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Drug repositioning is an alternative for the treatment of coronavirus COVID-19

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ABSTRACT

Given the extreme importance of the current pandemic caused by COVID-19, and as scientists agree there is no identified pharmacological treatment, where possible, therapeutic alternatives are raised through drug repositioning. This paper presents a selection of studies involving drugs from different pharmaceutical classes with activity against SARS-CoV-2 and SARS-CoV, with the potential for use in the treatment of COVID-19 disease.

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The recent spread of the novel coronavirus, SARS-CoV-2 has created a worldwide public health emergency. In December 2019, the outbreak of this emerging disease (COVID-19) began in Wuhan, China. It quickly spread, and a pandemic was declared by the World Health Organization in March 2020 [1,2].

Repositioning drugs already approved for use in humans is a useful tool to search for new therapeutic options, particularly in the current global crisis [3]. Thus, drug repositioning, also known as redirecting, repurposing, and repurposing [4,5], emerges as an effective possibility for generating new treatments against COVID-19. Repositioning is defined as a new use of a drug, in addition to its original indication(s), and is an option for rapid identification of new therapeutic agents. The availability of drug-related information, such as pharmacokinetics, pharmacodynamics and toxicity [6], is an important advantage in the research efforts to quickly find an effective treatment for this deadly virus.

Table 1 presents a selection of recent studies that investigated the antiviral activity of several pharmacological classes, including antimalarial drugs and antibiotics, as options for repositioning as treatments of coronavirus (SARS-CoV, SARS-CoV-2 and HCoV-OC43) [7–10]. A search was conducted on three databases (PubMed, SCOPUS and Web of Science) between March 15 th and March 27 th, 2020 using the following search strategy: [(repositioning) AND (repurposing) AND (redirecting) AND (repurposing) AND (rediscovery) AND (COVID-19) AND (CORONAVIRUS) AND (treatment)] with review filters appropriate for individual databases. The inclusion criterion was studies that included the repositioning of drugs with antiviral activity against coronavirus. Duplicate cases were excluded, as were studies that did not address the issue.

The analysis revealed seven studies that address drug repositioning against SARS-CoV-2: the target drugs were chloroquine, hydroxychloroquine associated with azithromycin, teicoplanin, remdesivir, nitazoxanide and metformin. Several authors report the potential of chloroquine as a therapeutic option against this virus: in vitro it presented an EC50 of 1.13 μm and in vivo it caused a negative conversion of the virus in more than 100 patients who were participating in multicenter clinical trials conducted in China [7,8]. In the in vitro study performed by Liu et al. (2020), both chloroquine and hydroxychloroquine inhibited the virus from entering the cell and, at later cell stages of SARS-CoV-2 infection, blocked virus transport between cell organelles, which is considered a determining step for the release of viral genome in cells in the case of SARS-CoV-2. However, chloroquine was observed to have a higher efficacy [9].

Teicoplanin, on the other hand, presented an in vitro IC50 of 1.66 μM, a relatively low active concentration, which is promising for its use against SARS-CoV-2; however, this requires further in vivo verification and incorporation in clinical trials [10].
# Table 1

Studies of the repositioning of drugs with effects against coronavirus.

| Drug               | Class                  | Original indication | New indication in repositioning | Type of study | Active concentration | Probable mechanism of action                                                                 | Reference                |
|--------------------|------------------------|---------------------|---------------------------------|---------------|----------------------|------------------------------------------------------------------------------------------------|--------------------------|
| Amodiaquine        | 4-amino-quinoline      | Antiparasitic agent | SARS-CoV                         | In vitro      | EC$_{50}$ = 1.274 μM | -                                                                               | Dyall et al. 2014 [13]    |
| Captopril          | ACE-2 inhibitor        | Hypertension        | SARS-COV-2                       | Hypothesis    | -                    | Inhibits binding between COVID-19 and human ACE-2, and reduces symptoms of severe pneumonia | Sun et al. 2020 [14]      |
| Chloroquine        | 4-amino-quinoline      | Antimalarial        | SARS-CoV                         | In vitro      | EC$_{50}$ = 6.538 μM | -                                                                               | Dyall et al. 2014 [13]    |
|                    |                        |                     | SARS-CoV                         | In vitro      | IC$_{50}$ = 8.8 μM  | -                                                                               | Keyaerts et al., 2004 [15]|
|                    |                        |                     | SARS-CoV                         | In vitro      | EC$_{50}$ ≥ 4.1 μM  | -                                                                               | de Wilde et al., 2014 [16]| |
|                    |                        |                     | SARS-CoV                         | In vitro      | EC$_{50}$ = 1.13 μM | Probably blocks virus infection by increasing endosomal pH required for virus/cell fusion, and interferes with glycosylation of cellular receptors of SARS-CoV | Wang et al., 2020 [7]      |
|                    |                        |                     | SARS-CoV-2                       | In vitro      | EC$_{50}$ = 2.71 μM | Blocks virus transport between cell organelles                                  | Liu et al., 2020 [9]      |
|                    |                        |                     | SARS-CoV-2                       | In vitro      | EC$_{50}$ = 5.47 μM | -                                                                               | Yao et al., 2020 [17]      |
|                    |                        |                     | SARS-CoV-2                       | Comput-ational| -                    | -                                                                               | Gordon et al., 2020 [18]  |
|                    |                        |                     | SARS-CoV-2                       | In vivo       | -                    | -                                                                               | Gao et al., 2020 [8]       |
|                    |                        |                     | HCoV-OC43                        | In vivo       | EC$_{50}$ = 0.3 μM  | Probably affects endosome-mediated fusion                                       | Keyaerts et al., 2009 [19]|
| Cyclosporin A      | Calcineurin inhibitors | Immunosuppressant   | SARS-CoV                         | In vitro      | 16 μM                | Likely that the drug interferes with functional interactions between viral proteins and one or multiple members of the large cyclophilin family | de Wilde et al., 2011 [20]|
| Chlorpromazine     | Antipsychotic          | Schizophrenia       | SARS-CoV                         | In vitro      | EC$_{50}$ = 3.3 μM  | Affects replicative protein                                                     | Pfefferle et al., 2011 [21]|
| hydrochloride      |                        |                     | SARS-CoV                         | In vitro      | IC$_{50}$ = 8.8 μM  | -                                                                               | de Wilde et al., 2014 [16]|
| Clomipramine       | Neurontransmitter      | Antidepressant      | SARS-CoV                         | In vitro      | CC$_{50}$ = 24.3 μM | -                                                                               | Dyall et al., 2014 [13]    |
|                    | inhibitor              |                     |                                 |               | EC$_{50}$ = 13.2 μM | -                                                                               |                          |
| Disulfiram         | Tuiram disulfide       | Chronic alcohol     | SARS-CoV                         | In vitro      | IC$_{50}$ = 24.1 μM | Competitive inhibitor of SARS-CoV papain-like protease                           | Lin et al, 2018 [22]      |
|                    | dependence             | dependence          |                                 |               |                      |                                                                                  |                          |
| Enalapril          | ACE-2 inhibitor        | Hypertension        | SARS-COV-2                       | Hypothesis    | -                    | Inhibits binding between COVID-19 and human ACE-2, and reduces symptoms of severe pneumonia | Sun et al., 2020 [14]      |
| Gemcitabine        | DNA metabolism         | Anticancer          | SARS-CoV                         | In vitro      | EC$_{50}$ = 4.9 μM  | -                                                                               | Dyall et al., 2014 [13]    |
| hydrochloride      | inhibitor              |                     | SARS-CoV                         | In vitro      | EC$_{50}$ = 7.9 μM  | -                                                                               | Dyall et al., 2014 [13]    |
| Hydroxychloroquine | 4-amino-quinoline      | Antimalarial        | SARS-CoV                         | In vitro      | 0.46 μg/mL (serum concentration) | -                                                                               | Gautret et al., 2020 [11]  |
|                    |                        |                     |                                 |               |                      | (continued on next page)                                                       |                          |
Table 1 (continued)

| Drug                  | Class                          | Original indication          | New indication in repositioning | Type of study | Active concentration | Probable mechanism of action | Reference       |
|-----------------------|--------------------------------|------------------------------|---------------------------------|---------------|----------------------|-------------------------------|-----------------|
| Hydroxychloroquine    | Estrogen receptor inhibitor     | Breast cancer                | SARS-CoV                        | In vitro      | $EC_{50} = 92.8 \mu M$ | -                            | Dylla et al., 2014 |
| Terconazole           | Sterol metabolism inhibitor    | Antifungal                   | SARS-CoV                        | In vitro      | $EC_{50} = 92.8 \mu M$ | -                            | Dylla et al., 2014 |
| Toremifene            | Estrogen receptor inhibitor     | Breast cancer                | SARS-CoV                        | In vitro      | $EC_{50} = 11.9 \mu M$ | -                            | Dylla et al., 2014 |
| Teicoplanin           | Glycopeptide antibiotic         | Bacterial infection          | SARS-CoV                        | In vitro      | $IC_{50} = 1.166 \mu M$ | Inhibited entry of 2019-nCoV pseudovirus, which provides a possible strategy for prophylaxis and treatment for 2019-nCoV infection | Zhang et al., 2019 |

(-) Not determined

Gautret et al. (2020) conducted a clinical trial using hydroxychloroquine in patients infected with SARS-CoV-2. The initial results show a significant reduction in viral carriage and the use of hydroxychloroquine in conjunction with azithromycin was more efficient in eliminating the virus [11]. There is also expectation for the results of the WHO solidarity initiative, which consisted of a worldwide call for a clinical study to simultaneously research the efficacy of four drugs, including remdesivir, chloroquine and hydroxychloroquine, for the treatment of patients affected with COVID-19 [12]. Thus, drug repositioning is a promising alternative for the treatment of COVID-19 disease, and a more complex investigation of the antiviral effect of these molecules against SARS-CoV-2 is encouraged.

Declarations

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