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The broad-spectrum antiviral recommendations for drug discovery against COVID-19

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ABSTRACT

Despite to outbreaks of highly pathogenic beta and alpha coronaviruses including severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and human coronavirus, the newly emerged 2019 coronavirus (COVID-19) is considered as a lethal zoonotic virus due to its deadly respiratory syndrome and high mortality rate among the human. Globally, more than 3,517,345 cases have been confirmed with 243,401 deaths due to Acute Respiratory Distress Syndrome (ARDS) caused by COVID-19. The antiviral drug discovery activity is required to control the persistence of COVID-19 circulation and the potential of the future emergence of coronavirus. However, the present review aims to highlight the important antiviral approaches, including interferons, ribavirin, mycophenolic acids, ritonavir, lopinavir, inhibitors, and monoclonal antibodies (mAbs) to provoke the nonstructural proteins and deactivate the structural and essential host elements of the virus to control and treat the infection of COVID-19 by inhibiting the viral entry, viral RNA replication and suppressing the viral protein expression. Moreover, the present review investigates the epidemiology, diagnosis, structure, and replication of COVID-19 for better understanding. It is recommended that these proteases, inhibitors, and antibodies could be a good therapeutic option in drug discovery to control the newly emerged coronavirus.

HIGHLIGHTS

- COVID-19 has more than 79.5% identical sequence to SARS-CoV and a 96% identical sequence of the whole genome of bat coronaviruses.
- Acute respiratory distress syndrome (ARDS), renal failure, and septic shock are the possible clinical symptoms associated with COVID-19.
- Different antivirals, including interferons, ribavirin, lopinavir, and monoclonal antibodies (mAbs) could be the potent therapeutic agents against COVID-19.
- The initial clinical trials on hydroquinone in combination with azithromycin showed an admirable result in the reduction of COVID-19.
- The overexpression of inflammation response, cytokine dysregulation, and induction of apoptosis could be an well-organized factors to reduce the pathogenicity of COVID-19.

1. Introduction

Coronaviruses are recognized as an enveloped virus with non-segmented positive-sense RNA (+RNA; ~30 KB) that belong to the *Coronaviridae* and *Nidovirales* family and order, respectively. During the past few decades, the two beta-coronaviruses including Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV) got the special attention because of their lethal respiratory syndromes and high mortality rates of about 10 and 36% for SARS-CoV and MERS-CoV respectively in animals as well as human (Huang et al. 2020; Li and Liu 2020). MERS-CoV was initially reported in Saudi Arabia in June 2012, in a patient with acute pneumonia and kidney failure (Rabaan et al. 2017; Alfaraj et al. 2019). It was reported in the

dromedary camel, which revealed that these camels have a high prevalence of MERS-CoV-antibodies in some regions of Africa and Saudi Arabia. The molecular presentation of MERS-CoV revealed that it is closely related to SARS-CoV, but according to phylogenetic analysis, it has a close relationship with bat isolated coronavirus than SARS-CoV, which exposed that it was isolated from the bat (*Vespertilionidae*) before transfer into human (Cui et al. 2019). Acute respiratory distress syndrome (ARDS), renal failure, and septic shock are the possible clinical manifestations associated with coronaviruses (Rahman 2018; Chen et al. 2020).

During the last few decades, the four human coronaviruses including HCoV-229E (ß-CoV), HCoV-NL63 (α-CoV), HCoV-HKU1 (ß-CoV) and HCoV-OC43 (α-CoV) circulate among the population and known as causative agents of the common cold (approximately one-third) among human beings. The HCoV-HKU1 and HCoV-229E both are beta-coronaviruses which used 9-O-acetylsialic acids as a receptor, whereas the remaining two HCoV-OC43 and HCoV-NL63 are alpha-coronaviruses which used host proteins, including polypyrimidine tract-binding (PTB) and hnRNP-A1 as receptors (Zeng et al. 2018; Li et al. 2019). It is documented that HCoV-OC43 accounts for 30% of respiratory infections and causes frequent reinfections during life and is considered in close relationship with MERS-CoV and SARS-CoV (Kim et al. 2019; Beury et al. 2020).

However, according to recent evidence, in late December 2019, cases of pneumonia were reported in Wuhan, Hubei, China. The real-time RT-PCR and deep next-generation sequences confirmed the entry of novel coronavirus in persons present in the wet market or seafood, which called COVID-19 (2019 novel coronavirus) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Du Toit 2020; Huang et al. 2020; Lai et al. 2020) (see Supplementary material). The evidence suggested that the SARS-CoV-2 has over 79.5% identical sequence of SARS-CoV and a 96% identical sequence of the whole genome of bat coronaviruses (Zheng and Song 2020; Zhou et al. 2020). Like other two beta-coronaviruses (see Glossary) (SARS-CoV and MARS-CoV), the COVID-19 also caused the severe respiratory syndrome considered as much more severe than the previous coronaviruses (Chung et al. 2020; Lin et al. 2020). The coronavirus carries two functional domains, including the receptor-binding domain (S1) and the membrane fusion domain (S2). It is reported that two cleavage sites are located at COVID-19 domains, first is present at S1/S2 boundary and the second is present upstream of putative protein at S2. After the attack of any carnivorous inhibitors including

TMPRSS2, these spikes of glycoproteins (S1 and S2) cleaved but remain attached with non-covalently instead of disulfide bonds. Finally, the S1-domain detached from the S2-domain of the protein (Millet and Whittaker 2015; Xia et al. 2020).

Unlike humans, the occurrence of coronavirus in non-human primates, including goats, bats, camels, and other animals do not lead to lethal diseases. The emerging pieces of evidence suggested that bats play a significant role in the transmission of coronavirus between intermediate hosts and human beings, which can bind with the spike (S) proteins that increase the chances of mutation and transmission efficiency. However, there is a lack of knowledge that how host factors help in the transmission of coronavirus in the human body (Anthony et al. 2017; Rahman 2018). Despite the spontaneous emergence, the rapid response must overcome the outbreak of novel and previously reported coronaviruses. During the outbreak of coronavirus, the reverse genetic system (see Glossary) got special attention to exploring the zoonotic coronavirus due to distinct receptor interactions, including the SARS spike/ACE2 receptor interaction (Menachery et al. 2019; Gralinski and Menachery 2020). Recently *in vitro* and *in vivo* studies on different antivirals, including interferons, ribavirin, Favipiravir, chloroquine, and hydroquinone, remdesivir, ritonavir, lopinavir, inhibitors, and monoclonal antibodies (mAbs) proved as potent therapeutic agents in the reduction of previously and recently circulated coronaviruses.

The infection of coronavirus is spread over 200 countries, which is not only an alarming condition for human health, but also affecting the financial conditions and relationships between different countries (WHO 2020). Most of the countries locked their borders with neighboring nations, which would affect the import/export of several commonly used and essential things and will lead to economic loss and shortage of food. Therefore, there is a need to develop a strong and effective drug/antiviral to treat and control the deaths caused by COVID-19. In this arena, despite research papers, the review manuscripts are equally essential for highlights and recommend the antivirals, which not only gives the new and innovative ideas to the scientific community but also gives preventive information to the common population against the threat of COVID-19. However, to minimize these problems, the present review investigates the recent approaches for the treatment and prevention of COVID-19 by varieties of receptor inhibitors including interferons, ribavirin, Favipiravir, chloroquine, and hydroquinone, remdesivir, TMPRSS2, ritonavir, lopinavir,

monoclonal antibodies, Cepharanthine (CEP), Fangchinoline (FAN), bis-benzylisoquinoline alkaloids tetrandrine (TET), and synthetic and natural drugs. Moreover, the epidemiology, structure, replication, and mechanism of action of newly emerged coronavirus (COVID-19) are also discussed in the present review.

2. Epidemiology of Coronaviruses

SARS-CoV was initially reported at 2003/2004 in the Chinese population and horseshoe (Lau et al. 2005), and afterward, it was continually identified among the several species of the horseshoe in the past 13 years (Zeng et al. 2016; Luk et al. 2019). The 8,096 confirmed cases were found with 774 deaths among 11 different countries, including China, Japan, Bulgaria, Hungary, Thailand, Kenya, Italy, Slovenia, and Luxembourg during 2004 (Organization WH 2003). Unlike to SARS-CoV, the MARS-CoV was initially identified in a patient of Saudi Arabia in June 2012. According to an estimation in 2012, more than 2,100 cases were confirmed, and 730 deaths were reported. Moreover, in 2016, more than 1,782 cases were reported, and 634 deaths were associated with MERS-CoV over the 27 countries of Asia, Africa, Europe, and America. After the initial outbreak of MERS-CoV in the Kingdom of Saudi Arabia, the Korea faced the second-largest epidemic of MERS-CoV in 2015, with 186 laboratory-detected confirmed cases and 36 confirmed deaths at 20% mortality rate (Zumla et al. 2016; Organization WH 2017).

The accumulated data suggested the outbreak of newly emerged 2019 coronavirus in Wuhan, China in late December. According to WHO reports till May 5th 2020, globally 3,517,345 confirmed cases have been reported with 243,401 deaths (6.92% mortality rate).

The detailed epidemiology country wise is presented in Figure 1 (WHO 2020).

3. Structure of newly emerged COVID-19

The studies conducted on newly emerged novel 2019 coronavirus reported that COVID-19 have more than 79.5% identical sequence to bat-coronavirus. Moreover, the polyprotein namely PP1AB has more than 86% identical sequence as SARS-CoV (Chan et al. 2020; Chen, Yiu, et al. 2020). Zhou et al. (2020) reported that 20 different predicted sites for N-glycosylation are present in coronavirus. The spike (S) proteins in coronavirus formed the trimers and are located on the surface of the virus and serve as entry proteins for the infection. The trimers developed by spike proteins are broken via different cellular proteases to enable the fusion between infected cells and virus membranes (Bian et al. 2009). The cellular proteases develop two types of subunits, including S1 and S2 on the spike molecule of coronavirus. Among them, the S1 subunit bears the receptor-binding domain (RBD) which bind with ACE-2 (angiotensin-converting enzyme 2) (see Glossary) of host cells. Besides, the receptor-binding motifs (RBM), coronavirus contain trypsin abundantly on the surface of RBD which facilitate the direct bonding with ACE-2 of host cells (Kirchdoerfer et al. 2016; Walls et al. 2016). ACE-2 is known as type 1 integral protein (805 amino acids) which carry one zinc-binding consequence sequence as HEXXH-E (Güler et al. 2020). ACE-2 is a chief cell receptor for the binding of coronavirus to target cells (caused the severe acute respiratory syndrome), which is expressed in the lower respiratory tract of humans and regulate transmissions either from human-to-human or cross-species (Tang et al. 2020).
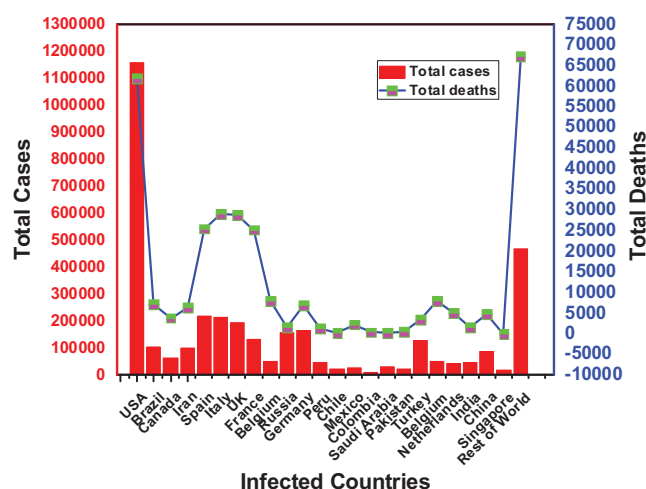

Figure 1. The country wise epidemiology of newly emerged COVID-19 as of May 5th 2020. This information is taken from WHO (2020).
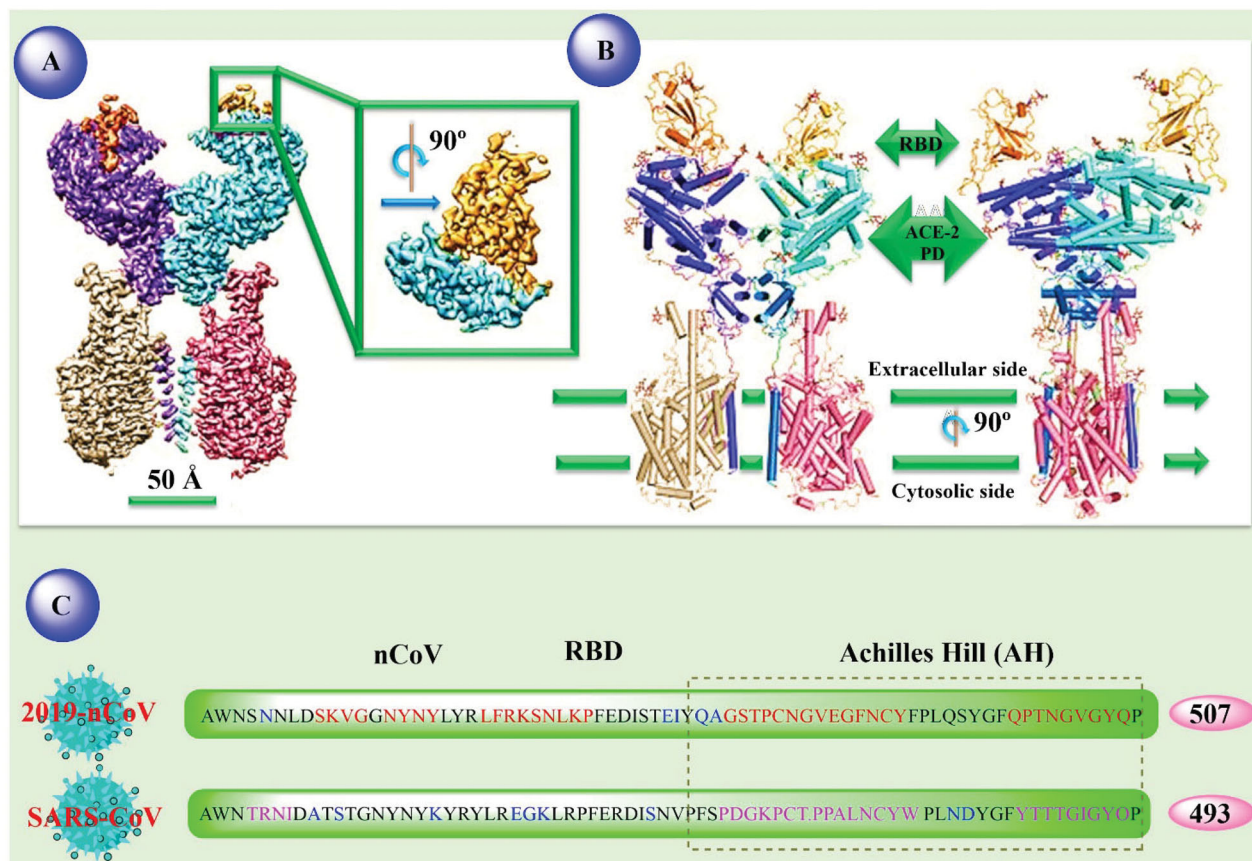
Figure 2. The Cryo-EM structure of RBD-ACE2-BOAT1 complex in SARS-CoV-2 (COVID-19). (A) Left: the reconstructed structure of the ternary complex at 2.9 A. Inset: Refined Cryo-EM map of RBD. (B) Overall structure of RBD-ACE2-BOAT1 complex. The sticks represent the glycosylation moieties, the cyan color represents the protease domain (PD), and blue is a collecting-like domain (CLD) in one of the ACE-2 protomers. (C) Comparison of epitopes in RBN domain between COVID-19 and SARS-CoV. The pink color in SARS-CoV characterizes epitopes whereas the blue and red colors in nCoV represent the epitopes and RBD cartoon, respectively. The brown dotted line is the AH for both coronaviruses (Zhou et al. 2020).

The recent evidence showed that the expression of ACE-2 (released by epithelial cells of the lung) for COVID-19 increases with diseases like diabetes mellitus and hypertension. Therefore, the susceptibility of COVID-19 for ACE-2 become increase in already infected persons. Hence, the binding of COVID-19 with ACE-2 receptor of the host cell is substantial a determining factor for the pathogenesis of the infection (Fang et al. 2020).

The emerging evidence evaluated that the spike glycoproteins are considered as an important target for antibody-based therapies and designing the new vaccines for the treatment of coronavirus (Yuan et al. 2017; Graham et al. 2019; Vlasova et al. 2020). It is reported that several other critical structures of spike molecules, including heptad repeat 1 and 2 (HR1 and HR2) domains, Central Helix (CH) are involved in the fusion of infected and host cells (Yuan et al. 2017; Xia et al. 2019). Most recently the Zhou and his research group checked the ASA profiling of RBD of a novel coronavirus

(COVID-19) and founded a vulnerable region YQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQ named as "Achilles heel" (see Glossary), which counted helpful during the binding of S protein and ACE-2 receptor (see Figure 2) (Zhou, Qi, et al. 2020).

3.1. Nucleocapsid proteins (N) of COVID-19

The most recent evidence revealed that the one-third genome of SARS-CoV-2 is encoded by four different types of viral proteins, including envelope (E), spike (S), membrane (M), and nucleocapsid (N) proteins (Sarma et al. 2020). The newly structural detailed studies on COVID-19 revealed that the nucleocapsid proteins (N) are located in the coronavirus genome, which considers as one of the most abundant proteins due to their involvement in virus replication, transcription as well as in RNA synthesis. The nucleocapsid proteins (N) formed the ribonucleoprotein (RNP) complex, which known as an important factor during viral assembly. The

nucleocapsid proteins of coronavirus systematized into two terminal domains, including the C-terminal domain (CTD) and N-terminal domain (NTD) during RNA binding. The emerging evidence suggested that the NTD is responsible for RNA genome binding of protein-protein interaction formation and folded into monomeric conformation (Nguyen et al. 2019; Lin et al. 2020).

Since the outbreak of COVID-19, there is a need to develop an effective antiviral against coronavirus. Hence, the discovery of a new anti-RNA binding inhibitor could be a potent therapeutic target against COVID-19. Most recently, Sarma et al. (2020) experimented to identify the potential inhibits against COVID-19 by viral-

RNA binding to the N-protein. They revealed that ZINC0000146942 (pyrimidine derivative; 3,4dihydropyrimidone class molecule) and ZINC00003118440 (theophylline derivative; bronchodilators inhibitor) inhibitors showed better results in binding with viral-RNA at NTD of N-protein in COVID-19.

4. Replication of Coronavirus

The coronavirus replication cycle starts after the entry of virus into the host cell, the replication cycle initiates with the translation of viral genome at 5′-proximal open reading frames (OLFs) including ORF1a and
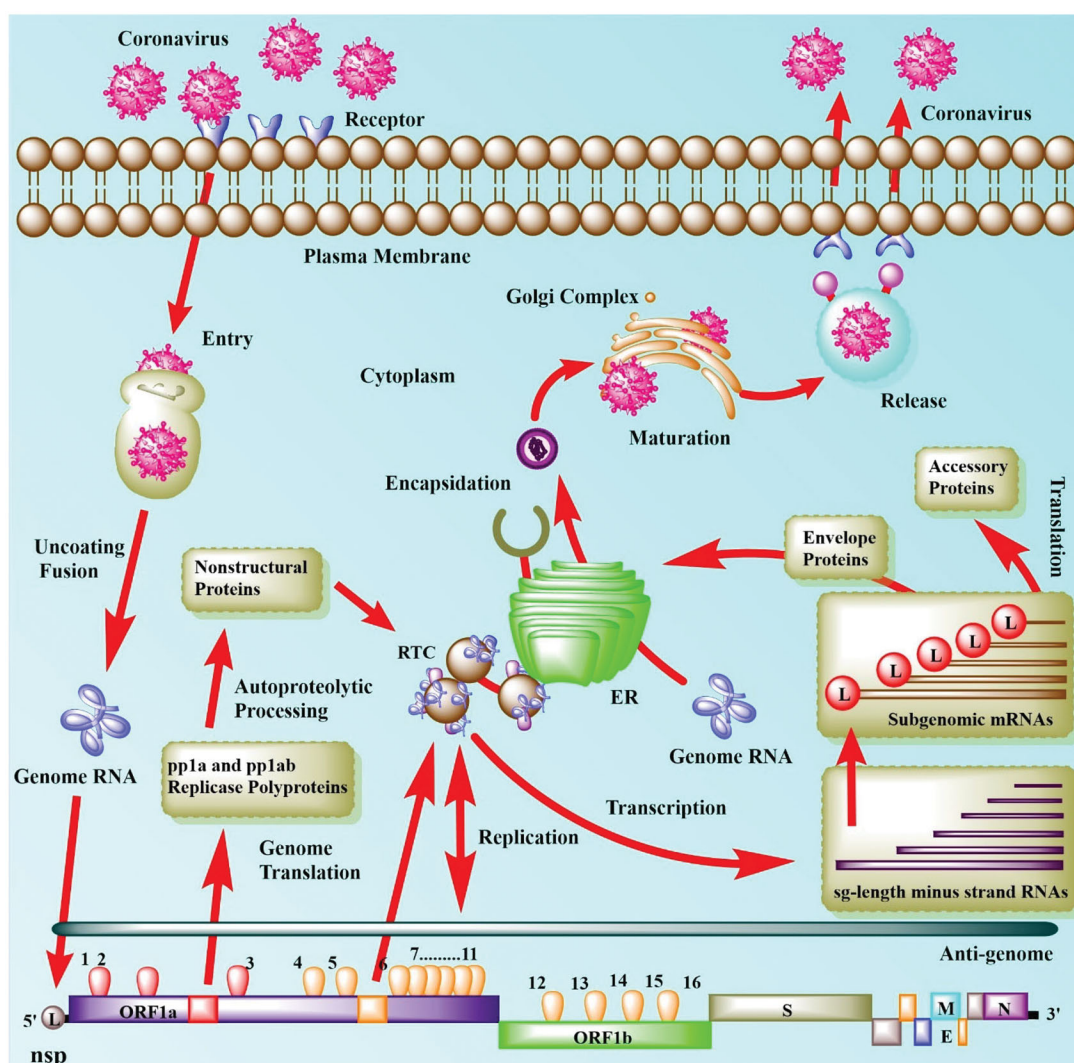
Figure 3. The schematic diagram of replication cycle of coronavirus. The virus (pink) across the plasma membrane (brown color) by receptor-mediated endocytosis (dark blue) and release into the cytosol of infected persons and yield in two replicase polyproteins including pp1a and pp1ab (in a light brown box) by genome translation. The viral nonstructural proteins (nsps) accumulates into RTC (dark brown ball with viral nsps) that resembled in minus-strand RNA formulation due to internal proteases like HAT, and TMPRSS2. The sub-genome mRNAs (brown lines with red balls), (sg)-length minus strands (purple) and full-length genome produced, and accessory proteins exist in the 3′-proximal quarter of the genome. Finally, the encapsulation of viral RNA occurs by budding in the smooth endoplasm reticulum (green) and packed in the form of nucleocapsids (light blue) by the Golgi apparatus (orange) and released from the cell via an exocytic pathway (Snijder et al. 2016; de Wilde et al. 2017).

ORF1b, which resultingly syntheses two large replicase polyproteins namely pp1a and pp1ab as illustrated in Figure 3. The formation of polyprotein, pp1ab, at the C-terminal domain involves a −1 ribosomal frameshift (RFS) into ORF1b near the *3′* end of ORF1a. This is the principal regulatory mechanism that is responsible for downregulating the expression level of ORF1b-encoded proteins in contrast to ORF1a-encoded nonstructural proteins. Both polyproteins (pp1a and pp1ab) cleaved with the help of several internal proteases (TMPRSS2) (see Supplementary Material; Abbreviation), and resulted in the assembly of viral nonstructural proteins (nsps) in the form of RTC (de Wilde et al. 2017). The proteolytic cleavage of both polyproteins (pp1a and pp1ab) by internal ORF1a-encoded proteases fallouts in the 15 mature replicases proteins. These replicase proteins comprise several types of enzymes, including helicase (nsp 13), exoribonuclease (nsp 14), RNA-dependent RNA polymerase (nsp 12), and RNA cap-modifying methyltransferases (nsp 14 and 16) which helped in the enzymatic activities and functions, necessary for viral RNA synthesis and capping (Snijder et al. 2016). Finally, after the replication and transcription, the viral genome is packed into nucleocapsids (enveloped from smooth endoplasm reticulum by budding) and ultimately leave the cell through the exocytic pathway (Ulasli et al. 2010; de Wilde et al. 2017).

5. Recommended treatments and drug discovery for Coronavirus

Unlike the influenza antivirus drugs such as zanamivir and oseltamivir, the anti-coronavirus targeting drugs are not available, but recently reported some protective candidates are present to control the coronavirus. The coronavirus antivirals must contain targeting factors that should be highly conserved for previously and novel emerged coronaviruses and essential in viral pathogenesis. The nonstructural proteins (nsps) (see Glossary) are thought to be the most conserved proteins in the replications and function of coronavirus. The structural and accessory proteins are considered as less conserved than the nsps and only involved in the synthesis of virion. However, the antivirals that helped or control the conserved host factors or proteins during transcription and replication of the virus could be a potential option to recover the emerging coronavirus (COVID-19) infections and clinical manifestations (Neuman et al. 2014; Totura and Bavari 2019). Following, we discussed the few targeting coronaviruses nonstructural, structural, and accessory proteins and therapeutic drugs that could be considered as a

revolutionary approach to control the recently reported COVID-19.

5.1. Interferons

According to previously published literature, the pegylated and non-pegylated interferons have considered as significant therapeutic agents in the treatment of HCoV infections. The interferons (IFN) showed good results both in animals and human coronavirus models. However, it is well documented that the early administration of IFN was proved as much beneficiaries as compared to delayed administration regarding treatment the loading of viral infections and improve clinical manifestations. Moreover, the early administration of IFN in combination with different agents like ribavirin represented an admirable advantage in the reduction of disease severity (Omrani et al. 2014; Zumla et al. 2016; Deng et al. 2019).

IFN- λ and IFN-αß showed a significant role in reducing the coronavirus infections in mice models. It is reported that the IFN-αß played a critical role in the restriction of replication of coronavirus by inducing the interferon stimulating genes (ISGs). A similar study on IFN-αß also demonstrated that IFN-αß could effectively control the viral disease by increasing the function and recruitment of IMM genes (Channappanavar and Perlman 2017). Channappanavar et al. (2016) reported that early administration of IFN-αß on SARS-CoV-infected mice showed the protective response in contrast to the delayed administration, which results in promoting the dysregulaton of anti-SARS-CoV immune response. However, in addition to IFN-αß, the IFN-αß-receptor blockers or antagonists are also being considered as good therapeutic options in the management of novel 2019 coronavirus. Besides IFN-αß, another type of interferon, namely IFN- λ reported in recent years to control the coronavirus, which enhance the expression of epithelial cells and inhibit the monocyte-macrophages-mediated inflammatory activity of IFN-αß (Davidson et al. 2016; Comar et al. 2019). However, the two beta-coronavirus such as MERS and SARS-CoVs effect the IFN- λ stimulating antiviral gene and AECs in an epithelial cell without over-inspiring the immune system (Channappanavar and Perlman 2017). Hence, the use of IFN- λ could be a revolutionary therapy to manage the MERS, SARS, and novel 2019 coronaviruses.

5.2. Ribavirin

During the *in vitro* study of ribavirin against SARS-CoV, it proved as an important antiviral therapeutic drug

(Cinatl et al. 2003; Kumaki et al. 2017), and no virologic effects were reported during the application of ribavirin as monotherapy (Falzarano et al. 2013; Mo and Fisher 2016). Like on SARS-CoV, the ribavirin also has the broad-spectrum antiviral activity on MERS-CoV. The *in vitro* study revealed that high medications of ribavirin effectively induced 50% inhibitory concentration (IC50) that was recorded as 41.45 μg/mL(Kumar et al. 2017). Few clinical trials of ribavirin are also reported in the literature and found that a high level of an intravenous dose of ribavirin of about 1000 mg determined 24 μg/mL (IC_{50}) (Falzarano et al. 2013). However, a study conducted by single-center RCT on SARS-CoV-infected persons reported that the ribavirin and interferon-1α have no noteworthy differences to discharge and symptom improvement (Zhao et al. 2003). Based on these significant broad-spectrum findings, the ribavirin could be a great therapeutic option to reduce the newly emerged novel coronavirus, namely COVID-19.

5.3. Chloroquine and hydroquinone

The emerging evidence reported that chloroquine and hydroquinone are considered as important and novel therapeutic targets against the newly emerged COVID-19. The chloroquine has been used as an important anti-malarial and autoimmune infection drug over the decades. However, the mechanism of action of chloroquine and hydroquinone against virus infection is still not understood clearly, but recently some evidence showed that these both drugs significantly involved in several mechanisms against viral infections (SARS-CoV) including blocking the pH-dependent phase due to their weak diprotic bases, inhibited/promote the release of IL-6 and TNF-α, and induce immunomodulatory effects (Mauthe et al. 2018; Tang et al. 2020). The most recent study on chloroquine and hydroxyquinone revealed that these drugs effectively inhibited the glycosylation of SARS-CoV-2 and worked as potent inhibitors at both stages, including entry and post-entry of the newly emerged coronavirus (COVID-19) on VeroE6 cell line. This *in vitro* study also reported that the chloroquine and hydroxyquinone proved as a good inhibitors at a low dose concentration against COVID-19 due to obtained EC_{50} as 2.71 and 4.51 μM respectively on VeroE6 cell line (Wang et al. 2020). Moreover, the similar experiment performed by Gautret and his research group in France on 26 COVID-19 infected-patients revealed that the significant administration of hydroxyquinone (200 mg up-to 10 treatment days) in combination with azithromycin (500 mg first day followed by 1250 mg up-to 4 treatment days) expressively improved the virology effects with almost 100% cure rate as compared to alone hydroxyquinone treatment which showed about 57% cure rate (Gautret et al. 2020). Similarly, more clinical trials (NCT04308668) by using hydroxyquinone as preemptive therapy against COVID-19 is under-investigation with the administration of 800 mg first day followed by 600 mg daily for 4 treatment days. Although the hydroxyquinone showed the remarkable results in combination with azithromycin, but still further investigation is required to check all the effects of this combination for pharmaco-therapy applications (Lu et al. 2020).

5.4. Favipiravir

Since the outbreak of a novel coronavirus from late 2019, it has been spread over 213 countries with a high infection rate and several health concerns including severe acute respiratory syndrome. Deprived of any approved antiviral, the scientists are exploring the effects of many medicinal compounds to overcome and tackle the COVID-19 epidemic (Lipsitch et al. 2020). Most recently, several studies have been conducted on Favipiravir as corona-antiviral due to previously its safe use and better results against the influenza virus. Favipiravir (purine nucleic acid analog; T705) is known as a pyrazine carboxamide derivative that initially was approved against the influenza virus in Japan due to its broad anti-viral activities. Generally, Favipiravir present in an inactive form (prodrug), which converted into its active form (ibofuranosyl-5′-triphosphate; T-705-RTP) after phosphorylation and ribosylation (Furuta et al. 2017). The study showed that the early administration (0.022 μg/mL) of T-705-RTP significantly inhibited the *RdRp* gene during the influenza virus treatment (Du and Chen 2020). However, the emerging detail structure of COVID-19 revealed that newly developed coronavirus also has *RdRp* gene similar influenza virus, which suggested that the Favipiravir could be a potent option against COVID-19 (Zhu et al. 2020). Recently, *in silico* based experiment on Favipiravir reported an admirable result in the discovery of therapeutic drugs against newly emerged COVID-19. Harismah and Mirzaei (2020) revealed that the F tautomers (F1, F2, and F3) of Favipiravir showed the stronger bonding with polymerase, 6NUR, and protease (6LU7) targeting enzymes of COVID-19, and suggested that Favipiravir could be a good therapeutic option against COVID-19 in future, but still comprehensive study is required to examine the adverse effects and clinical trials for pharmaco-therapy application.

Most recently, a clinical study revealed that the 45 patients (COVID-19-infected) who received the Favipiravir (600 mg twice daily up to 14 days) therapy in combination with IFN-α by aerosol inhalation (5 million U twice daily) showed effective results in chest imaging improvement (91.43%) as compared to control (62.22%) with less adverse effects (Cai et al. 2020). A similar study also observed that the randomly administration of Favipiravir (1600 mg first day followed by 600 mg twice daily up to 10 days) and Arbidol (200 mg thrice daily up-to 10 days) to COVID-19-infected patients (120:120) showed that Favipiravir has better results ($p < 0.0001$) than Arbidol ($p = 0.1396$) with a significant reduction in cough and pyrexia COVID-19 infected patients (Chen et al. 2020).

5.5. Gs-5734

GS-5734 (remdesivir) is a small nucleoside analog that *in vitro* generally known for its antiviral activities against different viral families, including *Coronaviridae*, *Pneumoviridae*, *Filoviridae*, and *Paramyxoviridae* (Warren et al. 2016; Brown et al. 2019). Sheahan et al. (2017) stated that in *in-vitro* models, the GS-5734 effectively reduced the viral RNA and viral titers against the both beta-coronaviruses namely MERS-CoV and SARS-CoV of HAEs. However, the *in vivo* activity of GS-5734 showed that it predominantly treated the MA-15 in SARS-CoV-infected mice. Besides to SARS-CoV and MERS-CoV, the GS-5734 also have similar admirable effects against another coronavirus like HCoV-NL63 and showed the inhibitory replication possessions in pre-emergent bat coronavirus including BatCoV-SHC014, BatCoV-HKU5, and BatCoV-WIV1 (Totura and Bavari 2019). Based on the existing antiviral potential of remdesivir on MERS-CoV and SARS-CoV, it is noted that it has high significance to control current underlying viral load of COVID-19 (Sheahan et al. 2020). Most recently, Wang et al. (2020) experimented to investigate the effect of seven different drugs including remdesivir on Vero E6 cell lines to check the viral titer and infection rate. They revealed that remedesivir have lower EC_{50} value (0.77 μM) following by choloquine (1.13 μM) and ribavirin (109.5 μM) on SARS-CoV-2, which suggested that remedesivir and choloquine required the low concentration to inhibit the viral infections. However, the NIH-sponsored clinical trials of remdesivir against SAR-CoV-2 are currently under-investigation by different countries, including the Republic of Korea, the USA, and the China in a double-blinded manner in which patients randomized to receive either remdesivir (200 mg dose) or placebo on the first day, following by a 100 mg dose

administrated twice daily up-to 10 treatment days (Amirian and Levy 2020). Resultingly, based on its *in vivo* and *in vitro* findings, it is stated that GS-5734 (remdesivir) may be a novel therapeutic agent against pathogenic and newly emerged coronavirus (COVID-19).

5.6. Ritonavir, lopinavir, and darunavir

Ritonavir, lopinavir, and darunavir were initially proposed as HIV-protease (see Glossary) inhibitors (Maksimovic-Ivanic et al. 2017), but after the outbreak of SARS-CoV the ritonavir and lopinavir were tested as therapeutic drugs to treat the coronavirus, which targeted the non-structural protein namely 3CL-pro (Lin et al. 2020). It is well documented that the ritonavir and lopinavir in combination showed significant results to reduce the SARS-CoV and clinical outcome of deaths as compared to the control cases (Totura and Bavari 2019). The oral treatment of both ritonavir and lopinavir in combined form reported modest improvement in the MERS-CoV by controlling the pulmonary infiltrates, weight loss, and intestinal pneumonia (Kim et al. 2016). According to the guideline and diagnosis of COVID-19 published by the National Health Commission of the People Republic of China recommended using the Kaletra as antiviral to treat the newly emergence coronavirus in China (http://www.nhc.gov.cn/) (Li et al. 2020). Initially, Kaletra was developed as an HIV-protease drug that is composed of two kinds of inhibitors including lopinavir (CAS#: 192725-17-0), and ritonavir (CAS#: 155213-67-5) (Vivithanaporn et al. 2016). The *in vitro* study showed that these two inhibitors might be used as antiviral to control viral infections like SARS and MERS coronaviruses (Chong et al. 2015; Arabi et al. 2018).

Most recently, Lin and his research group performed an *in vitro* experiment on two domains (PLVP and CEP-C30) of novel SARS-CoV-2 by using three different antivirals namely ritonavir, lopinavir, and darunavir. They reported that the ritonavir and lopinavir have a greater binding ability with the CEP-C30 domain than the PLVP domain. They also revealed that the ritonavir has the better suitability for tightly binding with CEP-C30 domain rather than the lopinavir. On the contrary, the darunavir inhibitor has a greater binding ability for the PLVP domain than the remaining CEP-C30 domain as presented in Figure 4. Overall, based on previous literature, it is suggested that the lopinavir, ritonavir, and darunavir inhibitors could be an innovative antiviral to treat the SARS-CoV-2 or COVID-19.
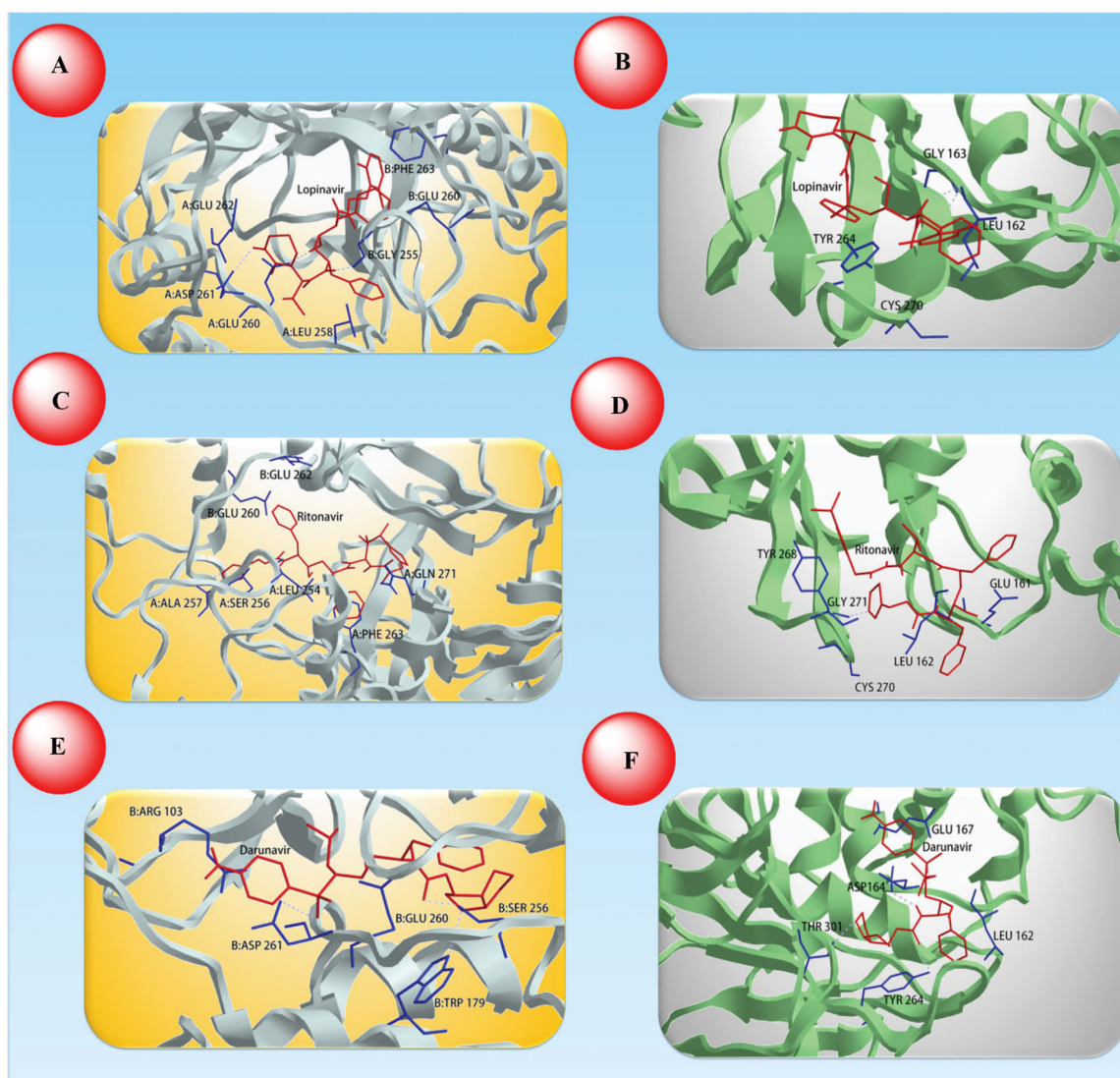
Figure 4. The interaction between three different drugs (lopinavir, ritonavir, and darunavir) and proteases (PLVP and CEP-C30) before energy minimization. The white color represents the main chain of CEP-C30 protease whereas the green color represents the main chain of PLVP protease. The blue colors are the side chain of both proteases which binds with all three drugs such as lopinavir, ritonavir, and darunavir while the red chain represents the drugs. However, the white interrupted lines represent the hydrogen bonding. The points (A, C, E) show the interactions between CEP-C30 protease and lopinavir, ritonavir, and darunavir, respectively, whereas the points (B, D, and F) represent the binding of PLVP protease with lopinavir, ritonavir, and darunavir respectively (Lin et al. 2020).

5.7. Cepharanthine, Fangchinoline, and tetrandrine

The Cepharanthine (CEP), Fangchinoline (FAN), and bis-benzylisoquinoline alkaloids tetrandrine (TET) are the important medicinal herbs which are isolated from *Stephania tetrandra* and *Menispermaceae* (Bhagya and Chandrashekar 2016; Liu et al. 2016). The emerging evidence reported that CEP, well showed the antiviral activity against human immunodeficiency virus type-1 (HIV-1) and herpes simplex virus type-1 (Bailly 2019;

Kim et al. 2019), and also demonstrated that TET is licensed an important antiviral in the reduction of different types of virus infections, including Ebola virus, dengue virus, and herpes simplex virus (Sakurai et al. 2015; Hoenen et al. 2019), and FAN also helped in the inhibition of HIV-1 (Wan et al. 2012). However, based on their significant results upon other viruses, these natural products could be potent antivirals against COVID-19 in the combination, but not limited to interferons, cidofovir, zanamivir, and ribavirin. The World Health Organization (WHO) declared that much research and

Table 1. The *in vitro* study of diverse classes of inhibitors against MERS and SARS-CoV with activity.

		IC$_{50}$	
Inhibitor name	Inhibitor class	SARS-CoV	MERS-CoV
Benztropine mesylate	Neurotransmitter inhibitors	21.6 1	16.63
Triflupromazine hydrochloride	Neurotransmitter inhibitors	6.39	5.75
Chlorpromazine hydrochloride	Neurotransmitter inhibitors	12.97	9.51
Thiothixene	Neurotransmitter inhibitors	5.31	9.29
Clomipramine hydrochloride	Neurotransmitter inhibitors	13.23	9.33
Gemcitabine hydrochloride	DNA metabolism inhibitor	4.95	1.21
Nilotinib	Kinase signaling inhibitor	2.10	5.46
Imatinib mesylate	Kinase signaling inhibitor	9.82	17.68
Toremifene citrate	Estrogen receptor inhibitor	11.96	12.91
Tamoxifen citrate	Estrogen receptor inhibitor	92.88	10.11
Mefloquine	Anti-parasite agent	15.53	7.41
Terconazole	Sterol metabolism inhibitor	15.32	12.20

This information is taken from the research of Frieman et al. (2019).

development (R&D) is required on urgent bases to treat or inhibit the coronavirus including MERS-CoV, SARS-CoV, COVID-19, and other bat coronaviruses (Organization WH 2018; Kim et al. 2019).

Kim and his research group conduct an experiment by using three different natural drugs, namely TET, CEP, and FAN to treat human coronavirus like HCoV-OC43. They reported that co-treatment (during treatment) of TET, CEP, and FAN significantly reduced the HCoV-OC43 at an administration amount of 10 μM in a dose-dependent manner (Kim et al. 2019).

5.8. Inhibitors

Based on accumulated data, the different types of inhibitors including neurotransmitters, DNA metabolism, and kinase signaling inhibitors consider as a potent therapeutic option to treat the newly emerged SARS-CoV-2 or COVID-19. The data revealed that based on drug targets, the inhibitors are categorized into four different major groups including, fusion (S2 fusion domain), replicase (viral helicase), protease (PL$_{pro}$), and entry inhibitors (S1 RBD) for the potential binding of different drug targets between host and virus during the treatment of coronavirus (Rahman 2018). Different drugs bind with different inhibitors, for instance, N$_3$ (strong coronavirus inhibitor) significantly inhibited the protease activity of coronavirus by blocking the PL$_{pro}$ domain (Rao et al. 2020). Similarly, the DPP4 (entry inhibitor) interface the binding between the S1 RBD domain and coronavirus cell-surface (Lu et al. 2014).

Frieman et al. (2019) reported that a significant concentration of diverse neurotransmitter inhibitors results in the formation of useful antiviral to reduce or control the coronavirus activity by at least 50% (IC$_{50}$). They reported that early administration of neurotransmitter inhibitors, including triflupromazine hydrochloride, and chlorpromazine hydrochloride in a range of 5.76–12.9 μM are proved as

good therapeutic targets to control the coronavirus (MERS-CoV and SARS-CoV) by inhibiting the dopamine receptor. Similarly, the kinase signaling inhibitors including dasatinib and imatinib mesylate within the administration dose of about 2.1–17.6 μM significantly showed the antiviral activity against MERS and SARS coronaviruses by at least 50% (IC$_{50}$) via blocking the endosomal fusion or inhibiting the viral RNA formation. Moreover, the estrogen receptor inhibitors including tamoxifen citrate and toremifene citrate and DNA metabolism inhibitor namely gemcitabine hydrochloride (1.2–4.9 μM) reduced the coronavirus by inhibiting the viral DNA replication and repair (Johansen et al. 2013; Madrid et al. 2013; Frieman et al. 2019). The *in vitro* study of different inhibitors against coronaviruses are presented in Table 1. These different inhibitors could be used in combination with several drugs, including brivudine, penciclovir, cidofovir, zanamivir, and ribavirin, interferons to develop a novel therapeutic agent to control the newly induced coronavirus (Frieman et al. 2019).

5.9. Monoclonal antibodies (mAbs)

The data demonstrated that the prevalence and transmissibility effects for coronavirus were relatively low after the intensive effort to develop a coronavirus vaccine (Majumder et al. 2014). In contradictory, the monoclonal antibodies (mAbs) (see Glossary) could be a potent drug to administrate against the coronavirus load (de Wit et al. 2018; Kim et al. 2019). mAbs proved as an effective therapeutic therapy to treat cancer and manage the autoimmune disease (De Martin et al. 2018). Like GS-5734, the mAbs may be administrated to reduce or control the viral infections at early stages due to its high specificity, greater potency, and pre-licensing evaluation. mAbs would also help to determine the immunogenic epitopes via crystallographic analysis, which might be a critical factor in designing better

Table 2. The different monoclonal antibodies (mAbs) in various stages of research and development to neutralize the coronavirus.

Antibody name	Source	Organization	Study type	Target	Reference
REGN3048/REGN3051	Humanized mouse	Regeneron	Mouse/NHP efficacy	RBD	(Pascal et al. 2015)
G2, G4, D12, F11,	S/S1 immunized mouse	NIH NIAID	NHP efficacy	S1, S2, RBD	(Wang et al. 2015)
2E6, 4C2	RBD immunized mice	Chinese Academy of Sciences	Mouse efficacy	RBD	(Li et al. 2015)
LCA60	Human survivor	HUMABS BioMed	Mouse/NHP efficacy	RBD	(Corti et al. 2015)
3B11 (AV-3)	Human antibody library	Dana-Farber Cancer Institute and AbViro LLC	NHP efficacy	RBD	(Tang et al. 2014)
m336, m337, m338	Human antibody library	NIH National Cancer Institute	In vitro	RBD	(Xia et al. 2014)

immunogens (Li et al. 2015; Wang et al. 2015; Yu et al. 2015).

Recently, some recommended functional groups of mAbs against MERS-CoV are under-investigation and approval process through pre-clinical development stages are remained as illustrated in Table 2 (Xia et al. 2014; Li et al. 2015; Pascal et al. 2015; Wang et al. 2015; Yu et al. 2015). Some of these groups have been isolated either from memory B cells of the infected and recovered patients (Corti et al. 2015) or from the antibodies of human phase library (Tang et al. 2014). The recent researches on mAbs reported that all mAbs which are published and under the approval process are targeted the S-receptor binding domain (RBD) (He et al. 2019), and carried the immunogenic epitopes on viruses. They also proposed that an early administration of mAbs with the inhibitory concentration of about 10 ng/μL (IC$_{50}$) significantly neutralized the MERS-CoV infections. The mAbs bind to the RBD and showed expression on both the surface and the recombinant S of the virus (Wang et al. 2015). Therefore, there is a need to develop and identify the cost-effective antibodies which can bind with RBD on S-site to inhibit or reduce the potential therapeutic resistance of newly emerged SARS-CoV-2.

5.10. The drugs with TMPRSS2 inhibitory activity

TMPRSS2 is known as a critical gene that is present on human chromosome 21 and encodes the protein (492 amino acids) present on the plasma member. TMPRSS2 contains multiple androgen receptor elements (AREs) which are located between the first intron and the transcription start site (Shen et al. 2017; Ito et al. 2018). According to the emerging evidence, the TMPRSS2 plays a significant role in the proteolytic activation of coronaviruses including SARS-CoV and MERS-CoV (Belouzard et al. 2012). Kawase and his research group (Kawase et al. 2012) reported that the entry of SARS-CoV inside the cell promoted as 2.6-folds in the presence of TMPRSS2, and proportionally, the entry of SARS-CoV into Calu-3 cells decreased to 5 times with siRNA targeting TMPRSS2. Similarly, Shulla et al. (2011) observed that the levels of RNA in SARS-CoV were 9

times greater in the presence of an active TMPRSS2 gene than the expressive inactive TMPRSS2. Like on SARS-CoV infection, the TMPRSS2 also plays a similar protective role in the MERS-CoV and human coronavirus (HCoV-229E) infections (Shen et al. 2017).

According to the emerging evidence, camostat (see Glossary) is suggested as a significant drug in the reduction of coronavirus. It was reported the ten-fold reduction of SARS-CoV titers in the Calu-3 cells with the inhibition of TMPRSS2 by camostat (Shulla et al. 2011). Camostat was proved as an effective inhibitor to treat SARS-CoV with a 60% survival rate in mice (Zhou et al. 2015). Recently reported nafamostat (a serine protease inhibitor) is also considered as more potent than camostat, which can significantly impair the viral entry of about 100 folds within 1 nM concentration and neutralized the MERS-CoV by inhibiting the TMPRSS2 (Yamamoto et al. 2016).

5.11. The role of DAAs and IAAs in the treatment of coronavirus

The data suggested that different host and viral factors are responsible for the transmission and replication of coronavirus, so several indirect and direct-acting antivirals (IAAs and DAAs) (see Glossary) might be a potential target against coronaviruses (Rahman 2018). Dipeptidyl peptidase 4 (DPP4) could be an effective inhibitor to reduce the coronavirus entry and attachment due to its targeting binding interference between RBD of S1-sub-unit and DAA4 (Pillaiyar et al. 2015). Also, the adenosine deaminase (ADA), a natural ligand for DPP4, proved as a natural antagonist against the MERS-CoV (Raj et al. 2013). The literature also suggested that the viral fusion process could also be blocked by targeting the S1-domain or host cell protease of coronavirus, and recently a peptide namely HR2P has been reported/licensed in restricting the fusion process of MERS-CoV disease (Lu et al. 2014).

Few synthetic inhibitors of furin (see Glossary) have been approved for the reduction of MERS-CoV (Becker et al. 2012). In addition to synthetic inhibitors, the furin directed human miR-24 and microRNA developed to suppress the fusion expression (Loveday et al. 2015).

However, the miR-24 could prove a potent therapeutic inhibitor to block the fusion reaction (Meyer et al. 2013). Teicoplanin is an important glycol-peptide antibiotic that has been developed as a powerful inhibitor in blocking the entry of different viruses by suppressing the cathepsin-L activity in MERS-CoV, SARS-CoV, and Ebola viruses (Zhou et al. 2016).

6. Conclusion and future recommendations

Despite to highly pathogenic beta and alpha coronaviruses including severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and human coronavirus namely HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1, the newly emerged COVID-19 (caused by SARS-CoV-2) associated with the deadly respiratory syndrome and high mortality rates in human. Based on evidences, we revealed that the SARS-CoV-2 has more than 79.5% identical sequence to SARS-CoV and a 96% identical sequence of the whole genome of bat coronaviruses. Unlike with other antivirus drugs, the anti-coronavirus targeting drugs are not available, but recently reported some protective candidates are recommended to control the COVID-19. However, there is a need to develop a strong antiviral or vaccine to tackles the present alarming situation shaped by a newly emerged COVID-19. Based on accumulated data, we suggested that interferons, ribavirin, remdesivir, chloroquine and hydroquinone, Favipiravir, ritonavir, lopinavir, inhibitors, and monoclonal antibodies (mAbs) could be a potent therapeutic agent in the reduction of newly emerged COVID-19, by inhibiting the viral RNA replication, and viral protein expression. However, it is recommended to understand the interaction between virus and host factors that facilitate the viral molecule to enter and replicate inside the human body during an infection. The over-expression of inflammation response, cytokine dysregulation, and induction of apoptosis could be an efficient factor to reduce the pathogenicity of COVID-19 by drugs including remdesivir, chloroquine and hydroquinone, Favipiravir, ritonavir, lopinavir, and ribavirin. In addition, to avoid the future potential of newly emerged coronavirus, it is also recommended to develop an essential universal genome diagnostic test to distinguish between all the diverse types of viruses.

7. Outstanding questions

1. Can the use of natural products will be an important therapeutic option in the treatment of COVID-19?

2. Why the formation of vaccines become unsuccessful so far against previously reported coronavirus (SARS-CoV and MERS-CoV)?

3. Can the formation of drugs against coronavirus also be useful against the Influenzas virus or HIV? Because these viruses shared the many common proteases for viral replication.

4. Can HIV drugs will be a temporary or permanent option against COVID-19?

5. Could the manufacture of a vaccine in combination with other antivirals be a potent therapeutic option against COVID-19?

6. Can the serum of other animals be used soon to make a vaccine against COVID-19? What will be the impact of the coronavirus vaccine on a patient's health?

7. Will the serum of recovered patients can be considered to make a vaccine/drug against COVID-19?

8. Are the receptor proteins on the surface of infected cells, will increase or decrease the susceptibility of antivirals?

9. Are the use of inhibitors and interferons could be a good preventive measure against COVID-19?

10. Could the use of Kaletra will be a good option in the present situation to control the effect of COVID-19?

Disclosure statement

Glossary

Achilles heel: A recently revealed scoop on the surface of viruses that cause several infections, including the common cold, and a conceivable target for operative drugs

ACE2: Angiotensin-converting enzyme 2 (ACE2) is an enzyme that is attached to the outer layer (cell membrane) of cells in the heart, lungs, kidney, and intestine, and also help in the binding of drugs to infected cells for treatment. ACE2 also serves as the entry point into cells for some coronaviruses.

Beta-coronaviruses: Beta-coronaviruses are one of four genera of coronaviruses of the subfamily Orthocoronavirinae. They are enclosed, positive-sense, single-stranded RNA viruses of zoonotic origin and 2019-nCoV is of the B lineage

Camostat: Camostat is known as a serine inhibitor. It approved for several chronic diseases like pancreatic and postoperative reflux, but recently it showed significant results against SARS-CoV.

DAAs (direct-acting antivirals): Direct-acting antivirals (DAAs) are a comparatively novel class of medication that acts to target specific steps in the viral life cycle. The goals of DAAs are to target the virus and improve sustained virologic response (SVR) rates.

Furin: Furin is a protein that in humans is encoded by the FURIN gene, it synthesizes as inactive protein and activated by an inhibitor for proper function

Monoclonal antibodies (mAbs): Monoclonal antibodies are assembled due to identical immune cells that are all clones of a unique parent cell.

Nonstructural proteins (nsps): In virology, nonstructural proteins are those proteins that are coded my virus genome and help in the expression of viral genes during the replication of viruses.

Protease: The protease belongs to the family of enzymes which catalyzed the proteolysis by breaking the peptide bonds between protein and release a molecule of water in return.

Reverse genetic system: The reverse genetic system is a system in molecular genetics, which facilitate in the function of any gene via identified its phenotypic effect on precise nucleic acid sequences

Author contribution statement

Abu Hazafa, and Khalil-ur-Rahman conceived the presented data. Nazish Jahan, Abu Hazafa, Ikram-ul-Haq, and Muhammed Mumtaz developed the theory and performed the computations. Huma Naeem, Muhammad Farman, and Faheem Abbas helped to draw the artwork. Abu Hazafa and Khalil-ur-Rahman investigate and supervised the review. Sania Sadiqa, Muhammed Naeem, and Saira bano helped in revision. All authors provided critical feedback and helped shape the analysis and manuscript.

Informed consent

For this type of study informed consent is not required.

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