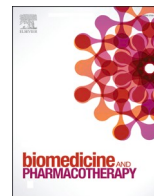




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Recent advances in management of COVID-19: A review

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ARTICLE INFO

Keywords:

COVID-19
SARS-CoV-2
Ivermectin
Famotidine
Nanobodies
Monoclonal antibodies
Remdesivir
SSRI
Fluvoxamine
Dexamethasone
Serotonin
Fluoxetine
Tocilizumab
Melatonin

ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic caused and is still causing significant mortality and economic consequences all over the globe. As of today, there are three U.S Food and Drug administration (FDA) approved vaccines, Pfizer-BioNTech, Moderna and Janssen COVID-19 vaccine. Also, the antiviral drug remdesivir and two combinations of monoclonal antibodies are authorized for Emergency use (EUA) in certain patients. Furthermore, baricitinib was approved in Japan (April 23, 2021). Despite available vaccines and EUA, pharmacological therapy for the prevention and treatment of COVID-19 is still highly required. There are several ongoing clinical trials investigating the efficacy of clinically available drugs in treating COVID-19. In this study, selected novel pharmacological agents for the possible treatment of COVID-19 will be discussed. Point of discussion will cover mechanism of action, supporting evidence for safety and efficacy and reached stage in development. Drugs were classified into three classes according to the phase of viral life cycle they target. Phase I, the early infective phase, relies on supportive care and symptomatic treatment as needed. In phase II, the pulmonary phase, treatment aims at inhibiting viral entry or replication. Drugs used during this phase are famotidine, monoclonal antibodies, nanobodies, ivermectin, remdesivir, camostat mesylate and other antiviral agents. Finally, phase III, the hyper-inflammatory phase, tocilizumab, dexamethasone, selective serotonin reuptake inhibitors (SSRI), and melatonin are used. The aim of this study is to summarize current findings and suggest gaps in knowledge that can influence future COVID-19 treatment study design.

1. Introduction

The COVID-19 pandemic first appeared as a case of pneumonia of unknown cause in December 2019 in Wuhan, China. Later, it evolved to a global outbreak and was declared a pandemic by the World Health Organization (WHO) on March 11, 2020. The WHO reported over 94 million confirmed cases of COVID-19 including 2 million deaths, globally as of 2021 [1]. It is caused by a novel virus from the family of

Coronavirus (CoV). This same family of virus caused the previous outbreaks of Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) in 2003–4 and 2012, respectively. The WHO defines Coronavirus as “a large family of viruses that cause illness ranging from the common cold to more severe diseases” [2]. Coronaviruses are single-stranded RNA viruses. They are highly diverse due to their susceptibility to mutation and recombination. They mainly infect humans, mammals, and birds. The SARS-CoV-2 or COVID-19 virus is

Abbreviations: ADE, Antibody dependant enhancement of the disease; ARDS, Acute Respiratory Distress Syndrome; CDC, Centers for Disease Control and prevention; CoV, Coronavirus; COVID-19, Coronavirus disease-2019; CVT, Cerebral Venous Thrombosis; EC50, half maximum neutralization concentration; EUA, Emergency Use Authorization; FDA, Food and Drug Administration; IC50, Half maximal inhibitory concentration; IC90, Concentration that inhibits 90% of the virions; ICU, Intensive care unit; IL-6, Interleukin 6; IMP, Importin; IRE1, Inositol-requiring enzyme; 1KD, Equilibrium dissociation constant (binding affinity); LPS, Lipopolysaccharides; MERS, Middle East Respiratory Syndrome; Nbs, Nanobodies; NEJM, The New England Journal of Medicine; NIH, National Institutes of Health; NOS, Reactive nitrogen species; OTC, Over the Counter medication; PCR, Polymerase chain reaction; RBD, Receptor binding domain; RdRp, RNA-dependent RNA polymerase; ROS, Reactive oxygen species; S1R, Sigma 1 receptor; SARS, Severe Acute Respiratory Syndrome; SARS-CoV-2, Severe acute respiratory syndrome corona virus 2; sdNbs, Single domain nanobodies; SPR, Surface plasmon resonance; TMPRSS2, Transmembrane serine protease 2; TNF-alpha, Tumor Necrosis Factor alpha; WHO, World Health Organization.

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<https://doi.org/10.1016/j.bioph.2021.112107>

Received 5 June 2021; Received in revised form 9 August 2021; Accepted 23 August 2021

Available online 27 August 2021

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thought to have originated in bats then spread to humans, possibly by contaminated meat sold in China's meat market. Symptoms of COVID-19 may involve multiple systems including respiratory, gastrointestinal, musculoskeletal, and neurologic. Respiratory symptoms can be manifested as dry cough, chest pain, rhinorrhoea and/or nasal congestion, sore throat and shortness of breath. Gastrointestinal symptoms can present as diarrhea, nausea, vomiting, haemoptysis and abdominal pain. Finally, patients could experience nonspecific symptoms such as fever, chills, fatigue, muscle ache, loss of taste and/or smell, headaches and confusion [3].

The Coronavirus enters the host cell via a trimeric spike glycoprotein, or peplomers, which give the viruses their corona-like appearance. The spike is constituted of two subunits: S1 and S2. The top of S1 subunit termed RBD, binds to the angiotensin-converting enzyme 2 (ACE2) receptor on the surface of the host cell. S2 subunit fuses with the host cell membrane. As the S1 subunit binds to the receptor, a host transmembrane serine protease 2 (TMPRSS2) activates the spike and cleaves ACE2, by acting on S2 subunit. This cleavage facilitates the fusion of the virus with the cell membrane, as shown in Fig. 1 [4]. Beside the more common direct membrane fusion pathway, a second suggested mechanism for COVID-19 entry is the endocytic pathway, thought to be pH dependant [5].

The viral RNA of coronavirus can be detected by polymerase chain reaction (real-time PCR). Since the outbreak of COVID-19, several treatment and prevention methods (i.e., vaccines) are under various phases of clinical trials. Some even got approved for Emergency Use Authorization (EUA) by the U.S Food and Drug Administration (FDA). Pharmacological agents could be classified into three classes according to the stage they tackle in COVID-19 infection. Stage I is the early infection phase during which the domination of upper respiratory tract symptoms is present. Management during this phase relies on supportive care to assist the immune system or prophylactic therapy possibly with ivermectin. Stage II is the pulmonary phase in which the patient develops pneumonia with all its associated symptoms. The aim during this stage is to inhibit viral entry or replication. In this class we mainly focused on famotidine, monoclonal antibodies, nanobodies, camostat mesylate and antiviral drugs. Stage III is the hyperinflammation phase, the most severe phase, in which the patient develops acute respiratory distress syndrome (ARDS), sepsis and multi-organ failure. Treatment

during this phase aims to suppress the immune response. Drugs like dexamethasone, the monoclonal antibody tocilizumab, dexamethasone, repurposed selective serotonin reuptake inhibitors (SSRI), melatonin or other immunomodulatory agents are being investigated in halting the cytokine release syndrome. Some patients also developed disseminated intravascular coagulation, against which anticoagulants are given [6].

The FDA issued EUA for three vaccines: Pfizer-BioNTech, Moderna and Janssen COVID-19 vaccine. However recently, on April 13, 2021, the FDA and the Centers for Disease Control and prevention (CDC) recommended withholding Johnson & Johnson (Janssen) COVID-19 vaccine until further safety investigations. This decision came after six reported cases of blood clotting, namely cerebral venous sinus thrombosis [7]. In this review, we summarized the findings of selected pharmacological agents against COVID-19 in terms of mechanism of action, efficacy, safety and stage of development. Our aim is to shed light on promising drugs and identify gaps in knowledge.

2. Treatment of different phases of COVID-19

2.1. Early infection (phase I)

Phase I is identified by upper respiratory symptoms most commonly cough, malaise and headaches, with the absence of shortness of breath. Less commonly patients might also present with sore throat, arthralgia, chills, rhinorrhoea, nausea and vomiting or loss of taste and/or smell. During this phase, the virus is replicating in the upper respiratory tract, mainly the nasal passages. The patient shows no to mild symptoms, with a presentation that is very similar to a flu or common cold. The goal during this phase is to support the immune system and to provide symptomatic management according to patient's presentation. Some patients are limited to this phase while others progress to the more severe stage II or III [8,9].

2.1.1. Symptomatic treatment/supportive care

Symptomatic treatment involves the use of analgesics and antipyretics to relieve symptoms of headache, fever and myalgia. For cough or dyspnea, self-proning (patient with respiratory distress is placed on his stomach) provides symptomatic improvement. Education on breathing exercise is also important. For mild cases of COVID-19 infection, general

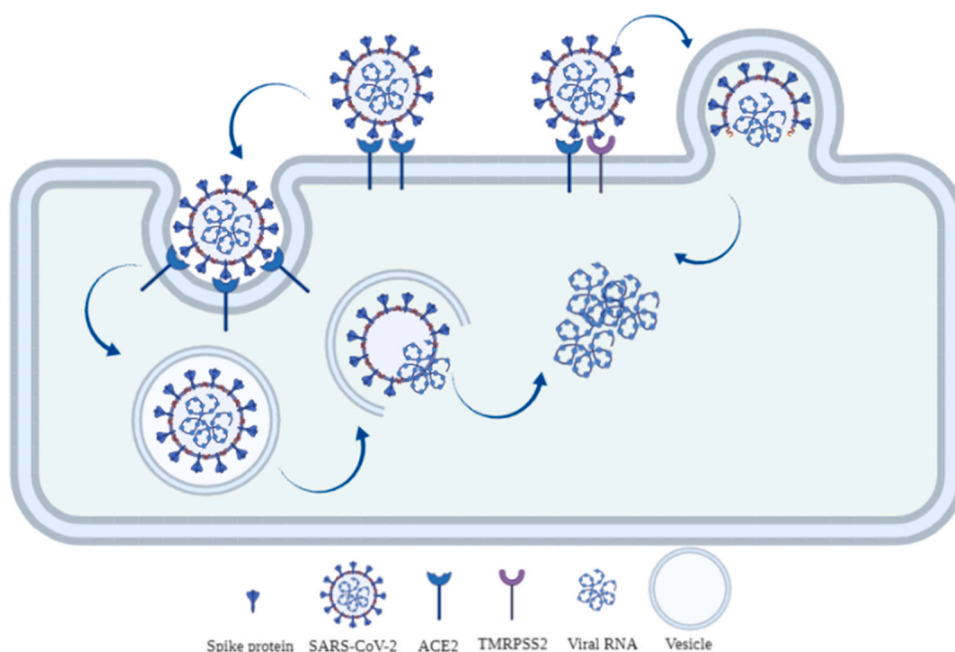


Fig. 1. Mechanisms of COVID-19 entry into the host cell. COVID-19 can invade the host cell by two mechanism: direct fusion or through the endocytic pathway.

supportive care is provided. This includes adequate hydration (especially when fever is present), rest, repositioning and ambulation [10]. Table 1 summarizes the symptomatic treatment and supportive care used during the mild phase (early infection).

2.2. Pulmonary phase (phase II): entry/fusion inhibition & antiviral agents

In phase II, the virus proceeds to infect the lungs triggering the innate immune response. As a result, patients develop pneumonia with its associated symptoms such as a worsened cough, fever, dyspnea and decreased oxygen levels. It is during this stage that most patients require hospitalization. Management during this phase is focused on preventing viral entry and invasion, in addition to limiting viral replication by antiviral therapy [11–13], as indicated below:

2.2.1. Ivermectin

Ivermectin is approved by the FDA as an anti-parasite drug to treat onchocerciasis (river blindness), Malaria, head lice and scabies [14,15]. The class of Ivermectin is avermectins. Ivermectin has shown an antiviral activity towards many RNA and DNA viruses [16]. In recent studies, ivermectin has shown in vitro antiviral activity against COVID-19.

The use of 5 μ M ivermectin reduced viral particle proliferation (5000-fold reduction in COVID-19 levels) within a 48-hour incubation period. The mechanism of action of ivermectin against COVID-19 is through inhibiting importin (IMP) α and β . IMP α and β are needed for the virus to gain access into the nucleus of the host cell [17]. Ivermectin was also found to antagonize transmembrane receptor CD147 [18].

In clinical settings, a retrospective cohort study including ($n = 280$) hospitalized patients infected with COVID-19 in South Florida hospital. 173 patients received ivermectin 200 mcg/kg orally and usual clinical care, while 107 patients received the usual clinical care only. Patients treated with ivermectin had significantly lower mortality rate (15.0% vs 25.2%) compared to conventional care only ($p = 0.03$) [19]. Furthermore, in a cross-sectional study, 100 mild to moderate COVID-19 patients were treated with a combination of oral doxycycline 100 mg and ivermectin 0.2 mg/kg. Within 6 days, 83.5% tested negative for COVID-19 and had major improvement in symptoms ($p = 0.59$). Additionally, no side effects or admission to intensive care was needed [20]. A case-control study conducted among healthcare workers in an Indian hospital, evaluated ivermectin as a prophylactic agent. Study subjects were health care workers that tested positive (case) or negative (control) for COVID-19. 77 of the control group and 38 of the case group, who took two doses of ivermectin prophylactically had 73% reduced risk of infection by COVID-19 [21]. It is not clear whether ivermectin should be used as treatment or prophylaxis and further studies are needed to establish ivermectin efficacy and mechanism against COVID-19.

2.2.2. Monoclonal antibodies

Antibodies are an important part of the host immune system and play a role in the eradication of pathogens including viruses. Monoclonal

Table 1
Symptomatic treatment/supportive care during the mild phase of COVID-19.

Early infection (mild phase)	
Symptoms	Treatment/ supportive care
Headache, fever and myalgia	<ul style="list-style-type: none"> Adequate hydration Acetaminophen nonsteroidal anti-inflammatory drug (NSAID)
Cough, and Dyspnea	<ul style="list-style-type: none"> Self-proning Breathing exercises education Over the counter (OTC) medications: <ul style="list-style-type: none"> Dextromethorphan Prescribed medication: <ul style="list-style-type: none"> Benzonatate (100–200 mg three times daily)

antibodies are synthetic proteins produced to mimic the natural immune response. As a result, they are very effective with vast applications. They are used in autoimmune diseases, asthma, oncology, neurology, radio-immunology and diagnostics [22–24]. Nonetheless, the FDA approved agents for viral infections are limited to Ebola and Respiratory Syncytial Virus (RSV) [25,26]. In comparison to other therapeutic agents, monoclonal antibodies are more specific, as they are designed to target a single protein.

There are many monoclonal antibodies developed or under development for treatment and/or prophylaxis of COVID-19. The majority target the S-spike protein, limiting viral attachment to the ACE2 receptor and further entry. Currently, the FDA permitted EUA for two combinations of monoclonal antibodies. REGEN-COV2 (casirivimab with imdevimab) approved in November 2020. While lately, in February 2021, the combination of bamlanivimab with etesevimab, by Eli Lilly and Company, was also approved [27,28]. Clinical trials that lead to FDA approval are provided in Table 2. Bamlanivimab monotherapy was initially approved, but due to development of resistant, the decision was revoked by the FDA [29]. According to the FDA, monoclonal antibodies are indicated in mild to moderate COVID-19 infected adults or even children (12 years or older with a minimum body weight of 40 kg), at high risk (as defined in the FDA fact sheet) for developing severe disease [30,31].

Expressly, an IV infusion of monoclonal antibodies is given to patients that test positive for COVID-19 with no critical symptoms, but at risk of developing severe infection. Some of these risk factors include age > 65 years, obesity, immunodeficiency and others. According to several studies, early treatment with monoclonal antibodies in these patients would reduce viral load, hospitalization and death [32]. It is suggested that monoclonal antibodies possess antiviral effect by reducing viral replication in the nasopharynx. As hospitalized patients with more severe symptoms experienced no benefit, their use is possibly limited to early therapy. Although their ineffectiveness in later, more severe stages, could be related to the hyperinflammatory state that is of higher impact [33].

2.2.3. Nanobodies

Despite advances in bioengineered monoclonal antibodies, as mentioned above, there are still some barriers to their use. Cost, heat sensitivity, and intravenous administration which requires patient hospitalization are all disadvantages of monoclonal antibodies. Additionally, in order to achieve effective alveolar concentration, a high dose must be injected which is associated with side effects. Their use was also linked with antibody-dependant enhancement of the disease (ADE), which could result in additional side effects [34].

Nanobodies (Nbs) are a new class of recombinant antibodies that are derived from heavy-chain antibodies, found in sharks and camels [35]. Mammalian antibodies (also known as conventional or traditional) are heterotetrameric proteins consisting of one pair of heavy chains and another pair of light chains. Interestingly, camelid species including camels, llamas and alpacas have antibodies that are devoid of light chains, with only the two sets of heavy chains. The variable domain of the camelid antibody is called the VHH domain (illustrated in Fig. 2), more commonly known as nanobody [24]. Nbs are a rapidly growing field in research with extensive evaluation in therapeutics and diagnostics. They have many advantages over conventional antibodies. To start, their small size (about 15 kDa) allows for good tissue penetration. Moreover, they have excellent aqueous solubility, stability, are easily bioengineered and suitable for large scale production assisted by yeast or bacteria. These outstanding biochemical properties possibly assist their administration by inhalation. Inhaled Nbs allow for lower doses, are more patient friendly and do not require hospitalization [36,37]. Finally, although attained from different species, their heavy chain is very alike to human antibodies, thus, is of low immunogenicity [38–41]. Caplacizumab is an FDA approved Nb for the management of thrombotic thrombocytopenia, supporting their therapeutic potential [42].

Table 2
Clinical trials that resulted in FDA approved of three monoclonal antibodies.

Drug	Name of Clinical trial	Type of clinical trial	Study subjects	Dose	Status
BAMLANIVIMAB (LY-CoV555)	BLAZE-1	interim data review from a Phase 2 randomized, double-blind, placebo controlled.	n = 465 (ambulatory)	Single IV infusion either 700 mg, 2800 mg, or 7000 mg	REVOKED [29]
BAMLANIVIMAB (LY-CoV555) AND ETESEVIMAB (LY-CoV016)	BLAZE-1	Phase 2 randomized, double-blind, placebo controlled. Phase 3 randomized, double-blind, placebo controlled.	n = 577 (ambulatory) n = 518 (ambulatory)	Single IV infusion 700 mg + 1400 mg Single IV infusion 2800 mg + 2800 mg	APPROVED EUA [33]
CASIRIVIMAB AND IMDEVIMAB (REGN-COV2)	R10933-10987-COV-2067	phase 1/2 randomized, double-blind, placebo controlled.	n = 799 (ambulatory)	Single IV infusion 1200 mg + 1200 mg Or 4000 mg + 4000 mg	APPROVED EUA [27]

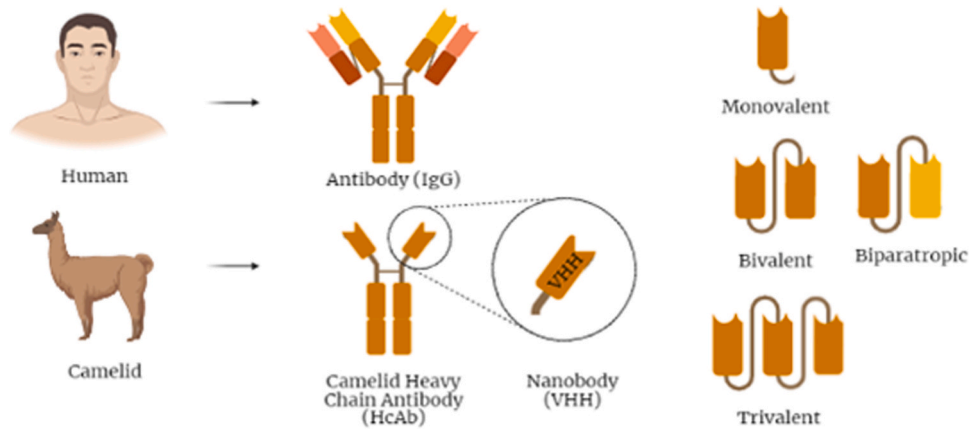


Fig. 2. The structure of nanobodies (Nbs) and different multivalent nanobodies. Camelid species unlike conventional antibodies (IgG) only consist of two light chains. The variable domain highlighted is known as the VHH domain or more commonly nanobody. Nbs can be bioengineered as monovalent or multivalent. Multivalent Nbs can be further classified into bivalent (two identical Nbs), biparatropic (two different Nbs) or trivalent (three identical Nbs).

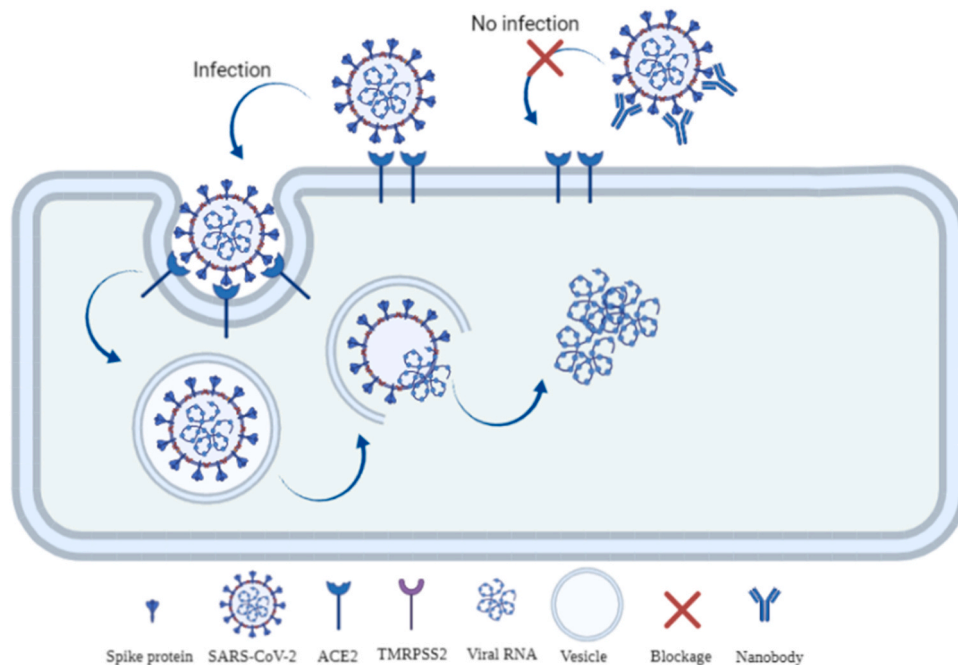


Fig. 3. Nanobodies inhibit the viral entry into the host cell. Nanobodies bind to viral spike proteins inhibiting spike-ACE2 binding.

Although many Nbs have been bioengineered and successfully tested preclinically, their efficacy in humans is yet to be trialed [43–45].

The main mechanism of action of Nbs against COVID-19 is by inhibiting spike protein-ACE2 binding interaction as shown in Fig. 3. Schoof, et al., using yeast surface-display libraries, identified two classes of neutralizing Nbs. Class I Nbs such as Nb6 and Nb11 (the most potent member of class I), attached to RBD, while class II Nbs such as Nb3 attached to a different, unidentified epitope on spike proteins. The lateral class had less inhibitory effect against COVID-19. Cryo-electron microscopy (cryo-EM) was used to identify the binding site of the most potent class I Nb. Both Nb11 and Nb6 were found to bind the up and down conformation of RBD. Uniquely, the binding of Nb6 to the more stable down state, stabilized two nearby RBD in the down conformation. This was likely to facilitate binding of other Nb6 molecules. These findings were not manifested by Nb11, that only bound RBD. The mechanism of Nb6's binding, influenced Schoof, M. and colleagues to design bivalent and trivalent forms of Nb6, that could possibly keep all RBD in the down state. Indeed, upon investigating the equilibrium dissociation constant (K_D) of bivalent and trivalent Nb6, more than 200,000-fold improvement in K_D was noted. Furthermore, Nb6 was modified with the aim of enhancing potency. The matured (modified) Nb6 (mNb6) exhibited 500-fold augmentation in spike binding affinity. As mNb6 showed a similar binding mode to Nb6, engineered trivalent mNb6 were the most potent multivalent Nb in neutralizing COVID-19. The observed mNb6 neutralizing effect was by two mechanisms; blocking RBD-spike interaction and stabilizing RBD in inactive down-state (ACE2 receptor only binds to the up-state). Table 3 provides a summary of the monovalent and multivalent Nb affinities and neutralizing activities [46].

In another study, a humanized llama VHH was used to examine the potency of Nbs against COVID-19. 91 high-affinity Nbs hit the spike protein binding site and 69 out of the 91 Nbs had a unique sequence. Upon further investigation of the 69 unique Nbs, 15S protein binders were discovered to block the spike protein-ACE2 receptor interaction, enhancing the neutralization effect against COVID-19 infection [47]. A Further study by Chi, et al., reported five single domain Nbs (sdNbs) that act against COVID-19 spikes. These monovalent Nbs had low affinity against pseudotyped particle of COVID-19. A successful attempt to improve the neutralizing activity of these sdNbs was noted upon fusion with human IgG Fc-domain. Fc-fused sdNbs showed 10-fold increase in activity compared to conventional sdNbs [48]. Although Fc-fused Nbs are more potent, they are more likely to be associated with ADE.

Koenig, et al., screened Nbs produced by immunized lama and alpaca. Out of 23 potential Nbs, four were the most potent VHH U, V, W and E in competing with COVID-19 for the RBD. VHH E had the highest activity (out of the four) with an IC50 (half maximal inhibitory

concentration) of 60 nM. Surface plasmon resonance (SPR) assay identified two binding sites on RBD. One region that binds each of VHH U, V and W, while VHH E binds to a separate region. Based on this information, and those obtained from SPR, X-ray crystallography and cryo-EM, Koenig et al., engineered two types of Nbs. Multivalent Nb VHH EE and EEE, since VHH E was the most potent Nb. However, upon exposure, the virus rapidly developed resistance and was no longer recognized by the Nbs. To overcome or limit the resistance, bivalent biparatropic Nbs were developed that targeted two independent regions of the RBD (VHH E + U, VHH E + V, VHH E + W). Notwithstanding, it is speculated that bivalent biparatropic Nbs' neutralizing mechanism enhances viral fusion as VHH E, U and W stabilized the RBD in the up conformation. Since the up conformation is the active conformation for COVID-19, it is believed that this triggers further conformational changes that eventually cause viral-membrane fusion. This observation is of interest as VHH E compared to VHH U and W target different binding sites, a phenomenon that was not observed in other coronaviruses. The exact mechanism is not clear and necessitates further investigation [37]. Table 3 provides a summary of the different Nbs' mechanism of action, binding affinity and IC50.

To conclude, the use of Nbs that stabilize the RBD in the more stable down-conformation, like the potent trivalent mNb6, might be of higher benefit. This would prevent possible Nb induced viral fusion. Also, they are devoid of ADE induced by Fc-fused sdNbs. Additionally, comparing potencies, mNb6 had the lowest IC50 versus each of VHH EV and VHH VE respectively. (1.6 nM vs 2.9 and 4.1 nM).

2.2.4. Famotidine

Famotidine is a Histamine-2 receptor (H2) antagonist, used in the treatment of peptic ulcer, mild reflux esophagitis and Zollinger-Ellison syndrome [49]. The potential mechanism of action of famotidine is being investigated. There are several studies that support the use of repurposed famotidine in COVID-19 patients.

In a case series, 10 non-hospitalized patients administered 80 mg famotidine three times daily for 11–21 days. All patients reported marked improvement in symptoms [50]. In a cohort retrospective study including a total of 1620 inpatients, 84 received a median dose of 136 mg famotidine for a duration of 5–8 days. On the other hand, 1566 patients were classified as control (did not receive famotidine). The results showed that the death/intubation ratio was (8/84). 10% of patients administered famotidine while 22% did not receive famotidine (332/1536). Results were statically significant ($p < 0.01$) showing that famotidine administration was associated with an improved outcome in terms of need for intubation or death [51]. However, bases on these results alone, it cannot be confirmed that famotidine has a direct effect on COVID-19, because it was an observational study. In another

Table 3
List of the different types of neutralizing nanobodies.

No. of study	Nanobody type	Mechanism of nanobody	Nanobody name	K_D	IC 50	References	
1	Yeast surface displaced library using synthetic nanobody sequences	Block the interaction of spike and RBD to ACE2	Nb6 Nb6 trivalent Nb6 Redesign	41 nM N/A 0.56 nM	2.0 μ M 1.2 nM 1.6 nM	Schoof et al. [43]	
2	Humanized antibody VHHs of llama	Block the interaction of spike and RBD to ACE2	N/A	0.25 nM	1 nM	Dong et al. [44]	
3	Single domain nanobodies (sdNbs)	Inhibitory effect against spike receptor-binding domain (RBD) of SARS-CoV-2	1E2 2F2 3F11 4D8 5F8	35.52 nM 5.175 nM 3.349 nM 6.028 nM 0.996 nM	18.8 nM 22.6 nM 28.6 nM 9.6 nM 39.3 nM	Chi et al. [45]	
4	Camelid nanobodies (one llama and one alpaca)	Inhibitory effect against spike receptor-binding domain (RBD) of SARS-CoV-2	Single domain nanobody Multivalent nanobodies	VHH E VHH U VHH V VHH W VHH EV VHH VE	2 nM 21 nM 9 nM 22 nM N/A N/A	60 nM 286 nM 198 nM 257 nM 2.9 nM 4.1 nM	Koenig et al. [37]

retrospective cohort study, 110 hospitalized patients received a combination of famotidine 20 mg twice daily and cetirizine 10 mg (a histamine 1 (H1) receptor antagonist) twice daily. The results showed that the combination of both drugs together reduced the mortality rate by 26–45% compared to similar published reports [52]. Moreover, in a retrospective matched-observational cohort study, 83 out of 878 (9.5%) patients received 20 mg/day of famotidine within +/- 7 days of hospital admission. The remaining 4.8% of the cases received 40 mg/day famotidine. The primary outcomes in the famotidine group were, 12 (14.5%) patients died, 18 (21.7%) patients needed intubation and 6 (7.2%) patients had both death/intubation cases. In the Non-famotidine group 179 (26%) patients died, 221 (32.1%) patients needed intubation and 95 (13.8%) patients died and needed intubation. Famotidine was associated with lower mortality risk (odds ratio 0.366, 95% confidence interval (CI) 0.155–0.862, $p = 0.021$) [53].

A hypothesis suggests that a high dose of famotidine could produce antiviral effect by inhibiting two COVID-19 proteases, papain-like protease and 3-chymotrypsin-like protease [50,54]. Nonetheless, in silico studies did not support this hypothesis. Loffredo et al., suggests that high dose famotidine is more likely to be involved in limiting the hyper-inflammatory phase [55]. In summary, further studies are needed to identify famotidine's mechanism of action and additional larger, multicentred studies are needed to confirm and support the effectiveness of famotidine towards COVID-19.

2.2.5. Other drugs

The following table summarizes other drugs that act against COVID-19 during the pulmonary phase (Table 4). Camostat mesylate and baricitinib inhibit viral fusion while the other drugs inhibit viral replication.

2.3. Hyperinflammatory phase III

During this phase, inflammation extends beyond the lungs into a systemic hyperinflammatory syndrome, also known as cytokine storm syndrome. As a result, patients can develop a range of complications mainly ARDS, sepsis or even multiorgan failure. It is characterized by an elevation in inflammatory mediators like IL-2, IL-6, IL-7, TNF- α , C-reactive protein and a decrease in T-cell count [56].

2.3.1. Tocilizumab

Tocilizumab is a humanized monoclonal antibody that binds to interleukin 6 (IL-6) receptor. The approved use of tocilizumab is

rheumatoid arthritis due to its anti-inflammatory effect. Tocilizumab can bind to both soluble IL-6 receptor and membrane bound receptor, antagonizing the effect of IL-6. IL-6 is an important pro-inflammatory mediator and its production is triggered by tissue injury and infection. Release of IL-6 into the circulation mobilizes B and T-cells. Targeting IL-6 receptor accordingly has a role in limiting the inflammatory and immune response [57,58].

Unlike REGEN-COV2 and etesevimab used in selected mild to moderate COVID-19 outpatients, tocilizumab is investigated for more severe COVID-19 cases in hospitalized patients. COVID-19 intensive care unit (ICU) patients have high plasma levels of cytokines, known as cytokine storm. IL-6 particularly, was elevated in more severe COVID-19 cases or those requiring mechanical ventilation [57]. There are many studies that investigated the effect of tocilizumab as shown in Table 5 with conflicting findings. Thence, larger randomized clinical trials were conducted to delineate tocilizumab's findings.

Tocilizumab was part of the [RECOVERY] trial, a large randomized clinical trial that included all big hospitals in the United Kingdom. This trial aims to find potential treatment for severe COVID-19 hospitalized patients. Eligible patients had a positive COVID-19 test, hypoxia (defined as oxygen saturation < 92%) and systemic inflammatory C-reactive protein levels of ≥ 75 mg/L. Study participants were randomized to receive standard care only or standard care along with intravenous tocilizumab at a dose of 400–800 mg (according to weight). If patient's condition did not improve, a second dose of tocilizumab was given, 12–24 h after the initial dose. 4116 adults were eligible according to the study criteria. Of those, 596 out of 2022 patient (29%) on the tocilizumab arm, were discharged after 28 days. Contrastingly, 694 out of 2094 subject (33%) who received the usual care, died ($p = 0.007$). Overall, patients allocated to receive tocilizumab had 4% reduction in mortality and the need.

for invasive mechanical ventilation ($p = 0.0005$) [59]. Comparable results were seen with EMPACTA (Evaluating Minority Patients with Actemra) in terms of reduced mortality and need for mechanical ventilation. EMPACTA is a phase III, international clinical trial. The aim of the study was to explore whether tocilizumab is safe and effective in COVID-19 hospitalized pneumonia patients, not on mechanical ventilation [60]. REMAP-CAP trial that recently published its results in *New England Journal of Medicine (NEJM)* also supported positive findings with tocilizumab when used in COVID-19 ICU patients that were not organ supported [61]. Finally, COVACTA trial involved 62 hospitals, and also published its results in *NEJM*, showed no major improvement in

Table 4
Other drugs that act against SARS-CoV-2 during the pulmonary phase.

Viral life cycle target	Drug name	Pharmacological class	Indication	Mechanism of action against SARS-CoV-2	Concentration against SARS-CoV-2 (μ M)	Phase of development
Attachment and entry	Baricitinib	Janus kinase (JAK) 1/2 inhibitor	Rheumatoid arthritis	Dual effect: • Inhibition of kinase signaling that will prevent viral endocytosis • Inhibition of cytokine release by blocking the JAK 1&2 [53]	NA	Phase III [54] APROVED in japan [55]
	Camostat mesylate	Protease inhibitor	Pancreatitis	Block TMPRSS2 involved in viral fusion [56]	EC50: 1	Phase III [57]
Proteolysis	Boceprevir	Protease inhibitors	hepatitis C virus (HCV)	NSP5 inhibitor (M ^{pro} /3CL ^{pro}), that cleaves viral proteins into the active form [58]	EC50: 15.57	Preclinical screening [58]
	PF-07304814	Protease inhibitors	/	NSP5 inhibitor, (M ^{pro} /3CL ^{pro}). [59]	NA	Phase I [60]
Translation of polyproteins	Plitidepsin	Didemnins	Multiple myeloma	Inhibitions of eEF1A, a protein needed for translation [61]	IC90: 0.00176	Phase III [62]
	Zotatifin	Anticancer	NA	Inhibition of protein biogenesis and blocks eIF4A, an enzyme needed to initiate translation [63]	NA	Phase I [64]
RNA replication	Remdesivir	Adenosine analog (Antiviral)	Filoviruses, pneumoviruses paramyxoviruses, and coronaviruses.	Inhibits RNA-dependent RNA polymerase (RdRp) [65]	EC50: 0.074	Phase III [66]

Table 5
Clinical studies on tocilizumab.

Study no./name	Study design	Total number of patients	Case	Control	Outcome	Reference
1	Observational cohort study	44	n = 22 (Tocilizumab intravenous 600 mg)	22	<ul style="list-style-type: none"> On day 14, lower respiratory rate in tocilizumab group (P=0.03), and fewer required mechanical ventilation. On day 7, a significant decrease in C-reactive protein levels (P = 0.04). 	Albertin et al. [74]
2	Retrospective cohort study	87	n = 29 (Tocilizumab 8 mg/kg)	58	<ul style="list-style-type: none"> Significant reduction in hospital and ICU stay. Mechanical ventilation had been reduced significantly at earlier time (P = 0.002) 	Eimer et al. [75]
3	Observational retrospective cohort study	544	n = 179 (16/88 received IV 8 mg/kg and 17–91 received 162 mg SC dose)	365	<ul style="list-style-type: none"> 57/365 of the control group needed mechanical ventilation 73/365 of the control group died Tocilizumab group were having less death rates and invasive mechanical ventilation (P = 0.020) 24/179 and 14/365 (P < 0.0001) had an acquired infection. 	Guaraldi et al. [76]
4	Multicentre cohort study	3924	n = 433	3491	<ul style="list-style-type: none"> 1544 patients from control group died compared to 125 from tocilizumab arm. 27 follow-up days, tocilizumab group had lower death rate compared to control group. Estimated mortality rate after 30 days was 37.1% for control group and 27.5% tocilizumab group. 	Gupta et al. [77]
EMPACTA	Randomized, phase III, international controlled trial	389	n = 249 8 mg/kg IV	128	On day 28, 12% on the tocilizumab vs 19.3% died or needed mechanical ventilation (P = 0.04)	Salama et al. [70]
REMAP-CAP	Global adaptive platform trial	803	n = 353 Tocilizumab (8 mg/kg) n = 48 Sarilumab (400 mg) n = 294 Tocilizumab (8 mg/kg)	402	No dependence on organ support and improved survival.	<ul style="list-style-type: none"> REMAP-CAP Investigators [71]
COVACTA	Randomized, phase III trial	452	n = 294 Tocilizumab (8 mg/kg)	144	No improvement in survival or mortality.	Rosas et al. [72]

reducing mortality or survival [62]. Most studies reported no improvement in survival except the REMAP-CAP trial [63].

2.3.2. Dexamethasone

One of the treatment approaches that has been widely implicated in the management of the hyperinflammatory phase is dexamethasone. Dexamethasone belongs to the Corticosteroids family, specifically; it is a glucocorticoid. Corticosteroids are used in several inflammatory conditions affecting a wide range of system, including dermatological, ophthalmic, rheumatologic, hematologic, gastroenterological and others. More importantly, they are commonly used in pulmonary infections like asthma, chronic obstructive pulmonary disease and viral pneumonias [64,65]. Dexamethasone is cheap, readily available and has a long half-life. In comparison to other corticosteroids, dexamethasone is 25 times more potent and has relatively no mineralocorticoid effect [66,67].

Dexamethasone has both anti-inflammatory and immunomodulatory effect. These effects result from a genomic or non-genomic pathway depending on the dose. At a low dose, dexamethasone has a genomic effect, altering genes that code for proinflammatory cytokines and chemokines. The lipophilic nature of dexamethasone allows it to cross the cell membrane and bind to the glucocorticoid receptor in the cytoplasm. Upon binding, the complex relocates to the cell nucleus where it binds to glucocorticoid response elements. Glucocorticoid response elements modulate gene transcription of several inflammatory mediators like cytokines, macrophages, mast cells, lymphocytes and prostaglandins. Additionally, this binding upregulates anti-inflammatory mediators IL-10, annexin A1 and lipocortin-1. When a higher dose of dexamethasone is used, the anti-inflammatory and immunomodulatory

effect result from a nongenomic pathway. Compared to the genomic pathway, it is faster but shorter in duration of action. Instead of binding intracellularly, dexamethasone binds either membrane-bound glucocorticoid receptor or cytosolic glucocorticoid receptor. A third mechanism is by a nonspecific cell membrane interaction, that alters certain signaling pathways [64,68–70]. Furthermore, based on computational molecular modeling, dexamethasone was found to inhibit the COVID-19M^{pro} [71].

A low dose of dexamethasone is indicated in severe cases of COVID-19, while no benefits were observed in mild to moderate cases. High doses are not recommended as they are associated with harmful effects [72]. According to the WHO and National Institutes of Health (NIH), corticosteroids are indicated as standard care for up to 10 days or until discharge in patients with COVID-19 pneumonia, requiring respiratory support [66]. These recommendations were largely shaped by the results of the RECOVERY trial. In the RECOVERY trial, hospitalized COVID-19 patients were allocated to receive dexamethasone along with usual care (n = 2104) or usual clinical care only (n = 4321). A dose of 6 mg dexamethasone was administered for up to 10 days or until discharge. Findings demonstrated that dexamethasone use is associated with lower mortality rate in patient on mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51–0.81) or oxygen therapy (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72–0.94) by day 28. Contrarily, no reduction in mortality was noted in patients not on respiratory support (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.92–1.55) [73].

Timing of initiating therapy is crucial. Early administration can aid viral replication and interfere with the adaptive immune response [64]. Evidence driven by current studies suggest maximum benefit from corticosteroid therapy when initiated in patients with persistent

symptoms, beyond 7 days [74]. Although dexamethasone is mainly indicated in the hyperinflammatory phase, initiation during the pulmonary phase exclusively in hypoxic patients has also been advocated [56]. While guidelines were based on the results of the RECOVERY trial, the extend of secondary bacterial infections (seen with previous viral pneumonias) was not assessed. Therefore, careful use is warranted particularly when administered with other immunosuppressants.

2.3.3. Selective Serotonin Reuptake inhibitors (SSRI)

2.3.3.1. Sigma-1 receptor (S1R) agonist.

Sigma-1 receptor (S1R) is a transmembrane chaperon protein and function as a receptor for many ligands. It is located in the mitochondria-associated membrane that is found in many organ tissues, but mainly in the central nervous system. Mutations or polymorphism of the S1R can lead to neuronal degeneration, resulting in pathological conditions such as amyotrophic lateral sclerosis, Huntington's diseases, Alzheimer's and dementia [75]. S1R agonist used in animal models displayed neuroprotective actions [75–77].

Interestingly, S1R is also involved in regulating oxidative stress in the endoplasmic reticulum. Specifically, inositol-requiring enzyme 1 α (IRE1), a main stress sensor, promotes the release of inflammatory cytokines upon subjection to lipopolysaccharide (LPS). Unfortunately, IRE1 is difficult to target as it is involved in other important psychological conditions. For this reason, Rosen, et al., shifted their focus on S1R, suggesting the involvement of this receptor in IRE1-induced inflammation. The study assessed the effect of S1R-IRE1 pathway modification in mice after injection of LPS, or peritoneal administration of fecal slurry. Mice with deleted S1R had significant higher sepsis induced-mortality rates (higher tumor necrosis factor alpha (TNF- α) and IL-6 concentration $p < 0.05$). Oppositely, upregulation of S1R or suppression of IRE1 increased survival due to a decrease in inflammatory response (decrease in IL-8 concentration $p < 0.05$). These findings supported further assessment of the anti-inflammatory effect of fluvoxamine. Fluvoxamine is a SSRI but also a potent S1R agonist. Injection of fluvoxamine in septic animal models revealed positive improvement. The anti-inflammatory effect was reproducible in human cells as well [78]. These findings, although induced by LPS, are certainly promising. Sepsis is a lethal complication and a major cause of mortality in intensive care patients. Despite sepsis being more commonly bacterial, viral sepsis can be a complication of viral infection as well [79,80]. In a study by Chen et al., in (Wuhan, china), out of 99 cases admitted to the hospital, 4% had septic shock [81]. More importantly, TNF- α and IL-6 are two very important pro-inflammatory cytokines involved in COVID-19 associated cytokine storm. Cytokine storm is a major complication of COVID-19 resulting in multiorgan failure, ARDS or even death [82].

A Double-blinded randomized study involved 152 mild PCR confirmed COVID-19 cases to receive either fluvoxamine (day 1 = 50 mg OD, day 2&3 = 100 mg twice daily, day 4–15 = 100 mg three times per day if tolerated) or placebo for 15 days. The objective was to assess the ability of fluvoxamine to halt disease progression and improve clinical outcome in symptomatic, non-hospitalized patients. The study was carried out remotely from patients' home. None of the fluvoxamine arm subjects had deterioration in their condition compared to 8.3% of the placebo arm ($p < 0.09$). Unfortunately, these finding cannot be considered statistically significant due to the limited sample size and the rather homogenous study subjects. It is also important to point out that since the study was conducted from distance, there is a higher chance of user bias [83]. Fluvoxamine does not require hospitalization, taken orally, readily available and relatively cheap in comparison to other COVID-19 used agents. Fluvoxamine is advantageous compared to other SSRI in that it does not cause QT-interval prolongation [84].

2.3.3.2. Lysosomotropic agents.

SSRI are also investigated as lysosomotropic agents. Specifically, sertraline and fluoxetine have been approved

as lysosomotropic agents. Lysosomotropic agents are weak bases ($pK_a > 6$, hydrophobic) that can penetrate endosomes or lysosomes in their unionized form. Once they cross, the acidic pH of endosomes or lysosomes causes protonation. Protonation traps the drug inside (ionized drugs cannot cross the membrane), neutralizing the acidic environment (increase in pH is represented in green Fig. 4). The acidic environment is crucial for the fusion of coronaviruses including COVID-19. Upon viral entry through the endocytic pathway, the decrease in endosomal pH allows the virus to attach vacuolar membrane and release the genetic material into the cytosol. This step is vital for viral replication and completion of its life cycle [85]. The closer the endosome gets to the nucleus, the higher the drop in pH (as shown in Fig. 5), which acts as a signal for the virus to exit the vacuole. Furthermore, the peptides needed for viral fusion are usually activated by endolysosomal proteases that require acidic pH for their function. Neutralizing the pH will thus inhibit this step.

Other agents besides SSRI have also been investigated. Examples are chloroquine, hydroxychloroquine and sodium bicarbonate [86–88]. Chloroquine and hydroxychloroquine, although studied extensively as lysosomotropic agents, are largely limited by their toxicity, side effect profile, interpatient-variations and their long half-life (30–60 days). Fluoxetine on the other hand has a better side effect profile, is less toxic and has a notable faster elimination half-life (1–3 days) [88]. However, Schloer, et al., stated that complete inhibition of viral entry will only be achieved by inhibiting both pathways, the endocytic pathway as well as the direct fusion with the host plasma membrane [89].

2.3.3.3. Functional inhibitors of Acid sphingomyelinase (FIASMA).

Functional inhibitions of Acid sphingomyelinase (FIASMA) is a pharmacological class with a wide range of therapeutic applications. Members of this class share the inhibitory effect on sphingomyelinase (SMA), the small size and general tolerability. The antidepressant fluoxetine belongs to this class.

In addition to the lysosomotropic effect of SSRI (mentioned above), Schloer, et al., also reported acid SMA inhibition (ASM), achieved with fluoxetine at higher concentration. ASM is a membrane bound lysosomal enzyme as indicated in Fig. 6. During cellular stress ASM relocates to the cell membrane, where it catalyses the cleavage of sphingomyelin into lipophilic ceramide and hydrophilic phosphorylcholine head. Ceramide is involved in cell signaling that could lead to apoptosis [90]. Once fluoxetine crosses the lysosomal membrane, it disrupts ASM membrane binding and releases it into the lysosomal lumen. Detachment renders the enzyme inactive and further subjects it to proteolytic enzymes Fig. 6 [89]. In vitro studies showed that FIASMA can prevent the infection with influenza and Ebola virus. In a study by Carpinteiro et al., COVID-19 virus infected the cells by activation of SMA, therefore inactivation of SMA could limit viral infection [91].

Fluoxetine also prevents efflux of cholesterol from the endosomes and lysosomes. As a result, less cholesterol is available for the plasma membrane and other cell functions. Cholesterol is particularly important for enveloped viruses as they form their envelopes from the host membrane. This mechanism is exhibited in influenza virus, through viral envelopes with decreased cholesterol content (crucial for viral survival) and less viral release. Indeed, 10 μ M fluoxetine when used in a cell culture model of COVID-19, significantly reduced viral load. It was also noted that the inhibitory effect was dose-related [89]. In vitro and observational studies indicated that fluoxetine prevents COVID-19 infection at usual psychiatric doses [92]. The risk of mortality and intubation was reduced dramatically in COVID-19 patients receiving regular antidepressant doses of fluoxetine (20 mg), as documented by a retrospective clinical study [93].

To summarize, SSRI can inhibit COVID-19 through several mechanisms as shown in Table 6 S1R modulation, endolysosomal pH reduction and FIASMA. They have a good safety profile, are readily available, can be taken orally and are cost effective. This certainly makes them an

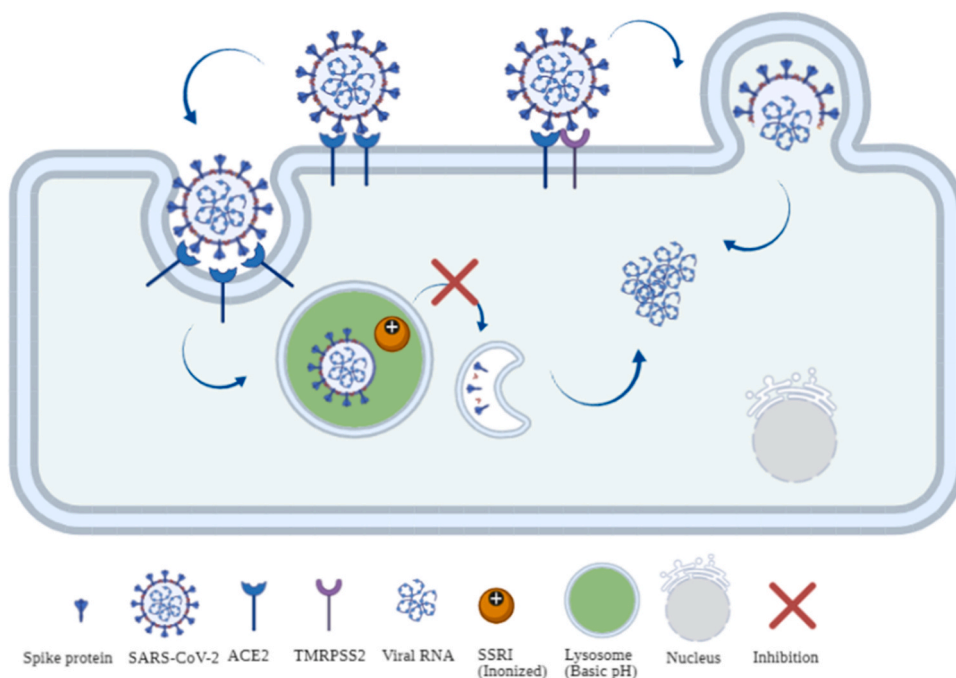


Fig. 4. Viral inhibition by Lysosomotropic agent. Lysosomotropism agents increase the endosomal/lysosomal pH (represented in green) which prevents viral vacuole escape into the cytosol.

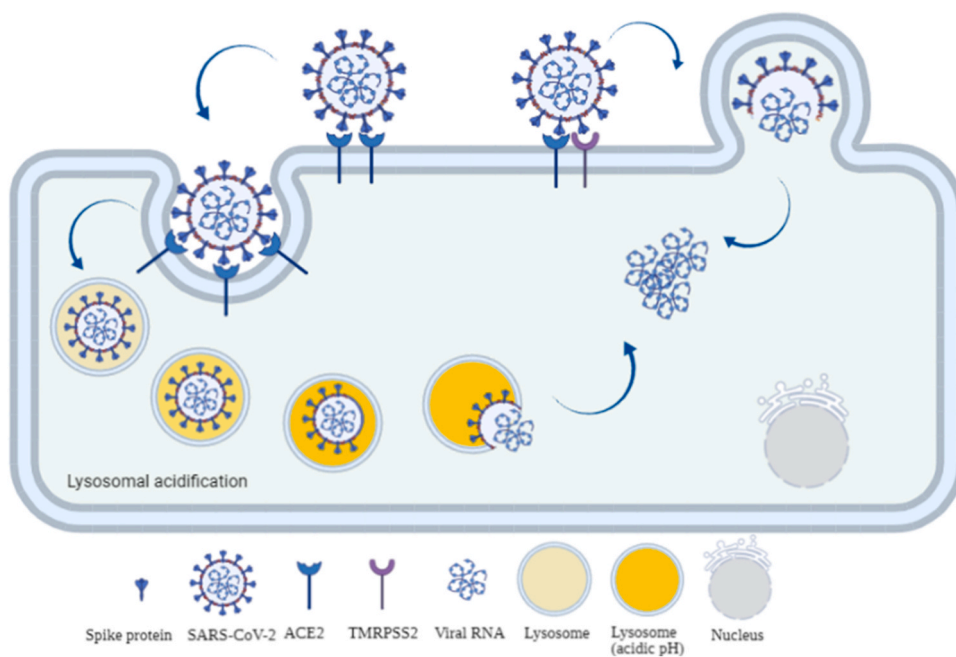


Fig. 5. Ph-dependant viral release into the cytosol. The pH decreases gradually as the endosome gets closer to the nucleus (indicated by a more intense yellow color). The virus uses the increasing acidic environment as a signal to exit the endosome.

attractive class for repurposing during this pandemic, when there are yet no definitive treatments available. However, their exact place of therapy is not yet clear, and further clinical trials need to be conducted.

2.3.4. Melatonin

There are several studies reporting the possible beneficial effect of melatonin, especially in elderly [94]. Melatonin biosynthesis has long been restricted to the pineal gland mainly at night. Nevertheless, increasing data indicate its release from the mitochondria. This means that most of the cells, including macrophages, synthesize melatonin.

Melatonin possesses anti-inflammatory, antioxidant, immunomodulatory effect and preserves mitochondrial function during conditions of oxidative stress (see Table 7) [95]. Impressively, Veltri, et al., reported that the liver, heart and brain have the highest mitochondrial density. This means they would be most protected by melatonin during sepsis, which is a major cause of morbidity in COVID-19 patients [96,97].

Suppression of the hyper-inflammatory state would ultimately also improve lung function. Especially when considering patients in the ICU that suffer additional pulmonary stress and inflammation due to mechanical ventilation [98]. However, melatonin has no documented

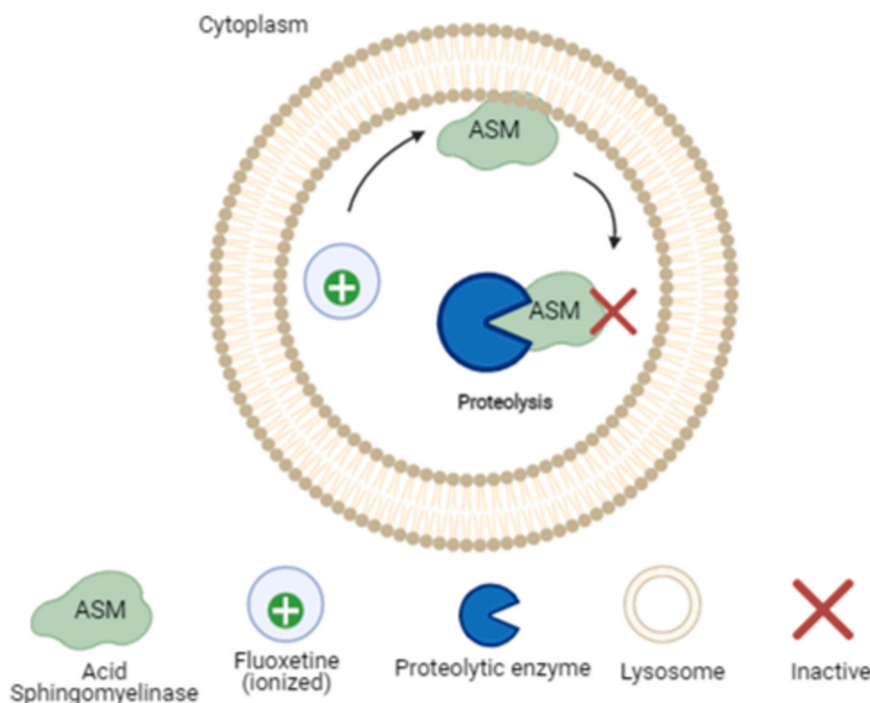


Fig. 6. Functional inhibitors of Acid sphingomyelinase (FIASMA) by fluoxetine. ASM is a membrane bound enzyme. Fluoxetine displaces ASM which turns it into inactive. Displacement from the membrane also subjects it to proteolysis by proteolytic enzymes.

Table 6
SSRI Summary and comparison.

SSRI	Classification	Mechanisms related to COVID-19	Advantages	Limitations
Fluvoxamine	Sigma-1 receptor agonist	Anti-inflammatory effect by reducing important proinflammatory cytokines such as (TNF- α and IL-6). Thus, ameliorates sepsis and its complications	No QT prolongation vs other SSRI	Further investigation is needed.
Sertraline & Fluoxetine	Lysosomotropic agent	Neutralization of endolysosomal pH, interfering with viral replication by: 1. Hindering viral release into the cytosol 2. Inactive fusion peptides	Less toxic with a shorter half-life compared to chloroquine and hydroxychloroquine.	Only inhibit the endocytic pathway, thus viral replication is not completely stopped. Not selective
Fluoxetine	Functional inhibitors of Acid sphingomyelinase	1. Degradation of acid sphingomyelinase, an important signaling enzyme. 2. Accumulation of cholesterol	Generally, well tolerated. Reduced the risk of mortality and intubation.	Drug interaction (<i>inhibit CYP2C19 and CYP2D6</i>)

direct antiviral activity and is therefore suggested as adjuvant therapy [94,99].

It has been noticed that viruses can inhibit melatonin release both from the pineal gland and the mitochondria. Exogenous melatonin administration in several infections exhibited a protective effect and limited the intensity of the infection [100]. It is suspected that COVID-19 similarly inhibits melatonin synthesis, thus reducing melatonin plasma levels.

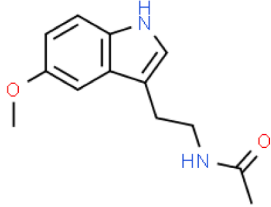









Administration of melatonin in COVID-19 patients would therefore reduce the cytokine storm and the generation of free radicals. Consequently, limiting not only alveolar damage, but also protect other vital organs. Several preclinical studies have demonstrated the positive effect of melatonin in reversing organ damage and increasing survival in septic shock [54,101]. Melatonin in several models successfully managed sepsis and restored vital organ function [102].

The effect of melatonin is even more advantageous in the geriatric population. Upon aging, the body's functions decline, and less melatonin is released, resulting in more severe cases. Both age and chronic conditions worsen prognosis and are associated with decreased melatonin levels [100,103]. This was evidenced by better response in aged rats, as reported by Escames, et al., [102]. In addition, supplemental melatonin administered to rodents delayed both aging and its associated chronic conditions [104]. Various clinical trials also confirm

effectiveness. In one study, a dose of 60 mg/day parenteral melatonin, was administered to ICU COVID-19 patients. Melatonin reduced the severity of sepsis, improved discharge by 40% and abolished mortality rates [105]. These promising findings encouraged many researchers to conduct further clinical trials in hospitalized ICU COVID-19 infected patients [106]. As of 2021, there are two ongoing clinical trials, both approved by Spanish agency of medicine. Escames et al., (EudraCT, 2020-001808-42) aims to find an effective dose of melatonin against COVID-19 [105]. The second trial (EudraCT, 2020-001530-35) tests 2 mg of Circadin® (melatonin) as a prophylactic agent in high-risk individuals [107].

Another important role of melatonin, especially in elderly, is its effect on the circadian rhythm [95,97]. Defective sleep patterns largely weaken the immune system and increase susceptibility to infection. This is further amplified by stress and lockdown [108]. This indicates that melatonin will not only assist in preventing infection, but also aim to regulate defective sleep patterns. Melatonin is safe even at high doses, readily available and can be taken orally. An oral dose of 50–100 mg half an hour before bedtime, has been suggested for the geriatric population [109]. However, firm guidelines on the use of melatonin in COVID-19 patients are lacking. Therefore, further investigations are needed to drive firm conclusions.

Table 7
Melatonin mechanism against SARS-CoV-19.

 <p>Melatonin (M1 and M2 receptors)</p>	Anti-inflammatory	 TLR, NF-κB, c-Fos and MMP-3	 Proinflammatory cytokines and NLRP3 inflammasomes.
	Anti-oxidative	 ROS, RNS and NF-κB	 Mitochondrial dysfunction
	Regulation of the circadian rhythm	 M2 (mainly) Sirtuins (S1, S3, S4, S5).	
	Regulates mitochondrial metabolism	 Sirtuins (S1, S3, S4, S5).	
	Immunomodulatory	 Neutrophils, lymphocytes, CD8+-T cells	
	Pulmonary protection	 Immune cell migration into the pulmonary tissue: neutrophils and macrophages. Lipid peroxidation of pulmonary surfactant.	
	Supress Viral replication	 BAML1	

3. Conclusion

Despite the large number of clinical trials and available vaccines, cure against COVID-19 is still lacking. Patients with mild COVID-19 should be limited to supportive care and symptomatic treatment according to presentation. Selected monoclonal antibody combinations (casirivimab with imdevimab or bamlanivimab with etesevimab) are FDA approved for EUA in mild to moderate no-hospitalized COVID-19 patient at risk for clinical deterioration. Although inhaled neutralizing Nbs are almost certainly superior to monoclonal antibodies, they still lack clinical evidence for their efficacy. Ivermectin use as per WHO recommendations should be limited to clinical trials. For hospitalized COVID-19 patients that meet the WHO severity criteria, systemic corticosteroids or a combination of corticosteroids with an IL-6 blocker (tocilizumab or Sarilumab) is strongly recommended. While WHO only suggests the use of remdesivir and baricitinib in clinical trial, the NIH recommends the use of either remdesivir or baricitinib in combination with dexamethasone in hospitalized patients that require oxygen therapy. Other agents like camostat mesylate and plitidepsin seem promising, but still await the results of phase III clinical trials. Preliminary studies on repurposed melatonin and SSRI suggest their positive effect against COVID-19 in both outpatient and inpatient settings. Therefore,

we suggest further investigations and larger clinical trials to determine their efficacy and place of therapy.

Although the fate of this pandemic is unpredictable, as the virus continues to mutate, history of previous coronavirus strains forecast that COVID-19 might end up similarly to influenza. Thus, even with the end of this pandemic, effective treatment will probably always be needed.

CRedit authorship contribution statement

Soraya Mouffak: Conceptualization, collection of data and original draft preparation **Qamar Shubbar:** Conceptualization, collection of data and original draft preparation **Ekrum Saleh:** manuscript reviewing and editing **Raafat El-Awady:** Conceptualization, Supervision, manuscript reviewing and editing.

Conflict of interest statement

All authors declare that they have no conflict of interest.

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