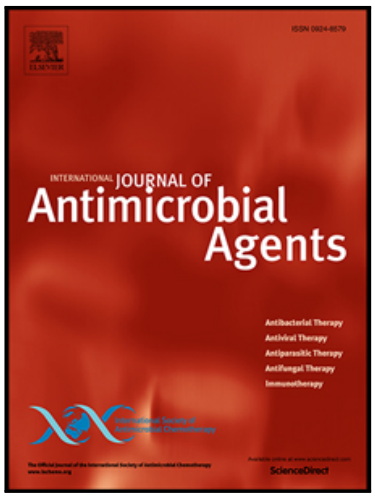

Severe Acute Respiratory Syndrome Coronavirus -2 (SARS-CoV-2): A global pandemic and treatments strategies

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Highlights

- The viral SARS-CoV-2 pandemic has led to detailed and exhaustive need to assess epidemiology
- The spread of virus at global level is due to human to human transmission
- Existing treatment is essentially supportive; role of antiviral agents is yet to be established
- Detection of biomarker could also be useful in early screening of infection

Severe Acute Respiratory Syndrome Coronavirus -2 (SARS-CoV-2): A global pandemic and treatments strategies

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Abstract

The emergence and rapid spread of novel coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as a potentially fatal disease is swiftly evolving public health crises worldwide. The origin of SARS-CoV-2 infection was first reported in people exposed to wet animal market in Wuhan City, China in December 2019. It was suggested that the infection is likely to be of zoonotic origin and transmitted to

human through yet unknown intermediary. As of (22/05/2020), there are around 4,995,996 confirmed cases reported by WHO with 327,821 deaths. SARS-CoV-2 infection is transmitted via inhalation or direct contact of infected people's droplets. It has an incubation period ranging from 2 to 14 days or more. The rate of spread of SARS-CoV-2 is more than partially resembled coronavirus (SARS-CoV and MERS). The symptoms are similar to influenza like, breathlessness, sore throat and fatigue therefore, infected person is isolated and administrated with effective treatments. Infection is mild in most but in elderly (>50 years) and those with cardiac and respiratory disorder, it may progress to pneumonia, acute respiratory distress syndrome, and multi organ failure. People with strong immunity or those developed herd immunity are asymptomatic. Fatality rate ranges to 3-4% on case basis. Diagnosis of SARS-CoV-2 is recommended in respiratory secretions by special molecular tests like PCR, chest scan and common laboratory diagnosis. Currently, the existing treatment is essentially supportive and role of antiviral agents is yet to be established as there is no vaccination or therapy available. This review focuses on epidemiology, symptoms, transmission, pathogenesis, ongoing available treatments and future perspectives of SARS-CoV-2.

Keywords

Coronavirus; SARS-CoV-2; Chloroquine; Severe Acute Respiratory Syndrome; Antiviral agents, Biosensor

1. Introduction

Since 19th century, pathogenic viral outbreaks and their complex interactions with humans and animals (species jump) have resulted in cross-species transmission possessing a great threat to human health and safety [1, 2]. With fast pace globalization and human activities, pathogenic transmission across continents has escalated and resulted in several pandemics, especially the viral pandemics [3, 4]. In the last two decades, an upsurge of some newly

identified coronavirus were identified and reported such as the Middle East respiratory syndrome (MERS-CoV) reported in Saudi Arabia [5], haemorrhagic fever viruses (Lassa, Ebola) in West Africa, novel coronaviruses including severe acute respiratory syndrome CoV (SARS-CoV) and highly pathogenic influenza (Avian Influenza A- H7N9; Pandemic-H1N1) in China [4,6]. According to WHO, these viral pandemics have resulted in substantial deaths for instance SARS originated from bats crossed over to human via palm civet (host) in the Guangdong province of China has notified 8422 infected including 916 deaths in 26 countries [7] with 11% mortality. The MERS-CoV also originated from bats with a dromedary camels as intermediate host and infected 2,494 people including 858 deaths (fatality rate 34%) from 27 countries [8]. Similarly, in total 28,637 cases of Ebola infection were notified including 11,315 deaths [9] with a mortality rate of up to 40%. These pandemic situations already caused significant mortality and economic losses; and it is critical to prevent the spread of emerging viruses. The present review sheds light on the current pandemic of SARS-CoV-2, epidemiology, global status, possible treatment strategies with their future potentials.

Coronaviruses (CoVs, subfamily *Coronavirinae*, order *Nidovirales*) are common human pathogen from a class of enveloped, positive-sense and single-stranded RNA viruses that belong to the family *Coronavirdiae* and known to cause acute respiratory, hepatic and neurological diseases with varying severity in human as well animal species [10-12]. CoVs are further divided into four genera namely, alphacoronavirus (αCoV), betacoronavirus (βCoV), gammacoronavirus (γCoV), and deltacoronavirus (δCoV) [13]. Among them, two novel βCoVs i.e. SARS- CoV and MERS-CoV have been reported with high mortality as discussed earlier. The evolutionary analysis has notified that the αCoVs and βCoVs mostly found in bats and rodents, whereas, the avian species are the gene sources of most δCoVs and γCoVs [11]. They have ability of repeatedly crossing the species barriers and have emerged out as important human pathogens. In December 2019, an outbreak of pneumonia like system

caused by novel coronavirus (2019-nCoV, temporarily name) occurred in Wuhan, Hubei Province and spread throughout China to the rest of the world [14] and later WHO declared this outbreak a global pandemic. In February 2020, WHO named the disease as COVID-19 short for "coronavirus disease 2019" [15] and in meantime The International Committee on Virus Taxonomy named the virus as SARS-CoV-2 [16] and a group of virologists in China also suggested renaming of SARS-CoV-2 as human coronavirus 2019 (HCoV-19) to distinguish from SARS-CoV and keeping it consistent with the WHO naming [17]. On 11 March 2020, WHO characterized SARS-CoV-2 as a pandemic situation [18]. Till 22/05/2020 around 4,995,996 confirmed cases of SARS-CoV-2 and 327,821 deaths have been reported among 216 countries [19] and the number is increasing by every minute worldwide (Fig.1A). In China, the total confirmed cases reported as 84,520 with total death of 4645. Moreover, the United State of America has the highest number of cases 1,525,186 and 91,527 deaths with a mortality rate of >12 %. As depicted in Fig.1B, the infection of SARS-CoV-2 across in India, which is a neighbour country to China, where the number of active cases (118,447) is increasing on daily bases (Fig.1C), at a low death rate (~3.0 %). In this review, we will be discussing epidemiology, transmission, pathogenesis, clinical manifestations, ongoing available treatments and future perspectives of SARS-CoV-2. The present review summarizes all information at one place focusing the wider audience and readability.

Figure 1

2. Origin and spread of SARS-CoV-2 (COVID-19):

CoVs are enveloped, positively sensed RNA viruses with diameter ranging from 60 to 140 nm. CoVs are characterized by a club-like spikes projections of protein on its surface with a crown (latin for crown "*coronam"* hence named coronavirus) like appearance under the electron microscope [20]. The unusually large viral RNA genome ~30 kb with unique replication strategy due to presence of 5′ cap structure along with a 3′ poly (A) tail allowing

to act as an mRNA for translation of the replicase polyproteins and strong affinity to bind with human cell receptors that differentiates it from other CoVs [21]. These CoVs are known to cause a variety of diseases in mammals and birds ranging from enteritis in cows and pigs and upper respiratory disease in chickens to potentially lethal human respiratory infections [21]. Previously, four different families of viruses namely HKU1, 229E, NL63 and OC43 have been identified with a transmission in human being causing mild respiratory disease [22]. On 8th December 2019, adults in Wuhan (Hubei Province, China) reported with severe pneumonia of unknown cause in local hospitals and these initial cases formed a preliminary notion of common exposure that they have visited seafood market trading live animal in Huanan [22]. Immediately, a surveillance system was activated and respiratory samples of diseased patients were collected for their etiologic investigations. Later (31st December 2019), WHO notified this incident as an outbreak following that on 1st January 2020, the Huanan seafood market was closed. Based on virologist investigations, on 7th January the virus outbreak was identified as a CoV infection that had >70% similarity with the SARS-CoV and >95% homology with the bat CoV. The environmental sample was also reported to be positive from the Huanan seafood market [23]. It was observed that the number of cases increasing exponentially, however, some cases did not have direct exposure to live animal seafood market which suggested that the human-to-human transmission has occurred [24]. The first case was reported on 8th Dec, 2019 but on tracing the virus back to where it originated and learn more about its spread- the first case was found to be hospitalized on 17th Nov, 2019. The massive migration of Chinese population during the Chinese New Year has pulled the epidemic globally as the cases in other country and continents were reported in people who were returning from Wuhan. Transmission to the healthcare professionals treating the infected patients was reported between 20th -23rd Jan, 2020. To prevent the

transmission, immediately, Wuhan was placed under lock down with 11 million population and restrictions on their entry and exit from the province.

Despite the extensive preventive measures, the spread of SARS-CoV-2 in countries outside China were reported in population with no travel history suggesting the local human-to-human transmission has started [25]. Considering the seriousness of pandemic, the countries evacuated their citizens from Wuhan or any other hot SARS-CoV-2 zone through special flights started testing virus or isolation for 14 days to secure asymptomatic people. Importantly, while the number of new cases noticed in China has reduced lately, however, they have increased exponentially in other countries [19]. The figure 2 represents the percentage distribution of total confirmed cases and death in various countries as on 25 April 2020. These numbers might be an underestimate of the total infected or confirmed cases and death due to limitations of surveillance and testing in developing countries. Though the probable origin indicates from bats, the intermediary animal through which it crossed over to humans is uncertain. Pangolins and snakes are the current suspects [11, 22].

Figure 2

3. Symptoms and diagnosis

Usually, the symptoms of SARS-CoV-2 infection appear after an incubation period of 2-14 days with an approximate period of 5.2 days [26]. Most commonly, the onset of SARS-CoV-2 illness is marked by fever, dry cough, fatigue and muscle pain with other symptoms like headache, lymphopenia, dyspnoea. Some people might have diarrhoea or nausea one or two days before the infection [27-29]. After onset of infection, on 5^{th} day patient face difficulties in breathing and an acute respiratory distress syndrome (ARDS) on day 8^{th}. Later, if the patient's condition worsens, he may have abdominal distress and pneumonia with other functional failure depending upon immunity and health conditions [30]. From onset of

infection to the death, the period ranges from 6-41 days with average rate of 14 days [31]. This period is dependent on the several factors such as age and health. The period is shorter for patients with comorbidities and above 70 years [31].

Diagnosis and treatment program (6^{th} version) published by the National Health Commission (NHC) of the People's Republic of China has defined the diagnosis of viral pneumonia based on radiologic features as one of the diagnostic criteria for SARS-CoV-2 [32]. Accurate diagnosis of chest CT scan may play an important role in the management of SARS-CoV-2 infected patients, especially when there is no scientifically proven therapy available for the treatment. Clinical features revealed by a chest CT scan indicated as pneumonia in infected patients. The other abnormal features such as ARDS, acute cardiac injury, RNAaemia, and grand-glass opacities that lead to death have also been reported [24]. The major notable symptoms are presence of multiple peripheral ground glass opacities in subpleural regions of both lungs which induce the both systemic and localized immune response leading to increased inflammation [33]. Importantly, there are similarities in the symptoms between SARS-CoV-2 and earlier reported βCoVs such as dry cough, fever, dyspnoea, and bilateral ground-glass opacities investigated through chest CT scans [24]. However, SARS-CoV-2 exhibited some inimitable clinical features targeting the lower respiratory region as evident by upper respiratory tract symptoms like rhinorrhoea, sneezing, and sore throat [29, 34].

Additionally, from investigation of chest radiographs of patients, an infiltrate in the upper lobe of the lung which is associated with increasing dyspnoea with hypoxemia was observed. [35]. Above discussions suggested that chest CT should be the preferred modality for diagnosis of SARS-CoV-2, nevertheless, the use of CT to diagnose SARS-CoV-2 is controversial. The detailed CT scan features for SARS-CoV-2 have been reported with limited literature [27, 36]. The patients infected with SARS-CoV-2 usually developed

gastrointestinal symptoms like diarrhoea, whereas, a low percentage of MERS-CoV or SARS-CoV patients experienced similar GI distress. Therefore, it is important to test faecal and urine samples to exclude a potential alternative route of transmission, especially through health care workers, patients etc.

4. Transmission of SARS-CoV-2:

After reporting the first case of transfer of SARS-CoV-2 infection from animal to human, several cases have been reported for local transmission and most seriously community transmission, which further led to pandemic state [18]. Based on the cases of infected people exposed to Wuhan seafood market, where live animals are routinely sold, it was suggested that origin of SARS-CoV-2 could be zoonotic. Various efforts and retro search have been made to identify a reservoir host or intermediate carriers from where infection might be transmitted to humans. Earlier, two species of snakes were identified as a possible reservoir of SARS-CoV-2, however, till date, there is no consistent evidence of CoVs reservoirs other than mammals and birds [29, 37].

According to reports, the human-to-human transmission of SARS-CoV-2 is possible, when an individual is under incubation stage or showing symptoms, whereas some individuals are contagious and remain asymptomatic (i.e. superspreaders). Transmission is notified to be occurred via inhalation of respiratory droplets (small size >10 μm) of exhaled virus from an infected person (within 1 m). The virus remains airborne for prolong periods, in contact of infected surfaces like skin-to-skin, touch of an infected inanimate object than mediates it through the mouth, nose, or eyes [4, 30]. The SARS-CoV-2 infection is reported to survive for several hours on contaminated metal surfaces, sterile sponges. The latex surgical gloves (forgot to change during handling of infected patient), increase the opportunity for transmission via touch. Moreover, the relative contributions of large

respiratory droplets, smaller airborne aerosol (<5 μm) and direct surface contacts to the transmissibility of SARS-CoV-2 still need to be evaluated to enable an effective control over transmission and infection.

The faecal transmission routes should also be considered, as the SARS-CoV-2 virus has been positively detected in stool samples of infected patients [31]. Earlier, it has been reported that SARS-CoV can survive in stool samples up to 4 days [6]. In other studies, the presence of CoVs have also been reported water, sewage and pure or pasteurized settled sewage where virus remains infectious for 3 days to 3 weeks [38]. Presence of stools of an infected patient in wastewater may generate a further transmission routes via generation of virus-laden aerosols during wastewater treatment. For example, a contaminated faulty sewage system in a high-rise housing estate reported in Hong Kong in 2003 was linked to be SARS outbreak in surrounding [39]. Therefore, the role of the aerosol arising from contaminated sewage in the transmission of SARS-CoV-2 is a potential cause of transmission of infection and need to investigate further.

Further, airborne dust is also possible alternate transmission route in respiratory diseases. Earlier reports have proved that transmission of infectious diseases is linked to the presence of microorganisms in an airborne particulate matters (PM)/ airborne dust [40]. The poor nationwide air pollution is frequent in some countries (India, China, Saudi Arabia, Iran), and the role of airborne particulate matter or dust might influence the rate of transmission of viral infection. Inhalation of virus-laden fine particulate matter could transport the virus into the deeper alveolar tissue and tracheobronchial regions, and increases the chances of infectivity [4]. Surface adsorption of SARS-CoV-2 virus on PM and airborne dust can contribute to long-range transport of the virus. Thus, an investigation of the survival of SARS-CoV-2 in/or air particulate matter will help to understand and established their role in transmission of through them.

Recently, a small study was conducted by Chen et al., on pregnant women who were confirmed to be infected with the SARS-CoV-2. Though no evidence for transmission of viral infection from mother to child has been found, still the cloud of uncertainty persists [41]. Understanding of this factor is highly important as pregnant mothers are relatively more susceptible to infection via respiratory pathogens and severe pneumonia. All pregnant mothers underwent caesarean process, so it remains unclear whether transmission can occur during vaginal birth.

5. Pathogenesis of SARS-CoV-2 and clinical manifestations

The recognition and receptor binding on host cells is the first step of viral infection followed by fusion with the cell-membrane [29]. It is reasoned that the lung epithelial cells are the primary target of the virus. Thus, it has been reported that human-to-human transmissions of SARS-CoV occurs by the binding between the receptor-binding domain of virus's spike proteins and the cellular receptor known as angiotensin-converting enzyme 2 (ACE2) receptor [20, 22]. Importantly, the sequence of the receptor-binding domain of SARS-CoV-2 spikes is similar to that of SARS-CoV. It suggests that entry into the host cells is most likely via the ACE2 receptor [20] as depicted in Figure 3. The SARS-CoV-2 virus or virion contain four different proteins (envelope, spike, membrane and nucleoside) and an RNA strand as shown in Figure. The spike protein helps to establish a contact with the human cell and it has region which recognize the ACE2 receptor in human cell especially respiratory cell. As virion binds with ACE2 protein, an another TMPRSS2 protein (on exterior cell wall) help to open the spike protein and cleave the membrane and allowing entry of virion particle. After that, virion releases its RNA strand, which is translated into protein and further form more RNA strands. During cell development (Fig.3), one strand of virion enters the Golgi bodies and evolving new virion those come out of cell where membrane and envelop proteins

intrigued. One virion particle has ability to make several hundred new virions in the way and each capable to infect new cell.

Pathogenesis of SARS-CoV-2 producing acute respiratory disorder and pneumonia like symptoms seems to be particularly complex and responsible for initiating an excessive immune reaction in the host. The cytopathic effect (CPE) and cytokine storm are related to clinical conditions of SARS-CoV-2 infected patients [42]. The pro-inflammatory cytokines and chemokines including interleukins 6 (IL-6), tumour necrosis factor (TNF), and macrophage inflammatory proteins are elevated and plays an important role in immunopathology of SARS-CoV-2 patients [43]. During infection period, cytokines express in lung epithelial cells, leucocytes, and dendritic cells via the activation of pattern recognition receptors (including the Toll-like receptors TLR3, TLR7, and TLR8), retinoic acid-inducible gene I, and the NOD-like receptor family members. Also, the direct virus-induced tissue damage and synergistic cytokine effect cause extensive tissue damage or multiple organ dysfunction. Abundance of ACE2 protein on lung alveolar epithelial cells and enterocytes of small intestine remarkably helps to understand the routes of infection and disease manifestations. The IL-6 activate leukocytes and promote differentiation of B lymphocytes and alter the cell replication. IL-6 also stimulates the production of acute phase proteins, and plays a role in the thermoregulation and anti-inflammatory response [44]. Furthermore, the deficiency of IL-6 and antiIL-6R monoclonal antibody led to the persistence of influenza like infection. Additionally, the lymphocytes lack ACE2 receptors and compromises T lymphocytes. Mostly, SARS-CoV-2 patient's similar symptoms, such as fever, malaise, influenza like features, however, some patients rapidly develop acute respiratory disorders (ARDS) and multiple organ failure. Clinical examination results in a decreased in peripheral lymphocytes counts, and lymphocytopenia (due to reduction of CD4 T and CD8 T cells). Importantly, ACE2 is a regulator of blood pressure and an attack of SARS-CoV-2 virus on

ACE2 receptor in endothelial cells responsible for coagulation, hypotension, cardiac injury, kindly dysfunction and secondary infections [42].

Figure 3

6. Therapeutics and Treatment options:

Till date, there is no specific antiviral treatment or vaccine available for treatment of SARS-CoV-2 infection. The molecular interaction between the virus cell receptors and host cell, mainly with the surface spike glycoprotein(s) is particularly important for the development of antiviral treatment. Treatment of such severe influenza still presents multiple challenges. There are several trails ongoing to discover a potential antiviral treatment for SARS-CoV-2. Presently, the only option available is using broad-spectrum antiviral (Nucleoside analogues and HIV-protease inhibitors) drugs combination with antimalarial and some potential antibiotics. In this work, we have reviewed all the possible ongoing treatment in the management of SARS-CoV-2 infection.

6.1. Hydroxychloroquine/ chloroquine

Recent publications [45-47] have brought prime attention to the potential benefit of chloroquine/hydroxychloroquine in the treatment of novel emerged virus pandemic. Chloroquine (CQ) is an amine acidotropic form of quinine and known for decades as a front-line drug prescribed for the treatment and prophylaxis of malaria worldwide [48]. Hydroxychloroquine (HCQ) is a 4-aminoquiniline analogue of chloroquine (having a hydroxyl group at the end of side chain of CQ). The pharmacokinetics of HCQ is similar to CQ and can be used for long periods with an improve tolerability. The sulphate form of HCQ is available for oral administration with a higher dose than CQ for rapid gastrointestinal absorption and renal elimination. Clinical indications and toxic doses of these drugs are slightly differed [45]. Regrettably, the efficacy of CQ/HCQ gradually

declined due to the continuous emergence of chloroquine-resistant plasmodium falciparum strains. Yet the activity of these molecules is not limited to malaria as they have been utilized in the treatment of autoimmune disorders (HIVs), viral infection associated with inflammation and broad-spectrum activity against a range of microbial (viral, bacterial, and fungal) infections and inhibiting their replication cycles [49-52]. During long-term therapy, clinical safety of HCQ is better than that of CQ and allows higher daily dose, yet, it has fewer concerns about drug-drug interactions. The broad-spectrum antiviral effects and clinical response of CQ and HCQ in SARS-CoV warrant a particular attention for repurposing the use of this drug in the treatment of the infection [45, 50].

6.1.1. Antiviral potential of HCQ/ CQ against SARS-CoV-2

Due to broad spectrum against viruses, including most CoVs, particularly SARS-CoV-1, and for the reason that CoV cell entry occurs through the endolysosomal pathway [53], it is reasonable in present situation of a public health emergency and the absence of any known efficient therapy to further investigate the possible effects of CQ against SARS-CoV-2. In 2005, Vincent and co-workers reported a strong antiviral effect of CQ on SARS-CoV-1 infection of primate cells treating at pre or post infection suggesting both the prophylactic and therapeutic advantage [54]. In-vitro studies has already described that the lethal infections of new-born mice infected with the recombinant HCoV-O43 could be successfully averted by administering chloroquine via mother's milk. Likewise, it has also proved to be effective against MERS-CoV [48]. Although, the in-vitro results against MERS-CoV are still controversial.

In addition to several antiviral agents, CQ and HCQ have been proposed as treatments that could reduce virus transmission. In-vitro studies have shown that CQ and HCQ both can inhibit SARS-CoV-2 transmission via alkalinisation of the intracellular phagolysosome [55],

which further prevents virion fusion and uncoating thereby decreasing viral spread. In recent report, the China National Centre for Biotechnology Development has indicated that CQ is one of the potential drug candidates for the treatment of new SARS-CoV-2 infection. It has been investigated in hospitals in Beijing, in central China's Hunan Province and South China's Guangdong Province. According to preliminary reports [56,57], approximately 100 infected SARS-CoV-2 infected patients treated with CQ experienced a more rapid decline in fever, improvement in lung function. The improved computed tomography (CT) images and shortening of recovery time compared with control groups, providing no serious adverse effects led to the inclusion of CQ in the treatment guidelines for SARS-CoV-2 by Chinese medical advisory board. As a result, CQ is probably the first molecule to be used in China and abroad as the front-line treatment of severe SARS-CoV-2 infection.

Under the Ministry of Health and Family Welfare, the Indian Council of Medical Research (ICMR) has recommended chemoprophylaxis and therapeutic use of HCQ in SARS-CoV-2 treatment with a dosage of 400 mg twice on day 1, then 400 mg once a week thereafter for asymptomatic healthcare workers treating infected patients and for asymptomatic household contacts of confirmed cases [58]. Even for treatment of diagnosed cases, there is no clinical information available except some of the pre-clinical examination reported with different aspects such as reduction of viral loads by administering HCQ in combination with azithromycin [47]. On the basis of these preliminary findings, CQ and HCQ have been prescribed to treat patient of SARS-CoV-2 to reduce their length of hospital stay and improve the SARS-CoV-2 related pneumonia. WHO has also recommended the guidelines for healthcare providers to use CQ [59] and HCQ [60] in adults and adolescents who weighed 50 kg and above. Recently published surviving sepsis campaign guidelines on the management of critically infected patients concluded that there is lack of evidence to offer any recommendation on standalone use of these drugs in patients admitted to the intensive care

unit (ICU) [61]. It seems that these discrepancies about use of antimalarial drugs in the clinical management of patients in the ICU with severe SARS-CoV-2 requires exhaustive research. This evidence, or the lack thereof, hardly justifies state-endorsed, widespread use of hydroxychloroquine for prophylaxis. A long-term use of these drugs in malaria treatment demonstrates the safety during acute administration to humans, however, one cannot ignore the minor risk of macular retinopathy, prolongation of QT interval in arrhythmic patient, renal and hepatic impairment, which depends on the cumulative doses [59,60]. A survey for adverse effects of CQ/ HCQ therapies in infected patients suffering with multiple organ dysfunction such as cardiac injury and kindly malfunction has potential to be evaluated. Currently, at least ten clinical trials are testing CQ as an anti-SARS-CoV-2 therapy [62].

6.1.2. Mode of action of CQ/ HCQ

CQ/ HCQ has multiple mode of mechanisms that may be useful in treatment of SARS-CoV-2 [45, 63]:

a. HCQ inhibit a pre-entry step of the viral into host cell via interfering with viral particles by binding to their cellular cell surface receptor by disabling angiotensin converting enzyme-2 (ACE-2) terminal glycosylation leading to change in surface morphology [54]. An association of virus and host cell is disrupted as ACE-2 is an enzyme requires by SARS-CoV-2 to attach to the host cell. CQ also inhibits quinone reductase-2, which is a structural neighbour of UDP-N-acetylglucosamine 2-epimerases [64] that are involved in the biosynthesis of sialic acids (an acidic monosaccharides) present at the extremity of sugar chains present on cell transmembrane proteins and one of important components required for ligand recognition.

b. HCQ/ CQ can impair the early stage of virus replication by increasing the endosomal pH required for the virus-host cell infusion. The inhibition likely involves the endocytosis and annulment of virus-endosome fusion.

c. CQ can also interfere with the post-translational modification of viral proteins, which involve two enzyme proteases and glycosyltransferases. The process occurs within the endoplasmic reticulum/ trans-Golgi network vesicles and may require a low pH. It localizes the M proteins in Golgi complex beyond the site, of virion budding which suggest that this drug possibly inhibit the replication of SARS-CoV-2 virion.

d. HCQ acts as an ionophoric agent for Zinc (Zn^{2+}) ions and thus increases the influx of Zn^{2+} ions into the cytoplasm of host cell regardless whether, the host target cells are infected or not [62]. Zn^{2+} ions adhere to the RNA dependent RNA polymerase enzyme of the virus and stops the SARS-CoV-2 intracellular polymerization.

e. HCQ not only attenuate the inflammatory response but also decrease the level of cytokines which is generally higher in patients infected with SARS-CoV-2. In one study, conducted by Yao et al., it was reported that the HCQ is more potent than CQ in inhibition of SARS-CoV-2 [66]. Other than this, CQ could also inhibit interleukin-1 beta (IL-1β) mRNA expression in THP-1 cells and reduces IL-1β release, tumour necrosis factor.

6.2. Ivermectin

Ivermectin is a synthetic derivative of macrocyclic lactones commonly known as avermectin's possessing a broad-spectrum antiparasitic activity. Ivermectin is an FDA-approved antiparasitic agent. In recent years, it has shown potent antiviral activity against broad range of viruses such as Influenza A, dengue virus (DENV) [66,68]. It is known to inhibit the interaction between the HIV-1 integrase protein (IN) and the importin (IMP) α/β

heterodimer responsible for import of integrase protein [69]. Since, the above mechanism of Ivermectin is confirmed to inhibit IN nuclear import and HIV-1 and DENV replication [70]. Other literature has also reported that this drug potentially inhibits the nuclear import of host cell and viral proteins, as observed in case of SV40 large tumour antigen (T-ag) protein of simian virus and non-structural protein 5 of dengue virus (DENV) [69,70-72]. However, this drug did not show any potential efficiency against Zika virus. Under a clinical trial in Thailand (2014-17) against DENV infection, it was observed that a single dose of Ivermectin is safe enough to result in significant reduction of viral NS1 protein in serum but no change in clinical benefits were notified [73].

6.2.1. Ivermectin potential against SARS-CoV-2

Although a series of clinical trials are now underway to identify the potential therapies or vaccination to respond against SARS-CoV-2. A group of researchers [73] from Monash University, Australia firstly reported that the Ivermectin has shown a broad-spectrum in-vitro antiviral activity inhibiting SARS-CoV-2. In an in-vitro experiment, they added a single dose Ivermectin to Vero-hSLAM cells infected with SARS-CoV-2 for 2 hrs. After analyzing the cell pellets and supernatant for 3 days using RT-PCR techniques to analyse the replica of SARS-CoV-2 RNA, a 93 % reduction in viral RNA in supernatant was quantified in Ivermectin treated sample over control (DMSO treated) and a 99.9 % reduction in cell-associated viral RNA. Efficiency increased to ~5000 fold by 48 hrs with no toxicity observed as reported earlier [68,70]. In the above study, a serial dilution method also produced similar efficiency with an IC50 vale of Ivermectin determined to be ~2μM.

6.2.2. Mode of action of Ivermectin

Earlier studies on SARS-CoV proteins, revealed a potential role for IMPα/β1 in a signal-dependent nucleocytoplasmic shutting of the SARS-CoV nucleocapsid protein [74], which

potentially impact the host cell division [75]. Additionally, the SARS-CoV protein (ORF6) also antagonize the antiviral activity of the STAT1 transcription factor sequestering IMPα/β1 on the membrane of rough ER/Golgi bodies [76]. Based, on the facts that the ivermectin's nuclear transport inhibitory activity may be effective against SARS-CoV-2. Caly et al., hypothesized the inhibition of SARS-CoV-2 via ivermectin by inhibiting IMPα/β1-mediated nuclear import of viral proteins (Fig.4) as already shown for other RNA viruses [73]. Further identification and confirmation of this mechanism in SARS-CoV-2 infection, still needs to be evaluated and various clinical trials are ongoing.

Figure 4

6.3. Lopinavir/ Ritonavir (protease inhibitors) and anti-viral drugs

These are antiretroviral class of drugs with a protease inhibitor action widely used for the treatment of HIV. It was recently suggested to be a potential candidate for the treatment of SARS-CoV-2 infection [77,78]. There is some previous evidence, which confirmed the effectiveness of lopinavir/ritonavir against other CoVs [67,79]. During in-vivo experiment for an open-label, non-randomised study treated with lopinavir/ritonavir and ribavirin have shown a reduced risk of severe hypoxia or death in 41 patients of SARS-CoV compared to 111 patients treated with ribavirin alone [79]. However, there is no potential evidence from randomised trials of the efficacy for treatment of SARS-CoV or MERS-CoV with lopinavir/ritonavir [80].

6.3.1. Potential mechanism of action

SARS-CoV-2 virus enter the host cells and replicate producing the strands which contain multiple copies of the viral genetic (RNA) material, which accumulate at the periphery of the host cell, further to be cleaved and released [81]. 3-chymotrypsin-like protease ($3CL^{pro}$) is an enzyme having a crucial role in processing of viral RNA [82]. Lopinavir/ritonavir are

protease inhibitor that inhibit the action of $3CL^{pro}$ and thereby disrupting the process of viral replication and release from host cells [82]. Some of the recent evidences suggested that these drugs have shown in-vitro antiviral activity against SARS-CoV-2 [77,78,83]. Most importantly, CoV proteases including $3CL^{pro}$ do not possess C2-symmetric pocket, which is a target site for HIV protease inhibitors, leading a question towards the potential potency of these HIV protease inhibitors in treating CoVs [84]. This conclude that the C2-pockets are not important for antiviral action.

6.3.2. Clinical efficiency of Protease inhibitors/ antiviral drugs against SARS-CoV-2

In Wuhan, China, an open-label random clinical trial was conducted on 199 adult patients hospitalized with SARS-CoV-2 pneumonia like symptoms [85] and treated with lopinavir 400 mg/ 100 mg twice a day for 14 days (n=99) or standard care (n=100). The baseline characteristics were similar among two groups, however, most of the patients were severely unwell and required urgent clinical attention. Even after 28 days of treatment, the intention to treat (ITT) analysis revealed no positive symptomatic relief in the primary outcome between two groups. Moreover, there was some evidence that lopinavir can reduce mortality with shortened ICU stays and time to discharge from hospital by 1 day. But no clinical improvement was observed after 28 days in lopinavir treated patients. No difference in viral clearance among both groups was marked and conditions worsen due to appearance of adverse side effects. The clinical efficacy ELACOI (Efficacy of Lopinavir Plus Ritonavir and Arbidol Against Novel Coronavirus Infection) was conducted on 44 SARS-CoV-2 infected patients. These were divided into 3 groups. No difference was observed in the primary results. The 3 groups were treated with lopinavir, umifenovir and control groups, respectively. No improvement in pyrexia, cough and lung CT after 7^{th} and 14^{th} day were observed and clinical conditions of patients further deteriorated [82]. In other studies [87,88] conducted on hospitalized SARS-CoV-2 patients treated with lopinavir and other protease

478 inhibitors showed no potential improvement in the clinical status and patients exhibited a
479 high rate of unfavourable outcomes with no difference in time for viral clearance amongst
480 who did not received this treatment.

481 Darunavir (HIV-1 protease inhibitor) is reportedly not active against SARS-CoV-2 in an
482 unpublished in-vitro study [89], whereas on February 4, 2020, a group of researchers in
483 China [90] reported that in an in-vitro experiments darunavir inhibited SARS-CoV-2
484 infection at a concentration of 300 μM and inhibition efficiency was calculated to be 280-fold
485 compare to untreated group. In-vitro studies using mouse models treated with Remdesivir (a
486 nucleoside analogue) found a stronger evidence for antiviral MERS-CoV activity compared
487 to lopinavir [91]. Wang et al. announced that the remdesivir potently blocks SARS-CoV-2
488 infection with effective concentration to inhibit 50 % cell (EC50) of 0.77 μM with a high
489 selectivity index (SI > 129.87) [92]. Holshue et al. reported that remdesivir exhibited
490 promising results in the treatment of SARS-CoV-2 infected patients in the United States [93].
491 In China, a randomized, placebo-controlled, double-blind, multicentre phase III clinical trial
492 was started on February 5, 2020 to evaluate efficacy of remdesivir in SARS-CoV-2 treatment
493 [90]. Under the trials, infected patients received an initial intravenous infusion of 200 mg of
494 remdesivir and 100 mg subsequent dose for 9 consecutive days and control group was treated
495 in similar manner with a placebo regimen. The outcomes of trial are expected to be concluded
496 by the end of April 2020.

497 In-vitro antiviral efficacy of remdesivir/ lopinavir against SARS-CoV-2 virus on Vero E6
498 cells at 50 % effective concentration was reported [83]. The ribavirin/favipiravir which are
499 under clinical trials showed no viral inhibition even at higher concentration i.e.100 μM. A
500 synergistic effect of remdesivir and emetine could help to achieve 64.9% inhibition in viral
501 yield. This prove that the combinational therapy may help to reduce the effective
502 concentration of drug and increase clinical benefits. Several groups of researchers are

503 working on this class of drugs, moreover, due to insufficient evidences the lopinavir is used
504 in healthcare for treating the SARS-CoV-2 infected patients for clinical purpose only.
505 Various dosage regimen of chloroquine, HCQ and other antiviral agents are undergoing as
506 line for treatment for chemoprophylaxis and therapeutic use are summarized in Table 1.

507 **Table 1**

508

509 **6.4. Other potential drug candidates/ therapies**

510 **6.4.1. Baricitinib:**

511 BenevolentAI's is a target identification platform and knowledge graph, which is a large
512 repository of structured medical information with abundant connections extracted from the
513 available scientific literature by a machine learning process [94]. Based on BenevolentAI
514 graph (Fig.5), Richardson et al., searched for potential approved drug candidate having
515 efficiency towards inhibiting the SARS-CoV-2 virus propagation [95]. Herein, Baricitinib
516 was identified as potential candidate which may reduce the capability of the SARS-CoV-2 to
517 infect lung cells. Baricitinib is high affinity AP2-associated protein kinase-1 (AAK1)
518 inhibiting drug with Janus kinase ½ (JAK ½) inhibition and which also bind to cyclin G-
519 associated kinase, which is a regulator of endocytosis [96]. Plasma concentration of
520 baricitinib on therapeutic dosing i.e. 2 mg or 4 mg single dose is sufficient to inhibit AAK1.
521 It has been clinically tested on a selected SARS-CoV-2 infected population using an
522 appropriate patient population to reduce both the viral entry and the inflammation in patients
523 with MuLBSTA score and also predict of viral mortality [97]. Due to high affinity of
524 baricitinib for AAK1 and JAK, ability to ameliorate allied chronic inflammation in
525 interferonopathies, pharmacokinetic properties make it a potential candidate to combine with
526 the direct-acting antivirals (lopinavir or ritonavir and remdesivir) to combat with the SARS-
527 CoV-2 pandemic [98].

528 **Figure 5**

529

530 **6.4.2. Interferon (IFN-α)**

531 According to the 5th edition of guidelines issued by WHO, antiviral drug IFN-α is
532 recommended for the treatment of SARS-CoV-2 infection [99]. IFN-α is a broad-spectrum
533 antiviral agent usually used to treat hepatitis [100], though it is reported to inhibit SARS-CoV
534 reproduction in-vitro [101]. Treatment regimen recommended for IFN-α is vapor inhalation
535 of IFN-α at a dose of 5 million U dispersed in 2 mL of sterile water for injection in adults
536 twice in a day. If IFN-α is administered with other antiviral or nucleoside analogues in
537 combination, it could be more effective in treatment of SARS-CoV-2 infection. Currently,
538 interferon beta-1a and interferon alfa-2b are under investigation as a potential candidate for
539 the treatments of SARS-CoV-2 affected people. Interferons can improve the immune system
540 by turning on dormant parts and align them towards the defence mechanism against SARS-
541 CoV-2 virus. Moreover, as interferons improve the immune system, the flu-like system in
542 SARS-CoV-2 become worsen as naturally occurring interferons are responsible for flu-like
543 system. For instance, if patient is on ventilator or ongoing asthmatic treatment are
544 administered with interferon-based medicine than that could be more catastrophic. WHO is
545 investigating different interferons to treat SARS-CoV-2 but no existing treatment exists. An
546 open randomized clinical study has been launched in China on efficacy and safety of IFN-
547 α2β in the SARS-CoV-2 treatment over 328 adults' patient and results are possible to be
548 come by June 2020 [102].

549 **6.4.3. Arbidol**

550 Arbidol (ARB) is a Russian-made potent broad-spectrum antiviral agent that demonstrated
551 activity against enveloped and non-enveloped viruses [103]. ARB is well known antiviral

552 agents in Russia, China and some of the western countries. It was developed by the Russian
553 Research Chemical Pharmaceutical Institute. Since 1990, ARB was used as OTC medicine in
554 prophylaxis and treatment of ARDS including influenza [103]. ARB exhibited molecular
555 mechanism of action against influenza viruses (influenza virus A and B), which is different
556 from other antivirals. ARB antiviral mechanism involves inhibition of virus-mediated fusion
557 with target membrane, which block the virus entry into the target cells [104]. According to
558 literature, ARB has been approved in Russia and China for treatment of SARS, influenza and
559 other viruses [105]. Recently, Deng at al., reported a combination therapy of ARB with
560 lopinavir/ritonavir with a small patient sample size [106] and very limited literature are
561 available which confirmed the successful recovery of patient treated with ARB and lopinavir
562 therapy. Zhu et al., performed their study on 50 patients divided into two group, i.e. treated
563 with lopinavir (34 patients) and second ARB (16 patients) group with a dosage of 400
564 mg/100mg of Lopinavir/ritonavir, 2 times/ day for 7 days, while the ARB group received 0.2
565 g ARB, 3 times/ day and analysed data retrospectively [107]. After 14 days of treatment, no
566 viral load was detected in the ARB treated group, moreover, the viral load was 44.1% in
567 lopinavir treated patients and no significant side effects observed in both the groups. This
568 combination therapy has been recommended by the National Health Commission and
569 National Administration of Traditional Chinese Medicine for the treatment of SARS-CoV-2
570 [105] with a limited clinical data available. In-vitro study suggested that ARB can
571 significantly inhibit SARS-CoV-2 infection at a concentration of 10-30 μM ARB [86].

572 **6.4.4. Convalescent Plasma or Blood Plasma Therapy**

573 Convalescent plasma therapy (CPT) is akin to passive immunisation and according to
574 researchers, it could be a preventive measure for the SARS-CoV-2 infection. Principle of
575 therapy is very simple and based on the premise that the plasma of a patient recovered from
576 SARS-CoV-2 contains antibodies which are highly specific and has ability to fight against

SARS-CoV-2 [108]. When antibodies obtained from recovered patients are ingested into patient under treatment it will start fighting against infection in second patient. This will be a potential measure of treatment to those who are critically affected by the virus and prevent the high-risk contacting person such as healthcare workers, immediate families of patients and other high-risk contacts.

Previously, CPT was successfully employed in the treatment of SARS [106], H1N1 [110], and MERS [108] with promising efficacy and safety. Meta-analysis from 32 studies of SARS-CoV infection and severe influenza showed a statistically significant reduction in the mortality rate over placebo under CPT [112]. A pilot study on a group of 10 patients confirmed with SARS-CoV-2 infection by RT-PCR was conducted in China to explore the feasibility of CPT [108]. One single dose of 200-mL CP transfusion injected to severe SARS-CoV-2 patient was well tolerated, and clinical symptoms promisingly improved with the increase of oxyhaemoglobin saturation within 3 days of treatment. A rapid neutralization of viremia and no significant side effects were also observed. FDA has issued and approved guidelines to health care providers and investigators to further investigate CPT efficacy from individuals who have been recovered from SARS-CoV-2 infection [113,114] and also issued guidelines for donor of CP antibodies [113]. Although, CPT might not be effective in every disease condition (due to multiple organ failure or immunodeficiency), therefore a clinical trial is required to see its feasibility and efficacy. In another report, an uncontrolled case series of 5 critically ill patients with SARS-CoV-2 and ARDS were treated with CPT containing neutralizing antibody followed by an improvement in clinical status of patients [115]. In India, Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), has received approval to use CPT for treatment of patients suffering from SARS-CoV-2 infection [116].

6.4.5. Vaccination for SARS-CoV-2

Until now, there is no evidence of any vaccination available for the treatment of SARS-CoV-2 viral infection. After WHO's response to the SARS-CoV-2 outbreak, a Research and Development (R&D) Blueprint has been initiated to accelerate the further development of vaccines and therapeutics for SARS-CoV-2 outbreak [117]. Under WHO's coordination, several group of scientists and experts with diverse backgrounds worldwide are working for the development of vaccines against SARS-CoV-2. According to one report, Bacille Calmette-Guérin (BCG) vaccine may come out as a potential candidate, however WHO does not recommend use of BCG vaccine in SARS-CoV-2 treatment as not much evidence is available on its potency [118]. Two clinical trials studies are addressing this question, and WHO will evaluate the evidence and announce when it is available. Several vaccines are undergoing trials from various organization and research group such as ChAdOx1 nCoV-19 by University of Oxford (510 estimated participants) [119] with completion by May, 2021; mRNA-1273 vaccine from Modern and Vaccine Research Centre (this vaccine targets the Spike (S) protein of the CoVs) [120] and other vaccine forms [121].

7. Miscellaneous

A continuous attempt to find out the potential treatment therapy is going worldwide. Some other individual drug or class of drugs have been found to be effective in in-vitro experimentation against similar virus physiology, such as fusion peptide (EK1) [124], RNA synthesis inhibitors (such as TDF, 3TC), antibiotics (azithromycin) [46], anti-inflammatory drugs like hormones, neuraminidase inhibitors (NAIs) such as oseltamivir (oral administration), and immunomodulators [36]. Additionally, the Chinese medicine, such as ShuFengJieDu Capsules and Lianhuaqingwen Capsules, have shown their potential in the prevention and treatment of new respiratory infectious diseases such as influenza A (H1N1) [123]. The above medicine in combination with antiviral agents can decrease the time required for viral shedding or improve the patient conditions by improving the health

627 conditions. Nonetheless, the efficacy and safety of above described drugs in SARS-CoV-2
628 infection is further needed to be evaluated and confirmed by clinical experiments.

629 WHO has launched a "Solidarity", an international clinical trial finding out an effective
630 treatment for SARS-CoV-2 [124]. Herein, the four treatment options will be evaluated to
631 assess their efficacy and safety against viral infection and later other potential drug
632 candidates might enter the regimen. Until and unless there are satisfactory outcomes from the
633 various trails across the world, WHO and other regulatory bodies such ICMR, EU are
634 cautious against physicians and healthcare professional recommending or administering an
635 unproven treatment to patients suffering with SARS-CoV-2. The agencies are also concerned
636 by the individuals who are self-medicating with any kind of medication which thought to be
637 effective such as CQ and causing serious side effects on themselves.

638 Very recently, a group of researchers from Indian Institute of Technology, Delhi and
639 Advanced Industrial Science & Technology (AIST), Tsukuba, Japan revealed that
640 Ashwagandha (*Withania somnifera*, family- solanaceae) and honeybee propolis contains
641 certain bioactive such as withanolides (from Ashwagandha) and Caffeic Acid Phenethyl Ester
642 (CAPE, from honeybee propolis-fungal resinous mixture) that interact with a highly
643 conserved protein, M^{pro} of SARS-CoV-2 virus [125] utilizing molecular docking tools. They
644 found that Wi-N (withanone) and CAPE significantly bind to the substrate-binding pocket of
645 M^{pro} SARS-CoV-2 with an equivalent efficacy and binding energies to an already claimed N3
646 protease inhibitor. The superimposition confirmed that all the ligands exhibits similar binding
647 mechanism and binding free energies calculated using MM/GBSA for N3 inhibitor, CAPE
648 and Wi-N were also comparable. This study predicted that these natural compounds possess
649 the potential to inhibit the enzymes essential for virus survival and will helps in initial
650 screening of anti-SARS-CoV-2 drugs.

8. Conclusion and Future perspectives to control to SARS-CoV-2 pandemic

Since, December 2019, a respiratory disease caused by SARS-CoV-2 is an ongoing threat to human race. This viral strain infects host cells through ACE2 to cause SARS-CoV-2 infection, and also causing damage to the respiratory and myocardium, although the specific mechanisms are still uncertain. The patients infected by SARS-CoV-2 infection have an adverse prognosis, thereby, a particular attention is required in patients already suffering with CVD, ARDS and with low immunity responses. Based on the epidemic and spread in several country, WHO declared this infection as a pandemic. The SARS-CoV-2 virus has an incubation period of 2-14 days and usually the infection is confirmatory tested by PCR test and chest scan. Till date, there is no medical treatment or vaccination is available to treat pandemic except the essential supportive treatments with antiviral agents, moreover the higher dosage of this antiviral has their own adverse effects. Therefore, there is an immediate need of medical treatment or vaccination for SARS-CoV-2. The BenevolentAI knowledge graph [94] has intrigued features of integrated biomedical data which could be a possible link in identifying the treatment. The detection and quantification of biomarker such as cytokinin's, interferons are important and useful in early screening of infection. The viral strands have altered shelf life at various surfaces. The presence of virus in human faecal matter is also confirmed where virus can survive for long duration. In underdeveloped nation, where faecal decomposition take place in an open area the rate of contact of virus through the above might increase. Hence, screening of faeces of SARS-CoV-2 infected patient is a promising challenge to understand transmission. Outer part of SARS-CoV-2 is made up of lipids, that can be disrupted by surfactant or hand washing. As discussed above the CPD

675 (Convalescent Plasma or Blood Plasma Therapy) could be a potential approach [108] in
676 treatment of SARS-CoV-2, as the patient recovered from SARS-CoV-2 infection has
677 developed antibody as a response of their immune system. These antibodies administered into
678 an infected patient will help to provide a quick response against the infection. However, the
679 parameter of clinical diagnosis in this procedure will be required such as the patient clinical
680 status and diagnosis from other disorders.

681 The natural resources such as plants and resinous matter possessing the antiviral
682 characteristics are promising candidates to be screened as lead molecules for drug-designing
683 and development for the treatment of SARS-CoV-2. These existing natural resources will
684 serve as an important purpose of saving time and cost-effective methods in the current
685 scenario of international health emergency and lack of treatment modalities.

686 In future, development of biosensor (a device which can transform the biochemical signal
687 into measurable signal) with ability of either detecting the SARS-CoV-2 virus or biomarker
688 associated with SARS-CoV-2 infection [126], wearable devices with ability to detect the
689 clinical symptoms/ physiological signs related to the onset of SARS-CoV-2 such as fever,
690 cough, and fatigue [127], and development of vaccine could be a potential achievement
691 towards early detection and management of SARS-CoV-2 pandemic. Based on our
692 experience [128, 129] and existing literature [130,131], an analytical methodology could be
693 proposed that the biosensor could be a promising solution addressing the fast screening of
694 SARS-CoV-2 infected patients and an alternative to the routinely employed RT-PCR
695 technique. Firstly, an optical biosensor can detect the presence of SARS-CoV-2 virus in
696 exhale air or sneeze droplets or swab sample of a person, where a biochemical signal
697 generation is converted into a measurable optical signal such as colour change, coagulation,
698 visual signal generation. For example- fluorescently labelled biorecognition element (nucleic
699 acid, antibody, peptide) can be immobilized on the surface of nanoparticle (having ability to

quench the fluorescence such as titanium dioxide nanoparticle, carbon nanotubes, graphene etc). In the absence of an antigen (virus in the present case), the fluorescence of labelled-bioreceptor will be quench due to fluorescence energy transfer between fluorescently labelled bioreceptor and nanoparticle. Whereas, in the presence of antigen, the high affinity molecular interaction between antigen and bioreceptor will led to conformational changes in the structure of bioreceptor and results in fluorescence recovery due to desorption from the nanoparticle surface or decrease in FRET phenomenon [128]. This signal can be qualitatively analysed for the presence of virus molecules either by switch on-off system [130] or could quantitatively calculating these signals against the concentration of antigen [131]. In the second strategy, an aptasensor and immunosensor could be designed in a following manner: first, the capturing of virion particle utilizing immobilized aptamer/ antibody on gold quartz crystal surface mounted on an electrochemical quartz crystal nanobalance. The binding of virion molecule to receptor will results in change in resonant energy or mass over the crystal surface and later the surface could be regenerated with a regenerating agent i.e. 4 % w/v glycine or 0.1 M glycine with lowering of pH will break the binding interaction or 1 % SDS [132,133]. Secondly, the addition of a surfactant (such as CTAB) in the antigen eluted fraction will perform the cell lysis by disrupting the cell membrane of virion molecule and later the addition of gold nanoparticle will convert it into a colorimetric detection based on the CTAB induced aggregation of AuNPs [134]. We have proposed these strategies based on earlier experience and the available literature; however, the reliability and reproducibility of designed strategies could not be predicted until the experimentations are done.

The current molecular diagnosis used for the detection of SARS-CoV-2 infection using RT-PCR takes 3-4 hrs time including the various steps of preparation of viral RNA, incubation and washing etc. Therefore, the highly sensitive, fast and effective diagnostic methods that could directly detect these antigens in complex matrix with less or no sample

preparation steps is of immense need. Recently, two biosensing platforms based on dual functional plasmonic photothermal coupled with surface plasmon resonance [135] and a field-effect transistor (FET)-based biosensor [136] were reported for detection of SARS-CoV-2 virus in clinical samples such as human nasopharyngeal swab specimens. The dual-functional LSPR biosensor [135] exhibits a high sensitivity towards SARS-CoV-2 sequences and offers a lower detection limit down to the concentration of 0.22 pM and allows precise detection of the specific target in a multigene mixture. The FET-based biosensor exhibited a detection limit of 1 fg mL^{-1} and 100 fg mL^{-1} SARS-CoV-2 spike proteins in phosphate-buffered saline and clinical transport medium, respectively. Additionally, it successfully detected 1.6×10^1 pfu mL^{-1} SARS-CoV-2 in culture medium and 2.42×10^2 copies mL^{-1} in clinical samples. The above platforms provide a reliable and easy-to-implement detection platform to improve the diagnostic accuracy providing less or no sample pre-treatment and will relieve the pressure on the PCR-based methods.

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Legends of Table and Figures

Legend of Table

Table 1: Recommended guidelines of various dosage regimen in SARS-CoV-2 treatment

Figure 1. (A) Worldwide mapping of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) pandemic (Source: World Health Organization accessed on 22 May, 2020, Time: GMT+5.30); (B) Occurrence of SARS-CoV-2 across different states of India as on May 22; (C) One month data of active, cured, deceased SARS-CoV-2 cases across India as on May 22 (Source: Ministry of Health and Family Welfare, Government of India accesses accessed on 22 May, 2020, Time: GMT+5.30 and https://www.covid19india.org/).

Figure 2. Data representing percent of SARS-CoV-2 cases in 11 major countries affected. The Data for the countries are: India (Jan 30- Apr 25); Unites States of America (Jan 30- Apr 26); Spain (Jan 31- Apr 25); Italy (Jan 29- Apr 25); Germany (Jan 28- Apr 25); The United Kingdom (Jan 31- Apr 25); France (Jan 24- Apr 25); Iran (Jan 19- Apr 25); China (Jan 11- Apr 26); Russia (Jan 31- Apr 25); Australia (Jan 25- Apr 26) (Source- WHO, Ref. 19).

Figure 3. Schematic representation of SARS-CoV-2 genesis and transmission inside human system.

Figure 4. Proposed antiviral mechanism of ivermectin against SARS-CoV-2. In the absence of ivermectin, IMPα/β1 binds to the CoV cargo protein in the cytoplasm and cross the membrane barrier through the nuclear pore complex (NPC) into the nucleus where the complex dissociate and viral cargo infect and reduce the host cell's antiviral response. In

presence of ivermectin, ivermectin binds to and destabilises the Impα/β1 heterodimer, hence preventing the binding of Impα/β1 to the viral protein and not allow to cross membrane to enter nucleus, thereby no infection and improved antiviral response. (Figure illustrated from Ref. 70.)

Figure 5. BenevolentAI knowledge graph integrates biomedical data from existing structure and unstructured sources. Constructed on the basis of fleet of algorithms to establish new relationships suggesting new ways of treatment for SARS-CoV-2. SARS-CoV-2 = novel COVID-19 virus, AAK1=AP2-associated protein kinase-1, JAK1/2 = janus kinase 1/2, GAK = cyclin G-associated kinase. (Figure illustrated from Richardson et al., 2020 and Seglar et al., 2018).

Table 1. Recommended guidelines of various dosage regimen in SARS-CoV-2 treatment [52,55,87]

S.No.	Drug	Administration	Dosage	Duration of treatment
1.	Chloroquine phosphate	Oral	500 mg twice in day	<10 days
2.	Hydrochloroquine (HCQ)	Oral	For asymptomatic healthcare personals-400 mg twice on day 1, then 400 mg once a week For home quarantine contact with positive cases-400 mg twice on day 1, then 400 mg once a week	For 7 weeks For 3 weeks
2.	Lopinavir/ ritonavir	Oral	200 mg twice in day (2 capsule 50 mg each time)	<10 days
3.	Ribavirin	Intravenous infusion	500 mg twice/thrice in day in combination with lopinavir/ritonavir or IFN-α	<10 days
4.	IFN-α	Vapor inhalation	5 million U twice in day	<10 days
5.	Arbidol	Oral	200 mg thrice in day	<10 days

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