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Recent Updates in the Pharmacological Management of COVID-19

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Abstract: SARS CoV-2 is the causative organism of Coronavirus disease 2019 (COVID-19), originated first in Wuhan, China, in December 2019. The WHO does not endorse any drug as safe and effective in managing patients with COVID-19 at this point. Hence, numerous drugs approved for other illnesses are being used as repurposed drugs to treat SARS-CoV-2 infection patients. The databases such as Medline/PubMed Central/PubMed, Google Scholar, Science Direct, Directory of open access journals (DOAJ), and reference lists have been searched to discover articles applicable to pharmacological management of COVID-19. The SARS-CoV-2 infection could be managed by drugs inhibiting the viral entry and viral fusion like umifenovir, baricitinib, camostat mesylate, and nafamostat mesylate, the drugs preventing the viral replication such as favipiravir, remdesivir, lopinavir/ritonavir, ribavirin, sofosbuvir and chloroquine, hydroxychloroquine, and by some of the investigational drugs including nitazoxanide, ivermectin, emetine, and auranofin.

Keywords: SARS CoV-2; COVID-19; Antiviral; Antioxidant; Anti-inflammatory; Immunomodulators.

1. Introduction

Coronaviruses belong to the family of Coronaviridae and the subfamily of Orthocoronavirinae, which consists of four different genera such as Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus [1]. In humans, coronaviruses most commonly cause the common cold and some recent severe diseases like severe acute respiratory syndrome (SARS-CoV), Middle East respiratory syndrome (MERS-CoV), and severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) [2].

SARS CoV-2 is the causative organism of Coronavirus disease 2019 (COVID-19), originated first in Wuhan, China, in December 2019. The World Health Organization (WHO) declared COVID-19 as a global pandemic on 11th March 2020 [3]. SARS CoV-2 was known previously as a 2019-novel coronavirus (2019-nCOV) by WHO, and it was renamed as SARS CoV-2 based on its phylogenetic analysis, on 11th Feb 2020 [4].

Bats may be the potential natural host, while pangolin could be a potential intermediate host for SARS-CoV-2, as suggested by various studies [5]. The transmission of SARS CoV-2 between humans occurs mainly through respiratory droplets and direct or indirect contact with mucous membranes in the eyes, mouth, or nose [6]. The incubation period of SARS-CoV-2 is estimated to be between 2 and 14 days, and the WHO recommend active monitoring for 14 days [7].

As of 04th July 2020, there are about 11 million confirmed cases of COVID-19 recorded in 216 countries, and 0.5 million deaths occurred among them, as per the WHO Novel Coronavirus (COVID-19) Situation Board. The most prominent symptoms of COVID-19 include fever, cough, and shortness of breath. Sufferers with COVID-19 may additionally have other symptoms like chills, repeated shaking with chills, myalgia, headache, sore throat and new loss of taste or smell [8].

The SARS-CoV-2 infection could be divided into 3 phases: an asymptomatic phase, a non-severe symptomatic phase with upper airway involvement, and a severe, lethal phase progressing to acute respiratory distress syndrome (ARDS). During the severe, lethal phase, the immune effector cells release high levels of pro-inflammatory cytokines and chemokines such as IL1-β, IL1RA, IL7, IL8, IL9, IL10, FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα and VEGFA resulting in a cytokine storm (Uncontrolled systemic inflammatory response) leading to ARDS, multiple organ failure and even death [9].

Immediate medical attention is recommended for the sufferers of COVID-19 when they develop emergency warning signs such as difficulty breathing, multi-organ failure, including cardiac injury, kidney injury, sepsis, and septic shock [10]. Almost 90% of critically ill COVID-19 patients have one or more underlying comorbid conditions, including hypertension, obesity, diabetes, chronic lung disease, and cardiovascular disease [11].

2. Materials and Methods

The literature was searched in databases such as Medline/PubMed Central/PubMed, Google Scholar, Science Direct, Directory of open access journals (DOAJ) and reference lists to identify articles relevant to pharmacological management of COVID-19 using terms like pharmacological management, SARS CoV-2, COVID-19, AntiCOVID, AntiSARS CoV-2, Antiviral, Antioxidant, Anti-inflammatory, and Immunomodulators. The publications related to the pharmacological management of COVID-19 done in English included in this review while the duplicates are excluded.

3. Results and Discussion

The WHO does not suggest any drug as safe and effective to manage patients with COVID-19, at this point of time. Hence, numerous drugs approved for other illnesses are being used as repurposed drugs to treat SARS-CoV-2 infection patients.

Angiotensin-converting enzyme 2 (ACE2) receptors are expressed generally in the lungs, heart, kidney, and intestine. SARS-CoV-2 enters the host cells via the binding with ACE2 receptors using the receptor-binding domain (RBD) of viral structural spike (S) protein. S protein priming in cell lines is mediated by serine protease enzyme called Transmembrane Protease, serine 2 (TMPRSS2). Synthesis of viral polyproteins and encoding of replicase-transcriptase complex occur inside host cells resulting in the synthesis of viral RNA and the launch of viral particles [12]. Based on the viral lifecycle, the drug therapy of COVID-19 may target viral entry pathways, nonstructural proteins, and immune regulation pathways [13].

3.1. Inhibition of viral entry and viral fusion.

Inhibiting the interaction between ACE2 receptor and RBD of S-protein of SARS-CoV-2 could be one of the drug targets to treat patients with COVID-19 (Table 1).

Table 1. Repurposed drugs are having the potential of inhibiting SARS-CoV-2 viral entry/viral fusion.

S.No	Name of the Repurposed drug	Proposed Mechanism
1	Umifenovir	Slowing of clathrin-coated vesicle (CCV) intracellular trafficking through the impaired release of clathrin-coated pits (CCPs) from the plasma membrane [15].
2	Baricitinib	Inhibition of AP2-associated protein kinase 1 (AAK1) which is an essential regulator of clathrin-dependent endocytosis [23].
3	Chloroquine and Hydroxychloroquine	Bind with sialic acid-containing gangliosides [60].
4	Camostat Mesylate	Blockade of Transmembrane protease, serine 2 (TMPRSS2) [27].
5	Nafamostat mesylate	Blockade of Transmembrane protease, serine 2 (TMPRSS2) [30, 31].
6	Neutralizing antibodies (B38 and H4)	Blockade of binding between the RBD of S-protein of SARS-CoV-2 and ACE2 receptor [32].

3.1.1. Umifenovir (Arbidol).

Umifenovir is an antiviral drug having broad-spectrum activity against several viruses, including enveloped/non-enveloped and DNA/RNA viruses. It is approved to prevent and treat human influenza A and B infections in Russia and China [14]. Umifenovir inhibits the viral entry via slowing of clathrin-coated vesicle (CCV) intracellular trafficking through the impaired release of clathrin-coated pits (CCPs) from the plasma membrane. Umifenovir also inhibits the viral fusion by impairing conformational changes in viral fusion proteins and increasing membrane rigidity [15].

In-service health professionals' clinical study demonstrated that the administration of oral umifenovir decreased the incidence of SARS-CoV-2 infection as prophylaxis [16]. A retrospective analysis of COVID-19 patients demonstrated that the patients on umifenovir cleared off their viral load earlier than the patients receiving Lopinavir/Ritonavir [17]. A retrospective study revealed that the discharge rate was improved and the mortality rate was decreased in COVID-19 patients taking umifenovir [18].

An *in-vitro* study which compared six anti-influenza drugs including umifenovir, oseltamivir, zanamavir, baloxavir, laninamivir and peramavir suggested that only umifenovir has potential antiviral efficacy against COVID-19 [19]. A retrospective multicenter cohort study suggested that the combination of umifenovir and interferon-α2b (IFN-α2b) could inhibit the lung inflammation associated with mild COVID-19 patients, compared to IFN-α2b alone [20].

On the contrary, a retrospective study found that the patients on umifenovir had to stay in the hospital longer than the patients who did not receive umifenovir [21].

3.1.2. Baricitinib.

Baricitinib is a Janus-associated kinase (JAK) inhibitor. It is used to treat various inflammatory conditions, including rheumatoid arthritis, atopic dermatitis, and systemic lupus erythematosus [22]. Baricitinib has antiviral and anti-inflammatory properties and may inhibit the SARS-CoV-2 viral entry into the target host cells by inhibiting AP2-associated protein kinase 1 (AAK1) is an important regulator of clathrin-dependent endocytosis [23].

An open-label pilot study of COVID-19 patients demonstrated that oral treatment with baricitinib significantly improved the clinical and laboratory parameters without ICU support [24]. Moreover, an 87-year-old woman who received Baricitinib along with supplemental oxygen, Lopinavir/ritonavir, and Hydroxychloroquine recovered successfully. In contrast, her husband (90 years) and son (59 years) who did not receive Baricitinib died of respiratory failure [25].

3.1.3. Camostat mesylate.

Camostat mesylate is an orally active, potent serine protease inhibitor, approved in Japan to treat chronic pancreatitis [26]. Camostat Mesylate can block the cellular entry of SARS-CoV-2 through the blockade of Transmembrane protease, serine 2 (TMPRSS2) [27].

In vitro study of camostat mesylate revealed that it inhibited the SARS-CoV-2 infection of human lung cells [28]. The randomized, placebo-controlled, clinical Trials such as NCT04321096 and NCT04338906 are underway to demonstrate the efficacy of camostat mesylate in patients with COVID-19.

3.1.4. Nafamostat mesylate.

Nafamostat mesylate is an anticoagulant drug approved in Japan to treat acute pancreatitis and disseminated intravascular coagulation (DIC) [29]. Nafamostat mesylate has shown higher efficiency of inhibition of SARS -CoV -2 infection of lung cells than camostat mesylate, *in vitro* [30, 31]. A prospective, double-blind, randomized placebo-controlled study (NCT04352400) is underway to test the clinical efficacy of intravenous nafamostat mesylate in adult hospitalized COVID-19 patients.

3.1.5. Neutralizing antibodies.

The neutralizing antibodies like B38 and H4 isolated from the convalescent plasma of COVID-19 patient blocked the binding between the RBD of S-protein of SARS-CoV-2 and ACE2 receptor, and the neutralizing antibodies could be the promising candidates to prevent and treat COVID-19 [32].

3.2. Disruption of viral replication.

The recovery of patients with COVID-19 might be accelerated by the repurposed drugs which inhibit the synthesis of viral RNA through the blockade of synthesis of viral polyproteins and encoding of replicase-transcriptase complex (Table 2).

Table 2. Repurposed drugs are having the potential of inhibiting SARS-CoV-2 viral replication.

S.No	Name of the Repurposed drug	Proposed Mechanism
1	Favipiravir	Selective inhibition of RNA-dependent RNA polymerase (RdRP) [33].
2	Remdesivir	Inhibition of RNA-dependent RNA polymerase (RdRP) [36, 37].
3	Lopinavir	Inhibition of 3-chymotrypsin-like protease [43].
4	Ribavirin	Inhibition of RNA-dependent RNA Polymerases (RdRPs), potent competitive inhibition of inosine monophosphate dehydrogenase (IMPDH), enhancement of viral mutagenesis, and inhibition of mRNA capping [49].
5	Sofosbuvir	Inhibition of RNA-dependent RNA polymerase (RdRP) [51].
6	Chloroquine and Hydroxychloroquine	Inhibition of expression of viral gene [61].
7	Nitazoxanide	Inhibition of viral replication of SARS-CoV-2 [67].
8	Ivermectin	Inhibition of the nuclear import of viral integrase protein and importin (IMP) α/β1 heterodimer [70].
9	Emetine	Inhibition of viral replication of SARS-CoV-2 [74].
10	Auranofin	Inhibition of viral replication of SARS-CoV-2 and the reduction of cytokines expression [76].

3.2.1. Favipiravir.

Favipiravir is a broad-spectrum antiviral drug, and it is approved in Japan to treat influenza viruses. It blocks the viral replication of RNA viruses by selectively inhibiting the RNA-dependent RNA polymerase (RdRP) [33].

A prospective, multicenter, open-label, randomized controlled clinical trial of patients with COVID-19 who received favipiravir or arbidol randomly for 10 days along with conventional therapy, reported that favipiravir therapy produced higher clinical recovery rate and effective reduction of incidence of pyrexia and cough [34] while an open-label control study of COVID-19 patients who received oral favipiravir or lopinavir/ritonavir along with aerosol inhalation of interferon-α revealed that favipiravir therapy ensuing in faster viral clearance, significant improvement in chest imaging and a significantly smaller number of adverse reactions compared to lopinavir/ritonavir treatment [35].

3.2.2. Remdesivir.

Remdesivir is an investigational broad-spectrum antiviral drug, and it is an inhibitor of RNA-dependent RNA polymerase (RdRP) [36, 37].

The administration of remdesivir in COVID-19 patients resulted in faster clinical recovery than those received placebo, as per a multicenter, randomized, double-blind, placebo-controlled clinical trial [38] while an open-label cohort study of patients hospitalized for severe COVID-19 denoted that the use of remdesivir produced clinical improvement in 68% (36 of 53) of patients [39]. Moreover, a randomized, double-blind, placebo-controlled clinical trial of adults hospitalized with COVID-19 with lower respiratory tract infection demonstrated that the intravenous administration of remdesivir lead to a median recovery time of 11 days compared to 15 days of placebo treatment [40].

The U.S. Food and Drug Administration has issued an Emergency Use Authorization of remdesivir to treat hospitalized COVID-19 patients based on the initial findings [41].

3.2.3. Lopinavir/Ritonavir.

Lopinavir is a protease inhibitor used widely to treat patients with human immunodeficiency virus (HIV), and ritonavir is another protease inhibitor combined with Lopinavir to formulate Lopinavir/ritonavir. Ritonavir is a CYP3A4 inhibitor, which can inhibit Lopinavir's metabolism and increase its plasma concentrations [42]. Lopinavir disrupts viral replication through the inhibition of 3-chymotrypsin-like protease [43].

A retrospective cohort study found that the viral clearance was more rapid in COVID-19 patients treated with Lopinavir/ritonavir than in hydroxychloroquine treated patients [44] while the viral shedding of COVID-19 patients was shortened significantly by the Lopinavir/ritonavir therapy, as per another retrospective study [45]. Also, a single-center, randomized, controlled trial which compared the efficacy of monotherapy of Lopinavir/ritonavir or umifenovir demonstrated that the administration of either drugs improved a little of clinical outcome of patients with mild/moderate COVID-19 [46].

In the contrary, an open-label, randomized, controlled clinical trial revealed that the hospitalized adult COVID-19 patients who received Lopinavir/ritonavir had shown similar mortality, throat viral RNA detectability, and clinical improvement as the standard-care, at 21 days [47].

3.2.4. Ribavirin.

Ribavirin is a nucleoside inhibitor categorized as a broad-spectrum antiviral drug used as an adjunctive therapy to treat hepatitis C infection and interferon-α and as a monotherapy treat other viral infections [48]. Ribavirin exerts its antiviral activity through numerous mechanisms, including inhibition of RNA-dependent RNA Polymerases (RdRPs), potent competitive inhibition of inosine monophosphate dehydrogenase (IMPDH), enhancement of viral mutagenesis, and inhibition of mRNA capping [49].

A prospective, open-label, multicenter, randomized clinical trial of adults with COVID-19 demonstrated triple antiviral therapy with ribavirin, interferon beta-1b, and lopinavir/ritonavir ensuing in decreased viral shedding and faster discharge of patients compared to lopinavir/ritonavir therapy alone [50].

3.2.5. Sofosbuvir.

Sofosbuvir is an antiviral drug approved to treat hepatitis C virus (HCV) infection, and it inhibits viral replication through the inhibition of RNA-dependent RNA polymerase (RdRP) [51]. Sofosbuvir is suggested as a potential treatment option for COVID-19 as HCV and SARS-CoV-2 have similar replication mechanisms [52, 53].

3.2.6. Oseltamivir.

Oseltamivir is an antiviral drug used to treat viral infections caused by influenza A and B infections [54]. The administration of Oseltamivir in COVID-19 patients found no positive outcomes reported by Wang D *et al*. [55]. At the same time, another study performed by Guan WJ *et al*. revealed that oseltamivir was ineffective in declining the rates of Intensive Care Unit (ICU) admission, ventilator need and death [56].

3.2.7. Chloroquine/Hydroxychloroquine.

Chloroquine is a quinine derivative, and it is used widely for the prophylaxis and therapy of malaria. The *in-vitro* and *in-vivo* studies of chloroquine have been confirmed its broad-spectrum antiviral activity against various RNA and DNA viruses [57]. Hydroxychloroquine is an analog of chloroquine, and it is used widely to treat malaria and autoimmune diseases. Hydroxychloroquine has been shown a more tolerable safety profile than chloroquine, as its interaction with other drugs is very few [58].

Chloroquine and hydroxychloroquine produce antiviral effects, probably by impairing the viral entry pathways and viral replication pathways [59]. SARS-Cov-2 may also bind to another surface attachment factor called sialic acid-containing gangliosides. Chloroquine and hydroxychloroquine may inhibit the SARS-Cov-2 viral entry through the binding with sialic acid-containing gangliosides [60]. Chloroquine and Hydroxychloroquine may also inhibit viral replication by inhibiting the viral gene [61].

Chloroquine therapy was recommended by Chinese experts to treat the patients with COVID-19. They do not have any contraindications to chloroquine use [62]. A clinical study from china revealed that the COVID-19 patients treated with chloroquine had better clinical recovery than the control group [63].

An open-label, a non-randomized clinical trial demonstrated the use of hydroxychloroquine along with azithromycin (macrolide antibiotic) cleared 100% of viral load

in six days in COVID-19 patients while the patients receiving hydroxychloroquine alone cleared off 57.1% of viral load and the patients in the control group cleared off 12.5% of viral load [64] and a retrospective study of COVID-19 patients taking chloroquine has shown significant prolongation of QTc interval. Hence, the ECG monitoring is recommended in those patients [65].

Moreover, on 15th June 2020, the US FDA has issued a caution against chloroquine or hydroxychloroquine to treat the patients with COVID-19 outside the hospital setting or clinical trial, based on the emerging scientific data.

3.2.8. Nitazoxanide.

Nitazoxanide is an antiprotozoal drug that is approved for the treatment of giardiasis. Various *in-vitro* studies demonstrated the antiviral efficacy of nitazoxanide against many viruses, including influenza, hepatitis B and C, dengue, norovirus, respiratory syncytial virus, and coronaviruses such as SARS-CoV-1, MERS, and SARS-CoV-2. Recently, an *in-vitro* study performed by Wang M *et al*. reported that Nitazoxanide inhibited the SARS-CoV-2 at a low-micromolar concentration [66].

Nitazoxanide and its active metabolite (Tizoxanide) inhibit the viral replication of various RNA and DNA viruses [67]. A Mexican randomized clinical trial (NCT04341493) is underway to compare nitazoxanide's efficacy with the combination of nitazoxanide and hydroxychloroquine in treating COVID-19 patients.

3.2.9. Ivermectin.

Ivermectin is an antiparasitic agent used widely to treat Strongyloides, scabies, and other parasitic infections [68]. Numerous *in-vivo* and *in-vitro* studies reported that ivermectin has antiviral activities against both RNA and DNA viruses [69]. Ivermectin inhibits the nuclear import of viral integrase protein and importin (IMP) α/β1 heterodimer resulting in antiviral response [70].

An *in-vitro* study done by Caly L *et al*. revealed that ivermectin produced a ~5000-fold reduction in viral RNA and inhibited the SARS-CoV-2 viral replication within 48 hours [71]. The antiviral efficacy of ivermectin against COVID-19 should be confirmed further by randomized controlled clinical trials [72].

3.2.10. Emetine.

Emetine is an antiprotozoal drug used to treat amoebiasis. The antiviral activities of emetine against RNA and DNA viruses were confirmed by previous studies [73]. An *in-vitro* study performed by Choy KT *et al*. demonstrated that emetine inhibited the viral replication of SARS-CoV-2. The combination of remdesivir and emetine produced synergistic inhibition [74].

3.2.11. Auranofin.

Auranofin is a gold compound that is used to treat rheumatoid arthritis. It inhibits Thioredoxin Reductase (TrxR), resulting in increased oxidative stress in central and transitional memory T cells (TCM and TTM), leading to the activation of redox-sensitive apoptosis pathways and cell death of TCM and TTM cells [75].

An *in-vitro* study carried out by Rothan HA *et al*. demonstrated that at low micromolar concentration, auranofin inhibited the viral replication of SARS-CoV-2 and the reduction of cytokines expression in human cells [76]. Pre-clinical and clinical studies could further confirm the safety and efficacy auranofin for the management of SARS-COV-2.

4. Conclusions

Many repurposed drugs are currently being used in the management of COVID-19 patients apart from their approved indications. At this point, no medicine is recommended by WHO to treat patients with COVID-19, except the repurposed drugs. The SARS-CoV-2 infection could be managed by drugs inhibiting the viral entry and viral fusion like Umifenovir, Baricitinib, Camostat mesylate, and Nafamostat mesylate, the drugs stopping the viral replication such as Favipiravir, Remdesivir, Lopinavir/ritonavir, Ribavirin, Sofosbuvir and Chloroquine, Hydroxychloroquine, and by some of the investigational drugs including Nitazoxanide, Ivermectin, Emetine, and Auranofin. Currently, more than 2000 clinical trials are underway to illustrate the safety and efficacy of the therapies used to manage COVID-19 patients.

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Conflicts of Interest

The authors declare no conflict of interest.

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