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1 **Current Trends and Future Approaches in Small-Molecule Therapeutics for COVID-19**

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3 Running Title: Trends in Small-Molecule Therapeutics for COVID-19

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13

14 **Abstract**

15 The novel coronavirus (SARS-CoV-2) pandemic has created a global public health emergency. The pandemic is

16 causing substantial morbidity, mortality and significant economic loss. Currently, no approved treatments for

17 COVID-19 are available, and it is likely to take at least 12-18 months to develop a new vaccine. Therefore, there

18 is an urgent need to find new therapeutics that can be progressed to clinical development as soon as possible.

19 Repurposing regulatory agency-approved drugs and experimental drugs with known safety profiles can provide

20 important repositories of compounds that can be fast-tracked to clinical development. Globally, over 500

21 clinical trials involving repurposed drugs have been registered, and over 150 have been initiated, including some

22 backed by the World Health Organisation (WHO). This review is intended as a guide to research into small-

23 molecule therapies to treat COVID-19; it discusses the SARS-CoV-2 infection cycle and identifies promising

24 viral therapeutic targets, reports on a number of promising pre-approved small-molecule drugs with reference to

25 over 150 clinical trials worldwide, and offers a perspective on the future of the field.

26

27 **Graphical Abstract**

28
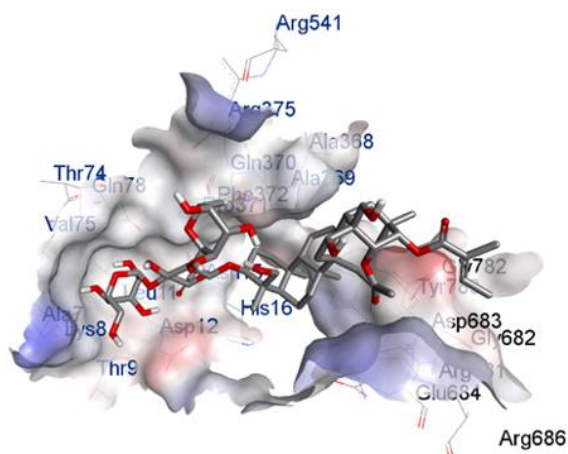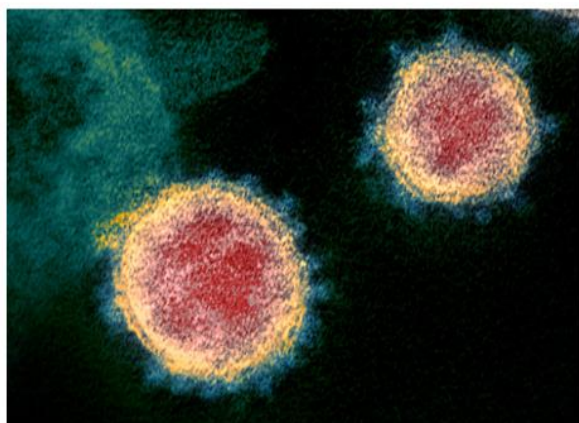
1. INTRODUCTION

COVID-19 (coronavirus disease 2019) is an infectious disease caused by the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) virus that was first identified in Wuhan, China in December 2019. The rapid evolution of the COVID-19 crisis from regional outbreak to global pandemic has caught governments and healthcare systems off guard [1]. With over 10 million confirmed cases as of the 28th of June [2], treatments for SARS-CoV-2 infection and COVID-19 are urgently needed. Symptoms of the disease typically include fever, dry cough and dyspnoea; less common are malaise, myalgia, anosmia, nausea and pain in the head, throat and/or abdomen. Patients suffering from severe cases of COVID-19 may also present with symptoms such as respiratory distress, tachypnoea and hypoxia. The latter cases can progress from viral pneumonia to acute respiratory distress syndrome (ARDS), multiple organ failure and death [1].

SARS-CoV-2 belongs to a family of viruses known as the coronaviruses, members of the order *Nidovirales* that are spread broadly among humans, different domestic/wild animals and birds and can cause respiratory, hepatic and neurological diseases [3]. Among the seven coronavirus species which are capable of infecting humans, four viruses (229E, OC43, NL63 and HKU1) are common respiratory viruses that produce common cold symptoms but can also cause pneumonia. Three zoonotic viruses – SARS-CoV (severe acute respiratory syndrome coronavirus), MERS-CoV (Middle East respiratory syndrome coronavirus) and, the most recent to emerge, SARS-CoV-2 – can cause fatal respiratory illness in humans [4, 5]. Recent studies suggest that SARS-CoV-2 is more contagious than SARS-CoV [6].

The scientific community have responded to the threat posed by SARS-CoV-2 with rapid identification and subsequent publication of crystal and cryo-EM structures of important SARS-CoV-2 drug targets, including the spike protein [7], main protease [7] and Nsp15 ribonuclease [8]. However, targeted approaches to designing new drugs for clinical use will take considerable time. Rapid repurposing of clinically-approved small-molecule drugs in randomised trial-led efforts to identify effective COVID-19 medications may buy time with which to develop investigational treatments.

1.1. *The SARS-CoV-2 Virus Infection Cycle*

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA betacoronavirus. Its RNA genome encodes three major surface proteins termed the spike (S), membrane (M), and envelope (E) proteins [9]. A fourth gene

59 encodes the nucleocapsid (N) [10]. The spike protein forms homotrimers on the viral surface [11] and is

60 comprised of two domains, an N-terminal S1 domain that mediates receptor binding [12] and a C-terminal,

61 transmembrane S2 domain for membrane fusion [9, 11]. The SARS-CoV-2 infection cycle (Figure 1) begins

62 with the recognition of angiotensin-converting enzyme 2 (ACE2) on the host cell surface by the spike protein

63 [13]. Interaction of the spike protein with ACE2 is thought to trigger a conformational change in the former,

64 revealing a site between the S1 and S2 domains that can be cleaved by host cell membrane proteases. Now

65 activated for membrane fusion, the cleaved S2 subunit inserts into the host cell membrane *via* its N-terminal

66 fusion peptide so that it is connected to both the viral and cell membranes. The N- and C-terminal heptad repeats

67 of the S2 subunit then fold to form a six-helix bundle, contracting the S2 subunit and bringing the two

68 membranes into close proximity, whereupon they fuse [9].

69

70 Following a successful recognition event, virus internalisation can occur either by direct fusion with the plasma

71 membrane or by endocytosis [13]. In the case of direct fusion, the host protease responsible for cleavage of the

72 S1 and S2 domains is thought to be transmembrane protease serine 2 (TMPRSS2), whereas in endocytosis the

73 cysteine protease cathepsin L is thought to be responsible [9]. In addition, it has recently become apparent that

74 SARS-CoV-2 contains sites that can be processed by furin-like proteases; since furin is widely expressed in

75 different cell types, this could increase the cell tropism of the virus beyond the respiratory and digestive systems

76 [11, 14]. Fusion of the viral and cellular membranes triggers the release of viral genomic RNA into the host cell

77 cytoplasm [13] and uncoating of the viral nucleocapsid [15]. If not targeted for degradation in the cytoplasm, the

78 viral RNA then attaches to the host ribosome, whereupon the viral genes ORF1a and ORF1ab are translated into

79 polyproteins [12] pp1a and pp1ab [1], respectively. These polyproteins are processed by the coronavirus main

80 protease (M^{pro}) and a papain-like protease (PL^{pro}), both cysteine proteases [12, 16]. M^{pro} is also known as 3C-

81 like protease ($3CL^{pro}$) because of its similar cleavage site specificity to the 3C protease ($3C^{pro}$) found in

82 picornaviruses [17]. Proteolysis gives rise to a number of non-structural proteins which form the replicase-

83 transcriptase, the only protein translated directly from the viral genome [15]. Alongside an ATP-dependent

84 RNA helicase and various cofactors [15], this RNA-dependent RNA polymerase copies the viral RNA in

85 membrane-associated replication-transcription complexes [1, 18] *via* negative-strand intermediates [13]. Copies

86 of the full-length genomic RNA and a set of sub-genomic mRNAs are produced [13], the latter determined by

87 transcriptional regulatory sequences located between open reading frames (ORFs) [1].

88

89 Once the replicase-transcriptase has replicated the viral genome and transcribed mRNAs, the sub-genomic

90 mRNA templates are used for translation of structural and accessory viral proteins [13, 15], a process which

91 occurs on the endoplasmic reticulum [15]. The full-length viral RNA is encapsidated and assembles with spike,

92 envelope and membrane proteins in the endoplasmic reticulum-Golgi intermediate compartment [15]. At this

93 stage, post-translational modifications will have occurred, such as S protein trimerization and glycosylation [9]

94 and vesicles move to the plasma membrane for release of infectious virus particles from the host cell *via*

95 exocytosis [15]. Upon viral release from the host cell, viral particles can be eliminated by a specific adapted

96 immune response so that the disease does not progress in severity; if this does not happen, however, continued

97 viral propagation downregulates ACE2, dysregulating the renin-angiotensin system and causing a cytokine

98 storm which can lead to a host inflammatory response and ARDS (NCT04344041) [19].

99

100 *1.2.   Targeting the SARS-CoV-2 Virus with Small-Molecule Therapies*

101 The severity of the current COVID-19 global pandemic necessitates immediate and decisive action to counter

102 the threat posed by the SARS-CoV-2 virus. To this end, various different approaches for disrupting the SARS-

103 CoV-2 infection cycle have been proposed using previously-approved drugs. Each of the structural and non-

104 structural proteins encoded by its RNA genome are potential targets for existing antiviral agents [20] since many

105 SARS-CoV-2 proteins have a high degree of sequence similarity to their SARS-CoV and MERS-CoV

106 homologues [12].

107

108 **Viral entry inhibitors** are molecules able to interfere with either receptor recognition or spike protein

109 proteolysis. This could involve drugs that target the spike protein, ACE2 inhibitors or inhibitors of host cell

110 proteases like TMPRSS2, cathepsin L or furin, though combinations of protease inhibitors may be necessary to

111 overcome the seemingly independent viral entry mechanisms. A high resolution crystal structure of the receptor

112 binding domain (RBD) of the SARS-CoV-2 spike protein with ACE2 has been published and has provided an

113 important target to screen FDA- and EMA-approved drugs against to identify clinical candidates (Figure 2) [21].

114 Candidates that have been developed in the past for SARS-CoV or MERS-CoV may require more development

115 beyond straightforward drug repurposing since the S1 subunit receptor binding domain in SARS-CoV-2 has

116 only 73.5% sequence identity with its SARS-CoV counterpart [12]. Viral entry inhibitors are desirable because

117 the opportunity for the virus to acquire resistance to these agents is minimal [22].

118

119 **Viral replication inhibitors** are another viable strategy, since the crystal structure of SARS-CoV-2 M^{pro} has

120 been published [7] (Figure 2) and it shares 96% sequence identity with the corresponding enzyme in SARS-

121 CoV. The SARS-CoV-2 RNA-dependent RNA polymerase is another promising target for drug repurposing

122 since it also shares 96% sequence identity with the SARS-CoV homologue [12]. While PL^{pro} only has 83%

123 sequence identity with its SARS-CoV homologue, active site conservation means it too is a promising target for

124 drug repurposing [12]. Other possible targets include the viral helicase enzyme [23], 3′-to-5′ exonuclease,

125 endoRNAse, 2′-O-ribose methyltransferase [24] and Nsp15 [8]. The structures of SARS-CoV-2 non-structural

126 proteins have also been published [25] and it is expected that the crystal or cryo-EM structures of other targets

127 will be published soon.

128

129 **Viral release inhibitors** are compounds capable of preventing the release of viral particles from host cells.

130 While few agents have currently been identified that inhibit this step of the SARS-CoV-2 infection cycle, this

131 approach has proven successful before in the case of the neuraminidase inhibitors, such as oseltamivir, which

132 bind the membrane-anchored neuraminidase enzyme found in influenza viruses to prevent release of progeny

133 viruses from infected cells [26]. With respect to SARS-CoV-2, the envelope protein may represent a promising

134 target due to its role in viral release as a viroporin [27].

135

136 **Immune response modulators** are also necessary to combat the virus-induced lung inflammation that causes

137 life-threatening respiratory disorders in severe cases of SARS-CoV-2 infection. ARDS is the major cause of

138 death in clinical cases of COVID-19 [28, 29], caused by the uncontrollable activation of the antiviral immune

139 response. Since this abnormal inflammatory response is mediated by macrophages and granulocytes, immune

140 suppression *via* cytokine inhibitors can help in managing it. Various cytokines including IL-6 and TNF-α have

141 been implicated in this immune response [19], with IL-6 thought to be responsible for cytokine release

142 syndrome (CRS) which can lead to multiple organ failure [1, 30, 31]. High doses of corticosteroids have been

143 traditionally considered effective in retarding multiple organ failure and decreasing ARDS-induced mortality,

144 though their use to treat COVID-19 patients remains a matter of debate [32, 33]. Alternative approaches to the

145 issue of SARS-CoV-2-induced ARDS must therefore be considered.

146

2. VIRAL ENTRY INHIBITORS

2.1. *Spike Protein-Targeting Drugs*

Umifenovir (Arbidol®; Figure 3), an antiviral medication used to treat influenza virus infections and approved for use in Russia and China [34], has been demonstrated to effectively inhibit SARS-CoV *in vitro* [35] and MERS-CoV [36] through disrupting virus-cell membrane fusion to block viral entry [37]. Although it appears to have a relatively low selectivity index (SI; CC_{50}/EC_{50}) against SARS-CoV-2 *in vitro* (SI >3.7 in Vero E6 cells; EC_{50} = 10.7 µM, CC_{50} = >40 µM, multiplicity of infection (MOI) 0.002) [38], variation in CC_{50}s between different cell lines (8 µg/mL to 115 µg/mL) [39-41] has previously been noted. Work by Wu *et al*. would appear to confirm a similar mode of action against SARS-CoV-2; docking of umifenovir against possible drug target within SARS-CoV-2 indicated it would interact most favourably with the spike protein with an mfScore of -145.125 [36]. Touret *et al*. report an EC_{50} for umifenovir against SARS-CoV-2 of 10.7 µM [38]. Umifenovir is currently set to be investigated in a number of phase 4 clinical trials in China and Iran both as a monotherapy (NCT04260594, NCT04255017 and NCT04286503) and in combination with other therapies (NCT04254874 and NCT04350684) for treatment of patients with COVID-19. However, a retrospective study of 81 COVID-19 patients suggests that umifenovir is not an effective SARS-CoV-2 antiviral treatment [42].

Nitric oxide (GeNOsyl®, INOmax®, Noxivent™; Figure 3), a colourless gas known to have important roles in a number of different biological processes, has previously been shown to inhibit the replication of SARS-CoV. It achieves this through two distinct mechanisms; by reducing the palmitoylation of nascently expressed spike protein and thus interfering with receptor binding, and by reducing viral RNA production [43]. During the 2002-2004 SARS-CoV outbreak, low dose nitric oxide (<30 ppm) was found to reverse pulmonary hypertension, improve severe hypoxia and shorten the duration of ventilatory support needed in SARS-CoV-infected patients relative to a control group (NCT04305457). LC_{50}s are reported to be 315 ppm in rabbits, 320 ppm in mice and 854 ppm in rats, from which the National Institute for Occupational Safety and Health (NIOSH) has set an IDLH (Immediately Dangerous to Life or Health) value of 100 ppm for humans [44]. Nitric oxide is the subject of multiple planned phase 1-3 clinical trials in the US (NCT04398290, NCT04421508, NCT04397692, NCT04388683, NCT04305457, NCT04306393, NCT04312243 and NCT04338828) and Canada (NCT03331445 and NCT04383002) for the treatment of COVID-19 at concentrations ranging from 20 ppm to 300 ppm; doses of the drug in excess of the aforementioned IDLH value will be restricted to short periods of time (15-30 minutes, up to twice daily).

177

2.2.   Angiotensin-Converting Enzyme 2-Targeting Drugs

178

The use of both angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs)

179

for the treatment of SARS-CoV-2 infections remains controversial; while their use may block viral entry into

180

cells through interfering with the prerequisite virus-ACE2 interaction, some experimental models have found

181

these drugs to prompt increased ACE2 expression in several organs which could exacerbate the viral infection.

182

Trials in the US (NCT04338009) and Ireland (NCT04330300) have been planned to investigate this area further;

183

the latter, a 2,414-person phase 4 clinical trial at University Hospital Galway (NCT04330300), will evaluate the

184

ACEIs **captopril** (Capoten®), **lisinopril** (Prinivil®), **enalapril** (Vasotec®), **perindopril** (Coversyl®), **ramipril**

185

(Altace®), **trandolapril** (Mavik®), **fosinopril** (Monopril®), **quinapril** (Accupril®) and **benazepril**

186

(Lotensin®) (Figure 4) and ARBs **irbesartan** (Avapro®), **candesartan** (Atacand®), **eprosartan** (Teveten®),

187

losartan (Cozaar®), **olmesartan** (Benicar®), **telmisartan** (Micardis®) and **valsartan** (Diovan®) (Figure 5).

188

Further phase 1-4 trials of some of these drugs are planned and/or recruiting participants in the Netherlands

189

(NCT04335786), Pakistan (NCT04343001), Egypt (NCT04345406) and the US (NCT04328012,

190

NCT04335123, NCT04312009, NCT04311177 and NCT04340557). While a Chinese retrospective study of

191

1,128 adults suffering from hypertension and COVID-19 has concluded that use of both ACEIs and ARBs was

192

associated with a lower risk of all-cause mortality compared to COVID-19 patients not using these medications

193

[45], other reviews of the available clinical evidence do not agree [46].

194

195

The Chinese herbal medicine **glycyrrhizin** (Figure 6), a glycosylated saponin comprised of one molecule of

196

glycyrrhetinic acid and two molecules of glucuronic acid [47] found in the roots of Chinese liquorice

197

Glycyrrhiza uralensis [48], has been predicted to bind ACE2 in a number of separate *in silico* studies. Chen and

198

Du predicted glycyrrhizin to bind ACE2 with a binding energy of -9 kcal/mol and interact with residues R559,

199

Q388, R393 and D30 [48], while separate work by Cinatl *et al*. found glycyrrhizin to have a high SI against

200

SARS-CoV strains FFM-1 and FFM-2 *in vitro* during and after virus adsorption (SI >67 in Vero cells; $EC_{50} =$

201

300 µg/mL, CC_{50} = >20,000 µg/mL) [50]. The double ammonium salt of the compound, diammonium

202

glycyrrhizinate, is currently being studied in two small-scale clinical trials against COVID-19 in China

203

(ChiCTR2000029768 and ChiCTR2000030490).

204

205

206　　*2.3.　Endosome-Targeting Drugs*

207　　**Chloroquine** (Aralen®; Figure 7), an antimalarial drug, has been identified as a promising small-molecule

208　　therapy for SARS-CoV-2 in a number of recent *in vitro* studies [51-53]; Wang and colleagues report that it has a

209　　high SI against SARS-CoV-2 *in vitro* (SI >88.50 in Vero E6 cells; EC_{50} = 1.13 µM, CC_{50} = >100 µM, MOI

210　　0.05) [53], although it is known to induce life-threatening cardiac toxicity on rare occasions [54]. Chloroquine

211　　and its analogues possess tertiary amine functional groups and are thus weakly basic; the neutral, freebase forms

212　　can diffuse across membranes into acidic cytoplasmic organelles such as endosomes, whereupon they become

213　　protonated and unable to diffuse out [55, 56]. Concentration of chloroquine within endosomes in this manner

214　　increases the pH within the endosome [55, 56], blocking the pH-dependent fusion of the viral and endosome

215　　membranes that leads to release of viral genetic material within the host cell [57]. This mode of action is well-

216　　documented in a wide variety of different viruses [56-59], though additional modes of action have also been

217　　reported/predicted in SARS-CoV-2 [57, 60]. To further evaluate chloroquine as a treatment for COVID-19, a

218　　number of phase 2, 3 and 4 clinical trials in countries including China (NCT04319900, ChiCTR2000029741,

219　　ChiCTR2000029609, ChiCTR2000029542, ChiCTR2000031204, ChiCTR2000029975, ChiCTR2000029988,

220　　ChiCTR2000029939, ChiCTR2000030054, ChiCTR2000029899 and ChiCTR2000029898), Israel

221　　(NCT04333628), Poland (NCT04331600), Greece (NCT04344951), Vietnam (NCT04328493), France

222　　(NCT04333914), the US, Australia, Ireland, South Africa (NCT04333732), the UK (NCT04303507), Brazil

223　　(NCT04323527 and NCT04342650) and Canada (NCT04324463) are either planned, recruiting or currently

224　　active; of note is a French 273-person phase 2 trial for COVID-19 patients also suffering from advanced or

225　　metastatic cancer (NCT04333914).

226

227　　**Hydroxychloroquine** (Plaquenil®; Figure 7), an analogue of chloroquine with similar promise against SARS-

228　　CoV-2 *in vitro* (SI = 61.45 in Vero E6 cells; EC_{50} = 4.06 µM, CC_{50} = 249.50 µM, MOI 0.02) [52], as well as

229　　associated drawbacks [54], is also the subject of a number of planned or active phase 1-4 clinical trials

230　　worldwide. These include studies in Canada (NCT04329611, NCT04308668 and NCT04321993), the US

231　　(NCT04329832, NCT04334512, NCT04329923, NCT04334382, NCT04333225, NCT04335084,

232　　NCT04336332, NCT04318444, NCT04328961, NCT04334148, NCT04335552, NCT04334967,

233　　NCT04332991, NCT04333654, NCT04328467, NCT04308668, NCT04328012, NCT04345692,

234　　NCT04341441, NCT04345653, NCT04343677 and NCT04342169), Singapore (NCT04342156), France

235　　(NCT04328285, NCT04325893 and NCT04344379), Germany (NCT04342221 and NCT04340544), Spain

236   (NCT04331834 and NCT04330495), Israel (NCT04323631), Brazil (NCT04329572, NCT04321278 and

237   NCT04322123), Mexico (NCT04315896, NCT04318015 and NCT04340349), Pakistan (NCT04328272), South

238   Korea (NCT04330144 and NCT04307693), China (NCT04261517, ChiCTR2000030054, ChiCTR2000029899,

239   ChiCTR2000029898, ChiCTR2000029868, ChiCTR2000029803 and ChiCTR2000029559), Norway

240   (NCT04321616 and NCT04316377), Denmark (NCT04322396), Austria (NCT04336748), Turkey

241   (NCT04326725) and Iran (NCT04343768). Of note are two large scale, multinational trials assessing the utility

242   of both chloroquine and hydroxychloroquine as prophylactic therapies for frontline healthcare workers

243   (NCT04333732 and NCT04303507); other, smaller studies investigating both pre-exposure (NCT04328467,

244   NCT04333225, NCT04328285, NCT04331834, NCT04318015, NCT04336748 and NCT04343677) and post-

245   exposure (NCT04318444, NCT04330144, NCT04308668, NCT04322396, NCT04330495, NCT04326725,

246   NCT04342156 and NCT04343677) prophylaxis on both healthcare workers and the general population are also

247   being conducted in multiple countries. Combination with the macrolide antibiotic **azithromycin** (Zithromax®),

248   another drug observed to have a high SI against SARS-CoV-2 *in vitro* (SI >19 in Vero E6 cells; $EC_{50} = 2.12$

249   μM, $CC_{50} = >40 \, \mu M$, MOI 0.002) [38], is also being assessed. Trials evaluating azithromycin either as a

250   monotherapy (NCT04332107 and NCT04344379) or in combination with chloroquine or hydroxychloroquine

251   (NCT04324463, NCT04329832, NCT04334512, NCT04334382, NCT04329572, NCT04336332,

252   NCT04328272, NCT04335552, NCT04322396, NCT04321278, NCT04322123, NCT04339816,

253   NCT04341727, NCT04341207, NCT04344444, NCT04338698 and NCT04344457) as well as other drugs

254   (NCT04339426 and NCT04338698) are being initiated worldwide. Preliminary results appear mixed; while

255   there are reports that suggest hydroxychloroquine monotherapy is associated with an increase in COVID-19

256   patient survival when started in the early stages of the disease [61], a meta-analysis of 11 clinical studies with a

257   total of 2,354 patients receiving hydroxychloroquine does not support this conclusion [62].

258

259   *2.4.   Host Protease Inhibitors*

260   **Camostat mesylate** (Foipan®; Figure 8), a serine protease inhibitor, is another possible treatment option.

261   Approved for clinical use in Japan since the 1990s for treating chronic pancreatitis and postoperative reflux

262   esophagitis [63], it has a high SI *in vitro* (SI >62 in MDCK cells; $EC_{50} = 3.2 \, \mu g/mL$, $CC_{50} = >200 \, \mu g/mL$) [64]

263   and is active against both SARS-CoV [9, 65] – Zhou *et al.* found it conferred a 60% survival rate on mice

264   injected with the virus [66] – and SARS-CoV-2 [67]. In the case of the latter, camostat mesylate blocks cellular

265   entry *via* inhibition of the TMPRSS2 protease; Hoffmann *et al.* found that pre-treatment of Caco-2 cells with the

266 drug reduced SARS-CoV-2 virus entry by ~90% relative to untreated control cells *in vitro* [67]. Combination of

267 camostat mesylate with **aloxistatin** (E-64d; Figure 8), a non-specific cysteine protease inhibitor first isolated by

268 scientists at Taisho Pharmaceutical [68] and a known inhibitor of cathepsin B and cathepsin L [67], may be

269 advantageous [65]; Hoffmann *et al*. report that this combination caused full inhibition of SARS-CoV-2 entry

270 into Caco-2 cells, improving on camostat mesylate alone [67]. Clinical trials evaluating camostat mesylate alone

271 or in combination with other drugs for treatment of COVID-19 patients are currently being organised in the US

272 (NCT04353284, NCT04435015 and NCT04374019), Denmark (NCT04321096), Germany (NCT04338906) and

273 Israel (NCT04355052).

274

275 **3.   VIRAL REPLICATION INHIBITORS**

276 *3.1.   RNA-Dependent RNA Polymerase Inhibitors*

277 **Favipiravir** (Avigan®; Figure 9) is a nucleoside analogue and pyrazinecarboxamide derivative developed by

278 Toyama Chemical [69]. The active form of the drug, favipiravir ribofuranosyl-5′-triphosphate, is generated *via*

279 intracellular phosphoribosylation [70]. Favipiravir has been clinically approved in Japan for the treatment of

280 influenza virus infections that are resistant to other classes of antivirals. Despite a low SI against SARS-CoV-2

281 *in vitro* (SI >6.46 in Vero E6 cells; EC_{50} = 61.88 µM, CC_{50} = >400 µM, MOI 0.05) [53], favipiravir is currently

282 being evaluated in a number of clinical trials in COVID-19 patients. In China, favipiravir has recently been

283 trialled in 80 confirmed COVID-19 patients, 35 of whom received favipiravir for 14 days while the rest received

284 a placebo. An initial report concluded that patients receiving favipiravir showed a substantially shorter viral

285 clearance time and improved infection progression [71], though at the time of writing this article has been

286 temporarily withdrawn [72]. Further trials in the UK (NCT04373733), Italy (NCT04336904), Thailand

287 (NCT04303299), the US (NCT04358549 and NCT04346628), Canada (NCT04448119), Iran (NCT04359615

288 and NCT04376814), Bangladesh (NCT04402203), Russia (NCT04434248), Egypt (NCT04349241 and

289 NCT04351295), Turkey (NCT04411433), Bahrain (NCT04387760), Saudi Arabia (NCT04392973), Germany,

290 Romania (NCT04425460) and China (NCT04333589, NCT04310228, NCT04319900, ChiCTR2000029600,

291 ChiCTR2000030113, ChiCTR2000029548, ChiCTR2000029544 and ChiCTR2000030254) assessing the utility

292 of favipiravir either as a monotherapy or in combination with other biologic or small-molecule therapies appear

293 to be in various stages of progression.

294

295   **Ribavirin** (Copegus®; Figure 9) was first synthesised in 1972 and is a guanosine analogue broad-spectrum

296   antiviral agent indicated to treat hepatitis C and E, Lassa, Hanta and respiratory syncytial viruses [73]. The

297   active triphosphate form of the drug is generated intracellularly [74] and inhibits viral RNA-dependant RNA

298   polymerase as well as mRNA capping, thus blocking RNA synthesis and consequently viral replication [73].

299   The inhibitory effects of ribavirin on SARS-CoV *in vitro* appear to vary between different cell lines; although it

300   showed potent inhibitory activity in MA104 (African green monkey kidney cell line; EC_{50} 9.4 ± 4.1 µg/mL),

301   PK-15 (pig kidney cell line; EC_{50} 2.2 ± 0.8 µg/mL), Caco-2 (human colon carcinoma cell line; EC_{50} 7.3 ± 3.5

302   µg/mL), CL14 (human colon carcinoma cell line; EC_{50} 8.2 ± 4.2 µg/mL) and HPEK (human primary epithelial

303   kidney cell line; EC_{50} 5.2 ± 2.9 µg/mL) cells, no observable inhibition was found in Vero cells (African green

304   monkey kidney cell line; EC_{50} >1,000 µg/mL) [75] and this may explain the low SI observed for SARS-CoV-2

305   by Wang and colleagues (SI >3.65 in Vero E6 cells; EC_{50} = 109.5 µM, CC_{50} = >400 µM, MOI 0.05) [53].

306   Recruitment is currently underway in China for a number of clinical studies involving co-administration of

307   ribavirin, lopinavir/ritonavir and/or various interferons to treat COVID-19 (NCT04276688,

308   ChiCTR2000029387 and ChiCTR2000030922) while other trials in Egypt (NCT04392427) and Bangladesh

309   (NCT04402203) are planned or recruiting patients. Of note is a Canadian 50-person phase 1 trial evaluating

310   different doses of an inhaled solution of ribavirin (Virazole®) in COVID-19 patients (NCT04356677).

311

312   **Remdesivir** (GS-5734™; Figure 9) is a broad-spectrum nucleoside analogue originally developed by Gilead

313   Sciences to treat the Ebola virus [76]. It is the monophosphoramidate precursor of the adenosine-based

314   nucleoside analogue GS-441524 [77] and is converted to its active triphosphate form intracellularly [74] where

315   it inhibits viral RNA-dependent RNA polymerase [78]. Wang *et al*. report a high SI for remdesivir against

316   SARS-CoV-2 (SI >129.87 in Vero E6 cells; EC_{50} = 0.77 µM, CC_{50} = >100 µM, MOI 0.05) [53]. In response to

317   its potential, both Gilead Sciences and the US Army Medical Research and Development Command have

318   offered expanded access to remdesivir for COVID-19 patients (NCT04323761 and NCT04302766). Six

319   different phase 3 clinical trials evaluating remdesivir in up to 3,100 COVID-19 patients were initiated as of

320   early April 2020 (NCT04292899, NCT04292730, NCT04252664, NCT04315948, NCT04280705 and

321   NCT04257656), of which two are recruiting participants and two are active at the time of writing. Preliminary

322   data from one of the aforementioned studies shows statistically improved time to recovery *versus* placebo [79],

323   though similar data from another trial does not support this conclusion [80]. As of the 1st of May 2020, the FDA

324   has granted remdesivir emergency use authorisation for the treatment of COVID-19 in hospitalised patients with

325   severe disease [81].

326

327   *3.2.   Main Protease (M^{pro}) Inhibitors*

328   **Lopinavir**/**ritonavir** (Kaletra®; Figure 10) is an antiretroviral combination medication developed by Abbott

329   Laboratories for the treatment and prevention of HIV and AIDS. The combination has previously received

330   interest for treatment of coronavirus infections (NCT00578825 and NCT02845843). Lopinavir (SI = 12.99 in

331   Vero E6 cells; EC_{50} = 5.73 µM, CC_{50} = 74.44 µM, MOI 0.01) has been reported to have a higher SI than

332   ritonavir (SI = 8.59 in Vero E6 cells; EC_{50} = 8.63 µM, CC_{50} = 74.11 µM, MOI 0.01) [82]. As of early March

333   2020, current license holders AbbVie Inc. have offered expanded access to lopinavir/ritonavir for the treatment

334   of COVID-19 patients [83]. A number of phase 2-4 clinical trials of the combination therapy in both

335   prophylactic and interventional capacities have been organised in the US (NCT04328012), France

336   (NCT04328285), Canada (NCT04321993, NCT04330690 and NCT04321174), Iran (NCT04331470 and

337   NCT04343768) and China (NCT04295551, NCT04276688, NCT04252885, NCT04261907,

338   ChiCTR2000029741, ChiCTR2000029548, ChiCTR2000029541, ChiCTR2000029468, ChiCTR2000029387,

339   ChiCTR2000029308, ChiCTR2000030187 and ChiCTR2000029539). However, preliminary results from a 160-

340   person Chinese study indicate that there are no benefits to lopinavir/ritonavir treatment of COVID-19 patients

341   beyond those of standard hospital care (NCT04261907) [84].

342

343   *In silico* modelling conducted by Huang and colleagues has predicted that a number of Chinese herbal medicine

344   ingredients might be capable of inhibiting the SARS-CoV-2 M^{pro} enzyme, including **quercetin** (a bitter-tasting

345   flavonol found in a variety of fruit and vegetables [85]; -5.6 kcal/mol [86]) and **baicalin** (a flavone glucuronide

346   found in the roots of Chinese skullcap *Scutellaria baicalensis* [87]; -6.4 kcal/mol [86]) (Figure 11). Both

347   compounds have previously been investigated for use in treating infections of SARS-CoV; IC_{50} values reported

348   for quercetin against SARS-CoV M^{pro} range from 23.8 ± 1.9 µM [88] to 73 ± 4 µM [89], while Chen *et al.*

349   observed a low SI for baicalin against ten strains of SARS-CoV *in vitro* after 48 hours (SI >4 in FRhK-4 cells;

350   EC_{50} = 12.5-25 µM, CC_{50} = >100 µM) [90]. A 50-person trial evaluating quercetin as both a COVID-19

351   treatment and prophylactic is currently recruiting in Turkey (NCT04377789).

352

4.   IMMUNE RESPONSE MODULATORS

While inhibition of the SARS-CoV-2 infection cycle is undoubtedly a promising means of controlling the current pandemic, no review of small-molecule therapies here would be complete without also considering therapies for managing the associated disease COVID-19. Indeed, the major cause of death in clinical cases of SARS-CoV-2 infection is ARDS [28, 29], triggered by virus-mediated ACE2 downregulation disrupting the renin-angiotensin system, inducing a cytokine storm and leading to a host inflammatory response (NCT04344041) [19]. A number of different anti-inflammatory, immune modulatory and other drugs are currently being trialled with a view to preventing ARDS in severe cases of COVID-19 and thus reducing the associated mortality rate.

4.1.   Corticosteroids

A recent publication by Russell and colleagues has recommended that **corticosteroids**, widely used to treat patients during the SARS-CoV and MERS-CoV outbreaks, should not be used in the case of COVID-19-related pneumonia, lung injury or septic shock except in clinical trial settings [32]. However, this advice is disputed in a subsequent publication by Zhao *et al*. which instead advises cautious use [33]. Despite the controversy surrounding their use, a number of different corticosteroids including **dexamethasone** (Dextenza®; NCT04381936, NCT04325061, NCT04347980, NCT04395105, NCT04360876, NCT04327401, NCT04445506, NCT04344730 and ChiCTR2000029656), **ciclesonide** (Alvesco®; NCT04330586, NCT04377711, NCT04435795 and NCT04381364), **budesonide** (Pulmicort®; NCT04331470, NCT04361474, NCT04416399, NCT04355637, NCT04193878 and NCT04331054), **prednisone** (Deltasone®; NCT04344288 and NCT04359511) and **methylprednisolone** (Medrol®; NCT03852537, NCT04329650, NCT04377503, NCT04345445, NCT04438980, NCT04355247, NCT04374071, NCT04273321, NCT04263402, NCT04244591, NCT04323592, NCT04343729 and NCT04341038) (Figure 12) are currently being trialled in COVID-19 patients across the world. Initial results from a 12,000-person UK randomised study evaluating dexamethasone in COVID-19 patients, with 2,104 patients receiving 6 mg of dexamethasone once daily for ten days *versus* 4,321 patients receiving standard-of-care, indicate that it is effective in reducing mortality rates in COVID-19 patients requiring ventilation (28-day mortality rate reduced by one third) or supplemental oxygen treatment (28-day mortality rate reduced by one fifth) [91].

4.2. Cytokine Production Inhibitors

A number of cytokines have been reported to be involved in the human immune response to COVID-19, including IL-1, IL-2, IL4, IL-6, IL-10, IL-12, IL-13, IL-17, GCSF, MCSF, IP-10, MCP-1, MIP-1α, HGF, IFN-γ and TNF-α (NCT04334044), and thus inhibitors of their production may prevent ARDS [92]. **Colchicine** (Colcrys®; Figure 13), an anti-inflammatory approved for the management of acute gout that targets the NLRP3 inflammasome to reduce the release of cytokines IL-1β and IL-6 [93], is currently the subject of various phase 2 and 3 clinical trials for COVID-19-associated ARDS in Italy (NCT04322565), Canada (NCT04322682 and NCT04328480), Greece (NCT04326790) and Argentina (NCT04328480). **Baricitinib** (Olumiant™), **ruxolitinib** (Jakafi®) and **tofacitinib** (Xeljanz®) (Figure 13), inhibitors of the Janus kinase family of enzymes that mediate an inhibition of cytokine signalling [94], are due to be trialled in different studies in Italy (NCT04320277 and NCT04332042), Germany (NCT04338958), Canada (NCT04331665), Mexico (NCT04334044), China (ChiCTR2000029580) and the US (NCT04340232), though their use is still the subject of debate [95-97]. **Deferoxamine** (Desferal®; Figure 13), an iron and aluminium chelator, has previously been observed to block IL-6 production in a porcine sepsis inflammatory response syndrome model [98] and intravenous deferoxamine therapy is currently the subject of a 50-person phase 1 trial for treatment of COVID-19 in Iran (NCT04333550). **Escin** (Reparil®), a mixture of saponins found in the horse chestnut *Aesculus hippocastanum* thought to suppress the release of pro-inflammatory cytokines *via* a reduction of high mobility group box 1 (HMGB1) secretion [99], is being evaluated in separate COVID-19 clinical trials in Italy (NCT04322344) and China (ChiCTR2000029742).

4.3. Cardioprotective Medications

While most infections of SARS-CoV-2 have resulted in COVID-19 as a mild respiratory illness, a subgroup of patients experience a severe illness and require invasive cardio-respiratory support in an ICU setting. There is evidence that severe COVID-19 requiring ICU treatment is correlated with incidence of acute cardiac injury; however, the details surrounding the latter are as yet poorly understood. A study by Imperial College London is seeking to investigate this further in a 3,170-person clinical trial assessing the utility of cardioprotective medicines **aspirin**, **clopidogrel** (Plavix®), **rivaroxaban** (Xarelto®), **atorvastatin** (Lipitor®) and **omeprazole** (Prilosec®) (Figure 14) in preventing cardiac complications in COVID-19 patients. The trial is currently at the recruitment stage (NCT04333407).

4.4. Other Drugs

Other drugs being investigated for their anti-inflammatory properties (Figure 15) include the nonsteroidal anti-inflammatory drugs **ibuprofen** (Advil®), **naproxen** (Aleve®), **aspirin** and **indometacin** (Indocid™) in clinical studies in the UK (NCT04334629), France (NCT04325633), Pakistan (NCT04343001) and the US (NCT04344457), respectively; the vasodilator **sildenafil** (Viagra®; NCT04304313); **thalidomide** (Thalomid®; NCT04273581 and NCT04273529); the sphingosine-1-phosphate receptor modulator **fingolimod** (Gilenya®; NCT04280588); and antifibrotic drug **pirfenidone** (Esbriet®; NCT04282902, ChiCTR2000031138 and ChiCTR2000030892).

Vitamin C (ascorbic acid; Figure 15) has previously been observed to exert effects on the immune system supporting adaptive and innate immunity [100]. Individuals suffering from acute respiratory infections such as pneumonia have reduced vitamin C plasma concentrations when compared to control subjects [101]; a trial by Mochalkin and co-workers using vitamin C at doses of 0.25-0.8 g/day in pneumonia patients reduced average duration of hospitalisation by 19% relative to a control group, while a higher dose of 0.5-1.6 g/day reduced average duration of hospitalisation by 36% [102]. A number of other studies have indicated a role for vitamin C in providing resistance to coronavirus infections [103, 104]. It is currently being studied as part of multiple COVID-19 clinical trials in the US (NCT04328961, NCT04344184 and NCT04342728), Turkey (NCT04337281), Italy (NCT04323514), Canada (NCT03680274) and China (ChiCTR2000029768). **Vitamin D** is also due to be studied as an immune modulatory agent for the treatment of COVID-19 patients in separate trials in France (NCT04344041) and Spain (NCT04334005).

5. CONCLUSION AND FUTURE PERSPECTIVE

The COVID-19 pandemic is currently predicted to cost the global economy up to and in excess of 1 trillion USD [105]. In recent years, a number of different commentators have opined that the world is ill-prepared to deal with the next pandemic [106-108] and it would appear their collective fears were well-founded. The current pandemic thus highlights the importance of strong anti-infective research and therapeutics development programmes. While research into therapies to tackle SARS-CoV-2 is a short term priority, governments worldwide must also take a longer term view. Specifically, countries need to come together to develop an investment and reimbursement model to encourage anti-infectives research and development so that humanity is better prepared to tackle future infectious disease pandemics.

442

443 Fortunately, global research into small-molecule therapies for SARS-CoV-2 and COVID-19 is progressing at an

444 unprecedented rate. The fact that there are over 200 clinical trials currently being conducted worldwide into

445 different small-molecule therapies is an incredible feat of organisation given the short amount of time the

446 SARS-CoV-2 virus has been known to science and the medical personnel and scientists responsible are rightly

447 deserving of high praise. However, it is essential that these clinical studies remain scientifically rigorous; the

448 overwhelming demand for any form of treatment must not be allowed to detract from the quality of data

449 gathered nor the validity of conclusions reported. Recent instances of trial design and protocol controversy [109-

450 111], trial suspension with minimal explanation (NCT04252664 and NCT04257656) and improper

451 dissemination of preliminary trial findings [112] cannot be allowed to become commonplace. Only when the

452 randomised trials currently in progress begin to report properly vetted findings can conclusions be drawn.

453

454 Once effective small-molecule treatments for COVID-19 are identified, it is important that COVID-19 patients

455 be started on courses of the drug(s) as soon as possible. This will depend on the widespread use of rapid

456 diagnostic tests to determine whether a patient is infected with SARS-CoV-2. To this end, worldwide

457 development of a variety of diagnostic approaches is proceeding in parallel with the aforementioned efforts to

458 identify small-molecule treatments [113-121]. Widespread and expeditious testing is thought to have been key

459 to South Korea's low COVID-19-related mortality rate [122] – approximately 2.2% as of the 28th of June 2020

460 [2] – and increasing levels of testing worldwide in recent months are therefore encouraging [123].

461

462 If a previously experimental drug such as Gilead's remdesivir proves to be useful in treating COVID-19

463 patients, the next hurdle to overcome will be the lack of an established unit price. Gilead has sought to downplay

464 remdesivir's commercial potential throughout the current pandemic, even providing its existing stock of 1.5

465 million doses free of charge [124], but this scenario cannot continue indefinitely. In deciding on a reasonable

466 price, the promise of a faster return to normalcy must be weighed against the current plight of global economies

467 and the limited funds available for population-wide distribution. Yet the production costs associated with

468 remdesivir could prohibit its widespread use; the Institute for Clinical and Economic Review (ICER) estimates

469 that a 10-day course of remdesivir costs 10 USD to produce [125], placing it far above many drugs on the WHO

470 Essential Medicines List [126] as well as a number of other drugs being trialled against SARS-CoV-2 [127].

471 With the market price of remdesivir all but guaranteed to exceed the production figure – the ICER estimate a

472   price of up to 4,500 USD as cost-effective [125] – it remains to be seen if use of remdesivir will be feasible on a

473   global scale.

474

475   A decisive factor in determining how long a small-molecule therapy for SARS-CoV-2 will take to reach the

476   clinic may well be the degree to which scientists of different nationalities, disciplines and industry sectors are

477   able to cooperate. The field is where it currently is largely thanks to the effective organisation and execution of a

478   number of large collaborative projects [7, 128-130]; with countries around the world imposing lockdown

479   measures in a bid to ease the pressure on struggling healthcare systems, innovative schemes facilitating such

480   large-scale collaborations are now more important than ever. PostEra, a US/UK startup specialising in machine

481   learning-powered medicinal chemistry, is leading a crowdsourced initiative to harness the data generated by the

482   XChem fragment screening experiment at the Diamond Light Source to create novel M^{pro} inhibitors by asking

483   scientists around the world to analyse the data and suggest combinations of hit fragments for synthesis and *in*

484   *vitro* testing [131]. The *Coronavirus Tech Handbook*, a crowdsourced resource library based around COVID-19,

485   has been established by faculty members of Newspeak House in the UK to bring together expert contributors in

486   a range of different disciplines to help tackle the pandemic [132]. Time will tell if these innovative approaches

487   to drug design and research prove fruitful.

488	***Abbreviations***	
489	$3C^{Pro}$	3C Protease
490	ACE2	Angiotensin-Converting Enzyme 2
491	ACEI	Angiotensin Converting Enzyme Inhibitors
492	ARB	Angiotensin II Receptor Blockers
493	ARDS	Acute Respiratory Distress Syndrome
494	CC_{50}	Half Maximal Cytotoxic Concentration
495	ChiCTR	Chinese Clinical Trial Registry
496	COVID-19	Coronavirus Disease 2019
497	CRS	Cytokine Release Syndrome
498	E	Envelope
499	EC_{50}	Half Maximal Effective Concentration
500	HMGB1	High Mobility Group Box 1
501	HPEK	Human Primary Epithelial Kidney cell line
502	ICER	Institute for Clinical and Economic Review
503	IDLH	Immediately Dangerous To Life or Health
504	M	Membrane
505	MERS-CoV	Middle East Respiratory Syndrome Coronavirus
506	MOI	Multiplicity Of Infection
507	$M^{Pro}/3CL^{Pro}$	Coronavirus Main Protease
508	N	Nucleocapsid
509	NCTC	National Clinical Trials Consortium
510	NIOSH	National Institute for Occupational Safety and Health
511	ORF	Open Reading Frame
512	PDB	Protein Data Bank
513	PL^{Pro}	Papain-Like Protease
514	RBD	Receptor Binding Domain
515	S	Spike
516	SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
517	SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2

518	SI	Selectivity Index
519	TMPRSS2	Transmembrane Protease Serine 2
520	US	United States of America
521	WHO	World Health Organisation
522		

523 ***Contributions***

524 All authors researched data for the article, made substantial contributions to discussions of the content, wrote the

525 article and reviewed and edited the manuscript before submission.

526

527 ***Conflict of Interest Declarations***

528 None to declare.

529

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959

960

Human cell

SARS-CoV-2

Spike protein

ACE2

Vesicle

Coronavirus entry

Lysosome

Cathepsin L

TMPRSS2

Cathepsin L or Furin cleavage

TMPRSS2 cleavage

Membrane fusion

Membrane fusion

Genomic RNA

① **Viral entry**

Exocytosis

Golgi body

Assembly and packing

ER

Nucleus

Translation

③ **Viral release**

Genomic RNA

mRNAs

Replication

Transcription

mRNAs

genomic RNA (positive)

genomic RNA (negative)

Translation

Polyproteins (pp1a, pp1ab)

RNA replicase–transcriptase complex (formed by NSPs)

Proteasomal cleavage

Protease

Nucleocapsid (N)

Spike (S)

Membrane (M)

Envelope (E)

② **Viral replication**

Alveolus

Viral duplication

Activation

Alveolar macrophage

Activation

Cytokines/chemokines e.g. IL-6, TNF-α

Infected dendritic cells and activated macrophages trigger cytokine storm

Cellular integrity damaged

ARDS and multiple organ failure

④ **Immune overdrive**

Strategies for SARS-CoV-2 treatment:
① Blocking SARS-CoV-2 entry (e.g. hydroxychloroquine, umifenovir)
② Interfering with SARS-CoV-2 replication (e.g. favipiravir, remdesivir)
③ Interfering with viral release (e.g. oseltamivir)
④ Regulating immune overload (e.g. corticosteroids, baricitinib)

961

962   **Figure 1**. The SARS-CoV-2 virus infection cycle.
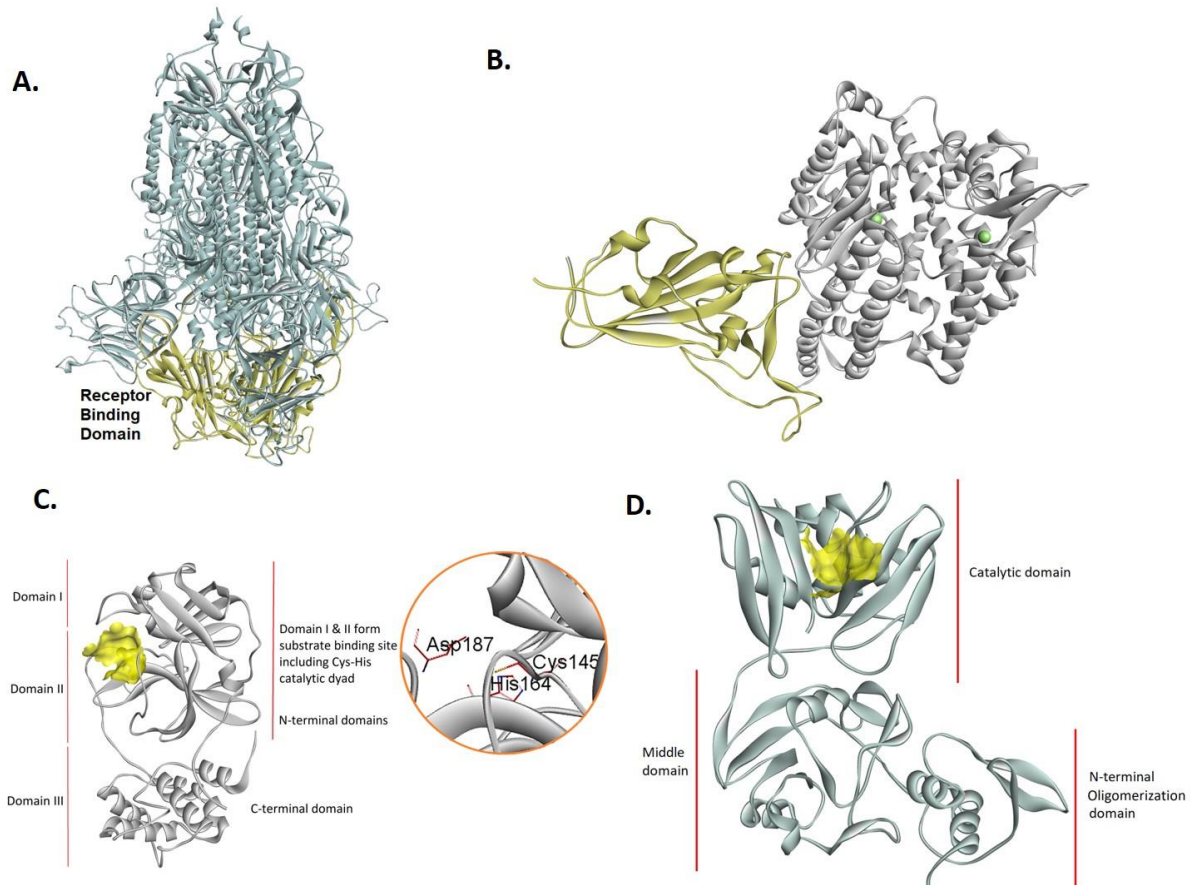
Figure 2. Different drug targets of SARS-CoV-2 that are currently being explored. A) Spike protein, B) spike protein-ACE2 docking interface (PDB ID 6LZG), C) main protease (PDB ID 6Y2E) and D) Nsp15 ribonuclease (PDB ID 6VWW).
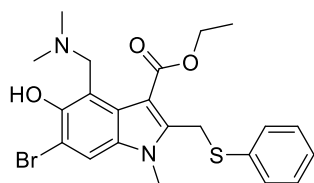
Figure 3. Spike protein targeting drugs umifenovir and nitric oxide.
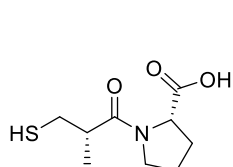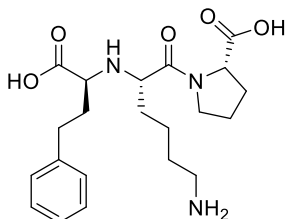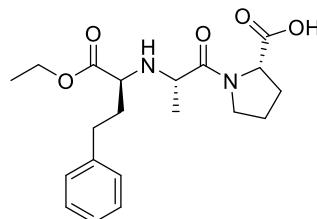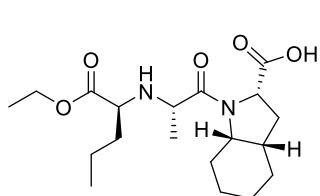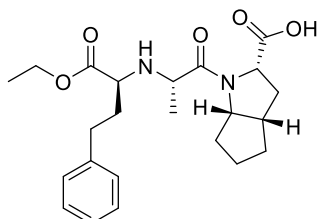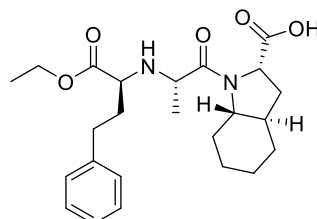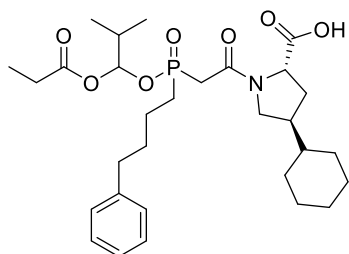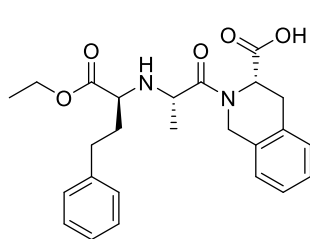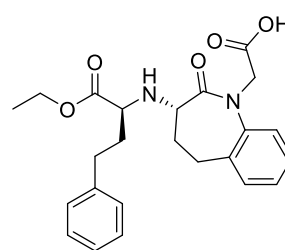
Figure 4. Structures of representative ACEIs.
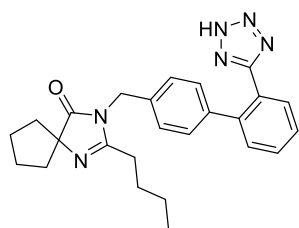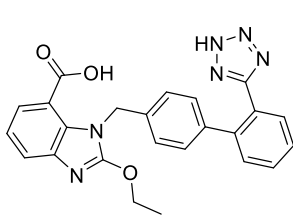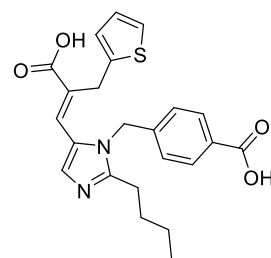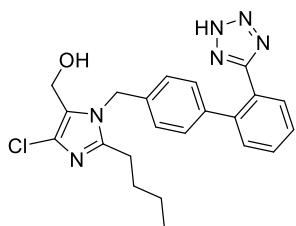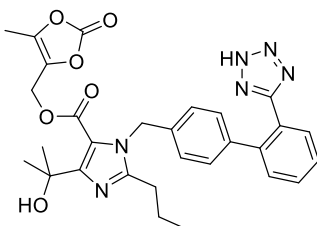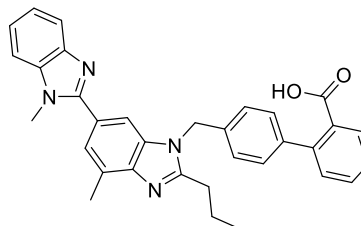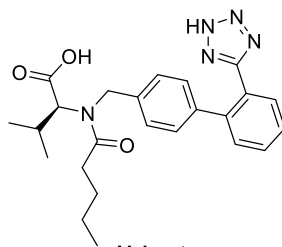
Figure 5. Structures of representative ARBs.
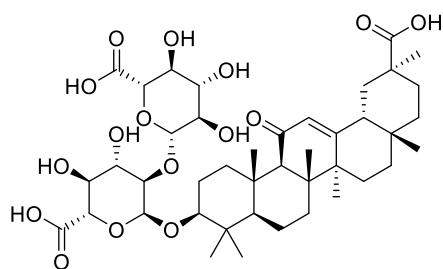
Figure 6. Structure of Chinese herbal medicine glycyrrhizin.
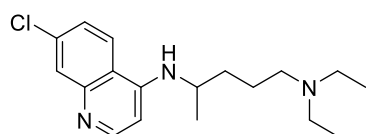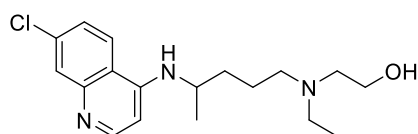
Figure 7. Endosome-targeting drugs chloroquine and hydroxychloroquine.

982
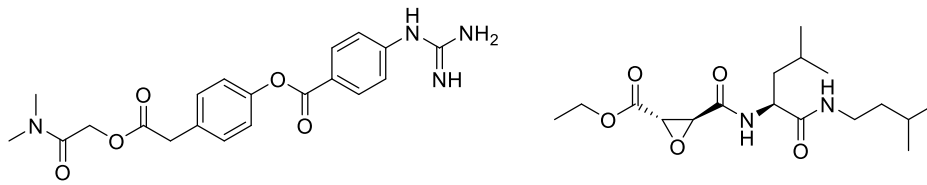
Camostat   Aloxistatin

983

Figure 8. Small-molecule therapies that target host proteases.

985
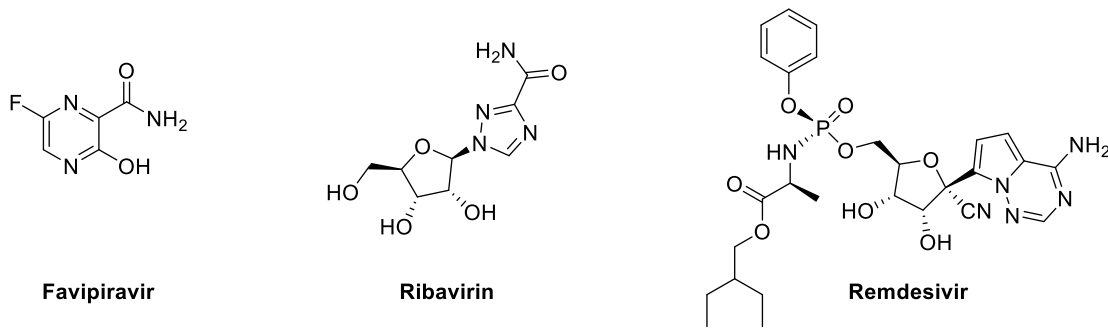
Favipiravir   Ribavirin   Remdesivir

986

Figure 9. Small-molecule therapies that target SARS-CoV-2 RNA-dependent RNA polymerase.

988
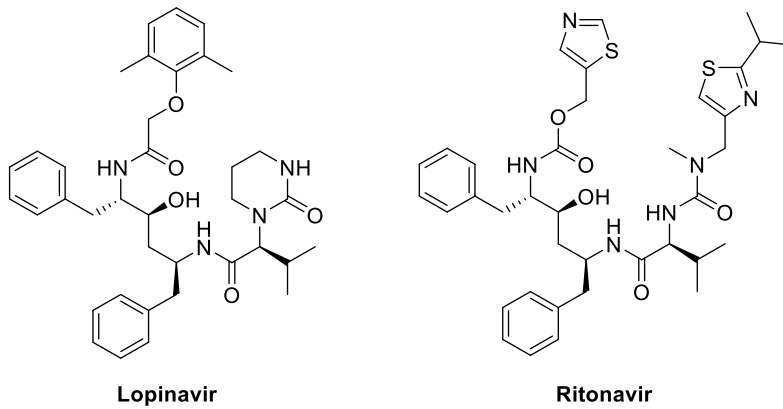
Lopinavir   Ritonavir

989

Figure 10. Small-molecule therapies that target SARS-CoV-2 M^{pro}.

991
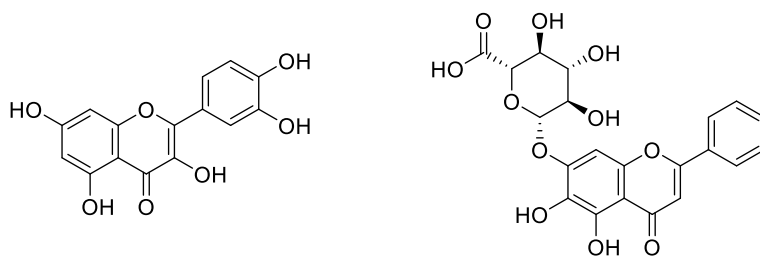
Quercetin   Baicalin

992

993   **Figure 11**. Structures of quercetin and baicalin.

994

Ciclesonide   **Budesonide**   **Dexamethasone**

Prednisone   **Methylprednisolone**
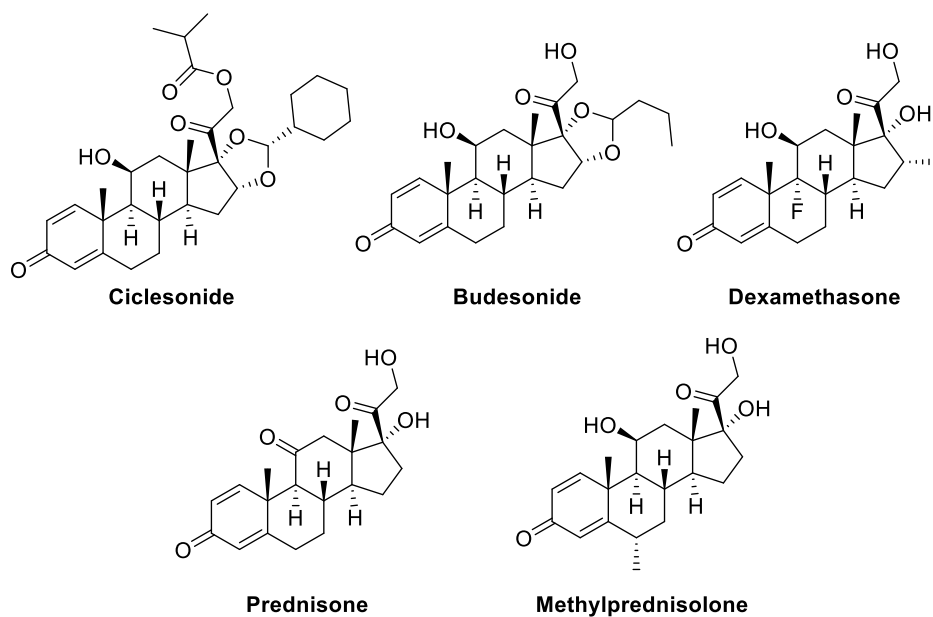
995

996   **Figure 12**. Corticosteroids being assessed for treatment of COVID-19-associated pneumonia.

997

Colchicine   **Baricitinib**   **Ruxolitinib**   **Tofacitinib**

Deferoxamine
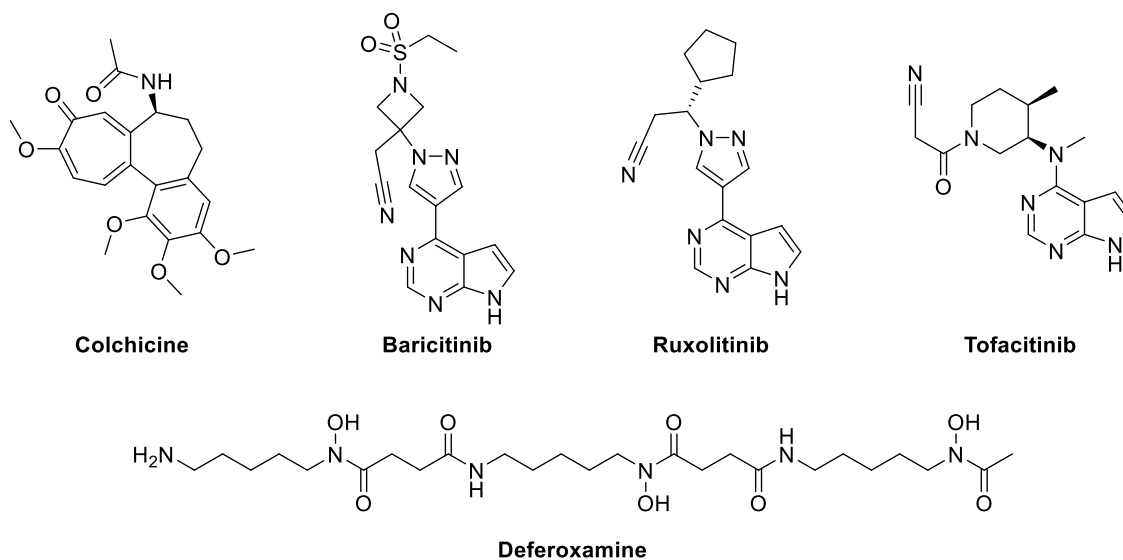
998

999   **Figure 13**. Cytokine production inhibitors being assessed for treatment of COVID-19-associated ARDS.

1000
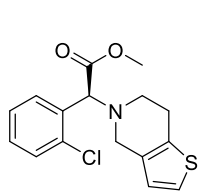
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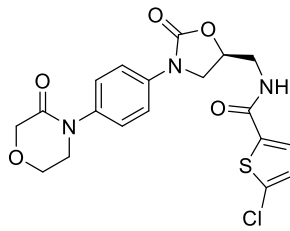
Rivaroxaban
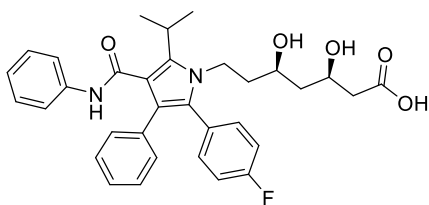
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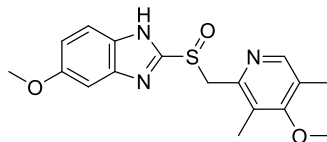
Omeprazole

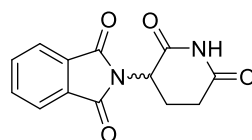**Figure 14**. Cardioprotective medicines being trialled in COVID-19 patients.
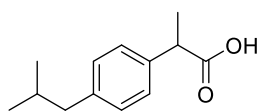
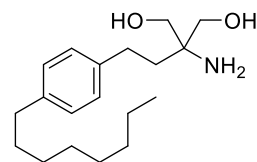**Ibuprofen**
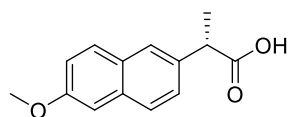
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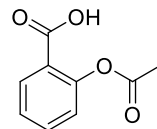
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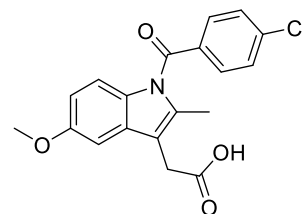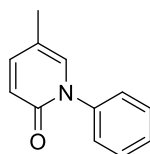
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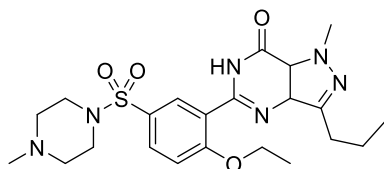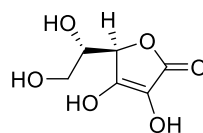
Sildenafil

Thalidomide

Fingolimod

Pirfenidone

Vitamin C

Figure 15. Other drugs being assessed for treatment of COVID-19-associated ARDS.