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A Brief Overview of Current Drug Repurposing Approaches for COVID-19 Management

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Abstract. This brief overview is intended to shed light on the current drug repositioning (also called drug repurposing) in the therapeutics of the novel coronavirus disease which emerged in 2019 (COVID-19). In this sense, the repositioning drugs for new indications can offer a better risk-*versus*-reward trade-off when compared to other drug development strategies, given that it makes use of drugs whose safety profile are already understood. Nonetheless, this approach allows healthcare professionals to promptly tackle the disease by investigating readily available drugs against it.

Keywords: coronavirus; antiviral; pandemic; outbreak; drug repositioning; healthcare.

1. COVID-19 outbreak and its current scenario

On December 31st, 2019, several pneumonia cases linked to a seafood market in Wuhan, China were reported to the World Health Organization (WHO). The fast-spreading infection, now known as coronavirus disease 2019 (COVID-19), is caused by a novel coronavirus (SARS-CoV-2) [1]. This recent global outbreak has raised many concerns regarding the limitations of standard therapeutic protocols against fast-spreading diseases as well as the importance of their epidemiological characteristics. Regarding the severe acute respiratory syndrome, SARS-CoV-2 is the etiological agent of the ongoing pandemic of 2019 CoV disease, which is already responsible for far more deaths than were reported during the previous public health emergencies of international concern provoked by two related pathogenic CoVs from 2002 and 2012 [2].

The cases of infection have been continuously increasing ever since its outbreak. Currently, there are no scientifically reliable approved drugs to treat the infection. In this scenario, there is a need to utilize the existing repertoire of FDA approved drugs to treat the disease [3]. Regarding COVID-19 infection, its symptoms are usually flu-like, while non-specific symptoms such as fever, dry cough and malaise are also common, up to the shortness of breath – which is an indicator of bad evolution. In this sense, differential diagnosis plays a crucial role in determining proper patient care, being this goal achieved by point of care immunochromatographic tests, real time polymerase chain reaction (RT-PCR) or by enzyme-linked immunosorbent assay (ELISA) in proper lab environment.

One can find that imaging (CT) could be the answer to the initial assessment of desaturating patients. The bilateral commitment of the lungs together with the epidemiological scenario are clues to the differential diagnosis, despite testing. Such assessment allows differentiation from the single lung disorder seen in Influenza patients. Notwithstanding, the medical personnel should be aware of the potential "cytokine storm" which may be caused also by severe Influenza A [4]. Table 1 showcases the main specific and unspecific symptoms associated to COVID-19.

Table 1 – Main specific and unspecific symptoms associate to COVID-19

Symptoms*	
Specific	Unspecific
	Fever
	Fatigue
Shortness of breath#	Muscle Pain
# often leads to bilateral lung commitment	Cough
	Expectoration
	Headache
	Hemoptisis
	Diarrhea

Notes: All symptoms were thoroughly reported by Huang and collaborators in 2020 [5].

2. Current COVID-19 therapeutics and perspectives on drug repurposing

Although there is up to date no FDA-approved specific treatment for COVID-19 infection, experimental drugs such as favipiravir and hydroxychloroquine are gaining increasing attention due to their allegedly efficacy. Favipiravir is a pyrazinecarboxamide derivative derivative whose main target is viral RNA-dependent RNA polymerase, while hydroxychloroquine is an aminoquinoline whose pharmacodynamics of its antiviral activity is still unclear. These drugs are selected to undergo investigation following empirical *in vitro* testing, chemoinformatic or other *in silico* approaches which correlate their chemical structure to biological activity. These methods are gaining attention due to their low cost when compared to standard medicinal chemistry approaches and provide reliable data under the time constraints imposed by global outbreaks such as COVID-19. In this sense, drug repurposing offers quick insights to employ readily available drugs against unorthodox biological targets [10, 11, 12, 13]. Table 2 summarizes the main drugs which are currently under investigation against COVID-19.

Table 2 – Drugs under investigation against COVID-19

Antiviral drug	MoA[2]	Regular indication	FDA-S[4]	References
IFN-Alfa[1]	Miscellaneous	Hepatitis	+	[6]
Lopinavir/ritonavir[2]	Protease Inhibitor	HIV	+	[11]
Ribavirin[2]	Nucleotide analogue	Broad spectrum antiviral	+	[6]
Chloroquine phosphate[1]	Miscellaneous	Antimalarial	+	[10]
Arbidol[3]	Miscellaneous	Influenza	-	[9]
Favipiravir[2]	Nucleotide analogue	Influenza	-	[14]
Remdesivir[2]	Nucleotide analogue	Ebola	-	[12]
Darunavir[2]	Protease Inhibitor	HIV	+	[13]
Atazanavir[2]	Protease Inhibitor	HIV	+	[8]
DRACOs[3 5]	Suppress viral RNA synthesis	Broad spectrum antiviral	-	[7]
Ivermectin[1]	Miscellaneous	Antiparasitic	+	[15]

Notes:

[1] Targets viral replication or entry/apoptosis; [2] Targets viral replication; [3] Targets viral entry/apoptosis; MoA – Mechanism of Action; [4] FDA-S - FDA status; [5] Double-stranded RNA Activated Caspase Oligomerizer.

Among potential drugs, the nucleotide analogue remdesivir is shown to be one of the most promising and hopeful anti-viral in therapeutic. It works by targeting viral RNA-dependent RNA polymerase (RdRp) while evading proofreading by viral exoribonuclease [16], resulting in premature termination of viral RNA transcription. Unlike other nucleotide analogues, remdesivir is a phosphoramidate prodrug with broad-spectrum activity against many virus families, including *Orthocoronavirinae*, in which the pathogenic SARS-CoV and Middle East respiratory syndrome coronavirus are included [17, 18].

The other nucleotide analogue, RdRp inhibitor favipiravir is easily recognized as a substrate of viral RNA polymerase in many RNA viruses [19]. Recently, preliminary results of clinical studies have shown favipiravir to have good potency in treatment of Chinese patients with COVID infection [18]. Favipiravir was approved for the treatment of COVID-19 in China in March, 2020. In addition, patients with COVID-19 infection are

being recruited for randomized trials to evaluate the efficacy of favipiravir plus interferon-α (ChiCTR2000029600) and favipiravir plus baloxavir marboxil (ChiCTR2000029544) [20].

Protease inhibitors (PIs) are important antiviral drug agents. In the *Orthocoronavirinae* context, the targets of PIs are papain-like protease and 3C-like protease [21]. It is noteworthy to mention that [22] compared the efficacy of prophylactic remdesivir as well as therapeutic remdesivir with that of LPV/ritonavir - IFNb combination therapy in a humanized MERS-CoV infection model. They observed the efficacy of remdesivir was superior to that of LPV/RTV-IFNb against MERS-CoV in terms of viral load reduction and improvement in extent of pathologic change in lung tissue [22]. Chinese Clinical Trial Register number, ChiCTR2000029308 failed based on the usage of LPV/RTN to provide benefits compared to standard care alone, hence there was no difference in the reduction of viral RNA loading for severe SARS-CoV-2 patients [23].

Chloroquine was shown to increase endosomal pH, which prevents virus/cell fusion. It also interferes with the glycosylation of cellular receptors of SARS-CoV. Although the in vitro data of chloroquine is promising (EC90 of 6.90 μM, using Vero E6 cells infected by SARS-CoV-2), an extensive prescription of chloroquine in clinical treatment of SARS-CoV-2 is a completely off-label use [24].

Originally identified as an inhibitor of the interaction between the human immunodeficiency virus-1 (HIV-1) integrase protein (IN) and the importin (IMP) α/β1 heterodimer responsible for IN nuclear import [25], Ivermectin is an FDA-approved broad spectrum antiparasitic agent that has since been confirmed to inhibit IN nuclear import and HIV-1 replication. Other actions of ivermectin have been reported, but ivermectin has been shown to inhibit nuclear import of host and viral proteins, including dengue virus (DENV) non-structural protein 5 [26].

The Oswaldo Cruz Foundation (Fiocruz) said in a note that it found in research on treatments for COVID-19 that the drug Atazanavir, used to treat HIV, was able to inhibit viral replication, in addition to reducing the production of proteins that are linked to the inflammatory process in the lungs and, therefore, to the worsening of the patients' clinical condition [27].

Considering the lengthy process of approving novel drugs to general health practice, the repurposing of preexistent medicines is surely a less strenuous approach in the path towards prompt medical treatment. In this sense, the commercialization of novel compounds in pharmaceutical formulations is preceded by thorough evaluation of their efficacy and safety profiles through several approaches such as *in silico*, *in vitro*, *ex vivo* and finally *in vivo* investigations. This process may take about ten years to achieve completion [28], while drug repurposing follows mainly clinical trials to attest the usefulness of the proposed treatment under the light of patient safety. Considering that emerging global outbreaks such as COVID-19 require fast and efficient intervention to counter mass contamination, drug repurposing is a remarkable alternative to tackle the epidemy in its beginning.

This has been a way out for several diseases, for instance, Brazilian researchers are working with derivatives of triazoles, known antifungals, for the treatment of sickle cell anemia. For neglected diseases, the repositioning of drugs is an excellent strategy, in which little is invested, or even in emergency diseases, such as the current COVID-19 outbreak [29, 30].

CONCLUSION

The repositioning drugs for new indications can offer a better risk-versus-reward trade-off when compared to other drug development strategies, given that it makes use of drugs whose safety profile are already understood. Nonetheless, this approach allows healthcare professionals to promptly tackle the disease by investigating readily available drugs against it. However, care must be taken and all clinical investigations must be performed in order to ensure the efficacy of the treatment under the light of patient safety.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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