REVIEW COVID-19 (SARS-COV-2) AND MEDICINAL PLANTS – LITERATURE

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ABSTRACT: In December 2019, a new coronavirus originating from the city of Wuhan in China

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started an epidemic that brought many countries into chaos and despair. SARS-CoV-2, as identified, gave rise to the severe acute respiratory syndrome called COVID-19. Its transmission happens through droplets of saliva, hand or contaminated surfaces. Since its discovery, COVID-19 has led many to death, therefore, researchers from around the world have joined efforts to develop strategies to contain the virus. In this race, drugs such as Chloroquine and Hydroxychloroquine have become possible options for showing an antiviral effect, however, studies contest their efficiency, generating uncertainties. Therefore, other alternatives have been investigated in this context, and the study of medicinal plants has been the target of research for the treatment of COVID-19 in search of bioactive natural products that can exert an antiviral action. The study aimed to analyze the published literature on COVID-19 (SARS-CoV-2) and its relationship with medicinal plants. Bibliographical survey. So far, no specific treatment against the disease has been found, only supportive, with drugs that aim to improve the individual's immune system and ensure that the virus does not replicate, for example, there are options such as chloroquine, hydroxychloroquine, remdesivir and convalescent plasma. On the other hand, studies have revealed that medicinal plants such as garlic, among others, showed efficiency in modulating proteins with a view to preventing viral replication and improving immunity against COVID-19. So far, there are no drugs that are completely safe and have been shown to have activity against the new coronavirus (SARS-CoV-2). However, medicinal plants can contribute to the development of specific therapies against SARS-CoV-2 in a safe and effective way.
KEYWORDS: COVID-19; Medicinal plants; Treatment; Biocompounds; SARS-CoV-2; Chloroquine.

REVISÃO COVID-19 (SARS-COV-2) E PLANTAS MEDICINAIS - LITERATURA

RESUMO: Em dezembro de 2019, um novo coronavírus originário da cidade de Wuhan, na China, iniciou uma epidemia que levou muitos países ao caos e ao desespero. O SARS-CoV-2, conforme identificado, deu origem à síndrome respiratória aguda grave chamada COVID-19. Sua transmissão acontece através de gotículas de saliva, mãos ou superfícies contaminadas. Desde sua descoberta, o COVID-19 levou muitos à morte, por isso, pesquisadores de todo o mundo uniram esforços para desenvolver estratégias para conter o vírus. Nesta corrida, medicamentos como Cloroquina e Hidroxicloroquina tornaram-se opções possíveis por apresentarem efeito antiviral, porém, estudos contestam sua eficiência, gerando incertezas. Portanto, outras alternativas têm sido investigadas nesse contexto, e o estudo de plantas medicinais tem sido alvo de pesquisas para o tratamento da COVID-19 em busca de produtos naturais bioativos que possam exercer ação antiviral. O estudo teve como objetivo analisar a literatura publicada sobre COVID-19 (SARS-CoV-2) e sua relação com plantas medicinais. Levantamento bibliográfico. Até o momento, não foi encontrado nenhum tratamento específico contra a doença, apenas de suporte, com medicamentos que visam melhorar o sistema imunológico do indivíduo e garantir que o vírus não se replique, por exemplo, há opções como cloroquina, hidroxicloroquina, remdesivir e convalescença plasma. Por outro lado, estudos revelaram que plantas medicinais como o alho, entre outras, mostraram eficiência na modulação de proteínas visando prevenir a replicação viral e melhorar a imunidade contra a COVID-19. Até o momento, não existem medicamentos completamente seguros e que tenham demonstrado atividade contra o novo coronavírus (SARS-CoV-2). No entanto, as plantas medicinais podem contribuir para o desenvolvimento de terapias específicas contra o SARS-CoV-2 de forma segura e eficaz.
PALAVRAS-CHAVE: Covid-19; Plantas medicinais; Tratamento; Biocompostos; SARS-CoV-2; Cloroquina.

REVISIÓN COVID-19 (SARS-COV-2) Y PLANTAS MEDICINALES - BIBLIOGRAFÍA

RESUMEN: En diciembre de 2019, un nuevo coronavirus originario de la ciudad de Wuhan, en China, inició una epidemia que sumió a muchos países en el caos y la desesperación. El SARS-CoV-2, tal y como fue identificado, dio lugar al síndrome respiratorio agudo severo denominado COVID-19. Su transmisión se produce a través de gotitas de saliva, de las manos o de superficies contaminadas. Desde su descubrimiento, el COVID-19 ha llevado a muchos a la muerte, por lo que investigadores de todo el mundo han aunado esfuerzos para desarrollar estrategias de contención del virus. En esta carrera, fármacos como la Cloroquina y la Hidroxicloroquina se han convertido en posibles opciones por mostrar un efecto antiviral, sin embargo, los estudios refutan su eficacia, generando incertidumbres. Por lo tanto, otras alternativas han sido investigadas en este contexto, y el estudio de las plantas medicinales ha sido el objetivo de la investigación para el tratamiento de COVID-19 en busca de productos naturales bioactivos que puedan ejercer una acción antiviral. El estudio tuvo como objetivo analizar la literatura publicada sobre el COVID-19 (SARS-CoV-2) y su relación con las plantas medicinales. Estudio bibliográfico. Hasta el momento, no se ha encontrado un tratamiento específico contra la enfermedad, sólo de soporte, con fármacos que buscan mejorar el sistema inmunológico del individuo y asegurar que el virus no se replique, por ejemplo, existen opciones como la cloroquina, hidroxicloroquina, remdesivir y plasma convaleciente. Por otro lado, estudios han revelado que plantas medicinales como el ajo, entre otras, mostraron eficacia en la modulación de proteínas con vistas a impedir la replicación viral y mejorar la inmunidad contra el COVID-19. Hasta el momento, no existen medicamentos que sean completamente seguros y que hayan demostrado tener actividad contra el nuevo coronavirus (SARS-CoV-2). Sin embargo, las plantas medicinales pueden contribuir al desarrollo de terapias específicas contra el SARS-CoV-2 de forma segura y eficaz.

PALABRAS CLAVE: Covid-19; Plantas medicinales; Tratamiento; Biocompuestos; SARS-CoV-2; Cloroquina.

1. INTRODUCTION

The new β-coronavirus SARS-CoV-2, which causes the infectious disease COVID-19, emerged in the city of Wuhan, Hubei Province, China, in December 2019, starting the transmission of a pneumonia of unknown etiology. After bioinformatics analysis, the causative agent was identified as SARS-CoV-2 (Severe Acute Respiratory Syndrome by Coronavirus 2), triggering the disease called COVID-19. Due to the rapid geographic spread of COVID-19, the World Health Organization declared, in March 2020, the pandemic of the new Coronavirus (SARS-CoV-2) (NETO et al., 2021).

The transmission of COVID-19 occurs through contaminated droplets, hands or surfaces, with virus incubation periods between 2-14 days (NETO et al., 2021). Symptoms of the new Coronavirus can range from asymptomatic to the development of severe pneumonia and death, however, the most frequent symptoms are fever, dry cough, muscle fatigue, throat irritation, headache, myalgia, nasal congestion and diarrhea (OLIVEIRA et al., 2020a).

According to data from the World Health Organization (WHO) as of 31 July 2022, over 574 million confirmed cases and over 6.3 million deaths have been reported globally. Given these alarming data, researchers around the world have been looking for new alternatives to control the virus. In the race for an effective treatment, chloroquine and hydroxychloroquine, antimalarials, have become possible options for showing an antiviral effect, however, studies dispute the benefits of chloroquine and hydroxychloroquine, generating uncertainty about the use of these drugs (OLIVEIRA et al., 2020a).

Due to the difficulty of finding an effective therapeutic model, other alternatives are being analyzed in an attempt to help in the treatment of COVID-19. A therapeutic possibility includes medicinal plants (OLIVEIRA et al., 2020a), as they are part of folk medicine and, in many cases, as the only treatment resource. From the advance in knowledge regarding biological properties and potential use, progress has been made in the incorporation of medicinal plants as complementary measures as a therapeutic form for some pathologies, including antivirals (PESSOLATO et al., 2021).

The study of secondary metabolites of medicinal plants has stood out, in the search for bioactive molecules for the development of phytotherapeutics or phytopharmaceuticals that are effective and safe for the treatment of diseases, including viral infections (JAIN et al., 2020). In this context, molecular modeling using computational chemistry and graphic visualization techniques has been used through the *in silico* study that seeks substances with inhibitory potential in essential virus proteins such as cysteine-protease 3-chymotrypsin ($3CL^{pro}$), an important enzyme for viral replication (QAMAR et al., 2020; SILVA et al., 2020).

2. MATERIAL AND METHODS

To carry out this study, we opted for a research in the form of integrative literature review. The integrative review determines current knowledge on a specific topic, as it is conducted in order to identify, analyze and synthesize results of independent studies on the same topic. In this way, based on bibliographic and scientific references, aiming at a continuous update of the reliability about COVID-19 and medicinal plants that help in alternative treatment and the immune system.

For the elaboration of the research, searches and analyzes of texts carried out in Portuguese were carried out, from the keywords: COVID-19, medicinal plants, treatment, biocompounds and SARS-CoV-2. The texts are electronically available in official bodies, magazines, articles on sites such as SCIELO (*Scientifie Electronic Library*), Ministry of Health and Resolutions of the National Health Surveillance Agency (ANVISA).

3. DEVELOPMENT

3.1 Etiological agent

The Coronaviridae family is made up of coronaviruses (CoV) as members. These are single-stranded, enveloped RNA viruses. Until then, there were, in this family, six viruses capable of causing diseases in humans. However, in 2019, SARS-CoV-2 was discovered, a new member of this family that gave rise to "Coronavirus Disease-2019" (COVID-19) (ZHOU et al., 2020). Only four circulate between humans and animals commonly (HKU1, NL63, OC43 and 229E). These viruses were first described in 1966 and are divided into four subfamilies, the alpha, beta, gamma and delta-coronaviruses. The first two groups are responsible for causing coronaviruses in mammals (SINGHAL, 2020; SOHRABI et al., 2020; VELAVAN; MEYER, 2020).

Beta-coronaviruses tend to cause infections in humans with mild or even asymptomatic symptoms. Alpha-coronaviruses are capable of causing severe symptoms in animals and being fatal. In history, there are already two cases of zoonotic overflow of viruses from this subfamily. The first occurred in 2002-2003, in China, where the virus, having bats as its primary host, found the Asian palm civet as an intermediate host, generating the Severe Acute Respiratory Syndrome (SARS-CoV-1), killing 916 people. In 2012, in Saudi Arabia, there was another zoonotic overflow involving bats, where camels were the intermediate hosts, leading to Middle Eastern Respiratory Syndrome (MERS-CoV) and the death of 858 people (CORMAN et al., 2018; SINGHAL, 2020; SOHRABI et al., 2020; VELAVAN; MEYER, 2020).

The genetic material of coronaviruses is positive RNA type, which also acts as messenger RNA, and is translated by host cell ribosomes. The total length of the genome is 30 Kb (kilobase), containing a non-coding portion of the 5' terminus, a 1a/b coding region of the ORF open reading box (open reading frame), an "e" portion encoding the envelope protein (E protein), an "m" region encoding the membrane protein (M protein), an "n" portion encoding the nucleocapsid protein (N protein) and a non-terminal coding -3'. Viral particles are spherical, with about 125 nm in diameter and covered by a phospholipid envelope and have projections that emanate from the envelope in the form of spikes, formed by protein S trimers (*Spike Protein*). These projections generate a crown aspect, hence the denomination coronavirus (BEZERRA et al., 2020; VELAVAN; MEYER, 2020).

The polyprotein encoded in the ORF1a/b area of the non-structural protein can be cleaved by two viral proteases, 3CLpro (papain protease type) and PLpro (chymotrypsin protease type). Cleavage occurs to generate RNA-dependent RNA polymerase and helicase, which can guide the replication, transcription, and translation of the viral genome. Structural protein S can particularly bind to the host cell receptor. This is the main protein for viruses to enter susceptible cells. Proteins M and E are related in the constitution of the viral envelope, while protein N is associated in the assembly of the virus (BEZERRA et al., 2020; ZHOU et al., 2020).

SARS-CoV-2 has a genetic similarity of 79.6% with SARS-CoV-1 and also has a similarity of 96% with RaTG13, a species of coronavirus found in bats (ZHOU et al., 2020). The main feature of SARS-CoV-2 that differs from other viruses is the receptor binding domain (RBD) of its spike proteins (S) (VELAVAN; MEYER, 2020; ZHOU et al., 2020). This receptor has a strong ability to bind to the angiotensin II-converting enzyme (ACE2), in addition to having similarity to receptors of some pangolin coronaviruses (ZHANG et al., 2020).

Protein S, in the envelope of SARS-CoV-2, consists of two binding domains (S1 and S2). The S1 domain supports the attachment of the virus to the receptor (angiotensin II-converting protein). The S2 domain collaborates in the mechanism of fusion of the viral membrane with that of the host cell. The angiotensin II converting protein is seen in abundance in the pulmonary alveolar epithelial cells, which allows us to understand respiratory aggravation, transmission, infection pathways and disease manifestations (GOMES et al., 2020).

It is believed that primary viral replication takes place in the mucosal epithelium of the upper respiratory tract (nasal cavity and pharynx), with greater multiplication in the lower respiratory tract (trachea, lungs, bronchi, bronchioles and pulmonary alveoli) and in the gastrointestinal mucosa, which causes a mild viremia. Coronavirus is a pathogen that targets the human respiratory system, triggering SARS-CoV-2, generating acute lung injury, worsening of Acute Respiratory Distress Syndrome (ARDS) or Severe Acute Respiratory Syndrome (SRGA) and the condition of failure pulmonary (GOMES et al., 2020; WHO, 2020; ZHOU et al., 2020).

3.2 Epidemiology

SARS-CoV-2 was initially transmitted to humans through bats marketed as delicacies in a central market in the city of Wuhan. Then, after contact, SARS-CoV-2 was shown to have a high potential for dissemination (BEZERRA et al., 2020).

The disease is transmitted through interpersonal contact through droplets containing the virus expelled by the infected individual, through sneezing, coughing or speaking. These droplets are inhaled by people close to the infected person, or remain on surfaces, and can also infect after contact with contaminated objects, when touching the regions of the eyes, nose and mouth (CHAN et al., 2020). In addition, it is assumed that the virus incubation time lasts, on average, five days, but this period can extend up to the 14th day. Studies show that 86% of viral contaminations are carried out by asymptomatic individuals (BEZERRA et al., 2020). The action of common disinfectants such as sodium hypochlorite and hydrogen peroxide are capable of destroying the virus (SILVA et al., 2020).

SARS-CoV-2 was identified in the feces of patients confirmed in the city of Wuhan, and in the first case in the United States, indicating that the virus can exist and replicate in the digestive tract. This fact proposes the chance of fecal-oral transmission, but it is not confirmed that the consumption of foods contaminated by the virus is transmitted and causes infection. Thus, the danger of contamination through infected feces is pointed out as low, because they require further studies on this hypothesis (SILVA et al., 2020).

There is still no evidence of an important role for SARS-CoV-2 infection and transmission by or to other animals (BIALEK et al., 2020). The first animal reported to test positive for SARS-CoV-2 was a 17-year-old dog that came into contact with the virus through its infected owner in Hong Kong. However, the test was weakly positive and the animal did not develop symptoms of COVID-19 (THE GOVERNMENT OF THE HONG KONG SPECIAL ADMINISTRATIVE REGION, 2020). A tiger and seven other big cats from a zoo in New York City, USA, also tested positive for the virus and apparently showed symptoms of the disease (CDC, 2019a).

A study, which investigated the susceptibility of dogs, pigs, chickens, ducks, ferrets and cats to the virus, pointed out that only the last two animals are highly susceptible to the microorganism, with its replication in their respiratory tracts, while in other animals, virus replication was quite low (SHI et al., 2020). On the other hand, another study that tested cats and dogs that had been in contact with owners infected by the virus, did not show positive tests by RT-PCR or presence of antibodies against SARS-CoV-2 (TEMMAM et al., 2020). Although there is no evidence of transmission of the virus from animals to humans, domestic animals must be cared for as family members, in order to use preventive measures to prevent contagion (CDC, 2019b).

3.3 Clinical Signs

COVID-19 can be asymptomatic in about 60% of infected individuals (QIU, 2020). Symptomatic people usually present with symptoms of fever, dry cough, tiredness, and, in more severe cases, difficulty breathing. The most severe cases have been more prevalent in the elderly and patients with comorbidities such as cardiovascular disease, diabetes mellitus, chronic respiratory diseases and cancer (GRASSELLI et al., 2020; WU; MCGOOGAN, 2020). Other less common symptoms are nasal congestion, sore throat, headache, conjunctivitis, loss of smell or taste, diarrhea, skin irritation or discoloration of fingers (CORONAVÍRUS BRASIL, 2021).

In adults, the symptoms presented by patients tested COVID-19 positive are fever, respiratory problems, dry cough, sputum, headache, myalgia, fatigue and hemoptysis (YUKI et al., 2020). You can also see gastrointestinal problems such as anorexia, diarrhea, vomiting and abdominal pain. Secondary conditions and underlying diseases need to be considered in adults, such as arterial hypertension, liver diseases, diabetes, chronic obstructive diseases and vascular diseases. In elderly patients, the manifestation of the condition is similar to other age groups, but with greater damage and existence. Respiratory crisis is the main complaint of such patients, analogous to pneumonia and bronchopneumonia (CAO et al., 2020; XU et al., 2020).

3.4 Treatment

According to the National Health Surveillance Agency (ANVISA), a drug is a pharmaceutical product that has the presence of the drug in its formula, usually associated with pharmacotechnical adjuvants, prepared with prophylactic, palliative, curative or diagnostic purposes. However, the practice linked to the consumption of medicines, without prescription or medical advice, is called self-medication (RUBERT; DEUSCHLE; DEUSCHLE, 2020).

However, it is known that the simultaneous administration of a polypharmacy by the same individual can lead to drug interactions and several adverse reactions, which can lead to the death of the patient (RUBERT; DEUSCHLE; DEUSCHLE, 2020). Thus, adverse drug reactions (ADRs) are defined as harmful and unintended reactions, which may occur at doses used in humans for prophylactic, diagnostic or intended to modify physiological functions (RUBERT; DEUSCHLE; DEUSCHLE, 2020).

However, as of December 2019, the scenario has undergone an immense transformation in the field of global health. Due to the rapid worsening of the disease, the situation was considered critical, and frontline health professionals became directly involved in the care, diagnosis and treatment of patients with Covid-19 (RUBERT; DEUSCHLE; DEUSCHLE, 2020).

There is still no specific effective antiviral treatment for the disease caused by SARS-CoV-2, although most patients, after the introduction of vaccines and with mutations of the different strains, have only mild or moderate symptoms, between 5% and 10 % may still have a more serious and potentially fatal condition, requiring the emergence of drugs that are effective. Optimized supportive care remains the mainstay of therapy in the treatment of this condition. Many clinical trials are still ongoing and several antiviral and immunomodulatory agents are in the evaluation stages for COVID-19, but an effective antiviral treatment using randomized controlled trials still needs to be found, as certain agents are being used throughout the world. the world based on *in vitro* evidence, extrapolated or observational studies (DA SILVA NETO et al., 2020).

There is currently no specific cure or treatment for SARS-CoV-2. WHO (2021b) has coordinated efforts to seek information about the virus that causes COVID-19 with several ongoing studies in different countries, in order to prevent and treat the disease.

The pharmacological treatment of SARS-CoV-2 infection is supportive, that is, it reduces the symptoms that may appear, such as antipyretics for fever, patient hydration and anti-inflammatory drugs to combat the systemic immune attack (HASÖKSÜZ, 2020). In mild cases, care should be taken on an outpatient basis, with home isolation being essential with guidance from contacts. In addition, it is necessary to carry out hand hygiene, frequently, with soap and water, as well as the bedroom and clothes. The patient must be confined to a closed-door and well-ventilated room, quarantined. These people need to be accompanied by the primary care team for 48-48 hours via telephone or teleconsultation (RAJENDRAN et al., 2020).

In severe cases, if the individual has an oxygen saturation <95%, tachypnea, decompensation of comorbidities, they should be hospitalized in isolation two meters away from other suspected cases (BARBOSA et al., 2020). Intubation for the use of a mechanical respirator is a primordial process when the individual presents hypoxemia, respiratory effort, encephalopathy, respiratory obstructions, among other aspects. Respiratory physiotherapy is essential in the ICU, in the maintenance of ventilatory parameters in mechanical ventilators, in early mobilization to prevent the formation of pressure lesions, adhesions and deformities that reduce range of motion. Certain bronchial hygiene maneuvers, hyperinflation and aspiration are also the function of the physical therapist (LONG et al., 2020; RAJENDRAN et al., 2020).

3.4.1 Vaccines

Vaccine development programs are continuously updated by the World Health Organization (WHO), with projects coming from public and private sources. In March 2021, the Brazilian government sought to adopt the Covax Facility, ten months later, when international negotiations were in the final stages, from that the international and Brazilian press described this episode as a late adhesion (DA PAZ SILVA FILHO et al. , 2021). Even with the universal health care system - the Unified Health System (SUS), by April 10, 2021, Brazil had vaccinated about 10.7% of its population, which is considered a low percentage of vaccination. The vaccine began to be applied in February 2021, about three months after the start of the vaccine campaign in Europe and the USA, where the vaccines adopted were the AstraZeneca (Covishield), imported and destined to be produced by the Oswaldo Cruz Foundation (Fiocruz-Rio) and the co-production with Insumo Farmacêutico Ativo (IFA) Sino-Brazilian of Coronavac, known to be an inactive virus that is being produced by Instituto Butantan-São Paulo (DA PAZ SILVA FILHO et al., 2021).

As for vaccine production, the national Technical Report of the vaccination campaign against COVID-19 made public the WHO panorama, reporting the existence of 173 candidate vaccines in the pre-clinical research phase and 63 candidate vaccines in the clinical research phase. , of these 20 reached phase III clinical trials. Where two were initially selected as capable of being introduced into the PNI public health network, these being the CoronaVac vaccines from Farmacêutica Sinovac/Butantan and AstraZeneca produced by the University of Oxford in partnership with the Oswaldo Cruz Foundation (Fiocruz) and the Instituto Serum from India, consisting respectively of the inactivated virus SARS-CoV-2 and the recombinant adenovirus (ANVISA, 2021).

Purified inactivated viruses have gained an important role in vaccine production and, currently, eight inactivated COVID-19 candidate vaccines have been clinically evaluated during the pandemic. Although efficacy results against COVID-19 are not yet available. Wu et al. (2021), described that several studies show that inactivated vaccines can induce neutralizing antibody responses and have good safety profiles. Among these vaccines we have CoronaVac, which is an inactivated SARS-CoV-2 vaccine developed by Sinovac Life Sciences (DA PAZ SILVA FILHO et al., 2021).

The ChAdOx1 nCoV-19 (AZD1222) or AstraZeneca COVID-19 vaccine was developed at the University of Oxford in the case it is made from a replication-deficient chimpanzee adenoviral vector ChAdOx1, where it contains the structural surface glycoprotein antigen SARS-CoV- 2 (spike protein; nCoV-19) gene. This vaccine had an acceptable safety profile and was found to be effective against COVID-19. In addition, ChAdOx1 nCoV-19 is tolerated in the elderly and young and has similar immunogenicity at all ages (DA PAZ SILVA FILHO et al., 2021)

Pfizer's vaccine is based on mRNA, where synthetic messenger RNA is used, which acts in the individual's body to generate antibodies against the virus. It can be developed and manufactured more quickly and effectively when compared to traditional vaccines. Pfizer selected this mRNA-based vaccine technology because of its high-response potential, safety and rapid production capability. mRNA technology can also be strategic for pandemic and epidemic scenarios due to the agility in modifying the encoded antigen if necessary, as well as the potential for carrying out booster doses. The technique, in which only a piece of genetic material is used instead of the entire virus, has never been done before (PFIZER, 2022).

For the Ad26.COV2.S vaccine, popularly known as the Janssen/Johnson vaccine, the technology used is that of a viral vector, specifically a non-replicating adenovirus serotype 26 (Ad26) vector that transports viral genes into cells, which triggers the immune response. This vaccine is considered third generation because it is vectorized (OLIVEIRA et al., 2022).

Anvisa published the Protocol for Epidemiological and Sanitary Surveillance of Post-Vaccination Adverse Events with the objective of determining measures and guidelines for the performance of agents of sanitary and epidemiological surveillance of vaccines against the SARS-CoV-2 virus, in order to evaluate the product safety from the analysis of post-vaccination adverse events (AEFI). From this, Anvisa intends to control and detect suspected cases of AEFI, acting in the search and causality assessment of each one of them (DA PAZ SILVA FILHO et al., 2021).

3.4.2 Fármacos e Alvos moleculares dos fármacos utilizados para o tratamento

SARS-CoV-2 consists of a virus wrapped in single-stranded RNA and aims to infect cells through the viral structural spike (S) protein, capable of binding to the angiotensin II-converting enzyme receptor. Thus, virus particles use host cell receptors and endosomes to enter cells. Once inside the cell, viral polyproteins are synthesized, which encode the replicase transcriptase complex, and from then on, the virus synthesizes RNA through its dependent RNA polymerase, which is formed causing the assembly and release of viral particles (DA SILVA NETO et al., 2020).

Thus, these stages of the viral cycle provide possible mechanisms for drug therapies. Promising drug targets include non-structural proteins such as 3-chymotrypsin-like protease, papain protease, RNA-dependent RNA polymerase, all of which share homology with other novel coronaviruses (nCoVs). Additional drug targets may also include: preventing viral entry, in addition to regulating the immune response (DA SILVA NETO et al., 2020).

Studies suggest the use of some drugs that help to treat COVID-19, especially in hospitalized patients. Hydroxychloroquine (HQ) and chloroquine (CQ) are immunomodulatory drugs that inhibit the release of inflammatory cytokines, such as IL-1, IFN-1 and TNF. They are commonly used for diseases such as rheumatoid arthritis and systemic lupus erythematosus (SCHREZENMEIER;

DÖRNER, 2020). In the intracellular environment, these drugs block the mobilization of lysosomes in phagocytic cells, which reduces the inflammatory effects (BARBOSA et al., 2020). There are published studies of patients who used hydroxychloroquine in addition to azithromycin and had a drastic reduction in viral load (GAUTRET et al., 2020). In contrast, there are studies that refute the benefit of HQ and CQ, and report that these substances did not influence the effective recovery of patients (SAVARINO et al., 2003; DEVAUX et al., 2020)

Remdesevir is an antiviral drug that has been shown to be favorable in the treatment of critically ill hospitalized patients. Its activity occurs in the inhibition of the RNA polymerase enzyme, which blocks viral replication (KO et al., 2020). With regard to SARS-CoV-2, it proved to be effective in an *in vitro* study. Its activity is also investigated against the MERS-CoV coronavirus (AGOSTINI et al., 2018; RAJENDRAN et al., 2020).

Convalescent plasma therapy has already been used for other diseases such as Ebola and similar coronavirus diseases such as MERS and SARS. Its basis is the administration of serum from individuals who improved from COVID-19, due to the presence of antibodies that can neutralize the virus and reduce viremia. Therefore, such therapy points to a decrease in mortality in critically ill patients, an increase in neutralizing antibodies and an improvement in symptoms (BLOCH et al., 2020; TAY et al., 2020; TUFAN et al., 2020).

Dexamethasone is a synthetic glucocorticoid drug, widely used in inflammatory diseases such as asthma and rhinitis. A clinical study conducted in the UK reported the success of this anti-inflammatory in reducing deaths of critically ill individuals in ICU (LEDFORD, 2020).

A study by Lovato et al. (2021) presented several recent discoveries of drug reuse with potential beneficial effects against COVID-19. Such therapeutic agents include remdesivir, lopinavir, ritonavir, IFN-β, ribavirin, chloroquine, hydroxychloroquine, azithromycin, tocilizumab and ivermectin. According to the authors, these drugs have emerged as possible treatment alternatives, which can prevent the virus from entering the host cell, preventing viral replication and reducing the exacerbation of the host's immune response.

The Ichilov Medical Center in Tel Aviv has successfully completed phase one studies of the research project on a nasal spray, EXO-CD24 based on exosomes enriched with the protein CD24, which is administered by direct aspiration into the lungs. The CD24 protein is found on the surface of cells and has a known and important role in regulating the immune system, helping to calm the system and contain the cytokine storm resulting from the SARS-CoV-2 coronavirus (TARRO, 2021).

As already mentioned, there are few randomized trials that have demonstrated an effective antiviral treatment for the treatment of COVID-19. The body's immune responses to the new coronavirus are different for each individual, which can result in different clinical conditions and, consequently, different responses to treatment and vaccines (DA SILVA NETO et al., 2020).

In this sense, new approaches have been studied since the beginning of the pandemic, using hypotheses from the potential immunomodulatory effects of certain substances, antioxidants, chelating agents, use of vitamins, from herbal and homeopathic medicines or stem cells. Thus, medicinal plants have been gaining ground in the treatment of various pathologies, including COVID-19.

3.5 What are medicinal plants

The WHO defines medicinal plant as being "any and every plant that has, in one or more organs, substances that can be used for therapeutic purposes or that are precursors of semi-synthetic drugs" (VEIGA JUNIOR et al., 2005). The practice of using medicinal plants is one of the oldest ways within the medicinal practice of humanity, as they are able to alleviate and cure certain illnesses, commonly their use occurs through teas and infusions carried out on the patient (PESSOLATO et al., 2021).

There are records of the use of medicinal plants in China (2838-2698 BC) when Emperor Shen Nung cataloged 365 medicinal plants. In India, around 1500 BC, the Hindu physician Susruta already had an understanding of 760 medicinal plants. In Brazil, the medicinal use of plants is based on indigenous, African and European cultures (OLIVEIRA et al., 2020a).

According to ANVISA (2020a), when the medicinal plant is industrialized in order to acquire a medicine, the herbal medicine is obtained as a result. The industrialization process prevents contamination by microorganisms and foreign substances. In addition, it is possible to standardize the amount and correct form of the drug that should be used, providing greater safety in consumption. However, herbal medicines must be regularized at ANVISA before being marketed.

The Brazilian Ministry of Health has encouraged the insertion of complementary intervention practices for the treatment of diseases in the Unified Health System (SUS) efficiently, including the implementation of the National Policy on Medicinal Plants and Herbal Medicines (PNPMF) in 2006, and the National Policy on Integrative and Complementary Practices (PNPIC), as well as, in 2009, the National List of Medicinal Plants of Interest to the Unified Health System (SUS), whose objective is to ensure safe access and rational use to the population of medicinal and herbal plants, enabling the sustainable use of biodiversity, the development of the production chain and the national industry (OLIVEIRA et al., 2020a).

In the context of the National Pharmaceutical Assistance Policy and the SUS, the Pharmacy Viva, created in 2010, covers "all stages, from the cultivation, collection, processing, storage of medicinal plants, handling and dispensing of masterful preparations and workshops of medicinal plants and herbal medicines" (ANVISA, 2020b). Therefore, SUS can offer medicinal plants in the form of fresh plant (in natura), dry plant (plant drug), manipulated herbal medicine and industrialized herbal medicine (ANVISA, 2020b).

3.6 *In silico* study of biomolecules extracted from plants against essential proteins of SARS-CoV-2

Bioactive substances with antiviral properties have been identified and their mechanisms of action elucidated. Alkaloids, proteins, saponins, flavonoids found in plant extracts showed antiviral potential. Hydrolyzable tannins attracted significant attention from Khalifa et al., 2020, who investigated 10 structurally different hydrolyzable tannins as natural anti-COVID-19 by binding to the major 2019-nCoV protease using molecular fit modeling via Molecular Operating Environment software (MOE, 2009).

Molecular modeling, according to IUPAC, is the "investigation of molecular structures and properties using computational chemistry and graphical visualization techniques, in order to provide a plausible three-dimensional representation under a given set of circumstances" (CARVALHO et al., 2003). Thus, in silico studies aim to predict the behavior of real systems, through computer simulations, allowing the electronic and structural characterization of a molecule, as well as studying the interaction between the molecule and its receptor, providing information that contributes to the discovery of new drugs (RODRIGUES, 2001).

Among these *in silico* researches, the study of secondary metabolites of medicinal plants has stood out, in the search for bioactive molecules for the development of effective and safe phytomedicines or phytopharmaceuticals for the treatment of diseases, including viral infections (JAIN et al., 2020; SILVA et al., 2020).

3.7 Medicinal plants used to assist in the treatment of COVID-19

The Indian neem (*Azadirachta indica* A. Juss), also known as Margosa, is a plant of Asian origin, specifically native in India. Its phytochemicals are found in various plant organs such as seeds, leaves, bark, flowers and roots. The constituents of Indian neem were shown to be possible inhibitors of the membrane (M) and envelope (E) proteins of SARS-CoV-2, and they are Nimbolin, which has the strongest binding free energy with the M and E proteins, and Nimocin and Cycloartanols (24-Methylenecycloartanol and 24-Methylenecycloartan-3-ona). The tests showed that the binding efficiency of the natural elements of Indian neem against SARS-CoV-2 related targets in viral binding and replication was superior compared to the drugs Lopinavir/Ritonavir and Remdesivir, therefore, Margosa may be favorable in controlling infection caused by SARS-CoV-2 (NETO et al., 2021).

Nigella sativa, also commonly called "Black Cumin", is a plant native to the Mediterranean Basin, therefore, it is found in nature in countries like the Middle East, Spain or India. Active components such as thymoquinones, present in *Nigella sativa* seeds, may be one of the molecules capable of blocking the recognition region of HSPA5 or BIP, an immunoglobulin binding protein, responsible for the entry of some viruses such as Ebola and Zica, possibly being useful in reducing the risk of COVID-19, according to the studies analyzed (OLIVEIRA, 2020b).

Alllium sativum, also called common Garlic, is a plant from the East and Southern Europe. Garlic contains antiviral, antibacterial and immune system stimulant properties, being used as a therapeutic medium in traditional medicine for the treatment of parasitic and viral infections, such as the influenza virus. Through 17 substances found in garlic essential oil - allyl disulfide, allyl trisulfide, (E)-1-propenyl allyl disulfide, methyl-allyl trisulfide, allyl tetrasulfide, 1,2-dithiol, (Z)-allyl-1-propenyl disulfide, 2-vinyl-4H-1,3-dithiene, 3-vinyl-1,2-dithiacyclohex-4-ene, carvone, 2-propenyl propyl trisulfide, allyl methyldisulfide, diacetone alcohol trisulfide, 1 (E)-1- propenyl, 2-propenyl allyl sulfide, 1-propenyl methyl disulfide and trisulfide -, triggers the inhibition of ACE2, causing the coronavirus to disassociate from the host and, concomitant with, the attack of the PDB6LU7 protein, which is the main protease of SARS-CoV-2, in this way, is blocked the protein maturation and advance of the infectious process, contributing to the resistance to the virus (SILVA et al., 2020).

Silva et al. (2020) presents that recent studies propose that the therapeutic approach in relation to COVID-19 infection shows promising results when there is ACE2 inhibition, through the inactivation of the serine 2 transmembrane protease or inactivation of the ACE2 receptor itself. Based on this situation, Persian fruits and plants were approached with efficiency of up to 100%, for the species Wild Cherry (*Cerasus avium* (L.)), *Alcea digitata* (Boiss.) and Granza (*Rubia tinctorum* L.); and up to 70% for the sorrel orange (*Citrus aurantium* L.), *Berberis integerrima* Bge; Harmal (*Peganum harmala* EU), being indicated the consumption of fruits, teas and extracts. It is also important to emphasize that more studies are needed to assess the immune potential and its associations with the treatment or advancement of viral infections.

Cannabis sativa L., also known as Cannabidiol, marijuana or pot, is one of the first non-food plants cultivated by humans, having its origin related to Central Asia. The active compounds present in the leaves of this plant, especially CBD, is a viable option to be analyzed in the treatment of COVID-19, due to its anti-inflammatory properties and potential to improve lung functions. Studies suggest the use of CB2 receptors (cannabinoid receptor type 2) as pharmacological targets for the treatment of SARS-COV-2 infection, since selective stimulation of CB2 can decrease the inflammatory response in patients positive for COVID-19 and improve the prognosis, in addition to the possible control of the inflammatory cascade, taking into account its ability to reduce the excessive production of cytokines (SOUZA BJM et al., 2020).

Eucalyptus globulus, also named Eucalyptus, is a naturally occurring plant from Tasmania and southern Australia. The eucalyptus oil, extracted from the leaves by the process of steam distillation, performs a great action on the respiratory system, with anti-inflammatory and antiseptic properties due to the presence of eucalyptol, which has a regulatory effect on the nuclear factor kappa B (NK- kB) and protein kinases. It also has stimulant properties and strengthens the immune system, so it is especially recommended against respiratory diseases such as asthma, bronchitis, tuberculosis and sinusitis. Thus, the presence of flavonoid compounds quercetin and hyperoside may be associated with an anti-inflammatory response, desirable in Covid-19 cases (OLIVEIRA et al., 2020a; SOUZA MRN et al., 2020).

Piper nigrum (Black Pepper), also called Round Pepper, native from India, is part of a group of plants used to treat viral infections. In silico tests with the active element piperine, present in the fruit, showed a relevant binding affinity for the SARS-CoV-2 glycoproteins, presenting the property of blocking viral replication (OLIVEIRA, 2020b).

The flower *Lycoris radiata*, known as the red spider lily, one of the species most used in traditional Chinese medicine, contains as active principle licorine, an alkaloid that has shown the ability to prevent viral replication. In recent decades, licorine has attracted interest because of its analgesic, anti-inflammatory and antiviral properties. This species also has a high selectivity index related to the ability of the compound to contain biological activity without generating toxic effects. The antiviral action mechanism of this constituent is not clearly described in the researches, however, based on the acquired results, it is valid to consider it as a SARS-CoV-2 inhibitor, since studies already report its expressive biological action as an anti-SARS -CoV (OLIVEIRA, 2020b).

The plant species *Scutellaria baicalensis*, popularly named scutelaria and skullcap de baical, native to China, has as its main active compound Baicaleína (5, 6, 7-trihydroxyflavone) a flavonoid found in the root of the plant, considered one of the capable natural metabolites of blocking SARS-CoV-2 $3CL_{pro}$ protease in in vitro tests with COVID-19-contaminated cells (OLIVEIRA, 2020b). Another study reports that the ethanol extract of *S. baicalensis* and baicalein inhibit the pro-SARS-CoV-2 3CL activity in vitro with IC 50 of 8.52 μg / ml and 0.39 μM, respectively. Both block SARS-CoV-2 replication in Vero cells with EC 50 of 0.74 μg/ml and 2.9 μM, respectively. Although baicalein is mostly active in the post-viral entry stage, ethanol extract also prevents viral entry (LIU et al., 2021).

4 CONCLUSION

The pandemic generated as a result of the rapid and potential dissemination of SARS-CoV-2 has led the world to a situation of extreme concern, especially on the part of Public Health Institutions. However, there was a great technological leap in the search for early identification mechanisms, more adequate management and the best therapeutic strategy to be adopted.

Considering the global scenario, where there is no scientifically proven assertive treatment, the use of folk medicine through medicinal plants is a promising opportunity, with the potential to reduce viral replication and modulate the inflammatory response. Furthermore, some biocompounds produced by medicinal plants found in this work were superior to other synthetic drugs currently adopted for the treatment of COVID-19. Therefore, it is considered that the study of medicinal plants is important and should be invested as an alternative tool for the treatment of diseases such as COVID-19.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Table 1. Medicinal plants tested against COVID-19 in the period 2020 – 2021.

Plant Popular name	Parts of the plant	Mechanism of action	Extract Compound	Biological Material Used	Research results	Location	References
Azadirachta indica *A. Juss* (Indian neem)	Seed, leaf, bark, root and flowers	Inhibit the membrane (M) and envelope (E) proteins of SARS-CoV-2.	Nimbolin Nimocine Cycloartanols	Cells contaminated with COVID-19	Tests showed that the binding efficiency of natural elements of Indian neem against SARS-CoV-2 related targets in viral binding and replication was superior compared to Lopinavir/Ritonavir and Remdesivir drugs.	India	(Neto et al., 2021)
Nigella sativa (Cominho Preto)	Seed	Block HSPA5 or BIP recognition region.	Thymoquinones	Cells contaminated with COVID-19	HSPA5 or BPI, an immunoglobulin binding protein, responsible for the entry of some viruses such as Ebola and Zica, and possibly useful in reducing the risk of COVID-19.	Middle East	(Oliveira, 2020)
Alllium sativum (Garlic)	Oil	Inhibit ACE2 and attack PDB6LU7 protein	Allyl disulfide and 17 other substances	Cells contaminated with COVID-19	The substances trigger ACE2 inhibition, causing the coronavirus to disassociate itself from the host and, at the same time, attack the PDB6LU7 protein, which is the main protease of SARS-CoV-2.	East Southern Europe	(Silva et al, 2020)
Cannabis sativa (Canabidiol)	Leaves	Use CB2 receptors (cannabinoid receptor type 2) as pharmacological targets for the treatment of SARS-COV-2 infection.	CBD	Cells contaminated with COVID-19	Selective stimulation of CB2 can decrease the inflammatory response in patients positive for COVID-19 and improve the prognosis, in addition to the possible control of the inflammatory cascade.	Central Asia	(Mano-Sousa et al, 2020)
Eucalyptus globulus (Eucalyptus)	Leaves	Strengthen the immune system.	Quercetin and hyperoside flavonoids	Cells contaminated with COVID-19	The presence of flavonoid compounds, quercetin and hyperoside may be associated with an anti-inflammatory response, desirable in Covid-19.	Tasmania South Australia	(Souza et al, 2020; Oliveira et al, 2020)
Piper nigrum (Black Pepper)	Fruit	Binding affinity for SARS-CoV-2 glycoproteins	Piperine	Cells contaminated with COVID-19	Tests show a relevant binding affinity for SARS-CoV-2 glycoproteins, showing the property of blocking viral replication.	India	(Oliveira, 2020)
Lycoris radiata (red spider lily)	Flower	Alkaloid with the ability to prevent viral replication.	Liquorine	Cells contaminated with COVID-19	The antiviral action mechanism is not clearly described, however, based on the acquired results, it is valid to consider it as a SARS-CoV-2 inhibitor, since studies already report its expressive biological action as an anti-SARS-CoV.	China	(Oliveira, 2020)
Scutellaria baicalensis (Skull-cap)	Root	Flavonoid capable of blocking SARS-CoV-2 $3CL_{pro}$ protease	Baicaleína	Cells contaminated with COVID-19	Studies report inhibition of pro-SARS-CoV-2 3CL activity and blockade of SARS-CoV-2 replication by baicalein.	China	(Liu et al., 2021)

Source: Elaborated by the authos.

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