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Repurposing of FDA approved drugs as COVID-19 therapeutics: Safety concerns and contraindications of drugs in clinical trials

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Abstract

Coronavirus disease (COVID-19) is the current global public health threat with no specific, effective, and approved treatment available till date. The outbreak of COVID-19 has led the world into an unimagined and uncertain situation by disrupting the economies, claiming human lives, and leaving many into secondary mental health problems. As per the latest WHO report, approximately 8.2 million people are infected, and nearly 0.44 million lives are lost to COVID. The infection has spread to over 200 countries and territories around the world. The world is in search of efficient diagnostics and therapeutics, including vaccines, biologics and drugs. With the rapid increase in rates of infection and time constraints, drug repurposing seems to be a potential and viable option to find the promising anti-COVID therapeutics. In the wake of a rapid increase in the number of clinical trials involving drugs for repurposing, we aim to provide information on the safety concerns related to the drugs currently investigated in trials. This review also highlights the possible mechanisms of actions, adverse drug reactions, and contraindications of the drugs under repurposing evaluation.

Keywords: Adverse drug reactions, Anti-COVID drugs, Coronavirus, Drug repurposing, Drug toxicity, Pharmacotherapy.

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1. Introduction

On 31 Dec 2019 World Health Organization (WHO) was informed about the cluster of pneumonia cases of unknown causes detected in Wuhan city, Hubei province, in China. On 11 March 2020, WHO announced COVID-19, a global pandemic, the first such declaration since calling H1N1 a 2009 pandemic [1]. Novel coronavirus or SARS-CoV-2 (severe acute respiratory syndrome) outbreak has recently been referred to as Coronavirus disease-2019 (COVID-19) by the WHO. On the contrary, the current outbreak is caused by a different and mutated strain of coronavirus as that of SARS or middle east respiratory syndrome (MERS) [2]. In humans, coronaviruses cause infections of the respiratory tract and can range from moderate to fatal. Mild diseases include some common cold cases (which have other possible causes, often rhinoviruses), while more deadly variants can cause SARS, MERS, and COVID-19.

As per the latest WHO situation report on COVID-19 pandemic released on 22 April 2020, COVID-19 has infected around 8.2 million people and claimed 0.44 million deaths in over 200 countries and territories around the world [3] with a case fatality rate ranging from 4.3% to 11% [4]. Furthermore, the data suggests that the infection is spreading at alarming rates around the globe. The affected countries and territories have taken various measures to contain the spread of the COVID-19, such as the closure of business, restrictions on travel, and mass gatherings. In contrast, the largely affected countries enforced a nationwide lockdown. Furthermore, governments and health institutions also encouraging people to practice personal hygiene and social distancing. The symptoms of COVID-19 include dry cough, headache, diarrhea, tiredness, nasal congestion, sore throat, and inability to breathe [5]. People with COVID-19 symptoms are quarantined, and treated in COVID dedicated health facilities. About 80% of the infected people recover and need no special treatment. Erstwhile, the elderly and people with pre-existing health conditions such as diabetes, heart problems, hypertension, and obesity are more likely to develop serious illness and may be admitted to emergency health services to get proper medical care.

At present, there is no specific medicine or vaccine for COVID-19, and no medicines or vaccines have been fully tested for safety and efficacy. Nonetheless, antiviral therapy is mainly used as symptomatic and supportive treatment according to the clinical condition of the patient [6,7]. Other supportive treatments include oxygen therapy, hydration, fever/pain control, and antibiotics in the presence of bacterial co-infection. However, there is very little evidence on the effectiveness of drugs currently used in an emergency or intensive care unit (ICU) wards of COVID-19 patients. In the wake of the increasing number of infections, research groups from vivid backgrounds are actively working on the development of various therapeutic strategies including identification of

novel drug molecules [8–10], repurposing of existing and FDA approved drugs [11–13], and design and development of vaccines [14]to treat and prevent the COVID-19. The time required for drug discovery programs to develop, evaluate, and obtain approval for a new potent anti-COVID-19 agent could take more than ten years. In the present scenario, the development of a new therapeutic agent for COVID-19 is not a feasible option concerning the urgency of the situation. Therefore, drug repositioning of existing medicines looks to be the best option due to their availability, well-known pharmacokinetics, pharmacodynamics, and adverse effects.

Currently, nearly 1200 clinical trials involving COVID therapeutic interventions are registered with clinical trials registry (https://clinicaltrials.gov/). Majority of clinical trials on the repurposing involve the use of drugs that are already approved by the united states food and drug administration (USFDA) for different indications. Despite the above-discussed advantages of drug repurposing, the researchers should also keep the patient safety in mind while treating them with these unproven therapeutics. The main objective of this review is to highlight and discuss the safety concerns related to the use of plausible COVID therapeutics, which are currently being investigated in different phases of clinical trials. This review is exclusively limited to chemical drugs and does not discuss other treatment options such as vaccines, monoclonal antibodies (immunotherapy), and plasma therapy.

2. Literature resources

A literature review was performed using PubMed, Google Scholar and various preprint servers to identify relevant articles published since the beginning of the year 2020. Keywords included coronavirus, 2019-nCoV, SARS-CoV-2, SARS-CoV, and COVID-19 in combination with treatment/therapeutics and pharmacology. The data and information about clinical trials involving the drugs for repurposing were extracted from https://clinicaltrials.gov/. Standard drug monographs and pharmacology books [15] were referred for the information on indications, and contraindications. Whereas the drug-specific adverse drug reactions acquired from VigiAccess (http://www.vigiaccess.org/) database.

3. Potential drug targets of COVID-19

Human Coronaviruses (HCoV) are positive-sense, 30 kB long, single-stranded RNA viruses. HCoVs contain two groups of proteins, which include structural proteins, such as Spike (S) protein which play a significant role in the endocytosis of the virus into the host cell and non-structural proteins, such as proteases (nsp3 and nsp5) and RNA-dependent RNA polymerase (RdRp or nsp12) [16]. RdRp is a crucial viral enzyme in the life cycle of RNA viruses; hence, these proteins are targeted in various viral infections, including the hepatitis C virus (HCV), the Zika virus (ZIKV), and coronaviruses (CoVs) [16,17]. Moreover, SARS-CoV-2 also contains proteases such as

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main protease (M^{pro}) and papain-like protease (PLP or PL^{pro}), which play a crucial role during the attack on the host cell. Therefore, the structural and non-structural proteins, as well as the proteases, can serve as the COVID drug targets to hamper the viral infection, replication, and transmission [18].

4. Drug under repurposing

4.1. Antiviral agents

At present, the antivirals and anti-HIV drugs seem to be on top of the repurposing list to manage the clinical symptoms and provide supportive care. Various studies involving virtual screening have reported the possible anti-COVID mechanisms of existing antiviral drugs [19,20]. Moreover, these drugs have been preferred by health professionals for the management of COVID in the emergency wards and were reported to be effective in the alleviation of viral symptoms. Based on these shreds of evidence, therapeutic options that could be evaluated and used for COVID-19 include molecules that have the ability to interfere with viral entry, replication, and release of the viral particles from the host cell. Antivirals possibly exert their anti-COVID action via inhibition of different CoV proteins and enzymes such as spike protein (umifenovir), non-structural protein (danoprevir), RNA dependent RNA polymerase inhibition (RdRp) (ribavirin, remdesivir & tenofovir), Inosine-5'-monophosphate dehydrogenase (ribavirin), main protease (lopinavir & ritonavir), papain-like protease, neuraminidase (oseltamivir), and 3–chymotrypsin-like protease (lopinavir), as well as nucleotide synthesis inhibition (remdesivir, favipiravir & emtricitabine) [19,21]. Amidst the limited and contradictory reports on the clinical efficacy of the remdesivir, the USFDA has approved its emergency use against COVID [22].

The most common unwanted effects of antiviral drugs include gastrointestinal disturbances (e.g., nausea, vomiting, abdominal pain), blood disorders (sometimes anaemia or neutropenia), and CNS effects (e.g., insomnia, dizziness, headache) and hypersensitivity reactions. However, each antiviral drug may produce some specific adverse effects, as listed in table 1. Antivirals should not be given to drug-sensitive patients as these drugs known to cause serious anaphylactic reactions [15]. Due to some contraindications of antivirals (Table 1), special care should be taken while these drugs are administered to special populations such as children, pregnant women, and geriatric patients suffering from COVID-19.

4.2. Antiparasitic drugs

Preliminary studies on the evaluation of antiparasitic drugs for their anti-COVID properties turned out to be interesting and beneficial. They are also being pursued repurposing and involved in various clinical trials [23,24].

Notably, there are more than one hundred ongoing clinical trials are registered to evaluate the anti-COVID potential of hydroxychloroquine [25]. Antiparasitic antimalarial drugs are the most explored drugs for drug repurposing after antivirals due to their ability to interfere with various pathways involved in coronavirus infection and immunomodulatory properties [26,27]. The possible mechanisms of action of antiparasitic drugs including prevention of viral entry (chloroquine & hydroxychloroquine) [28], inhibition of non-structural proteins (mefloquine), endoribonuclease inhibition (mefloquine), blocking the post-translational viral maturation (nitazoxanide), inhibiting CoV main protease (niclosamide), inhibition of importin α/β1-mediated nuclear import of viral proteins (ivermectin), and inhibition of CoV papain-like protease (levamisole) [24,29].

Adverse drug reactions are as important as their beneficial effects while choosing for any kind of pharmacotherapy, and antiparasitic drugs are no exception. Well-known adverse effects of these pharmacological agents include gastrointestinal disturbances (e.g., nausea, vomiting, abdominal pain), hypersensitivity reactions, and blood-related adverse events [15,30]. As these drugs remain for a longer period in the body, the side effects such as Stevens-Johnson syndrome, and encephalopathy associated with antiparasitic use should be noticed carefully. The use of chloroquine and hydroxychloroquine should be avoided in COVID patients with existing heart conditions. On the other hand, the use of mefloquine in patients with existing psychiatric issues and depression (Table 2).

4.3. Antimicrobial drugs

Antimicrobials and antibiotics are widely used drugs for the treatment of microbial infectious diseases caused by bacteria, viruses, and protozoan parasites. In general, most of the antimicrobials are known to be less effective or ineffective against viral infections. Still, the need for promising anti-COVID therapeutics made the researchers revisit the antimicrobial agents and evaluate them for their antiviral properties. Very few antimicrobial drugs were found to be beneficial against the COVID-19 employing preliminary *in silico*, and *in vitro* screening [31]. These antimicrobial drugs were found to exert their anti-COVID effects by preventing the viral entry (Povidone-iodine) or by inhibition of CoV main protease (Azithromycin & Atovaquone) or by interfering with viral replication pathways (Nitazoxanide). Povidone-iodine (PI) is one of the widely used disinfectants in the hospital set-up. Reports suggest that gargling with PI for 3-4 times a day will reduce the transmission of the virus from infected patients to healthy people [32]. Whereas, azithromycin and atovaquone found were to inhibit the CoV main protease, which cuts the polyproteins translated from viral RNA to yield functional viral proteins [33]. Nitazoxanide, on the other hand, believed to interfere with viral replication pathways.

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Antimicrobials are well known for their skin (anaphylaxis, pruritus & urticaria), GI (irritation, and abdominal pain), blood-related adverse events. Furthermore, dose-dependent hepato-renal toxicities and antimicrobial resistance are associated with their inappropriate clinical use. Antimicrobial agents such as azithromycin administration may cause QT-interval prolongation and palpitations, whereas, the chronic use of nitazoxanide may lead to tachycardia (Table 3). Moreover, the use of drugs in COVID patients with pre-existing conditions related to liver, kidney, and heart should be strictly monitored or ceased, if needed (Table 3) [15,30].

4.4. Immunosuppressants

It could be possible that the hyperactivation of the immune system in COVID patients is responsible for the severe damages caused by SARS-CoV-2 infection [34]. Comorbid cardiometabolic health conditions (diabetes, hypertension, obesity, and heart ailment) in conjunction with the hyperactive immune system among multiple organ systems may exaggerate the mortality among the COVID patients [35,36]. Immunosuppression, through several cytokine axes, seems to have improved the well-being of CoV infected people in the clinical set-up. These drugs are well-known to exert their immunosuppressant actions via their anti-inflammatory abilities by reduction of cytokine secretion that essential for recruitment and differentiation of different immune cells. Immunosuppressants are known to act via different mechanisms such as inhibition of T-lymphocyte recruitment (sirolimus), Inhibition of Calcineurin/IL-2/T-lymphocyte production pathway (tacrolimus) [37], and reducing the systemic IL-2, IL-6, IL-10, and tumor necrosis factor-α (TNFα) levels (thalidomide) [38].

However, the immunosuppressants at therapeutic doses may exert adverse effects, including skin rashes, GI disturbances, fluid accumulation, negative neurological effects (confusions and insomnia), blood, and blood vessel-related effects. Furthermore, the chronic administration of these agents may lead to some serious side effects such as myocardial infarction, liver, and kidney damage. Thalidomide, a well-known teratogen and use of which may lead to some life-threatening side effects such as opportunistic infections (pneumonia), congestive heart disease, renal failure, pulmonary embolism, and may even lead to coma. On the other hand, the use of immunosuppressants is contraindicated in immunocompromised patients, pregnancy, and people who are already suffering from any major organ failure (Table 4).

4.5. Corticosteroids or Steroidal anti-inflammatory drugs

Corticosteroids are considered lifesaving drugs and used in the treatment of health conditions such as bronchial asthma, chronic obstructive pulmonary disease (COPD), and various autoimmune disorders (e.g., rheumatoid arthritis). Corticosteroids produce their beneficial health effects via their anti-inflammatory and

immunomodulatory properties; hence they are also known as steroidal anti-inflammatory drugs. Nevertheless, the hyperactive host immune system is the primary target of these drugs. The corticosteroids mainly act by reducing the cytokine secretion from the infected host cells (dexamethasone, budesonide & hydrocortisone), or by inhibition of cyclooxygenase (COX)–2 synthesis (methylprednisolone), or by anti-inflammatory cum antioxidant properties to prevent the pulmonary interstitial fibrosis (prednisone) [39]. However, the pleiotropic modes of action of corticosteroids may be one of the important reasons behind their repurposing.

Corticosteroids are known to act by multiple mechanisms and can produce side effects at an even greater magnitude. However, the noteworthy side effects include Cushing's syndrome, osteoporosis, acute adrenal insufficiency, hyperglycemia, depression, atrial fibrillation, acute kidney injury, and opportunistic fungal infections [15,30]. The contraindications are always looked forward to prior to their administration to patients with underlying conditions osteoporosis, cerebral palsy, acute respiratory distress syndrome, less active immune system, prior tuberculosis, and pregnant women (Table 5) [40].

4.6 Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are one of the most commonly prescribed classes of medication for the management of pain and inflammation. These drugs fundamentally modulate the immune system through their anti-inflammatory properties, mainly by inhibiting the cyclooxygenases (COX-1/2), enzymes that regulate the synthesis of prostaglandins, and other prostanoids, such as thromboxanes [15]. Duet to the physiological roles of COX-2 (inflammation, pain, and fever) and COX-1 (platelet aggregation), COX-1/2 inhibitors are thought to be promising drugs for the treatment of COVID. The NSAIDs are considered safe as compared to steroidal anti-inflammatory drugs. However, these drugs are used to provide symptomatic relief to the patients but not specific therapeutic options of COVID [41,42]. The NSAID drug, which is currently under trials, mainly acts by inhibition of platelet aggregation (aspirin, enoxaparin, tinzaparin, and defibrotide) via inhibition of COX-1 or by reducing the inflammation through inhibition of COX-2 (Ibuprofen, dexmedetomidin and formeterol).

The well-recorded adverse effects of NSAIDs include gastric irritation, Reyes Syndrome in children, respiratory and metabolic acidosis, anaphylactic shock, liver damage, hypertension, and renal impairment. On the other hand, anti-coagulant anti-inflammatory heparin analogues may lead to hemorrhage across multiple organ systems (Table 6). NSAIDs under trials for drug repurposing are diversely contraindicated in special populations such as children, pregnant women, people suffering from cardiac ailments, hepato-renal failure, and bone marrow depression (Table 6).

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4.7 Protein kinase inhibitors

kinases have been identified as important drug targets for treating different forms of human ailments such as cancer, autoimmune and inflammatory diseases because of their (kinases) crucial role in signal transduction and control of different cellular functions [43]. Besides, recent studies on the evaluation of the anti-COVID potential of protein kinase inhibitors have suggested that the kinase inhibitors may offer benefits against CoV infection. Numerous virtual screening and *in vitro* studies have stated that these drugs might be able to prevent the viral entry into the host cell via inhibition of CoV main protease/type-II transmembrane serine protease or by inhibiting the Janus kinase (JAK½) or Serine/threonine (MARK1) kinase (Table 6) [44–46]. Based on the available pieces of evidence, these protein kinase inhibitors are taken up for drug repurposing and are also being investigated in clinical trials.

Anaemia, thrombocytopenia, splenomegaly, hepatomegaly, atrial fibrillation, hypersensitivity, opportunistic infections, pain in extremity, memory impairment, insomnia, depression, and haemorrhage are the key adverse drug reactions associated with the use of protein kinase inhibitors. Further, drug resistance with these drugs is also a concern but uncommon. The use of kinase inhibitors is strictly contraindicated in patients with underlying *Mycobacterium* (Tuberculosis) infection, hypertension, vital organ failure (liver or kidney), and hypersensitivity to the drug (Table 7).

4.8. Other drugs

In addition to various classes of drugs discussed above, this section includes other drugs that are capable of alleviating the clinical symptoms of COVID that are currently under various clinical trials. All these drug acts by different mechanisms of action which include, decreasing the availability of the ACE-2 receptors for the CoV (Losartan &Valsartan) [47,48], inhibition of viral main protease (Fluvoxamine, Simvastatin) [49,50], DPP-4 inhibition, which is a functional receptor of CoV in humans and prevents the viral penetration into host cells (Linagliptin) [51], anti-inflammatory action (Pyridostigmine), or by facilitating the vasodilation via increasing the nitric oxide (NO) release (Sildenafil) [52], thereby decreasing pulmonary artery pressure. Although no anti-COVID mechanism of spironolactone is discovered, yet it can be used as a replacement of angiotensin receptor blockers in hypertensive patients as it doesn't lead to the overexpression of ACE-2 receptors in the lungs.

The drugs are known to cause a wide range of ADR ranging from most common gastrointestinal (GI irritation and bleeding), dermatological (anaphylaxis, urticaria, and rashes), and neuropsychiatric (dizziness, headache, insomnia, suicidal tendencies) to serious side effects such as visual impairment, bradycardia, myocardial

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infarction, kidney damage, angioedema, and hypotension (see Table 8 for detailed information on drug-specific ADR). Information on contraindications related to the use of these drugs in special populations and health conditions should be considered before commencing the treatment (Table 8).

Conclusions

Management of the current COVID pandemic is the immediate need of the hour and requires fast-track solutions to prevent the spread of the infection and treatment of the already infected. Many public and private funded organizations are rigorously working to find potential solutions, and drug repurposing is one of them. The existing evidence does not provide conclusive evidence for or against the use of the drugs discussed in this review for the treatment of COVID-19. However, there appears to be some evidence that these drugs may be beneficial if used with precautions and necessary care. Hence, the pharmacological management of COVID should be carefully assessed and monitored for their compatibility with patient populations in terms of adverse effects and contraindications before their use in any given clinical set-up, including emergency wards or critical care units.

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Author contributions

RND, MD, SK, PB, and NR done the literature search and drafted the initial manuscript. All the authors were involved in reviewing and revising the manuscript.

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Table legends

Table 1. List of antivirals in repurposing trials against COVID-19; their mechanism(s) of action, adverse drug reactions, and contraindications.

Table 2. List of antimalarial and antiparasitic drugs in clinical trials against COVID-19; their mechanism(s) of action, adverse drug reactions, and contraindications.

Table 3. List of antimicrobial agents in clinical trials against COVID-19; their mechanism(s) of action, adverse drug reactions, and contraindications.

Table 4. List of immunosuppressant drugs in clinical trials against COVID-19; their mechanism(s) of action, adverse drug reactions, and contraindications.

Table 5. List of corticosteroids in clinical trials against COVID-19; their mechanism(s) of action, adverse drug reactions, and contraindications.

Table 6. Anti-inflammatory drugs in clinical trials against COVID-19; their mechanism(s) of action, adverse drug reactions, and contraindications.

Table 7. List of protein kinase inhibitor drugs in clinical trials against COVID-19; their mechanism(s) of action, adverse drug reactions, and contraindications.

Table 8. Other drugs for symptomatic/supportive therapy in clinical trials against COVID-19; their mechanism(s) of action, adverse drug reactions, and contraindications.

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Table 1. List of antivirals in repurposing trials against COVID-19; their mechanism(s) of action, adverse drug reactions, and contraindications.

Drug candidate - No. of Ongoing clinical trials	**Target & MoA against COVID-19**	**Adverse drug reactions**	**Contraindications/Special populations**	**Current indications**
Ribavirin-9	Inhibition of RNA dependent RNA polymerase inhibition (RdRp)[53,54]. Inhibition of Inosine-5'-monophosphate dehydrogenase (IMPDH) [55].	Dyspnoea, abdominal pain, thrombocytopenia, neutropenia, leukopenia, pancytopenia, palpitations, myocardial infarction, fatigue, pyrexia, asthenia, vomiting, chills.	Pregnancy, unstable cardiac issues, hemoglobinopathies, autoimmune diseases.	Viral infections such as respiratory syncytial virus (RSV), hepatitis C, viral hemorrhagic fevers
Remdesivir-35	Inhibition of RdRp [53,56]. Blocks viral nucleotide synthesis to stop viral replication [54,57,58].	Elevated transaminases (reversible), kidney injury Probable: acute respiratory distress syndrome, anaemia.	Severe renal impairment.	Ebola virus infection
Tenofovir-2	Inhibition of RdRp [53].	Dyspepsia, skin rashes, renal failure, anxiety, dizziness, decreased appetite, muscle weakness	Hypersensitive to drug, lactic acidosis and severe hepatomegaly.	Anti-HIV
Lopinavir-76	Inhibits 3–chymotrypsin-like protease (3CLpro) [54,57] and Main protease (Mpro) [56].	Pancreatitis, hepatotoxicity, cardiac conduction abnormalities.	Pregnancy, co-administration with potent CYP450 3A Inducers.	Anti-HIV
Ritonavir-78	Inhibits Mpro [56].	Pancreatitis, hepatotoxicity, jaundice, rashes, hyperbilirubinemia, acute kidney injury, hypertriglyceridemia, hyperlipidaemia, Hypercholesterolemia.	Pregnancy, HBV/HCV co-infection, cardiomyopathy, diabetes mellitus.	Anti-HIV
Favipiravir (Favilavir)-25	Purine analog that acts as an alternate substrate leading to inaccurate viral RNA synthesis [57].	Hyperuricemia, elevated transaminases, reduction in neutrophil count. suspected teratogenicity.	Contraindicated during pregnancy & lactating mother.	Ebola virus infection
Umifenovir-8 (FDA approval pending)	Targets S-protein/ACE2 receptor interaction and prevents the viral entry to the target cell [57,59].	Allergic reactions, angioedema, gastrointestinal upset, liver damage.	Hypersensitive to drug, children <2 years of age (increased sensitivity).	Influenza infections
Emtricitabine-2	Emtricitabine is a cytidine analog that competes with deoxycytidine 5'-triphosphate for CoV reverse transcriptase.	Hypersensitivity, acute renal damage, hepatomegaly with steatosis, lactic acidosis.	Pregnancy, lactation period, existing co-infection of hepatitis-HIV.	Anti-HIV
Danoprevir-2	Inhibition of non-structural protein (NS3-4A) protease inhibitor [60].	Blood and lymphatic system disorders, cardiac disorders, gastrointestinal disorders.	Liver disorders	Anti-HCV
Oseltamivir-17	Inhibits neuraminidase enzyme that helps the release of viral replicates from the host cells [8,61].	Severe hypersensitivity reactions, hallucination, abnormal behavior, insomnia, blood, and lymphatic system disorders, dysrhythmia.	Stevens-Johnson Syndrome, epidermal necrolysis, erythema multiforme.	Influenza A & B infections

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Table 2. List of antimalarial and antiparasitic drugs in clinical trials against COVID-19; their mechanism(s) of action, adverse drug reactions, and contraindications.

Drug candidate -No. of Ongoing clinical trials	**Target & MoA against COVID-19**	**Adverse drug reactions**	**Contraindications/Special populations**	**Current indications**
Chloroquine-76	Elevates the endosomal pH and interfere with ACE2 glycosylation to prevent viral fusion [57] and inhibits SARS-CoV-2 papain-like protease (PLP) [62]. Also exerts reduces COVID-induced inflammation [56].	Macular degeneration, tinnitus, QT prolongation, hematologic effects (g6pd deficiency), hypoglycemia, hepatitis, retinal toxicity, neuropsychiatric side effects.	Pregnancy, hypersensitivity to chloroquine, Patients suffering from retinal or visual impairment.	Antimalarial and Extraintestinal amebiasis.
Hydroxychloroquine-222	Similar to Choloroquine.	Alopecia, urticaria, anaphylaxis, visual impairment, cardiomyopathy, palpitations, rheumatoid arthritis, arthralgia, joint swelling, hypoglycemia.	Hypersensitive to drug, should not be given along with drugs causing QT prolongation.	Antimalarial
Mefloquine-1	Main protease, non-structural protein (NSP-15) and endoribonuclease inhibition [10].	Decreased appetite, vomiting, vertigo, tinnitus, skin rashes, anxiety, depression, insomnia, nightmares, hallucinations, agitation, palpitations, tachycardia.	Chemoprophylaxis, psychiatric disorders such as depression, anxiety, and psychosis.	Antimalarial
Nitazoxanide-12	Possible inhibition of viral protein expression by blocking the post-translational viral maturation and intracellular movement in addition to preventing protein implantation into the plasma membrane [20,57,63].	Nausea, diarrhea, GI reflux, chromaturia, anaphylaxis, Chromaturia, pruritus, rashes, urticaria, tachycardia, carcinogenesis, mutagenesis, fertility impairment.	Hypersensitive to drug.	Diarrhea caused by various helminthic, protozoal, and viral infections.
Niclosamide-3	Inhibition of CoV main protease [64,65], and ATP synthase [66].	Abdominal pain, nausea, skin rashes, urticaria, cardiac cyanosis.	Hypersensitive to drug.	Anti-helminthic.
Ivermectin-25	Inhibition of Importin α/β1-mediated nuclear import of viral proteins [20,67].	Headache, dizziness, pruritus, erythema, rashes. Rarely orthostatic hypotension, worsening of asthma, Stevens-Johnson syndrome.	Hypersensitive to drug, pregnancy.	Anti-parasitic agent for Strongyloidiasis.
Levamisole-3	Inhibition of SARS-CoV-2 PLP [62].	Headache, excessive salivation, lacrimation, dizziness, encephalopathy, leukopenia, agranulocytosis, hyperlipidaemia, skin rashes.	Hypersensitive to drug, liver failure, psoriatic arthropathy.	Anti-helminthic

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Table 3. List of antimicrobial drugs in clinical trials against COVID-19; their mechanism(s) of action, adverse drug reactions, and contraindications.

Drug candidate -No. of Ongoing clinical trials	**Target & MoA against COVID-19**	**Adverse drug reactions**	**Contraindications/Special populations**	**Current indications**
Azithromycin-95	Possible inhibition of CoV main protease [31].	Hypersensitivity, pruritus, urticaria, flushes, dizziness, headache, hypoaesthesia, decreased appetite, dehydration, QT-interval prolongation, palpitations, liver damage, acute renal damage.	Hypersensitive to drug, patients with impaired liver functioning.	Approved for respiratory, urogenital, dermal and other bacterial infections.
Povidone-Iodine-14	Inhibits the viral growth and viral attachment to cellular receptors and inhibition of viral release and spread from infected cells [32,68].	Rash, on-site irritation, hypersensitivity.	Hypersensitive to drug.	Approved for influenza A virus
Atovaquone-1	CoV main protease inhibition [50].	Neutropenia, methemoglobinemia, thrombocytopenia.	Cardiac disorders.	Antimicrobial (*Pneumocystis carinii*), Hematologic cancer, Malaria.

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Table 4. List of immunosuppressant drugs in clinical trials against COVID-19; their mechanism(s) of action, adverse drug reactions, and contraindications.

Drug candidate -No. of Ongoing clinical trials	**Target & MoA against COVID-19**	**Adverse drug reactions**	**Contraindications/Special populations**	**Current indications**
Sirolimus-4	Immunosuppression via inhibition of T-lymphocyte to counter the COVID-induced hyperinflammation [16].	Dehydration, pneumonitis, myocardial infarction, atrial fibrillation, pericardial effusion, arterial thrombosis, proteinuria, renal failure, increased risk of infections, impaired wound healing, fluid accumulation, obesity.	Hypersensitive to drug, Immunocompromised patients.	Prophylaxis therapy to prevent graft rejection.
Tacrolimus-2	Inhibition of immune responses by interfering with Calcineurin/IL-2/T-lymphocyte production pathway [69].	Respiratory failure, tremor, confusions, insomnia, anaemia, thrombotic microangiopathy, myocardial infarction, pyrexia, diabetes mellitus, hyperkalaemia, liver damage, kidney failure, increased risk of infections.	Pregnancy, hepatic failure, renal insufficiency. Children below 2 years of age, and immunocompromised patients.	Immunosuppressive drug to prevent graft rejection and acute dermatitis.
Thalidomide-5	Degradation of messenger RNA in blood cells and thus reduce IL-2, IL-6, IL-10, IFN-γ and tumour necrosis factor-α (TNF-α) and increases the IL-12 secretion that activates natural killer cells [38,70].	Constipation, dermatitis, congestive heart failure, myocardial infarction, bradycardia, dyspnoea, pulmonary embolism, anaemia, neutropenia, thrombocytopenia, peripheral neuropathy, dizziness, paraesthesia, delusions, renal failure, teratogenicity, death.	Pregnancy, and immunocompromised patients.	immunosuppressant and antiangiogenic.

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Table 5. List of corticosteroids in clinical trials against COVID-19; their mechanism(s) of action, adverse drug reactions, and contraindications.

Drug candidate -No. of Ongoing clinical trials	**Target & MoA against COVID-19**	**Adverse drug reactions**	**Contraindications/Special populations**	**Current indications**
Dexamethasone-12	Inflammatory modulation by reducing the cytokine secretion [71].	Anaphylaxis, pyrexia, reduction in platelet count, dizziness, neuropathy, insomnia, opportunistic infections, acute adrenal insufficiency, Cushing's syndrome, osteoporosis, hyperglycemia, muscle weakness, depression, euphoria, atrial fibrillation, acute kidney injury, hypotension, opportunistic fungal infections.	Pregnancy, pre-existing osteoporosis, cerebral palsy, acute respiratory distress syndrome, immunocompromised patients.	Anti-inflammatory and immunosuppressive for the treatment of asthma, arthritis, atopic dermatitis, contact dermatitis.
Hydrocortisone-7	Inflammatory modulation by reducing the cytokine secretion [71].	Hypokalaemia, hyperglycemia, hyponatremia, dizziness, headache, insomnia, anxiety, pruritus, rash, urticaria, acute adrenal insufficiency, flushing, hypotension.	Pregnancy, hypersensitive to drug, immunocompromised patients.	An anti-inflammatory drug used to treat ulcerative colitis, acute severe asthma.
Methylprednisolone-25	Reduction of inflammatory cytokine release in the lungs by suppressing the synthesis of cyclooxygenase (COX)-2 [56,72].	Tachycardia, palpitations, hypersensitivity, hyperglycemia, diabetes mellitus, osteonecrosis, arthralgia, headache, drowsiness, kidney injury, dyspnoea, increased fluid, and sodium retention.	Pregnancy, hypersensitive to drug, tuberculosis patients, immunocompromised patients.	anti-inflammatory immunosuppressant used during organ transplants.
Prednisone-5	Anti-inflammatory and antioxidant properties may prevent the pulmonary interstitial fibrosis [70].	Insomnia, confusion, anxiety, pneumonia, sepsis, anaemia, tachycardia, atrial fibrillation, adrenal insufficiency, blurred vision, hypersensitivity, hyperglycemia, diabetes mellitus, neuropathic pain, arthralgia, renal impairment, alopecia, hypertension.	Pregnancy, hypersensitive to drug, diabetic and immunocompromised patients.	Similar to Methylprednisolone.
Budesonide-8	Inflammatory modulation by reducing the cytokine secretion [73].	Anaphylaxis, insomnia, dizziness, tremor, dyspnoea, cough, asthma, palpitations, opportunistic candidiasis, muscle spasms, rashes, hypertension.	Hypersensitive to drug, immunocompromised patients.	Ulcerative colitis, liver cirrhosis, lung diseases, asthma allergic rhinitis.

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Table 6. Anti-inflammatory drugs in clinical trials against COVID-19; their mechanism(s) of action, adverse drug reactions, and contraindications.

Drug candidate -No. of Ongoing clinical trials	**Purpose & MoA against COVID-19**	**Adverse drug reactions**	**Contraindications/Special populations**	**Current indications**
Aspirin-8	Anti-inflammatory and via inhibition of platelet aggregation [74].	Gastric bleeding, dizziness, headache, tinnitus, respiratory and metabolic acidosis (high doses), post-viral encephalitis (Reyes syndrome) in children. Liver damage, renal insufficiency.	Should not be given along with anticoagulants such as Warfarin, as it may lead to excessive bleeding.	Non-steroidal anti-inflammatory drug (NSAID), Antiplatelet, Blood-thinning agent.
Ibuprofen-4	Anti-inflammatory activities by reversible inhibition of COX-1, weak inhibition of COX-2 [15].	Periorbital eye swelling, anaemia, palpitations, tinnitus, gastric bleeding, facial oedema, liver dysfunction, anaphylactic shock, suicidal attempts, renal impairment, dyspnoea, bronchospasm, rashes, angioedema, urticaria, hypertension, bone marrow depression.	Liver failure and hypertensive patients being treated with diuretics [15].	Anti-inflammatory and Antipyretic.
Enoxaparin-22 Tinzaparin-24	Pulmonary coagulopathy with ARDS in COVID patients is fatal. Prophylactic use of heparins will improve the blood oxygenation to reduce the mortality rate among COVID patients [75].	Thrombocytopenia, tachycardia, visual impairment, severe gastric hemorrhage, muscle hemorrhage, cerebral hemorrhage, headache, state of confusion, haematuria, acute kidney injury, pulmonary embolism, epistaxis, itching, rashes, hematoma, bleeding, opportunistic urinary tract infections, chest pain.	Pregnancy, Pre-existing thrombocytopenia, and Renal failure, Patients with impaired blood clotting. Should not be given along with anticoagulants, and platelet inhibitors [76].	Anti-inflammatory & Anticoagulant for the prophylaxis of deep vein thrombosis (DVT).
Defibrotide-2	Reduction of systemic inflammation to reduce progression of acute respiratory failure rate in patients [77].	Hemorrhage, hypotension, interstitial lung disease, cystitis hemorrhagic, renal failure, haematuria, gastrointestinal hemorrhage	Should be avoided with systemic anticoagulant or fibrinolytic therapy [78].	For the treatment of hepatic veno-occlusive disease (VOD).
Dexmedetomidine-5	Anti-inflammatory actions via inhibition of cytokine (IL-1B, IL-6, TNF-α, and NF-κB) release [79].	Bradycardia, hyperthermia, seizure, electrolyte imbalance, polyuria, agitation, respiratory depression, hypotension.	Bradycardia, Heart failure, and hypotension.	Selective α-2 (Auto receptor) agonist used in anaesthesia.
Formoterol-3	Inhibits the release of mast cells and TNF-alpha from monocytes and increase the mucous clearance.	Tremors, tachycardia, cardiac dysrhythmia, diarrhea, nausea, dry mouth, insomnia, nervousness, hypertension.	Coronary insufficiency, cardiac arrhythmias, and hypertension. Should calculate the risk to benefit ratio before its use during the pregnancy [80].	Adrenergic β-2 agonist for asthma.

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Table 7. List of protein kinase inhibitor drugs in clinical trials against COVID-19; their mechanism(s) of action, adverse drug reactions, and contraindications.

Drug candidate -No. of Ongoing clinical trials	**Target & MoA against COVID-19**	**Adverse drug reactions**	**Contraindications/Special populations**	**Current indications**
Imatinib-5	Inhibition of type-II transmembrane serine protease (TMSP2), and 6LU7, the main protease of CoV [64] to prevent the fusion virions with the endosomal membrane [44].	Anaemia, Thrombocytopenia, Cardiac failure, Opportunistic infections, Loss of appetite, Muscle spasms, Myalgia, Headache, Dizziness, Insomnia, Depression, Renal failure, Dyspnoea, Pleural effusion, Oedema, Hypertension, Skin rashes.	Use in patients with renal impairment and Hypertension should be carefully monitored [81].	Anticancer agent to for the treatment of chronic myeloid leukemia [15].
Nintedanib-1	Inhibits receptor tyrosine kinases (RTKs) to treat pulmonary fibrosis in COVID patients [45,46].	Fatigue, Myocardial infarction, Diarrhoea, Opportunistic infections, Loss of appetite, loss of weight, Headache, Dizziness, Dysgeusia, Dyspnoea, Rashes, Alopecia, Hypertension.	Pregnancy, moderate to severe hepatic impairment [82].	Idiopathic pulmonary fibrosis (IPF).
Ruxolitinib-18	Prevents the viral entry by the prevention of Clathrin/AP-2 associated protein Kinase 1 mediated endocytosis by JAK1/2 inhibition [83], Serine/threonine (MARK1) Protein kinase inhibitor [55].	Anaemia, Thrombocytopenia, Splenomegaly, Hepatomegaly, Atrial fibrillation, Hypersensitivity, Opportunistic infections, Pain in extremity, Dizziness, Headache, Memory impairment, Insomnia, Depression, Haemorrhage, Dyspnoea.	Patients infected with Mycobacterium (Tuberculosis).	Anti-inflammatory, anti-arthritic (Rheumatoid arthritis), Myelofibrosis.
Tofacitinib-4	Prevents the viral entry by the prevention of Clathrin/AP-2 associated protein Kinase 1 mediated endocytosis by JAK1/2 inhibition [83].	GI disturbances, Hypersensitivity, Weight gain, Rheumatoid arthritis, Skeletal muscle stiffness, Dizziness, Headache, Insomnia, Depression, Pollakiuria, Rash, Alopecia, Hypertension.	Patients infected with Mycobacterium (Tuberculosis).	Methotrexate tolerant Rheumatoid arthritis treatment and Myelofibrosis.
Baricitinib-15	Prevents the viral entry by the prevention of AP-2 associated protein Kinase 1 associated endocytosis by JAK1/2 inhibition [83].	Abdominal discomfort, Weight gain, Hypercholesterolemia, Rheumatoid arthritis, Dizziness, Headache, Deep vein thrombosis, Opportunistic bacterial infections.	Patients infected with Mycobacterium (Tuberculosis) [84].	Anti-inflammatory, anti-arthritic, Anti-myelofibrosis.

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Table 8. Other drugs for symptomatic/supportive therapy in clinical trials against COVID-19; their mechanism(s) of action, adverse drug reactions, and contraindications.

Drug candidate - No. of Ongoing clinical trials	**Purpose & MoA against COVID-19**	**Adverse drug reactions**	**Contraindications/Special populations**	**Current indications**
Losartan-14 & Valsartan-3	Blocking angiotensin receptor binding (ARB) will make ACE-2 occupied with the task of converting Angiotensin-I & II into angiotensin (1-7) thereby decreasing the availability of the ACE-2 receptors for the CoV [47,48].	Palpitations, Vertigo, Visual impairment, Nausea, Diarrhoea, Cough, Vomiting, Hyperkalaemia, Hyponatraemia, Dizziness, Headache, Insomnia, Suicidal tendencies, Kidney damage, Angioedema, Hypotension.	People with low blood pressure and impaired liver function.	AT2R blocker for hypertension and cardiac failure.
Fluvoxamine-1	Possible inhibition of CoV-2 main protease [49].	Loss of libido, Failure of orgasm, Galactorrhoea, increased suicidal tendencies, Excitement, Insomnia, Aggression, Weight gain.	Children below 18 years of age, Shouldn't be given to patients already taking monoamine oxidase (MAO) inhibitor antidepressants, the combination may lead to "Serotonin syndrome (Tremors, hyperthermia & Cardiovascular collapse)".	Selective serotonin reuptake inhibitor (SSRI) as an antidepressant.
Linagliptin-2	DPP-4 is a functional receptor of CoV in humans. DPP-4 inhibition will reduce viral penetration into the cells [51].	Pancreatitis, Blurred vision, Hypoglycaemia, Loss of appetite, Dizziness, Insomnia, Confusion, Pemphigoid (Blisters & Rashes on the skin and mucous membrane).	Patients with diabetic ketoacidosis, Hypersensitivity conditions. Diabetic patients under other hypoglycaemic agents should be monitored carefully.	DPP4 inhibitor as antidiabetic.
Pyridostigmine-1	Probable anti-inflammatory action via reducing the IL-6 levels (https://clinicaltrials.gov, 2020).	Bradycardia, Blurred vision, Excessive sweating (Hyperhidrosis) and salivation, Hypotension, May exacerbate asthma.	Patients with renal failure should be critically monitored in asthmatic patients.	Cholinesterase inhibitor for the treatment of Myasthenia gravis.
Simvastatin-3	Possible inhibition of CoV-2 main protease [50] anti-inflammatory effects [86].	Myotoxicity, myopathies and rarely rhabdomyolysis, angioedema [86].	Patients with comorbid Liver and kidney impairments [86].	HMGA CoA reductase inhibitor for the treatment of hypercholesterolemia & Hypertriglyceridemia.
Sildenafil-1	Via vasodilation by activation of nitric oxide (NO) release, thereby decreasing pulmonary artery pressure and, as a result, lower pulmonary capillary hydrostatic pressure [52].	Hypotension, flushing, headache, Visual disturbances, Myocardial infarction.	Should not be used in patients with "Retinal degenerative diseases."	PDE-5 Inhibitor for erectly dysfunction and pulmonary hypertension treatment.
Spironolactone-3	As a replacement of angiotensin receptor blockers in hypertensive patients. As it doesn't lead to the overexpression of ACE-2 receptors in the lungs [87].	GI upset, Gynaecomastia, Testicular atrophy, Bradycardia, Hyperkalaemia, Hyponatraemia, Dehydration, Orthostatic hypotension.	Potassium supplements should be stopped, Continuous monitoring of electrolytes and creatinine in patients with renal failure.	Potassium-sparing antidiuretic for the treatment of hypertension.