IRAETC Medical Bulletin

ISSN (e): 2959-3115

Volume: 1 (2023), Issue: 2 (Jul-Aug)

OPEN ACCESS

iraetcjournals.com

Molecular pathogenesis, recognition and Solidarity Therapeutic Approaches against COVID-19

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Review Article

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Citation:

Sarvesh Sharma & Himesh Soni., (2023); Molecular pathogenesis, recognition and Solidarity Therapeutic Approaches against COVID-19. iraetc med. bull; 1(2) 35-46.

Abstract:

A novel Corona Virus infection (COVID-19) is alike to viral pneumonia and it is caused by severe acute respiratory syndrome Corona Virus-2 (SARS-CoV-2). In this short review we discuss here common features of highly contagious and pathogenic SARS-CoV-2 provide current information of molecular immune pathogenesis, diagnosis and solidarity treatment of COVID-19 on the base of present perceptive of SARS-CoV infectivity, which may be useful to control and to combat pandemic situation.The pressure COVID-19 puts on health systems means that WHO considered the need for speed and scale in the trial. Whereas randomized clinical trials usually take years to design and conduct, the Solidarity Trial will reduce the time taken by 80%. Enrolling patients in one solitary randomized trial will help facilitate the rapid worldwide comparison of unproven treatments. This will conquer the hazard of multiple small trials not generating the strong evidence needed to determine the relative effectiveness of potential treatments.

Key Words: SARS-CoV-2, COVID-19, molecular immune pathogenesis.

|| © IRAETC Publisher || **Publication History** - Received: 22.05.2023 || Accepted: 28.07.2023 || Published: 03.08.2023||

INTRODUCTION

The international virus classification commission declared that the novel corona virus was named as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). COVID-19 is not the first severe respiratory disease outbreak caused by the corona virus. Just in the past two decades, corona viruses have originated three epidemic diseases, namely, COVID-19, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). At pre- sent, the cases of COVID-19 have been found in many countries around the world. This review attempts to describe the molecular pathogenesis, diagnosis and solidarity treatment approaches of COVID-19 [1].

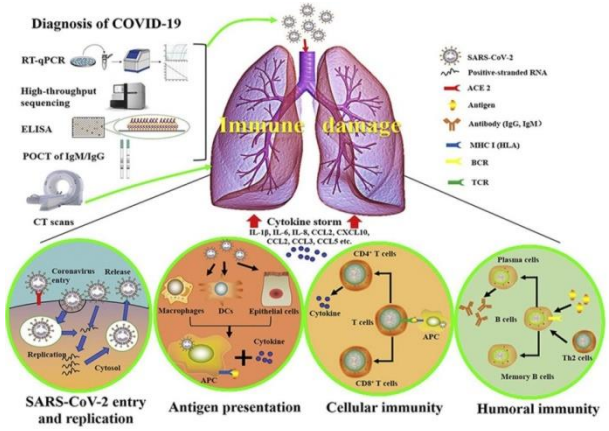


Fig.1: Overview of COVID -19

Characteristics of SARS CoV-2

The envelop bears crown-like, 20-nm in length spikes that resemble corona of the sun under electron microscopy, hence given its name corona virus. The virus can cause disease both in animal and human. It carries the largest genome among the currently known RNA viruses. Four coronaviruses are endemic in humans. These are human coronaviruses (HCoV) 229E, OC43, NL63, and HKU1. Two epidemic human corona viruses are SARS-CoV and

MERS-CoV. Alphacoronavirus includes HCoV 229E and NL63, and betacoronavirus includes HCoV OC43, HKU1, SARS-CoV, and MERS-CoV. The gammacoronavirus includes avian infectious bronchitis virus and several other coronaviruses, and deltacoronavirus includes several re cently discovered avian coronavirus. Within the coronavirus particle, a nucleoprotein (N) wraps the RNA genome to form a coiled tubular structure. The viral envelop (E) surround this helical nucleocapsid. Two or three structural proteins are associated with viral envelop. The matrix protein (M) embedded in envelop. The spike structural protein (S) anchored in envelop is target of neutralizing antibody. The hemagglutinin esterase is found in several of the beta-coronaviruses . The coronaviruses have 5 essential genes which are for 4 structural proteins (N, E, M, S) and for viral replication/ transcription (RNA dependent RNA polymerase, RdRp). The genome organization is 5'-RdRp-S-E-M-N-3'. This gene order of coronaviruses is highly conserved. Based on the virus genome sequencing data, bats are assumed to be the reservoir of SARS-CoV-2, but the intermediate hosts are yet to be known [2]. Data indicate SARS-CoV evolved from bat coronavirus in horseshoe bats through civet cats or other intermediated animal hosts. SARS-CoV-2 requires the angiotensin-converting enzyme 2 (ACE-2) as a receptor to enter cells. The attachment of the virus with host cell receptor is significant determinant for the pathogenesis of infection. The clear understanding of comparative effect of receptor and protease action will help to predict further possibility of adaptation of corona virus [3].

Molecular Pathogenesis of COVID-19

COVID-19 patient's clinical symptoms including high grade fever, nonproductive cough, dyspnea, myalgia, fatigue, breathlessness, normal or decreased leukocyte count, and radiographic indication of pneumonia, which is similar to the symptoms of SARS-CoV and MERS-CoV. Hence pathogenesis is not very clearly understood but symptoms and pathological information of infection to facilitate our recognition of COVID-19 [4-5].

Cellular entry and replication of Coronavirus [6-12]

S- Protein of corona virus has been reported as an important determinant of virus entry in host cells. Following envelop spike glycoprotein binds to its cellular receptor:

Table.1: Envelop spike glycoprotein and sub cellular receptor

S. No	Envelop Spike Glycoprotein	Cellular Receptor
1	SARS-CoV and SARS-CoV-2	ACE-2
2	SARS-CoV	CD209L (C type lectin also known as L-SIGN)
3	MARS-CoV	DPP4

The spike glycoproteins have two subunits; one subunit, S1, binds to the cell surface receptors; the other subunit, S2, fuses with the cell membrane. A host trans-membrane serine protease 2 (TMPRSS2) promotes entry of SARS-CoV into cells by two separate mechanisms. After the S1 subunit of the spike binds to the ACE-2 enzyme on the cell membrane surface, TMPRSS2 activates the spike and cleaves ACE-2. TMPRSS2 also acts on the S2 subunit of the spike glycoprotein, causing an irreversible conformational change, activating it, and facilitating fusion of the virus to the cell membrane. The virus then enters the cell. A model of these events is shown in Fig. 2.

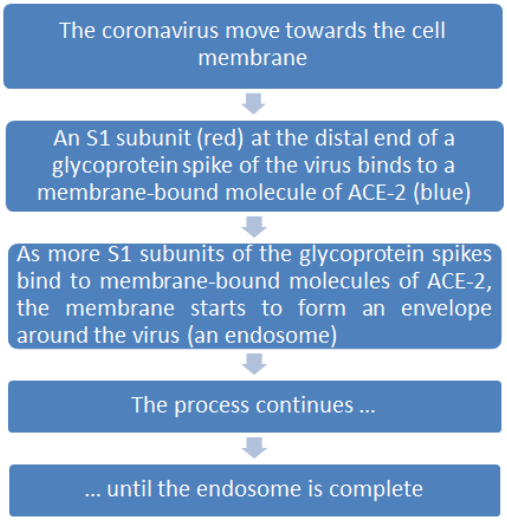


Fig.2 : Pathway of virus into human body

The virus can enter the cell in two ways:

(a) A cell membrane-bound serine protease (brown), TMPRSS2, cleaves the virus's S1 subunits (red) from its S2 subunits (black) and also cleaves the ACE-2 enzymes; the endosome enters the cell (endocytosis) where the virus is released by acidification or the action of another protease, cathepsin

(b) The same serine protease, TMPRSS2, causes irreversible conformational changes in the virus's S2 subunits, activating them, after which the virus fuses to the cell membrane and can be internalized by the cell

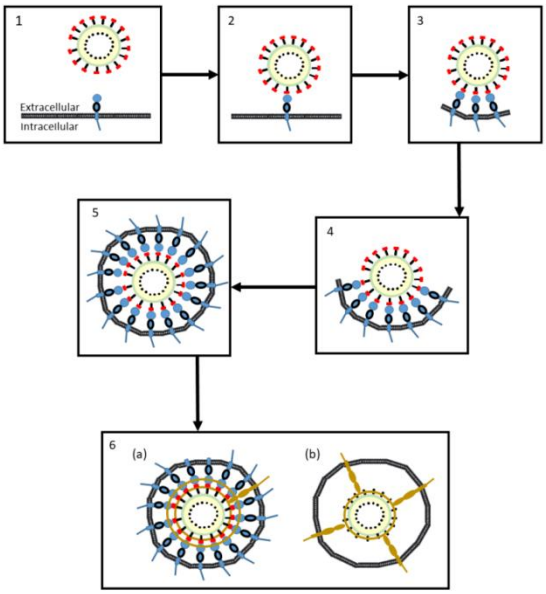


Fig.3: A proposed model of the coronavirus SRA-CoV-2 enters in to cells

Membrane fusion the clathrin dependent and independent endocytosis medicated SARS-CoV entry too. When virus enters the cells the viral RNA is released in to the cytoplasm and translated into two polyproteins and structural proteins, then viral genome start the replication. The newly enveloped glycoprotein is introduced in to membrane of endoplasmic reticulum or golgibody, and the nucleocapsid is formed by combination of genomic RNA and nucleocapsid protein. After that, viral particles produced in to endoplasmic reticulum-Golgi body intermediate compartment (ERGIC). Finally, the vesicles containing the virus particles then fuse with the plasma membrane to release the virus.

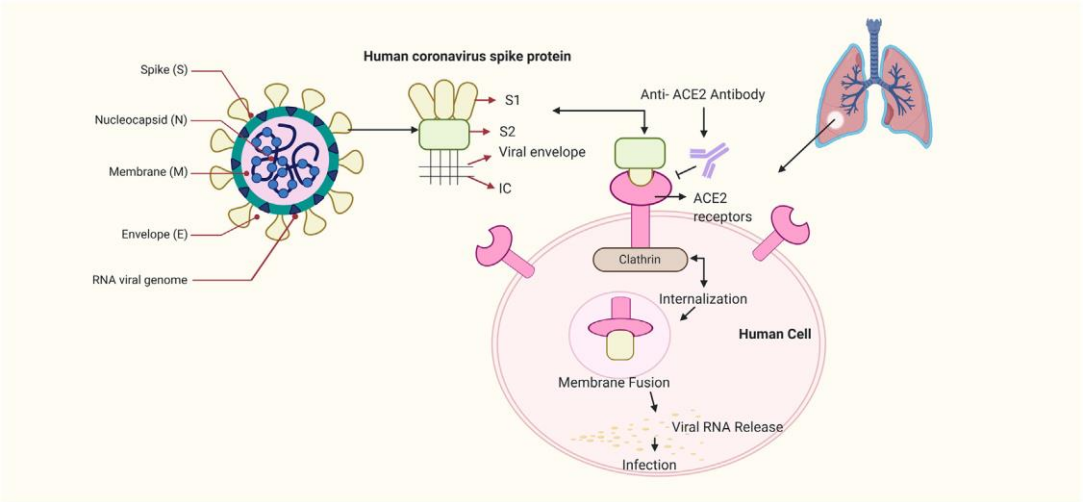


Fig.4: Structure and binding of COVID-19 virus to ACE2.

The above-mentioned figure showed the structure of the COVID-19 virus. Among the viral structure the S protein has a major role in binding of the virus to the host receptor cells. S protein has two subunits which are the S1 receptor-binding subunit and S2 the membrane fusion subunit; where the earlier one attached itself to the ACE2 receptor of the human host cell and the S2 subunit internalises and creates the membrane fusion among the viral subunit and the ACE2 receptors. This leads to the release of the viral RNA into the host cell and results into respiratory infection.

Antigen presentation in coronavirus infection [13-18]

Whilst the virus goes in to the cells, its antigen will be presented to the Antigen Presentation Cell (APC), which is the center of the human body's anti-viral immunity. Antigen peptides are presented by major histocompatibility complex (MHC; or human leukocyte antigen (HLA) in humans and then recognized by virus specific cytotoxic T

lymphocytes (CTLs). Hence the perceptive of antigen presentation of SARS-CoV will help to understanding of pathogenesis of COVID-19. **[*Hypothesis*]** The antigen presentation of SARS-CoV depends on MHC-I, MHC-II molecules and various HLA polymorphs. Above and beyond, gene polymorphism of MBL (mannose-binding lectin) connected with antigen presentation are related to the risk of SARS-CoV infection. This hypothesis will provide prospective clues for prophylaxis and treatment of COVID-19.

Humoral and cellular Immunity [19-23]

Antigen presentation consequently stimulates the body's humoral and cellular immunity, which are mediated by virus-specific B and T cells. Just alike to general acute viral infections, the antibody profile against SARS-CoV has unique pattern of IgM and IgG production. The SARS-specific IgM disappear at the end of week 12 while the IgG can very last for long duration, means it indicates IgG may primarily play a protective role, and the SARS-specific IgG mainly are S-specific and N-specific antibodies.

Table.2: Types of T- Cell and SARS-CoV interaction

Cells	Adaptation of CD-T cells in SARS-CoV infected patients
CD4 and CD8	Reduced
HLA-DR (CD4 3.47%) and CD38 (CD8 39.4%)	Incresed
CD4 and CD8 memory T cells	T cell proliferation, DTH response and production of INF-β

Cytokine storm in COVID-19 [24-26]

Acute Respiratory Distress Syndrome (ARDS) is the major immunopathological events of SARS-CoV-2, SARS-CoV and MARS-CoV infection and death cause of COVID-19. Core mechanism of ARDS is cytokine storm, fetal uncontrolled systemic inflammatory response resulting from the large amount of pro-inflammatory cytokine (INF-α, INF-β, INF-γ , IL-1 β, IL-6, IL-12, IL-18, IL-33, TNF-α, TNF-β. etc.) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.) by immune effectors cells released. The cytokine storm will activate aggressive attack by the immune system to the body, causes ARDS and multiple organ failure, and finally leads to lethal in severe cases of SARS-CoV-2 infection similar to SARS-CoV and MERS-CoV infection.

Immune evasion of coronavirus [27-32]

For the survival in host cell machinery, SARS-CoV and MERS-CoV apply various strategies to avoid immune responses. A conserved microbial structure called pathogen associated molecular pattern can be recognized by pattern recognition of receptors. (PRRs) On the other hand SARS-CoV and MERS-CoV can induce the production of double membrane vesicles that not show PRRs and then replicate in these vesicles, so avoiding the detection of host of their dsRNA. INF-α, INF-β has defensive effect of SARS-CoV and MERS-CoV infection, but the INF-I pathway is inhibited in disease induced mice. Gene expression correlated to antigen presentation is down-regulated after MERS-CoV infection. Thus, demolishing the immune evasion of SARS-CoV-2 is crucial in its treatment and specific drug development.

Clinical Diagnosis of COVID-19 [33-38]

Diagnosis of COVID-19 is based on epidemiological history, clinical symptoms and some secondary screening, such as nucleic acid detection, CT scan, immune identification technology (Qualitative rapid testing of IgG and IgM,), blood culture. Although the sign and symptoms of SARS-CoV-2 infected patients are atypical and similar to viral pneumonia. Therefore proper clinical examination and suitable screening are the demand of time.

Nucleic acid detection technology

Nucleic acid amplification tests (NAAT) for COVID-19 virus usual confirmation of cases of COVID-19 is based on detection of unique sequences of virus RNA by NAAT such as real-time reverse- transcription polymerase chain reaction (rRT-PCR) with confirmation by nucleic acid sequencing when necessary. The viral genes targeted so far include the N, E, S and RdRP genes. RNA extraction should be done in a bio-safety cabinet in a BSL-2 or equivalent facility.

There are two nucleic acid detection techniques for SARS-CoV is real time quantitative polymerase chain reaction (RT-qPCR) and High throughput screening. The reliable method for SARS-CoV-2 blood culture and High throughput sequencing of whole genome but the application of High throughput sequencing techniques in clinical diagnosis is restricted due to equipment dependency and high cost. Rt-qPCR is the most common and effective method for the detection of virus in auropharangial and nasopharengial saliva swab and blood.

Chu et al. explained two 1 step RT-qPCR assays (TaqMan based fluorescence signal) to detect two different regions (ORF1b and N) of viral genome separately. The reliability of non invasive saliva swab testing is 91.7 %. RT-

qPCR has sensitivity around 50 -79% for SARS-CoV-2 and specificity for SARS-CoV and MERS-CoV infection too. Hence it is necessary to upgrade the detection rate of RT-qPCR for SARS-CoV-2 infection. Some other limitation of RT-qPCR including Bio-safety hazards brought by maintenance and operation of patient's samples, and long time consuming for results.

Fig. 5: Truenat

CT scan and other biochemical diagnostic methods [39-43]

At present RT-qPCR is specific for COVID-19 diagnosis but its false negative rate can't be neglected. So many researchers proposed CT scans should be other auxiliary detection methods due to its sensitivity and resolutions. Chest CT is essential for early diagnosis and check the disease severity. The characteristic CT images show bilateral pulmonary parenchymal ground glass and consolidative pulmonary opacities, sometimes with a round morphology and peripheral lung distribution. Means CT scans have the value in high prevalence area of SARS-CoV-2. Although given not clear differentiation with other viral pneumonia. As the drawback of present NAAT and CT scan techniques for the diagnosis of COVID-19, some clinical or biochemical methods should apply qualitative immunological detection kits that target viral antigen or antibodies as rapid manner. IgG/IgM based and ELISA kits for SARS-CoV-2 have been developed and tested by some diagnostic companies and shown rapid testing but the sensitivity and reliability is insignificant. Hence the development of sensitive and specific methods is demanding and urgent need for the diagnosis of COVID-19.

Present treatment strategies of COVID-19 [44-45]

At present there is no clinically proven preventive and or therapeutics available for SARS-CoV-2 infection. There are so many supportive and symptoms control treatment like oxygen therapy, fluid management, use of broad spectrum antibiotics to cover secondary infection, remains in the practice. As per the genomic organization and molecular mechanism of corona virus, several potential targets to repurpose the existing antiviral agents.

Virally targeted drug molecule [46]

Molecules in this category generally follow any one of below three mechanisms i.e. viral-viral replication inhibition, ion channel inhibition and serine protease inhibition. Marketed antiviral drugs mainly target 4 major groups of viruses: HIV, Herpes, Hepatitis and Influenza.

Table.3: Commercially available drug for therapy of COVID-19

Drug	Illness treated
α-Interferon	Respiratory Infection, SARS
Ritonavir and Lopinavir	SARS and MERS
Adenosine analogue (that can target the RNA- dependent RNA polymerase and block viral RNA synthesis) Remdesivir	SARS and MERS
Ribavirin	RSV and RSV pneumonia
Reverse transcriptase inhibitors: Zidovudine, Didanosine, Zalcitabine, Stavudine, Lamivudine, Abacavir and Emtricitabine.	SARS
Nucleotide reverse transcriptase inhibitor: Tenofovir Disoproxil Fumarate.	SARS
Non-nucleoside reverse transcriptase inhibitors (NNRTIs): Nevirapine, Delavirdine and Efavirenz.	SARS
Protease Inhibitors (PIs): Saquinavir, Ritonavir, Indinavir, Nelfinavir, Amprenavir, Lopinavir, Atazanavir and	SARS

Fosamprenavir.	
Fusion inhibitor: Enfuvirtide. Lamivudine and Adefovir Dipivoxil.	SARS
Umifenovir	ARVI, influenza, rhinovirus, adenovirus, parainfluenza, respiratory syncytial virus, coronavirus, including the causative agent of atypical pneumonia Used in the phase III trials of 2019-nCoV virus, SARS, MERS
3-Chymotrypsin-like protease: cinanserin and flavonoids	SARS, MERS
PLP inhibitors, such as diarylheptanoids	SARS, MERS
Papain-like protease	SARS, MERS and Human Coronavirus NL63
RNA-dependent RNA polymerase	SARS, Murine Coronavirus
Capsid spike glycoprotein (hCoV	EMC) SARS, Human Coronavirus
Guanosine	analog RNA synthesis inhibitors Coronavirus
Nitazoxanide	SARS MERS and Influenza
Alcohol Vaporization or Nebulization Inhalation Therapy	COVID-19
Chloroquine	SARS, Human Coronavirus OC43.
Baricitinib	COVID-19
Ruxolitinib	COVID-19
Saquinavir	SARS and Feline Coronavirus
Indinavir	SARS and COVID-19
Carfilzomib	COVID-19
Oseltamivir	COVID-19
Azvudine	COVID-19
Baloxavir marboxil	COVID-19
Thymosin α1	MERS
Methylprednisolone	SARS, MERS
Tocilizumab	COVID-19
Interferon Subtypes of β-1b, α-n1, α-n3, and human leukocyte interferon α	SARS
Acyclovir	SARS, MERS, Coronavirus 229E and COVID-19
Cathespin L	SARS
ACE-II Inhibitors	

Antibody and plasma therapy [47-48]

There are some restorative patients donating own plasma against SARS-CoV-2, similar to SARS-CoV and MERS-CoV trials. Their results are also favorable. The virus enters the host cell by binding the S protein to ACE-2 receptor. Besides, the formation of recombinant human monoclonal antibody (mAb) is a fairly direct route to neutralize SARS-CoV-2. CR3022 is a SARS corona virus specific human mAb, which can bind with the receptor binding domain (RBD) of SARS-CoV-2.

Vaccine [49]

Universal SARS-CoV-2 vaccine is necessary to reduce viral transmission and control the disease severity situation. So many vaccination strategies are in process like live attenuated virus, viral vector, inactivated virus, subunit vaccine, r-DNA, and epitope based protein vaccine. At present so many targets for SARS-CoV-2 but their clinical proof still should be explored.

AYUSH Medicinal System [49-50]

Indian medicinal system is ancient plus traditional system and plays an important role to maintain the immunity. Traditional Indian medicinal practices include Ayurveda, Siddha, Unani and Yoga, Naturopathy and Homeopathy.

Indian herbs have been used for the management (prevention as well as treatment) of various types of diseases. The benefits of these herbs in viral respiratory diseases are to build immune stimulation and inflammation modulating effects of the management of immune system.

Table.4: Preventive and prophylactic approaches of AYUSH recommended for COVID-19.

Indian medicinal Plant	Form of Extract	Trade Name	Indian Traditional Medicine Practice	Preparation	Recommended Uses	Effective Against
Preventive and Prophylactic						
Tinospora cordifolia	Aqueous	Samshamani Vati	Ayurveda	Samshamani Vati 500 g with warm water	Twice a day for 15 days	Chronic fever
Andrographis paniculata	Aqueous	Nilavembu kudineer	Siddha	Nilavembu kudineer 60 ml decoction	Twice a day for 14 days	Fever and cold
Cydonia oblonga	Aqueous	Behidana Unnab	Unani	Behida a – 3 g Unnab – 5 Nos Sapistan – 9 Nos Boil these 3 in 250 ml water, boil it until it remains half and filter it	Twice a day for 14 days	Antioxidant, immune-modulatory, anti-allergic, smooth muscle relaxant, anti-influenza activity
Zizyphus jujube	Aqueous	Sapistan				
Cordia myxa						
Arsenicum album 30	Tablet	Arsenicum album 30	Homeopathy	--	Daily once in empty stomach for 3 days (Should be	Effective against SARS-CoV-2, immune-modulator.

					repeated after 1 month till the infection persists).	
Symptomatic Management for COVID-19						
Ayush-64	Tablet	-	Ayurveda	-	2 Tablets twice a day	Respiratory infections
Agastya Haritiki	Powder	Agastya Rasayana	Ayurveda	5 gm in warm water	twice a day	Upper respiratory infections
Anuthaila	Oil	Sesame oil	Ayurveda	-	2 drops in each nostrils daily	Respiratory infections
Adathodai Manapagu	Aqueous	Adathodai Manapagu	Siddha	-	10 ml twice a day	Fever
Bryonia alba	Tablet	Bryonia	Homeopathy	-	-	Reduce lung inflammation
Rhus toxico dendron	Tablet	Rhus tox	Homeopathy	-	-	Viral infections
Atropa belladonna	Tablet	Belladonna	Homeopathy	-	-	Asthma and chronic lung diseases
Bignonia sempervirens	Tablet	Gelsemium	Homeopathy	-	-	Asthma
Eupatorium perfoliatum	Tablet	Eupatorium perfoliatum	Homeopathy	-	-	Respiratory symptoms
Add on interventions to the conventional care						
Vishasura Kudineer	Tablet	Polyherbal formulation	Siddha	Decoction 60 ml	twice a day	Fever
Kaba sura Kudineer	Tablet	Polyherbal formulation	Siddha	Decoction 60 ml	twice a day	Fever, cough, sore throat, shortness of breath

The Solidarity Trial will compare four treatment options against standard of care, to assess their relative effectiveness against COVID-19. By enrolling patients in multiple countries, the Solidarity Trial aims to rapidly discover

whether any of the drugs slow disease progression or improve survival. Other drugs can be added based on emerging evidence.

Involvement in solidarity

The Solidarity Trial offers simplified procedures to facilitate even overloaded hospitals to participate, with no paperwork required. As of April 21 2020, over 100 countries are working together to find triumphant therapeutics as soon as possible, via the trial.

The greater the number of participating countries, the faster consequences will be generated. WHO is facilitating access to thousands of treatment courses for the trial through donations from a number of manufacturers? WHO is also inviting developers and companies to collaborate on ensuring affordability and accessibility of the treatment options if they prove effective?

How solidarity trials work?

Adults with COVID-19 admitted to applicant hospitals can unite this study. Appropriate patients will be asked to sign to demonstrate they comprehend the possible risks and benefits and consent to joining the study. The medical team responsible for each patient will verify whether any of the study treatments would definitely be unsuitable. After those checks, concise identifying details and any other conditions are digitally recorded for the patient, who is then randomly allocated to one of the study options. This may or may not involve one of the learning treatments. Neither the patient nor the medical staff chooses which of the study options a patient will receive, as a computer makes this allocation at random. Critical anonymized information for the trial will only be collected at the randomization stage and when the patient is discharged or dies: which study drugs were given (how many days); whether ventilation or intensive care was received (and, if so, when it began), date of discharge, or date and cause of death while still in hospital. Interim trial analyses are monitored by a Global Data and Safety Monitoring Committee, which is an independent cluster of experts. Countries, or particular groups of hospitals, may want to work together in making additional serial measurements or observations, relating to areas such as virology, blood gases or chemistry and lung imaging. It also possible to incorporated documentation of other aspects of disease status, for example, through linking in electronic healthcare records and routine medical databases. While well-organized supplementary research studies of the natural history of the disease or of the effects of the trial treatments could well be precious, they are not center requirements. Adults (age ≥18 years) recently hospitalized, or already in hospital, with confirmed COVID-19 and, in the view of the responsible doctor, no contra-indication to any of the study treatments will be randomly allocated between. Local standard of care, OR local standard of care plus one of we plan according to physiological condition and start the therapy to manage the clinical situation.

Table.5: Clinical and Physiological effect of Corona virus patients

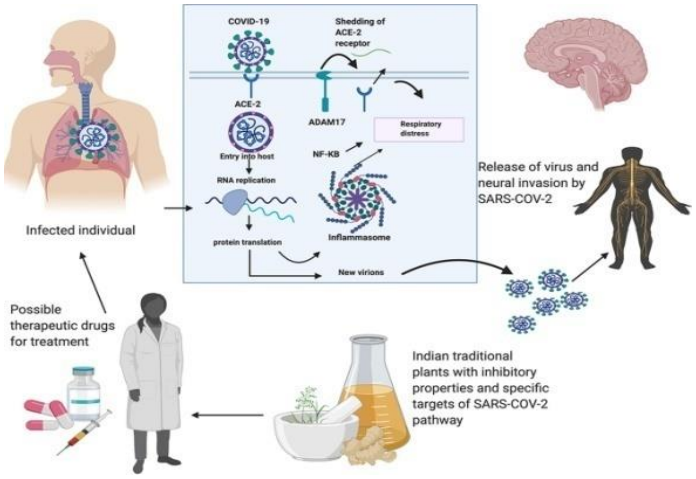
S. No.	Acute Organ Injuries	Pathological/Biochemical test
1	Renal	Renal function test
2	Lung	X-ray chest and CT scan/ HRCT ABG(Arterial Blood Gases) PAO2
3	Cardiac	ECG, Cardiac Echo, Troponin, Ionic calcium
4	Liver	Serum Bilirubin , HGOT & HGPT
5	Haemolysis(RBC breakdown)	CBC, serum ferritin, LDH, Glycosylated Hb
6	Metabolic acidosis	ABG
7	Metabolic hyperpyrexia	Blood, urine, stool and sputum

Various comorbidities recorded are: diabetes, heart disease, chronic lung disease, chronic liver disease and asthma, extending to HIV and tuberculosis in the African region. Brutality of illness at entry is determined by recording: shortness of breath, being given oxygen, already on a ventilator, and, if lungs imaged, major bilateral abnormality.

CONCLUSION

Finally the incidence and spread of SARS-CoV-2 depends on the interaction/interfacing between the virus and individual's immune system. Viral factor comprise types of virus, mutation, viral load, viral titer and *in-vitro* viability or virulence. The person to person or races to races immune system factors includes individual genetics, age, gender, nutritional status, neuroendocrine regulation and physical to physiological status. These entire factors contribute whether a person is infected with virus, duration and the severity of the disease, and recurrent infection chances. So analysis and understanding the role of non-structure and its proteins encrypted in this the virus will aid us the mechanism of action. Our review summarized the importance of medicinal plant based medicine may target to reduce the disease burden. In this stage of pendamic, accurate diagnosis helps to control the disease transmission. It is essential to develop novel, safe,

specific, rapid responding, and simple new technology for the detection of SARS-CoV-2. All health concern and available system of medicine will deliberately get involved in the two factors to make them develop into a direction benefits to human health, which can help patients recover as soon as possible. Because ***prevention is always better than cure.*** We all authors appeal and advocacy to scientific fraternity and available pathy's specialist dropdown your own ego and complexes and try to make a common platform where needy patients get well soon through solidarity means.



Combined apporaches to combat COVID-19

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