COVID-19 THERAPEUTICAL OPTIONS: OVERVIEW ON CURRENTLY ANTIMALARIALS AND ANTIPARASITIC DRUGS USED

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Abstract: Given the amount of scientific knowledge produced and published daily about the new corovavirus, this study sought to review evidence on some of the drugs used to treat Acute Respiratory Infection Syndrome caused by the COVID-19 virus. Thus, antimalarials and antiparasitics were evaluated regarding chemical and pharmacological aspects, including mechanism of

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ISSN: 2763-5724
Vol. 01 - n 04 - ano 2021
Editora Acadêmica Periodicojs

action, toxicity, adverse effects and recommendation for use in the treatment of COVID-19.

Keywords: COVID-19; Therapeutic Approaches; Drug Therapy

Background

Epidemiological and virological studies suggest that COVID-19 transmission occurs mainly from symptomatic people to others, by direct contact through respiratory droplets eliminated by the upper respiratory tract (such as nose and throat). In the first 3 days from the onset of symptoms when patients with infection cough, sneeze, or even during a conversation or by contact with contaminated objects and surfaces. Also, other forms of transmission are suggested, such as by hugging and close contact (e.g. contact with the mouth, nose, or conjunctiva of the eyes through the infected hands). It has not been recognized so far, COVID-19 mother-to-child transmission during breastfeeding (HEMMATI et al., 2020).

Several repeated collected biological samples from confirmed patients with the virus has demonstrated that the incubation period for COVID-19 (which is the time between exposure to the vírus – infection, and the onset of symptoms) is on average 5 to 6 days, but it can last up to 14 days. During this period, also known as the "pre-symptomatic" period, some infected people can be highly contagious, from 1 to 3 days before the onset of symptoms (WORLD HEALTH ORGANIZATION, 2020).

After the incubation

ISSN: 2763-5724
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period of the disease, it is recognized that the infection by COVID-19 exhibits three degrees of increasing severity, which correspond to distinct clinical forms. The first stage (mild) is referred to by an early infection that occurs at the time of inoculation of the virus and the onset of the disease, associated with mild and often non-specific symptoms such as malaise, fever, and dry cough. In the second stage, occurs the viral multiplication and localized inflammation in the lung and establishing of pneumonia, follow by cough, fever, and possibly hypoxia. A minority of patients with COVID-19 will make the transition to the third and more severe stage of the disease, which manifests itself as an extrapulmonary hyper inflammation syndrome. Besides, systemic inflammation markers may be increased and observed by inflammatory cytokines and elevated biomarkers such as IL-2, IL-6, IL-7, significantly in patients of this more severe stage (SIDDIQI; MEHRA, 2020).

Information about this new coronavirus is still limited to characterize the clinical disease spectrum, as many pieces of evidence are based on early analysis of cases of previous coronavirus infections, such as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). Thus, it is ratified that the clinical characteristics are not specific and can be similar to those caused by respiratory viruses, and it is recommended to consult the periodical updates disclosed by official health institutions, such as the Ministry of Health, the Brazilian Health Agency.

The PCR (Polymerase Chain Reaction) test, recommen-

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ded for laboratory diagnosis, amplifies sequences of RNA of the virus and, this, enables its identification. However, it was observed that PCR sensitivity is reduced when using samples with low viral load. PCR diagnostic accuracy seems to be influenced by the type of sample collected for the test and the time of clinical evolution. Samples often used include nasopharyngeal or oropharyngeal swab (MINISTÉRIO DA SAÚDE, 2020a, 2020b).

Serological tests, applied as rapid laboratory tests through IgM and IgG antibody identification for SARS-CoV-2, are not recommended for diagnostic confirmation of patients with recent onset symptoms because the immunologic window time reduces the sensitivity of the test when applied in early stages of the disease. It is worth noting that the role of rapid tests in the screening of asymptomatic people or in the identification of people with IgM antibodies in order to correlate acquired immunity remains unclear (MINISTÉRIO DA SAÚDE, 2020a, 2020b).

The rapid test category is divided into tests for the detection of SARS-CoV-2 antibodies in whole blood, serum and plasma samples, and nasopharyngeal and/or oropharyngeal swab tests for detection of viral antigen by immunofluorescence. However, the role of these tests for the detection of viral antigens remains uncertain, due to the absence of studies that assess their accuracy. Thus, considering the above limitations, sequential testing in patients with a compatible clinical picture is justified, since the presence of positive results in the PCR test and the serological tests is highly suggestive of infection by the SARS-CoV-2 virus, con-

sidering the high specificity of these tests and that there is no evidence of cross-reactivity in published studies (MINISTÉRIO DA SAÚDE, 2020a, 2020b).

Literature Review:

Antimalarials drugs - CHLOROQUINE

CHEMICAL STRUCTURE, CLINICAL INDICATION AND PHARMACOLOGY

It is an antimalarial derived from the chemical compound 4-aminoquinoline. Chloroquine is an immunomodulatory drug with other therapeutic indications such as amoebic liver abscess, systemic lupus erythematosus, rheumatoid arthritis, juvenile idiopathic arthritis, Sjogren's syndrome. Besides, antiviral action against viruses, including HIV type 1, hepatitis B, and herpes simplex type 1. This drug also can act as antipyretic and anti-inflammatory. Currently, the disuse in the above-mentioned treatments is verified, due to the toxic character, and manifestations of ototoxicity and retinopathy. Besides several other side effects that can affect the most diverse organic systems, causing several complications such as dizziness, headaches, dermatological alterations, gastrointestinal symptoms, among many others (COLSON et al., 2020; DELVECCHIO et al., 2016).

HYDROXYCHLOROQUINE

The drug presents a chemical structure similar to chloroquine, which is derived from 4-aminoquinolin, and a single addition of hydroxyl radical. Characterized as immunomodulatory and widely used in the treatment of malaria and rheu-

matologic affections. The use of hydroxychloroquine has raised many concerns due to the systemic distribution potential that leads to the appearance and increasing of toxic effects becoming lethal to the individual. Also, prolonged use in chronic renal or liver dysfunction patients can possibly induce clinical presentations of cardiotoxicity. Many studies revealed that these adverse effects of the therapeutic administration may trigger the generation of collateral damage, with the consequent appearance of conduction disorders and branch blocking. Due to the suppressive cardiological effect of the drug on the sinoatrial node with heart failure, which can generate more serious cardiotoxic complications. Besides, subsequent occurrence of arrhythmias and, in more harmful cases, the appearance of acute circulatory failure. Thus, it is appropriate to state that the pharmacological use of hydroxychloroquine should be primarily guided by scientific evidence that corroborates its efficacy on the basic pathology that is sought to combat (MENEZES; SANCHES; CHEQUER, 2020; SUÁREZ-MUTIS; MARTÍNEZ-ESPINOSA; CLAUDIA GARCIA SERPA OSORIO-DE-CASTRO, 2020).

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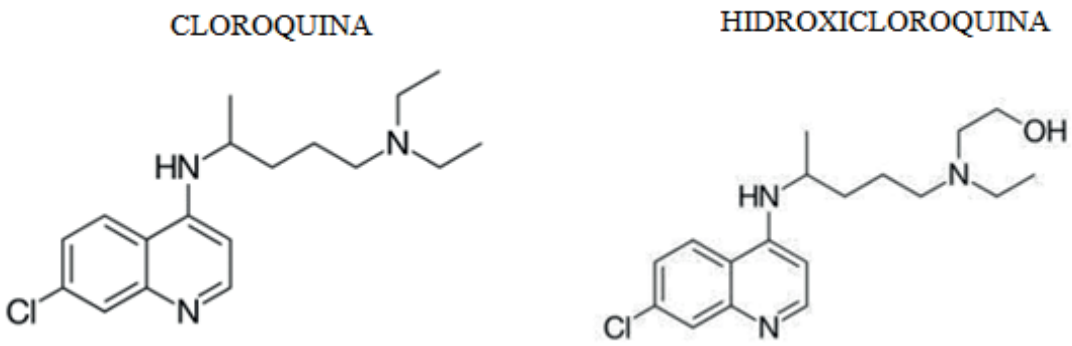

Figure 1. Chemical structures of chloroquine and hydroxychloroquine

PHARMACOLOGY OF ANTIMALARIALS

Biological and pharmacological analysis of numerous authors demonstrated that both chloroquine and hydroxychloroquine participations in the immunomodulation of several cytological and biochemical reactions that occur in the organism infected by SARS-CoV-2. These drugs can be triggering blocking the activity of coronavirus spike protein, whose biological function is linked, and allow the entrance in the cells. This hypothesis received even more engagement due to the already recognized antiviral character against the human immunodeficiency virus. Since its pharmacological action inhibits the entry of the virus into the host cells. From this, several researchers have deepened their studies on the future expectations about the performance of hydroxychloroquine and chloroquine, showing, for example, the existence of possible inhibitory action on the replication of SARS-CoV-2 (COLSON et al., 2020; ZHOU; DAI; TONG, 2020).

The pharmacological

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spectrum of the mentioned antimalarial drugs, include the inhibition of the angiotensin 2 converting enzyme (ECA 2) through its terminal glycosylation. Which become perceptible and makes the cell receptor unfeasible, preventing the connection of the virus to the cell. Moreover, the presence of drugs inside the cell can culminate with increasing of the endosome's pH, contributing to the minimization of infection by SARS-CoV-2. Because can hinder or even inhibits the performance of the spike protein, and prevents the virus from penetrating the cell.

Several studies showed that hydroxychloroquine and chloroquine can modulate the generation of the pro-inflammatory response, precisely by reducing the secretion of cytokines. Thus, the cellular response would be inhibited or blocked by the terminal glycosylation of ECA 2 or even by the endosomal alteration of pH. These events can lead in a decrease of the typical exacerbated immune response, commonly triggered by the permanence of viral infection. Due to these arguments, it can be affirmed that the numerous researches carried out on the potential therapeutic capacity of these drugs on COVID-19 had a strengthened theoretical basis, since, from these ideals, the drugs could be revealed as great drug alternatives for viral treatment (MENEZES; SANCHES; CHEQUER, 2020; ROSA; SANTOS, 2020).

MECHANISM OF ACTION AND ACTIVITY AGAINST COVID-19

Molecular docking studies, involving the use of hydroxychloroquine and chloro-

quine, associated with structure of ACE2 and SARS-CoV-2 the structure was performed in many studies. The analyze of potential interactions between drugs and the crystalline structures of viral proteins, aiming mainly at the discovery of possible effects on RNA-polymerase, since it is the main enzyme responsible for RNA synthesis. However, during in silico analyses, it became evident that both hydroxychloroquine and chloroquine do not have a spectrum of activity capable of providing great influence on the COVID-19 virus. The aminoquinolines derived showed no ability to interact with the viral proteins, active bound sites. Although they demonstrated a certain affinity, in the allosteric site, on some amino acids (ASP350, ASP382, ALA348, PHE40, and PHE390) of ACE2 (CELİK; ONAY-BESİKCİ; AYHAN-KILCIGİL, 2020).

On the other hand, it was discovered that hydroxychloroquine, in comparison with chloroquine, exhibited a greater capacity of interaction with the allosteric site of ACE2. Thus evidencing the effect of promoting an effective conformational alteration in the enzyme structure, gaining the function of blocking. Consequently, the interaction of the spike protein of SARS-CoV-2 on ACE2, potentially hindering the binding of the virus in the biological enzymatic structure of the host cell, thus causing the interruption of the continuation of viral infection. However, it is important to point out that, even in the presence of allosteric blocks on the active region of the ACE2 enzyme. There may be other types of interactions that contribute to the increase and continuation of the infecting capacity of

the virus, such as the awakening of a competitive activation, in which the viral particle begins to compete with the hydroxychloroquine to bind with the enzymatic receptor, thus being able to remain with the maintenance of its pathogenic cycle (CELİK; ONAY-BESİKCİ; AYHAN-KILCIGİL, 2020).

TOXICITY AND ADVERSE REACTIONS

Chloroquine and hydroxychloroquine cause several adverse effects that can be detrimental to the integrity of the human body infected by SARS-CoV-2. The adverse effects can be general or specific, reaching, in this case, the most diverse organic systems, such as ophthalmic, dermatological, gastrointestinal, neuromuscular, cardiological, and hematological, taking into account, also, that the appearance of effects on these last two systems (cardiological and hematological) tends to be quite rare (LACAVA, 2010; PONCHET et al., 2005; SUÁREZ-MUTIS; MARTÍNEZ-ESPINOSA; CLAUDIA GARCIA SERPA OSORIO-DE-CASTRO, 2020).

The following in table 1, showed a large list of adverse reaction that can be caused by the use of anti-malarial drugs:

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Chart 1. Adverse reactions that can be caused by the use of chloroquine and hydroxychloroquine.

Systems	Adverse Effect
General Adverse Reactions	Itching, Dizziness, Headache, Loss of Appetite, Nausea, Vomiting, Abdominal Pain, Diarrhea, Tinnitus, Irritability, Blurred Vision, Fever
Ophthalmic	Photosensitivity and ocular toxicity with accumulation and formation of mild retinal edema, retinopathy and even macular degeneration.
Dermatological	Pigmentary changes in the skin and mucous membranes, with discoloration and hair loss, erythroderma, fixed pigmentary erythema, exfoliative dermatitis, exacerbation of psoriasis, etc.
Gastrointestinal	Anorexia, Colic, Diarrhea and Nausea. Rarely, there may be liver failure and hepatitis.
Neuromuscular	Fatigue and Myalgia. In rare cases, myopathy and sensory-motor neuropathy may occur.
Neurological	Headache, Insomnia, Nervousness, Irritability and more rarely seizures, psychosis and depressive conditions.
Cardiovascular (rare clinical event)	Conduction disorders with bundle branch block, biventricular hypertrophy and heart failure
Hematological (extremely rare)	Hemolysis, Reversible Agranulocytosis, Leukopenia, Thrombocytopenia, Aplastic Anemia.

In general, both drugs (chloroquine and hydroxychloroquine) can promote the same sides effects. However, a difference that deserves to be highlighted is the fact that the incidence of complications tends to be different according to the drug. Chloroquine therapy, for example, is more characterized by the concern with the appearance of toxic effects that fall more

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on the ear and the retina of the patient. On the other hand, the use of hydroxychloroquine has emphasized more the recurrence of the appearance of cardiotoxic effects on patients. However, it is relevant to emphasize that both drugs can produce toxicity on the same organic systems, not having a cardiotoxic effect only for those individuals who use hydroxychloroquine. Finally, it is also necessary to clarify that the great majority of the adverse effects that can be triggered, present a reversible character, from the moment the suspension or even the reduction of the drug administration occurs. In some cases, about 10% to 18% of the patients must interrupt the use of antimalarials due to the appearance of potentially intolerable adverse clinical manifestations (PONCHET et al., 2005; SUÁREZ-MUTIS; MARTÍNEZ-ESPINOSA; CLAUDIA GARCIA SERPA OSORIO-DE-CASTRO, 2020).

RECOMMENDATIONS ON THE TREATMENT OF COVID-19

According to the most recent updates, the World Health Organization (WHO) has definitively finalized studies involving research on chloroquine and hydroxychloroquine as potential drugs to be used in SARS-CoV-2 infected patients. Despite the numerous analyses performed by several countries, the WHO reported that the results obtained showed little or no reduction in mortality of patients hospitalized with COVID-19, thus declaring the immediate interruption of investigations and clinical trials that addressed the use of antimalarials (PAHO, 2020b, 2020a).

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In June 2020, the Food and Drug Administration (FDA), an agency of the United States Department of Health and Human Services, officially revoked the authorization allowing the emergency use of chloroquine and hydroxychloroquine for the treatment of hospitalized patients, because scientific evidence was revealed that there was not enough clinical benefit on such patients. These conclusions were reached because of the serious adverse and cardiotoxic effects that can be generated, as well as the minimal or even no improvement in the rapid recovery of patients. Besides this scenario, several conclusions were obtained through scientific researches developed by several international entities, such as the clinical trials entitled RECOVERY, SOLIDARITY, and DISCOVERY, which were characterized by evaluating the effectiveness of the therapeutic capacity of hydroxychloroquine on patients with COVID-19, to prove or refute whether the antimalarial treatment is effective against SARS-CoV-2 (ADER, 2020; WORLD HEALTH ORGANIZATION, [s. d.]). Sequentially, all these trials, conducted internationally, have demonstrated that the pharmacological use of hydroxychloroquine does not produce beneficial effects for individuals infected with SARS-CoV-2, and it is advisable to discontinue its use. With the proper verification of the conceptual data and perceiving the doubtful safety and inefficiency of the drug against the viral infection by SARS-CoV-2, the argument that its use should be interrupted, even in cases of routine use, as a measure of prevention against the disease, because there is no applicability, proof and much

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fewer benefits that justify its use for the treatment of COVID-19 has become even stronger (GUPTA; MALVIYA, 2020; RIZZO, 2020).

ANTIPARASITIC

CHEMICAL STRUCTURE, PHARMACOLOGY AND CLINICAL INDICATION

IVERMECTIN

Ivermectin was discovered in 1975 by Professor Satoshi Ōmura as a fermentation product of Streptomyces avermitilis bacteria, being included in the class of avermectins (figure 2). Since then, is a broad-spectrum agent used in the treatment of several mammals' diseases caused by invertebrate animals or viruses. The drug is a mixture of 80% 22, 23-dihydro-avermectin B1a and 20% 22, 23-dihydro-avermectin B1b, with pharmacological activity (BANERJEE et al., 2020; RIZZO, 2020).

This drug has been widely used as an anthelmintic, pesticide, and insecticide. Ivermectin shows an affinity for several families of ionic channel receptors in the parasite, especially glutamate-controlled chlorine channels. With its action, hyperpolarization of the parasite cell membranes occurs with inhibitory neurotransmission blocking in myocytes, resulting in paralysis and death of the parasite. In theory, the receptors of the ionic channels of host mammals would also be targeted by the drug. However, in therapeutic concentrations, the affinity of the drug is about 100 times lower in the vertebrate host (animal or human) than in the helminth parasite, for example. Furthermore,

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the blood-brain barrier prevents the drug from entering the central nervous system of the hosts in general. Besides the drug does not reach GABA-ergic receptors of the chlorine channels in the brain and shows a benefit from the therapeutic effect as antiparasitic. Mechanisms of anti-tumor action have been identified, with the induction of cell death in cancer cell lines (BANERJEE et al., 2020).

It has demonstrated efficacy in several viruses both in vitro and in vivo, with emphasis on RNA viruses - for example, the Dengue virus strains (DENV), the West Nile virus (WNV), the Venezuelan equine encephalitis virus (VEEV), the Influenza virus, and the pseudorative virus (PRV), a DNA virus. The antiviral action mechanism proposes ivermectin as an inhibitor of nuclear transport mediated by the heterodimer of the host import (α/β1), responsible for the translocation of proteins of various viral species, indispensable for their replication (NATIONAL CENTER FOR BIOTECHNOLOGY INFORMATION, [s. d.]; WAGSTAFF et al., 2012).

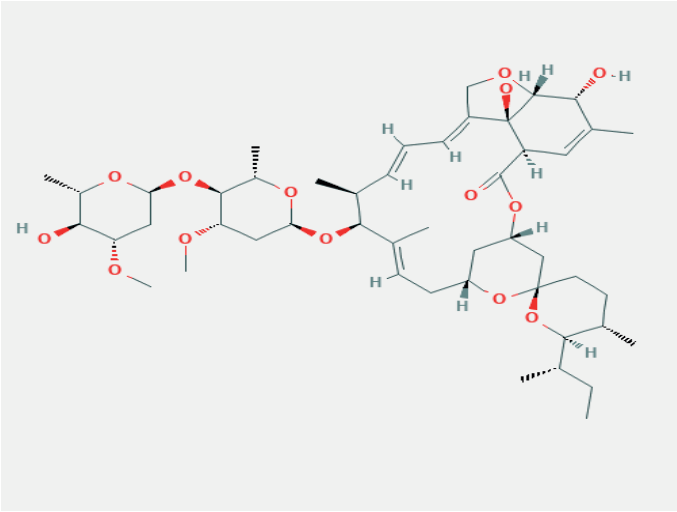

Figure 1. Chemical structure of Ivermectin.

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In Brazil, according to the National Health Surveillance Agency (ANVISA), ivermectin is intended for the treatment of intestinal strongyloidiasis, onchocerciasis, filariasis, ascariasis, scabies, and pediculosis. Contraindications include cases of hypersensitivity to avermectins and patients with conditions that compromise the integrity of the blood-brain barrier - for example, meningitis. It is also contraindicated in children under 15 kg or under 5 years of age because, due to the insufficient amount of clinical data regarding treatment in this age and body weight range, there is still no safety and effectiveness established for these patients (ANVISA, 2007).

MECHANISM OF ACTION AND SPECTRUM OF ACTIVITIES IN COVID-19

In the search for clinical evidence, models of the drug's action in relation to the SARS--CoV-2 virus have been proposed. A work has demonstrated in vitro inhibition of the replication of the SARS-CoV-2 virus by ivermectin, which, added to the built knowledge of the antiviral potential, endorsed a research front in the pharmacological treatment of COVID-19. Considering that this is an RNA virus, there is a possibility that the pharmacodynamics is in accordance with the mechanism of inhibition of the importin α/β1 (heterodimer of transport of the host), compromising the translocation of viral proteins in the cell of the host. However, there is the prospect of ivermectin acting as an ionophore agent, a substance capable of ions binding (usually cations) by a more internal binding site in its molecule. Thus, being externally more

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hydrophobic, and able to cross membranes, and affect the hydro electrolyte balance of cells and biological environment. Thus, it is speculated that two molecules of the drug may react with each other, forming a suitable complex to fulfill this ionophore role by causing the viral capsule osmotic lysis (RIZZO, 2020).

TOXICITY AND ADVERSE REACTIONS

The adverse effects caused by ivermectin are, in general, light and transitory. Gastrointestinal events (diarrhea, nausea, asthenia, abdominal pain, anorexia, constipation, and êmesis) rarely occur. Dizziness, drowsiness, vertigo, and tremor may also occur, as well as itching, eruptions, and urticaria. Specifically, in the treatment of onchocerciasis, adverse reactions are observed - namely, Mazzotti reaction and ophthalmic reactions. Besides, it is recommended that the administration of ivermectin concomitant with CNS depressant drugs be cautious (ANVISA, 2007). No scientific publications report adverse effects of ivermectin were found in the therapeutic context of COVID-19.

RECOMMENDATIONS ON THE TREATMENT OF COVID-19

Some protocols of clinical management recommendations elaborated in Brazilian municipalities foresee the use of ivermectin already in the initial phase of infection, in outpatient environments. However, ANVISA states that there are no conclusive studies regarding the use of drug for the treatment of COVID-19, as well as the use of

the drug for indications not provided in the package leaflet is the choice and responsibility of the prescribing physician (ANVISA, 2020). The Pan American Health Organization (PAHO), in a note published in June 2020, highlighted the insufficient evidence so far for the use of ivermectin in the treatment of COVID-19, as well as the risk of the use of higher dosages concerning that approved by the Food and Drug Administration (FDA) to obtain the potential antiviral effect. The document advocated the use of ivermectin and other therapies not yet proven only in the context of randomized clinical trials (PAHO, 2020c).

NITAZOXANIDE

CHEMICAL STRUCTURE, PHARMACOLOGY AND CLINICAL INDICATION

Nitazoxanide or 2-acetyloxy-N-(5-nitro-2-thiazolyl) benzamide, was synthesized in the early 1970s and developed as an oral antiparasitic drug (figure 3). It obtained national indication status for treatments when, in 2002, the American Food and Drug Administration (FDA) approved for management of diarrhea and enteritis caused by Cryptosporidium spp. and Giardia lamblia. In addition to the antiparasitic effect, nitazoxanide has demonstrated in vitro efficacy against a wide range of gram-positive and gram-negative anaerobic bacteria, as well as against strains of Mycobacterium tuberculosis and Clostridium difficile.

The mechanism of action of this drug involves the inhibition of the enzyme pyruvate-ferredoxin oxidoreductase

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(PFOR), essential in anaerobic metabolism. It is also proposed that the nitazoxanide acts as a decoupler, breaking the membrane potential and the homeostasis of the parasite's intra-organism (MAHMOUD; SHITU; MOSTAFA, 2020; ROSSIGNOL, 2014).

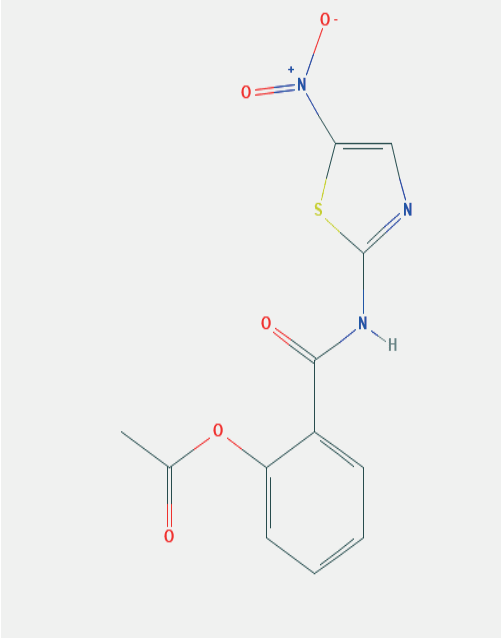

Figure 3. Chemical structure of Nitazoxanide.

Nitazoxanide has also demonstrated in vitro broad-spectrum antiviral activity. Influenza, Respiratory Syncytial Virus (RSV), norovirus, rotavirus, and hepatitis B and C viruses were susceptible to laboratory tests. Studies with the Influenza virus, demonstrated that nitazoxanide inhibits the ERp57 protein present in the endoplasmic reticulum of the host cells. Thus, blockage the hemagglutinin viral maturation, and the intracellular traffic of the viral components

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would be impaired. Some studies demonstrated that nitazoxanide, the active metabolite of nitazoxanide, inhibited the maturation of two rotavirus viral glycoproteins. These are structural and replication protein of the virus in the host cell. Another studies with human norovirus, the inhibition of viral replication and the stimulation of cell antiviral response was attributed to the nitazoxanide metabolite, especially by the expression of the interferon 1 regulator factor (GAMIÑO-ARROYO et al., 2019; MAHMOUD; SHITU; MOSTAFA, 2020; NATIONAL CENTER FOR BIOTECHNOLOGY INFORMATION, 2005).

Currently, nitazoxanide is indicated in Brazil for the treatment of viral gastroenteritis caused by rotavirus and norovirus; helminthiasis caused by nematodes, cestodes, and trematodes; diarrhea caused by acute intestinal amebiasis or amebic dysentery; giardiasis; cryptosporidiosis; blastocystosis, balantidiasis, and isosporiasis.

TOXICITY AND ADVERSE REACTIONS

Nitazoxanide is a medicine contraindicate in diabetes, liver or kidney disease, and hypersensitivity patients, and also for children under 12 years. Pregnant women and women in the lactation period have category B risk, so it should only be administered if the benefits justify the potential risk for the fetus or infant. Patients in use may experience abdominal pain such as colic, diarrhea, nausea, amenesis and headache, as well as color change in physiological fluids (e.g., urine and sperm). Less common, allergies, anemia, hyperhidrosis, itching, increased

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salivary glands and other adverse reactions can occur. Nitazoxanide has high binding rates to plasma proteins. Therefore, there should be caution when administered together with other drugs with this same property - for example, warfarin and phenytoin. Moreover, the ingestion of nitazoxanide with food increases its absorption capacity by the organism (increase of the "area under the curve" and the maximum concentration in the blood (ANVISA, 2007). No scientific publications with reports of adverse reactions by nitazoxanide have been found in the therapeutic context of COVID-19.

RECOMMENDATIONS FOR USE ON COVID-19 TREATMENT

Over the last of few years, in vitro studies have tested the activity of this drug in relation to some species of coronavirus. It has been demonstrated that tizoxanide inhibits the replication of canine coronavirus S-378, within certain culture and dosage specifications. Other studies were showed similar results for the murine coronavirus, the mouse hepatitis virus strain A59 (MHV-A59), bovine coronavirus strain (BCoV-L9), human enteric coronavirus (HECoV-4408) and Middle East Respiratory Syndrome coronavirus (MERS-CoV). Nitazoxanide also seemed to inhibit the expression of viral N protein from some strains of the group (ROSSIGNOL, 2016).

Besides the antiviral activity, it has also been observed that nitazoxanide inhibits the production of pro-inflammatory cytokines in mononuclear cells of peripheral blood, being the reduction of IL-6 representative of

this activity. The appearance of SARS-CoV-2 and its clinical manifestation in humans was resulted in vitro experimentation endorsement execution of clinical tests with this drug. By July 2020, there were 14 clinical trials that included nitazoxanide in their testing protocol. Accordingly, to its antiviral activity, immunomodulatory role, or yet another less known mechanism, nitazoxanide is expected to contribute, within certain therapeutic schemes, to good clinical outcomes in COVID-19 (MAHMOUD; SHITU; MOSTAFA, 2020; ROSSIGNOL, 2016).

The World Health Organization (WHO) and the Pan American Health Organization (PAHO) have not yet released specific notes with recommendations regarding nitazoxanide. However, this drug fits in the recommendations with insufficient clinical evidence and that require results from randomized clinical trials.

The pandemic caused by SARS-CoV-2 has led to the use of several drugs for the treatment and even prevention of infection, although many of these have not been sufficiently evaluated for administration efficacy and safety for such purposes. In view of the multiplicity of treatment protocols adopted by each medical care institution, as well as the vast number of papers hitherto published, the present study sought to gather the data published so far on some of these drugs used. Antimalarials, antiparasitic, antiviral, anti-inflammatory and anticoagulant were evaluated for their chemical and pharmacological aspects, including mechanism of action, toxicity, adverse effects and use recommendation for the treatment of COVID-19.

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In view of the growing scientific interest in immunotherapy, the use of this therapeutic tool to treat the disease was also discussed.

Concluding Remarks

The pandemic caused by SARS-CoV-2 has led to the use of several medications for the treatment and even prevention of infection, although many of them have not been sufficiently evaluated regarding the efficacy and safety of administration for such purposes. With these uncertainties, the number of divergent opinions grows with which therapeutic tactics should be used in COVID-19. Therefore, an approach must be carried out using protocols that differentiate the phase in which viral pathogenicity is dominant versus when the host's inflammatory response overcomes the pathology, so that the use of different drugs obtains viable potential effects. Given the multiplicity of treatment protocols adopted by each health care institution, as well as the large number of articles published so far, studies that seek to gather the data published so far on antimalarial and antiparasitic drugs used for the treatment of COVID- 19 are important for a better therapeutic decision.

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