An integrative literature review on the SARS-CoV-2 virus from 2015 to 2022

Uma revisão integrativa da literatura sobre o vírus SARS-CoV-2 de 2015 a 2022

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ABSTRACT
Coronaviruses of the order Nidovirales and families Coronaviridae, Arteriviridae, Mesoniviridae, Roniviridae were first isolated in 1937 and described in 1965. In 2019, the SARS-CoV-2 coronavirus was responsible for the coronavirus disease in 2019 (COVID-19) in Worldwide. Due to the great importance of SARS-CoV-2, this study integrated information about the virus, as a response: its origin, diagnosis and treatment, diagnosis and treatment. For this, a bibliographic survey was carried out in the Scielo, PubMed and Google Scholar databases regarding SARS-CoV-2, in order to describe its characteristics. SARS-CoV-2 does not yet have a well-clarified pathophysiology, it is known that it can cause an acute or chronic lung injury and that this condition resembles SARS-CoV, which results in aggressive inflammation initiated by viral replication. Both SARS-CoV and SARS-CoV-2 replicated similarly in alveolar epithelium, but SARS-CoV-2 replicates extensively in bronchial epithelium. Reverse transcription followed by polymerase chain reaction (RT-PCR) is widely used to identify viruses that cause respiratory secretions. Currently, with an ongoing viral pandemic, the importance of identifying the pathophysiological characteristics of SARS-CoV-2 and its serious impact on global public health becomes increasingly evident, especially with regard to the remarkable overload of health services, both private and public.

Keywords: Coronavirus, SARS-CoV-2, betacoronavirus, COVID-19.

RESUMO
Coronavirus da ordem *Nidovirales* e famílias *Coronaviridae*, *Arteriviridae*, *Mesoniviridae*, *Roniviridae* foram isolados pela primeira vez em 1937 e descrito em 1965. Em 2019, o coronavírus SARS-CoV-2 foi o responsável pela doença de coronavírus em 2019 (COVID-19) em todo o mundo. Devido à grande importância do SARS-CoV-2, este estudo integrou informações importantes a respeito do vírus, como: origem, morfologia, resposta inflamatória causada pelo mesmo, diagnóstico e tratamento. Para isso, foi realizado um levantamento bibliográfico nas bases de dados da Scielo, PubMed e Google Acadêmico a respeito do SARS-CoV-2, com intuito de descrever suas características. O SARS-CoV-2 não possui ainda uma fisiopatologia bem esclarecida, sabe-se que pode causar uma lesão pulmonar aguda ou crônica e que essa condição se assemelha à SARS-CoV, o que resulta em inflamação agressiva iniciada pela replicação viral. Tanto o SARS-CoV quanto o SARS-CoV-2 se replicaram de maneira semelhante no epitélio alveolar, mas o SARS-CoV-2 replico-se extensivamente no epitélio brônquico. A transcrição reversa seguida de reação em cadeia da polimerase (RT-PCR) é largamente usada para identificar vírus que causam secreções respiratórias. Atualmente, com uma pandemia viral em curso, torna-se cada vez mais evidente a importância do identificar as características fisiopatológicas do SARS-CoV-2 e seu grave impacto para saúde pública

mundial, especialmente no que se refere à notável sobrecarga de serviços de saúde, tanto privados quanto públicos.

Palavras-chave: Coronavírus, SARS-CoV-2, betacoronavirus, COVID-19.

1 INTRODUCTION

Coronaviruses (CoV) are the largest group of viruses belonging to the order Nidovirales, which includes the families Coronaviridae, Arteriviridae, Mesoniviridae, Roniviridae. The Coronavirinae family is subdivided into four genera, alpha, beta, gamma and delta coronaviruses. Viruses were initially classified based on serology, but are now divided by phylogenetic grouping (Gorbalenya et al., 2020).

The first human coronaviruses were isolated for the first time in 1937. However, it was in 1965 that the virus was described as coronavirus, due to the morphological characteristics of the viral particle observed under microscopy, alluding to a crown. Coronaviruses cause respiratory and intestinal infections in animals and humans, and among the most common species that infect humans are alpha coronavirus 229E and NL63 and beta coronavirus OC43, HKU1; both responsible for milder and usually self-limiting upper respiratory tract infections (Hasoksuz et al., 2020).

Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) are highly transmissible and pathogenic that began to infect humans in the early 21st century. They were not considered highly pathogenic to humans until the outbreak of Severe Acute Respiratory Syndrome (SARS) in 2002 and 2003 in Guangdong Province, China. Ten years after the emergence of SARS, another pathogenic coronavirus, the MERS-CoV coronavirus, emerged in Middle Eastern countries (Cui et al., 2019).

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is the virus responsible for coronavirus disease 2019 (COVID-19). First identified in Hubei, China) in December 2019, and shortly after the creation of a pandemic by the World Health Organization (WHO) in March 202. as well as SARS-CoV. The analysis placed the virus in the genus Betacoronavirus and subgenus Sarbecovirus, which confirms its probable origin in the bat coronavirus (BatCoV RaTG13) (Valencia et al., 2020). The viral nucleocapsids are assembled and sprout from the lumen of the endoplasmic reticulum golgi intermediate (ERGIC). As viral nucleocapsids wrap the viral RNA to produce new coronavirus virions, they are exocytosed, completing the replication cycle (Gao et al., 2020).

Currently, with a viral pandemic still ongoing, the importance of SARS-CoV-2 in the disease process and its serious impact on global public health is becoming increasingly evident, especially with regard to the remarkable overload of health services, both private and public. Therefore, studies that promote a better understanding of the various epidemiological aspects, as well as genetic and structural characteristics and the biosynthesis and immunopathology of SARS-CoV-2 are fundamental and of paramount importance for future perspectives in terms of specific and effective treatments. against COVID-19 caused by SARS-CoV-2, in addition to reinforcing prophylactic strategies against the virus.

2 METHODOLOGY

2.1 STUDY DELIMITATION

An integrative literature review was performed according to Machado et al. and Pereira et al. (2022), with searches performed in the SciELO (Scientific Electronic Library Online), PMC (US National Library of Medicine National Institute of Health) and Google Scholar databases, using the following descriptors: Coronavirus, SARS-CoV-2, Betacoronavirus, COVID-19.

For this study, 30 articles were selected between the years 2015 and 2022 addressing SARS-CoV-2. 19 of these articles addressed the central theme of the research, however, all those that did not address the focus of this work were excluded, in a total of 11 articles.

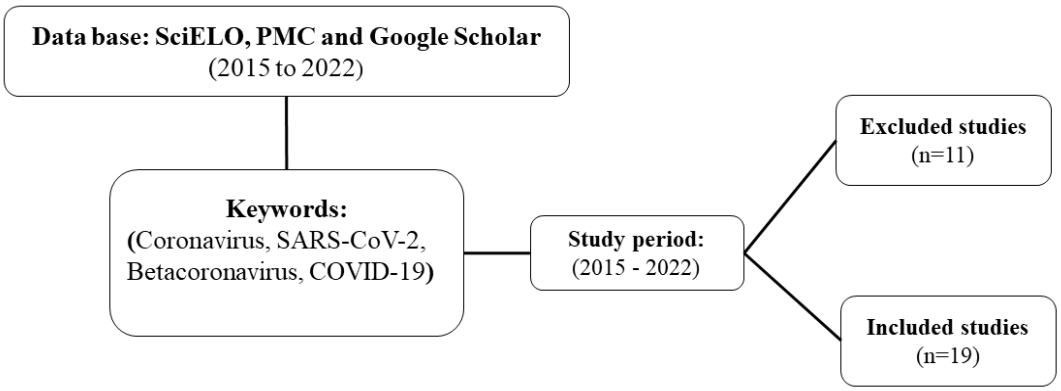
2.2 INCLUSION CRITERIA

Of the 30 articles selected to be evaluated for this study, only 19 met the inclusion criteria, which addressed relevant scientific content such as the history of the virus, its diagnosis, pathophysiology, mode of transmission, prophylaxis against the virus. The selection consisted of literature review articles and original articles without time and language restrictions.

2.3 EXCLUSION CRITERIA

All articles that did not address the focus of this study were excluded, including short communications, book chapters and studies that were not outside the proposed study period (2015 to 2022). Flowchart 1 demonstrates the steps followed to carry out this work.

Flowchart 1 - methodological steps



Source: Authors, 2022.

3 RESULTS AND DISCUSSION

WHO declared COVID-19 a public health emergency of international concern on January 30, 2020 and a pandemic on March 11, 2020. During this period, it was reported that about 80% of patients with COVID-19 have mild to moderate symptoms, while 20% develop severe manifestations such as severe pneumonia, acute respiratory distress syndrome (ARDS), sepsis, and even death (Gao et al., 2020).

Coronaviruses are enveloped, positive-sense, single-stranded RNA viruses that were first described in 1966 by Tyrell and Bynoe. They belong to the genus Betacoronaviiru (Zhu et al., 2020), as well as other zoonotic coronaviruses, such as SARS-Cov and MERS-CoV (Chen; Liu; Guo, 2022). One of the strands infers for the bat being the habitat of SARS-CoV-2, spreading to humans via Pangolin (Liu; Chen, W; Chen, J.-P, 2019). According to LI et al., 2020, bats are identified as the main natural reservoirs of Betacoronavirus, also harboring the discovery of a virus related to SARS-CoV. To further legitimize this statement, a study by Memish et al. (2013) demonstrated the presence of a betacoronavirus with 100% nucleotide match to MERS-CoV in stool samples of Taphozous perforatus species in Saudi Arabia.

In a research led by Ji et al. (2020), showed that SARS-Cov-2 was a recombinant virus between a known one, present in bats, and another of unknown origin. For Zhang et al. (2020), Pangolin-Cov is about 91% and 90% identical to SARS-CoV-2 and BatCoV and RaTG13 at the whole genome level, respectively, inferring that pangolin species is a natural reservoir of SARS-like coronaviruses. -CoV-2. Compared with other coronaviruses, SARS-CoV-2 has higher genomic affinity to two bat-derived coronaviruses, bat-SL-CoVZC45 and bat-SL-CoVZXC21 (about 88% genetic match), and more distant from SARS-CoV. -1 (about 79% compatibility) and MERS-CoV (about 50% similarity) (Lu et al, 2020). Therefore, it is unlikely that the origin of SARS-CoV-2 is laboratory (Andersen et al., 2020).

It is known that coronaviruses usually affect the respiratory or digestive tract of mammals, including humans, and are still considered to be zoonotic viruses, since studies indicate that the first infected human patients acquired these viruses directly from animals. SARS-CoV-2 isolated from clinical samples has crown-shaped protein epitopes seen on its surface, with diameters ranging from 60 to 140 nm. The cytopathic effects induced by SARS-CoV-2 appear to be different from SARS-CoV and MERS-CoV. After SARS-CoV-2 internalization, structural changes in host cells are seen earlier in human airway epithelial cells (at 96 hours) than in other cell lines, including Vero6, a monkey kidney cell line, and Huh-7, a liver cell line, (at 144 hours), and this makes a difference in response time to cytopathic effects caused by the presence of SARS-CoV-2 (Tang et al., 2020; Lai et al., 2020; Lai et al. al., 2020 and Abd El-Aziz et al., 2020).

SARS-CoV-2 does not yet have a well-clarified pathophysiology, it is known that it causes an acute lung injury and that this condition resembles SARS-CoV, which results in aggressive inflammation initiated by viral replication. Lucena et al. (2020), attempted to discuss and report possible mechanisms of inflammatory responses mediated by SARS-CoV-2 in individuals with pre-existing cardiometabolic diseases and to speculate possible therapeutic target that could be applied to obtain a better immune response, reduce the inflammatory profile and, consequently, reduce the critical levels of the disease.

3.1 TROPISM AND VIRAL BIOSYNTHESIS

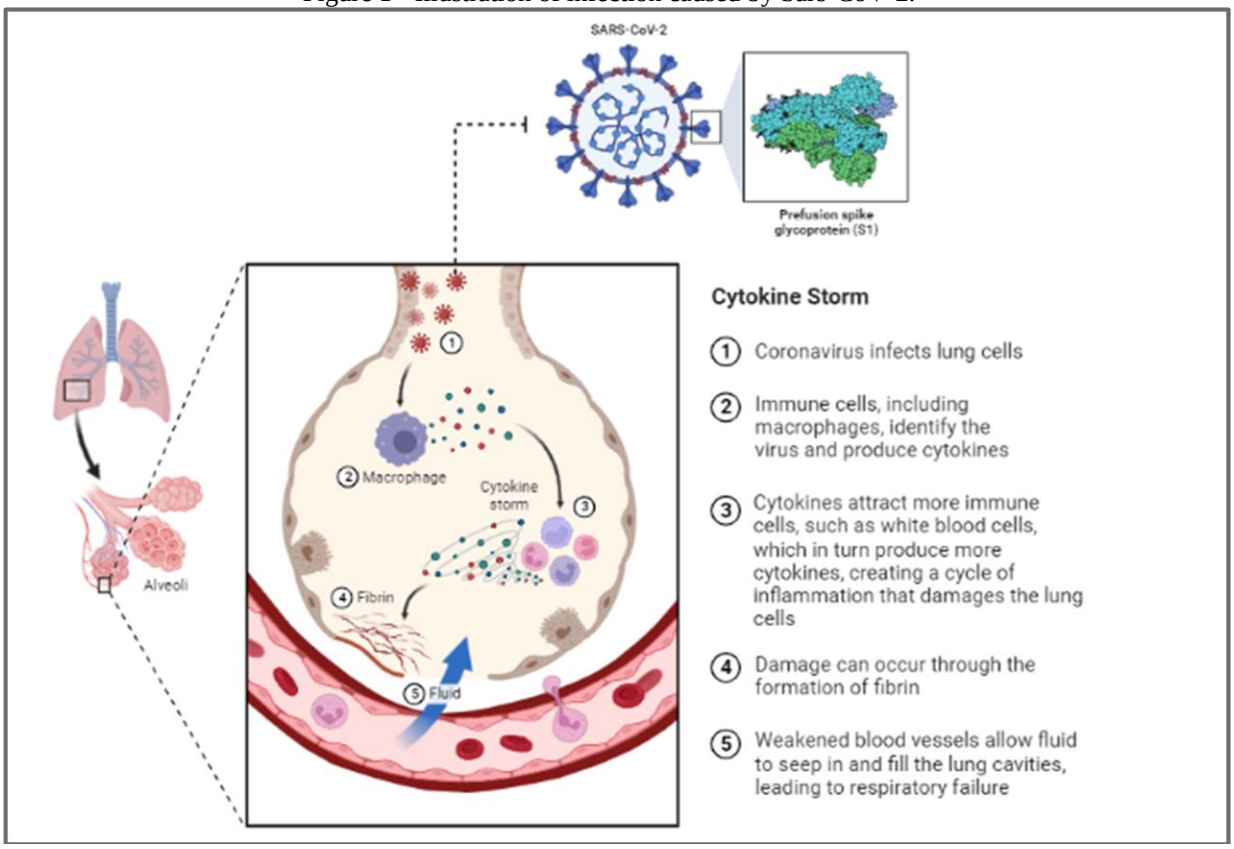
Conjunctival epithelium and conducting airways appear to be potential portals of SARS-CoV-2 infection. Both SARS-CoV and SARS-CoV-2 replicated similarly in alveolar epithelium, but SARS-CoV-2 replicated extensively in bronchial epithelium, which may elucidate robust transmission of this pandemic coronavirus (Hui et al., 2020).

Once viral particles enter the respiratory tract, the virus binds to lung cells in a process known as adsorption, using surface spike (S) proteins, which have the ability to specifically interact with target receptors on the cell. The main ones are the receptors for angiotensin-converting enzyme 2 (ACE-2) and dipeptidyl peptidase 4 (DPP4), present in bronchial ciliated epithelial cells and type II pneumocytes, respectively. Adsorption promotes a complex biochemical signaling, which allows changes that lead to the internalization of the viral particle in the host cell through the process of endocytosis (Gao et al., 2020).

Understanding the mechanism of virus entry into the respiratory tract may, in this regard, offer a promising curative strategy to treat viral infections, including Covid-19.

SARS-CoV entry is facilitated by S-glycoprotein binding to ACE2; later, conformational changes of glycoprotein S occur in the endosomal microenvironment by cathepsins B and L of the cellular serine protease. ACE2 is expressed in epithelial cells of the lung, tongue, kidney, heart and liver. Binding of S-glycoprotein to ACE2 can cause loss of cilia, squamous metaplasia, and increase in macrophages in the alveoli that cause diffuse alveolar damage in the lung (Fani et al., 2020).

Figure 1 - Illustration of infection caused by Sars-CoV-2.



Source: (Biorender, 2023).

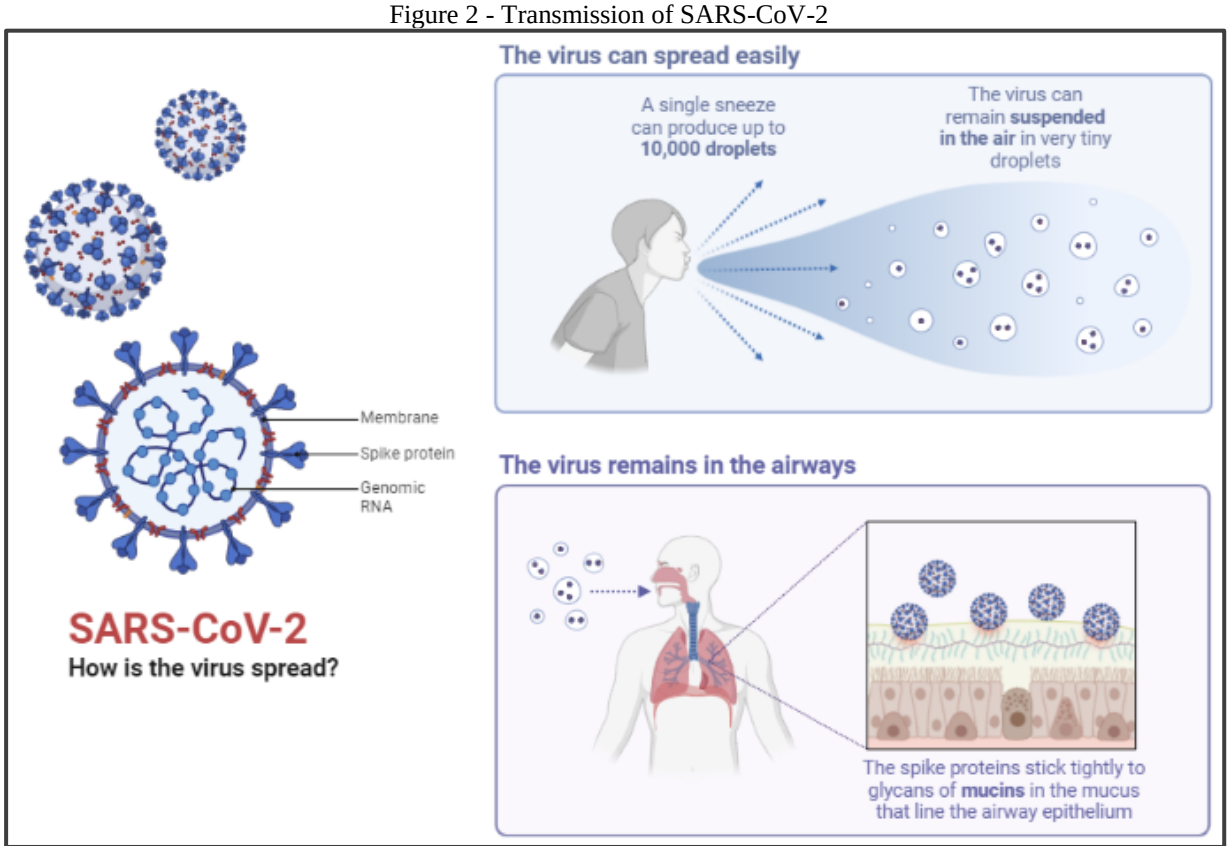
3.2 ROUTES OF TRANSMISSION

As an emerging acute respiratory infectious disease, COVID-19 mainly affects the respiratory tract, through droplets, respiratory secretions and direct contact (Guo et al., 2020). There have been reports of conjunctival transmission of SARS-CoV-2, viral shedding through tears, and ocular manifestations in patients with COVID-19 (Emparan et al., 2020).

Patients with severe or fatal COVID-19 infection are more likely to transmit the virus, as they shed a greater number of infectious particles compared to patients who have a mild or asymptomatic infection. The identification and quarantine of these patients in healthcare facilities where outbreaks have occurred, together with the implementation of adequate

infection control and constant case reports in different countries, has been effective in reducing transmission and containing outbreaks of the disease (Cruz et al., 2021). Figure 2 illustrates the transmission process.

Figure 2 - Transmission of SARS-CoV-2



Source: (Biorender, 2023).

3.3 IMMUNOPATHOLOGY

The virus is able to enter macrophages and dendritic cells, however, it only leads to an abortive infection. Furthermore, infection of these cell types may be important in inducing pro-inflammatory cytokines that may add up to disease (Fehr et al., 2015).

SARS-CoV-2 infection and lung cell destruction trigger a local immune response, recruiting monocytes and macrophages that respond to the infection, release cytokines, and respond to primary adaptive T and B cells. In most cases, this process is able to resolve the infection. However, in some cases, a dysfunctional immune response occurs, which can cause severe lung infection. It was observed that patients with severe COVID-19 requiring intensive care in hospitals exhibited higher blood plasma levels of IL-2, IL-7, IL-10, granulocyte colony stimulating factor (G-CSF), PI -10, MCP1, macrophage inflammatory protein 1a (MIP1α) and tumor necrosis factor (TNF)15,8. (Tay et al., 2020 and Abd Al-Aziz et al., 2020). In this way, the inflammatory feedback triggered by SARS-CoV-2 contamination triggers the excessive

synthesis of inflammatory or proinflammatory cytokines, receiving the name of "cytokine storm". The production of such mediators is responsible for high tissue and cellular damage, pulmonary and systemic inflammation, leading to lethal viral pneumonia, viral sepsis and severe acute respiratory syndrome. In addition to contributing to the incidence of probable hepatic, cardiovascular and neural complications (Almeida et al., 2020).

3.4 DIAGNOSIS

Rapid and accurate diagnostic tests are essential to control the ongoing COVID-19 pandemic (Wyllie et al., 2020). In the case of an acute respiratory infection, Reverse Transcription followed by polymerase chain reaction (RT-PCR) is commonly used to identify viruses that cause respiratory secretions. The viral envelope gene sequencing has been effectively implemented by 35 laboratories, however, the diagnostic algorithm employs other viral genomic sequences to confirm COVID-19 positivity by detecting the viral RNA polymerase and nucleoprotein gene sequences. RNA is extracted from clinical samples, through material from the respiratory tract (swabnasopharyngeal and oropharyngeal in outpatients and sputum, if present, endotracheal aspirate or bronchoalveolar lavage in patients with severe respiratory disease) (Cruz et al., 2020).

Rapid and reliable laboratory diagnostics for SARS-CoV-2 are important to support the rapid implementation of appropriate public health interventions. In the acute phase of COVID-19, laboratory diagnosis mainly depends on molecular methods. In addition, serological assays are now being developed to allow epidemiological assessments through serosurveillance as well as retrospective diagnosis in target groups. There is an urgent need for high quality test kits suitable for in vitro diagnostics (IVD), automated laboratory equipment and laboratory information systems (software). The LIS, which records, manages and stores data, is one of the key elements in reliable diagnostics with high throughput (Jaaskelainen et al., 2020)

It is crucial to note that the definitive diagnosis of COVID-19 is made by real-time polymerase chain reaction (RT-PCR), and a normal (negative) chest CT scan does not exclude the diagnosis. However, currently, the RT-PCR result took longer than the CT reports to be available, therefore, CT has taken on an important role in a comprehensive evaluation of patients, as it demonstrates high sensitivity (although low specificity), for detect the most frequent pulmonary findings of the disease (Shoji et al., 2020).

3.5 TREATMENT AND CLINICAL TESTS PERFORMED WITH GOOD RESULTS

There are currently no specific treatments for COVID-19, however clinical guidelines for the management of patients with suspected and confirmed COVID-19 are available to healthcare providers. However, these guidelines are not intended to replace expert consultation or clinical judgment and are periodically updated as new treatment options are available and approved based on research results and clinical trials (Yan et al., 2021).

Possible treatment strategies for SARS-CoV-2 infection is still a priority. Until then, there is no consensus on the best pharmacological treatment for patients with the disease, and drugs are available that contribute to the treatment of the symptoms of the disease. However, there are some drugs that have already been proven to be effective against SARS-CoV-2, although they are still in recent studies, such as the antiviral Favipiravir, Arbidol and Redesevir, which are promising drugs for therapeutic use. against the new coronavirus. (Bolarin et al., 2021). Therapies that are still in the research phase include new drugs and old agents available, being researched in clinical trials or through compassionate use (Dias et al., 2020).

3.5.1 Protease inhibitors

Protease inhibitors such as darunavir and atazanavir, used in the treatment of HIV, would be able to inhibit the viral replication of SARS-CoV-2 by inactivating the proteases, which are important for replication. The Agenzia Italiana del Farmaco Italiana (AIFA) has approved a study known as ARCO-Home, this aims to test the effectiveness of darunavir-cobicistat, favipiravir, lopinavir-ritonavir and hydroxychloroquine as in-home therapies in an earlier population with COVID-19, all to prevent the progression of the infection. And key drugs used in the context of the national emergency management plan for COVID-19 include lopinavir/ritonavir, used in COVID-19 patients with moderately severe symptoms and in the early stages of the disease, managed both at home and in hospital (Stasi et al., 2020).

To date, the Food and Drug Administration (FDA) has issued a note with authorized emergency use for two antibody cocktail pairs and an antibody monotherapy for the treatment of mild to moderate COVID-19. The first cocktail pair is called Lilly (tibody bamlanivimab or LY-CoV555/LY3819253) being used in combination with etesevimab, also called LY-CoV016. This combination greatly decreased the logarithmic viral load of SARS-CoV-2 at the onset of moderately severe infection in a phase II clinical trial (Li et al., 2022).

3.5.2 Antivirals investigated to treat COVID-19 in clinical trials or in vitro studies

Analog nucleosides are explored as possible treatment options for COVID-19. Options include geldesivir, remdesivir, ribavirin, and favipiravir, with remdesivir the drug that has received the most attention. Remdesivir was originally developed for the treatment of hemorrhagic fever virus, namely Ebola virus (EBOV) and Marburg, but underestimated in EBOV treatment compared to antibody strategies. These have in vitro antiviral activity on SARS and MERS. By competing with ATP and replacing it with adenosine during RNA synthesis, remdesivir inhibits viral RNA-dependent RNA polymerase (RdRp). Human mitochondrial RdRp show lower affinity for remdesivir compared to their viral counterparts, attenuating side effects for the host cell (Chang et al., 2020; Hashemian et al., 2020).

The drugs remdesivir (GS-5734) and favipiravir belong to the group of viral RNA inhibitors; lopinavir and ritonavir are responsible for inhibiting the viral protein; hydroxychloroquine and chloroquine which are inhibitors of virus entry into the host cell. There are also immunomodulators that are being tested, these are represented by nitazoxanide and ivermectin (Naik et al., 2021).

3.5.3 Vaccines

Advances in COVID-19 vaccines are quite encouraging as this is the first time that vaccine development has accelerated at this speed. Research advances that incorporate vaccination have ensured that the most critical public health intervention is developed in a timely manner. Points that should be considered for future COVID-19 vaccines include the development of heat-stable vaccines, that is, vaccines that can be easily administered in low-resource tropical environments (Ndwandwe et al., 2021).

There are several types of vaccines that have been developed with the aim of creating immune memory to fight the SARS-CoV-2 virus. Among these types of vaccines are live attenuated vaccines, which are viruses that are weakened (SARS-CoV-2) by the passage of animal or human cells, until the genome mutates and is capable of causing disease (Kashte et al., 2021). Vaccines based on SARS-CoV-2 proteins are purified from microorganisms, but in most cases, currently, they are produced by in vitro techniques, with recombinant DNA (Forni et al., 2021);

The US Food and Drug Administration (FDA), considered one of the largest regulatory agencies in health, declares that, for approval of a vaccine, there must be evidence of a reduction in the occurrence and severity of the disease in at least 50% of patients (Lima et al. al., 2021).

In Brazil there are some vaccines used to combat the virus. Some of them are: Chadox1 from Astrazeca and Oxford University containing adenovirus (Chimpanzee vector); CORONAVAC from Sinovac Biotec, using inactivated virus; BNT162 vaccines (PF-07302048) from Pfizer-Wyeth, Fosun and BioNTech containing mRNA; AD26.COV2.S (VAC31518) from Janssen-Cilag (Johnson & Johnson) containing human vector adenovirus; mRNA-1273 from the company Moderna containing mRNA; Gam-COVID-Vac (Sputnik V) from the Gamaleya Institute, from human vector adenovirus 2 and UB-612 from the Covaxx company with Peptide-Multitope compound (Vaccination, 2021).

4 FINAL CONSIDERATIONS

SARS-CoV-2 is a virus that is genetically modifying itself and has been causing public health problems. We could observe that SARS-CoV-2, currently, already demonstrates very important information that makes prevention and treatment measures necessary. However, its pathophysiology is still not well elucidated; however, the more studies that appear and the more information that is generated, the more it is considered an advance for science and for the fight against coronavirus.

One of the exceptional advances we've had is the development of vaccines that have contributed to generating immune memory in millions of people around the world. This has also drastically reduced the number of deaths worldwide. The development of drugs capable of eliminating SARS-CoV-2 is also in the testing phase, and some tests, as mentioned in the results and discussion, show that some drugs have great efficacy in an in vitro model, which could be a hope for the in vivo treatment of humans.

REFERÊNCIAS

Abd El-Aziz, T. M., & Stockand, J. D. (2020). Recent progress and challenges in drug development against COVID-19 coronavirus (SARS-CoV-2)-an update on the status. *Infection, Genetics and Evolution*, *83*, 104327.

Andersen, K. G., Rambaut, A., Lipkin, W. I., Holmes, E. C., & Garry, R. F. (2020). The proximal origin of SARS-CoV-2. *Nature medicine*, *26*(4), 450-452.

Bolarin, J. A., Oluwatoyosi, M. A., Orege, J. I., Ayeni, E. A., Ibrahim, Y. A., Adeyemi, S. B., ... & Adeoye, A. B. E. (2021). Therapeutic drugs for SARS-CoV-2 treatment: Current state and perspective. *International Immunopharmacology*, *90*, 107228.

Chang, Y. C., Tung, Y. A., Lee, K. H., Chen, T. F., Hsiao, Y. C., Chang, H. C., ... & Chen, C. Y. (2020). Potential therapeutic agents for COVID-19 based on the analysis of protease and RNA polymerase docking.

Chen, Y., Liu, Q., & Guo, D. (2020). Emerging coronaviruses: genome structure, replication, and pathogenesis. *Journal of medical virology*, *92*(4), 418-423.

Cruz, M. P., Santos, E., Cervantes, M. V., & Juárez, M. L. (2021). COVID-19, una emergencia de salud pública mundial. *Revista Clínica Española*, *221*(1), 55-61.

Cui, J., Li, F., & Shi, Z. L. (2019). Origin and evolution of pathogenic coronaviruses. *Nature reviews microbiology*, *17*(3), 181-192.

de Lucena, T. M. C., da Silva Santos, A. F., de Lima, B. R., de Albuquerque Borborema, M. E., & de Azevêdo Silva, J. (2020). Mechanism of inflammatory response in associated comorbidities in COVID-19. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, *14*(4), 597-600.

De vacinação, P. M. COVID19. *Direcao Geral de Saude*.

Dias, V. M. C. H., Carneiro, M., & Lacerda Vidal, C. F. (2020). Orientações sobre diagnóstico, tratamento e isolamento de pacientes com COVID-19. *J Infect Control*, *9*(2), 56-75.

dos Santos Pereira, C., Farias, J. R., Machado, P. R. P., Braga, G. L. C., Corôa, M. C. P., Ribeiro, R. M., ... & Varela, E. L. P. (2022). Amitriptyline: Useful for the prophylactic treatment of migraine?. *Research, Society and Development*, *11*(10), e465111033013-e465111033013.

Emparan, J. P. O. D., Sardi-Correa, C., López-Ulloa, J. A., Viteri-Soria, J., Penniecook, J. A., Jimenez-Román, J., & Lansingh, V. C. (2020). COVID-19 and the eye: how much do we really know? A best evidence review. *Arquivos brasileiros de oftalmologia*, *83*, 250-261.

Fani, M., Teimoori, A., & Ghafari, S. (2020). Comparison of the COVID-2019 (SARS-CoV-2) pathogenesis with SARS-CoV and MERS-CoV infections. *Future Virology*, *15*(5), 317-323.

Fehr, A. R., & Coronaviruses, P. S. An overview of their replication and pathogenesis. *Maier H, Bickerton E, Britton P (eds) Coronaviruses Methods in Molecular Biology*, *1282*.

Forni, G., & Mantovani, A. (2021). COVID-19 vaccines: where we stand and challenges ahead. *Cell Death & Differentiation*, *28*(2), 626-639.

Gao, Q., Bao, L., Mao, H., Wang, L., Xu, K., Yang, M., ... & Qin, C. (2020). Development of an inactivated vaccine candidate for SARS-CoV-2. *Science*, *369*(6499), 77-81.

Gorbalenya, A. E., Baker, S. C., Baric, R. S., de Groot, R. J., Drosten, C., Gulyaeva, A. A., ... & Ziebuhr, J. (2020). The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nature Microbiology*, *5*(4), 536-544.

Guo, Y. R., Cao, Q. D., Hong, Z. S., Tan, Y. Y., Chen, S. D., Jin, H. J., ... & Yan, Y. (2020). The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak–an update on the status. *Military medical research*, *7*(1), 1-10.

Hashemian, S. M., Farhadi, T., & Velayati, A. A. (2020). A review on remdesivir: a possible promising agent for the treatment of COVID-19. *Drug design, development and therapy*, *14*, 3215.

Hasöksüz, M., Kilic, S., & Saraç, F. (2020). Coronaviruses and sars-cov-2. *Turkish journal of medical sciences*, *50*(9), 549-556.

Hui, K. P., Cheung, M. C., Perera, R. A., Ng, K. C., Bui, C. H., Ho, J. C., ... & Chan, M. C. (2020). Tropism, replication competence, and innate immune responses of the coronavirus SARS-CoV-2 in human respiratory tract and conjunctiva: an analysis in ex-vivo and in-vitro cultures. *The Lancet Respiratory Medicine*, *8*(7), 687-695.

Jääskeläinen, A. J., Kekäläinen, E., Kallio-Kokko, H., Mannonen, L., Kortela, E., Vapalahti, O., ... & Lappalainen, M. (2020). Evaluation of commercial and automated SARS-CoV-2 IgG and IgA ELISAs using coronavirus disease (COVID-19) patient samples. *Eurosurveillance*, *25*(18), 2000603.

Ji, W., Wang, W., Zhao, X., Zai, J., & Li, X. (2020). Homologous recombination within the spike glycoprotein of the newly identified coronavirus 2019-nCoV may boost cross-species transmission from snake to human. *Journal of Medical Virology*, *doi*, *10*.

Kashte, S., Gulbake, A., El-Amin III, S. F., & Gupta, A. (2021). COVID-19 vaccines: rapid development, implications, challenges and future prospects. *Human cell*, *34*(3), 711-733.

Lai, C. C., Shih, T. P., Ko, W. C., Tang, H. J., & Hsueh, P. R. (2020). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. *International journal of antimicrobial agents*, *55*(3), 105924.

Li, D., Sempowski, G. D., Saunders, K. O., Acharya, P., & Haynes, B. F. (2022). SARS-CoV-2 neutralizing antibodies for COVID-19 prevention and treatment. *Annual Review of Medicine*, *73*, 1-16.

Li, Q., Guan, X., Wu, P., Wang, X., Zhou, L., Tong, Y., ... & Feng, Z. (2020). Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. *New England journal of medicine*.

Lima, E. J. D. F., Almeida, A. M., & Kfouri, R. D. Á. (2021). Vacinas para COVID-19-o estado da arte. *Revista Brasileira de Saúde Materno Infantil*, *21*, 13-19.

Liu, P., Chen, W., & Chen, J. P. (2019). Viral metagenomics revealed Sendai virus and coronavirus infection of Malayan pangolins (Manis javanica). *Viruses*, *11*(11), 979.

Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H., ... & Tan, W. (2020). Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *The lancet*, *395*(10224), 565-574.

Machado, P. R. P., dos Santos Pereira, C., da Silva, D. C. B., Varela, E. L. P., Corôa, M. C. P., Braga, G. L. C., ... & da Cruz, J. N. (2022). Atuação do farmacêutico no uso racional e manejo de

antigripais: guia de prática clínica. *Research, Society and Development*, *11*(8), e13711830526-e13711830526.

Melo, H. M., Paiva, M. J. M., & Carvalho, C. J. S. (2021). Pandemia do SARS-COV-2: uma revisão integrativa sobre os principais medicamentos, aprovados ou em fase de estudos, que podem ser utilizados no tratamento da COVID-19. *Pubsaúde*, *6*, a151.

Memish, Z. A., Mishra, N., Olival, K. J., Fagbo, S. F., Kapoor, V., Epstein, J. H., ... & Lipkin, W. I. (2013). Middle East respiratory syndrome coronavirus in bats, Saudi Arabia. *Emerging infectious diseases*, *19*(11), 1819.

Ndwandwe, D., & Wiysonge, C. S. (2021). COVID-19 vaccines. *Current opinion in immunology*, *71*, 111-116.

Shoji, H., Fonseca, E. K. U. N., Teles, G. B. D. S., Passos, R. B. D., Yanata, E., Silva, M. M. A., ... & Szarf, G. (2020). Structured thoracic computed tomography report for COVID-19 pandemic. *Einstein (São Paulo)*, *18*.

Stasi, C., Fallani, S., Voller, F., & Silvestri, C. (2020). Treatment for COVID-19: An overview. *European journal of pharmacology*, *889*, 173644.

Tang, A. N., Tong, Z. D., Wang, H. L., Dai, Y. X., Li, K. F., Liu, J. N., ... & Yan, J. B. (2020). Detection of novel coronavirus by RT-PCR in stool specimen from asymptomatic child, China. *Emerging infectious diseases*, *26*(6), 1337.

Tay, M. Z., Poh, C. M., Rénia, L., MacAry, P. A., & Ng, L. F. (2020). The trinity of COVID-19: immunity, inflammation and intervention. *Nature Reviews Immunology*, *20*(6), 363-374.

Teixeira, L. C. S. (2021). Comparação das vacinas Coronavac e Astrazeneca aprovadas para uso emergencial no Brasil.

Valencia, D. N. (2020). Brief review on COVID-19: the 2020 pandemic caused by SARS-CoV-2. *Cureus*, *12*(3).

Wyllie, A. L., Fournier, J., Casanovas-Massana, A., Campbell, M., Tokuyama, M., Vijayakumar, P., ... & Ko, A. I. (2020). Saliva or nasopharyngeal swab specimens for detection of SARS-CoV-2. *New England Journal of Medicine*, *383*(13), 1283-1286.
Yan, Y., Pang, Y., Lyu, Z., Wang, R., Wu, X., You, C., ... & Pang, C. H. (2021). The COVID-19 vaccines: recent development, challenges and prospects. *Vaccines*, *9*(4), 349.

Zhang, T., Wu, Q., & Zhang, Z. (2020). Probable pangolin origin of SARS-CoV-2 associated with the COVID-19 outbreak. *Current biology*, *30*(7), 1346-1351.

Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., ... & Tan, W. (2020). A novel coronavirus from patients with pneumonia in China, 2019. *New England journal of medicine*.