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The Chemical Sciences' Advances on Coronavirus Disease 2019 (COVID-19)

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ABSTRACT

The novel β-coronavirus (SARS-CoV-2) causes coronavirus disease (COVID-19), which is presently a pandemic affecting numerous nations worldwide including a grim fatality of over 9 lakhs deaths till August, 2020. But even after the 9 months of the outbreak of this deadly disease, there is no particular medication or vaccine so far that can be recommended for the treatment of COVID-19 patients. Therefore, chemists are struggling to understand and dissect the viral structure of this SARS-CoV-2, unwind its pathogenesis and pinpoint its vaccines and therapies as well. In this current study, the author endeavor to sum up the ongoing advances of chemical sciences about COVID-19 focusing mainly on the developments of its therapeutics.

KEYWORDS

Coronavirus, SARS-CoV-2, COVID-19, Drugs, Vaccines, Therapeutics.

INTRODUCTION

Coronaviruses (CoVs) are members of highly infectious family of viruses and their particles are mostly pleomorphic and often spherical with sizes ranging from 80 to 120 nm in diameter [1]. These CoVs are categorized into four subfamilies-α-/β-/γ-/δ-coronaviruses (CoVs). Among these four sub-classes, γ- and δ-CoVs are tend to taint birds whereas α & β-CoVs mainly infect mammals [2]. Particularly, β-CoV is mainly responsible for human infections. When it enters into the human body it assumes unpredictable characters and causes normal to severe infections from minor cold and fever to fatal respiratory blockages like severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS). A new β-coronavirus *i.e.* SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) has appeared in Wuhan (Hubei province, China) in December 2019 which is answerable for the disease COVID-19 [3]. SARS-CoV-2 and SARS-CoV are nearly identical twins [4]. But the noticeable difference is that the spike glycoprotein of SARS-CoV-2 has a furin-like cleavage site which was not found in the previous SARS-CoV of the same clade [5]. Both viruses use the angiotensin-converting enzyme-related carboxypeptidase (ACE2) receptor to get access to the cells. For entering into the human cell, first the surface spike protein of SARS-CoV-2 binds to the human ACE2 receptor through its receptor-binding domain (RBD). After cell entry of SARS-CoV-2, the virus first uncovered its RNA to generate its RNA replicase

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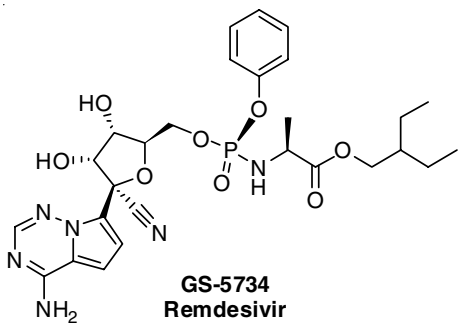
resulting in the formation of an RNA replicase-transcriptase complex. The complex then forms RNA negative strands through the process of transcription and replication. This newly formed RNA negative strands then translates into the auxiliary proteins of the virus. Combination of this auxiliary proteins with RNA in the cytoplasm amass translates into new viral particles that are released from the contaminated cells by exocytosis to taint other cells. COVID-19 infection can be understood through the low blood lymphocyte count *i.e*. by lymphopenia. This key feature of COVID-19 infection is very much informative to doctors to understand the patient's seriousness [6]. Now, this SARS-CoV-2 is pandemically affecting most of the countries worldwide, but the researchers are still not able to find any specific drug or vaccine for the treatment of COVID-19 patients. Chemistry always undertakes a spearheading role in virology suggesting pathways for the remedies from several fatal viruses like SARS-CoV-2. Therefore, this survey aims to endeavor a concise rundown of recent advances of chemical sciences to develop diagnostic and therapeutic remedies to prevent the spread of SARS-CoV-2.

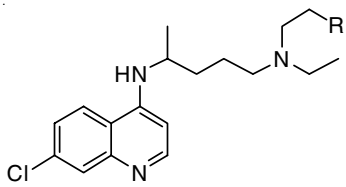
Remdesivir as anti-SARS-CoV-2 drug: The first COVID-19 patient in the USA gave good responses within a day of treatment with remdesivir (Fig. 1) [7]. This case arouses a new hope in the public mind that remdesivir could be turned into a specific drug for COVID-19. However, the main concern for the severe cases is to reduce the quantity of newly formed viral replicas in the body as soon as possible to rescue the patient from the ventilation. Although the efficacy of remdesivir drug is need to be tested in the current phase III clinical trials by the pharmacokinetics and kinetics of COVID-19. In the opening speech on COVID-19 on February 20, 2020, the Director-General of the World Health Organization (WHO) commented on remdesivir drug in the treatment of COVID-19 with expecting good preliminary results of the two clinical trials of remdesvir. On February 24, the WHO makes a choice of certainty for Gilead Sciences′ trial of remdesvir as antiviral medication demonstrating that remdesivir has a high potential and may lead to the best drug for the treatment of COVID-19. More significantly, one report showed that remdesivir improved one CIVID-19 patient from the ventilation state [8].



GS-5734
Remdesivir

Fig. 1. Remdesivir

Chloroquine/Hydroxychloroquine as anti-SARS-CoV-2 drug: Chloroquine and hydroxychloroquine (Fig. 2) have shown to inhibit viral infection into cell culture, which lured investigators to expect that they have an *in vivo* antiviral effect [9-11]. Despite the absence of the adequacy of the efficacy of



Chloroquine, R = H
Hydroxychloroquine, R = OH

Fig. 2. Hydroxychloroquine/chloroquine

their clinical tests, chloroquine [12-15] and hydroxychloroquine [16-18] have been profusely used for the treatment of SARS-CoV-2 infection. In February 2020, it was announced in China that chloroquine is preferable to be more effective than control treatment in clinical trials of patients with COVID-19 [13]. Officials confirmed that chloroquine treatment prevented worsening of pneumonia, improved findings on lung imaging, facilitated conversion to virus-negative status and diminished sick period, without significant side effects [13]. These results prompt to a panel of recommendations in that country for its use in COVID-19 and subsequently leading to the world-wide utilization of hydroxychloroquine for COVID-19 [14]. A recent paper reported that both chloroquine and antiviral drug remdesivir inhibited SARS-CoV-2 *in vitro* and recommended these drugs to be assessed in human patients suffering from COVID-19 [20]. Right now, not less than ten clinical trials in human patients are in progress for testing chloroquine as an anti-COVID-19 therapy [21].

Ribavirin as anti-SARS-CoV-2 drug: Ribavirin (Fig. 3) is a guanosine analog that interferes with the replication of RNA and DNA viruses [22]. In the first three reported case series of COVID-19 treatment (an aggregate of 180 cases Wuhan, China; 1 case from Washington, USA), no patient has yet been treated with ribavirin [23]. Hopefully, the announcement of new clinical studies will offer new evidence of the efficacy of ribavirin also when added with other drugs like lopinavir, ritonavir, interferon-β1b, *etc*. for a clinical deal with COVID-19 [23,24].

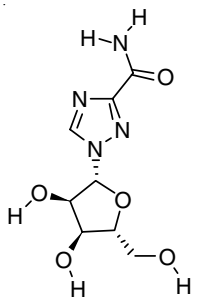


Fig. 3. Ribavirin

Theaflavin as anti-SARS-CoV-2 drug: Theaflavin (Fig. 4), a polyphenolic compound present in black tea, is thought to be responsible for the medicinal value of black tea. Theaflavin and theaflavin gallate derivatives have shown wide-spectrum of antiviral activity against several viruses including influenza A and B viruses and hepatitis C virus [25,26]. Very recently, Wu *et al*. [27] proposed that theaflavin may have antibacterial activity against SARS-CoV-2 by targeting RdRp of SARS-

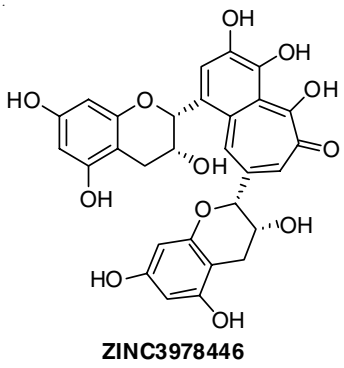


Fig. 4. Theaflavin

Cov-2, which was well documented by a molecular docking study. In the case of coronaviruses, the presence of the protease *i.e.* RNA-dependent RNA polymerase (RdRp), which is mainly responsible for catalyzing the replication of RNA from RNA layout, throws therapeutic challenges to the researchers in the field. The investigators demonstrated that theaflavin has the lowest idock and lower binding energy in the catalytic pocket of SARS-CoV-2 RdRp because of its formation of additional hydrogen bonds and π-cation interaction with the catalytic pocket of SARS-CoV-2 RdRp [27].

Angiotensin-converting enzyme 2 as anti-SARS-CoV-2 drug: Angiotensin-converting enzyme 2 (ACE2) is a metalloproteinase and a homologue of carboxypeptidase ACE [28]. Cheng *et al*. [29] reported organprotective effect of ACE2 and its impact on the prognosis of COVID-19. The investigators found that SARS-CoV-2 attacks cells by binding spike proteins (S-proteins) to the ACE2 and thereby suggesting that ACE2 may be a potential invention in the treatment of SARS-CoV-2 infection [30]. Xi *et al*. [31] also studied the cyclodextrin-soluble angiotensin-converting enzyme 2 (CD-sACE2) inclusion compounds in the treatment of SARS-CoV-2 infections by blocking S-proteins. Cyclodextrin (CD) is a sort of macrocyclic molecule linked by the pyranose unit through the α-1,4-glycoside chain. They are capable of enclosing highly hydrophobic molecules (guest molecules) in their hydrophobic cavities (host), shaping host-guest complexes. Therefore, the development of a complex of CD and sACE2 can effectively improve the water solubility of sACE2 and hence it meets the necessities for drug atomization inhalation. The inclusion compounds first release sACE2 after entering into the body *via* atomization or other medical applications and the released sACE2 then combines with SARS-CoV-2 S-proteins to destroy the virus's efficiency to contaminate and destroy human cells. Therefore, CD- sACE2 inclusion compounds can effectively treat COVID-19. Král & Han [32] also emphasized the presence of ACE2-based peptide inhibitors in SARS-CoV-2 and established their study through a computational design.

Niclosamide as anti-SARS-CoV-2 drug: For several decades, niclosamide (Fig. 5) has been extensively used in humans to treat tapeworm infections. Niclosamide is an FDA recommended anthelminthic drug and right now listed in the World Health Organization's list of essential medicines [33]. Niclosamide restricted the cytopathic effect (CPE) of SARS-CoV at very low concentration dose of 1 μM. It inhibited SARS-CoV replication with an EC_{50} value of less than 0.1 μM in Vero E_6 cells

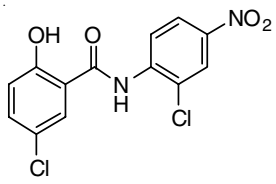


Fig. 5. Niclosamide

[34]. It also inhibits MERS-CoV replication by up to 1000-fold at 48 h p.i. at a concentration of 10 μM in Vero B4 cells [35]. As SERS-CoV-2 belongs to the same breed as β-coronavirus as in SARS-CoV and MERS-CoV and there is almost 80% sequence identity to that of SARS-CoV [36], it is expected that niclosamide could be a potential drug in combating COVID-19 [37].

Lopinavir/ritonavir as anti-SARS-CoV-2 drug: In 2003, a SARS study group from the University of Hong Kong first noticed that the cytopathic effect of the SARS coronavirus was initiated by lopinavir at 4 μg/mL after 48 h of incubation [38]. It was observed that by the treatment of SARS patients with lopinavir/ritonavir drug (Fig. 6), the usage of steroid and hospital-acquired infections *i.e*. nosocomial infections had decreased. It was also noticed that these SARS patients also had a rising of peripheral lymphocyte count with the concomitant decrease of viral load after treatment with lopinavir/ritonavir drug [38]. With this observation, analysis of lopinavir and ritonavir were done as SARS-CoV inhibitors [39,40]. A recent report from Rungrotmongkol's group [41] revealed that both lopinavir and ritonavir communicated well with the residues at the active sites of SARS-CoV 3C-like protease (SARS-CoV $3CL^{pro}$). Besides, ritonavir could communicate with the oxyanion hole residues N142 and G143 employing the formation of two hydrogen bonds. All these findings predict that the two HIV-1 protease inhibitors, lopinavir and ritonavir, could be effective medications to battle COVID-19 [41].

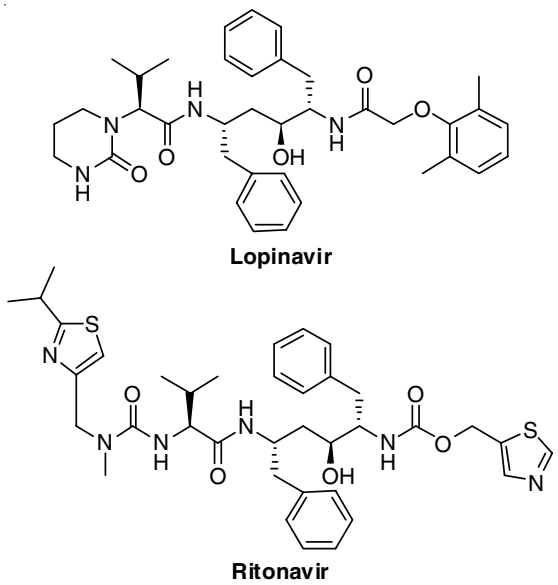


Fig. 6. Lopinavir and ritonavir

Tocilizumab as anti-SARS-CoV-2 drug: Tocilizumab with molecular formula $C_{6428}H_{9976}N_{1720}O_{2018}S_{42}$ is an immunosuppressive drug. It was first endorsed for the treatment of

rheumatoid arthritis and systemic juvenile idiopathic arthritis, then for cytokine release syndrome (CRS) in patients receiving CAR T cell therapy, and is currently being further repurposed for the COVID-19 pandemic [42]. It is a humanized monoclonal antibody against the interleukin-6 (IL-6) receptor. SARS-CoV-2 infection results in monocyte, macrophage, and dendritic cell activation which released IL-6 that results in increased systematic cytokine production. This increased cytokine adds to the pathophysiology of COVID-19, including hypotension and acute respiratory distress syndrome (ARDS), which might be treated with IL-6 antagonists like tocilizumab [42]. The outcomes from clinical utilization of tocilizumab in the treatment of COVI-19 are empowering [43-48].

Moreover, favilavir is an antiviral drug that is a recommended drug in Japan for the treatment of patients with common influenza. Right now, it is used to treat symptoms of COVID-19 in China [49]. Interferon and umifenovir are also used for antiviral therapy to COVID-19 patients in China [50]. Ghosh *et al*. [51] recently reviewed the biochemical assays for 3CLpro and PLpro protease inhibitors against SARS-CoV-2. Mubarak *et al*. [52] reviewed natural products and their derivatives against coronavirus. Richert *et al*. [53] also reported a short note about the contributions of chemists to battle against SARS-CoV-2 by proposing three ways of dealing with the problem *i.e*. hand sanitizers, drug candidates and outbreak. Furthermore, the nanotechnology can also contribute significantly in the battle against COVID-19 [54].

Advances on vaccines for COVID-19: Researchers are ransacking the possible immunizations for this pandemic COVID-19. So far there are mainly four sorts of vaccines under progress to combat COVID-19 *i.e.* DNA-based vaccines, peptide based vaccines, virus-like particle vaccines, and mRNA-based vaccines [55]. On March 3, 2020, Inovio pharmaceutical, Inc. announced that they have structured the DNA vaccine called INO-4800 for COVID-19, which is awaiting test on human bodies in America in April 2020 [56]. In late February 2020, GSK declared cooperation with the Chinese firm Clover Biopharmaceuticals to assess a COVID-19 vaccine candidate [57]. Recently, Generex has also declared that they are developing COVID-19 vaccine by utilizing its li-key immune system activation and is earnestly looking towards its human clinical trials [58]. Novavax has additionally asserted that their COVID-19 vaccine candidate targeting the S protein of SARS-CoV-2 has been developed and it has started animal testing [59]. Recently Chakraborty *et al*. [60] pointed out a good observation that among the spike glycoprotein of SARS-CoV-2, 13 major Histocompatibility Complex-(MHC) I and 3 MHC-II epitopes are the best candidates to design a multi-epitopic peptide vaccine for the treatment of COVID-19. Robson [61] also studied the viral protein sequence which is suitable for a peptide synthetic vaccine for COVID-19. Ebb and flow progress and the future difficulties of peptide-based vaccines are discussed by Lai *et al*. [62]. Mederna [63] likewise declared that they also made ready the vaccine in the name of mRNA-1273 to prevent the spread of SARS-CoV-2 in human bodies.

Conclusion

The emergence of the novel COVID-19 caused by highly transmissible SARS-CoV-2 has become a major public health crisis throughout the world now. This pandemic caused by SARS-CoV-2 takes over 9 lakhs human lives so far. Yet at the same time, there is no "specific drug" or vaccine that can be recommended for the treatment of COVID-19. Along these lines, the present survey on the headways of antiviral therapeutics and immunizations might be an invaluable compendium of helpful data in this area.

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