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# Corona virus SARS-CoV-2 disease COVID-19: Infection, prevention and clinical advances of the prospective chemical drug therapeutics

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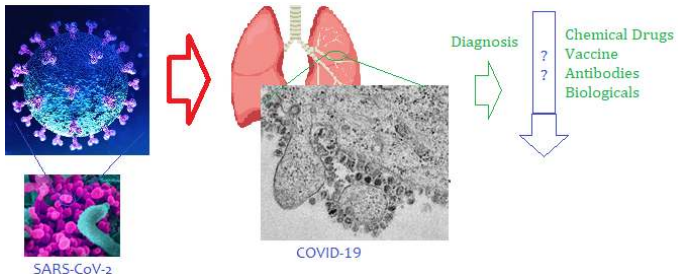
## ABSTRACT




The recent outbreak of Corona virus SARS-CoV-2 disease COVID-19 in the China and subsequent intermittent spread of infection to other countries has alarmed the medical and scientific community mainly because of lethal nature of this infection. Being a new virus in the category, the immediate emergency therapy is not available for the treatment of this disease, leading to widespread fear of infection and has created social issues for infected peoples. Herein, the epidemiology of COVID-19 infection, transmission characteristics of SARS-CoV-2 virus spread, effectiveness of preventive measures, coronavirus family, structural characteristics of virus, current literature advances for the diagnostics development (RT-PCR, CT-Scan, Elisa) and possible drug development based virus life cycle (Entry inhibitors, replication inhibitors, nucleoside, nucleotide, protease inhibitors, heterocyclic drugs, including biological therapeutics (monoclonal antibodies therapy, vaccine development) and herbal formulations have been reviewed. The chemical drug molecules with prospective application in the treatment of COVID-19 have been included in the discussion.

*Keywords: Vaccine, Monoclonal Antibody Therapy, Antiviral, Medicinal Chemistry, Epidemiology, Pharmacology, Cell Mechanism*

## INTRODUCTION

An infectious disease outbreak in the China in December 2019 has emerged with a record number of deaths in China and intermittent spread of infection to other countries.[1] The infected person showed pneumonia symptoms advancing to Severe Acute Respiratory Syndrome (SARS). The infection caused by virus is lethal in nature and stand responsible for a number of deaths by respiraotry infection. With first reported spread of infection in China,[2] the virus has advanced to nearly all other countries and continents, the large number of confirmed infection cases observed in South Korea, Italy, Iran, and few cases in South Africa, USA and other countries. In recent update from WHO and other live updates monitoring institutes, the virus has infected more than 90,000 people wordwide with more than 3,000 deaths in different regions and countries. The China, the major hit country, alone recorded more than 2,500 deaths by end of February 2020.

The sudden emergence and widespread transmission of the virus has created an epidemic situation. Though not confirmed, the origin of virus is speculated from different animals that are consumed as food in China. The early transmission studies reported a link between the local fish and wild animal market in China with most of the early infections; indicating the possiblity of transimission of virus from animals to humans. Later, the

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virus spread new infections mainly through human-to-human transmission.

This disease proved to be more lethal and showed resemblance with Severe Acute Respiratory Syndrome (SARS). In consideration of urgency and to give an identity to current unique symptomic disease, the World Health Organization (WHO) announced a new name for the epidemic disease caused by new corona virus: **Co**rona **V**irus **D**isease 20**19** (COVID-19) on 11 February 2020.

The new virus belonged to corona viruses family and as linked with emergance of new infection in 2019, it was provisionally named as 2019-nCoV. Subsequently, systemic nomenclature was chosen on the basis of an analysis of the new coronavirus's evolutionary history and the pathogen that causes severe acute respiratory syndrome (SARS) and thus, new virus has been given the name as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (Figure 1) by the International Committee on Taxonomy of Viruses on 11 February 2020.

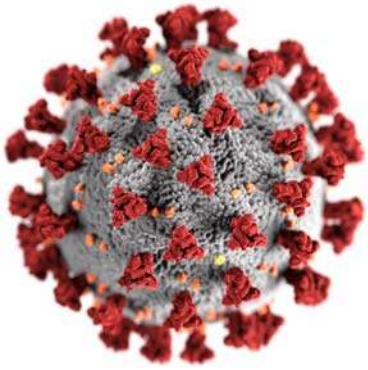

**Figure 1**. A graphical representation of structure of corona virus (SARS-CoV-2). Source: Centers for Disease Control and Prevention – Public Health Image Library. Credit: Alissa Eckert, MS, Dan Higgins, MAM

The epidemic outbreak of COVID-19 is in the line of recent health emergencies caused by different pathogens and WHO has declared the COVID-19 outbreak as the sixth public health emergency of international concern, following H1N1 (2009),[3] polio (2014), Ebola in West Africa (2014),[4] Zika (2016)[5] and Ebola in the Democratic Republic of Congo (2019).[6]

The sudden emergence and continuous spread of this novel coronavirus in 2019 December in humans, has created an urgent need for development of methods for quick diagnosis of SARS-CoV-2 virus and infection disease COVID-19. The doctors have been controlling the virus infection COVID-19 using few exisiting drugs and subsequent result reports are coming with varied degree of controls. The researchers have been extensively engaged by different international agencies and institutes to understand the mecahnism of infection, virulence, pharmacology, and possible early drug and vaccine development. This review discusses the literature reports on advances regarding diagnosis methods and therapeutic development along the prospective possibilities of existing anti-viral drugs.

## THE CORONAVIRUSES

Coronaviruses (CoV) (Corona: Crown like shape; Figure 2)[7] belong to a big family of viruses that cause wide range of diseases mainly related to respiratory system and infection may vary from the common cold to more severe respiratory diseases. The Middle East Respiratory Syndrome (MERS-CoV)[8] and Severe Acute Respiratory Syndrome (SARS-CoV)[9] are two recent prominent infections caused by coronaviruses. In 2019, a new coronavirus (nCoV) i.e. a new strain of coronavirus has appeared which was not identified in humans previously. The Coronaviruses are zoonotic, that signifies these viruses are mostly present in animals and then transmitted from animals to human beings.[10] For example, the earlier coronavirus SARS-CoV was transmitted from civet cats to human beings; and MERS-CoV was transmitted from dromedary camels to humans. There are several other coronaviruses that are known to be present in animals but are harmless for humans or have not yet infected human beings. Some coronaviruses may cause illness in humans, and many other viruses such as canine and feline coronaviruses are known to infect animals only. In rare instances, animal coronaviruses emerge to infect human beings and then can spread via human-to-human transmission. The same case is suspected to have occurred for the new coronavirus that causes COVID-19 disease.

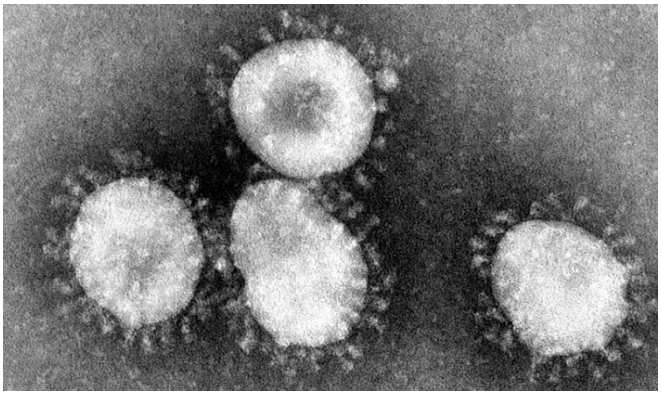

**Figure 2**. Representative structure (Electron micrograph of infectious bronchitis virus) of Coronaviruses (crown-like shape). Source: Wikipedia/CDC Credit: CDC/Dr. Fred Murphy

## COVID-19 INFECTION TRANSMISSION

The first incidences of COVID-19 were observed in the Wuhan city, Habei province of China. Its initial rampant spread was mostly to the nearby populations, the whole Habei province is worse affected followed by further spread to nearby provinces. The epidemiology of infection represented on the map of China region by the C. Lai et. al.[11] (prepared for infection upto 11 February 2020, figure 3) indicated the Habei as the most infected province, the adjacent provinces Hanan, Guangdong and Zhejang as the next most infected areas. The other adjacent provinces has lesser infection spread. The key point to be observed on the epidemiology map is that the most affected area is the point of origin of infection (the epicenter Habei) while other adjecent provinces has reducing impact as the distance increases. The infection to other countries spread

mostly via the travellers to and from Wuhan city at the time of peak infection. The South Korea, Italy and Iran has seen most infected population after the China.[12] The international alert about the COVID-19 infection has helped in the containment of the spread. Many other countries have now reported the confirmed cases of infected people (and subsequent cases of deaths from COVID-19) but the number has been very less and most of new cases are now confined to localized regions.[13]


**Figure 3**. Distribution of laboratory-confirmed cases of 2019 coronavirus disease (COVID-19) in China by province/region as of 11 February 2020. Reproduced with permission from report by C. Lai et. al.[11] Copyright: Elsevier.

The human-to-human spread is now the primary way of transimission of the infection, the transmission may be from symptomatic or asymptomatic person. The transmission occur from the symptomatic COVID-19 patient via the respiratory droplet when the patient coughs or sneezes. The transmission in such cases is to the nearby persons only (upto the distance the droplets can fly in air). While in in case of asymptomatic person[14] having the SARS-CoV-2 virus, the transmission from such patients occur via the handshake or contamination of surfaces by hands as such people do not show symptoms of COVID-19 (coughing, sneezing).[15] This manual transmission may also spread in case of symtomatic patients. The vertical transmission of virus from mother to child has not been observed as per the studies carried out by H. Chen et. al. on a small group of pregnant women. They suggested, the absence of interauterine vertical transmission of COVID-19 from mother to unborns.[16]

In emergence and rampant spread of new virus, the increase in human population is considred to be major factor. The increased population density increases the possibility of transmission of new infections due to increased human proximity while the sparse population area generates auto-separation or containment of infections.

In summary, the human-to-human transmission of SARS-CoV-2 virus occurs:

1. Through respiratory droplets generated by sneezing and coughing by infected person, generally when present in close proximity.
2. By manual touching of infected surface (having the SARS-CoV-2 virus from symptomatic or asymptomatic person) and then hand touching the mouth, nose or eyes.
3. Transmission do not occur through simple air (virus remain contained in snizzing droplets).
4. No vertical mother-to-child transfer in case of pregnant women.

## SYMPTOMS OF PATIENTS INFECTED WITH COVID-19

The symptoms of COVID-19 are mainly for respiratory disorders and similar to severe acute respiratory symptoms. The common signs of infection observed in COVID-19 patients include respiratory symptoms, snizzing, fever, cough, shortness of breath and other breathing difficulties. In case of severely infected patients, infection can cause pneumonia, severe acute respiratory syndrome (SARS), kidney failure and even death in many cases. There are many people who had high viral load but do not develop COVID-19 symptoms like coughing or snizzing.[17] Such asymptomatic people serve hidden carriers of virus and may further contribute in enhanced transmission of virus to other peoples.[15]

In clinical investigation study of COVID-19 infected patients from different regions of China by the Guan et. al.[18] showed a varied pattern of the illness. The study reports that the median age of the infected patients studied was 47 years indicating the presence of infection in people of all ages. Further, out of total patient studied, 41.9% were female, a point indicating towards gender neutrality of infections spreading in different patients. The report states that the primary composite end point occurred in 6% patients. The patients from outside of the Wuhan city either had a contact with the residents of Wuhan city at some point or had visited the city recently.[18] In the patients admitted for COVID-19, very few (only 1.9%) of the patients had a history of direct contact with wildlife; indicating the support for human-to-human transmission of SARS-CoV-2 virus.[19]

The most of the patients had a common symptom of **fever** and **cough**. Many of the patients often presented without fever, however, developed it in due course of infection. Majory of patients developed fever (43.8% on admission and 88.7% during hospitalization) and nearly two-third of patients had cough (67.8%) as common symptoms. The blood test showed **Lymphocytopenia** (abnormally low level of lymphocytes in the blood) in majority of the patients (83.2% of the patients) on admission to the hospitals. Diarrhea was not common in most of the cases as only 3.8% of patients had diarrhea. The patients developed full symptoms of the COVID-19 in 2 to 7 days[20] i.e. the median incubation period of infection development was 4 days with interquartile range of 2 to 7 days in all patients.[18]

## PREVENTIVE MEASURES

In absence of availability of emergency medicine or complete therapy for COVID-19; the prevention of spread of SARS-CoV-2 virus and regulation of infection is the prime step in controlling this epidemic disease.

The containment of the infected patients has been recommended as one step to control the rampant transmission

among people. However, it is difficult to impose the isolation of infected patients as along it generate many social issues. Like many media reports from China mentioned the practice of forced locked down of infected persons in their houses by the other peoples. The isolation of infected persons supported with availability of complete medical care (in hospitals) could be ethical way of control.[21] In this direction, proper research studies should be carried out to understand the best approach for infection prevention, including assessing whether lockdowns in major Chinese cities[22] have had a positive or negative effect on slowing the spread of virus.[23]

The masks has been in extensive demand in a notion towards prevention of this viral infection transmission.[24] The medical masks could be of help in prevention of direct exposure to respiratory droplet from infected patients (symptomatic patients). While in other cases with improper use of masks may lead to increased chances of infection transmission. Particularly, the infection from asymptomatic persons and via infected surfaces pose higher risk of transmission with improper use of masks.[24] This happens because the person wearing the masks touches own mask (towards adjusting the strip or mask on face) and mouth/face parts more frequently than the person without mask. This frequent touching of mouth and face part pose higher possibility of reaching of virus to person's respiratory system on exposure of hands with contaminated surfaces (in shops, malls, buses and other public places) or hand shake with asymptomatic persons. So, care should be taken to avoid frequent touching of own face particularly mouth, nose and eyes (whether wearing mask or not).[25]

The standard procedures that are recommended for prevention of any infection spread would be more effective in controlling the spread and keeping one safe. The most important include regular hand washing, a practice simple but very effective. Washing of hands after any visit to public places would keep the virus (even if exposed to contaminated surfaces) away from getting transmitted or one getting infected. Other practice include covering mouth and nose when coughing and sneezing to prevent the spread particularly if the person is asymptomatic or in initial stages of infection. Also thoroughly cooking meat, eggs and food from animals would destroy the virus. In general practive, one should avoid close contact with anyone showing symptoms of respiratory illness such as coughing and sneezing. The simple preventive measures would be effective in controlling the spread and thus containment of virus itself.

## STRUCTURE OF VIRUS

The structure identification of SARS-CoV-2 virus is essential towards understanding its historical resemblance with other viruses and that of corona virus family, occurance and probable mode of infection, mechanism of entry at tissue site of infection and multiplication process in the infected cells. The etiologic agent virus responsible for COVID-19 infection has been identified as a coronavirus by using electron microscopic imaging examination of a thin-section virus isolate (Figure 4). The Scanning electron microscopic images of SARS-CoV-2 virus showed that virions are spherical in shape with diameter of 70-80 nm. The virions are composed of a helical like nucleocapsid within an envelope with surface projections (Figure 4).

The transmission electron microscopic images of the SARS-CoV-2 show the virus internal structure as double walled with lobe like surface projects, the cytoplasm containing vacuole like spherical structures (Figure 5). Further, as the SARS-CoV-2 belong to coronavirus family with SARS resemblance, it is expected to be carrying other distinct ultrastructural features of coronaviruses such as: double-membrane vesicles, nucleocapsid inclusions, and large granular areas of cytoplasm.[26] Further, as it is the case for other coronaviruses, the SARS-CoV-2 virus particles cytoplasmic part should be containing viral proteins as well as the RNA as genetic material.[26] Recently, it is revealed that, the SARS-CoV-2 is a positive-strand RNA virus causing severe respiratory syndrome in human.

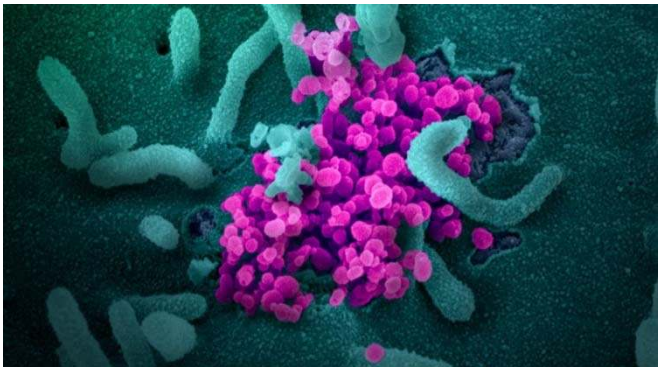

**Figure 4**. The coronavirus SARS-CoV-2, shown in a scanning-electron-microscope image. Image reproduced as provided for public domain use by National Institute of Allergy and Infectious Disease, US. Credit: NIAID-RML/de Wit/Fischer

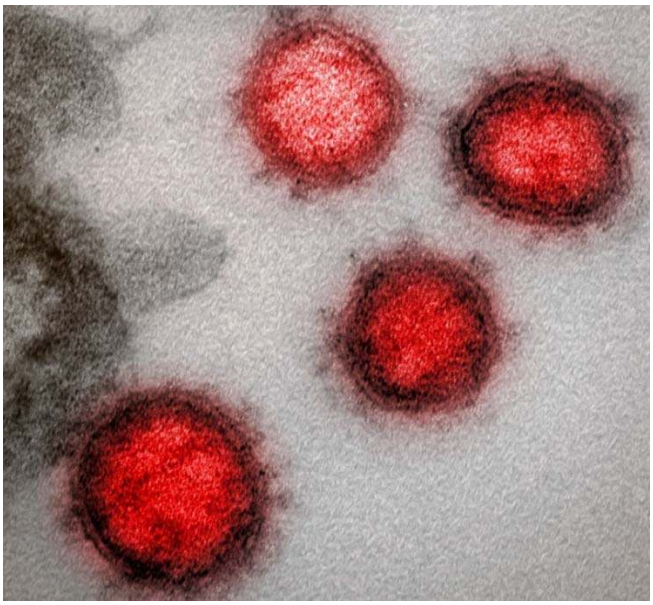

**Figure 5**. Electron-microscope image of the new coronavirus, now designated SARS-CoV-2. Image reproduced as provided for public domain use by National Institute of Allergy and Infectious Disease, US. Credit: NIAID-RML/de Wit/Fischer

Electron microscopic studies have proved critical in identifying the etiologic agent of the earlier Severe Acute Respiratory Syndrome (SARS), H1N1 outbreak and then have been an essential tool in guiding subsequent laboratory and epidemiologic investigations of earlier world epidemics. In the case of SARS-CoV-2 as well, the electron microscopic images provide fundamental data about the structural aspects of virus and would be guiding point in development of therapeutics.

## LIFE CYCLE OF SARS-COV-2 VIRUS AND INFECTION

The 2019 novel coronavirus is zoonotic in origin[27] and have a multiplication cycle in respective animal, though not clear as of now. In human beings the virus primarily infects the cells of respiratory system, the covering cells of sacs in the lungs. Angiotensin-converting enzyme 2 (ACE2) is the cellular receptor for SARS coronavirus.[28] The virus binds to these receptors and make entry in the cell where it duplicates its genome materials and synthesize different required proteins using the cellular machinery, and then buds out new virions from cell surface.[29] The researchers at University of Hong Kong has grown the virus in cell culture and microscopic image of the cells infected with SARS-CoV-2 show a large number of virus release from the surface of cell (figure 6).[30]

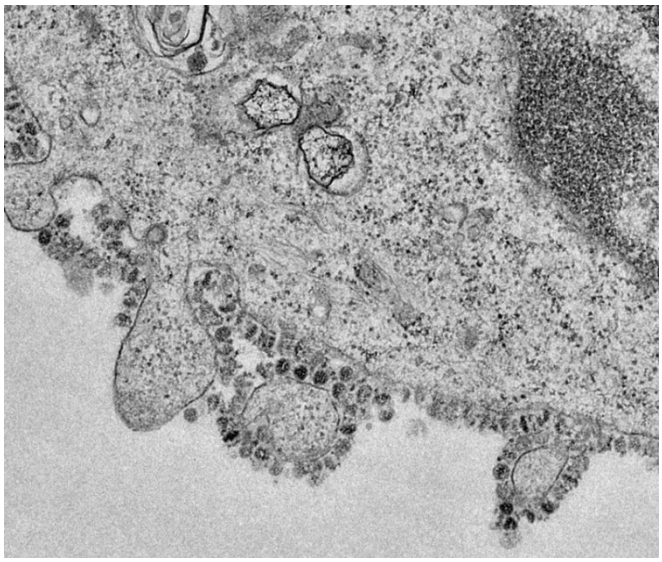

**Figure 6**. A microscope image of a cell infected with the novel coronavirus, grown in culture at the University of Hong Kong. Multiple virus particles are being released from the cell surface. Credit: John Nicholls, Leo Poon and Malik Peiris - The University of Hong Kong.[30]

The similar release of virus had been observed with SARS vrius infected cells. In earlier report with SARS, the ultrastructural examination of a bronchiolar lavage specimen from a SARS patient had shown numerous coronavirus-infected cells, with features similar to those in infected culture cells.[26]

The virus multiply in the infected cells, using the cellular machinary of cell for viral RNA synthesis as well as protein synthesis required for new virus generation. The complete mechanism for the SARS-CoV-2 is yet to be understood, the preliminary data with other coronaviruses like SARS would be handy in creating the map for mechanism of novel virus multiplication.

## DIAGNOSIS

The characteristic proper diagnosis of COVID-19 infection is first line of control and a deciding factor in initiation of course of treatment. The distinction of COVID-19 from general cold infections is essential for proper treatment. The symptoms vary in patients (discussed above) and preliminary examination may not provide the clear diagnosis of COVID-19 infection. The doctors generally take into consideration the travel history of patient along with other symptoms of cough, snizzing, fever etc. On initial inference, the sputum examination and other diagnostic tests help in proper establishment of early infection. The number of days from possible first day of infection is taken in account for recommending the respective diagnostic tests:

**RT-PCR**

The standard method of diagnosis is by reverse transcription polymerase chain reaction (rRT-PCR) from a nasopharyngeal swab or sputum sample, with results within a few hours to 2 days.[31]

**ELISA**

Antibody assays can also be used, using a blood serum sample, with results within a few days.[32]

**CT-Scan**

The infection can also be diagnosed from a combination of symptoms, risk factors, and a chest CT scan showing features of pneumonia.[33] The preliminary diagnosis reports from hospitals in China indicate that most of COVID-19 infected patients were diagnosed with pneumonia and characteristic CT imaging patterns,[34] radiological examinations have become vital in early diagnosis and assessment of disease course.[35] CT scan of different COVID-19 infected patients varied in pattern[36] and nearly half of patients could be ascertained of infection from images. On admission to hospitals, the ground-glass opacity was the most common radiologic finding on chest computed tomography (CT)[37] of 56.4% of patients.[35] The longitudnal CT findings of a COVID-19 infected patient with pneumonia showed organized pattern of CT images in follow up scan during the course of treatment.[38] Also it was observed that many patients did not have abnormal radiologic findings.[39]

## TREATMENT OF COVID-19

There is urgent demand for suitable therapeutics for the treatment of new disease COVID-19. The lethal nature of the infection has produced a pronounced sense of scare in the patients and peoples in general. The infection is new type of respiratory disease (SARS) with acute lethal nature, the existing drugs have been successful in partially managing the symptoms and till now, no definite line of treatment and therapeutics have been defined. The prevention of spread is the early emphasis for protection by all nations. The international organizations such as WHO has promulgated call for speedy vaccine, drug and diagnostic development for SARS-CoV-2 and COVID-19. The officials at World Health Organization (WHO) has outlined their top research priorities for controlling the outbreak of the

coronavirus-associated disease. In a recent two-day international forum in Geneva, Switzerland, meant for assessing the COVID-19 outbreak, the WHO director-general T.A. Ghebreyesus emphasized the importance of developing candidate therapeutics and easy-to-apply diagnostics for identifying active, asymptomatic and resolved infections of COVID-19.

The mechanism of viral infection i.e. entry of virus in the cells and its multiplication using host cellular machinary along with damage of the host cells, is the key part to look forward for the development of therapeutics. As little is known specifically for this virus (SARS-CoV-2), so the most of the drugs attempted so far by the doctors in controlling the COVID-19 are based on the information for the similar kind of infections that occurred in past and treatment has oriented towards 'management' of symptoms. The various drugs and formulations having possibility of use in control of COVID-19 includes the anti-viral drugs (for similar kind of infections or other anti-virals depending on presumed mechanisms and processes might being adopted by the SARS-CoV-2). Few prospective drugs for consideration to direct application now or development of new therapeutic drugs includes:

ENTRY INHIBITORS: The SARS-CoV-2 virus infects the respiratory system and the aleveoli cells in lung sacs would be the host for viral infection. The virus enters in host cells generally by forming a complex between the virus projections (the crown like spikes or lobes) with the receptors on the host cell. Though exact structure of virus spikes[40] / lobes and receptors on host cells for the SARS-CoV-2 is not known completely yet, the earlier coronavirus (β-family) responsible for SARS infection in past would have similarity in form of entry in host cells.[41] Recently, it has been discovered that Angiotensin-converting enzyme 2 (ACE2) is the cellular receptor for SARS coronavirus, (SARS-CoV) and (SARS-CoV-2).[28] Angiotensin-converting enzyme 2 (ACE2) shares some homology with angiotensin-converting enzyme (ACE) but is not inhibited by ACE inhibitors. The earlier SARS cases, the infections were initiated by the transmembrane spike (S) glycoprotein, which binds to host receptors and fuses the viral and cellular membranes.[42] The identification of structure of viral spikes / lobes molecules would be taking time, however, the development of heterocyclic molecules as drugs will be facilitated or the screening of existing heterocycles with probability of binding might provide a lead in getting entry inhibitor drugs.[43]

REPLICATION INHIBITORS: The corona viruses are RNA viruses and uses the host cells for replication of their genome. Coronavirus genomes also encode a protein called RNA-dependent RNA polymerase (RdRp), which allows the viral genome to be transcribed into new RNA copies using the host cell's machinery. The replication mechanism of viral genome serves potential target for the control of viral infection. The nucleoside analogues (that are potential polymerase inhibitors and used as antiviral drugs[44]) could be potentially effective with SARS-CoV-2. The RNA polymerase inhibitor Remdesivir (a nucleotide adenosine analogue antiviral for Ebola virus and other array of RNA viruses) has shown promising results in clinical control of SARS-CoV-2 pneumonia in in-vitro cell culture and with selected clinical cases,[45] however, require further evaluation of potential application with more patients. Many other nucleoside analogues including DNA synthesis inhibitors such as tenofovir disoproxil, lamivudine and similar other antiviral (figure 7) have potential to inhibit the SARS-CoV-2 virus multiplication and are being evaluated through molecular docking studies[46] and testing in lab culture infected cells.

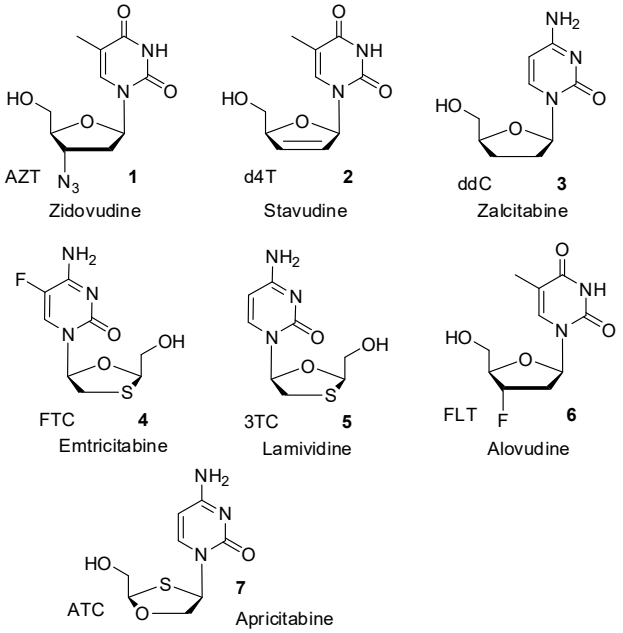


**Figure 7a**. Chemical structure of Nucleoside analogue anti-HIV drugs

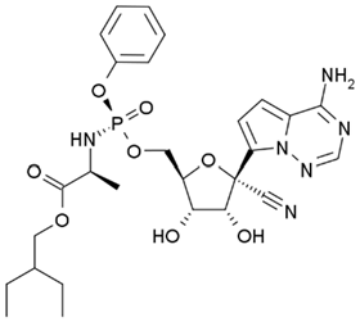

**Figure 7b**. Chemical structure of nucleotide adenosine analogue Remdesivir antiviral drug

PROTEASE INHIBITOR: Protease enzymes are involved in the maturation stage of virus replication inside the host cell and associated with protein or peptide translation. The lopinavir and ritonavir (both approved as anti-HIV[44] drugs) (figure 8) combination have shown the potential application in inhibition of SARS-CoV-2.[47,48] A report by J. Lim et.al. regarding treatment of a COVID-19 patient in Korea indicated that on administration of lopinavir/ritonavir (Kaletra, AbbVie) to the patient, interestingly, β-coronavirus viral loads decreased significantly and on further treatment no or little coronavirus

titers were observed.[48] This is the report with single patient, a detailed analysis is required for recommendation of this drug formulation for treatment of COVID-19.

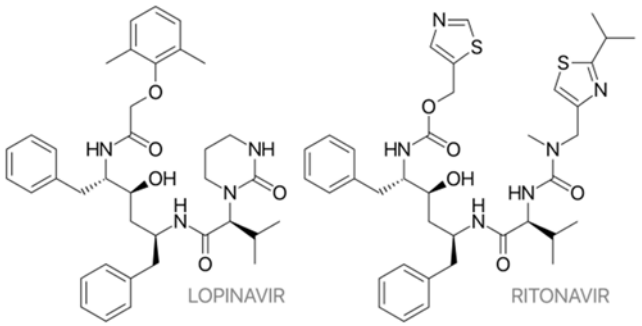


**Figure 8**. Chemical structure of Protease Inhibitor drugs.

The molecular docking of potential inhibitors might provide a point of lead as detailed docking similuation reports have shown essential inputs in case of earlier SARS and other other virus infections.[49–51]

HETEROCYCLIC ANTI-VIRALS:

Many heterocyclic molecules has been used in the treatment of viral infections in past and with presumption of possible effectiveness for SARS-CoV-2, few are being pursued for COVID-19 infection treatment via *in vitro* evaluation as well as by direct clinical applications. The Chloroquine (Figure 9) is a well known anti-malarial drug[52,53] and has been well described for the *in vitro* effects on inhibition of uncoating and/or alteration of post-translational modifications of newly synthesised proteins, especially inhibition of glycosylation in many viruses, including HIV and chikungunya fever.[54] A recent study by Wang et al. on application of remdesivir and chloroquine in vitro conditions revealed the effectiveness of these drugs in the control of SARS-CoV-19.[45] Also the preliminary results from a multicentric trial announced by Gao et.al indicated the effective and safe application of chloroquine in treating COVID-19 associated pneumonia. On obtaining the successful results for Chloroquine, the group has recommended this drug for the treatment of pneumonia caused by COVID-19.[55]

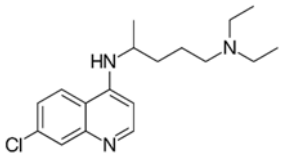

**Figure 9**. Chemical structure of Chloroquine.

Other heterocyclic antivirals such as Umifenovir (Arbidol), Galidesivir and Garunavir used as antiviral for HIV / H1N1 / H1N5 / SARS are actively pursued for evaluation for SARS-CoV-2. Oseltamivir (brand name Tamiflu), a most widely used neuraminidase inhibitor for treatment of influenza has also been recommended for COVID-19 symptoms.[56] In addition to heterocycles, angiotensin-converting enzyme 2 (ACE2)-based peptide, 3CLpro inhibitor (3CLpro-1) and vinylsulfone protease inhibitor, may presumably show and can be evaluated for potential antiviral activity against SARS-CoV-2.[57]

NANO DRUG DELIVERY SYSTEMS have extensively been used for improving the delivery and efficacy of antiviral drugs particularly the nucleoside analgues on conjugation with delivery systems has shown the potential application in drug resistant HIV infection.[58–61] The number of available nanodelivery systems can be used with the new developed drug formulation which could be efficacious in delivering the drugs[62–64] with faster therapeutic indices for COVID-19.

BIOLOGICAL THERAPEUTICS

Therapy using the Antibodies or antibodies fragement is one possibility for COVID-19 infection, however, it is mentioned that it will take time and some effective applicable options would be available by 2021 only.[65] X. Tian et.al. has reported a SARS-CoV-2 specific human monoclonal antibody, CR3022, which they propose for potent binding with SARS-CoV-2 RBD (KD of 6.3 nM).[66] Reportedly the 'epitope of CR3022 does not overlap with the ACE2 binding site within SARS-CoV-2 RBD'.[66] The proposed unique binding results of this antibody indicate the possibility of CR3022 being developed as candidate therapeutics, alone or in combination with other neutralizing antibodies, however, in vitro or clinical studies are required to use CR3022 for the prevention and treatment of COVID-2019 infections.[66]

Same way the Vaccine development has been initiated mainly taking the similarity of coronaviruses for SARS, MERS and their conserved regions present in SARS-CoV-2.[67] Using the similarity pattern of immunogenic structural proteins of SARS coronavirus, S.F. Ahmed et al.[68] has identified a set of B cell and T cell epitopes derived from the spike (S)[69] and nucleocapsid (N) proteins that map identically to SARS-CoV-2 proteins.[68] The report mentions that the identified epitopes has not shown any mutation in available SARS-CoV-2 sequences, so the immune targeting of these epitopes may potentially be explored for protection against SARS-CoV-2 virus. The SARS-CoV-2 spike glycoproteins has been elucidated along with antigenicity,[70] impetus lead towards development. Further, by population coverage analysis of the associated MHC alleles, a set of epitopes that is estimated to provide broad coverage globally has been proposed for the T cell epitopes.[71] Though these finding about a screened set of epitopes again provide a direction towards development of vaccines against SARS-CoV-2, however, final outcome would depend upon the invitro/clinical studies.[68] There are many other vaccine candidates in development, in few months, one or two of those might be in human trials. Still, it will be more than a year until they might be available for wider use.

HERBAL DRUGS

The herbal formulations used as alternative medicine has been successful in providing the cure to a number of infections along with symptom specific treatment using herbs. The initial lead from herbal medicine has been successful in developing final applicable formulations like Praneem (an herbal extract of neem tree) as microbicide for HIV therapy.[72] In case of COVID-19, the Chinese herbal medcines have been proposed and

evaluated in clinical settings for relieving the COVID-19 symptoms.[73] The herbal medicine (suitable for chronic diseases) may not be effective for treatment of acute disease, however, might be suitable as supplement towards symptoms mitigation, the final recommendation could be made on clinical evaluations.[74] In India, general herbs that help in better immunity profiling and herbs for general physiological balance during any infection have been prescribed for viral infections.[75] For the COVID-19 infected peoples as well, the Geloy (Tinospora cordifolia) extract[76] (have been successful in controling the severity of Dengue infections), Hing (having anti-microbial properties)[77] and many other herbal formulations have been recommended for the coronavirus infections by herbs experts.[78]

## CONCLUSION

The sudden outbreak of COVID-19 in China and subsequent spread to other countries has become a clinical threat to medical community, health workers and general population worldwide. In many new cases, the clinical staff got infected from the patients visiting the hospital. The surging spread of virus via human-to-human transmission, has created an urgent need for the development and approval of standard therapy protocols. In absence of complete structural and life cycle details of virus, the therapeutic development get delayed, the preventive measure remain the only prominent tool to counterfeit the SARS-CoV-2 infections. Few existing drugs have been evaluated for treatment of COVID-2 and shown promising good results in clinical applications. The chemical drugs (and herbal medicines) for the 'management of viral infection symptoms' has been on frontline to mitigate this novel viral infection disease and has helped a numbers patients in safe recovery from COVID-19. Further, as the knowledge about SARS-CoV-2 is advancing, new therapeutics including vaccines and monoclonal antibody therapy could be seen in sight in near future. So far, a complete effective treatment of COVID-19 is not known, however, potential therapeutics are emerging as clinical evaluation of existing anti-viral drugs continues and knowledge about this novel corona virus advances.

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