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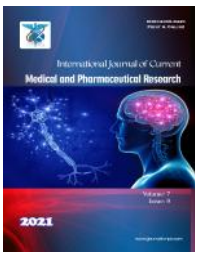


Review Article

# A COMPREHENSIVE REVIEW ON COVID-19 WITH THEIR TREATMENT APPROACHES

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**ABSTRACT**

Currently, the world is having the biggest health crisis which threatening the public with the spread of COVID-19 is unstoppable. The first case of the SARS-CoV2 came to China and after that; it has been spread all over the world. The World Health Organization (WHO) has recognized that the recent outbreak as a global public health emergency. Currently, the study on novel coronavirus is still in the primary stage. Based on the existing data, we going to summarize the clinical characteristics, pathogenesis, diagnosis, treatment, and prevention of information regarding COVID-19. In this review, we aim at investigating the most recent trend of COVID-19 for helping the community effectively recognize and deal with the 2019 novel coronavirus (SARS-CoV-2), and providing a reference for forthcoming studies.



## INTRODUCTION

In December 2019, a person suffering from anonymous pneumonia was traced to China, specifically in Wuhan, Hubei province. Till 31st Dec., 27 cases of this unidentified pneumonia were detected in Wuhan[1].Scientist after the analytical studies of the sample taken from the throat of the patients finds out that it is caused due to novel coronavirus[2].Later WHO truncated this virus to 2019 n-CoV on 7th January 2020[3].The International Committee of Taxonomy of virus termed this virus as "severe acute respiratory syndrome coronavirus 2(SARS-CoV2)"[4].According to the WHO reports since the arrival of the SARS-CoV2 virus, across the world38 394 169peoples are infected with this virus &1,089 047 peoples have lost their life[5]. This outbreak was one of the biggest outbreaks after the H1N1 (2009), polio (2014), Ebola (2014), zika (2016)[6].

Coronavirus is of 4 type's i.e. alpha coronavirus, Beta coronavirus, Gamma coronavirus & Delta coronavirus[7]. COVID-19 is caused by the Beta coronavirus. The outbreak of SARS-CoV2 has an unclear relationship with the Huanan Seafood Wholesale market as many cases have a link with the market and it is not clear that this virus is transmitted from the animals of the seafood market to human beings or not[8-9]. These viruses can be isolated from various wild animals & domestic animals[10]. Predictions were made that Bats might be the host of this epidemic[11].


**Figure 1** Outspread History of n-CoV

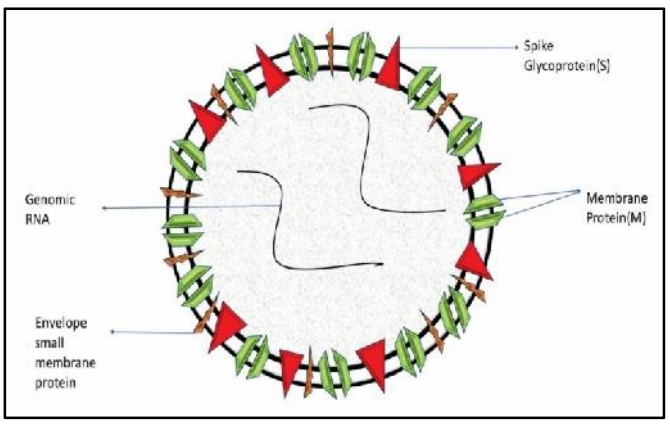


**Figure 2** Structure of Coronavirus

***Origin & Classification***

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In the 1930s in the U.S, coronavirus was first discovered in chicken infected by IBV[12]. Later on, two more animal virus strands are found that are Mouse hepatitis virus and the transmissible gastroenteritis virus. In the 1960s First human coronavirus was founded[13-14].It was later known as the novel cold virus &[15-16]. Coronavirus has the potential to mutate expeditiously, change tissue tropism, cross-species barrier & adjust to the different epidemiological environments[17]. Since the 1960s, 6 types of Human coronavirus were reported that are OC43, NL63, HKU1, 229E, SARS-CoV, and MERS-CoV[18].Coronavirus is the huge family of single-stranded RNA viruses that affect mammals and animals& it can be founded in wild animals and mammals[19]. Coronavirus ranges in diameter (65-125nm) and their viral genome lies in the range of 26-32kilobase in length[20-21].Coronavirus adds up to kingdom *Orthocoronavirinae*; family *Coronaviridae*; order *Nidovirales*[22-23]. Coronaviridae comprises of two subfamilies that are coronavirinae and torovirinae. Coronavirinae has further divided into four genera that are (α)-coronavirus, (β)-coronavirus, (γ)-coronavirus, and the(δ)-coronavirus [24].

αcoronavirus contains (HCoV-NL63) & (HCoV-229E), βcoronavirus covers the HCoV-HKU1,SARS-CoV), (HCoV-OC43) & (MERS-CoV). (γ)-Coronavirus isolated from birds and whales and the δ coronavirus includes pigs and avian species [25]. Out of these 6 human coronaviruses, 4 of them initiate less or mild illness to the humans such as cold, fever,etc[26]. SARS-CoV and MERS-CoV have the potency to cause lethal respiratory disease to every age group[27].

MERS-CoV and SARs-CoV both are transmitted from the bats to dromedary camels and palm civets respectively[28]. SARS epidemic first started in Guangdong, China in 2002 &bats were the host &the death rate was 11%[29-31]. In South Arabia 2012,the MERS epidemic happens, bats were the host &the death rate is more than 30%[32].In 2019 in Wuhan, an untraceable pneumonia case of the patient was diagnosed. The origin of this transmission of diseases was still unknown but according to reports, it might be possible it is through the Huanan seafood market where live animals are sold such as frogs, bats, snakes, etc very frequently[33].The virus has a 96.2 % identical genome sequence as that of BatCoV RaTG13, that was previously discovered in Rhinolophus affinis from the Yunnan province in China[34].

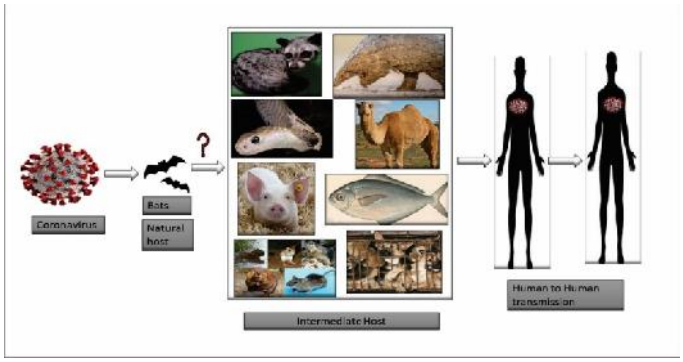


**Figure 3** Possible origin of SARS-CoV2

It was thought that COVID -19 was only transmitted from animals to humans as most of the earlier detected cases is from the Wuhan market, but after some time further case studies reveal that number of cases are increasing and they even don't have any linkage with the seafood market[35]. With all these analyses and researches Bats might the natural host of this virus [36]. A protein sequence alignment shows that snakes, pangolins & turtles can be the intermediate host of this virus [37].

### *Clinical Features of COVID 19*

COVID 19 is caused by SARS-CoV2. The mean incubation period of SARS-CoV2 is 5-7 days[38]. Initially, many patients have symptoms and many are asymptomatic [39]. Initially, Pneumonia was the major clinical sign for the detection of the disease. The most usual symptoms of COVID 19 are fever, cough, fatigue, diarrhoea, vomiting, muscle pain, abdominal pain, loss of smell and appetite, sore throat, Chest pain, Headache, Rhinorrhoea, myalgia, shortness of breath, Conjunctivitis, nasal congestion[40]. More than 70% of the patients have mild or very fewer symptoms. The symptomatic patients tend to show severe symptoms such as dyspnoea, low oxygen saturation level which could lead to respiratory failure or even organ failure which could lead to the death of the patient[41-42]. Critical patients have some critical clinical manifestations like multi-organ failure including septic shock, renal damage, liver damage, testicular tissue damages and hypoxemia. Persons with pre – comorbidities are at higher risk for COVID 19. According to published reports, the comorbidities include hypertension, diabetes, cardiovascular disease, cancer, and kidneyfailure &asthma etc[43]. One of the major clinical features is Cytokine storms. This infection comes with the aggressive inflammatory response which releases a large amount of pro-inflammatory cytokines that leads to cytokine storm which might result in multi-organ failure or unfavourable prognosis of severe COVID-19.[44]

### *Epidemiology*

The highly infectious, contagious, or rapidly transmissible disease COVID 19 or SARS-CoV 2 first reported in China. Further, the increase in no. of cases that have a linkage with the wildlife animal food market in Wuhan supported this contention, but the first laboratory-confirmed case of the unknown Pneumonia was on 1st December 2019 did not have any exposure to the seafood market of Wuhan. On 31st December, the local authorities of china emerge an "epidemiological alert" and by taking quick action on 1st January 2020, the Wuhan seafood market was closed. Subsequently, more than 200 other countries have been largely affected by the virus as it was spreading at a very fast rate. Countries which are affected till now are the USA, Brazil, Russia, Spain, UK, India, Italy, Peru, Germany, Iran, Turkey, France, etc. The first country to get the infection from the virus after china was Thailand. According to data published by WHO the most affected region is the Americas and the least affected region is Africa[45-47]. Below there is the comparison between the epidemiological features of SARS, MERS, SARS-CoV 2[48].

**Table 1** Epidemiology Comparison between *SARS-CoV, MERS-CoV* and *SARS-CoV2*

| ***Factor*** | ***SARS – CoV*** | ***MERS – CoV*** | ***SARS – CoV2*** |
|---|---|---|---|
| A host of the Virus | Horseshoe bats are natural host, masked palm civets are Inter.host humans are the terminal hosts. | Bats are the natural host; camels are the intermediate hosts & human beings are the terminal hosts. | Bats are the natural host, pangolins and snakes are the intermediate hosts while humans are terminal hosts |
| Reproduction No. | 2-5 | >1 | 2.68 |
| Incubation Period | 4.6 Days | 5.2 Days | 6.4 Days (0-24 Days) |
| Virus Origin | Guangdong, China | South Arabia | Wuhan City, China |

***Transmission***

SARS-CoV 2 transmission depends on the following 3 factors:-Origin of Infection, route of transmission, and vulnerability

***Origin of Infection***

Initially, a large number of cases of COVID 19 have exposure to the Huanan Seafood market in Wuhan, China where live animals are sold regularly suggested that there is a zoonotic origin of COVID 19.Although a genomic study provided proof that this pathogenic virus is introduced from another yet untraceable location into the wet animal market[49].Several studies suggested that human to human transmission was occurring as cases are exponentially increasing even the patients are not exposed to the Wuhan market but some of them come in contact with the patients of COVID 19& after the human chain was formed. At present, there is no conclusive evidence of a natural host but it can be said that wild animals are the main source of animals and the discussion will still go on regarding the patients getting the infection in the incubation period[50].

***Route of transmission***

China's health authorities have issued the latest guidelines which describe the 3 main routes of transmission for COVID 19.The 3 transmission routes are:-Droplets Transmission, Contact Transmission, (Fomities Transmission) and Aerosol Transmission

- Droplets transmission can be spread when an infected person sneezes or coughs tiny droplets are released from the nose and mouth of the COVID patient and they are inhaled by other individuals in close presence.An estimated study said that a single cough releases upto 3,000 droplets that can infect many peoples[51].
- Contact Transmission or fomites transmission, like the virus, can persevere on the inanimated objects for more than 96 hrs[52].Although the confirmed persistence time of SARS CoV-2 on any surface remained uncertain[53]. Contact transmission occurs when a subject touches any inanimated object which is contaminated by the virus and eventually touches their nose, mouth, eyes, or face,that person can also get infected by the virus.But studies show that this virus can get inactivating by cleaning the subject by using chemicals like sodium hypochlorite,60-70% alcohol, hydrogen peroxide, and benzal alkonium chloride.
- Aerosol transmission may occur when respiratory droplets incorporate into the air, forming aerosols & this is inhaled heavily increases the risk of infection[54]
- Add to this scientist have discovered SARS-CoV2 traced in the samples of stool, saliva, gastrointestinal tract, urine, tears, conjunctival secretions of the COVID patients. Intrauterine transmission from mother to infant during pregnancy is still uncertain. Based on the bioinformatics studies it was indicated that the digestive tract may be the transmission route of this infection and this coronavirus RNA has been constantly detected in the gastrointestinal tissues of COVID patients since ACE 2 receptors are highly stated in the absorptive enterocytes from ileum and colon. Regarding the asymptomatic peoples spreading the virus remains the question and this is a serious threat to humans.[55-56]

***Vulnerability Population and viral latency***

An investigation has been carried on and it was reported that the elderly peoples, children less than age 10 and person with comorbidities are highly prone to the disease[57]. Comparing the median latency period of SARS, MERS, and SARS-CoV 2,SARS-CoV has the median latency period of 4 days and the standard time for the onset of signs and symptoms was to admission in hospital is 3.8 days[58]. For MERS the median latency period was 7 days[59].

***Genomic Characterisation***

Coronavirus is the huge family of RNA viruses that can be found in various animal species. Coronaviruses possess the largest of around 26.4-31.7 kilobase among all the RNA viruses. Coronavirus belongs to the Family *Coronaviridae* and contains 4 genera that are has been recognized. A characterization study in genes has helped to identify that bats and rodents are the gene provenance of alpha and beta coronavirus, whereas avian species are said to be the gene source of delta and gamma coronaviruses[60-62]. A coronavirus contains at least of 6 ORF's excluding the gamma-Coronavirus which lacks the nsp1.N-CoV is a spherical and pleomorphic enveloped particles containing the single-stranded positive-sense RNA linked with a nucleoprotein with a capsid comprised of matrix protein and with 5′-cap structure and 3′poly-A tail. This envelope support club-shaped glycoprotein projections and some of them contain a hem agglutinin-esterase protein[63]. The novel coronavirus was first isolated in the bronchoalveolar lavage fluid (BALF) of the initial three COVID patients of the Jinyintan hospital of Wuhan on 30$^{th}$ December 2019[64]. According to the GISAID, accessionno(EPI_ISL_402131) the Isolated SARS-CoV-2 is 96.2 % similar at the whole genome level to a bat coronavirus isolate RaTG13 collected from the Yunnan (China) whereas it is 88% similar to the two bats derived SARS-like CoVs, bat-SL-CoVZC45 and bat-SL-CoVZXC21 taken from the Zhoushan, eastern China in 2018[65].

Various studies have identified that SARS-CoV2 has a distinctive RAR moiety in the spike proteins[66]. The four structural genes that are the envelope, spike, membrane, and nucleocapsid are encoded by the ORFs 10,11[67]. The 5'- end comprises more than two-thirds of the genome consisting of ORF1ab encodes for ORF1abpolyproteins and on other hand, the 3' tail contains the gene encoding structural proteins. ORF1ab is the largest gene in the novel coronavirus and it translates the two polyproteins that are pp1a & pp1b. They also encode for the 16 nsp and the left-over open reading frames encodes for the remaining structural proteins. These 16 nsp formed the viral replicase transcriptase complex and they rearrange the membrane arising from the rough endoplasmic reticulum into the double-membrane vesicles where the replication and transcription occur[68-69]. Fresh studies have suggested that there is slightly but a notable change in SARS-CoV and SARS-CoV 2 as 8a protein is absent in SARS-CoV 2 and there is an alteration in the amino acids present in 8b and 3c proteins of SARS-CoV2. Additional to this fresh data it was also identified that the SARS-CoV 2 contains the 6 additional proteins encoded by the ORF3a, ORF6, ORF7a, ORF7b, and ORF8 genes [70]. A predicted Study considers that S, ORF3a, E, N, M genes of novel coronavirus are3822, 828, 228, 669, and 1260 nt in length, respectively. Till now, on GISAID, around 149,000 genomic variations are present of the SARS-CoV2 [71]. A mutation in the spike protein of N501T in SARS-CoV2 may

increase or enhance the binding activity for ACE2[72]. The spike protein of the CoVs, consisting of 2 subunits that are N-terminal S1[binds to host cell]subunit and C-terminal S2 subunit[membrane fusion] .

***Treatment of COVID 19***

At present, there is no vaccine or any specific anti-viral drug for the treatment or control of COVID 19. The need fora vaccine or an approved medication is very urgent as the no. of cases of COVID 19 is increasing exponentially.If the patient is diagnosed with a virus basic step is to isolate them and start their treatment acc. to their symptoms to avoid the death of the patient. New drugs are coming into the pharmaceutical field one after another but their efficacy in treating the disease and their side effects are being studied in randomized controlled clinical trials [73]. Here we are going to summarize the potential therapeutic options available for the treatment of COVID-19.

***Chemical Medications***

***Chloroquine Phosphate & Hydroxychloroquine***

Hydroxychloroquine and chloroquine phosphate are the drugs that are mainly used as an antimalarial drug and have been using for the treatment of rheumatoid arthritis and lupus erythematosus[74]. The pharmacological mechanism of action of chloroquine and hydroxychloroquine against the SARS-CoV2 virus is still under scanner. Based on the initial studies it was believed that chloroquine may prevent the virus from binding to the ACE2 receptor by blocking the terminal glycosylation. New researches have suggested that the HCQ may additionally stop SARS-CoV-2 from binding with gangliosides, which in turn may block virion contact with the ACE-2 receptor. The organelles endosomes and lysosomes normally require an acidic environment for homeostasis, but both HCQ and chloroquine incorporate the endosomes and lysosomes which results in the alkaline nature of intracellular compartments. Eventually, this increase in pH level results in their dysfunction leads to defective protein degradation, endocytosis, and exocytosis needed for viral infection, replication, & propagation [75-76].

A small clinical trial was done on the patients of more than 10 hospitals of Wuhan which was the epicentre of the epidemic and it was concluded in the trials that anti-viral & anti-inflammatory effects of chloroquine/HCQ may account for its potent efficacy in treating patients with COVID-19 pneumonia [77]. In addition to its benefits it may have serious complications also such as cardiomyopathy, retinopathy and it can cause immune suppression can also inhibit antibody-antigen reaction [78].

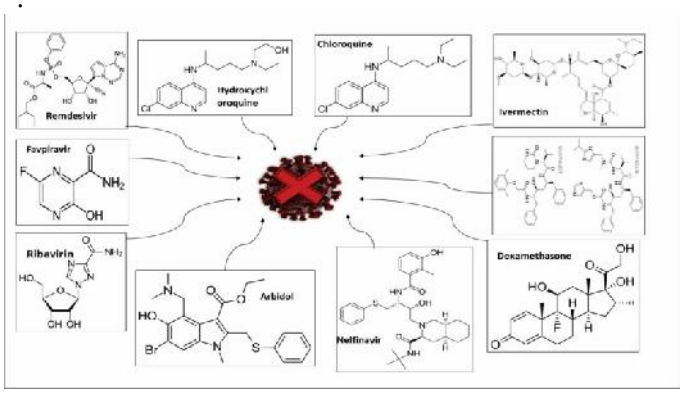


**Figure 4** Medication used in COVID-19

***Ivermectin***

Ivermectin is a broad-spectrum anti-parasitic medication that is approved by the Food and Drug Administration. Ivermectin is used to treat various infectious diseases in mammals [79-80]. Ivermectin was originally recognized as an inhibitor of interactivity between the (HIV-1) integrase protein (IN) and the importin (IMP) α/β1 heterodimer responsible for IN nuclear import [81].SARS-Cov2 is also a single-stranded RNA virus and ivermectin can be a potential option for the treatment of COVID 19. A recent *in-vitro* study was performed where Vero/hSLAM cells were infected with the novel coronavirus and 5 μM ivermectin was exposed to it. In 48 hours, a 5000-fold reduction in viral RNA compared with control was observed. This can conclude that treatment with ivermectin successfully kills almost all the viral particles in 48 hours . While using this anti-parasitic drug ivermectin against COVID19, patients may suffer from adverse effects such as nausea, dizziness,itching,rash,abdominal pain, eosinophilia, fever, tachycardia[82]. For more potent knowledge about the ivermectin use for COVID 19 human trials should be formed in the bigger number of patients to get more precise observation.

***Remdesivir***

Remdesivir was originally used for the treatment of Ebola virus infection, but due to its anti-viral effect and reducing the viral load [83]. Remdesivir is a monophosphoramidate prodrug and it is metabolized into its active form i.e. remdesivir (GS-441524) that conceals the viral polymerase and evades proofreading by viral exonuclease, leads to a decrease in viral RNA production. *In-vitro* studies have shown that this nucleotide analogue drug can inhibit the coronaviruses such as SARS-CoV and MERS-CoV and this suggested that it can be used against the SARS-CoV2 [84]. After this *in-vitro* study,itis proven that remdesivir is effective against the SARS-CoV 2 and a study reported that in a group of patients there is 13% mortality, 68% oxygen improvement and 60% reported adverse events during this follow up [85]. Remdesvir has a good effect on SARS-CoV2 but it has a no. of serious adverse effect like Hepatotoxicity(increased hepatic enzyme), Respiratory toxicity(respiratory failure and Pneumothorax), Cardiovascular toxicity(Hypotension, Atrial fibrillation, Hypernatremia), Nephrotoxicity (hematuria, renal impairments, acute kidney failure), Reproductive toxicity, Gastrointestinal symptoms (nausea, vomiting, constipation) which may cause a problem to COVID patients[86]. As of now, remdesivir is going through the trials for the specific use for COVID 19 and it has been sanctioned for emergency use in the countries like USA [87].

***Lopinavir/Ritonavir***

Lopinavir is anHIV type 1 aspartate protease inhibitor [72]. Ritonavir also is an anti-retroviral drug that is an active peptidomimetic inhibitor against HIV-1 and HIV-2 aspartyl proteases [88]. Currently, an *in-vitro* study has been proven that Lopinavir/Ritonavir can inhibit the replication of SARS & MERS to produce its anti-viral effect. According to these studies'combination of Lopinavir/Ritonavir has been used for the treatment of patients. The common toxicities are gastrointestinal intolerance, nausea, vomiting, diarrhoea and major are Pancreatitis, hepatotoxicity, cardiac conduction abnormalities. A recent study however has proven that lopinavir/ritonavir treatment did not significantly enhance clinical improvement, reduce mortality, or diminish throat

viral RNA detectability in patients with COVID-19[89]. A clinical trial runs in Hong Kong hospitals of the triple combination of lopinavir/Ritonavir with interferon-beta -1b as a potential option for treatment of COVID-19 [90].

***Ribavirin***

The antiviral mechanism of ribavirin is not restricted to interference with polymerases, the structure of ribavirin drug also hinders with RNA capping that relies on natural guanosine to prevent RNA degradation. Additional to this to promote the destabilization of viral RNA, ribavirin blocks the natural guanosine generation by directly inhibiting inosinemonophosphate -dehydrogenase in a pathway that is important for the production of the guanine precursor to guanosine [91].*In-vitro* activity of ribavirin against the SARS-CoV is restricted and it is because it required a high concentration of drugs to inhibit the viral replication. This higher dose can cause haemolytic anaemia in patients [76]. A study conducted where it was recorded that ribavirin has some serious adverse events in COVID patients like anaemia and gastrointestinal disorders including nausea, vomiting, diarrhoea, abdominal pain and discomfort, GI bleeding, and decreased appetite, Increased AST & ALT. These adverse events might reduce its rampant use[93]. However, the safety and therapeutic effectiveness of ribavirin for COVID 19 still need further clinical trials to confirm.

***Favipiravir***

Favipiravir is a guanine analogue wide-spectrum antiviral medication which is a prodrug of a purine nucleotide, favipiravirribofuranosyl-5′-triphosphate. It is developed forthe treatment of avian influenza or novel influenza resistant to neuraminidase inhibitors [95]. Favipiravir can also be effective against the Ebola virus and yellow fever virus. The prodrug favipiravir act by entering the infected cells by endocytosis & then transformed into active favipiravir ribofuranosyl phosphates through phosphoribosylation and phosphorylation. The Favipiravir anti-viral activity of Favipiravir is exhibited trough selectivity targeting the conservative catalytic of RdRp, break in the nucleotide incorporation process during the process of RNA replication and this result in increased number and frequency of transition mutation including the substitution of 4 nitrogenous bases which causes destructive mutagenesis in RNA viruses. A recent *in-vitro* study has shown that favipiravir was effective against SARS-CoV2 infection[96]. In addition to this a study has shown that this medication shows an effect in Vero E6 cells infected with SARS-CoV-2, resulted ina high concentration is needed for safe and effective treatment. In March 2020, the National Medical Products Administration of China approved favipiravir as the first anti-COVID 19 drugsin china. . Favipiravir has various adverse effects such as increased AST & ALT,Blood bilirubin increased, abdominal discomfort,duodenal ulcer, diarrhoea, WBC count decreased,Blood Uric acid increased & glucose urine present[97]. Clinical trials are going across various countries to test the efficacy and safety of favipiravir.

***Umifenovir (Arbidol)***

Arbidol can block the adhesion of viruses to host cells and arrest them from invading human cells and at the same time, it can enhance the synthesis of interferon, which can inhibit influenza virus invasion and treat influenza virus infection. Umifenovir is active against many enveloped and non-enveloped viruses and has interferon inducing effect [98]. In the various study, it is founded that 10–30 μmol of arbidol could effectively inhibit SARS-CoV-2 proliferation by 60 times. In addition to this it has been suggested that Umifenovir targets the S protein/ACE2 interaction and inhibits membrane fusion of the viral envelope. A small study has been conducted arbidol was well tolerated and associated with mild gastrointestinal adverse events in some patients like nausea, diarrhoea, stomach ache, and moderately increased in ALT level[99].

***Darunavir***

Darunavir is an inhibitor of protease dimerization and activity of HIV-1. It can also selectively block the cleavage of HIV encoded gag-pol precursor protein in virus-infected cells, thus stopped the development of mature infectious virus particles. In China, it was reported that darunavir could inhibit the replication of the virus at a concentration of 300 μmol/L . Similar to darunavir another anti-retroviral drug Emtricitabine combined with the denofoviralafenamide shows a good therapeutic effect in the clinical trials for the COVID-19 [100].

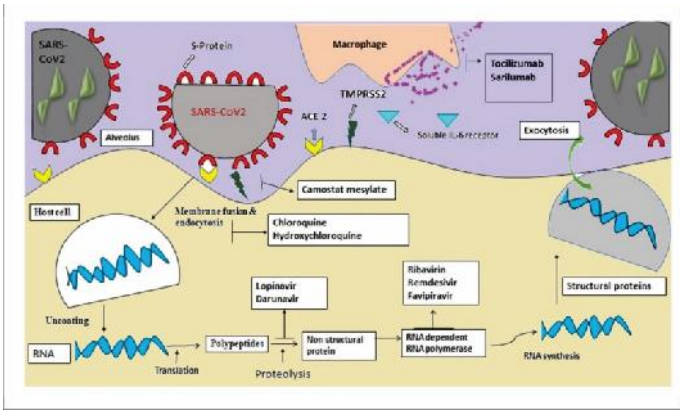


**Figure 5** Possible mechanism for treatment of COVID-19

***Biological Medications***

***Convalescent Plasma Therapy***

Convalescent plasma therapy can be a hopeful treatment option forCOVID-19[101]. Plasma therapy is a passive antibody therapy and it has been used during the various infectious diseases such as H1N1 infection, SARS-CoV, avian influenza A (H5N1). On this basis, Convalescent plasma therapy can be effective against the SARS-CoV2[102]. The therapeutic action of plasma therapy is s through binding of the transfused antibodies to the pathogen, leads to cellular cytotoxicity, phagocytosis, or direct neutralization of the pathogen. While using plasma therapy for COVID 19 treatment there are some obvious limitations such as allergic reactions which may lead to serum sickness & anaphylaxis. The most major drawback of CPT is a risk of reinfection that is passive Abs may suppress/attenuate the humoral immune response of recipient thereby inhibiting the synthesis of specific Abs against SARS-CoV-2.This can increase the risk of reinfection of the particular individual[103]. Hence, the convalescent plasma therapy can be only used at a small scale and for the usage of it's at alarge scale, we have to wait until we understand the adverse reactions and clinical application effect.

***Tocilizumab Injection***

Tocilizumab is a humanized recombinant monoclonal antibody in opposition to the human IL-6 receptor which exactly binds to soluble and membranous IL-6 receptor to inhibit signal transduction, thus inhibiting the activity of the IL-6 receptor.In

2017 Tocilizumab was approved by the U.S for severe life-threatening cytokine release syndrome[104]. IL-6 plays a major role in the development of some auto-immune disorders and inflammatory responses. SIL-6R is an activator of IL-6 which enhances the sensitivity of cells to IL-6. After various studies, it has been found that Tocilizumab injection is an antagonist of cytokine interleukin-6, and it can inhibit cytokine storm and thus prevent COVID -19 patients from turning to severe and critical diseases.

A small retrospective study was conducted to understand the efficacy of TCZ regarding the treatment of COVID 19 patients.20 patients were given the 400mg of tocilizumab through the I.V. route, along with the other anti-viral drugs. The result was quite promising that within a few days the fever was going back to normal and other symptoms are also improving remarkably. The oxygenation was improved to 75%. In addition to this percentage of peripheral lymphocytes came back to normal in 52.6% ofpatients. These data show that tocilizumab can be an effective option for the treatment of novel coronavirus pneumonia. It may have some common side effects like nausea,dizziness & bacterial/fungal infection & another study recorded effects like bacteraemia, fever, cough, and shortness of breath[105].

***Sarilumab***

It is an IL-6 receptor antagonist used for the treatment of patients of severe or moderate active rheumatoid arthritis who have an inadequate response to anti-rheumatic drugs [106].Because it is an IL-6 antagonist it has an action against the cytokine storm; hence it was suggested that it can be used against the COVID 19 patients. Currently according to the data available on https://clinicaltrials.gov/ the clinical trials for this medication is in Phase 3.

***Anakinra***

Anakinra is an improvised human IL-1 receptor antagonist that inhibits the activity of interleukin-1 (IL-1) . This medication has gained the access to test the efficacy and safety of patients or at the same time blocking IL-6 and IL-1 versus standard of care on blood oxygenation & systemic cytokine release syndrome in patients with COVID -19 infection and acute hypoxic respiratory failure and systemic cytokine release syndrome.

***JAK Inhibitors***

N-CoV could enter the cell through endocytosis and AP2-associated protein kinase is a well-known regulator of endocytosis. Inhibition of AP2-associated protein kinase can disturb the passage of the virus & this will prevent the virus infection to the host. Drugs like Ruxolitinib and Baricitinib are the JAK inhibitors as well as AAK1 inhibitors; therefore these drugs can be suggested for the treatment of COVID-19 patients. The biggest concern regarding the usage of JAK inhibitors is that it can block the variety of inflammatory cytokines including INF-α which has a major role in restraining the virus activity, hence detailed clinical trials and studies are needed to confirm its activity. Ruxolitinib has been approved for usage in COVID 19 patients with respiratory failure who do not need invasive assisted ventilation & on the other hand, AIFA has licensed the randomized phase 2 trials to check the safety, efficacy, tolerability of Baricitinib regarding the COVID 19 patients.In addition to its beneficial effects it has serious adverse events such as the occurrence of neutropenia, viral reactivation, lymphocytopenia & these events may lead to the incidence of co-infections[107]

***Glucocorticoids***

Glucocorticoids have anti-inflammatory and immunosuppressive action so it might therapeutic option for COVID-1. A study was conducted in Spain to determine the role of steroids in the treatment of COVID 19. In this study period out of 848 patients, 463 patients fulfilled the inclusion criteria. Among them, 396 patients were given the steroid's and 67 patients were not. The outcome was progressive as the mortality rate was lower in the patients treated with steroids than in control this concluded the study that chances of the survival of the COVID patients is higher in patients treated with glucocorticoids [108]. Currently, various studies have proven that glucocorticoid administration should only be used for critical complications to suppress CS manifestations in patients with COVID-19, such as ARDS, acute heart injuries, patients with higher D-dimer levels, and acute kidney complication. WHOdoesn't recommend glucocorticoids for the routine treatment of COVID-19? Drugs like methylprednisolone likely to prevent an extended cytokine response and may initiate resolution of pulmonary and systemic inflammation in pneumonia and Dexamethasone has potential utility on ARDS by decreasing mortality and ventilator days of critical ARDS in patients without COVID-19. Adverse events of this are Gastrointestinal bleeding, lower Super-infections, Hyperglycaemia, Hypernatremia,low risk of neuromuscular weakness[109].

**Figure 4** Possible Mechanism of action of drugs on SARS-CoV2

***Ayurvedic Medication***

Across the world, no. of conventional or newly proposed drugs have been going through the clinical trials, but their clinical efficacy and toxicity remain inevitable issue leads to severe adverse effects. Because of this, this encourages us to study the treatment of COVID-19 with traditional herbal plants [110]. In Ayurveda Charaka Samhita & Ashtanga Hrdayam which deals with the pathophysiology, diagnosis, classification, management, medicines, diet, and prognosis [111]. According to literature in Ayurveda,COVID-19 is categorized as agantukajvara with aVataKaphapradhanasannipata presentation [112].On this basis, an in-silico study was conducted to assess the Indian herbal plants in the pursuit of potential COVID-19 inhibitor. Multiple Indian herbal plants such as giloy, harsingar,aloevera,neem, turmeric, ashwagandha, ginger, black pepper,red onion, tulsi,cannabis.Were taken in the In-Silico study. The study is conducted on parameters like lipophilicity, aqueous solubility, and binding affinity of the extracted compounds. On the basis of binding affinity, the inhibition potential of these plantsit can be ranked as harsingar > aloe vera > giloy > turmeric > neem > ashwagandha > red onion > tulsi > cannabis > black pepper. PatanjaliAyurvedic institute has purposed that Giloy, Ashwagandha, and Tulsi have natural phytochemicals that have the potential to battle against COVID-19. They have suggested the following points: -

- Ashwagandha has Withanone has a definite effect on viral receptor-binding domain and ACE2 receptor complex.
- In Giloy (Tinospora cardifolia) one of the phytochemical compounds Tinocordiside has found

that it also binds in the ACE2-RBD complex with considerable affinity.

- Scutellarein, a natural flavone founded in tulsi establishes to dock well into the enzyme cavity of the RDRP enzyme of coronavirus. Blocking to RDRP can be an attractive option for controlling COVID-19.

Though all these things are used as an immunity booster[113]. In addition to this CSIR has started the clinical trials of Ayurvedic remedies like Yashtimadhu, Ashwagandha, Guduchi Pippali and a well know ayurvedic anti-malarial formulation "AYUSH-64". Various researchers have proven that Yashtimadhu contains glycyrrhizic acid due to which it gives anti-viral, anti-inflammatory, anti-oxidant & immune-modulating properties and Guduchi or giloy hasanti-viral, adaptogenic and immunomodulating properties. AYUSH-64 is a well-known ayurvedic anti-malarial drug contains Saptaparna, katuki or Picrorhiza kurroa which is effective against upper respiratory tract infection. Clinical trials are underway to conclude the efficacy of (lack there) of these medicines [114].

**Figure 5- Drugs used on SARS-CoV2**

***BCG Vaccination***

BCG vaccination obtains from the Mycobacterium Bovis & used against tuberculosis[116].In a randomized control trial that BCG vaccine can decrease the seriousness of the infection of several viruses. This led to the possibility that the BCG vaccine might protect health care workers and other vulnerable individuals againstCOVID19. A randomized control trial has proven that BCG vaccine's immunomodulatory properties can save against respiratory infections. Currently, there isa total of three clinical trials are going on to determine either BCG vaccine prevents SARS-CoV-2 infection in healthcare workers involved in the care of COVID-19 patients or not . At present WHO does not recommend BCG vaccination for the prevention of COVID-19 [117].

***Radiation Therapy***

It is a therapy mainly for tumours and cancers. In published reports, it was discussed the use of lungs low dose radiation therapy (LDRT) as a therapeutic approach for COVID 19 pneumonia. There are some reports which observed the high efficacy of the LDRT method in treating pneumonia by X-rays. LDRT's main mechanism is the induction of anti-inflammatory response but this will be led to the suppression of immune response against infectious agents, therefore it will not be effective against the cytokine storms in COVID-19 [118].

***Vaccines***

With the exponential growth, the best option for blocking the infections disease caused by SARS-CoV 2 is vaccine development [119].On 11$^{th}$ January 2020, the genomic sequence of the SARS-CoV2 was released and after that company like Moderna Therapeutics, Stermirna Therapeutics, Novavax, Vir Biotechnology, Johnson & Johnson, etc have engaged in actively developing the vaccine and some of them have already entered the clinical evaluation phase.

Till 17-10-20, a total of 42 vaccine candidates are in the clinical evaluation phase and 156candidates are in the pre-clinical evaluation phase.

## CONCLUSION

An unprecedented outbreak in acute respiratory disease, caused by a novel coronavirus SARS-CoV-2. The coronavirus disease 2019 (COVID-19) swept across China rapidly and received worldwide attention. Fever, fatigue, cough, diarrhoea are the symptom which is similar to SARS. Bats and the intermediate host is the origin of COVID-19 and infect human by binds to ACE2 with high affinity as a virus receptor. It is transmitted through close contact and respiratory droplets. This virus is highly infectious mainly affect the ageing and people with certain underlying medical conditions, which needs more attention and care. So far, there are not any precise antiviral medication or vaccines for COVID-19 and therefore clinical management of COVID-19 has been restricted to support and palliative care until now. Consequently, it is required to develop a safe and stable COVID-19 vaccine**.** Currently, effective control the source of infection, cut off the transmission route, and use the existing drugsis the only way to inhibit the spread of these diseases.

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The authors declare that they have no competing interests.

**Statement of informed consent**

There are no potential conflicts of interest.

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