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Comprehensive Review on the Various Therapy Endeavored Against Coronavirus Disease 2019 (COVID-19)

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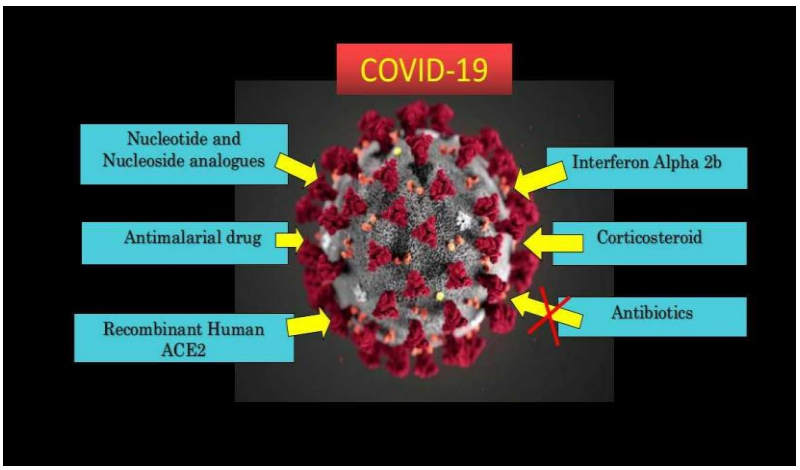
ABSTRACT

The novel Coronavirus Disease (COVID-19) also known as Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) has transpired as a new pandemic, threatening the world. The finding of a new drug or vaccine would considerably take a long duration of time. Hence the possible drug therapy includes re-purposed already existing drugs against different ailments. There are no guaranteed solutions to ensure the spread of infectious diseases, before they reach densely populated areas. But we need to have cost-effective ways of widening the scope of its cure. This review highlights the various re-modified uses of the already existing xenobiotic for therapy of COVID-19 and explains their plausible mechanism on the new virus.

Keywords: Coronavirus Disease 2019, Severe acute respiratory syndrome coronavirus 2, World Health Organization



Graphical Abstract

INTRODUCTION

In December 2019, Wuhan, China witnessed a new unknown outbreak of pneumonia, Severe Acute Respiratory Syndrome named Coronavirus 2 (SARS-CoV-2), caught limelight of the entire globe. The novel beta form with SARS-CoV-2 is coined as Coronavirus Disease 2019 (COVID-19). There were 118,000 cases, over 4,000 mortality, hence the World Health Organization (WHO) announced COVID-19 as a state of pandemic on 12th March 2020 [1].

As of 12 March, 2020, data from the WHO shows 1, 53,517 active cases have been identified in 32 countries/regions, with maximum cases being detected in China followed by Italy and the United States taking the lead. The International Committee on Taxonomy of Viruses (ICTV) called this new virus as SARS-CoV-2 and the disease as COVID-19 [2]. The virus being zoonotic, is transmitted between wild animals and humans.

Diagnosis is carried out by identification of the virus in the mucosal secretions by laboratory tests. Diagnostic findings include rise in C - reactive protein (CRP) and low leukocyte counts. A tomographic chest scan aids to identify cases with no symptoms or mild disease. Prevention measures include home quarantine of qualmed individuals and people with mild illnesses, followed by strict preventive measures including wearing masks to avoid person to person spread [3].

Prevention is crucial as there are no approved vaccines for this infection. All medical practitioners should have a track on the recent developments and strategies followed to combat the disease. The unique characteristics of the COVID-19 virus make deterrence difficult like the infectivity before onset of symptoms in the incubation period, general features of the disease, prolonged incubation phase, diathesis for mucosal surfaces such as the conjunctiva, saliva and nasal droplets, duration of the diseases and transmission despite of symptomatic cure [4].

Aside from already existing drugs, scientists are also looking to formulate new medications specifically for COVID-19. The process may take longer but it's a testament to how the medical experts are unstoppable in their desire to find the cure. For now, people's only protection against the virus includes strengthening the immune system, frequent hand washing, and wearing a protective mask when sick [5].

The common signs and symptoms include respiratory symptoms, high fever, cough, and dyspnea. In more critical cases, infectivity can lead to severe acute respiratory syndrome, renal failure, pneumonia and even mortality [6].

The possible drug therapy for this COVID-19 includes the re-purposed already existing drugs against different ailments. In this work, we have tried to compile the various xenobiotic pragmatic for the treatment of the new COVID-19 infections.

Modes of transmission

Being a respiratory infection COVID-19 is assumed to be transmitted by means of droplets which is referred elicited from the particle sizes as either Respiratory droplets having diameter >5-10 μm or droplet nuclei with a diameter of <5μm. The infection is supremely transmitted through droplet transmission, referred as human-to human transmission via sneezing, coughing or taking. The next prominent route of transmission is the gastrointestinal tract. According to the report by Huang et al. anal swabs samples collected from infected family member's unveiled positive for COVID infection [7,8].

The mode of spread of infection could either direct or indirect Figure 1. The direct mode includes Transmission through droplets, feco-oral secretions, lacrimal secretions, sputum, semen, and mother to fetus could be categorized as direct mode. Transmission with aid of a vehicle like towel, money, clothing, dishes, books or toys etc. could be indirect mode of transmission. Underrating any of this mode could lead to spread of infection [9].

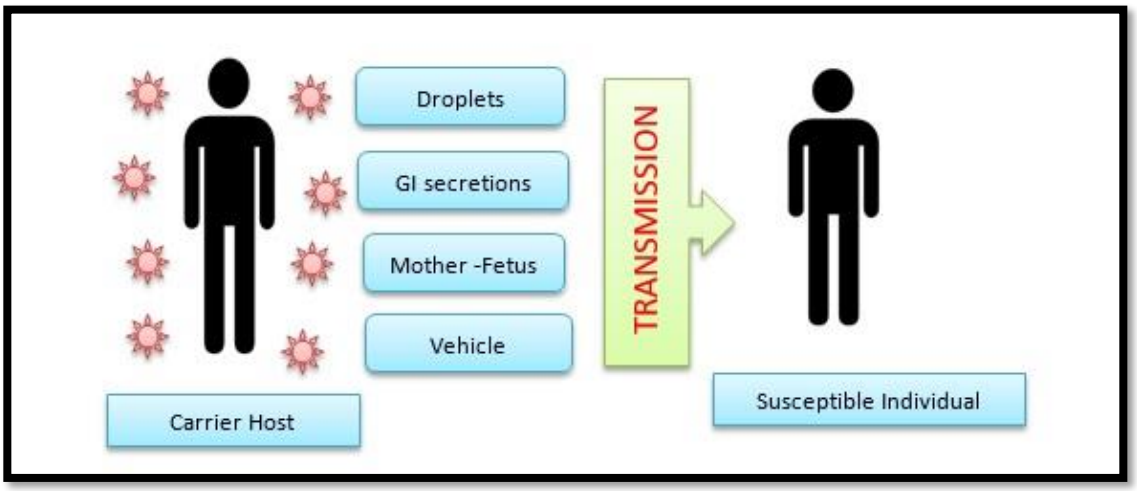


Figure 1: Mode of Transmission.

Potential drugs to treat COVID-19 infections

1. Nucleotide and nucleoside analogues inhibitors
2. Antimalarial drug
3. Angiotensin-converting enzyme 2 (ACE2)
4. Interferon Alpha 2b

5. Corticosteroid therapy
6. Antibiotics

Nucleoside analogues

Remdesivir

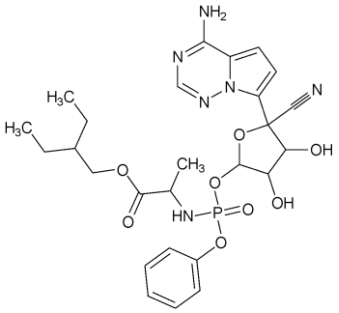


Figure 1: Remdesivir.

Remdesivir (Figure 1), befittingly familiar as GS-5734, a monophosphate prodrug encounters rapid metabolism to the active C-adenosine nucleoside triphosphate analogue. It gets incorporated into the viral RNA inhibits viral RNA polymerases and leads to initial chain termination.

Being a broad-spectrum antiviral, Remdesivir has activity against virus families, including filoviruses, paramyxoviruses, pneumoviruses, and coronaviruses. It has propitious potential therapy for COVID-19 owing to its broad-spectrum and potent in vitro activity. The safety and efficacy of Remdesivir for the treatment of COVID-19 are being evaluated in multiple ongoing Phase III clinical trials by Gilead Science [10].

Various clinical trials conducted on COVID patients with acute respiratory syndrome shows that remdesivir can act as an effective candidate for the treatment [11]. The Food and Drug Administration (FDA) on May 1, 2020, issued an Emergency Use Authorization (EUA) for remdesivir. Although the FDA has not commented that it had authorized remdesivir for the therapy of COVID-19 but the intention was to make the access of the drug more facile for the medical team and make it available for patients with severe symptoms. The FDA further revamped the EUA so that remdesivir could be utilized by maximum patients hospitalized with COVID-19 [12].

Nitazoxanide

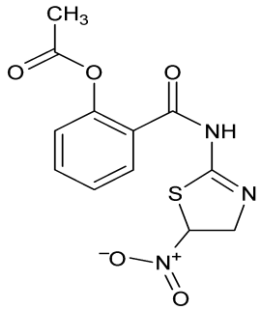


Figure 2: Nitazoxanide

Nitazoxanide (Figure 2), consistently used as an anthelmintic agent, is an orally active nitrothiazoyl-salicylamide broad-spectrum antiprotozoal agent, repurposed as an antiviral prodrug. The active metabolites of nitazoxanide are tizoxanide and tizoxanide conjugates, which are safer. These active metabolites inhibit the replication of a wide range of resistant strains of influenza viruses [13]. Nitazoxanide has exemplified in vitro antiviral activity over Middle East respiratory syndrome (MERS) and SARS-CoV-2. Further, nitazoxanide exhibits activation of interferon alfa and interferon beta formation. With an amalgamation of considerable safety profile, antiviral activity and immunomodulatory effects, nitazoxanide vindicates its further study as candidate for treatment of SARS-CoV-2 [14,15].

Lopinavir/Ritonavir

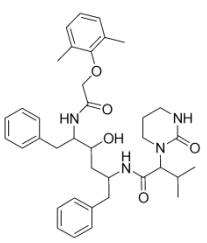


Figure 3: Lopinavir.

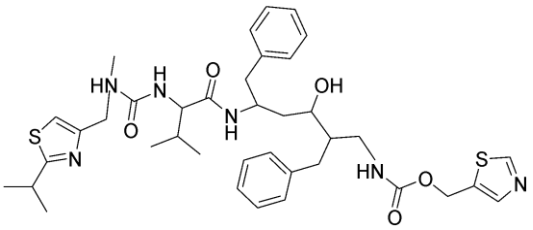


Figure 4: Ritonavir.

Lopinavir (Figures 3 & 4) an inhibitor of Human Immunodeficiency Virus type 1 protease (HIV-1), stumbles the maturation of HIV-1. Ritonavir 4 also being a protease inhibitor, is administered conjointly with Lopinavir to inhibit its metabolic inactivation by elevating its bioavailability. HIV-1 protease is an aspartic protease that cleaves both structural and functional proteins from precursor viral polypeptide strands and fulfills an essential role in the viral life cycle. Immature and nonlethal virus results due to inhibition of HIV protease as it prevents cleavage of the Gag-Pol polyprotein. Since the similar enzyme protease is utilized by the SARS-CoV-2 for their replication, a meld of these drugs can be put to use for MERS-CoV and SARS-CoV-2 furthermore [16].

Favipiravir

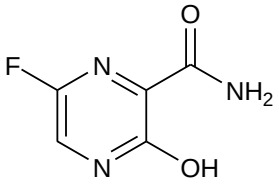


Figure 5: Favipiravir

Favipiravir (Figure 5) is a broad spectrum antiviral used in infections caused by RNA viruses. It selectively inhibits the enzyme RNA-dependent RNA polymerase (RdRp), which stops RNA polymerase activity. An intracellular phosphoribosylation of favipiravir converts it to the active form, favipiravir ribofuranosyl-5′-triphosphate, which is recognized as a substrate by RdRp. Favipiravir instigates a rapid mutation rate of the virus RdRp, causing the total viral population to decline and increases the nonviable viral load [17]. This mechanism of baneful mutagenesis is anticipated to play a quintessential role in the mechanism of favipiravir. Various nations like Russia, China and India have approved Favipiravir for treatment of COVID-19 [18].

Following are few Nucleoside analogues which demonstrate activity towards human Coronavirus and their EC50 or IC50 (Table 1)

Table 1: Nucleoside analogues with demonstrate activity towards human Coronavirus and their EC50 or IC50

Nucleoside analogues wich demonstrate activity towards human Coronavirus	
Nucleoside analogue	**EC50 or IC50**
Ribavirin	50–819 µM
Remdesivir	0.07 µM
Nitazoxanide	0.2-1.5µM
Favipiravir	29 µM

Antimalarial

Chloroquine

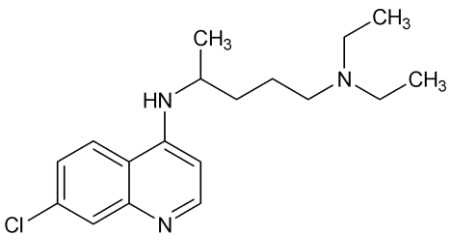


Figure 6: Chloroquine.

An antiparasitic drug, chloroquine (Figure 6) acts by binding to the cellular receptor present on the surface and thus stops a preclusive step in the viral life cycle. It is evident as per the clinical studies that chloroquine interferes with the biosynthesis of sialic acids by inhibiting 2-epimerase quinonereductase, an enzyme essential for its synthesis. This leads to the broad antiviral spectrum of chloroquine, since viruses similar to the Human Coronavirus- OC43 utilizes sialic acid for their activity. Chloroquine also works by decreasing the glycosylation of angiotensin-converting enzyme 2 (ACE2) present on the viral cell surface [19]. In vitro studies demonstrate that both chloroquine and hydroxychloroquine can inhibit SARS-CoV-2 transmission by alkalinisation of the intracellular phagolysosome, which inhibits virion fusion and uncoating preventing viral escalation. Being used for the past several decades, Chloroquine can make for a safe and cheap drug therefore, it's potentially used against COVID-19 can be studied [20].

Recombinant human Angiotensin-converting enzyme 2 (ACE2)

Apeiron's ACE2 drug product APN- 01

Angiotensin-converting enzyme 2 plays a crucial part in the initial stages of SARS-CoV viral infection which was widespread in the year 2003. The novel coronavirus (COVID-19 or SARS-CoV-2) also mimics the SARS-CoV on relying on the Angiotensin-converting enzyme 2 for its virulent nature.

Hence, therapy using recombinant human ACE2 becomes quintessential to stop the progress of the diseases and also to avoid the associated mortality and co-morbidity. Hence recombinant human ACE2 comes as a rational and fanatical drug for the new pandemic.

A dual-arm randomized trial was conducted by Apeiron Biologics AG to identify if APN01 improves the overall condition of patients with acute COVID-19 infection which showed positive results [21,22].

Interferon Alpha 2b

Interferons are a group of naturally occurring proteins, and an integral part of protein-based therapeutics. Interferons are a divergent group of cytokines having distinct characteristics, complex functionality and broadly includes Type I interferons (interferon-a and interferon-ß) and Type II interferons. Interferon Alpha 2b therapy has shown to accelerate the natural formation of interferon in humans and boost the immunity of the patients, hence has been effective against COVD-19. For immunosuppressive diseases like various malignancies, HIV-AIDS, Hepatitis, Herpes zoster or Shingles and Dengue, α-interferon has been used. α-interferon is available as an atomization inhalation. The weakly recommendation being 5 million U per time for adults in sterile injection water, twice a day [23,24].

Corticosteroid therapy

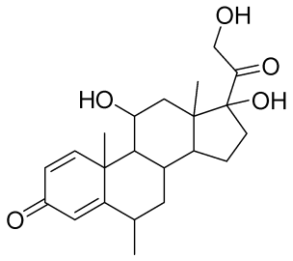


Figure 7: Corticosteroids.

Corticosteroids (Figure 7) are steroid hormones that play an eminent role in the process of inflammation and the immune system. Although human clinical trials have portrayed corticosteroids as effective in diminishing clinical damage, the major disquiet is their adverse effects, such as acute respiratory syndrome. A study conducted on porcine for therapy against respiratory coronavirus using dexamethasone illustrated that one or two doses at earlier stages are efficacious in lessening proinflammatory responses yet prolonged utilization could elevate viral replication [25]. For cases showing rapid progression of infection, methylprednisolone can be opted for the treatment. 40-80 milligram (mg) of methylprednisolone every day or the total daily intake not exceeding 2 mg/kg can be used. The research conducted by the SARS management indicated that for elevated lung shadows and dyspnea, timely use of nasal oxygen along with corticosteroids has proven useful. Strategic use of corticosteroids can drastically reduce the clinical symptoms among patients with COVID, and also reduce the rate of progression [26,27]. The use of corticosteroids for COVID seems dicey as it can escalate the risks of acute respiratory syndrome and viral replication could be boosted.

Antibiotic therapy

The new coronavirus is a virus and hence no antibiotic should be used for treatment or prevention. Antibiotics should be used wisely, specifically the amalgamation of broad-spectrum antibiotics. Cautious bacteriological scrutiny can be conducted to combat secondary bacterial infection.

Although antibiotic combination therapy can be provided for any secondary infection acquired during the infection by the virus [28,29].

CONCLUSION

Repurposing of existing drugs is quintessential as for a new drug to be approved would require time and the spread of this pandemic needs to be tackled soon. Development of a vaccine is anticipated in near future, but till then preventive measures are necessary. The first step is to ensure sufficient quarantine to prevent transmission to other contacts, patients, and medical staff. Mild to moderate symptoms can be managed at home. Over consumption of antibiotics needs to be stopped in confirmed cases.

The strategy to be followed involves balanced nutrition to boost immunity and controlling fever and cough. Thus redefining the uses of the already existing drug candidates to combat the rapidly invading COVID-19 will significantly improve the existing cases and will also provide the desired time to design vaccines and reduce disease burden.

Format for Consent for Publication

Not applicable.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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