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# Potential repurposed SARS-CoV-2 (COVID-19) infection drugs

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The global outbreak of COVID-19 viral infection is associated with the absence of specific drug(s) for fighting this viral infection. About 10 million people are already infected, about 500 000 deaths all over the world to date. Great efforts have been made to find solutions for this viral infection, either vaccines, monoclonal antibodies, or small molecule drugs; this can stop the spread of infection to avoid the expected human, economic and social catastrophe associated with this infection. In the literature and during clinical trials in hospitals, several FDA approved drugs for different diseases have the potential to treat or reduce the severity of COVID-19. Repurposing of these drugs as potential agents to treat COVID-19 reduces the time and cost to find effective COVID-19 agents. This review article summarizes the present situation of transmission, pathogenesis and statistics of COVID-19 in the world. Moreover, it includes chemistry, mechanism of action at the molecular level of the possible drug molecules which are liable for redirection as potential COVID-19 therapeutic agents. This includes polymerase inhibitors, protease inhibitors, malaria drugs, lipid lowering statins, rheumatoid arthritis drugs and some miscellaneous agents. We offer research data and knowledge about the chemistry and biology of potential COVID-19 drugs for the research community in this field.

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## 1 Introduction

This work aims to find a suitable vaccine or drug to save the global population promptly. One of the most promising strategies is drug repurposing, known as repositioning, reprofiling or redirecting strategies.<sup>1</sup> This review article is focused on the chemistry and biology of drug molecules or drug groups that target diseases other than COVID-19 and may be useful to design possible drugs or drug combinations for treatment of COVID-19 viral infection.

### 1.1 Background

Infectious diseases are those which are caused by microorganisms. Their importance comes from the degree and the extent of damage

caused to the host cells and organs. Damage caused by microorganisms is due to their growth, multiplication or replication, their metabolic biproducts, distribution and their interference with functions of host systems.<sup>2</sup> By the failure of immune system to eliminate the pathogenic organism, the infection can emerge.<sup>3</sup> Emerging infectious disease usually appears in a certain time, in a given population of certain environment causing epidemics. Sometimes the infectious agent is highly contagious; spread rapidly resulting in the transfer of infection from one population to another and from one country to other causing pandemics. It was noticed in the last decades that many emerging infectious diseases which was controlled in the past, begins to reappear again. These reemerged infectious diseases found to be caused by the previously controlled pathogens after their acquisition of new properties due to gene mutation, genetic recombination, reassortment or the passage of the organism by many stages of adaptation to new environment and hosts.<sup>4</sup> Many emerging infectious diseases were found to threaten the global public health causing pandemics such as SARS-COV (severe acute respiratory syndrome), MERS-COV (Middle East respiratory syndrome), hemorrhagic fever, Ebola, influenza and Zika virus infections. The impact of epidemics caused by the previous diseases depends on the number of the infected individuals in a certain time, mode of transmission, severity of cases and mortality rate.<sup>5</sup>

On 12 December 2019, A Chinese patient (from Wuhan, Hubei province, china) suffering from severe respiratory disease was hospitalized followed by the admission of 1975 cases with

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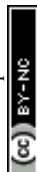
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the same symptoms until 25 January, 2020. By the increase in the number of cases with the same symptoms (fever, dry cough, fatigue and sore throat), samples were obtained from the bronchoalveolar lavage fluid from a patient (a worker at a seafood market) admitted to the central hospital of Wuhan, China for isolating the causative agent. Metagenomic RNA sequencing for the extracted RNA showed a new RNA virus belongs to coronaviridae that was named as 2019-nCoV on 7<sup>th</sup> January 2020. Then, it was renamed as SARS-CoV-2 after testing its nucleotides' similarity to SARS-CoV and MERS-CoV that showed 89.1% of nucleotide identity between SARS-CoV (was previously found in bats causing an outbreak in China, 2003) and the new virus.<sup>6</sup>

On 30 January 2020, the new coronavirus outbreak was declared as a public health emergency of international concern (PHEIC) which means that the new disease is an extraordinary event and is considered as a public health risk to other countries by the international spread of disease and require a coordinated international response.<sup>7</sup> On 11 February 2020, World Health Organization (WHO) announced the official name for the new virus as coronavirus disease 2019 (COVID-19).<sup>8</sup> This name was announced according to the guidelines of WHO set in 2015, which stated that naming new human disease should not refer to certain geographical area, animal, group of people to avoid the negative effects on travelling, tourism, trade, animal welfare, any cultural or national or professional or ethnic groups.<sup>9</sup> On 11 March 2020, WHO officially changed the classification of COVID-19 from PHEIC to a pandemic disease which was the first pandemic since H1N1 pandemic in 2009.<sup>10</sup>

## 1.2 Epidemiology

As of 21 June 2020, WHO has reported that there are 8 894 711 confirmed cases of COVID-19 infection globally distributed in 6 different regions in 213 countries and territories. Out of the total number of the confirmed cases, active cases were 3 704 142 (364 966 mild conditions (98.5%) and 54 492 serious cases (1.4%)) and closed cases were 5 190 569 from which 4 724 625 (91.1%) were recovered and 495 944 (9.5%) deaths,<sup>11</sup> Fig. 1. Also, number of deaths among males were found to be more than that observed among females which may be attributed to females sex steroid concentrations and X chromosome diploidy that results in strong immune response observed by females,<sup>12</sup> Fig. 2.

## 1.3 Origin and transmission

COVID-19 or SARS-CoV-2 is a member of  $\beta$ -coronavirus, subgenus Sarbecovirus-Orthocoronavirinae subfamily.<sup>14,15</sup>  $\beta$ -Coronaviruses were known to cause epidemics of severe acute respiratory illness such as epidemics caused by SARS-CoV in 2003 and MERS-CoV in 2012.<sup>16</sup> Metagenomic RNA sequencing of the isolated strain, revealed 96.2% similarity to bat-CoV RaTG13 and 89.1% similarity to SARS-CoV which suspected that it is a zoonotic disease and bat is the natural host of the virus. Also, previous findings suggested that COVID-19 uses angiotensin-converting enzyme-2 receptor (ACE2) similar to SARS-CoV. On the other side, the first isolated virus was isolated

from a worker on a seafood market which did not contain bats that indicated the probability of the presence of some other intermediate hosts.<sup>17</sup> Lui *et al.*, reported that protein sequences alignment and genome sequencing showed that many species shared similar residues of receptors such as turtles, pangolins and snakes.<sup>18</sup> Another study done by Wrapp *et al.*<sup>19</sup> supported the probability of the presence of more than one intermediate host. As they revealed that binding affinity of SARS-CoV-2 S protein to ACE2 is much stronger than that observed by SARS-CoV. Human to human transmission was firstly reported on 30 January 2020 when a husband of a confirmed COVID-19 case tested positive for SARS-CoV-2 with no history of travelling outside USA.<sup>20</sup> Many studies reported that 85% of human to human transfer occurs within social events and among family members. In addition, transmission of SARS-CoV-2 infection among health care team was found to be 3.8% of cases which is lower than that reported in SARS-CoV in 2003 while majority of cases were infected from their families due to the long period of contact with them.<sup>6,10,21,22</sup>

## 1.4 COVID-19 (SARS-CoV-2) structure

SARS-CoV-2 viruses are enveloped positive sense RNA viruses with helical symmetrical nucleocapsid. Coronaviruses are characterized by their specific features of having club-shaped spike projections on their surfaces. Coronavirus particles have 4 main structural proteins which are: *Spike (S) protein* (trimetric S glycoprotein) is a class I fusion protein which is activated by human proteases and cleaved at S1/S2 containing receptor binding domain (RBD) and at S2' portion responsible for virus fusion with cell membrane.<sup>23</sup> *M protein* (~25–30 kDa) gives the virus its shape and can adapt for 2 different conformations allowing it to promote membrane curvature to bind the nucleocapsid. *E protein* (~8–12 kDa) is a transmembrane protein. It was found that viruses without E protein have no lethal action. It has a role in the assembly and the release of viruses. N protein is the protein forming nucleocapsid with high affinity for viral RNA. It has a role in the packaging of encapsidated genome to viral particles.<sup>24–26</sup>

In addition, the virus has hemagglutination-esterase (HE) dimer in their structure which binds to sialic acid and shows esterase activity to facilitate viral S protein cell entry and viral spread.<sup>27</sup>

## 1.5 SARS-CoV-2 life cycle and pathogenesis

Viral attachment was initiated by binding S protein to ACE2 receptor. S protein is cleaved into S1, containing receptor binding site, which binds to peptidase domain of ACE2 receptor and S2 which is responsible for membrane fusion. After the binding of S protein with ACE2 receptor, they undergo conformational changes by pH-dependent cysteine protease cathepsin L, followed by fusion of viral envelope with the wall of endosome.<sup>28</sup> Another way of entry depends on direct proteolytic cleavage of transmembrane protease 2 (TMPRSS2) to ACE2 receptor and the activation of S protein followed by the fusion of viral envelope with the host cell membrane and the passage of





Fig. 1 Global total deaths of COVID-19 starting from 23 January to 21 June 2020 (data from Worldometer).<sup>13</sup>

nucleocapsid into the cytoplasm and the release of viral genome.<sup>29</sup>

Viral genomes act as mRNA. Translation was employed to the two third of the genome containing (open reading frame) ORF1a and ORF1b into polyproteins pp1a and pp1ab. Polyproteins with their proteases (PLpro and 3CLpro) were cleaved into 16 non-structural proteins forming replicase–transcriptase complex (RTC). The main protein of RTC is RNA-dependent RNA polymerase (RdRp) which mediates synthesis of negative sense subgenomic RNA from positive sense mRNA and the transcription of negative sense subgenomic RNA into positive sense mRNA and the replication of the positive mRNA to become the genome of the viral particles.<sup>30</sup>

The remaining part of the genome following ORF is translated into the structural proteins (S, E, M and N proteins) in the endoplasmic reticulum. Structural proteins move to Golgi intermediate compartment where M protein direct protein–

protein interaction for protein assembly forming viral particles. Viral particles transferred by exocytosis using secretory vesicles for release.<sup>30</sup>

The peak viral load of patients with COVID-19 occurs during the first week of illness and gradually decreases over the second week which explained why SARS-CoV-2 is highly infectious and showed high transmissibility during the first week of getting infection. It was found that the severity of symptoms is correlated with age. Older adults showed more severe symptoms due to their lower immunity, presence of other diseases such as cardiovascular diseases, diabetes, pulmonary diseases, cancer or other diseases affecting their overall immunity<sup>31</sup> and high expression of ACE2 receptors,<sup>32</sup> Fig. 3.

### 1.6 Response to COVID-19 infection

Response to SARS-CoV-2 infection was found to have 3 stages depending on the overall immunity of patients. The first is



Fig. 2 Global death rate among all cases and confirmed cases according to gender.<sup>13</sup>



Fig. 3 Death rate among all cases and confirmed cases according to the presence of pre-existing disease.<sup>13</sup>

asymptomatic stage with or without detectable virus. The second is symptomatic stage with mild to moderate symptoms with detectable virus. The third is symptomatic stage with severe complications, high viral load and marked damage to organs such as lung, intestine and kidney.<sup>33</sup> Clinical manifestation of SARS-CoV-2 ranged from mild symptoms to life-threatening complications. Main symptoms are fever (88% of patients), dry cough (67% of patients), fatigue (38% of patients) and sore throat (14% of patients). Non-respiratory symptoms such as diarrhea are challenging to find. By time, patients develop shortness of breath (an average of eight days) followed by lymphopenia and clinical pneumonia supported with CT findings (characteristic pulmonary ground glass opacity changes on chest). Hypoxic respiratory failure may develop that needs ICU admission. Mechanical ventilation due to refractory hypoxia is required in 10% of patients.<sup>34</sup>

According to previous data obtained during previous outbreaks caused by coronaviruses, innate immune response plays a critical role in the protection or the destructive response to the infection. SARS-CoV-2 was found to induce delayed type I IFN (interferon) and increase the influx of neutrophils and macrophages which are the sources of pro-inflammatory mediators (cause inflammation and further damage) with the loss of viral replication control. In addition, adaptive immune response was initiated by antigen presenting cell (APC) through their MHC class I and MHC class II by inducing CD8+ T cell response more frequently (to kill virus infected cells) than CD4+ T cell response which leads to the increase in the severity of disease and further damage to lung cells. In addition, humoral immunity is stimulated for the production of specific IgM at day 9 after disease onset and seroconversion to IgG by week 2.

Long incubation period of SARS-CoV-2 virus may be attributed to the time taken by the virus to evade immune detection mechanisms and to suppress immune response.<sup>17,35,36</sup> Some patients remain viral positive or suffer relapse after their discharge from the hospital which indicates that some people may not develop immunity against SAR-CoV-2.<sup>37</sup>

Statistics results showed variation of number of deaths with age, Fig. 4. The rate of infection in the age range of 0 to 9 years old is very low. This may due to strong immune response or cross reactivity between vaccines of the routine childhood immunization schedule and other viral genus. Some studies showed that infants gain high degree of protection because of their extended immunization program. Liniger *et al.*<sup>38</sup> showed that measles vaccine provides neutralizing antibodies against SARS-CoV and HIV. In addition, it was found that intralesional administration of MMR vaccine results in the improvement of cases suffering from warts caused by human papilloma virus. Also, *Bordetella pertussis* (a vaccine against whooping cough disease) and BCG (a vaccine against tuberculosis diseases) vaccines were reported to give rise to neutralizing antibodies against some respiratory viruses by the production of local cytokines in lungs protecting lungs from damage. This situation may be explained by the ability of vaccines to stimulate CD4+ T helper1 cells resulting in the secretion of different types of cytokines including  $\gamma$ -interferon, IL-2, IL-12 activating cytotoxic NK cells and stimulating CD8+ T cells for killing virus infected cells.<sup>39–41</sup> Another explanation for child response to infection may be attributed to the trained immunity or innate immunity memory in which innate immune system stores information about the pathogen causing primary infection or after vaccination to respond rapidly and strongly after the subsequent exposure to the same or some unrelated pathogens. Many studies reported metabolic, epigenetic and transcriptional reprogramming for specific innate immune cells such as monocytes, macrophages and NK cells regarding strong non-specific vaccination response.<sup>42</sup> Also, it was reported that this memory is transferable especially after observing trained monocytes (monocytes have short-life span in circulation of one day) in the circulation of an individual after 3 months of BCG vaccination. Innate memory was explained by the occurrence of reprogramming at the level of progenitor cells of the innate immune cells and the ability of innate immune memory to transfer *via* hematopoietic stem and progenitor cells. On the other hand, the signals mediating the transfer of innate





Fig. 4 Death rate among different age range according to data obtained from the first 44 672 confirmed cases in China.<sup>50</sup>

immune memory from the periphery to the bone marrow is not yet known in details and need further investigation.<sup>42–44</sup>

Many studies reported the protective role of breastfeeding even after breastfeeding has been stopped. As it gives protection against infection by wide range of pathogens including respiratory pathogens in the long term which means that its protective role increase by the increase in the time of breastfeeding showing persistent protective effect.<sup>45,46</sup> Agarwal *et al.*<sup>47</sup> reported that macrophage cells represent 80% of the early milk and by the transfer of macrophages to the infant, they can be differentiated into dendritic cells that can stimulate T-lymphocytes giving protection against wide range of pathogens. Also, human milk contains pro-inflammatory cytokines in levels that can induce inflammation and defend against pathogens, fatty acids which have destructive effect on microbial membranes and viral envelope,<sup>48</sup> lactoferrin, iron binding glycoprotein (belongs to transferrin family) and milk fat globule containing mucins which are known with their activity against bacteria, viruses and fungi.<sup>49</sup>

### 1.7 Potential interventions for treating or preventing COVID-19

There are no approved treatment or effective vaccines against SARS-CoV-2 till now but there is a great need for rapid development of antiviral agents and vaccines to stop the wide spread of infection and to save lives of the infected cases. There are many trials applied and showed useful results such as:

**1.7.1 Interference with viral binding to ACE2 receptors.** S (Spike) protein is an important target as it contains RBD epitope which is responsible for binding to ACE2 receptor. Using monoclonal antibodies against RBD epitope can neutralize the virus preventing viral cell entry. Depending on the fact that SARS-CoV and SARS-CoV-2 bind to the same receptor, neutralizing monoclonal antibodies against SARS-CoV can show protection against SARS-CoV-2 such as CR3014, CR3022, F26G18 and

F26G19 monoclonal antibodies which give their action by blocking the interaction of S1 subunit protein with cellular ACE2 receptor.<sup>51–55</sup>

**1.7.2 Bevacizumab.** Bevacizumab is an anti-VEGF (vascular endothelial growth factor) recombinant humanized monoclonal antibody, which has been used as anti-tumor treatment for 16 years. Evidence suggest that bevacizumab is a promising drug for severe and critical COVID-19 patients.<sup>56</sup>

**1.7.3 Vaccines under trials.** NIH started clinical trial on 16 March 2020 using mRNA as a vaccine. The vaccine is called mRNA-1273. The new vaccine directs the body's cells to express the virus protein to stimulate immune response. The mRNA-1273 vaccine has shown promise in animal models, and this is the first trial to be examined in humans.<sup>57</sup>

Kim *et al.* produced both rSARS-CoV-S1 and rSARSCoV-S1fRS09 immunogens after the publication of the SARS-CoV-2-spike glycoprotein sequence and incorporate them in dissolvable microneedle array (MNA) for pre-clinical testing publication. MNA delivery of either rSARS-CoV-2-S1 or rSARS-CoV-2-S1fRS09 induced significant increases in antigen-specific antibodies responses as soon as week 2. So, it is considered as a promising immunization strategy against coronavirus infection.<sup>58</sup>

**1.7.4 Passive immunization.** Using plasma or hyper-immunoglobulin of patients recovered from COVID-19 may be effective. The administered antibodies have the ability to recognize epitopes of the virus, neutralizing it and prevent its replication and spread. There are some challenges facing the application of passive immunization which are: availability of donors in the current time with the wide spread of the virus all over the world, donors should be from the same city or the same area due to the difference in life style of individuals and the possibility of the presence of another new strain of the virus similar to what happened in Italy (isolating of a new coronavirus



from an Italian patient that differs than that isolated from China).<sup>59</sup>

## 2 Repopiling of known antiviral agents in COVID-viruses

### 2.1 Polymerase inhibitors

Polymerase inhibitors, in general, can be classified into two categories: nucleotide/nucleoside analogs and non-nucleoside inhibitors (pyrophosphate derivatives). Nucleotide and nucleoside analogue inhibitors are chemically synthesized analogues of purines and pyrimidines in which the heterocyclic ring or sugar moiety has been altered and include 5-substituted 2'-deoxyuridine analogs (idoxuridine, trifluridine, and brivudine) (Fig. 5 and Table 1). They include arabinosyl nucleoside analogs (vidarabine) and acyclic guanosine analogs (acyclovir, ganciclovir, penciclovir, famciclovir, valaciclovir, and valganciclovir) (Fig. 5). Related to these drugs, cidofovir is a broad-spectrum nucleotide analog (acyclic nucleoside phosphonate), approved for treatment of HCMV retinitis in AIDS patients and used to treat many other DNA virus infections (*e.g.*, HSV, adeno-, pox-, polyoma-, and papillomavirus infections) (Fig. 5).<sup>60,61</sup>

Nucleoside analogs are prodrugs that mimic natural nucleosides and are used, in their triphosphate forms, as substrates for the synthesis of viral nucleic acid. This means that nucleoside analogs must not be only substrates for viral polymerases, they also need to be recognized and phosphorylated by host

nucleo(s/t)ide kinases.<sup>60,61</sup> Nucleotide and nucleoside analogue inhibitors (NIs) currently used to treat both acute and chronic viral infections. NIs exhibit a relatively high barrier to resistance emergence because the structural conservation of the polymerase targets binding site is high among virus families, and resistance mutations generally incur a fitness cost for the enzyme and the virus.<sup>62</sup>

For CoVs, amino acid conservation of the viral RdRp ranges from 70 to near 100% and is maintained across genera, suggesting NIs could potentially serve as broad-spectrum inhibitors of CoV infection.<sup>63</sup> However, proofreading activity of nsp14-ExoN activity protects CoVs from many NIs effective against other RNA viruses.<sup>64,65</sup> For effective inhibition of CoVs, an NI needs to either evade recognition by ExoN or undergo uptake into the elongating strand at a rate exceeding ExoN excision kinetics.

#### 2.1.1 Efficacy of nucleotide and nucleoside analogue inhibitors (NIs) against CoVs

**2.1.1.1 Favipiravir.** Favipiravir, also known as T-705, pyrazinecarboxamide derivative, a guanine nucleoside analogue (Fig. 6 and Table 1) was originally developed by Toyama Chemical of Japan.<sup>66</sup> In March 2015, the US Food and Drug Administration completed a phase III clinical trial studying the safety and efficacy of favipiravir in the treatment of influenza.<sup>67</sup> Moreover, on March 15, 2020 the drug was approved in China for the treatment of influenza.<sup>68</sup> Recently, favipiravir approved for use in clinical trials for treating coronavirus disease 2019

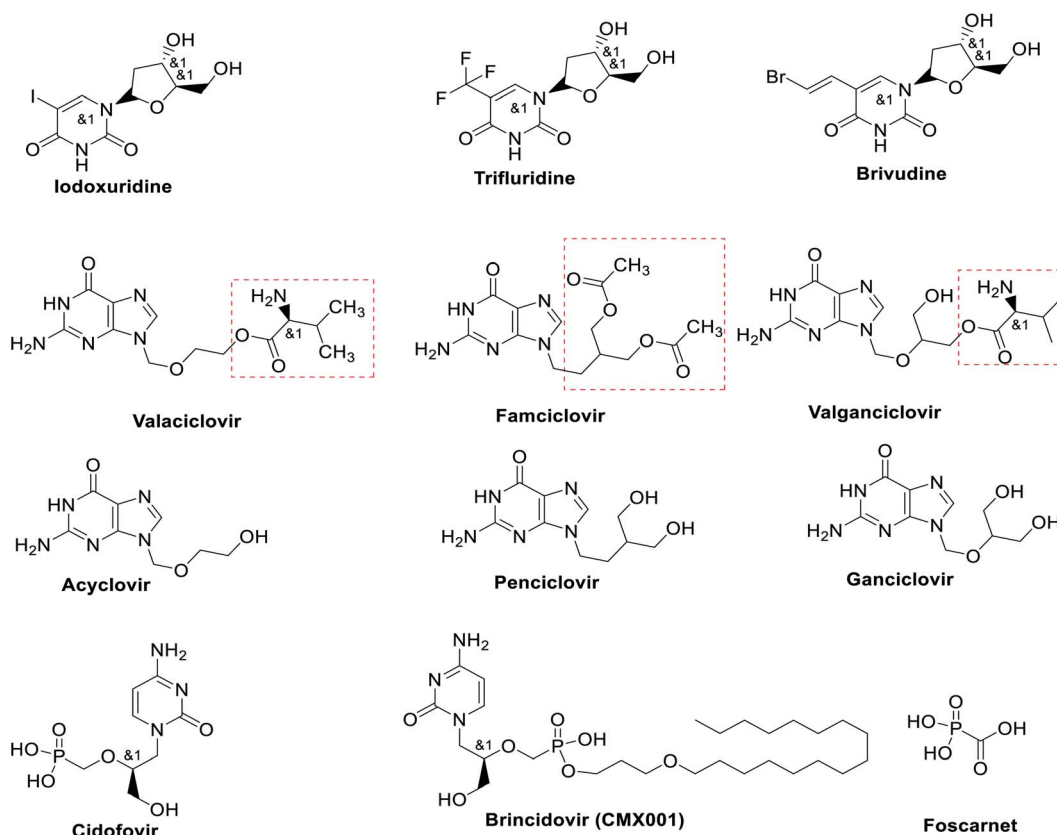


Fig. 5 Structure of some nucleoside, nucleotide and pyrophosphate analogs.



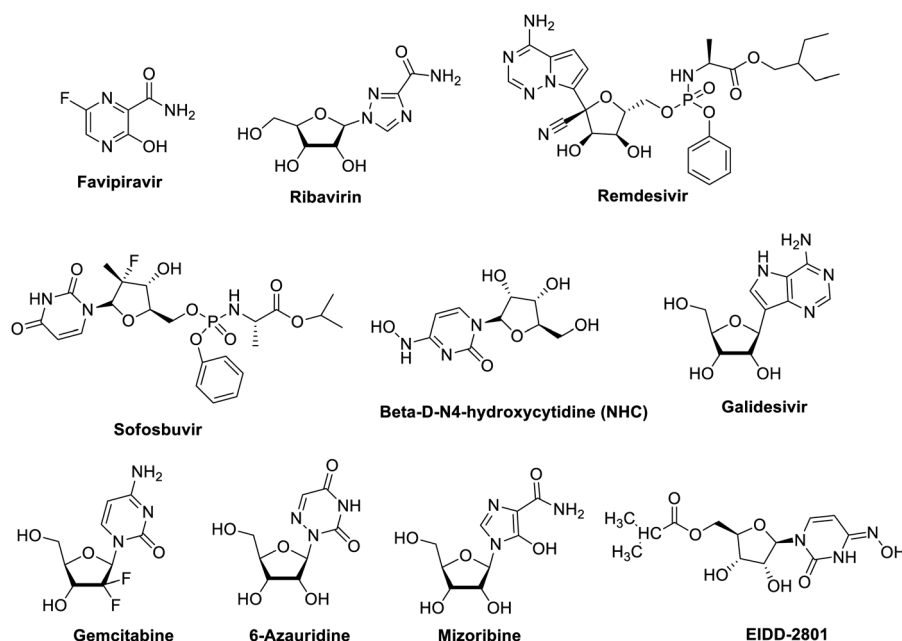
**Table 1** Existing drugs with therapeutic potentials for COVID-19 (drug repurposing) targeting RdRp<sup>95</sup>

Antiviral agents	Infectious diseases	Reported mechanism of action	Status
Favipiravir	2019-nCoV; influenza	Inhibits RdRp	<ul style="list-style-type: none"> <li>• Approved for influenza in Japan</li> <li>• Randomized trial for 2019-nCoV (ChiCTR2000029544, ChiCTR2000029600)</li> </ul>
Ribavirin	2019-nCoV, MERS-CoV, SARS-CoV, RSV, HCV	Inhibits viral RNA synthesis and mRNA capping	<ul style="list-style-type: none"> <li>• Approved for HCV and RSV</li> <li>• Randomized trial for 2019-nCoV in combination a pegylated interferon (ChiCTR2000029387)</li> <li>• Randomized trial for SARS (NCT00578825)</li> </ul>
Penciclovir Remdesivir (GS-5734)	2019-nCoV 2019-nCoV, MERS-CoV, SARS-CoV	Inhibits RdRp Terminates the non-obligate chain	Approved for HSV <ul style="list-style-type: none"> <li>• Phase III for 2019-nCoV (NCT04252664, NCT04257656)</li> <li>• Phase I for Ebola (NCT03719586)</li> <li>• Phase I for yellow fever (NCT03891420)</li> <li>• Phase I for Marburg virus (NCT03800173)</li> </ul>
Galidesivir (BCX4430)	Broad-spectrum ( <i>e.g.</i> SARS-CoV, MERS-CoV, IAV)	Inhibits viral RNA polymerase function by terminating non-obligate RNA chain	Preclinical
6'-Fluorinated-aristeromycin analogues	Broad-spectrum ( <i>e.g.</i> CoV, ZIKV, CHIKV)	Inhibits the activity of RdRp and host cell <i>S</i> -adenosyl-L-homocysteine hydrolase	Preclinical
Acyclovir fleximer analogues	HCoV-NL63, MERS-CoV	Doubly flexible nucleoside analogues inhibit RdRp	Preclinical

pneumonia.<sup>68</sup> Its mechanism of actions is thought to be related to the selective inhibition of viral RNA-dependent RNA polymerase.<sup>69</sup> Other research study suggests that favipiravir induces lethal RNA transversion mutations, producing a nonviable viral phenotype.<sup>70</sup> Favipiravir is a prodrug that is metabolized to its ribofuranosyl-5'-triphosphate (favipiravir-RTP) form which act as purine mimetic binding to ATP- and GTP-binding sites on polymerase in a competitive manner.<sup>71–73</sup> Notably, favipiravir is

selective to viral cells, it does not inhibit RNA or DNA synthesis in mammalian cells therefore it is not toxic to them.<sup>74</sup> Favipiravir can effectively inhibit the RNA-dependent RNA polymerase of RNA viruses such as influenza, Ebola, yellow fever, chikungunya, norovirus and enterovirus.<sup>75</sup>

In February 2020, favipiravir has been approved for a clinical trial as a drug to treat COVID-19.<sup>76,77</sup> On March 17, Chinese officials suggested the drug had been effective in treating

**Fig. 6** Structure of some polymerase inhibitors used in treatment of COVID-19.

COVID-19 in Wuhan and Shenzhen. Recently, a study reported its activity against 2019-nCoV ( $EC_{50} = 61.88 \mu\text{M}$  in Vero E6 cells).<sup>78</sup> Patients with 2019-nCoV are being recruited in randomized trials to evaluate the efficacy of favipiravir plus interferon- $\alpha$  (ChiCTR2000029600) and favipiravir plus baloxavir marboxil (an approved influenza inhibitor targeting the cap-dependent endonuclease) (ChiCTR2000029544). Moreover, A study on 80 patients comparing it to lopinavir/ritonavir found that it significantly reduced viral clearance time to 4 days, compared to 11 for the control group, and that 91.43% of patients had improved CT scans with few side effects.<sup>79,80</sup> As of 23 March 2020, it seems that Japan and China have issued an export ban on the substance. Japan and China are the only countries in which favipiravir is produced and approved as a medical compound. Some Chinese pharmaceutical companies assure that export rights are still granted *via* international diplomatic means by the Chinese Ministry of Industry and Information Technology.

**2.1.1.2 Ribavirin.** Ribavirin (Fig. 6) is a synthetic nucleoside guanosine analogue and has broad-spectrum antiviral activity against multiple RNA viruses. It is approved for treating respiratory syncytial virus, hepatitis C and E virus, Lassa virus, and hantavirus infections. Although the coronavirus is an RNA virus, in theory favipiravir and ribavirin have some anti-coronavirus activity. However, coronaviruses express exonuclease (nsp14-ExoN) in nonstructural protein 14, and are common throughout the coronavirus family. The current research results show that nsp14-ExoN has an RNA proofing function.<sup>81</sup> So, it is speculated that the coronavirus is resistant to nucleoside analogs. The results of *in vitro* experiments have shown that ribavirin has little antiviral effect on coronavirus. NIs effective against other RNA viruses.<sup>64</sup> Synergistic activity against MERS-CoV of ribavirin combined with IFN $\alpha$ 2b was observed *in vitro* and in rhesus macaques, suggesting that IFN increases the potency of ribavirin at lower, more tolerable concentrations.<sup>82,83</sup> However, five critically ill MERS-CoV-positive patients who were treated with a combination of ribavirin and IFN $\alpha$ 2b showed no clinical improvement.<sup>84</sup> Treatment of 20 MERS patients with a combination of ribavirin and IFN $\alpha$ 2a showed significantly improved survival at 14 days but not at 28 days,<sup>85</sup> whereas treatment of MERS patients with a combination of IFN $\alpha$ 2a or IFN $\beta$ 1a and ribavirin yielded no survival benefit in another study.<sup>86</sup> Thus, although ribavirin shows some efficacy *in vitro*, it does not provide clinical benefit to humans with SARS-CoV or MERS-CoV infections. Ribavirin approved for treating HCV and respiratory syncytial virus (RSV) that has been evaluated in patients with SARS and MERS, but its side effects such as anaemia may be severe at high doses<sup>87</sup> and whether it offers sufficient potency against 2019-nCoV is uncertain. However, a fixed dose of the anti-HIV combination, lopinavir-ritonavir, is currently in clinical trials with umifenovir or ribavirin.<sup>88</sup>

**2.1.1.3 Remdesivir (GS-5734).** Remdesivir (Fig. 6), nucleoside analogue, is a phosphoramidate prodrug of the adenosine NI GS-441524 which have multiple mechanisms of action, including lethal mutagenesis, obligate or non-obligate chain termination, and perturbation of natural nucleotide triphosphate pools *via* inhibition of nucleotide biosynthesis.<sup>89</sup>

Remdesivir has demonstrated antiviral activity *in vitro* against several viral families of emerging infectious diseases including pneumoviridae, filoviridae, pneumoviridae, paramyxoviridae, and coronaviridae.<sup>63,90,91</sup> Remdesivir has broad-spectrum activities against a diverse panel of RNA viruses such as Ebola virus (EBOV), Marburg, MERS-CoV, SARS-CoV, respiratory syncytial virus (RSV), Nipah virus (NiV), and Hendra virus under clinical development. The mechanism of remdesivir's anti-MERS-CoV activity is likely through premature termination of viral RNA transcription.<sup>92,93</sup> A recent study reported that remdesivir inhibited 2019-nCoV ( $EC_{50} = 0.77 \mu\text{M}$  in Vero E6 cells),<sup>78</sup> and a US patient with 2019-nCoV recovered after receiving intravenous remdesivir in January.<sup>94</sup> The drug is currently being studied in phase III clinical trials in both China and USA. Two phase III trials were initiated in early February to evaluate intravenous remdesivir (200 mg on day 1 and 100 mg once daily for 9 days) in patients with 2019-nCoV (NCT04252664 and NCT04257656), with estimated completion dates in April 2020.<sup>95</sup> Studies probing the interactions between remdesivir and the CoV replication machinery will likely yield crucial insights into how this NI circumvents or overcomes CoV proofreading activity, which can in turn be applied to modeling the development of new NIs and enhancing potency of existing NIs. Currently, remdesivir clinical trials are enrolling and are supported by the National Institutes of Health (NIH),<sup>96</sup> USA and AIFA, Italy.<sup>97</sup> The use of remdesivir in COVID-19 patients in a single-arm trial gave positive preliminary outcomes,<sup>98</sup> and this in contrast to the result published by another group.<sup>99</sup> However, the debate over remdesivir efficacy is still open, according to the reported preliminary results in the ACTT NIH clinical trial,<sup>96</sup> the FDA has given remdesivir an emergency use authorization restricted to patients affected by severe COVID-19.<sup>97</sup>

**2.1.1.4 Sofosbuvir.** Sofosbuvir (Fig. 6), a nucleotide analogue hepatitis C virus NS5B polymerase inhibitor, is used to treat chronic hepatitis C as a component of a combination antiviral regimen. In addition, the European Medicines Agency's Committee for Medicinal Products for Human Use has recommended the approval of sofosbuvir for the treatment of chronic hepatitis C.<sup>100,101</sup> The most important druggable targets of sofosbuvir is the RNA-dependent RNA polymerase (RdRp), where it is incorporated into RNA, and due to modifications at the 2' position, inhibits further RNA chain extension and halts RNA replication, and sofosbuvir can inhibit RdRp of the hepatitis C virus, it acts as an RNA polymerase inhibitor by competing with natural ribonucleotides. As the hepatitis C virus and the coronavirus use a similar viral genome replication mechanism, sofosbuvir may also inhibit coronaviruses, including 2019-nCoV.<sup>102</sup>

**2.1.1.5 Beta-D-4-hydroxycytidine (NHC).** NHC (Fig. 6) is a cytidine analogue with demonstrated potent, broad-spectrum antiviral activity against many viruses such as Venezuelan equine encephalitis virus (VEEV), influenza A virus (IAV), respiratory syncytial virus (RSV), chikungunya virus (CHIKV), influenza B virus (IBV), and CoVs. NHC exerts its antiviral effect primarily through mutagenesis of viral RNA serial passaging in the presence of NHC led to low level resistance for VEEV but not RSV, IAV, and bovine viral diarrhoea virus, thus indicating a high





resistance barrier.<sup>103–107</sup> Potent anti-CoV activity of NHC was demonstrated for SARS-CoV and HCoV-NL63.<sup>106,108</sup> Although the mechanism of CoV inhibition has not been determined, micromolar-range EC<sub>50</sub>s suggests that NHC like remdesivir may also have a novel way of interacting with the CoV replication. Its potent, broad-spectrum antiviral activity warrants further investigation for the treatment of CoV infections, either alone or in combination with other DAAs and immunomodulators. Moreover, the isopropyl ester prodrug of the ribonucleotide analogue, N4-hydroxycytidine (Fig. 6) with improved bioavailability was found to inhibit replication of human and bat SARS-CoV-2. This occurs in the airway epithelial cells in both mice and human. Clinical trials for the effectiveness of this drug are in progress.<sup>109</sup>

**2.1.1.6 Other drugs.** Galidesivir (BCX4430), Fig. 6, is an adenosine analogue that was originally developed for HCV, and has broad spectrum activity positive and negative sense RNA viruses. Galidesivir is currently in early-stage clinical studies evaluating its safety in healthy subjects and its efficacy against yellow fever, and has shown antiviral activities in preclinical studies against many RNA viruses, including SARS and MERS.<sup>87,110</sup>

Gemcitabine hydrochloride, Fig. 6, another NIs deoxycytidine analogue, is a chemotherapy drug that inhibits SARS-CoV and MERS-CoV, in addition to the uridine analogue 6-azauridine (Fig. 6) with activity against HCoV-NL63;<sup>106</sup> and finally, mizoribine (Fig. 6), the immunosuppressant imidazole nucleoside, which inhibits SARS-CoV.<sup>87</sup>

## 2.2 Proteases inhibitors

**2.2.1 SARS-CoV-2 main protease inhibitors.** Nominated the molecule of the month in February 2020,<sup>111</sup> the main protease (M<sup>Pro</sup>) of the new coronavirus SARS-CoV-2 is a heart shaped dimer that is responsible for different cuttings in the viral lipoproteins<sup>112</sup> into essential functional pieces forming viral spike, membrane, envelop, nucleoprotein, replicase, and polymerase.<sup>113,114</sup> These cutting products are essential for viral maturation, survival and replication.<sup>114</sup> Thus since the protease enzyme is crucial for viral proteolytic activities in early stage of the SARS-CoV life cycle, it is considered as a promising target for attacking the viral activity.<sup>115,116</sup> This fact was supported by the success of inhibiting viral proteases in the fight against previous viral infections such as human immunodeficiency virus (HIV)<sup>117</sup> and hepatitis C.<sup>118</sup>

The use of protease inhibitors for preventing coronavirus replication started with repurposing anti-HIV protease inhibitors. While the main residue in HIV protease is an aspartate residue,<sup>119</sup> coronaviruses protease uses a cysteine residue for nucleophilic attack.<sup>120,121</sup> The approach of using HIV protease inhibitors for older type of coronavirus SARS-CoV protease started with rational screening for old medicines including antivirals to block the proteolytic activity of SARS-CoV.<sup>120</sup> Since the M<sup>Pro</sup> sequence of both types of coronavirus is conserved by 96% and homology studies showed they also share a very similar 3D structure, the use of drugs that block M<sup>Pro</sup> of SARS-CoV as potential SARS-CoV-2 protease inhibitors is rational.<sup>112</sup>

Actually, previously approved anti-HIV protease inhibitors; lopinavir and ritonavir (Fig. 7); were found to be promising candidates for tackling the older type of coronavirus, SARS-CoV, active site.<sup>122–124</sup> Theoretically both lopinavir and ritonavir was bound efficiently to the same pocket in active sites of M<sup>Pro</sup> of both SARS-CoV and SARS-CoV-2.<sup>115</sup> Unfortunately, a randomized clinical study performed on 199 hospitalized patients in China and USA did not prove that use of the anti-HIV drugs of clinical significance over the standard care introduced for SARS-CoV-2 affected patients.<sup>124,125</sup> A similar contradiction between cell culture testing and *in vivo* screening results was reported earlier also with using alisporivir; is a cyclophilin inhibitor; against emerged coronaviruses SARS and MERS. Alisporivir inhibited both viruses in EC<sub>50</sub> of about 3.6 mM but it failed to show any improvements of SARS infection in mouse model.<sup>126</sup> Another anti-HIV protease inhibitor, nelfinavir, was repurposed for SARS infection. Nelfinavir showed a strong inhibitory activity on SARS-CoV replication<sup>127</sup> and though it gave strong reduction in viral pathogenicity and viral antigen expression for SARS-CoV but no reports tested on SARS-CoV-2 yet.

Based on the separated crystal structure of SARS-CoV-2, a German Laboratory<sup>112</sup> was able to design a ketoamide inhibitor (compound 2, Fig. 7) that successively inhibited SARS-CoV-2 viral replication in infected human Calu3 cells with an EC<sub>50</sub> of 4–5 μM. The design is based on a previously designed SARS-CoV protease inhibitor introduced earlier this year (compound 1, Fig. 2). The ability of these ketoamides to form a bond on the Cys<sup>145</sup> residue in the active site of SARS-CoV series forming a thiohemiketal offered an advantage over HIV protease inhibitors used lacking thiol reactivity.<sup>128</sup> An additional advantage is the ability of these compounds to form two hydrogen bonds at the catalytic active site of SARS-CoV-2 with Gly<sup>143</sup>, Cys<sup>129,145</sup> but still the lack of animal testing raising a big question on the availability of use of such inhibitors for controlling COVID-19.

Additionally, a theoretical study using the crystal structure of the M<sup>Pro</sup> for SARS-CoV2, scientists tried to repurpose commercially available medicines to fit into the enzyme pocket. Surprisingly, antibiotics and chemotherapeutic agents named colistin and valrubicin (Fig. 7) showed tight binding with 9 and 7 hydrogen bonds formed with essential amino acid residues in M<sup>Pro</sup> active site including THR<sup>24</sup>, THR<sup>25</sup>, and THR<sup>26</sup>.<sup>115</sup> Other theoretical studies investigating millions of small molecules as possible candidates for M<sup>Pro</sup> inhibitions are coming out lipoproteins<sup>112,130</sup> but the lack of biological testing hinders the use of these molecules as potential M<sup>Pro</sup> inhibitors and a need for more evidence to support their use is still required.

**2.2.2 Serine protease inhibitors.** Interestingly, protease inhibitors have been employed in the fight against coronaviruses for purposes more than inhibiting the proteolytic activity required for virus life. Reports announced the possible use of serine protease inhibitors for blocking virus penetration into the host cell.<sup>131</sup> The coronaviral entry into the host cell starts with the viral spike (S) protein. This S protein is composed of two subunits, S1 and S2. S1 is the subunit responsible for binding to receptors on the host cell surface (mostly angiotensin converting enzyme 2, ACE 2), while S2 is responsible for





Fig. 7 Structure of lopinavir and ritonavir, a-ketoamide protease 1 and 2, anti-HIV protease inhibitors.

viral fusion with the cell membrane. After S1 binding to ACE 2, a transmembrane serine protease (TMPRSS2) becomes responsible for S protein priming and induces cuts in both ACE 2 and S2 protein subunit causing irreversible changes that ease the process of viral fusion into the host cell.<sup>132–134</sup> Thus, the use of serine protease inhibitors is a promising strategy in preventing viral entry to host cell and preventing its pathogenicity and researches trying to repurpose previously marketed serine inhibitors for potential treatment of COVID-19 caused by SARS-CoV-2 is currently under consideration.

In 2016, nafamostat; Fig. 8, a blood thinner that works *via* serine protease inhibition approved in Japan for treatment for acute Pancreatitis, Fig. 4; was repurposed to inhibit middle east

coronavirus MERS-CoV.<sup>135</sup> Currently, it is also tested to prevent SARS-CoV-2 entry into human cells. Nafamostat can prevent the fusion of the envelope of the virus with host cell surface membranes, the first step in infection with the causative virus SARS-CoV-2. Similarly, another inhibitor of TMPRSS2, camostat, blocks SARS-CoV-2 infection of human lung cells, Fig. 8; it actually minimized entry of MERS-S, SARS-S and SARS-2-S proteins into lung cell lines.<sup>131</sup> Nafamostat showed 10 times lower concentration in inhibiting viral membrane fusion compared to camostat.<sup>136</sup> Generally, they both represent an interesting class of compounds that might be useful in our current fight against the COVID-19 endemic.

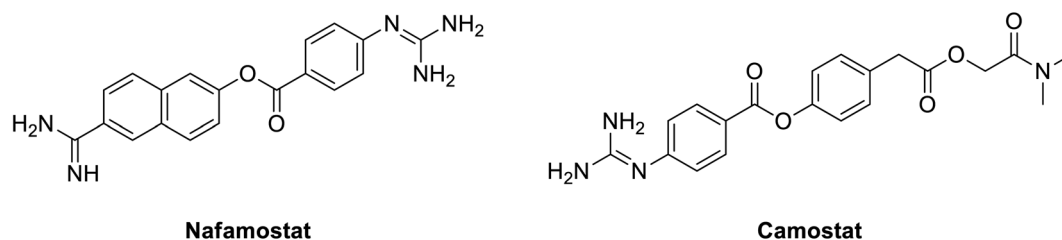


Fig. 8 Structure of serine protease inhibitors nafamostat and camostat.



### 2.3 Malaria drugs in COVID-19

Chloroquine, hydroxychloroquine and the structurally related atovaquone and mefloquine, Fig. 9, are old known therapeutically used antimalarial drugs. Hydroxychloroquine, the hydroxyl analogue of chloroquine being synthesized in the mid of 20<sup>th</sup> century was introduced as a less toxic derivative than the parent chloroquine in animal studies. Moreover, these two drugs are known to have immunomodulatory effects; hence they have been used in rheumatoid arthritis or in lupus erythematosus diseases.<sup>137</sup>

A collective review about the possible *in vivo* and *in vitro* antiviral activity of malaria drugs concluded that utilization of antimalarial drugs against viral infection may be effective especially in cases of viral resistance and emergencies.<sup>138</sup> An *in vitro* study showed that The IC<sub>50</sub> of chloroquine against SARS-CoV was  $8.8 \pm 1.2 \mu\text{M}$  which is less than the cytostatic activity; CC<sub>50</sub> ( $261.3 \pm 14.5 \mu\text{M}$ ) with selectivity index 30. The IC<sub>50</sub> of chloroquine for inhibition of SARS-CoV *in vitro* approximates the plasma concentrations of chloroquine reached during treatment of acute malaria. Addition of chloroquine to infected cultures could be delayed for up to 5 h post infection, without a significant drop in antiviral activity. Authors concluded that chloroquine, an old antimalarial drug, may be considered for prompt use in the prevention and treatment of SARS-CoV infections.<sup>139</sup> Also, another *in vitro* study resulted in important results where chloroquine can inhibit the replication and spread of CoV, and prevents CoV infection in newborn mice; this is considered a promising potential therapy for this resistant virus.<sup>140</sup> Recent reports about chloroquine and hydroxychloroquine recommend them as SARS-CoV potential agents. *In vitro* research studies results showed that hydroxychloroquine is three times more potent than chloroquine in its effect on SARS-CoV-2 infected cells (EC<sub>50</sub> = 0.72 and 5.47  $\mu\text{M}$ ). This proposal depends upon the immunomodulatory effect of chloroquine and hydroxychloroquine which may be useful in controlling the cytokines stress that occurs in patients with SARS-CoV-2.<sup>141</sup> Vincent *et al.*, (Vincent *et al.*)<sup>142</sup> concluded that chloroquine is effective in preventing the spread of SARS-CoV in

cell culture. This effect was found to occur in cells either treated with chloroquine prior or after SARS-CoV infection. This study indicated that chloroquine could elevate endosomal pH or can interfere with terminal glycosylation of the cellular receptor, angiotensin converting enzyme-2. These actions can affect virus receptor binding and hence repeal viral infection. A most recent study revealed that hydroxychloroquine may contribute efficiently in inhibiting SARS-CoV-2 *in vitro*. It may attenuate inflammatory response associated with COVID-19 and hence it can compete with the infection if the toxicity profile has been established by clinical studies.<sup>18</sup>

It is noteworthy worth that the *N*-cinnamoyl analogues of chloroquine **3a**, **b**, Fig. 10, are effective agents *in vitro* in relieving pneumocystis pneumonia associated with some pulmonary viral, bacterial, mycobacterial or parasitic infections. Compounds **3a** and **3b** will be further assessed in *in vivo* assays as potential potent anti-pneumocystis pneumonia.<sup>143</sup>

The mechanism of broad-spectrum antiviral of chloroquine and hydroxychloroquine is associated with suppressive effect on the production of the inflammatory mediators TNF- $\alpha$  and IL6. Authors in this study suggest hydroxychloroquine and analogues to have useful clinical applications in treatment of viral infections associated with inflammation or immune-hyperactivation. Moreover, a series of chloroquine analogues **4**, Fig. 10 (ref. 144) can inhibit tumor susceptibility gene (TSG101) and also seems to inhibit viral replication by blocking late-stage viral activity, possibly after completion of viral protein synthesis. Inhibition of this gene could retard the movement of the virus to the cell surface and subsequently affect budding.<sup>145</sup>

Moreover, the antimalarial antiparasitic agent atovaquone (Fig. 9) acts *via* retardation of pyrimidine biosynthesis and consequently inhibits viral replication. *In vitro* study using human placental model showed that atovaquone can limit Zika virus infection and suggesting that it can serve as broad spectrum antiviral effect.<sup>146</sup> Theoretically, computer-based design and screening proposed that chloroquine may act as SARS-CoV-2 entry blocker with S-score of 7.2639 kcal mol<sup>-1</sup>.<sup>147</sup> Atovaquone showed a potential binding affinity with S-score of



Fig. 9 Structure of malaria drugs effective in CoV.



Fig. 10 Structure of potential antiviral chloroquine analogues.

$-0.8.449 \text{ kcal mol}^{-1}$  This study states that atovaquone has the same scaffold features like chloroquine to elevate endosomal pH and interfere with ACE-2 glycosylation.<sup>147</sup> In very recent research study, a model was used for 2019-nCoV research, results showed that the antimalarial mefloquine HCl, and the antiparasitic selamectin are potential agents for treating COVID-19 infection.<sup>148</sup>

Due to the geographical overlaps between malaria and viral-related diseases, antimalarial drugs represent additional modes and mechanisms of action as antiviral agents. The lack of new effective antiviral drugs has strengthened interest in the potential antiviral activity of antimalarial drugs.<sup>149</sup> It is obvious that mechanism of action of chloroquine is not certain, it may act by elevation of endosomal pH or interference with terminal glycosylation of the cellular receptor, angiotensin converting enzyme-2.<sup>150</sup> Chloroquine inhibits quinone reductase, a structural neighbor of UDP-*N*-acetylglucosamine-2-epimerase that is involved in the biosynthesis of sialic acid. Viruses can use sialic acid moiety as receptor.<sup>151,152</sup>

Chloroquine and hydroxylchloroquine are considered promising in treatment of COVID-19. Their previous effects on MERS-COV, the analogue of COVID-19 in addition to the recent studies about their effects<sup>153</sup> recommend them as potential urgent solution to treat this viral infection on some inflammatory mediators involved in pneumonia associated with COVID-19 infections recommend them as potential urgent solution to treat this viral infection after completing the clinical studies. Also, medicinal chemists are invited to study the molecular target mechanism of chloroquine and its analogues as promising therapy for COVID-19 that enables development of newer better targeted derivatives with less side effects.

Many clinical trials and studies, in addition to *in vitro* and *in vivo*, are currently ongoing to validate the efficacy of chloroquine and hydroxylchloroquine as effective treatment for SARS-CoV-2. They are testing chloroquine if able to shorten SARS-CoV-2 disease course, mitigate inflammatory responses to infection, inhibit the exacerbation of pneumonia, improve lung imaging findings, and promote a virus negative conversion.<sup>154-158</sup> On the 13<sup>th</sup> March 2020, the FDA approved chloroquine as a treatment for COVID-19 infection with specific precautions. While early studies suggested beneficial effects of chloroquine and hydroxylchloroquine, recent studies could not confirm this, but instead highlighted potential meaningful

adverse events of chloroquine and hydroxylchloroquine in the treatment of COVID-19; this led to a temporary pause from May 23 to June 3 of the chloroquine and hydroxylchloroquine arm within the large, international Solidarity trial.<sup>159</sup> After a reassessment of the evolving data the FDA revoked the emergency use authorization for chloroquine and hydroxylchloroquine on June 15.<sup>160</sup> Therefore, we must pay the attention chloroquine and hydroxylchloroquine need to be administered with caution when treating COVID-19 infection to prevent the possible cardiovascular problems.<sup>160</sup>

## 2.4 The lipid lowering statins in COVID-viruses

Rosuvastatin (RSV), Fig. 11, is a statin FDA-approved to be used as lipid lowering agent, it acts through inhibition of HMG-CoA reductase enzyme consequently it lowers or cholesterol level. This molecule has the advantages of being inexpensive, safe and easily obtained.<sup>161</sup> A recent study showed that rosuvastatin improves lung pathological changes by decreasing T helper cells Th2 and Th17-mediated cytokines where this action is not related to its lipid-decreasing activity.<sup>162</sup>

Another study by Farag *et al.*, in a structure-based drug design approach aiming at targeting COVID-19 virus revealed that rosuvastatin on docking along with COVID-19 virus M<sup>Pro</sup> substrate-binding pocket (PDB ID: 6LU7). Rosuvastatin showed outstanding binding affinity regarding free energy with S score of  $-12.3096 \text{ kcal mol}^{-1}$ . Concerning binding mode, it experienced hydrophobic interactions and hydrogen bonding with Gly143 and Glu166 amino acids.<sup>147</sup> Although the study was totally computer-based, and need more validation studies before any clinical application, the study gives a starting point to consider the re-evaluation of statin against COVID-19.

Indeed, some research studies indicate that statins therapy is associated with a reduction in cardiovascular problems and



Fig. 11 Structure of rosuvastatin.



mortality rates in patients of influenza and/or pneumonia.<sup>147</sup> Totura *et al.*<sup>163</sup> proposed that toll-like receptor 3 (TLR3) signaling has a protective role in innate immune response in cases of severe SARS-CoV infection. The FDA approved statins are considered TLR-MYD88 agonists, they keep or retains TLR-MYD88 level during hypoxia.<sup>164</sup> Synchronously, an early and high dose of a statin might be an idea for treatment of MERS-CoV infections. However, statins may not be very effective for late-stage patients. Timely administration of statins may be crucial to surviving MERS-CoV infection.<sup>165</sup> Importantly, a recent research study showed that angiotensin receptor blockers and statins upregulate ACE2, the tissue receptor for COVID-19; these effects participated in protection against acute respiratory disease syndrome and can decrease mortality rate.<sup>166</sup> Statins are believed to reduce the risk of mortality in cases of influenza viral infection due to their anti-inflammatory and immunomodulatory effect.<sup>167</sup> Moreover, rosuvastatin reduced cytokines TNF- $\alpha$ , IFN- $\gamma$  and Th-1 immune response during 72 h, it exerts rapid immunomodulatory effects.<sup>168</sup> It is important to note that in all studies, there was no harm associated with statin therapy. Therefore, it is conceivable that patients admitted<sup>166</sup> with viral respiratory illnesses including COVID-19 could derive a beneficial effect from the continuation of their statin therapy. Statins especially rosuvastatin are advised to be given to acute COVID-19 patients; they have a role in decreasing cardiovascular problems like the fatal myocardial infarction associated with COVID-19 infection.<sup>169</sup>

## 2.5 Rheumatoid arthritis drugs

Disease-Modifying Antirheumatic Drugs (DMARDs), Fig. 12 are a diverse collection of drugs, grouped according their use and convention, for treatment of rheumatoid arthritis (RA) and other related inflammatory diseases. DMARDs are immunosuppressive and immunomodulatory agents that have been found to improve symptoms, decrease joint damage, different

types of pains and inflammations that affect, heart and blood vessels.<sup>170</sup>

They are classified as either conventional DMARDs or biologic DMARDs. Commonly used conventional DMARDs therapeutic agents have fast onset with respect to their anti-inflammatory and analgesic effects but they neither remove the underlying cause of the disease nor protect against the functional disability.<sup>171</sup> They include methotrexate (MTX), leflunomide, hydroxychloroquine, and sulfasalazine. Biologic DMARDs were introduced in the early 1990s and are usually prescribed after the failure of conventional DMARD therapy with advantages of more efficacy and fewer side effects.<sup>172</sup> Biologic DMARDs are highly specific and target a specific pathway of the immune system against inflammation like inhibition of tumor necrosis factor, suppression of IL-1 and TNF- $\alpha$ , induction of apoptosis of inflammatory cells, by increasing chemotactic factors, inhibition of purine synthesis, pyrimidine metabolism or purine metabolism. They include TNF- $\alpha$  inhibitors (certolizumab, infliximab and etanercept), modified antibody (Abatacept), modified human interleukin 1 receptor antagonist protein (Anakinra), Janus associated kinase (JAK) inhibitors (baricitinib and tofacitinib) and monoclonal antibodies as interleukin-6 receptor blockers (*e.g.* tocilizumab, sarilumab, and rituximab).<sup>173</sup>

A number of classic DMARDs have demonstrated not only antitumor but unexpected antiviral activities such as methotrexate (MTX, Fig. 12) against mosquito-borne flaviviruses, such as dengue virus (DENV) and Zika virus (ZIKV) through dihydrofolate reductase (DHFR) inhibition mechanism leading to decreased viral replication.<sup>174</sup> Other examples include leflunomide, Fig. 12, an isoxazole derivative, is nucleotide biosynthesis inhibitor, that is rapidly metabolized to its active form, and teriflunomide, which is a potent inhibitor of mitochondrial dihydroorotate dehydrogenase (DHODH), a key enzyme in the *de novo* biosynthesis of pyrimidine nucleoside triphosphates.<sup>175</sup> Both leflunomide has demonstrated antiviral activity toward

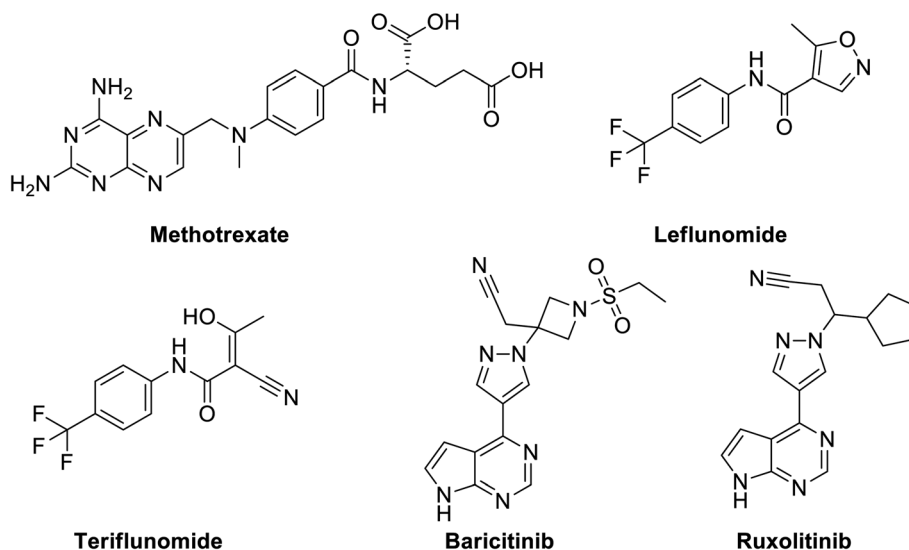


Fig. 12 Structure of methotrexate, leflunomide, teriflunomide, baricitinib and ruxolitinib as examples of DMARDs.





Fig. 13 Structure of ivermectin B1b.

diverse DNA and RNA viruses, such as herpes simplex virus (HSV),<sup>176</sup> human cytomegalovirus (HCMV),<sup>177</sup> polyoma BK virus (BKV),<sup>178,179</sup> human immunodeficiency virus (HIV),<sup>180</sup> respiratory syncytial virus (RSV),<sup>181</sup> and arenaviruses.<sup>182</sup> Currently, they have not been tested against SARS-CoV-2.

Currently, there are no specific antivirals or vaccines to treat SARS-CoV-2 infection. High-throughput screening (HTS) of various compound libraries against SARS-CoV-2 have been started and several biologic DMARDs were identified as possible targets in controlling SARS-CoV-2 complications such as tocilizumab, sarilumab and baricitinib, Fig. 12.

Interleukin 6 (IL-6), a glycoprotein composed of 212 amino acids in humans, has pleiotropic effects on many cells, including B cells, T cells, hematopoietic stem cells, hepatocytes, megakaryocytes, osteoclasts, synoviocytes, keratinocytes, and possibly chondrocytes, and thus has a wide range of biological activity, including regulation of immune response, support of hematopoiesis, generation of acute phase reactions, and induction of inflammation and oncogenesis. Therapies involving blockade of IL-6 functions have constituted a new therapeutic strategy for some inflammatory and autoimmune diseases.<sup>183</sup>

Unlike conventional DMARDs, interleukin-6 antagonists (*e.g.* sarilumab and tocilizumab) have no direct or indirect antiviral activities; they block IL-6 a key cytokine that plays an important role in immune responses as proinflammatory cytokine that induces strong inflammatory responses. So, they may have a role in the severe deterioration of lung function and COVID-19 pneumonia.

Tocilizumab (TCZ), has been developed by Osaka University for the treatment of inflammatory and autoimmune disorders.<sup>184,185</sup>

TCZ was the first humanized IgG1 monoclonal antibodies acting as interleukin-6 (IL-6) receptor antagonist approved in Japan in 2008, in Europe in 2009, and FDA-approved in 2010 for

the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) that didn't provide enough progress with other agents.<sup>186,187</sup>

TCZ can be administered intravenously or subcutaneously (SC) with similar efficacy, but convenience of SC formulation permits once-weekly self-administration.<sup>187</sup> Extensive clinical experience has firmly established the short- and long-term efficacy and safety of tocilizumab (monotherapy or in combination with conventional DMARDs) in adults with early-stage and longer-duration established RA. In the clinical trial and real-world settings, tocilizumab monotherapy or combination therapy provided rapid and sustained improvements in clinical and radiographic outcomes and health-related quality of life. The safety profile of tocilizumab is consistent over time and, in general, is consistent with that of other immunomodulatory agents. It exhibits low immunogenicity.<sup>188</sup>

Tocilizumab has anticancer potency against non-small cell lung cancer cells *via* apoptosis induction as an agonistic IL-6R regulator and it is currently under evaluation in a multicenter clinical trial for large-cell lung carcinoma.<sup>189,190</sup> In addition, tocilizumab completed phase II clinical trials for Pulmonary Arterial Hypertension (PAH) treatment.<sup>191</sup>

At present, this excellent safety and efficacy of tocilizumab encourages China's National Health Commission to include its use 8 mg kg<sup>-1</sup>/12 h (maximum of 800 mg per dose) in guidelines to treat coronavirus (COVID-19) patients either alone or in combination with favipiravir, a broad spectrum anti-viral agent. They report that the drug has been involved with a Chinese clinical trial involving 20 severe COVID-19 cases. 19 of them were discharged from the hospital within two weeks. Moreover, a 150-patient trial assessing tocilizumab is led by Hong Zhao of Peking University First Hospital and a 188-patient trial assessing tocilizumab alone is led by Dongsheng Wang of The First Affiliated Hospital of University of Science and Technology of China (Anhui Provincial Hospital).<sup>192</sup>



On 11 March 2020, in Italy, tocilizumab was the subject of an up-to-30-patient phase II trial designed to study the drug as a single 8 mg kg<sup>-1</sup> dose in patients affected by severe pneumonia correlated to SARS-CoV2. The study by researchers at Università Politecnica delle Marche and Azienda Ospedaliera Ospedali Riuniti Marche Nord has two primary outcome measures: TCZ arrest in deterioration of pulmonary function, and improvement in pulmonary function. These signs of improvement prompting the Italian Pharmacological Agency (AIFA) to expand testing in 5 other hospitals.<sup>193</sup>

TCZ prevents overreaction of the immune system that has led to organ failure especially the lung and death in coronavirus patients. Roche and the WHO are each launching separate trials for its use in severe COVID-19 cases. Finally, Genentech (Roche) announced that the FDA has approved the initiation of a double-blind, randomized phase III clinical trial of the oncology supportive care drug tocilizumab (Actemra) for use in combination with standard care for the treatment of hospitalized adult patients with severe COVID-19 pneumonia.<sup>194</sup>

**2.5.1 Sarilumab.** Sarilumab, is one of two IL-6 receptor antagonists being studied as potential COVID-19 treatments. The logic behind using sarilumab is similar to that of TCZ. It is approved by the FDA in 2017 to treat adults with moderately to severely active rheumatoid arthritis.<sup>195</sup> However, On March 16<sup>th</sup>, 2020, A research group announced that they launched a phase II/III clinical program of up to 400 patients assessing the drug in severe COVID-19 coronavirus infection in collaboration with the FDA and the Biomedical Advanced Research and Development Authority (BARDA). The phase III portion will evaluate longer-term outcomes such as reducing the need for hospitalization and mechanical ventilation, as well as mortality.<sup>196</sup>

**2.5.2 Baricitinib.** Baricitinib (Fig. 12) was FDA-approved in June 2018 for the treatment of moderately to severely active rheumatoid arthritis (RA). Baricitinib joins tofacitinib as the second oral once-daily medication in the Janus Kinase (JAK) inhibitor class for RA. Baricitinib exerts its effects by selective inhibiting JAK1 and JAK2 enzymes, targeting cytokine and growth factor receptor stimulation, thus reducing downstream immune cell function.<sup>197</sup>

On February 15<sup>th</sup>, 2020, a month after the first reports of a novel coronavirus spreading in China. The artificial intelligence (AI) research groups and others have used AI software to find an already-approved drug that might limit the virus's ability to infect people.<sup>198</sup> They used the first genomic sequence of the virus published in mid-January, and by January 29<sup>th</sup>, 2020 scientists suggested that the virus might enter human cells by binding to a cell-surface molecule called ACE2.<sup>199</sup>

The software pointed at the enzyme adaptor-associated protein kinase 1 (AAK1) as a possible target for the disease. AAK1 regulates endocytosis, the process that brings material into cells, which also is a common mode of viral infection. AI results select baricitinib, based on its affinity for the kinase and its toxicity amongst more than 378 known AAK1 inhibitors. Janus-associated kinase (JAK) inhibitor baricitinib is predicted to reduce the ability of the virus to infect lung cells by inhibition of ACE2-mediated endocytosis.<sup>198</sup>

Later, the researchers propose testing baricitinib in clinical trials against the virus as a dual antiviral and anti-inflammatory agent after confirming *in vitro* activities. Currently, ruxolitinib, Fig. 1, a drug that works by a similar mechanism, shows a promise in severe COVID-19-associated cytokine storm, where levels of cytokines were found to be significantly reduced. Also, It was found to be well-tolerated with low toxicities. It is subjected for phase III clinical trials for COVID-19.<sup>200</sup>

## 2.6 Miscellaneous drugs

Some other drug molecules or agents have a potential positive impact in management of COVID-infections. Research reports suggest that the use of antioxidants like ascorbic acid, *N*-acetylcysteine in combination with antiviral drugs can synergistically decrease the lethal effect of influenza viral infection.<sup>201</sup> Another research study showed that combination of the influenza drug oseltamivir with *N*-acetylcysteine can increase host defense mechanism and decrease mortality rates. This occurs through reduction of oxidative stress associated with viral infection.<sup>202</sup> Dietary supplements such as resveratrol, curcumin and sulphoraphane were found to have cytoprotective effect on vital organs. This approach could be extrapolated to the lungs of infected patients with coronaviruses infections. A recent research study revealed that combination thalidomide and the selective COX-2 inhibitor, celecoxib, can improve the severe COVID-19 pneumonia through modulation of activated NF-KB that promote severe lung injury.<sup>203</sup> The FDA-approved antiparasitic drug ivermectin (Fig. 13) is known in the literature by its broad-spectrum antiviral activity. Surprisingly, recent reports showed that this drug is a potent inhibitor of SARS-Cov-2. Ivermectin causes 5000× reduction in viral RNA during two days, it requires future clinical investigation in humans.<sup>204</sup>

## 3 Conclusion

The war between scientists and viral infection is a continuous war. Finding specific potent drug with high efficacy and acceptable toxicity profile is a dream. It is the first time in the world to join scientists, politicians, diplomats, businessmen and the normal people all over the world to have the same target. Although the FDA approved chloroquine and hydroxy-chloroquine to be used in the emergency clinical management protocols used in CoV, this approval has some restrictions. The information about the wide use of these drugs is not enough. Some of the polymerase nucleoside/nucleotide inhibitors are considered promising agents. Favipiravir has selectivity on viral cells as it is viral RNA-dependent RNA polymerase inhibitor without effects on human cell lines; it has no effect on RNA or DNA in human cells. It is approved to be tested in clinical trials in cases of COVID-19 infections. Moreover, the combination between lopinavir and ritonavir is under investigation for clinical studies. The broad-spectrum antiviral effect of remdesivir against different RNA viruses in addition to its interference effect on CoV replication machinery recommend this drug for intensive studies to be COVID-19 drug.



On the other hand, the ability of protease inhibitors to fight COVID-19 is under investigation. Inhibition of this enzyme is crucial for viral proteolytic and other essential vital activities. Lopinavir, ritonavir and nelfinavir are effective agents in COVID-19 infection but still need additional studies. Similarly, the serine protease inhibitors such as nafamostat and camostat are promising strategy in COVID-19 therapy. The important relatively save and potent lipid lowering statin, rosuvastatin, has a good impact on lung pathological changes through decreasing Th2 and Th17 mediated cytokines. Statins are recommended to be useful in reducing the mortality rates in cases of influenza infections due to their anti-inflammatory and immunomodulatory effects. Some rheumatoid arthritis drugs may be beneficial in management of COVID-19 cases such as TNF- $\alpha$  inhibitors, interleukin 1 receptor antagonists; Janus associated kinases (JAK) in addition to monoclonal antibodies which block interleukin 6 receptors. Tocilizumab is under clinical investigation to treat hospitalized severe COVID-19 associated pneumonia. Also, baricitinib and ruxolitinib are suggested to induce ACE-2 mediated endocytosis that reduces ability of the virus to infect viral cells with their additional anti-inflammatory actions.

In the near future, scientists are invited to collect their efforts and share knowledge in redirecting the mentioned drugs in this review to have suitable, cheap drugs with the lowest possible toxicity profile.

## Abbreviations

COVID	Coronavirus disease
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
MERS	Middle East respiratory syndrome
PHEIC	Public health emergency of international concern
WHO	World Health Organization
HE	Hemagglutination-esterase
RBD	Receptor binding domain
ACE2	Angiotensin converting enzyme 2
TMPRSS2	Transmembrane serine protease 2
ORF1a	Open reading frame 1a
ORF1b	Open reading frame 1b
pp	Polyprotein
PLpro	Papain-like protease
3CLpro	Chymotrypsin-like protease
RTC	Replicase-transcriptase complex
RdRp	RNA-dependent RNA polymerase
IFN	Interferon
APC	Antigen presenting cell
MHC	Major histocompatibility complex
CD8	Cluster of differentiation
T cell =	Cytotoxic lymphocyte
Tc	
IgM	Immunoglobulin M
IgG	Immunoglobulin G
TMPRSS2	Transmembrane protease, serine 2
ICU	Intensive care unit
NK cells	Natural killer cell
RBD	Receptor-binding domain
VEGF	Vascular endothelial growth factor

HCMV	Human cytomegalovirus
HSV	Herpes simplex virus
BK	Polyomavirus
NIs	Nucleotide and nucleoside analogue inhibitors
FDA	Food and Drug Administration
TRP	Ribofuranosyl-5'-triphosphate
ATP	Adenosine triphosphate
GTP	Guanosine-5'-triphosphate
CT	Computerized tomography
IFN $\alpha$ 2b	Interferon alpha-2b
nsp14	Nonstructural protein 14
HCV	Hepatitis C virus
RSV	Respiratory syncytial virus
NiV	Nipah virus
EBOV	Ebola virus
VEEV	Venezuelan equine encephalitis virus
IAV	Influenza A virus
CHIKV	Chikungunya virus
IBV	Influenza B virus
HCoV-NL63	EC <sub>50</sub> : the concentration of a drug that gives half maximal response
DAAs	Direct acting antivirals
ZIKV	Virus family Flaviviridae
TSG101	Tumor susceptibility gene
RSV	Rosuvastatin
HMG-CoA	3-Hydroxy-3-methyl-glutaryl-coenzyme A
UDP	Uridine diphosphate
TLR3	Toll-like receptor 3
MYD88	Myeloid differentiation primary response 88
Th1	T helper cell
DMARD	Disease-modifying antirheumatic drugs
IL-1	Interleukin-1 family
JAK	Janus associated kinase
DENV	Dengue virus
HCMV	Human cytomegalovirus
BKV	Polyoma BK virus
HTS	High-throughput screening
SC	Subcutaneously
RA	Rheumatoid arthritis
PAH	Pulmonary arterial hypertension; biomedical advanced research and development authority
BARDA	Artificial intelligence
AI	
AAK1	Adaptor-associated protein kinase 1
COX-2	Cyclooxygenase 2
NF-KB	Nuclear factor kappa-light-chain-enhancer of activated B cells
GIT	Gastrointestinal tract

## Conflicts of interest

Authors declare no conflict of interest.

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