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SARS-COV-2 OR COVID-19: THE SEARCH FOR ALTERNATIVE TREATMENT FOR THE NEW CORONAVIRUS

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ABSTRACT

SARS-CoV-2 belongs to the *Coronaviridae* family and of the order *Nidovirales*, which has positive non-segmented RNA, of the enveloped type that causes a severe acute respiratory syndrome in humans, which has already infected more than 9 million people worldwide, leading to 496,075 deaths by June 27, 2020, making the search for alternative treatment for this pathogen urgent. Thus, this study aimed to conduct a bibliographic survey of research that presents treatment alternatives for the new coronavirus. Thus, a qualitative and descriptive cross-sectional study was carried out, and a comparative analysis was carried out with the prospective results achieved as presented in a study carried out by Reis and collaborators. Publications from the last 7 months were considered, that is, from December 2019 to June 2020, the period in which studies of SARS-CoV-2 started. In this way, a total of 4,898 studies related to the treatment alternative for SARS-CoV-2 were found, in which the drugs remdesivir, atazanavir, favipiravir, EIDD-2801 and hydroxychloroquine associated with azithromycin stand out, where they presented attractive preliminary results and are recommended for clinical studies in humans as an alternative way of coping with the new coronavirus.

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INTRODUCTION

In Wuhan, the capital of Hubei province, China, there have been cases of pneumonia of unknown cause, where most of the diagnosed people worked or lived near the local Huanan wholesale seafood market, which sold live animals for consumption. This disease soon spread and the city became the center of an outbreak of severe acute respiratory syndrome with an unknown cause (Chen *et al.,* 2020). The discovery of the etiologic agent of this disease was made by the Chinese Center for Disease Control and Prevention (CDC) on January 7, 2020, where the new coronavirus classified as SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2) and known popularly as COVID-19 (Zhou *et al.*, 2020). However, only in February 2020, the virus was officially released by the World Health Organization (WHO) as the cause of the new respiratory disease (Gorbalenya, 2020). This is the 9th identified coronavirus that infects humans, belonging to the Coronaviridae family and of the order Nidovirales that have positive non-segmented RNA, of the enveloped type (Huang *et*

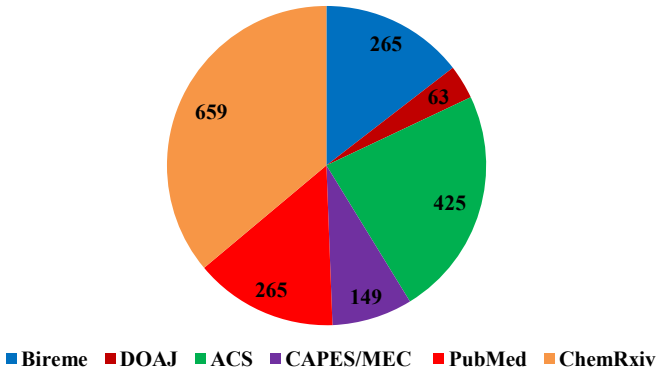
al., 2020). SARS-CoV-2 infection can range from mild symptoms of the upper respiratory tract to severe viral pneumonia with respiratory failure and can lead to death (Chen *et al.,* 2020; Andersen *et al.,* 2020). The symptoms vary according to the immune characteristics of the person infected by the virus, and may present fever, irritation in the throat, loss of smell and taste, headache, muscle pain, difficulty in breathing and radiological opacity of the lung in frosted glass in the most severe cases (Corman *et al.,* 2020). On June 27, 2020, the virus had infected 9,891,727 people worldwide, leading to 496,075 deaths (https://coronavirus.jhu.edu/map.html) (Johns Hopkins University [website] (2020). This number tends to increase, as there is no treatment for COVID-19. In this way, WHO recommends social isolation to try to reduce the contagion and prevent a collapse in the health systems of the country's most affected by the disease (Chen *et al.,* 2020; Gorbalenya, 2020). Currently, South America is the new epicenter of COVID-19, with Brazil being the country most affected, with 1,274,974 confirmed cases and 55,961 deaths (Johns Hopkins University [website] (2020). In this perspective, the search for an effective treatment has been the priority of scientists worldwide, developing studies of drug repositioning, clinical presentations, traditional Chinese medicine and studies with advanced therapy drugs (Cattani, 2020; Araújo *et al.,* 2020). Thus, this study aimed to carry out a bibliographic survey of research that presents treatment alternatives for the new coronavirus.

METHODS

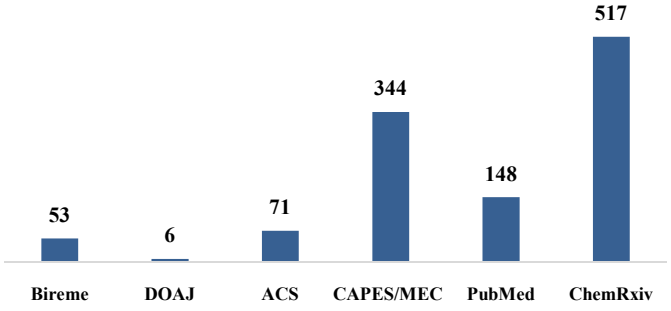
The study is qualitative in nature and cross-sectional, with a comparative analysis carried out with the prospective results achieved, as presented in a study carried out by Reis and collaborators (Dos Reis *et al.,* 2016). The prospective study followed the method of Martins and collaborators (Martins *et al.,* (2020) with some modifications. The search in the databases was carried out between the months of May and June 2020, where publications from the last 7 months were considered, that is, from December 2019 to June 2020. This is the period when studies of SARS-CoV-2 started. Only studies in English (American and British) were considered. The databases used in this search were: Centro Latino-Americano e do Caribe de Informação em Ciências da Saúde (Bireme), Directory of Open Access Journals (DOAJ), American Chemical Society (ACS), Portal de Periódicos CAPES (CAPES/MEC) and National Center for Biotechnology Information (PubMed). Searches for paper were also carried out on the preprint Server for Chemistry (ChemRxiv), because due to the need to seek studies aimed at alternative treatment against COVID-19, it is essential to elucidate preliminary results available as a preprint. Thus, studies that point to possible treatment alternatives for SARS-CoV-2 were selected to elucidate the treatment alternatives found against COVID-19 and which are more promising (Carvalho *et al.*, 2020). The descriptors used were: drugs against SARS-CoV-2, COVID-19 target protein inhibitors and vaccines against the new coronavirus.

RESULTS

The findings point to significant numbers of studies related to alternative treatment for SARS-CoV-2, using the databases, Bireme, DOAJ, ACS , CAPES/MEC, and PubMed, where 2,897 published studies were obtained and evaluated by peers in scientific journals. Searches for paper were also carried out on the preprint Server for Chemistry (ChemRxiv), with 2,001 preprints found. These searches took into account articles published between the months of December 2019 to June 2020. In graphs 1, 2 and 3, we can elucidate the amount of searches found for each descriptor. The descriptor "drugs against SARS-CoV-2" presented the largest number of published studies, with a total of 1,826 articles. We can see in Graph 1 that most of these studies are concentrated in the ChemRxiv database, containing 659 articles related to research on drug repositioning against the new coronavirus, where we highlight the drugs arbidol, remdesivir, favipiravir (Dong *et al.,* 2020), lopinavir/ritonavir (Mckee *et al.,* 2020), chloroquine, atazanavir, rimantandine, amantadine, zanamivir, oseltamivir (Araújo *et al.,* 2020), hydroxychloroquine (Eastman *et al.,* 2020), EIDD-2801, baricitinib, methylprednisolone, heparin, zinc, darunavir, emtricitabine, tenofovir, fingyrpridam, baloxaviram, marxaviram losartan, azithromycin, ribavirin, triazavirin, tranilast, ebastine (Huang *et al.,* 2020). We emphasize that these results were obtained through filtering, using tools available in the databases, excluding observational studies, divided into descriptive and analytical, taking into account only studies of innovative discovery of treatment alternatives for SARS-CoV-2. The DOAJ database had the lowest index of publications with 63 articles found (Graph 1).



Graph 1: Studies found for the descriptor "drugs against SARS-CoV-2".
Note: Bireme - Centro Latino-Americano e do Caribe de Informação em Ciências da Saúde; DOAJ - Directory of Open Access Journals; ACS - American Chemical Society; CAPES/MEC - Portal de Periódicos CAPES; PubMed - National Center for Biotechnology Information; ChemRxiv - preprint Server for Chemistry. **Source:** Developed by the authors (2020).

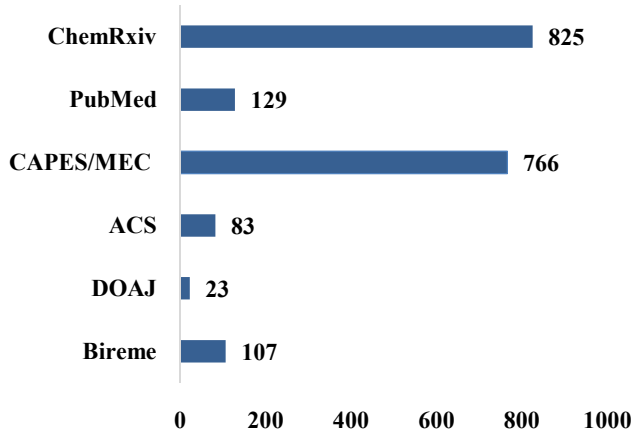


Graph 2: Deposits of articles referring to the descriptor "COVID-19 target protein inhibitors".

Note: Bireme - Centro Latino-Americano e do Caribe de Informação em Ciências da Saúde; DOAJ - Directory of Open Access Journals; ACS - American Chemical Society; CAPES/MEC - Portal de Periódicos CAPES; PubMed - National Center for Biotechnology Information; ChemRxiv - preprint Server for Chemistry. **Source:** Developed by the authors (2020).

Graph 2 shows the results obtained in the search for scientific articles on research involving the inhibition of SARS-CoV-2 key proteins by means of organic or synthetic compounds. 1,139 studies were found related to the descriptor "COVID-19 target protein inhibitors", which the lowest result is found in comparison to the other descriptors. This demonstrates that most studies are focused on research with drugs already available on the market, as these have already undergone regulatory processes and tests of their pharmacological and toxic properties and become attractive in studies in the short or medium term (Liu *et al.,* 2020). The database with the most publications was ChemRxiv with 517 results (Graph 2). According to the author Huang and collaborators (Huang *et al.,* 2020), there are 19 inhibitors under study with biological potential to treat the new coronavirus, among them, 4 stand out with excellent binding-free energy when they bind to a key SARS-CoV-2 protein by molecular docking studies, they are: patchouli alcohol; resveratrol; lignan; and curcumin.

For the descriptor "vaccines against the new coronavirus", 1,933 results from published articles were achieved, with the ChemRxiv database prevailing with the largest number of articles, and the DOAJ with the lowest amount, only 23 articles published on studies of vaccines that are effective against the SARS-CoRV-2 (Graph 3). It can be seen that the ChemRxiv database presented a greater number of published studies among all the other databases for the 3 descriptors used in this study, this was already expected, since preprint studies were not evaluated by peers and are not published in scientific journals, in this way, research is deposited at ChemRxiv simultaneously after submission (Huang *et al.,* 2020). This resource is a way for scientists to share preliminary or completed results of studies against SARS-CoV-2 so that they can disseminate information as soon as possible to the scientific community due to the need to find an alternative treatment for the new coronavirus. According to Canaday and collaborators (Canaday and Gravenstein, 2020), in their research entitled "On setting expectations for a SARS-CoV-2 Vaccine", there was a major international effort to develop a vaccine against SARS-CoV-2 in less than 6 months, thus generating more than 140 vaccines at different stages of development, with 9 recruited for clinical trials, with Oxford being the most advanced.



Graph 3: Studies found for the descriptor "vaccines against the new coronavirus".

Note: Bireme - Centro Latino-Americano e do Caribe de Informação em Ciências da Saúde; DOAJ - Directory of Open Access Journals; ACS - American Chemical Society; CAPES/MEC - Portal de Periódicos CAPES; PubMed- National Center for Biotechnology Information; ChemRxiv - preprint Server for Chemistry.
Source: Developed by the authors (2020).

DISCUSSION

Currently, large pharmacological companies and infectious disease research groups are focused on developing an anti-SARSCoV-2 vaccine, or discovering an alternative treatment that can inhibit the virus, thus the search for vaccines, monoclonal antibodies and drugs are the studies developed by scientists around the world (Nutho *et al.,* 2020). However, these studies need time to elucidate their pharmacological, toxicological properties, active potential, in addition to analyzing the effectiveness of these possible drugs, vaccines and SARS-CoV-2 inhibitors (Nutho *et al.,* 2020). We observed that most of the studies found by these descriptors, are aimed at research on drug redirection (Liu *et al.,* 2020), where it is possible to identify attractive anti-SARS-CoV-2 biological activity of drugs of a given pathogen and redirect them to the treatment of COVID -19. This reuse can be implemented through the systematic realization of drugs, target drug action (DTI) and therapeutic interaction analysis (DDI) (Canaday, and Gravenstein, 2020). In this perspective, we present the drugs that are being studied in clinical trials and computational prediction studies, they are: arbidol, remdesivir, favipiravir, lopinavir / ritonavir, chloroquine, atazanavir, rimantandine, amantadine, zanamivir, oseltamivir, hydroxychloroquine, EIDD-2801 baricitinib, methylprednisolone, heparin, zinc, darunavir, emtricitabine, tenofovir, baloxavir marboxil, damageprevir, dipyridamole, fingolimod, losartan, azithro-mycin, ribavirin, triazavirin, tranilast and ebastine (Wu, *et al.,* 2020; Araújo, *et al.,* 2020; Dong, *et al.,* 2020; Mckee *et al.,* 2020; Eastman, *et al.,* 2020; Huang *et al.,* 2020; Wang, 2020; Martinez, 2020).

Among these drugs, the prodrug remdesivir stands out, which has been showing antiviral activity due to paramyxovirus, pneumovirus and some species of coronavirus infections, including SARS-CoV, Bat CoV and MERS-CoV (Eastman *et al.,* 2020; Wu *et al.,* 2020; Martinez, 2020). Animal experiments were carried out, and it was found that the drug reduced the amount of virus in the lung tissue of mice infected with MERS-CoV, improving lung function (Dong, *et al.,* 2020; Martinez, 2020). In tissue culture, remdesivir emitted effective semi-maximum fusions (EC 50. s) of 0.069 M for SARS-CoV and 0.074 M for MERS-CoV. And tissue culture studies have found that remdesivir is also active (EC 50) in submicromolar. And it differs against a number of coronaviruses, including CoVs OC43 (HCoV-OC43) and 229E (HCoV-229E). Thus, remdesivir has shown promise in inhibiting different CoV targets, presenting itself as an alternative for studies against SARS-CoV-2 (Martinez, 2020).

Another drug that showed promise against SARS-CoV-2 was atazanavir in a study conducted by Araújo and collaborators (Araújo *et al.,* 2020). That from DFT calculations, molecular docking and ADMET predictions, they could elucidate between 6 drugs, which has a higher molecular affinity to bind and inhibit the main SARS-CoV-2 (M^{pro}) protein. Thus, atazanavir had the lowest free binding energy when it binds to the M^{pro} or $3CL^{pro}$ protein, responsible for mediating the replication and viral transcription of SARS-CoV-2, pointing to the strong action of the drug at the active site, causing damage to the protein and inhibiting the virus. We highlight the authors' recommendation for the use of this drug in studies with humans, having presented low toxicity and negative results for mutagenicity and carcinogenicity in a study by preADMET (Araújo *et al.,* 2020).

Then we have the drug favipiravir, which is also presented as an alternative treatment for COVID-19, this drug was developed for the treatment of avian influenza and neuraminidase, in addition to being used to treat other infectious diseases caused by RNA viruses, such as influenza, Ebola and norovirus (Wang, 2020). Recent *in vitro* studies point to a redirection of favipiravir against SARS-CoV-2, which is a Beta-coronavirus consisting of single-stranded enveloped RNA (Barlow *et al.,* 2020). We also present azithromycin, where *in vitro* studies have shown an inhibitory action against the Zika and Ebola viruses, which can prevent serious respiratory tract infections in patients suffering from viral infection (Gautret *et al.,* 2020). Thus, based on these results, several studies have been carried out to elucidate possible effects of azithromycin associated with hydroxyl chloroquine in people infected with SARS-CoV-2 (Wang, 2020). Hydroxychloroquine is derived from chloroquine hydroxy, which has a greater safety profile than chloroquine, both are drugs for the treatment of malaria (Gao *et al.,* 2020). Evaluations point to the effectiveness of chloroquine to inhibit SARS-CoV-2 infection at low molar concentration. However, hydroxychloroquine has a greater cytotoxic potential, being 3 times higher compared to chloroquine, and its use is more indicated in studies with humans infected with SARS-CoV-2 (Barlow *et al.,* 2020). A study with hydroxychloroquine showed inhibition of exacerbations of pneumonia, improving lung image and reducing disease progression in patients with COVID-19 (Gao *et al.,* 2020). Ressaltamos que este método terapêutico até o momento não possui resultados contundentes sobre sua eficácia. We emphasize that this therapeutic method has so far had no striking results on its effectiveness. However, it has toxicological results that indicate health risks, which can cause adverse effects and worsen the patient's clinical condition, such as causing arrhythmias that can lead to death, in addition to presenting positive results for carcinogenicity in a study conducted by Araújo and collaborators (Fihn, et al., 2020; Taylor and White, 2004; Juurlink, 2020; Araújo, *et al.,* 2020). In addition to these possible treatment alternatives, other drugs have biological potential against SARS-CoV-2. Among them, we have arbidol, which is used in China and Russia for the prevention and treatment of influenza, in addition to other respiratory viral infections (Blaising *et al.,* 2014).

Chinese scientists point to this drug as a possible treatment alternative against COVID-19. Other drugs that have antiviral activity are being analyzed, where darunavir, emtricitabine/ tenofovir and baloxavir present attractive preliminary results (Lythgoe and Middleton, 2020). Oseltamivir, on the other hand, did not obtain attractive results compared to SARS-CoV-2 as pointed out in studies by Barlow and collaborators and Araújo and collaborators (Barlow *et al.,* 2020)). We have also seen promising results with the use of EIDD-2801 which inhibited RNA-dependent-RNA-polymerase (RdRp) which catalyzes self-replication of single-stranded RNA and are key enzymes in viruses that have their single-stranded RNA genome, such as SARS-CoV-2. Like methylprednisolone, which inhibited anti-inflammatory cytokines, another compound that showed efficacy was heparin, which reverses the hypercoagulability of the potential mechanism of action of SARS-CoV-2. In addition to these, also have dipyridamole (inhibits phosphodiesterase), fingolimod (modulates sphingosine 1-phosphate receptor), losartan (blocks angiotensin receptor), ribavirin (inhibits protein synthesis and viral RNAm), triazarin (can inhibit RNA synthesis), tranilast (hematopoietic D synthesis prostaglandin inhibitor) and ebastine (inhibits H1) (Huang *et al.,* 2020). Among all these drugs identified as a possible treatment alternative against SARS-CoV-2, remdesivir, atazanavir, favipiravir, EIDD-2801 and hydroxychloroquine associated with azithromycin present themselves as the best therapeutic alternatives for studies in humans and to evaluate their effectiveness in treatment against COVID-19, where they presented preliminary results that reduced symptoms related to pneumonia in a percentage of infected patients (Holshue *et al.,* 2020). In addition to being effective in molecular fitting to key SARS-CoV-2 proteins with free stable binding energies in computational studies by docking and molecular dynamics (Beck *et al.,* 2020; Rodrigues *et al.,* 2020). Another alternative is to strengthen the immune system through the use of $Zn2^{+}$ associated with vitamin C as a prophylactic use in order to increase antiviral immunity, in addition to assisting the inflammatory response. Studies suggest that modulation of $Zn2^{+}$ may be effective against SARS-CoV-2, through *in vitro* tests it could be observed that $Zn2^{+}$ has antiviral activity inhibiting SARS-CoV RNA polymerase. However, clinical and experimental studies are needed to prove its effectiveness against the virus (Skalny *et al.,* 2020). In this perspective, China conducts studies with natural products and synthetic compounds that may have biological potential against SARS-CoV-2 and have low toxicity and availability of active components. Preliminary results point to the interaction effectiveness and molecular fit of alcohol from patchouli, resveratrol, lignan and curcumin to a key SARS-CoV-2 protein (Huang *et al.,* 2020).

Patchouli alcohol is a compound of traditional Chinese medicine, patchouli, tricyclic sesquiterpene, which has biological and pharmacological information, including antivirals, anti-inflammatories, antioxidant immunomodulators. The anti-SARS-CoV-2 activity shown, shows that the binding and effect of patchouli alcohol on RdRp was promising, being able to promote antiviral activity (Huang *et al.,* 2020). Curcumin is a phenolic compound isolated from turmeric that inhibits aminopeptidase N/CD13, the hypothesis being raised that it has efficacy as a prophylactic use against coronavirus, in order to inhibit its cell binding via the CD13 pathway and its entry into the host cell, in addition to hindering the replication of the virus in human cells as its action is observed in relation to other viral infections, such as HIV (Verma, 2020; Huynh *et al.,* 2020). Two other potential phytotherapies under evaluation is lignan, which has an inhibitory activity against the $3CL^{pro}$ or M^{pro} protein, responsible for the viral replication and transcription of SARS-CoV-2 and resveratrol, which prevents the expression of the virus's RNA and nucleocapsid. The treatment with these western herbal medicines is mainly based on the principles of asymptomatic treatment, being a way to prevent complications (Huang et *al.,* 2020). In addition to efforts to find an alternative treatment for SARS-CoV-2, studies aimed at developing vaccines are carried out with the aim of finding a definitive solution, however, this process is time-consuming and expensive (Amanat and Krammer, 2020; Ahmed *et al.,* 2020). Thus, tests of vaccine candidates are carried out following linear steps with several interruptions for data inspection and verification of the manufacturing method (Lurie, 2020). The discovery of a vaccine for SARS-CoV-2 would control the spread of the virus and the therapeutic process (Ahmed *et al.,* 2020). A previous study entitled "SARS-CoV-2 Vaccines: Status Report", carried out by Amanat and Krammer (2020), shows the similarity between SARS-CoV and SARS-CoV-2, through phylogenetic analysis

of the complete genome of the two strains, where it was possible to elucidate the similarity in the cell entry mechanism and the use of human cell receptors (Wit *et al.,* 2020). Because of this similarity between the two viruses, previous research that has provided an understanding of the protective immune responses against SARS-CoV can potentially be used to help develop a vaccine for SARS-CoV-2. In this sense, more than 140 candidates for vaccine against SARS-CoV-2 are being studied, with 9 recruited for clinical trials and available in the database of ClinicaTrial.gov (https://clinicaltrials.gov/) (Canaday and Gravenstein, 2020).

CONCLUSION

The SARS-CoV-2 pandemic caused scientists from all over the world to be engaged in the search for a treatment alternative, thus, a total of 4,898 studies were found related to the treatment alternative for SARS-CoV-2. However, a definitive solution has not yet been discovered, as the vaccine candidates are under analysis and need time for their results to be elucidated, with the studies of the University of Oxford being the most advanced. In contrast, drugs available in the pharmaceutical market for alternative use to fight SARS-CoV-2, in particular the drugs remdesivir, atazanavir, favipiravir, EIDD-2801 and hydroxychloroquine associated with azithromycin presented attractive preliminary results and are recommended for clinical studies in as an alternative way of coping with the new coronavirus.

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