



## 28 Introduction

29 Coronaviruses are enveloped, positive-sense single-stranded RNA viruses with a  
30 nucleocapsid of helical symmetry (1). Coronaviruses have widely been known to cause  
31 respiratory and intestinal infections in humans after the outbreak of “severe acute respiratory  
32 syndrome (SARS)” in Guangdong, China (2, 3). SARS was caused by SARS-CoV during 2002  
33 and 2003, emerged in a market where civets were sold out (2, 3). Only a decade later, the world  
34 witnessed another outbreak of “Middle East respiratory syndrome (MERS)” caused by MERS-  
35 CoV in the Middle East (4, 5). While the researchers were still investigating the underlying  
36 mechanisms of pathogenicity and developing effective therapeutic strategies against MERS, the  
37 world witnessed the deadliest outbreak of COVID-19 (6). The causative coronavirus of this  
38 outbreak was named SARS-CoV-2 due to its resemblance to SARS-CoV (7–9). The SARS-CoV  
39 infects ciliated bronchial epithelial cells and type-II pneumocytes through angiotensin-converting  
40 enzyme 2 (ACE2) as receptor (2, 10). MERS infects unciliated bronchial epithelial cells and  
41 type-II pneumocytes by using dipeptidyl peptidase 4 (DPP4) also known as CD26, as a receptor  
42 (2, 11). The mechanisms associated with the infectiousness of SARS-CoV-2 is not clear,  
43 however, structural analysis suggests it is likely entering human cells through the ACE2 receptor  
44 (12). This newly emerged virus has much more similarity with SARS-CoV than MERS-CoV,  
45 thus both SARS-CoV and SARS-CoV-2 may cause pathogenesis through similar mechanisms.  
46 The transmission of SARS-CoV to humans was reported from market civets, while that of  
47 MERS- CoV was from dromedary camels (13, 14). Similarly, the newly emerged SARS-CoV-2  
48 also transmitted to humans form the markets where wild animals were sold out (8). However, the  
49 zoonotic source of its transmission is not clear yet. According to the previous reports, the  
50 aforementioned three coronaviruses are thought to have originated in bats (2, 11, 15, 16).

51 Since the first epidemic of SARS, the pathogenic coronaviruses have harmed thousands  
52 of people worldwide (1, 17). Considering the adverse outcomes of the current COVID-19  
53 epidemic, developing effective therapeutic strategies is necessary to cope with the lack of  
54 effective drugs, high mortality rate and the potential of the virus to cause further epidemics. In  
55 this Review, we focus on the origin, evolution, and pathogenicity of SARS- CoV, MERS- CoV,  
56 and SARS-CoV-2. We also discuss the therapeutic options for SARS-CoV-2, due to its  
57 importance in the current scenario of COVID-19 outbreak in Wuhan, China. This review will be

58 useful in terms of preparation against future spillover and pathogenic infections with novel  
59 coronaviruses in humans.

#### 60 **Diversity and origin of highly pathogenic coronaviruses**

61 Coronaviruses are members of the subfamily “Coronavirinae” (family; Coronaviridae,  
62 order; Nidovirales) that contains four genera alpha-coronavirus, beta-coronavirus, gamma-  
63 coronavirus and delta-coronavirus (2). Gamma and delta coronaviruses generally infect birds,  
64 although some of them can cause infection in mammals. Whereas, alpha and beta coronaviruses  
65 are known to harm humans and animals. The SARS-CoV (beta coronavirus), 229E (alpha  
66 coronavirus), HKU1 (beta coronavirus), NL63 (alpha coronavirus), OC43 (beta coronavirus) and  
67 MERS-CoV (beta coronavirus) can cause infectiousness in humans (2). However, beta-  
68 coronaviruses are the most important group as this group contains the highly pathogenic viruses  
69 in humans including SARS-CoV-2, MERS-CoV and SARS- CoV (2, 18, 19). The highly  
70 pathogenic MERS and SARS coronaviruses originated from bats (2, 18, 19), however, the origin  
71 of the newly emerged SARS-CoV-2 is debatable. Investigations revealed that the detected  
72 SARS-CoV strains in market civets (20, 21), were transmitted from horseshoe bats (22). These  
73 viruses were found phylogenetically related to SARS-CoV in bats from China, Europe, Southeast  
74 Asia and Africa (2, 22, 23). In addition, the genome sequences of SARS-CoV isolated from  
75 humans were very much similar to those in bats (21). However, some variations were found  
76 among the *s* gene and *orf* gene, which encode the binding and fusion proteins, and dispensable  
77 protein for replication respectively (2, 23). Nevertheless, clade2 of *s* region (22, 24), *orf8* (23)  
78 and *orf3b* in SARS-CoV from bats contain major variations if compared with SARS-CoV from  
79 humans (23).

80 Different strains of MERS-CoV obtained from camels were found similar to those  
81 isolated from humans (14, 25, 26), except, genomic variations among S, ORF4b and ORF3  
82 regions (26). Furthermore, genome sequencing-based studies revealed that MERS-CoVs from  
83 humans are phylogenetically related to those from bats. They have identical genomic and protein  
84 structures except for the S proteins (27). In addition recombinations analysis of genes encoding  
85 *orf1ab* and S revealed that MERS-CoV originated from the exchange of genetic elements  
86 between coronaviruses in camels and bats (26, 28).

87 Although the zoonotic source of SARS-CoV-2 is not confirmed, its genome sequence  
88 exhibited close relatedness (88% identity) with two bat-derived SARS-like coronaviruses (bat-  
89 SL-CoVZC45 and bat-SL-CoVZXC21). Phylogenetic analysis revealed that SARS-CoV-2 was  
90 genetically distinct from SARS-CoV and MERS-CoV. However, homology modeling revealed  
91 that both SARS-CoV and SARS-CoV-2 had similar receptor-binding domain structures, despite  
92 amino acid variation at some key residues. Such as the absence of 8a protein and fluctuation in the  
93 number of amino acids in 8b and 3c protein in SARS-CoV2 (29). In contrast, the main protease is  
94 highly conserved between SARS-CoV-2 and SARS-CoV with a 96% overall identity (30). These  
95 observations suggest that bats are the source of origin, while an animal sold at the Wuhan  
96 seafood market might represent an intermediate host facilitating the emergence of the virus in  
97 humans (12, 31).

#### 98 **Epidemiology and clinical features of human coronaviruses**

99 After the emergence of SARS-CoV in the Guangdong province of China, it rapidly spread  
100 around the globe (2, 3). During November 2002, an epidemic of pneumonia with a high rate of  
101 transmission to the people, occurred in Guangdong, China (32), followed by subsequent outbreaks in  
102 HongKong. In HongKong, a total of 138 people contracted the infection within 2 weeks after the  
103 exposure to an infected patient in the general ward of a hospital (1, 32). Overall, SARS-CoV infected  
104 8098 people and caused 774 fatalities in 29 different countries by the end of the epidemic (1). Later  
105 on, during June 2012 a patient infected by MERS-CoV developed severe pneumonia and died in  
106 Jeddah, Saudi Arabia (1, 33). Analysis of cluster of nosocomial cases in Jordan during April 2012,  
107 confirmed that MERS-CoV caused the outbreak (34). The spread of MERS-CoV continued beyond  
108 the Middle East, causing further reports of infected individuals (1, 4). Until 2020, 2468 cases and 851  
109 fatalities have been reported globally (35, 36). Again, during December 2019, clusters of patients  
110 with atypical pneumonia were reported by local health facilities, in Wuhan, China. On December 31,  
111 2019, a rapid response team was dispatched by the Chinese Center for Disease Control and  
112 Prevention (China CDC) to conduct an epidemiologic and etiologic investigation (37). The patients  
113 were found epidemiologically linked to the wet animal wholesale market and seafood in Wuhan,  
114 China. Later on, the infectious agent responsible for this atypical pneumonia was confirmed reported  
115 a coronavirus SARS-CoV-2, which caused the first fatality during the start of January 2020 (15).  
116 During the first two 6 weeks of the outbreak, several cases were reported in more than 37 countries  
117 including the USA, Japan, Iran and South Korea (38). The infection rapidly spread all over the globe

118 from Wuhan, China. Therefore, the Chinese authorities implemented several strategies including  
119 massive lockdown in Wuhan and suspension of transport to and from Wuhan to control the spread  
120 (17). According to situation report 35, published on the WHO website, SARS-CoV-2 caused 79331  
121 confirmed cases and 2618 deaths around the globe. However, COVID-19 caused 77262 confirmed  
122 cases and 2595 deaths only inside Mainland China (38). Until February 24, WHO has reported 8  
123 deaths in Iran. It is now the second country after Chian, bearing the highest fatalities due to SARS-  
124 CoV-2 infection. (38). The spread of SARS-CoV-2 in Iran can pose a higher risk of pandemics in the  
125 Middle East and South Asian countries. The epidemic growth rate on the basis of data analyzed  
126 between December 10 and January 4, was estimated and the basic reproductive number ( $R_0$ )  
127 calculated, which was 2.2. It means that each patient has been spreading the infection to 2.2 other  
128 individuals (39). The estimated  $R_0$  value for SARS was around 3, however, SARS was successfully  
129 controlled by isolation and of patients (39). Moreover, The  $R_0$  for MERS ranged from 0.45 in Saudi  
130 Arabia to 8.1 in South Korea (36). Considering the lower  $R_0$  value, the rapid increase in suspected  
131 as well confirmed cases with COVID-19 may be inferred with viral transmission through the  
132 fecal-oral route and aerosol formation. Moreover, the asymptomatic persons are thought to be  
133 potential sources of SARS-CoV-2 infection (40), which may have caused the rapid spread of SARS-  
134 CoV-2. This asymptomatic spread may be one of the reasons that the control strategy based on the  
135 isolation of patients was not fully successful. To overcome these problems a complete quarantine for  
136 the general public is necessary. So that all of the infected individuals could develop symptoms  
137 without spreading the virus randomly. Thus the direct and indirect contacts of infected individuals  
138 can be easily identified and isolated.

139 Clinical features associated with patients infected with SARS-CoV, MERS-CoV and  
140 SARS-CoV-2 range from mild respiratory illness to severe acute respiratory disease (1, 17). Both  
141 MERS and SARS patients in later stages develop respiratory distress and renal failure (1, 17).  
142 Pneumonia appears to be the most frequent manifestation of SARS-CoV-2 infection,  
143 characterized primarily by fever, cough, dyspnea, and bilateral infiltrates on chest imaging (17).  
144 The period from infection to appearance of symptoms varies. Generally, it is thought to be 14  
145 days, however, a research group at Guangzhou Medical University reported the incubation  
146 period to be 24 days. In a family cluster of infections, the onset of fever and respiratory  
147 symptoms occurred approximately three to six days after presumptive exposure (41).

#### 148 **Diagnostic testing**

149 Diagnostic testing for the SARS-CoV-2 is primarily done in public health laboratories.  
150 Delays in testing result from the need for administrative oversight of testing at the national or  
151 regional level, as well as the time needed to transport specimens and the high volume of testing  
152 needed in some regions. More rapid testing should widely available in days of epidemics. High-  
153 level testing facilities at the regional hospital and commercial laboratories are needed, in addition  
154 to the commercially available tests that have undergone regulatory approval. Several tests have  
155 been validated by public health authorities, including those in China, Germany, Thailand, Japan  
156 and the United States (WHO, COVID-19, technical guidance, Feb 12, 2020). These tests are  
157 reverse-transcriptase PCR tests that use primers and probes designed to detect a variety of targets  
158 in the SARS-CoV-2. Although these have been designed and validated, there is currently very  
159 limited information available related to the performance of these tests. The sensitivity and  
160 specificity of the tests are not widely known, and some of them might detect other coronaviruses  
161 such as SARS-CoV. In addition, the utility of different specimen types for detection of the  
162 viruses is not known. As a result, testing of multiple specimen types is recommended by some  
163 agencies, including the CDC (CDC, guidelines for samples for COVID-19, Feb 11, 2020). The  
164 availability of serological tests is unclear, and presumably, such tests are in development.  
165 Moreover, the collection and submission of sera from potentially infected patients is  
166 recommended by some public health laboratories.

167 The CDC and WHO have both issued recommendations for laboratory safety when  
168 testing specimens from patients suspected of being infected with SARS-CoV-2 (WHO,  
169 document Laboratory biorisk management for laboratories handling human specimens suspected  
170 or confirmed to contain novel coronavirus 2012, Interim recommendations and CDC, guidelines  
171 for samples for COVID-19, Feb 11, 2020). Both guidelines recommend that manipulation of  
172 potentially infectious specimens should be done in a biosafety cabinet if there is potential for  
173 splashes or generation of droplets or aerosols. Viral isolation (culture) should be done only in  
174 BL-3 laboratories. Testing in chemistry and hematology laboratories can be done following  
175 routine laboratory precautions recommended for such work.

#### 176 **Therapeutic options for human coronaviruses**

177 Currently no promising antiviral treatment available, however, numerous compounds  
178 have been proven effective against SARS-CoV and MERS-CoV but have not been tested widely  
179 for newly emerged SARS-CoV-2. Remdesivir and chloroquine were found highly effective in  
180 vitro for the control of 2019-nCoV infection (42). Treatment with remdesivir alone or in  
181 combination with chloroquine or interferon beta was found effective against COVID-19  
182 infection. This strategy has not caused any obvious side effects yet (35, 42, 43). However, more  
183 investigations are necessary to confirm the impacts of remdesivir. As coronaviruses share key  
184 genomic elements thus, common therapeutic targets can be of greater importance. Therapeutic  
185 agents targeting nucleosides, nucleotides, viral nucleic acids and enzymes/proteins involved in  
186 the replication and transcription of coronaviruses can be promising strategies to treat coronavirus  
187 diseases (1). The surface spike glycoprotein (S) is an important potential target for anti-viral  
188 agents, due to its vital role in the interaction between the virus and the cell receptor. S consists of  
189 two subunits, S1, the amino-terminal receptor binding subunit, and S2, the carboxy-terminal  
190 membrane fusion subunit (44). In addition, Activation of membrane fusion and virus entry  
191 requires the cleavage at the junction of S1–S2 (44). Hence, the S1 subunit targeting monoclonal  
192 antibodies and S2 subunit targeting fusion inhibitors may be effective therapeutics to target  
193 coronaviruses (1). Furin (a serine endoprotease) cleaves off S1/S2 (45), thus, could be a suitable  
194 antiviral agent. Further, the helical nucleocapsid interacts with S protein, envelope proteins, and  
195 membrane proteins to form the assembled virion (1). Therefore targeting the structural genes  
196 using small interfering RNAs could be an effective therapeutic strategy against coronaviruses  
197 (1). The host receptors are also associated with the viral entry into host cells, thus agents  
198 targeting these receptors also inhibit coronaviruses (44). Inhibitors of endosomal cysteine  
199 protease and transmembrane protease serine 2 can partially block viral entry into the cell (46).  
200 K22 targets membrane-bound RNA synthesis in coronaviruses and inhibit double-membrane  
201 vesicles formation (47) thus could be effective against SARS-CoV-2.

202 Broad-spectrum antivirals, for instance, dsRNA-activated caspase oligomerizer  
203 (DRACO) selectively induces apoptosis in virus-containing host cells, thus can be evaluated for  
204 its effectiveness against SARS-CoV-2 (48). However, it may not be a very promising strategy  
205 alone, as it cannot block the virus from entry or disrupt the viral nucleic acid. On the other hand  
206 thiopurine compounds, naphthalene inhibitors, protease inhibitors, zinc, and mercury conjugates  
207 target 3CLpro (3C-like protease) and PLpro (papain-like protease) enzymes in coronaviruses and

208 can block the pathogenicity of coronaviruses (49, 50). Therefore, combinational therapy of these  
209 antiviral agents with DRACO may enhance the overall impact on the recovery of patients.  
210 Despite the higher rate of infectiousness, coronaviruses are thought to have the ability to  
211 suppress counteracting response from host innate interferons. This response can be augmented  
212 by the utilization of interferon inducers or recombinant interferons (1). The previously tested  
213 recombinant interferon against SARS-CoV, such as interferon alfa and beta (1) can be utilized  
214 either alone or in combination with other potential antiviral drugs including remdesivir. Both  
215 interferon-alpha and beta inhibit viral replication (1). The use of interferon inducers in  
216 combination effective antiviral agents may be evaluated for their synergistic effects against  
217 SARS-CoV-2. In addition, calcineurin inhibitors such as cyclosporine (51) could also be  
218 evaluated for SARS-CoV-2 in combination with antibiotics and traditional Chinese medicines.

## 219 **Vaccines**

220 Effective vaccines are important to prevent and control sporadic viral attacks and  
221 emerging virus-mediated epidemics, such as the recent outbreak caused by SARS-CoV-2.  
222 Although SARS-CoV was fully controlled during 2003, and MERS-CoV has been controlled  
223 from causing high mortalities, yet the newly emerged SARS-CoV-2 is spreading efficiently with  
224 a significant increase in the number of cases and fatalities each passing day. Vaccines are  
225 required to prevent SARS-CoV-2 from causing COVID-19. Live-attenuated vaccines, designed  
226 for SARS (1), may be evaluated for SARS-CoV-2 infected patients. In addition rhesus  $\theta$ -defensin  
227 1 and protein cage nanoparticles are innate immunomodulators with high anti-SARS-CoV  
228 efficiency (52, 53). Based on the higher similarities and phylogenetic relatedness between  
229 SARS-CoV and SARS-CoV-2, protein cage nanoparticles designed for SARS-CoV can be  
230 evaluated for SARS-CoV-2. Meanwhile, following the similar strategies utilized for SARS-CoV,  
231 novel protein cage nanoparticles specified for novel coronavirus can be designed on an urgent  
232 basis. Based on the urgency in the current scenario of COVID-19 outbreak, vaccination  
233 strategies based on viral vectors, recombinant protein, and viral-like particles, which have been  
234 developed or being developed for SARS and/or MERS can be modified for utilization against  
235 SARS-CoV-2 (54). Despite the current progress, further work is needed to develop safe and  
236 effective vaccines, available for individuals at high risk of SARS-CoV-2 endemics, to control the  
237 ongoing and risk of future epidemics. An interesting feature of plasma from recovered patients is



238 the presence of active antibodies, thus transferring plasma from people recovered from COVID-  
239 19 into infected individuals could enhance immunity against SARS-CoV-2. Monoclonal  
240 antibodies that could inhibit virus-cell receptor binding, and interrupt virus-cell fusion have been  
241 developed (1). Combining two or more monoclonal antibodies may be suitable for the quicker  
242 recovery of patients. Lastly, antiviral peptides that target different regions of S such as, HP2P-  
243 M2 peptide (effective against viral infections) (1), should also be considered against COVID-19.

244 Although some strategies against SARS-CoV are being developed including RBD based  
245 vaccines, they need further evaluation (2). Given the importance of the current outbreak in  
246 Wuhan, further studies are necessary to provide deep understating of replication, pathogenesis,  
247 and biological properties using reverse genetics and related molecular techniques. These  
248 investigations will help the control and prevention of SARS-CoV-2 mediated pneumonia disease  
249 and novel emerging diseases in the future.

## 250 **Conclusions and Perspective**

251 SARS-CoV and MERS-CoV were reportedly originated in recombination from bats  
252 viruses, before their introduction into Guangdong province through civets, and the middle east  
253 through camels respectively. Some of the SARS-CoV strains became epidemic after several  
254 independent spillovers to humans during the outbreak of 2002 in Guangdong, China (3).  
255 Similarly, MERS-CoV became endemic after a series of infections to humans during 2012 in  
256 middle eastern countries (33). Both viruses further transferred to several countries other than  
257 countries of origin. However, unlike the continuous propagation of MERS-CoV epidemics, the  
258 SARS-CoV outbreak was successfully controlled in 2003. Based on the origin of other  
259 coronaviruses, SARS-CoV-2 is likely originated in bats and introduced to Wuhan, China through  
260 an unknown intermediate. Until now, no effective clinical treatments or prevention strategies are  
261 available to be used against human coronaviruses.

262 Testing the drugs for coronaviruses requires suitable animal models prior to their use in  
263 humans. The currently established models are not very promising for the studies of pathogenesis  
264 and treatment of highly pathogenic coronaviruses. For instance, non-human primates were  
265 unable to reproduce the characteristics of the severe human disease and even mortality was not  
266 observed (55). However, some of the small animals developed the clinically apparent disease

267 (55), such as transgenic mice expressing human ACE2 and mouse-adapted SARS-CoV strains  
268 are one of the most suitable models (1). Additionally, transgenic mice expressing human DPP4  
269 are a suitable small animal model for MERS (1). Like the animal models for SARS-CoV,  
270 transgenic animal models may also be standardized for SARS-CoV-2. The development of  
271 clinical drugs for coronaviruses is challenging because of the repeated emergence of novel  
272 coronaviruses with diverse features, thus, each newly emerged virus requires specific drugs.  
273 Moreover, only a limited number of animal models are available and most of them can only be  
274 used in highly demanding biosafety level 3 labs (1). From the perspective of the current  
275 outbreak, designing effective therapeutics for SARS-CoV-2 is yet another challenge for  
276 scientists. Although a large number of antiviral treatment options for SARS and MERS have  
277 been reported with potent in vitro activities, a very limited number from them may have the  
278 potential in the clinical setting.

279 Now moving forward treatment options are available that could be utilized clinically during the  
280 ongoing SARS-CoV-2 epidemics. Some of the broad-spectrum antiviral drugs may be effective  
281 for SARS-CoV-2, and it is a congenial opportunity to test them in the current scenario of  
282 pneumonia in Wuhan, China. Broad range combinational therapies including, lopinavir and  
283 interferon antiviral peptides can also be evaluated and examined as these agents have shown  
284 significant effects against MERS in non-human primates (1). The designing and development of  
285 novel broad-spectrum antiviral drugs that can potentially target all coronaviruses, in general,  
286 maybe the only treatment option against reemerging and circulating coronaviruses.

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297 **References**

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499 Table 1. Therapeutic options for COVID-19

Therapeutic Name	Activity	Effectiveness	Reference
K22	It targets membrane-bound replication complex of virus in host cell to inhibit RNA synthesis	It has been found effective against SARS and MERS, thus could be effective against SARS-CoV-2.	(56)
Draco	It targets viral dsRNA to induce apoptosis in cells containing virus	It has been found effective against a large group of viruses, therefore may have potential to target SARS-CoV-2.	(49, 57)
Mycophenolic Acid	It targets Nucleosides and/or nucleotides to inhibit synthesis of guanine monophosphate	Effective against wide range of viruses, however combinatorial therapy with interferon beta-1b may be useful for SARS-CoV-2.	(54)
Lopinavir	It targets 3CLpro enzyme to inhibit its activity	Effective against wide range of viruses including SARS-CoV and MERS-CoV, thus could be suitable choice for treatment of SARS-CoV-2 infection.	(58)
Remdesivir	It terminates transcription of the viral RNA transcription at premature level	It has been found effective against broad spectrum viruses including MERS-CoV and SARS-CoV. The efficacy is	(35)

		very promising when combined with IFN $\beta$ , hence could be a suitable therapeutic strategy for SARS-CoV-2.	
Ribavirin	It targets RdRp (RNA-dependent RNA polymerase) enzyme to inhibit synthesis of viral RNA synthesis and capping of mRNA	Effective against wide range of viruses including MERS-CoV and SARS-CoV but high doses are required which may have severe side effects. It may be reevaluated for SARS-CoV-2 and recommended if low doses are found effective.	(35, 58)
Bcx4430	It targets RdRp (RNA-dependent RNA polymerase) enzyme to inhibit synthesis of viral RNA synthesis and capping of mRNA	It is broad-spectrum and effective against SARS-CoV and MERS-CoV, thus may be effective against SARS-CoV-2 however, evaluation using animals' models is required.	(59)
Bananins	It targets helicase to inhibit its unwinding and activities of ATPase	It can affect broad-spectrum viruses and can be evaluated for SARS-CoV-2	(1)
Aryl Diketoacids (Adks)	Targets helicase to inhibit its unwinding	Effective for broad range viruses and including SARS/MERS-CoV and may be a suitable choice for SARS-CoV-2	(1)

Griffithsin	It targets Oligosaccharides on S to block viral binding with host cell	It has been found effective against SARS/MERS-CoV and other high pathogenic viruses, thus can be used against SARS-CoV-2	(60)
Hexamethylene Amiloride	It targets viral envelope to inhibit ion channel activity	It is effective against different coronaviruses thus a one of the most suitable treatment options for SARS-CoV-2	(61)
J1103	It targets lipid membrane and causes modification of phospholipids	It has shown effects against different viruses and may be promising anti-SARS-CoV-2 agent.	(1, 58)
Recombinant Interferons	These induce the innate interferon responses against viral pathogens	Inducing immune responses through recombinant interferons has been found effective against a wide range of viruses and can be the most suitable option in case of SARS-CoV-2.	(1, 58)
Nitazoxanide	These induce the innate interferon responses against viral pathogens	Inducing immune responses through recombinant interferons has been found effective against a wide range of viruses and may be promising to use against SARS-CoV-2.	(62)

Cyclosporine, Alisporivir	It inhibits cyclophilin to affect calcineurin–NFAT pathway	These agents can inhibit broad-spectrum viruses specifically coronaviruses and thus could be suitable option to treat people infected with SARS-CoV-2.	(1)
Rapamycin	It inhibits kinase signaling associated pathways to block viral entry	It is effective against SARS/MERS-CoV and possibly be effective against SARS-CoV-2.	(1, 63)
Imatinib	It inhibits kinase signaling associated pathways to block viral entry	It is effective against SARS/MERS-CoV and possibly be effective against SARS-CoV-2.	(1)
Dasatinib	It inhibits kinase signaling associated pathways to block viral entry	It is effective against SARS/MERS-CoV and possibly be effective against SARS-CoV-2.	(1)

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