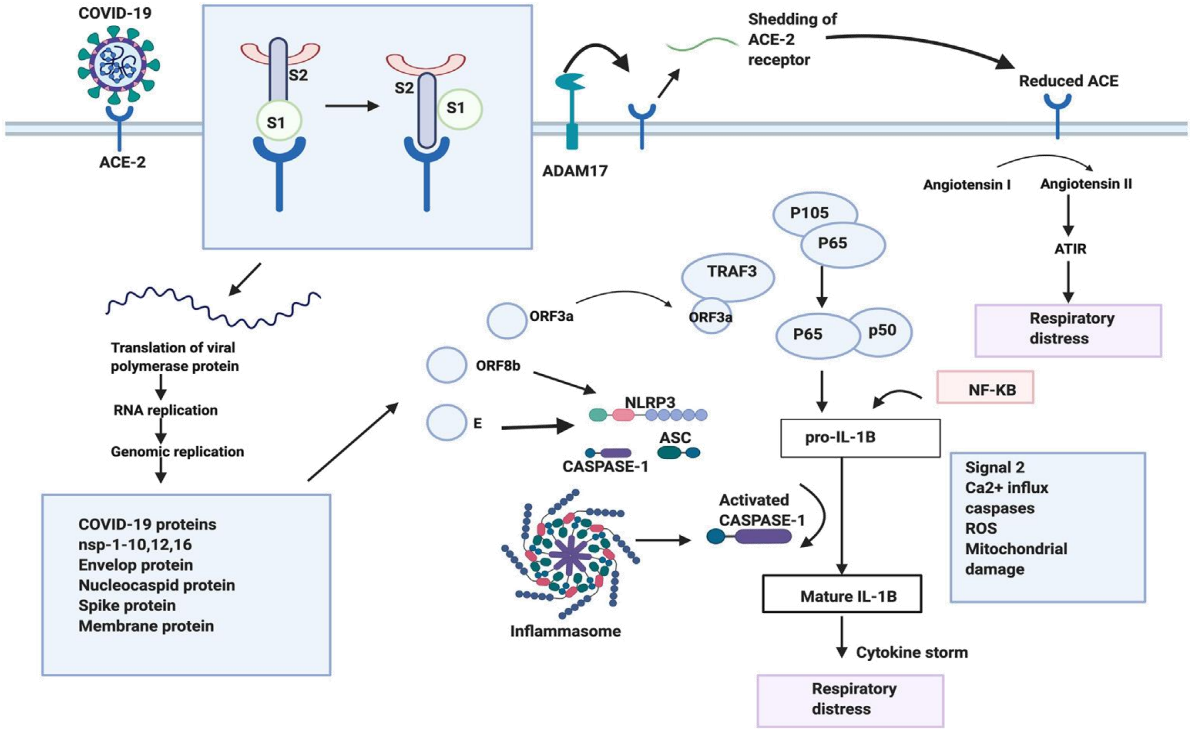
For replication the genomic RNA consists of a 5' end region that has the untranslated leader (L) sequence with the transcription regulation sequence (TRS) present at the descending region of the genome. (Brian and Baric, 2005). The replicase gene encoded enzymes uses the negative RNA genome as a template for developing few sets of small overlapping messenger RNA molecules which further gets translated into the structural proteins (N,M,E and S protein), while the positive stranded RNA genome is used as a template to produce the negative strand. During the replication process inside the human host, the N protein of the virus binds to the genome which the M protein gets attached with the membranes of the endoplasmic reticulum(ER). Further with the help of Nsp proteins the RNA gathers into a helical twisted structure and enters into the ER lumen. Viral progenies are transferred to the cell membranes by golgi bodies and exocytosed into the extracellular space of the human host cell environment. These mechanisms were discovered in the preceding viruses and may have a vital role in SARS-CoV-2 as well. (Brian and Baric, 2005; de Haan and Rottier, 2005). From the replication process of SARS-CoV-2 it is proved that if we target Nsp proteins then we can develop a strategy to overcome this viral infection.

4) SARS-CoV-2- proposed mechanism:

SARS-CoV-2 shares similarity with SARS-CoV but the rate of transmission and infectivity is much higher for SARS-CoV-2 most probably due to a gain of function mutation. The SARS-CoV-2 like other beta coronaviruses goes through a few steps to enter into and affect the host cell. In SARS-CoV upon binding to the receptor, proteases are sent to split the S protein into S1 and S2 domains. This splitting gives rise to a conformational change activating S2, followed by the inclusion of the FP into the membrane which leads to membrane fusion

ACE2, we can assume that SARS-CoV -2 uses the same mechanism to enter the host cell.Once the virus enters the cell, ACE2 gets reduced and shed by ADAM17 into the extra membrane space. Once the virus translates its proteins in the cell, it produces the ORF3a protein and codes for a Ca^{2+} ion channel similar to SARS-CoV and SARS-CoV-2. It interacts with TRAF3 and opens up the transcription of the NF-kB pathway resulting in transcription of the pro-1L-1B gene (Siu et al., 2019), ORF3a along with TRAF3 also brings in the inflammasome complex. This complex is made up of NLRP3, ASC and caspase1. A second signal like Ca^{2+} influx, caspases activation, ROS production and mitochondrial damage converting pro-IL-1B to IL-B resulting in cytokine production.The E protein which forms an ion channel, is also preserved in the two viruses and is involved in the overproduction of cytokines through the NLRP3 inflammasome pathway. (Nieto Torres et al., 2015). All these pathways when associated together forms a cytokine storm causing respiratory distress, a common symptom of COVID -19.

During the infection of the virus ,the most vital part is the interaction with host cell nucleases. It is feasible that SARS-CoV-2 may use proteases alike SARS-CoV such as TMPRSS11a, Trypsin, Plasmin, Cathepsin L and Furin in the breaking of the spike protein for the virus to enter the cell. These proteases can be used as targets to reduce the symptoms of COVID-19 since proteosomal inhibitorsused for HIV treatment are being used to treat COVID-19 (Fig 2).



5) SARS-CoV-2 and the immune system:

The HCoVs are usually very long (30,000 bp) positive- sense single-stranded RNA viruses. Two groups of protein characterize HCoVs ; the structural proteins and non-structural .proteins such as RNA dependent RNA polymerase (RdRp) (nsp12) (Elfiky, 2020). Coronaviruses such as SARS and MERS are specifically proficient at avoiding immune detection and moistening immune responses.Although there is not a clear picture of how SARS-CoV-2 disturbs the immune system. T cells particularly CD4+ and CD8+ play a sig. nificant antiviral role to fight the pathogens and increase the risk of developing autoimmunity/inflammation (Cecere et al., 2012). The CD4+ T cells forwards the production of viral-specific antibodies by activating T cell-dependant B cells. Whereas CD8+ T cells are cytotoxic and kill virus infected cells.The CD8+ T cells account for about 80% of total inflammatory cells in the pulmonary interstitium in SARS-CoV infected patients and play a significant role in clearing coronaviruses in infected cells and inducing immune injury. (Maloir et al., 2018). In addition, T helper cells produce proinflammatory cytokines via NF-kB signaling. (Man ni et al., 2014). The cytokines, IL-17 appoint monocytes and neutrophils to the infection site showing inflammation and triggers other downstream cascades of cytokines and chemokines, including IL-1, IL-6, IL-8, IL-21, TNF-β and MCP-1 (Bunte and Beikler,2019). From the provisional testimonies it was depicted that T cell response to S protein and other structural proteins (including M and N proteins) is persistent and provides valid proof for the design of new drugs and vaccines for SARS-CoV-2, which can add on effective and long- term memory cell responses against the virus.

6) Recent Diagnostic techniques:

During the SARS and MERS outbreaks effective diagnostic equipments were developed for authentic detection. The viral nucleic acid detection is primarily used in SARS-CoV-2 diagnosis (Wang et al., 2020a, 2020b, 2020c). CDC has advised to collect upper respiratory nasopharyngeal (NP) swabs for the diagnostic tests (CDC, 2020). The CDC detection examination targets the N region and contains one test for beta-coronaviruses and two exclusive probes for SARS-CoV-2. The Charitě algorithm contains probes for E protein and RNA dependent RNA polymerase (RdRp). Once both become positive, the sample is again tested against specific SARS-CoV-2 RdRp (Loeffelholz and Tang,2020). When the commercially available Real star kit, Virus + Rox Vial kit and Super Script III One-step RT-PCR System with Platinum TaqDNA Polymerase were compared for their performance, the RealStar kit did not have any unwanted signals and outpaced the other two in its efficiency (Konrad et al., 2020). These tests are also expensive, hence cheaper alternatives have been introduced to track the symptoms of COVID-19 using smart- phone surveillance (Dorigatti et al., 2020). Imaging techniques can also be applied as a diagnostic method in COVID-19. Additionally chest CT scans have been done to detect lung abnormalities in SAS-CoV-2 infection (Shi et al., 2020; Xu et al., 2020a,2020b). But, not all the cases can be perfectly detected with CT scans (Lei et al., 2020).Hence it is important to carry on molecular tests and consider travel history and clinical symptoms of patient as well. In order to design specific drugs, it is necessary to figure out the current strategies used to treat this novel COVID-19.

7) Classification of pipeline drugs:

At present there are no FDA approved drugs for COVID-19 yet. Presently treatment provided to the infected patients are mainly symptom based, and the seriously ill individuals are provide with organ support (Jin et al., 2020; Zumla et al., 2020). Since the development of specific drug or vaccine against COVID-19 shall take sometime drugs which have an evidence to be safe for humans can be remodelled to treat this disease. The following classification of drugs may be used for treating COVID 19 worldwide.

a) *Antiviral drugs*

Drugs under this category generally follow any one of the three mechanisms in the virus-viral replication inhibition, ion channel inhibition and serine protease inhibition. Marketed antiviral drugs mainly targetfour major groups of viruses: human immunodeficiency virus (HIV), herpes, hepatitis and influenza (Razonable, 2011).

b) *Antimalarial drugs*

These drugs also comes under three categories based on their mode of action aryl amino-alcohol compound, antifolate compound and artemisinin. A disadvantage of this drug is that antimalarial drug resistance is developed for any drugs under this category (Edwin et al., 2019).

c) *Anti-HIV drugs*

These drugs are listed into different categories according to their targets reverse transcription, retro transcription, proteolytic processing, viral-cell fusion, co-receptors interactions and incorporation of proviral DNA into the host genome. Drugs falling under these categories are approved by the FDA (Food & Drugs Administration) and are now officially used for the treatment of HIV (De Clercq, 2009).

d) *Anti-inflammatory drugs*

Anti- inflammatory drugs like JAK-STAT inhibitors, used against rheumatoid arthritis can be promising against increased levels of cytokines and handy in obstructing viral infection. A recent study reveals that an anti-inlammatory drug, baricitinib when used in combination with anti-viral drugs like Remidesivir, increases the potential of the drug to lower viral infection (Stebbing et al. 2020).

e) *Monoclonal antibodies*

The virus enters the host cells by binding the S protein to ACE2 receptors. By establishing counterbalancing antibodies against the receptors, there is a high possibility of reducing the severity of the disease (Zheng and Song, 2020). Currently, only a few drugs have been approved for use against SARS-CoV-2.

8) Clinically used drugs:

SARS-CoV-2 being a rapidly spreading virus, it is necessary to provide timely treatment for the affected individuals (Zumla et al., 2016). Few of the commonly used drugs are described below and a list of possible drugs is depicted in Table 2.

a) *Ribavirin*

Ribavirin is a broad spectrum drug whose therapeutic credibility was discovered in 1972. It is used in the treatment of Hepatitis C. It is generally used in combination with interferon α (IFN). This drug approved by the FDA, competes for the active site of RdRp, Ribavirin scored 109.5μM of half maximum concentration against SARS-CoV-2 (Elfiky, 2020).

b) *Sofosbuvir*

This is also an FDA approved drug against NS5B and acts a nucleotide polymerase inhibitor for the treatment of Hepatitis C. This drug was previously used for the treatment of Zika virus (Cheema et a., 2019).

c) *Lopinavir/Ritonavir*

Lopinavir is a protease inhibitor that targets the HIV virus. It was identified in 1998 and approved by the FDA in 2000. This drug averts the production of viral proteins by disturbing the proteolytic processing by mirroring its structure as a peptide carved by HIV protease. This drug along with another flu drug oseltamivir was reported to result in complete recovery after showing symptoms of COVID-19 related pneumonia (Wu et al., 2020a, 2020b).

d) *Remidesivir (anti-viral peptide)*

This drug is an adenosine nucleotide associate, which was used in treatments against Ebola, SARS-CoV and MERS-CoV. A recent study has shown that Remidesivir has scored 0.77μM at half maximum concentration against COVID-19 and blocked viral infection (Wang et al., 2020a, 2020b, 2020c).

e) *Chloroquine*

This drug listed as an anti-malarial drug , has shown potential in the treatment of vian influenza A (Yan et al., 2013). Chloroquine possesses anti-viral as well as immune modulating properties. This drug showed 1.13μM at half maximal concentration against SARS-CoV-2 and obstructed viral infection by increasing the endosomal pH required for viral fusion (Wang et l., 2020a, 2020b, 2020c; Vincent et al., 2005).

f) *Favipiravir*

This is also a broad spectrum anti-viral drug which has obtained approval from Shenzan Health Commission for treating COVID-19 patients (Wu et al., 2020a, 2020b).

g) *Ongoing clinical trials*

Presently, numerous companies have applied for clinical trials to remodel existing drugs as well as to develop vaccines and drugs to combat the fast and vast spreading COVID-19 (Rudra et al., 2017). For remodeling the existing drugs , randomized control treatment (RCT) are being performed by different research organizations and biotechnological companies such as National Institutes of Health (NIH), USA to recognize disease specific drugs. There is need of more research in traditional medicine to utilize them for treating COVID-19. The crucial drugs going through clinical trials are mentioned in Table 3.

Table -2: The detailed report of commercially available drugs in treatment of COVID-19

S. No.	Name of drug	Illnesses treated	References
1	Papain-like protease	SARS, MERS and Human Coronavirus NL63	(Chen, 2020; Harcourt et al., 2004; Kilianski et al., 2013)
2	Nitazoxanide	SARS, MERS and Influenza	(Rossignol, 2016)
3	Remdesivir	COVID-19, SARS, MERS	(Agostini et al., 2018; Wang,2020)
4	Favipiravir	COVID-19	(Wang , 2020)
5	Darunavir	COVID-19	(Beck et al., 2020; Lin et al., 2020)
6	Lopinavir	COVID-19, SARS, MERS	(Yao et al., 2020)
7	Alcohol Vaporization or Nebulization Inhalation Therapy	COVID-19	(Cao, 2020)
8	Chloroquine	SARS, Human Coronavirus OC43	(Keyaerts et al.,2009,2004; Vincent et al., 2005)
9	ASC09	ARDS, SARS,MERS	(March and Bogatcheva, 2018,2019)
10	Baricitinib	COVID-19	(Richardson et al., 2020;Stebbing et al., 2020)
11	Ruxolitinib	COVID-19	(Stebbing et al., 2020)
12	Indinavir	SARS and COVID-19	(Contini,2020; Tan et al., 2004)
13	Carfilzomib	COVID-19	(Wang,2020)
14	Oseltamivir	COVID-19	(Haagmans et al.,2004; Lu,2020)
15	Azvudine	COVID-19	(Hu et al., 2020)

16	Baloxavir marboxil	COVID-19	(Li and Clercq, 2020)
17	Tocilizumab	COVID-19	(Diao et al., 2020)
18	Acyclovir	SARS, MERS, Coronavirus 229E and COVID-19	(Peters et al., 2015)
19	Cathespin L	SARS	(Simmons et al., 2005)

Table 3. Ongoing clinical trials for COVID-19.

S.No	**Study**	**Drug**	**Status**	**Organization**
1	Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19	Sarilumab	Recruiting	Regeneron Study Site New York, New York, United States
2	Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Moderate Coronavirus Disease(COVID-19) Compared to Standard of Care Treatment	Remdesivir	Recruiting	1.Stanford Hospital, Stanford, California, United States. 2. Providence Regional Medical Center Everett, Everett, Washington, United States.
3	Fingolimod in COVID-19	Fingolimod 0.5mg	Recruiting	Wan-Jin Chen Fuzhou, China
4	Efficacy and Safety of Corticosteroids in COVID-19	Methylprednisolone	Recruiting	1.Hubei province hospital of integrated Chinese & Western Medicine Wuhan, Hubei, China 2.Renmin Hospital OF Wuhan University Wuhan, China
5	Mild/Moderate 2019-nCoV Remdesivir RCT	Remdesivir	Recruiting	Jin Yin- tan hospital Wuhan, Hubei, China
6	Severe 2019-nCoV Rmdesivir RCT	Remdesivir	Recruiting	Bin Cao Beijing, Beijing, China
7	Nitric Oxide Gas Inhalation for Severe Acute Respiratory Syndrome in COVID-19	Nitric Oxide Gas	Not yet recruiting	-
8	Evaluating and Comparing the Safety and Efficacy of ASC09/Ritonavir and Lopinavir/Ritonavir for Novel Coronavirus Infection	1.ASC09/ritonavir group 2.Lopinavir/ritonavir group	Not yet recruiting	-
9	Glucocorticoid Therapy for Novel Coronavirus Critically III Patients With Severe Acute Respiratory Failure	Methylprednisolone	Recruiting	Medical ICU Peking Union Medical College Hospital Beijing, Beijing, China
10	Lopinavir/Ritonavir, Ribavirin and IFN-beta Combination for nCoV Treatment	1.Lopinavir/ritonavir 2.Ribavirin 3.Interferon Beta-1B	Recruiting	University OF Hong Kong, Queen Mary Hospital Hong Kong, Hong Kong
11	A study for the efficacy of hydroxychloroquine for mild and moderate COVID-19 infectous diseases	Hydroxychloroquine	-	The Second Affiliated Hospital of Chongqing Medical University
12	The efficacy and safety of carrimycin treatment in patients with COVID-19: a multicenter, randomized, open-label controlled trial	Carrimycin	-	Beijing You'an Hospital, Capital Medical University
13	A Pilot Study of Sildenafil in COVID-19	Silenafil citrate	Recruiting	Department and Institute of Infectious Disease, Wuhan, Hubei, China
14	Comparison of Lopinavir/Ritonavir or Hydroxychloroquine in patients with Mild Coronavirus Disease (COVID-19)	1.Lopinavir/ritonavir 2.Hydroxychloroquine sulfate	Recruiting	Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, Republic of Korea
15	Various Combination of Protease Inhibitors, Oseltamivir, Favipiravir and Chloroquine for Treatment of COVID-19: A Randomized Control Trial	Oral	Not Yet Recruiting	Subsai Kongsaengdao, Bangkok, Thailand
16	Post-exposure Prophylaxis for SARS-Coronavirus-2	Hydroxychloroquine	Recruiting	University of Minnesota, Minneapolis, Minnesota, United States
17	The efficacy and safety of pirfenidone capsules in the treatment of severe new coronavirus pneumonia (COVID-19)	Pirfenidone	-	Third Xiangya Hospital of Cenral South University

9) Importance of Indian Medicine:

Indian traditional medicinal systems are considered as one of the oldest treatments in human history and it plays a vital role in encountering health care needs worldwide. (Ravishankar and Shukla, 2007). These practices include Ayurveda, Siddha, Unani and Yoga ,Naturopathy and Homeopathy, which are successfully practiced for the treatment of various diseases (Gomathi et al., 2020). These practices came into occurrence about 5000 years ago and have been observed and documented in ancient texts.

Traditional Indian medicine use plants, minerals and animal products for treating human diseases. About 25,000 plant based formulations have been used in folk-lore remedies in Indian medicine (Pundarikakshudu and Kanaki,2019). Recently, the total number of Indian medicinal plants was estimated to be around 3000, yet, traditional practitioners use around 8000 different species for their practice (Pundarikakshudu and Kanaki,2019). Tradiotional medicines are usually avoided in research and development of modern drugs as their adaptational capability are usually underrated.A single herb consists of many phytoconstituents that may work alone or in combination with other compounds to deliver the needed pharmacological effect (Parasuraman et al., 2014). Among antiviral therapeutic methods, majority of them are non-specific for viruses (Jiang et al., 2015). Plant derived pharmacological formulations made a major contribution for viral infections (Cragg et al.,1997). Based on the availability of convenient, potent and fast bioassay systems, the antiviral compounds have been used for fast blinding from plant extracts and fractions (Scior et al., 2012). Synthetic drugs have been replaced by medicinal plants, as life-saving drugs in various viral diseases (Gurib-Fakim, 2006). As many Indian medicinal plants display antiviral, anti-inflammatory and antioxidant properties, it may be encouraging to consider them for the treatment of COVID-19.Although standard clinical trials should be conducted to scientifically to confirm its potency.

10) Indian medicinal plants and their possible effect on COVID-19:

Since ancient times, Indian herbs are being used as a treatment for respiratory viral infections. Holistic approach of AYUSH system of medicines gives emphasis on prevention through lifestyle modification, dietary management, prophylactic interventions for improving the immunity and simple remedies based on presentation of the symptoms (AYUSH, 2020). A study has shown anti-mouse coronaviral activity (a surrogate of SARS-CoV) by the plants *Indigofera tinctoria (AO)*, *Vitex trifolia*, *Gymnema sylvestre*, *Abutilon indicum*, *Leucas aspera*, *Cassia al.ata*, *Spaeranthus indicus*, *Clitorea ternatea*, *Clerodendrum inerme Gaertn*, *Pergularia daemi* and *Evolvulus alsinoides* in Tamil Nadu (Vimalathan et al., 2009). Among them *Vitex trifolia* and *Spaeranthus indicus* have been found to reduce inflammatory cytokines using the NF-kB pathway (Alam et al., 2002; Srivastava et al., 2015).The plants *Glycyrrhiza glabra* (Nourazarian, 2015) and *Allium sativum* (Keyaerts et al., 2007) have been found to target the viral replication of SARS-CoV, arising as promising candidates against SARS-CoV-2. In Asia, Himalayan forests are abundantly flourished with rich medicinal plant species and a study has documented the presence of ethnomedicinal plants against bronchitis (Amber et al., 2017). The study screened the antiviral plant properties against bronchitis , which showed that *Hyosyamus niger*, *Justicia adhatoda* and *Verbascum thapsus* 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. Various medicinal plants have shown inhibitory effects against ACE, and these include *Coriandum sativum* (Hussain et al., 2018), *Boerhaavia diffusa*, *Cynara scolymus*, *Coscinium fenestratum*, *Punica granatum*, *Cassia occidentalis* and *Embelia ribes*. Among these *Punica granatum* exhibited a competitive mode of action while the rest were non-specific inhibitors (Khan and Kumar, 2019; Prathapan et al., 2013). It was observed that *Andrographis paniculata* (Kalmegh) suppressed increased NOD-like receptor protein 3 (NLRP3), caspase-1 and interleukin-1β molecules that are extensively involved in the pathogenesis of SARS-CoV and likely SARS-CoV-2 as well (Liu et al., 2020a, 2020b). Numerous plants have also shown inhibitory actions towards HIV proteases and can be promising drugs for COVID-19. They include *Acacia nilotica* (Shanti, 2016), *Eugenia jambolana* (Otake et al., 1995), *Euphorbia granulate* (Shanti, 2016). Some plants like *Ocimum sanctum* (Rege and Chowdhary, 2014), *Ocimum kilim and scharicum* (Thayil Seema and Thyagarajan, 2016), *Solanum nigrum* (Yu,2004), *Vitex negundo* (NAIR, 2012) have been known to target the reverse transcriptase activity of HIV and can be studied fo activity against SARS-CoV-2 as well. Though many medicinal plants have been identified, a lot of research has to be executed for the development of drug specific to SARS-CoV-2. The effect of these prescribed traditional medicines on SARS-CoV-2 is provide in Table.4.

Table.4 List of Indian medicinal herbs which might inhibit the HCoVs and other viruses

S.No.	Plant source	Mechanism of action	Target	Virus	Reference
1	*Acacia nilotica*	Inhibition	_	HIV-PR	Mishra et al., 2014
2	*Allium sativum*	Proteolytic and hemagglutinating activity and viral replication	_	SARS	Keyaerts et al., 2004
3	*Clerodendrum inerme Gaertn*	Inactivation	Ribosome	SARS-CoV-2	Olivieri et al.,1996
4	*Clitoria ternatea*	Metalloproteinase inhibitor	ADAM 17	_	Maity et al., 2012
5	*Eugenia jambolana*	Inhibition	Protease	_	Otake et al., 1995
6	*Glycyrrhiza glabra*	Inhibition of viral replication; Modulation of membrane fluidity	_	SARS, HIV-1	Akamatsu et al.,1991; Cinatl et al., 2003; Fiore et al., 2008
7	*Coriandrum sativum*	Inhibition	ACE	_	Pandey e al., 2011
8	*Hyoscyamus niger*	Inhibition and Bronchodilator	Ca^{2+}	_	Gilani et al., 2008
9	*Ocimum sanctum*	Inhibition	_	HIV-1	Rege and Chowdhary, 2014
10	*Salacia oblonga*	Suppresion	Angiotensin II, ATI signal	_	He et al., 2011
11	*Sambucus ebulus*	Inhibition	_	Enveloped virus	Ganjhu et al., 2015
12	*Solanum nigrum*	_	_	HIV-1	Yu, 2004
13	*Punica granatum*	Inhibition	ACE	_	Prathapan et al., 2013; Khan and Kumar, 2019
14	*Strobilanthes callosa*	Blocking	_	HCoV-NL63	Tsai et al., 2020
15	*Strobilanthes cusia*	Blocking	_	HCoV – NL63	Tsai et al., 2020
16	*Vitex negundo*	Inhibition	_	HIV- 1	Nair, 2012
17	*Vitex trifolia*	Reduction	_	SARS-CoV	Liou et al., 2018

11) Recommendations:

The spectrum of symptoms associated with COVID-19 ranges from difficulties in breathing and other respiratory ailments to serious conditions including SARS, kidney failure and even death sometimes. Individuals are likely to get infected by others who are inflicted with the virus. The disease may spread from person to person via small droplets from nose or mouth when a person with COVID-19 coughs or exhales. These particles in the air, settle on surfaces in the environment further infecting people who breathe these particles or touch these places and then touch their body parts. Hence it very important to stay less than 1m/ (3 ft) away from a person who is sick (WHO, 2020c). Reports are suggesting that aged persons and persons with existing or previous medical conditions (like high blood pressure, heart disease, lung disease, cancer or diabetes) are likely to develop serious illness more often than others (Wu and McGoogan, 2020; Chen et al., 2020). The protective measures recommended by WHO (2020d) are as follows:

a) Wash hands completely using an alcohol- based hand sanitizer. It will kill the virus.
b) Avoid touching eyes, nose and mouth when outside.
c) Remain updated about the virus.
d) Avoid travelling or gathering in crowded places.
e) Women with infants are encouraged to breastfeed their babies to enhance their immunity.

WHO is coordinating efforts to develop vaccines and medicines to prevent and treat COVID-19 (WHO, 2020d). National Institute of Health (NIH), has said that SARS-CoV-2 can survive for up to 3 hours maximum as aerosols to a maximum of three days on surfaces. Hence, it's time for all the citizens to join hands together to combat against coronavirus by practicing self-hygiene and social distancing.

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