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Review article

Pharmacotherapy of COVID-19: confine to existential drugs or search for new ones?

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Abstract

Background

The recent COVID-19 outbreak (pandemic) has inflicted great human lives and economic losses. Aside from being abated, new surges in cases are being recorded. The sudden emergence and fulmination of the disease and its rapid spread caught the health authorities worldwide, including the developed ones, off guard, with no novel drugs available. Therefore there was no choice other than using the old drugs.

Objectives

This study aims to reveal the possible mechanism of action, adverse drug reactions and beneficial combination of drugs used in COVID-19 treatment

Methods

We undertook a comprehensive living structural review of COVID-19, searching databases, and other sources to identify literature on drugs used in the treatment of COVID-19. We analyzed the sources, publication date, type, and the topic of the retrieved articles/studies in the available search machines.

Results

Although a large number of literature on COVID-19 deals with pathology, clinic, and epidemiological issues, few studies that tackle pharmacology and toxicology of the drugs used could be found in the literature. At least twenty six (26) drugs, alone or in various combinations, are found in the literature to be used in various countries in the world. These drugs had been used previously for other purposes but they also possess activities that could target various steps involved in the virus invasion-replication-multiplication and leaving the cell. Pharmacokinetic fundamentals had also been applied in some combination (decrease Lopnavir's metabolism by ritonavir), but some drugs that were initially extensively used at high doses without benefiting from some of their properties are recently being abandoned *(hydroxychloroquine, ionophore for Zn2+).*

Conclusion

The literature concerning drugs used in the treatment of COVID-19 lag far behind the great number of literature that discusses disease's pathogenicity, clinical picture, and epidemiology. The World indeed had been caught unprepared for COVID-19, hence obliged to use old drugs.

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Keywords

COVID-19; Antivirals; Cytokine inhibitor; RdRp inhibitor; ACE2 modulator; Protease inhibitor; Folding inhibitor; Fusion/budding inhibitor.

Introduction

The novel coronavirus (CoV) disease (COVID-19) is caused by severe acute respiratory syndrome SARS-CoV-2 (referred to as nCoV hereafter). The infection source of COVID-19 could be bats, pangolins, murine, etc. It is a major health concern implicated in an alarming pandemic global outbreak. It represents a great health threat with worldwide >11.0 million confirmed cases (mostly in Americas and Europe) including >half a million deaths, with >6.0 million recoveries, as of July 04, 2020; [1]. Patients infected with nCoV have symptoms of varying degrees, ranging from fever or a mild cough to pneumonia and extensive involvement of multiple organ functions (brain, cardiovascular, renal) with a mortality rate varies from 2-4% to as high as 12%.

This review aims to reveal the drugs effective in reducing COVID-19 severity, touches on adverse drug reactions (ADR) where possible, disease duration and mortality, with an emphasis on the molecular mechanisms of the effects displayed by the drugs. Although a great number of researches and publications dealt with epidemiology and molecular biology of COVID-19 and nCoV, no comprehensive mechanistic pharmacological data relevant to the disease and the drugs are available. Accordingly, we tried in this review to highlight the biological molecular structures of nCoV that are responsible for the virus's pathological effect and could be potential targets for drugs.

Methods

Based on publications (especially recently published literature, official documents, and selected up-to-date preprints) we reviewed the treatment of COVID-19 infection using the main search stream as the drugs and/or Authors' names were referred to as additional keyword in the search. The search was conducted using the search engines such as Google, PubMed-PMC-NCBI, Elsevier Coronavirus Research Hub, Wikipedia, Microsoft Academic Search, RefSeek-Academic Search Engine.

Pharmacotherapy of COVID-19

It is doubtless that nCoV caught the world off any pre-developed specific antiviral drug. The momentum of research on developing antiviral agents or vaccines against the nCoV carried on while the epidemic is being on the rise. Currently, no specific therapies for COVID-19 are available. The measures that have been implemented remain limited to preventive and supportive therapies. However, knowledge of nCoV structure made it possible to try some old drugs attacking some points in the virus's intracellular passage due to the extensive outbreak and mortality. Based on our knowledge of the structure of the virus and its life cycle the initial objective was how to prevent virus attachment and entry into cells. The spike (S) glycoprotein and ACE2 are the firs points to be targeted to prevent the virus from entering into cells. The first strategy would be to employ either a small receptor-binding domain (RBD) or a neutralizing antibody targeting the ACE2 receptor, thus blocking the binding of S protein and preventing virus entry into cells. The main limitation of using RBDs or antibodies is that the treatment must be given within a specific time window, before the initiation of viral replication [2]. In addition, the turnover of ACE2 receptors would influence how often the therapeutic RBD or antibody would have to be administered. Moreover, the side effects due to ACE2 blockade in pulmonary and non-pulmonary tissue must be considered and minimized before the implementation of therapy. A second strategy is to create an ACE2-like molecule that would bind to the S protein of the nCoV itself. The creation of soluble ACE2 protein "sink" could divert the virus from targeting host ACE2 and so blocks the nCoV from infecting cells. The additional benefit of using this strategy lies in the possible prevention of S protein-mediated ACE2 shedding that has been shown to be induced by nCoV and involved in the pulmonary edema characteristic of COVID-19 [3]. Another treatment choice is the use of mesenchymal stromal/stem cells (MSCs) in severe cases with COVID-19 infection. However variable results had been obtained. This could be due to the need for enhancing MSC effectiveness by IFNγ which may be absent in severely affected patients.

A large number of drugs claimed to either be effective against nCoV or COVID-19 had swirled in the literature and clinics. Some of these are either unexpected or induce ADR: chlorpromazine's ability to inhibit clathrin-mediated endocytosis, and to induce extensive extrapyramidal syndrome. One of the applications most frequently referred to is a combination of antivirals among themselves or with other drugs. Some preliminary studies have investigated potential combinations that include the protease inhibitor lopinavir/ritonavir, which is applied worldwide. Other reported antiviral treatments form

human pathogenic nCoV include nucleoside analogues, neuraminidase inhibitors, (remdesivir, umifenovir).

Natural active ingredients isolated from medicinal plants are also found to display antiviral properties. The site of effect from virus fusion till budding had been elaborated for these active ingredients such as flavonoids, anthraquinone terpenoids, polyphenols, imminosugars and tannates. These compounds have not been standardized but could be used as diet, complementary to drug therapy, and in the convalescence. They also could serve as a source of inspiration for the development of novel drugs. However, this important topic is not the subject of this review. It merits special concern and should be elaborated in detail.

Currently, twenty-six (26) existing drugs and already prescribed for various diseases had been used with varying success degrees (Table 1). Thousands of lives in different countries had been saved, owing to these drugs or to patients' condition that has not been adequately clarified yet. Here, the drugs used in COVID-19 treatment are classified according to their effect mechanisms and divided into two groups: I-drugs targeting nCoV and prevent one or more steps in its cellular cycle, and II-drugs treat the pathological changes induced by the virus directly or by the destructive mediators they release.

Table 1. Drugs used or useful in treatment of COVID-19 targeting nCoV.

1	Favipiravir	• Inhibits RdRp. • Induces lethal viral mutagenesis.
2	Remdesivir	• Inhibits RdRp.
3	Velpatasvir and Ledipasvir	• RdRp inhibition.
4	Oseltamivir, Peramivir, Zanamivir, Laninamivir	• Neuraminidase inhibitor.
5	Lopinavir/rotinavir	• Protease (3CLpro) inhibitor. • Blocks viral replication.
6	Nelfinavir	• Inhibits Protease • Inhibits fusion • Activates unfolded protein response •
7	Darunavir/Cobicistat	• Protease/CYP3A inhibition.
8	Chloroquine	• Zinc ionophore. • Immunomodulatory effects, suppressing production/release of TNF-α and IL-6. • interferes with the glycosylation of nCoV cellular receptors. • Inhibits autophagy. • Lysosomal alkalinization.
9	Zinc	• Inhibits RdRp and Protease.
10	Nafamostat Camostat mesylate	• Spike glycoprotein inhibition • TMPRSS2 antagonism
11	Imminosugars	• Inhibits α-glucosidase
12	β-D-N4-hydroxycytidine	• Inhibits viral RNA synthesis. • Induces lethal viral mutagenesis.
13	Umifenovir	• Inhibits CoV-membrane fusion
14	Triazavirin	• Guanosine nucleotide analog that inhibits RNA synthesis and viral replication.
15	Disulfiram	• Protease and pore inhibition.

*Almost all countries applied a treatment protocol varied according to disease's severity and progress of infection, and contained combinations of two or more of Hydroxychloroquine, Azithromycin, Lopinavir/ritonavir, Remdesivir, and Favipiravir. RdRp: RNA-dependent RNA polymerase. TMPRSS2: transmembrane protease, serine 2.

8.1. Drugs targeting nCoV

8.1.1. *Favipiravir*: Favipiravir, pyrazine carboxamide derivative, is guanidine nucleoside analog broad-spectrum antiviral. It has been approved for the treatment of human influenza, available in both oral and intravenous formulations. Favipiravir-ribosyl triphosphate (RTP) is a selective RdRp inhibitor. Moreover, Favipiravir inhibits the envelope protein and ORF7a protein binding to porphyrin, and so recovers porphyrin from CoV. It is also suggested that Favipiravir induces lethal RNA transversion mutations that produce a nonviable viral phenotype [4]. Favipiravir also acts as a potent GTP-competitive inhibitor of the viral polymerase. This is in contrast to ribavirin, structurally similar to Favipiravir that inhibits inosine monophosphate dehydrogenase (IMPD), which results in fast and profound GTP depletion and an imbalance in the nucleotide pools. In contrast, in infected cells, viral RNA synthesis is completely inhibited by Favipiravir or ribavirin, whereas exposure to lower drug concentrations induces the formation of noninfectious particles and accumulation of random point mutations in the viral genome. This mutagenic effect is 2-fold higher for Favipiravir than for ribavirin. Hence, Favipiravir and ribavirin both act as purine pseudo basis but profoundly differ with regard to the mechanism behind their antiviral and mutagenic effects on the influenza virus [5].

Favipiravir has high bioavailability (97.6%). Food decreases Cmax (FDA/CDER, 2002). While Favipiravir is not substrate for various transporters, it together with its metabolite M1 inhibit activities of various transporters such as hOAT1, hOAT3, and hURAT1 [6]. Favipiravir inhibits CYP2C8 activity in a concentration-dependent manner. It's major metabolite M1decreases CYP2E1 activity but increases the expression of other CYP isoforms (CYP1A2, 2C9, 2C19, 3A4). Favipiravir, but not M1, inhibits the de-esterification of Oseltamivir. It has a low volume of distribution, 0.359 L/Kg, which is expected to kinetically cause high blood levels. The plasma Favipiravir concentration profile in male subjects is comparable to that in female subjects. Favipiravir 400 mg was also orally administered to Japanese healthy elderly male and female subjects (aged 65-77 years), the plasma Favipiravir concentration profile in male subjects was comparable to that in female subjects, and no clear differences between male and female subjects were found in the pharmacokinetic parameters: Cmax, 18.0 μg/mL and 20.1 μg/mL; AUC 59.1 μg·hr/mL and 55.0 μg·hr/mL; t1/2, 2.0 h and 1.7 h).

Favipiravir is a prodrug being metabolized to its active form Favipiravir ribofuranosyl-5'-triphosphate, Favipiravir-RTP [7], with a pulmonary half-life 4.2 h. Its main metabolism pathway is hydroxylation by cytosolic aldehyde oxidase and xanthine oxidase to an inactive metabolite (Figure 1). The Cmin of ≥0.3 μmol/kg had been detected for up to 48 hours after the first dose (400 mg) on Day 1. Metabolism of Favipiravir may be inhibited by calcium channel blockers, cimetidine, ondansteron, tamoxifen, and tricyclic antidepressants.

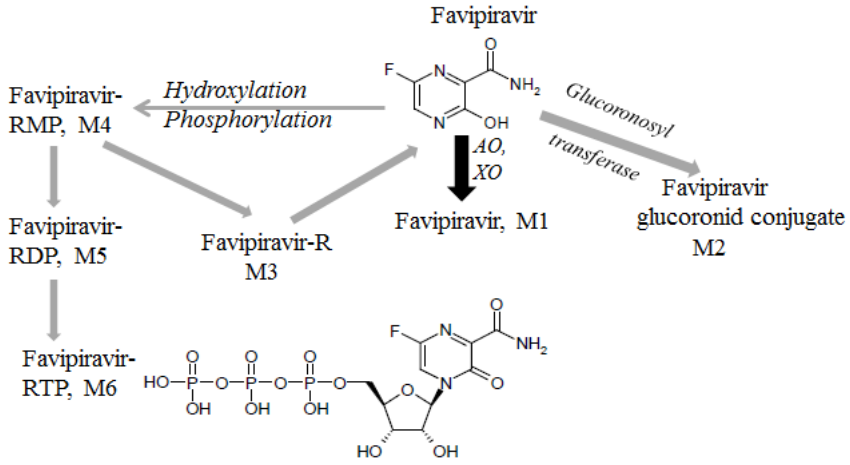

Figure 1. Favipiravir's main (solid arrow) and predicted (faint arrows) metabolic pathways. AO: Aldehyde oxidase; M1-6: Favipiravir and its metabolites; RMP, RDP, and RTP: Ribosyl mono-, di- and triphosphate respectively. XO: Xanthine oxidase. (adapted from references 6&7).

8.1.2. Remdesivir: There is now evidence that remdesivir may be effective in controlling nCoV infection. Remdesivir is a monophosphoramidate prodrug converted to the active nucleoside triphosphate, remdesivir-triphosphate-TP. Remdesivir-TP structurally being analogous of adenosine triphosphate (ATP), competes with adenosine-triphosphate for incorporation into nascent viral RNA chains. Once incorporated into the viral RNA the drug appears to evade proofreading by viral exoribonuclease, an enzyme thought to excise nucleotide analog inhibitors and inhibit RdRps, and either halt the growth of the RNA strand, after being initiated following the addition of only a few nucleotides or delay chain termination during replication of the viral RNA. Recently it has been reported that Remdesivir may be effective in controlling nCoV infection. It is reported to decrease recovery time from 15 days (placebo) to 11 days in COVID-19 patients [8]. Although coronaviruses have a proofreading process that is able to detect and remove other nucleoside analogs and render them resistant to many of the antivirals, Remdesivir seems to outpace this viral proofreading activity, thus maintaining its antiviral activity. Remdesivir-TP is a weak inhibitor of mammalian DNA and RNA polymerases with low potential for mitochondrial toxicity.

Administration of Remdesivir over shorter time interval provides similar parent exposure as the same dose administered over a longer duration (same dose 75 mg i.v. over 30 min. vs. 120 min), and clinically 75 mg i.v. over 30 min is a more effective dosing method for maximizing the intracellular levels of the active metabolite. A prolonged intracellular half-life of more than 35 hours was observed for the metabolite, supporting the once-daily dosing of remdesivir. The respective pharmacokinetic parameters obtained with 75 mg 30 min^{-1} infusions for Remdesivir and its active triphosphate metabolite (AUCinf (h.ng/ml)=1254.7 and 394.3; t1/2 (h)=1.0 and 48.8, with an accumulation ratio of 3.5 for the metabolite. These values are very close to those obtained for 75 mg.120 min^{-1} infusions (data according to WHO R&D Blueprint [9].

8.1.3. Velpatasvir and ledipasvir: inhibit NS5A protein of the hepatitis C virus (HCV). Both drugs are approved in combination with sofosbuvir, which is a prodrug nucleotide analog inhibitor of RdRp and NS5B. Interestingly, sofosbuvir has recently been proposed as an antiviral for the nCoV based on the similarity between the replication mechanisms of the HCV and the coronaviruses. Velpatasvir/sofosbuvir and ledipasvir/sofosbuvir may be attractive candidates to repurpose because they may inhibit two coronaviral enzymes. A drug that can target two viral proteins substantially reduces the ability of the virus to develop resistance. These direct-acting antiviral drugs are also associated with very minimal side effects and are conveniently orally administered [10]**.**

8.1.4. Oseltamivir: has been used for the treatment and prophylaxis of infection with influenza A and B viruses (including pandemic H1N1). Oseltamivir is effective when administered within 48 hours of the onset of influenza symptoms because its effectiveness decreases significantly after that point in time [11]. Oseltamivir inhibits viral neuraminidase. Thus Oseltamivir prevents budding from the host cell, viral replication, release of virus from the plasma membrane of infected cells, and infectivity. Because of the conservation of the active site of the neuraminidase, Oseltamivir has activity against the neuraminidase subtypes of several viruses using this enzyme.
Oseltamivir is prescribed as a phosphate (OP) derivative. It is a prodrug when ingested orally about 75% of Oseltamivir phosphate rapidly metabolizes by hepatic ester hydrolysis to the active metabolite, Oseltamivir carboxylate (OC), and <5% is recovered in urine as OP. Neither OP nor OC is a substrate for cytochrome P450 isoform. The absolute bioavailability of OP is ∼80%, not influenced by concomitant food intake, antacids, and cimetidine. OP displays minimal inter- and intra-subject variability. OP and OC are eliminated primarily by renal excretion, but small amounts (<20% of the oral dose) of both compounds are also eliminated in feces. Renal clearance of both compounds exceeds the glomerular filtration rate, indicating that renal tubular secretion contributes to elimination; for OC, this has been shown to proceed via the anionic transport process. Following oral dosing, the plasma concentration (Cp) of Oseltamivir declines rapidly (apparent elimination half-life of 1–3 h), while OC concentrations persist for a longer time (apparent elimination half-life of 6–10 h), permitting twice-daily dosing. OC is detectable in plasma within 30 min of dosing, and its Cmax, attained after 3–4 h, exceeds OP concentrations by >20-fold. The volume of distribution of OC after intravenous administration in man is 23–26 L. This volume approaches the extracellular volume of body water in

humans, indicating that the metabolite may penetrate infection sites, including the respiratory system, at concentrations similar to those in plasma [12].

8.1.5. Protease inhibitors*:*

8.1.5.1. Inhibitors of host TMPRSS2 serine protease

TMPRSS2 plays an important role in the entrance of CoV into the cell. It is expected that the inhibitor(s) of TMPRSS2 could block virus entry and might constitute a treatment option.

Nafamostat is a synthetic TMPRSS2 inhibitor. It is a short-acting anticoagulant with antiviral and anti-cancer properties. It has been used to prevent post-reperfusion syndrome in conditions such as liver transplantation and as an anticoagulant therapy for patients with renal replacement therapy. It has been reported that Nafamostat could inhibit the spike glycoprotein and membrane fusion of nCoV at a concentration less than one-tenth that of Camostat mesylate. It also inhibits the production of TNF-α and chemotaxis [13]. The other drug Camostat mesylate was initially developed and currently approved for the treatment of chronic pancreatitis in Japan. Camostat mesylate targets the TMPRSS2 protease, theoretically preventing viral entry. It reduces the amount of nCoV viral replication [14]. Ciclesonide is another drug that apart from its traditional glucocorticoid property, suppresses replication of the nCoV possibly via inhibition of viral nps15. It is converted by intracellular esterase to an active metabolite, desisobutyryl-ciclesonide, with high glucocorticoid recept
or affinity and reversible esterification to fatty acid ester derivative. Niclosamide: Inhibits viral replication and autophagy.

Main protease inhibitors: control the activities of the nCoV replication complex. One of the best-characterized drug targets in nCoV is the main protease M^{pro}, chymotrypsin-like cysteine protease also called 3CLpro. Along with the other protease papain-like cysteine protease (PLp), M^{pro} is essential for processing the polyproteins that are translated from the viral RNA. The protein sequences of M^{pro} are 96% identical between SARS-CoV and nCoV, and the spatial structure of lopinavir/ritonavir binding pocket in M^{pro} is also conserved between the two viruses [15]. M^{pro} is the site for the broad-spectrum potent inhibitors of COVID-19 M^{pro}; Nelfinavir, Lopinavir, and the peptidomimetic a-ketoamides [16]. However, CoV proteases, including M^{pro} lack the C2-Symmetric pocket that is the target of HIV protease inhibitors.

8.1.5.2. Inhibitors of viral protease

Lopinavir: is widely used in combination with ritonavir for thetreatment of COVID-19. It is the main protease M^{pro} inhibitor. Recent evidence suggests that lopinavir has antiviral activity against SARS-CoV-2. Lopinavir is lipid-soluble and penetrates the cerebrospinal fluid (CSF). It produces significant reductions in the CSF viral load [17]. The mean peak Cm_{ax} at dose 400 mg/100 mg twice daily is 9.8 ± 3.7 μg/mL, occurring approximately 4 hours after administration of a dose. A once-daily dosing regimen of 800 mg/200 mg may be used in drug-naive patients. Food intake does not affect the absorption of the tablet formulation. However, liquid formulation should be taken with food to improve absorption. The absolute bioavailability of lopinavir/ritonavir in humans has not been established. At a steady state, lopinavir is 98%–99% bound to plasma proteins. The mean trough Cp is 5.2 μg/mL and the mean elimination half-life ranges from 2 to 3 hours after a single dose and from 4 to 6 hours after multiple-dose administration. Lopinavir/ritonavir is primarily eliminated by the fecal route with urinary excretion accounting for <2% of the eliminated drug Lopinavir/ritonavir accumulates intracellularly and the intracellular/Cp ratio is 1.18 [18]. Lopinavir undergoes rapid first-pass metabolism in the liver by CYP3A4 and CYP3A5. Ritonavir inhibits the CYP3A4 isoenzyme in the human liver microsomes and results in increased concentrations of lopinavir when the two drugs are coadministered.

It is expected that Lopinavir/ritonavir could display significant interactions with drugs that are either metabolized by CYP3A4 and CYP3A5 or induce/inhibit these enzymes. The interaction with Lopinavir/ritonavir takes different forms: inhibition of the antiviral effect of lopinavir (Rifampin, St. John's Wort); cardiovascular side effects (Cisapride, ergots, statins, pimozide, Amiodarone, lidocaine, quinidine, PDE5I), increase (Amiodarone, lidocaine, quinidine, Clarithromycin, Rifabutine, Trazodone) or decrease (Phenytoin) the blood levels of these drugs; Disulfiram-like syndrome (Metronidazole); Adrenal suppression/osteoporosis (Fluticasone); increased CNS depression

(Benzodiazepines). On the other hand, several antivirals including protease inhibitor, nucleoside- and non-nucleoside-reverse transcriptase inhibitors increase and/or decrease lopinavir/ritonavir blood levels [19].

Lopinavir/ritonavir induces metabolic changes, including hyperlipidemia and glucose intolerance. It also induces a dose-dependent (especially at high dose 800/200 mg) diarrhea, immune reconstitution syndrome manifested as inflammatory response hypertriglyceridemia and hypercholesterolemia. [20]. In addition to Lopinavir there are several other protease inhibitors, but with other mechanisms of actions.

Nelfinavir: Anti-cancer drug with pleiotropic effects, of which some are also involved in prevention SARS-Cov-2 fusion and replication. Nelfinavir inhibits HIV protease, Its hydroxyl group interacts with the carboxyl group of the protease active site residues, Asp 25 and Asp 25′, by hydrogen bonds. It has been reported that Nelfinavir inhibits cell membrane-virus fusion caused by the SARS-CoV-2 spike glycoprotein. Nelfinavir also upregulates the UPR, an effort to degrade misfolded or aggregated proteins. Nelfinavir profoundly alters ER morphology and causes the appearance of ER-derived vesicles. Moreover, Nelfinavir might induce autophagy is through eukaryotic elongation factor 2 kinase (eEF2K), which is involved in the elongation phase of protein synthesis, and activators of eEF2K induce autophagy. Nelfinavir has been shown to treat nCoV, and is being tested to treat COVID-19 in combination with the anti-inflammatory Cepharanthine. Nelfinavir can produce a range of ADR. Common (>1%) side effects include insulin resistance, hyperglycemia, lipodystrophy, and diarrhea.

Darunavir: (in the form of Darunavir ethanolate) combined with Cobicistat (adsorbed onto silicon dioxide) is an antiretroviral drug used in the treatment and prevention of HIV. It is also used in the treatment of COVID-19. Darunavir is a competitive protease inhibitor by forming several hydrogen bonds with aspartate and glycine residues in the catalytic site of the protease [21]. CYP3A4 inducers increase metabolism of Darunavir. Cobicistat is a CYP3A inhibitor inhibits metabolism of Darunavir and consequently increases its activity. Cobicistat is an analog of ritonavir, in which valine moiety is exchanged for a morpholinoethyl group, and hydroxyl radicle is removed. These changes eliminate the antiviral activity but the inhibitory effect on the CYP3A isozyme remains preserved. Cobicistat is more soluble than ritonavir, making pharmaceutical formulation easier. Cobicistat and ritonavir are equally strong inhibitors of cytochrome P450 (CYP) 3A4, but Cobicistat is more selective. Cobicistat does not alter the pharmacokinetics of drugs metabolized by CYP1A2, CYP2B6, CYP2C8, CYP2C9, and CYP2C19 or drugs undergoing mainly glucuronidation [22].

8.1.6. Chloroquine (CQ): 4-aminoquinoline compound, has been used for the prophylaxis and treatment of malaria. Moreover, CQ and Hydroxychloroquine (HCQ) are included in the treatment protocol of other ailments such as Rheumatoid arthritis, Lupus erythematosus, and antiphospholipid syndrome. Recently both drugs found their way to COVID-19 treatment paradigm. The rationale for their use in COVID-19 treatment is their vast mechanisms of actions. The drugs are effective against the virus, produce immune modulation, and benefit in inhibiting exacerbation of pneumonia. CQ does not affect the level of ACE2 expression on cell surfaces but interferes with the glycosylation of SARS-CoV and ACE2 cellular receptors. ACE2 that is not in the glycosylated state may less efficiently interact with the SARS-CoV-2 spike glycoprotein, further inhibiting viral entry [23]. Accordingly, CQ/HCQ render the ACE2-SARS-CoV interaction less efficient and so CQ blocks virus-cell fusion and the virus entry into the cell.
CQ inhibits GSK-3β and potentiates lithium-induced GSK-3 β&α inhibition. This may rationalize a combination of three GSK-3 β inhibitors: *lithium, Hydroxychloroquine, and zinc* for synergistic activity. Moreover, it is reported that CQ has immunomodulatory effects that involve decreasing the production and release of tumor necrosis factor-α (TNF α) and interleukin (IL)-6. Additionally, CQ also prevents further deleterious mechanisms that may lead to acute respiratory syndrome, such as alteration of tight junctions, further release of pro-inflammatory cytokines, and increased microvascular permeability [24].
The acidity is a prerequisite for the viral envelope merge with endosomal and lysosomal membrane, or spike glycoprotein digestion and release of viral RNA. CQ is a cationic weak basic drug. It is

"lysosomotropic" enters endosomes and lysosomes and acts as a proton magnet, becomes protonated within lysosome, and becomes trapped (ion trapping) there. It takes and detains protons inside lysosome, prevents acidity, increases pH from 4.5 to 7.4, and thus impairs endosome's and lysosome's acidic milieu, and consequently disrupts lysosome-autophagosome fusion, lysosomal degradative function [25]. Cells treated with CQ or HCQ had significantly more virion localized to the early endosomes and fewer localized to endolysosomes. CQ also draws water into the lysosomes through an osmotic effect which leads to vacuolization too.
CQ is N-dealkylated primarily by CYP2C8 and CYP3A4 (to less extent by CYP1A1) to active metabolite firstly to N-desethylchloroquine (39%), and the latter further N-dealkylated to N-bidesethylchloroquine. The latter finally transforms to 7-chloro-4-aminoquinolineCQ is 60% bound to plasma proteins, with binding to both albumin and α1–acid glycoprotein. However, The drug is extensively distributed, with a volume of distribution of 200 to 800 L/kg when calculated from plasma concentrations and 200 L/kg when estimated from whole blood data (concentrations being 5 to 10 times higher). The high distribution volume could be attributed to the strong binding of CQ to pigmented tissues (including retina), mononuclear cells, muscles. Consequently, distribution, rather than elimination processes, determines the blood concentration profile and long $t_{1/2}$. Of CQ. Moreover, CQ has a total plasma clearance of 0.35-1L/h/kg, with 21-47% excreted unchanged. Intravenous CQ reaches a C_{max} of 650-1300µg/L, whereas oral CQ reaches a C_{max} of 65-128µg/L with a T_{max} of 0.5 h.

Potentially important kinetic interactions with CQ have been documented for d-penicillamine and cimetidine but have not been found for aspirin, ranitidine, or imipramine. CQ may cause potentially lethal hypotension and arrhythmia, which later lead to discontinuation of CQ/HCQ in some hospitals. Both CQ and HCQ block the KCNH2- encoded HERG/K v 11.1 potassium channel and potentially can prolong the QTc. At-risk individuals, these so-called HERG blockers can precipitate TdP. Moreover, the risk of long QT is expected to increase with the combination of CQ or HCQ with Lopinavir/ritonavir and Azithromycin. Quinines, generally, should be used with utmost caution in patients with G6PD deficiency and diabetes Mellitus. Parenteral Chloroquine should be given either by continuous intravenous infusion or by frequent intramuscular or subcutaneous injections of relatively small doses.
CQ is a zinc ionophore, which ensures Zinc ions entry into cells and targets zinc to the lysosomes thereby inducing apoptosis [26]. It is possible to suggest that this property could render the addition of Zn2+ ions to CQ/HCQ more efficient in the treatment of COVID-19.

HCQ is an analog of CQ in which one of the N-ethyl substituents of CQ is hydroxylated. The activity of HCQ is equivalent or even more potent than CQ. HCQ is preferred over CQ when high doses are required because of the lower level of ocular toxicity of HCQ than of CQ. HCQ, as well as CQ, is a chiral drug administered as racemates (as a 1:1 mixture of two paired enantiomers, sinister (S)-(+) and rectus (R)-(–)). R(-)-CQ binds more strongly to α1-acid glycoprotein, whereas R(+)-CQ binds more to albumin. It should be noted that whereas (R)-(−) and (S)-(+) isomers of CQ have similar efficacy and toxicity profile, HCQ displays a stereoselective deposition and/or metabolism. (R)-(−)-HCQ presents at higher concentrations in the blood than (S)-(+)-HCQ. It has been reported that (S)-(+)-HCQ is the eutomer, having desired pharmacological activity with less toxicity. (R)-(–)-HCQ enantiomer accumulates in the ocular tissue and causes more retinopathy. There is no interconversion between (S)-(+)-HCQ and (R)-(–)-HCQ enantiomers. The clinical implications of using the preparation of (S)-(+)-HCQ, substantially free of the (R)-(–)-HCQ, as the active ingredient is expected to provide lower ADR and the possibility of higher dose levels and/or longer periods of administration. The use of HCQ in the treatment of COVID-19 is still debated. Using the proper isomer of the drug at minimum effective dose and duration, considering the patient's cardiac state and addition of may had been increased the efficacy and minimized the toxic effects encountered during therapy. HCQ produces the same molecular effects as CQ and, as CQ, represses CD154 expressing T-cells and interferes with nCoV binding to the host cells [27]. About 50% of the HCQ in plasma is bound to plasma proteins. HCQ is metabolized in the liver into three active metabolites: desethylCQ (18%), desethylHCQ (16%), and bisdesethyl HCQ (BDCQ). HQ share CQ most of the pharmacokinetic parameters with some differences. Some pharmacokinetic parameters for HCQ compared to CQ [28]: renal clearance 21%

vs.51%; volume of distribution blood/plasma 47.257 L/ 5.500 L vs. 65000 L/15.000 L; fraction excreted unmetabolized 62% vs. 58%; t1/2 45±15 days vs. 41±11 days.
The drug interaction with CQ and HCQ is another subject that should be considered. Significant drug interactions with CQ and HCQ had been reported for digoxin, antiepileptics, antacids, cyclosporine, amiodarone, azithromycin, moxifloxacin, insulin and antidiabetic agents, tamoxifen, and praziquantel. Moreover, the combination of azithromycin with HCQ frequently prolongs the QT interval in a clinically significant manner. This effect increases either repeating treatment over time. Moreover, the Food and Drug Administration withdrew its emergency use authorization for the oral formulation of HCQ and CQ due to efficacy problems and harm/benefit imbalance.

8.1.7. Zinc (Zn^{2+}): Zn^{2+} is involved in many different cellular processes. It is crucial for the proper protein folding and activity of various cellular enzymes and transcription factors. Additionally, Zn^{2+} is also an important cofactor for numerous viral proteins as well. Nevertheless, the intracellular concentration of free Zn^{2+} is maintained at a relatively low level by metallothionins, likely due to the fact that Zn^{2+} can serve as an intracellular second messenger and may trigger apoptosis or reduction of protein synthesis at elevated concentrations. In vitro studies with purified had shown that Zn^{2+} could inhibit RdRps and 3C proteases [29]. Zinc ions were demonstrated to inhibit certain proteolytic cleavages in the processing of the CoV replicase polyproteins [30]. Interestingly, Zinc-ionophore pyrithione in combination with Zn^{2+} is a potent inhibitor of CoV RdRp elongation and reduces template binding [31]. Furthermore, it has been reported that Zn^{2+} inhibits autophagy and enhances the inhibitory activity of CQ on autophagy and CQ-induced apoptosis [26].
Zn^{2+} has an important place in a variety of infections: its deficiency predispose, whereas supplementation helps treat infections. It has been suggested that Zn^{2+} correction combined with nCoV treatment sustains the antiviral activity, whereas reduces the cytokine storm and nCoV RNA synthesis [32]. These data indicate that the inclusion of $Zn^{2+}$with other drugs (such as CQ or HCQ) maybe e beneficial in the treatment of COVID-19.

8.1.8. Imminosugars: Imminosugars are bicyclic or monocyclic D-glucose- and D-galactose-derived sugar mimetics in which the cyclic oxygen is replaced with nitrogen. The glucose-mimicking iminosugars inhibit glycoprotein processing but do not inhibit glycolipid processing. The galactose-mimicking iminosugars act oppositely. Imminosugars have high bioavailability. They are excreted unchanged in the urine.
The surface of enveloped viruses can be extensively glycosylated. Unlike the glycans coating pathogens such as bacteria and fungi, glycans on viruses are added and processed by the host-cell during biosynthesis. This process requires the correct N-glycosylation of the peptides and is required for their folding and export to the Golgi apparatus for the production of glycoproteins that form virus glycoproteins. N-Glycosylation starts in the ER where a 14-sugar tri-glucose(GGG) glycan, composed of three glucose molecules on A arm, nine mannoses on arms B&C, and two N-acetylglucosamines (Glc(3)Man(9)GlcNAc(2)), is transferred to nascent proteins, then the terminal glucoses are sequentially trimmed by ER-resident α-glucosidases (α –Glu) αGlu I and αGlu II from A arm to produce GG- and G-glycan respectively. The latter, G-Glycan, is received by the chaperones Calnexin and calreticulin, and directed to αGlu II to pursue either of the two ways:1- correct folding and exporting of the protein to Golgi for further processing, or 2-if the folding is incorrect the misfolded protein is either reglucosylated by UDP-glucose:glucosyltransferase (UGGT) for a 'second chance' folding or directed to the ER-associated degradation (ERAD) pathway by ER mannosidase I (ER Man I), which removes a mannose residue from the B-arm of the glycan [33]. Then the mannose on C arm is removed by ER degradation-enhancing α-mannosidase-like proteins 1–3 (EDEM1–3) followed by A- arm trimming and delivery to ER-membrane bound export system, PNGase-separation of free oligosaccharide from protein and ubiquitation of the latter.
The main step in these processes, α –Glu-mediated host-ER folding, is required by many viruses in order to form their glycoproteins and incorporating them to their structures. Inhibition of the glucosidase will prevent protein folding, and thus viral glycoproteins from being incorporated with protein-folding machinery leading to misfolding of viral glycoproteins and prevent their incorporation into the virus, and consequently interferes with viral secretion or cause secretion of noninfectious virions. Moreover, it was hypothesized that one particular viral glycoprotein (M) when in the

triglucosylated state may act as a kind of 'poison pill' in the ER preventing the secretion of the virus. In this case, a viral protein acts as a 'dominant-negative' poison of viral secretion and may itself be considered the antiviral drug. The long intracellular half-life of the 'poison pill' may be due to aberrant trafficking between the ER and Golgi that has recently been observed for glycoproteins retaining terminal glucose residues on their glycans. This additional mechanism could lead to a reservoir of unfolded protein that interfere with the ER quality control. These are areas that need to be investigated further to understand the structural requirements for viral assembly, secretion, and fusion to host cells in an iminosugar protein folding compromised context [34] in order to develop proper effective antivirals.

Support for the approach of targeting α-glu I in antiviral development is provided by the observations that two patients deficient in this enzyme have no clinical evidence of recurrent viral infections and that cells derived from these patients have a greatly reduced ability to support replication of a variety of different viruses [35].

By examining the effects of iminosugars on the transduction of lentiviral particles pseudotyped with envelope proteins from eight different viruses, it was demonstrated that the N-linked glycan processing of some host cellular proteins is indeed altered under the conditions where viral glycoprotein metabolism is affected. Detailed analyses of the glycan processing of ACE2 revealed that the N-linked oligosaccharides in iminosugar-treated cells can be processed through an alternative pathway that trims the N-linked glycans by cleaving the oligosaccharide chains between the internal mannose moieties by Golgi endomannosidases. The resulting N-linked glycans are further processed and matured into complex glycans in the Golgi apparatus. Moreover, alteration of N-linked glycans of ACE2 does not apparently affect its cell surface expression and binding of the SARS-CoV spike glycoprotein, but it does impair its ability to support viral envelope spike glycoprotein-triggered membrane fusion. At this moment, whether the reduced fusion activity is due to the aberrant glycan structure of ACE2 or to misfolding of the glycoprotein, a consequence of abnormal glycan processing, remains to be determined. A possible scenario is that alteration of ACE2 N-linked glycans compromises its dynamic interaction with viral envelope glycoproteins during membrane fusion and consequently inhibits CoV and Cov-NL63 glycoprotein-mediated entry to the cell. Alternatively, alteration of N-linked glycans may disrupt ACE2 interaction with another cellular component(s) that facilitates the membrane fusion between virus and host cells. Nevertheless, N-linked glycans of ACE2 are important for virus-induced membrane fusion. Moreover, Inhibition of Endoplasmic Reticulum-Resident Glucosidases alters glycan processing of ACE2, and hence impairs sever spike-mediated entry into cell [36].

Considering host-targeting antiviral therapies, the paramount concern is the toxicity underlying the "on-target" suppression of host functions required for viral replication. Because ER glucosidases catalyze the glycan processing of both viral and host cellular glycoproteins, it is rather surprising that inhibition of ER glucosidases selectively suppresses viral replication and that iminosugars are generally well tolerated, at least for short-term therapy, in animals and humans [37]. A possible explanation for the selective antiviral effects of ER glucosidase inhibitors is that the viral glycoproteins are quantitatively the predominant glycoproteins made in infected cells and are thus more vulnerable to partial inhibition of ER glucosidases. In addition, assembly of infectious virion particles relies on coordinative interaction among multiple copies of envelope glycoproteins, and misfolding of a small fraction of viral glycoprotein may lead to the failure of virion assembly.

Iminosugars are considered to be promising candidates for broad-spectrum antiviral activity when glycoprotein processing is concerned. Celgosivir, a bicyclic glucose-mimicking iminosugar, was confirmed to be an antiviral in primary human macrophages [38]. The mean by which these molecules are thought to exert their antiviral effects is through inhibition of host-resident glycoprotein processing enzymes, the ER-resident α-glucosidases, but many iminosugars are also capable of inhibiting host glycolipid processing. Their structural similarity to sugar molecules means that many iminosugars are competitive inhibitors of α-glu preventing correct folding and synthesis of glycoprotein. One of the advantages of the imminosugars is their being refractory to viral mutations, because they target host enzymes, not the viral ones. Addition of iminosugar leads to impaired virion secretion, or secretion of non-infectious virions [34]. It is noteworthy to mention that some plants are rich in active ingredients that are reported to be potent α-glu inhibitors. Of these Mulberry could be mentioned as an example. It

contains several potent α-glu inhibitor active ingredients in leaves, roots and fruits including 1-deoxynojirimycin.

8.1.9. β-D-N4-hydroxycytidine: A broad-spectrum orally bioavailable ribonucleoside analog antiviral. It improves pulmonary function, reduces viruses titer and body weight loss. It is reported to be effective against Remdesivir resistant CoV. It acts by inducing lethal mutagenesis where deleterious transition mutations accumulate in viral RNA, and reduces viral replication [39].

8.1.10. Umifenovir: Inhibits viral fusion with the host cell membrane and subsequent entry into the host cell (Boriskin et al., 2008). Moreover, a favorable clinical response had been reported following the addition of umifenovir to lopinavir/ritonavir combination [40].

8.1.11. Triazavirin: Guanine nucleotide analog, RNA synthesis inhibitor with broad-spectrum antiviral property, developed as a potential treatment of Influenza A and B infections [41]. Triazavirin is active against a rimantadine-resistant strain and a highly pathogenic avian influenza A virus H5N1. It has a C_{max} of 4.8μg/mL, with a T_{max} of 1-1.5h, and an AUC of 12.8μg/h.mL, and volume of distribution of 32 L.

8.1.12. Disulfiram: It is orally bioavailable as bis(diethylthiocarbamoyl) disulfide, reduced to diethyldithiocarbamate when it reacts with thiol groups. This metabolite of Disulfiram is a potent copper chelator, and it can thereby affect the activity of copper-dependent enzymes such as monooxygenases, amine oxidase, cytochrome oxidase, microsomal carboxylesterase, and plasma cholinesterase. Disulfiram is used in the treatment of alcoholism and cocaine addiction. It inhibits aldehyde dehydrogenase and dopamine-β-hydroxylase. Disulfiram acts as a competitive Covalent inhibitor of nCoV PL^{pro} [42], and caspase proteases [43]. It may work through inhibition of caspase1-gasdermin-IL-1β and Il-18 release by a variety of innate immune cells (such as macrophages, monocytes) which made it possible to Disulfiram to allocate its place among the drugs that are used in the fight against COVID-19. It has been reported that Caspases activate and cleave gasdermin D to generate N-terminal cleavage product (gasdermin D-NT). These fragments group together to form pores that punch holes in the membrane of the infected cells (both living hyperactive, and dead pyroptotic cells), causing pyroptosis and release of inflammatory cytokines such as IL-1β and IL-18 through these pores [44]. Disulfiram blocks gasdermin-D-NT fragments from forming -pore, and so prevents pyroptosis and release of inflammatory cells that cause sepsis [45], consequently hinders the release of the interleukins, and decreases the inflammatory responses.

8.2. Other drugs may be used in COVID-19 (Table 2)

8.2.1. Anti-inflammatory drugs: These drugs are very important in antagonizing the inflammatory mediators that are responsible for most of the pathologic and clinical symptoms of COVID-19. The mediator held responsible here is far more serious than prostaglandins. Of these, the Numb-associated kinase (NAK), including AAK1 and GAK, is involved in clathrin-mediated endocytosis. It is known that Notch signaling dampens macrophage activation and abrogates pro-inflammatory cytokine production. Numb negatively regulates Notch, whereas positively regulates TNFα, IL-6, IL-12, and NF-κB production [46]. Drugs like Baricitinib, fedratinib, and ruxolitinib are potent and selective JAK inhibitors, approved for indications such as rheumatoid arthritis and myelofibrosis. These drugs are powerful anti-inflammatories that, as JAK–STAT signaling inhibitors, are likely to be effective against the consequences of the elevated levels of cytokines typically observed in COVID-19 patients [47]. Use of this agent over 7–14 days induce only trivial side effects including low incidence upper respiratory tract infections (similar to that observed with methotrexate) and herpes zoster.
The high affinity of Baricitinib for NAKs (AKA1), its anti-inflammatory properties, and its ability to ameliorate associated chronic inflammation in interferonopathies, together with its advantageous pharmacokinetic properties, appear to make it a special case among the approved drugs. In addition, the potential for combination therapy with Baricitinib is high because of its low plasma protein binding and minimal interaction with CYP enzymes and drug transporters. Combinations of

Baricitinib with direct-acting antivirals (lopinavir or Ritonavir and Remdesivir) could reduce viral infectivity, viral replication, and the aberrant host inflammatory response.

Table 2. Drugs useful in treatment of the nCoVs-induced systemic pathology in COVID-19.

1	Anti-inflammatory drugs	• Inhibit inflammation mediators. • Inhibit Numb-associated kinase and endocytosis.
2	Tocilizumab	• Inhibit Interleukin-6 (IL-6).
3	Azithromycin	• Immune modulation.
4	Hyaluronidase	• Removal of hyaluronan casts.
5	Lithium	• Inhibits Glycogen synthase kinase 3-β inhibition. • PI3K/Akt/GSK-3α/β pathway inhibition; mRNA and gRNA synthesis inhibition.
6	Dornase	• Extracellular DNAase.
7	Thiazolidinediones	• Peroxisome proliferator-activated receptor gamma (**PPARγ**) activator.
8	Mycophenolate mofetil	• Inhıbition of inosine-5′-monophosphate dehydrogenase.
9	Thalidomide	• Immune modulation and inhibition of chemotaxis.
10	ARB + ACEI	• Ang-II and ACE2 level: increase/decrease.
11	Ivermectin	• Inhibits importin heterodimer IMPα/β1. • Inhibits nonstructural 3 helicase.

ACEI. Angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blockers.

8.2.2. Tocilizumab: Tocilizumab is a recombinant humanized monoclonal antibody, competitively inhibits both soluble and membrane-bound Interleukin-6 (IL-6) receptors, thereby inhibits IL-6-mediated signaling. The potential immunological effects of Tocilizumab include induction/expansion of B-regulatory cells, reduce expression of pro-inflammatory cytokines and chemokine genes, and obtund cytokine release syndrome that is evident in severe COVID-19 patients [48]. Tocilizumab eliminates both antibody-dependent and complement-dependent IL-6R expressing cellular cytotoxicity. Binding of Tocilizumab to soluble IL-6R is a dose-dependent; complete inhibition is seen at approximately 4 μg/mile Tocilizumab treatment increases serum levels of free IL-6 and soluble IL-6R (sIL-6R). Likely due to prolongation of elimination half-life by the formation of Tocilizumab/sIL-6R immune complex, and inhibition of IL-6R-mediated consumption of IL-6 due to occupation of IL-6R by Tocilizumab and the unavailability of free IL-6R [49].

Serum Tocilizumab concentrations display nonlinear pharmacokinetics in the dose range of 2-8 mg/kg when intravenously administered by drop infusion for 2 hours. The drug has a nonlinear pharmacokinetic. The $t_{1/2}$ is dose dependent, and approximates the half-life of human IgG1 (241.8 ± 71.4 hours) by the third dose of 8 mg/kg. The mean AUC for serum Tocilizumab concentration is 10.66 ± 4.07 gm./ml. The clearance decreases with increasing the dose and relevantly Cp, indicating a capacity limited clearance process. Interestingly, C-reactive protein (CRP) and serum amyloid (SAA) levels were undetectable in RA patients with serum concentrations of free Tocilizumab greater than 1 μg/ml, suggesting that IL-6 is essential for CRP and SAA production *in vivo*. In fact, CRP levels have been shown to function as a surrogate marker for the level of Tocilizumab activity. After IV dosing, Tocilizumab undergoes biphasic elimination from the circulation. In patients with Rheumatoid arthritis, the central volume of distribution is 3.5 L, and the peripheral volume is 2.9 L, resulting in a volume distribution at a steady state of 6.4 L. Tocilizumab may be hepatotoxic, and can cause infusion-related reactions. It should be used cautiously in patients with thrombocytopenia and neutropenia.

*8.2.3. Sarilumab***:** It is a fully-human monoclonal antibody that inhibits the interleukin-6 (IL-6) pathway by binding and blocking the IL-6 receptor. It is able to tamp down pulmonary inflammation in serious COVID-19 patients.

8.2.4. Corticosteroids: The use of the corticosteroids had been limited due to suppression of the immune system. This is valid for the first stage of the disease where the immune activity is crucial. However, during the second phase where cytokine storm takes place, suppression of the immune reaction is inevitable, and corticosteroids may be useful. Recently, Dexamethasone at a low dose (6 mg p.o. or. İ.v. once a day) given for up to 10 days had been found to decrease mortality after 28 days in the intubated patients (by 35%) and patients receive oxygen therapy (20%), but not effective in patients with light symptoms.

8.2.5. Azithromycin: It is a macrolide antibacterial. It prevents bacterial superinfection and has immunomodulatory properties in pulmonary inflammatory disorders. It downregulates inflammatory responses and reduces the excessive cytokine production associated with respiratory viral infections. However, its direct effects on viral clearance are uncertain. Immunomodulatory mechanisms may include reducing chemotaxis of neutrophils to the lungs by inhibiting cytokines (i.e., IL-8) and mucus hypersecretion. Azithromycin also decreases the production of reactive oxygen species, accelerates neutrophil apoptosis, and blocks the activation of nuclear transcription factors [50]. The risk of cardiac arrhythmias (e.g., QT prolongation) and significant drug interactions should be considered. It is used as an adjunct therapy.

8.2.6 Hyaluronidase: Hyaluronic acid (HA), also called hyaluronan, is an anionic, nonsulfated non-epimerized linear glycosaminoglycan existing in vivo as a polyanion of hyaluronic acid and composed of repeating disaccharide units of D-glucuronic acid and N-acetyl-D-glucosamine. It is unique among glycosaminoglycans in that it is nonsulfated, forms in the plasma membrane instead of the Golgi apparatus. HA has extraordinary hydrophilic, rheological, signaling properties and viscoelastic properties. It is a major constituent of the extracellular matrix and distributes widely through-out connective, epithelial, and neural tissues (15 g/75 kg) where dynamically it is involved in many biological processes and associated with the acute respiratory distress syndrome (ARDS). Indeed, the cytokines released in COVID-19 (IL-1, TNF) are strong inducers of HA-synthase-2 (HAS2) in lung alveolar epithelial cells, and fibroblasts [51]. It is noteworthy to mention that HA has the ability to absorb water up to 1000 times its molecular weight. This will eventually cause edema and together with fibrosis and other pathological insults may be implicated in nCoV-induced pulmonary edema and breathing problems. Therefore, reducing the presence or inhibiting the production of HA holds a great promise in helping COVID-19 patients breathe. Drugs such as hyaluronidase and hymecromone (4-Methylumbelliferone, 4-MU), an inhibitor of HAS2 [52] may be useful. Moreover, since Vitamin B3 is highly lung-protective, it should be used as soon as coughing begins [53].

*8.2.7. Lithium (Li^+)***:** The cornerstone in treatment of bipolar depression. Li^+ produces this effect by decreasing cAMP and inhibiting dopamine release, GSK 3β, IMPase and IPP, and inositol transport into cells. However, Li^+ is also known to produce antiviral activities, but at levels toxic to humans. GSK-3β is required for the production of CoV genomic RNA. The inhibition of GSK-3β by Li^+ will deprive phosphorylation of the viral nucleocapsid and subsequently prevent synthesis of full length viral genomic and subgenomic mRNAs [54]. Li^+ does not interfere with virus attachment to cells [55]. It was found that Li^+Cl could inhibit apoptosis that is caused by PDCov infection. Apoptosis is considered a host innate defense mechanism to eliminate virus-infected cells. However, some viruses use and trigger apoptosis to facilitate the release of viral progeny for further dissemination. This can be fundamental for viral pathogenesis, promote cell death and tissue injury, and disease progression.

8.2.8. Dornase alfa: It is recombinant human deoxyribonuclease I (DNase I). The enzyme is involved in endonucleolytic cleavage of extracellular DNA to 5′-phosphodinucleotide and 5′-phospho-oligonucleotide end products. Extracellular DNA is released by the degenerating leukocytes that accumulate during inflammatory responses to infections. It is a viscous anionic polymer and its breakdown appears to improve the viscosity and viscoelasticity of purulent sputum, help expulsion of

the sputum, and thus reduce airflow obstruction in individuals with cystic fibrosis. Dornase alfa cleaves extracellular DNA to 5′-phospho-dinucleotide and 5′-phosphooligonucleotide end products without affecting intracellular DNA, and hence it is expected to help keep the airways open. The optimal DNase activity is dependent on the presence of divalent cations such as calcium and magnesium. Following inhalation, Dornase alfa can be detected after 15 min in sputum (3 μg/mL), declining to an average of 0.6 μg/ml within 2 hours. The systemic absorption is very low (>2-15%), and accumulation in serum is very low, whatever the dose administered. Peak concentrations are achieved after 9 days after daily administration. Dornase is metabolized by proteases in the biofluids. The disappearance half-life of Dornase alfa from the lungs is 11 hours. In humans, sputum DNase levels decline below half of those detected immediately post-administration within 2 hours but effects on sputum rheology persisted beyond 12 hours. ADR occur at a frequency of < 1/1000 and are usually mild and transient in nature. The reported ADRs include chest pain (pleuritic/non-cardiac), fever, dyspepsia, voice alteration (hoarseness), pharyngitis, dyspnea, laryngitis, rhinitis, decreased lung function, rash, urticaria, and conjunctivitis.
In severe COVID-19, the host response is characterized by extensive neutrophilia in peripheral blood to an extent activation of the neutrophil-to-lymphocyte ratio becomes an independent risk factor for severe disease [56]. In addition to the peripheral blood, there are neutrophils infiltrations in pulmonary capillaries, acute capillaritis with fibrin deposition, extravasation of neutrophils into the alveolar space, and neutrophilic mucositis. Neutrophilia could be a source of excess neutrophil extracellular traps (NETs). NETs are web-like structures of DNA and proteins expelled from the neutrophil that ensnare pathogens. Several enzymes are involved in NETs formation and maybe drugs targets: neutrophil elastase, which degrades intracellular proteins and triggers nuclear disintegration; peptidyl arginine deiminase type 4, which citrullinates histones to facilitate the decondensation and release of the chromosomal DNA; and gasdermin D, which generates pores in the membrane of the neutrophils. Although NETs are beneficial in the host defense against pathogens, the excessive NET formation can trigger a cascade of inflammatory reactions that harm surrounding tissues, facilitates microthrombosis, and results in permanent organ damage to the pulmonary, cardiovascular, and renal systems, which are the most affected organ systems in severe COVID-19 [57]. Moreover, NETs lead to the formation of extracellular naked histones which are involved in ARDS and sepsis, and they are toxic to cells [58]. Dornase alfa dissolves NETs in the airways of patients with cystic fibrosis [59]. Other available related drugs such as Alidornase alfa (more potent than Dornase alfa) sivelestat (neutrophil elastase inhibitor), colchicine (inhibits both neutrophil recruitment to sites of inflammation and the secretion of IL1β) and anakinra (IL1α&β receptor antagonist) have excellent safety profiles. They are included in therapeutic strategies available to antagonize NETs in COVID-19 patients today.

8.2.9. Thiazolidinediones: Pioglitazone is an example. It is commonly used for treating insulin resistance. It is a Peroxisome proliferator-activated receptor gamma activator, increases insulin sensitivity by enhancing the storage of fatty acids in fat cells and reducing lipotoxicity, reduces TNFα and IL-6 [60] and has a potential in decreasing lung fibrosis [61], and to reverse the reduction of glutamate transporter (GLT-1) that observed in viral infection such as HIV [62]. Due to their central anti-inflammatory and the glutamate homeostasis correcting properties, Pioglitazone could be beneficial in case either the SARS-CoV-2 or the consequent inflammation response has spread to the brain is concerned. A rationale for using pioglitazone or other PPARγ agonists in the treatment of COVID-19 treatment had been proposed [63].

8.2.10. Mycophenolate mofetil: It is the morpholino ethyl ester and prodrug of mycophenolic acid (MPA), an immune suppressive. The ester masks the carboxyl group in its structure. The ester form is rapidly metabolized in the liver to the active moiety MPA, a potent, reversible, and un-competitive inhibitor of inosine-5′-monophosphate dehydrogenase (IMPDH). The IMPDH is nicotinamide adenine dinucleotide (NAD^+)-dependent enzyme that controls *de novo* synthesis of purine nucleotides, catalyzes the oxidation of inosine 5'-monophosphate (IMP) to xanthosine 5'-monophosphate, which is then converted by GMP synthase to guanosine 5'-monophosphate used in the proliferation of B and T lymphocytes. The IMP also serves as a substrate for the biosynthesis of adenosine 5'-monophosphate (AMP). IMPDH exists as two isoforms, IMPDH1 and IMPDH2, with 84% amino acid sequence identity, and forms independent tetramers. IMPD1 is more prevalent in the peripheral blood

cells, neutrophils, whereas IMPDH II is expressed exclusively in activated T and B lymphocytes. Proliferating B and T lymphocytes are singularly dependent on the de novo pathway, rather than the salvage pathway, for purine biosynthesis. Since MPA is more selective inhibitor of IMPD II, it is expected to relatively produce a selective reduction of GMP and interruption of DNA synthesis in lymphocytes, but not neutrophils [64], an effect that results in decreased cytokines synthesis and releases from the lymphocytes. The MPA and its related forms cause dose-limiting gastrointestinal toxicity such as diarrhea, leukopenia, sepsis, and vomiting are the barriers to the administration of higher doses, and to develop a more effective treatment.

8.2.11. Thalidomide: A drug once widely used for treating morning sickness in pregnant women, but it was the perpetrator of teratogenicity tragedy: over 10,000 children born to mothers who took the drug were affected with severe congenital deformities including phocomelia, cleft lip and palate, abnormal eyes and ears, and congenital heart diseases. Its use was also associated with peripheral neuropathy in adults [65]. However, later on, it was found to possess anti-inflammatory and immunomodulatory effects, and used in treating Erythema nodosum leprosum and multiple myeloma [66].
Thalidomide inhibits or downregulates cyclooxygenase enzyme-2 and Prostaglandin E2, TNF-α, IL-1, IL-6, and NF-κB. Moreover, thalidomide is reported to enhance the differentiation of T-helper cells type 1, with the subsequent increase in IFN-g and IL-2 levels [67]. It also suppresses IL-12 production from macrophages of patients with interstitial lung disease [68]. Thalidomide exerts an antifibrotic effect [69]. It could potentially inhibit chemotaxis of neutrophils and monocytes, upregulate NK and T cells. The inference of thalidomide's efficacy in the treatment of COVID-19 could be based on its above-mentioned anti-inflammatory, cytokines downregulating and antifibrotic activities. Moreover, a case of nCoV-pneumonia had successfully been treated with thalidomide combined with low dose glucocorticoid [70].

8.2.12. ACEIs and ARBs: It is possible that some Covide-19 patients admitted to the hospital could be receiving drugs for the treatment of pre-existing cardiovascular diseases. Covide-19 is more prevalent in the hypertensive patients and/or nCoV itself causes hypertension by modulating Ang II or ACE2. Derangement of renin-angiotensin-aldosterone system (RAAS) system is proposed to be involved in the pathological burden of COVID-19 such as hypercoagulopathy and microvascular immunothrombosis [71]. Higher level of Ang II had been detected in COVID-19 patients than in those without COVID-19. Moreover, Patients with elevated AngII levels are more likely to be critically ill with COVID−19 [72]. Accordingly, the drugs that could modify RAAS are of great importance in combating COVID-19 and hypertension whether induced by COVID-19 or previously exists in these patients. ACE2 should be considered when ACEI or ARBs are used in the treatment of hypertension in COVID-19 patients.
Various effects had been attributed to ACEI and ARBs in COVID-19 patients: no effect, beneficial or even harmful effects. However, overall, improved outcomes [73] or no change in the risk of mortality between ACEI/ARB-exposed and non-ACEI/ARB exposed COVID-19 patients [74]. Both ACEI and ARBs increase ACE2 expression. However, it is debated whether this may inhibit or facilitate infection with CoV-19. Two opposite hypotheses have been proposed for the effects of RAAS inhibition with ACEIs and ARBs in COVID-19 [75]: increased ACE2 could be harmful in the first stage/light cases of the disease, but beneficial in the severe cases. On the other hand, increased ACE2 and decreased AngII is expected to be beneficial in advanced severe cases. The harmful effect is expected with ACEI alone. The predominant effect of ACE inhibition may result from the combined effect of reduced Ang II synthesis, decreased Ang-(1–7) metabolism, but increased ACE2 mRNA due to inhibition of the hydrolytic activity of ACE that regulates ACE2 mRNA but not ACE2 activity. The reduced Ang II levels during ACEI therapy may be a stimulus for increased ACE2 mRNA. On the other hand, blockade of Ang I receptors increases plasma levels of ACE2 mRNA/activity and hence Ang II metabolism to Ang-(1–7). It is proposed that the situation depends on the state of Ang II. In the case of a low Ang II level, there will be more AT1R –ACE2 combination, leaving no or few ACE2 to combine with the virus. On the other hand, in the case of high Ang II level, Ang I will combine with more AT1R, leaving more free ACE2 to combine with the virus (Figure 2), and hence increase the infection probability.

Although the use of ACEI or ARBs alone clinically seems innocent, it may be better to look at what happens on combination or ACEI with ARBs. It has been reported that a combination of ACEI and Ang I blocker therapy (e.g. Lisinopril to losartan) not only increases the effects of the latter on Ang II but abolishes the increase in ACE2 mRNA (ACE2 activity remains as for losartan alone). The reduced ACE2 gene expression when Lisinopril was added to losartan suggests that ACEI therapy can override the signal that modulates ACE2 mRNA [76]. It is noteworthy that the ACEI- and ARBs-induced increase of ACE2 could be beneficial in the advanced COVID-19 because ACE is downregulated and/or degenerated by CoV. Also, the drugs possess anti-inflammatory and antifibrotic effects which are of great advantages ın treatment. Accordingly, it is rational to suggest that the use of the ACEI and ARBs could be considered in the advanced case. Moreover, the addition of an ARB to ACEI therapy may reduce Ang II, enable ACE2 to bind AT1R, and keep AT1R and ACE2 together, so that devoid CoV from the chance of binding to a greater number of ACE2, and hence decrease its cellular pathogenicity.

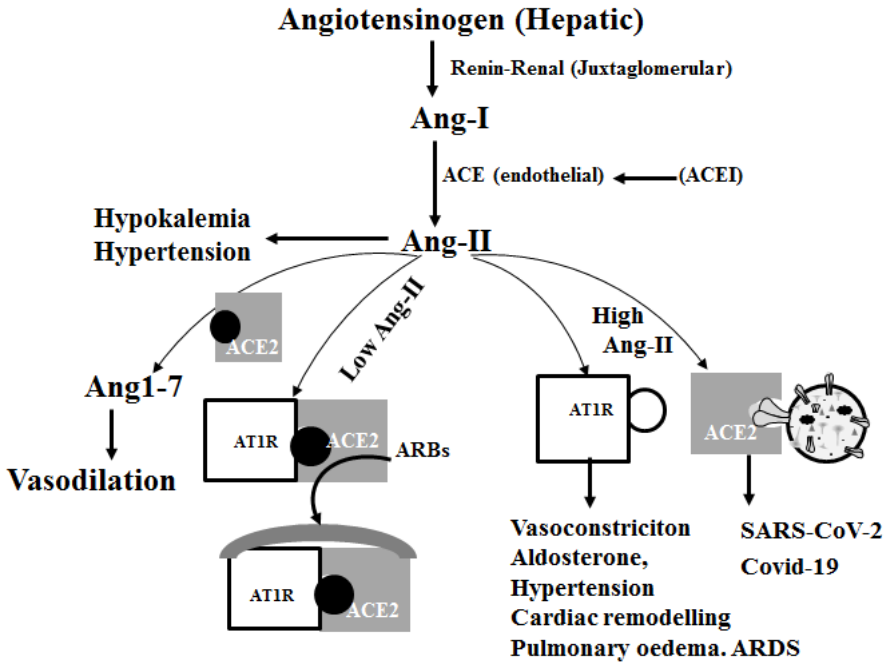

Figure 2. The renin-angiotensin activating system in COVID-19. The level of Ang II could determine virus-ACE2 interaction, initiation, and course of the disease. Abbreviations: ACEI: Angiotensin (Ang) converting enzyme (ACE) inhibitor; ARD: Acute respiratory distress syndrome. AT1R: Ang-II receptor.

The risk/benefit ratio is another factor in the use of these drugs when COVID-19 is considered. The general trend is to continue using those drugs for current benefits in control of severe or uncontrolled hypertension and heart failure, where the benefits outweigh the risks, whether the patient is positive or negative to the disease test.

8.2.13. Ivermectin: is a semisynthetic derivative of avermectins, a group of macrocyclic lactones produced by the soil bacterium Streptomyces avermitilis. It is generally a mixture of avermectin B1a (90%) and B1b (10%). It is used for treatment of onchocerciasis and other nematodes including strogyloidiasis. Ivermectin produces its anthelmintic effect by potentiation or direct activation of glutamate-gated chloride channels (GluCls), found only in protostome invertebrate phyla, but are closely related to mammalian glycine receptors, which causes paralysis of the parasite. The Cmax is achieved within 4h after oral administration. Ivermectin is 93% bound to plasma protein, its volume of distribution approaches total body water, 47L. The systemic clearance is low, 1.2 L/h. This is reflected as long $t_{1/2}$, 27h. Ivermectin is excreted almost totally in feces as unchanged drug, and the highest tissue level is detected in liver and adipose tissue. Although Ivermectin passes through blood-brain barrier, extremely low levels are detected in the brain. This may be due to secretion of Ivermectin out

of brain by P-gp efflux pumps that are present in the blood brain barrier and cerebral endothelia. This low level and the limited affinity of Ivermectin for CNS-receptors may explain the lack of central side effects and inexpediency of Ivermectin for brain infections. In addition to the previously established effect on GluCls, Ivermectin inhibits viral entry into the nucleus, both directly and by inhibiting the interaction between the viral protein and the importin heterodimer IMPα/β1 responsible for integrase nuclear import [77], and inhibits flavivirus replication by specifically targeting the activity of nonstructural 3 helicase [78]. Ivermectin has since been confirmed to inhibit the replication of several RNA viruses including nCoV *in vitro* [79]. The use of Ivermectin for COVID-19 is a real enigma. While some scientists are skeptical and put forward a lack of controlled well-designed studies, others claim great success in treating COVID-19 and saving the lives of their patients. This dilemma is much more evident in some Latin American countries. It should be noted that nuclear import is not of importance in case of nCoV replication, and the studies that hail Ivermectin as an antiCoV drug are mostly in vitro, or small-sized clinical studies. Moreover, there seems weirdness in the FDA's article to its stakeholders showing Ivermectin as "intended for animals" and advising against its use as a treatment for COVID-19 in humans.

9. Conclusion

COVID-19 had posed profound health, social, and economic challenges all over the world. Lack of adequate and relevant therapeutic options had aggravated the situation and forced authorities and hospitals to adopt treatment protocols and make decisions with little or no sound data. This review tackles the drugs used to combat the disease. These (old) drugs had been used to treat other viral infections or various related and/or unrelatedsystemic diseases. However, variable success degrees had been reported in regard to SARS-CoV-2 in different parts of the World. These drugs are generally used at doses empirically selected, and mostly as a cocktail of combinations of drugs targeting the virus and the systemic illness that it causes. It is important to understand the pharmacodynamic, kinetic, toxic effects of these drugs to obtain the best therapeutic effect and to avoid their adverse effects. Some of these drugs had been used to disease not related to viral infection. However, these drugs possess interesting effects on virus structure and replication. It is noteworthy to mention that while some of these drugs were useful in some hospitals, they were retracted by others. This may be a matter of selecting the correct dose and combination. Of course, we have had acquainted with a great deal of experience in the fight against SARS-CoV-2, but it is well known that coronaviruses subtly contrive to mutate, and have a tremendous potential to evade the antivirals. It could be suggested that the chemical structures of these drugs could also form a crucial part of the itinerary in the hard and costive path to the development of novel drugs.

Article highlights

- The COVID-19 pandemic is evolving, spreads exponentially and has a great potential for reappearing.
- No prediscovered drug is available. Using the old ones disclosed novel antiviral mechanisms for them.
- Combined therapy targeting the virus and its pathology is in vogue.
- Considering the risk of their frequent mutations, there is a need for novel, safe, resistance evading with multiple effect mechanisms anticorona drugs.

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