Metformin and its analogues as a therapeutic tool for COVID-19: a narrative review.

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Abstract

The new coronavirus (Sars-Cov-2) appeared in China in late 2019 and with it an intense search for effective pharmacological tools in the treatment of COVID-19. This virus can cause from mild symptoms, such as dry cough, fever and tiredness, to more severe symptoms, such as respiratory failure and systemic shock. Part of this problem is due to the increase in the neutrophil/lymphocyte ratio and serum levels of several inflammatory cytokines and chemokines. Other blood markers also deflagrate the inflammatory condition, among them C-reactive protein, ferritin and D dimers. Additionally, the history of chronic and/or acute hyperglycemia is an independent predictor for morbidity and mortality in patients with severe acute respiratory syndrome. In this pandemic scenario, numerous new and other drugs already available on the market have become therapeutic tools. Biguanide class drugs, classically used in the treatment of type 2 diabetes mellitus, received great notoriety for potentially useful systemic effects in the clinic, in cardiovascular level and against cancer. Some of their properties may be useful in the fight against Sars-Cov-2, such as the reduction of mRNA expression levels of inflammatory cytokines, chemokines and by the attenuation of NF-κB activation. These actions reduce the inflammatory response in the individual and the damage from a severe inflammatory response. Given the morbidity and mortality, partly attributed to the cardiovascular damage of the COVID-19, the objective of this work was to review the systemic effects of biguanides, as well as their therapeutic potential as an adjuvant.

INTRODUCTION

COVID-19 is an infectious disease caused by the new coronavirus (SARS-CoV-2), was first reported in Wuhan, China, later reaching pandemic proportions. Patients may present symptoms (fever, dry cough and tiredness), severe (dyspnea, hypoxia and/or great pulmonary involvement) and critical (respiratory failure, systemic shock and/or multiple organ failure) [1]. Respiratory discomfort syndrome, an incident complication, affected 15.6% of patients in a study that collected data from 1,099 patients with COVID-19 in China [2]. Despite the incessant search for effective drugs in their clinical treatment, no drug has yet been validated [3,4]. Several classes of drugs and strategies are being evaluated or developed aiming at the clinical management of COVID-19, such as antibiotics, antiviral, anti-inflammatory, antibodies, anticoagulants, anti-fibrotic, oxygen therapy, and immunomodulation, among others. Possibly, different treatment modalities have different efficiencies according to the stage of the disease and its manifestation [4]. Thus, it is necessary to understand the pathophysiology of the disease, as well as the affected organs and systems, in order to improve the identification of therapeutic targets and, thus, rigorously define the ideal treatment.

In the context of the search for adequate pharmacotherapy, biguanides, buformin (BUF), metformin (MET) and phenformin (PHEN) appear as possible adjuvant therapy for the treatment of COVID-19, due to their comprehensive pharmacological properties [5]. Only MET is used in large scale [6], appearing as the first therapeutic line for type 2 diabetes mellitus (DM2) and one of the most prescribed drugs worldwide [7].

Antihelmintic, antimalarial and antiviral effects of biguanides have been described, the latter being dependent on the administration of high doses [8,9]. Considering recent publications of this pharmacological class, its potential off label use, pharmacological advances that allow the administration of drugs by alternative routes, as well as the demand for new therapeutic tools for COVID-19, this study aimed to review the pharmacological effects of biguanides, as well as its therapeutic potential in viral infections.

METHODOLOGY

This is a narrative review of the literature performed in the PUBMED and Virtual Health Library databases through the combination of descriptors in health sciences (Table 1). After applying the search and selection criteria, original studies were included, without language and publication time restrictions, dealing with biguanides and their pharmacological effects. Those who did not have a control group were excluded, when the intervention was only in association, when it did not specify the treatment of data, as well as duplicity. The data were extracted: author, year of publication, objectives, method, experimental design, experimental model, follow-up time, intervention, posological scheme, main results and bibliographic references (submitted to the cited criteria). No evaluation by the Research and Ethics Committee was necessary.

IMPACT OF HYPERGLYCEMIA ON COVID-19

Evidence points to clinical and pathophysiological complications related to SARS (Severe Acute Respiratory Syndrome) in hyperglycemic patients, either by SARS-CoV or SARS-CoV-2. Analysis of clinical and biochemical characteristics of 135 patients who died of SARS-CoV, 385 survivors and 19 with non-SARS pneumonia, indicated a history of chronic and/or acute hyperglycemia as an independent predictor for morbidity and mortality in patients with SARS, and revealed metabolic control as the best prognostic factor [10].

A cohort of more than 7000 Sars-CoV- 2 infected patients (with or without DM2) showed correlated hyperglycemia with worse prognosis and higher risk of mortality [11]. This pathological condition favors inflammation and abnormal immune response, contributing to the development and progression of radiological findings [12]. When comparing groups of infected patients: without a history of diabetes (1), with secondary hyperglycemia (2) and diabetics (3), it was noticed that the proportion of critical patients and mortality in 2 and 3 was higher than in 1, besides needing a longer hospitalization time [13].

A retrospective analysis reinforced DM as the greatest risk for negative outcomes in COVID-19 infected [12]. However, acute or stress hyperglycemia may lead to additional complications in these patients (Figure 1). The glycosylation of the ACE2 receptor (Angiotensin 2 converting enzyme) facilitates the intrusion of the virus into the cell [14], since the spike protein of the virus binds to this receptor and promotes the fusion of the viral membrane with the host membrane [15]. In addition, monocytes and macrophages are the immune cells most present in the lungs. This virus effectively infects monocytes from peripheral blood and increases the expression of ACE2. Infected monocytes increase IFN expression α, β and λ and pro-inflammatory cytokines associated with the "cytokine storm" triggered by SARS-CoV-2. It was also demonstrated that these monocytes increased the function of HIF-1, a strong inducer of glycolysis and transcription of IL-1β, contributing to the pro-inflammatory state. In addition, changes in oxidative metabolism were observed in critically ill patients with COVID-19, by reducing oxygen consumption in infected monocytes and increasing production of mitochondrial ROS (mtROS). Thus, it is suggested that infected monocytes can promote epithelial cell death in an mtROS/HIF-1α dependent manner [16]. Under conditions of hyperglycemia during infection, inhibition of T-cell proliferation may occur, resulting in dysfunction and lymphopenia [16-18]. There was also an increase in viral load, expression of ACE2 and IL-1β in a glucose dependent dose. In this sense, hyperglycemia promotes increased viral replication and expression of cytokines [16].

Based on the data found so far, hyperglycemia should not be neglected at the time of admission, but should be adequately treated, aiming at better outcomes in diabetic patients or not, contaminated by COVID-19[11]. Biguanides can represent auxiliary tools in treatment, thanks to their anti-hyperglicemiant, cardio-protective and modulating properties of the immune system, in addition to their potential antiviral effect.

PHARMACOLOGICAL ASPECTS OF METFORMIN AND ITS ANALOGUES

Biguanides are anti-hyperglicemiant agents [5]. MET promotes reduction in hepatic glucose production, increased muscle uptake, decreased gastrointestinal absorption, in addition to being an insulin sensitizer [19]. The complex I of the electron transport chain was the first identified target of this drug, which acts as partial inhibitor of the mitochondrial complex [20-23]. The main effect of this inhibition is the activation of the AMPK and its pathways, which occurs through the stimulation of the regulatory subunit γ for the high levels of AMP/ADP [24,25].

The pharmacological aspects of MET were summarized in Chart 1. In a pharmacokinetic context, it differs from other biguanides by not suffering hepatic metabolism. The PMAT (plasma monoamine membrane transporter), located in the luminal side of the enterocytes, is one of the responsible for capturing the MET from the intestine. Moreover, the OCT transporters (organic cation carrier) have great importance in tissue distribution, particularly for MET. The OCT3 transporters deserve to be highlighted, because they are located in the brush border of the enterocytes and participate in the capture of the drug. The transport of MET and PHEN from the blood to the hepatocytes is mediated mainly by OCT1. On the other hand, the renal uptake of MET is mediated by OCT2 [27]. Urine excretion occurs via MATE1 and MATE2 (multidrug and toxin extrusion proteins transporters) [28]. The distribution volume of MET is 63 to 276L after an intravenous administration, while for a daily oral administration of 2g it is approximately 600L [27]. Its half-life with physiological renal function is approximately five hours [27,28], and the maximum recommended daily dose 2.55g [19].

PHEN and BUF present bioavailability of 40 to 50% after oral administration, accumulating mainly in the liver, pancreas, kidneys and muscles. Approximately 50% of PHEN is metabolized in the liver, which generates inactive metabolites. This way, the "slow metabolizers" present a higher risk of developing lactic acidosis, the most important adverse effect of biguanides. PHEN is eliminated through urine and bile [5].

MET is a safe, well tolerated and accepted drug [19], since the adverse effects usually occur during the beginning of therapy and are resolved spontaneously [27]. Lactic acidosis occurs in five out of 100,000 individuals, generally being reported in patients with low tissue perfusion (e.g., sepsis, myocardial infarction and congestive heart failure) [27,28]. Renal insufficiency is the most common comorbidity present in patients with lactic acidosis associated with MET, being reported especially in those with high plasma creatinine levels (>3mg/dL) [28,30]. MET should not be used in moderate or severe renal insufficiency, or in those with mild but not stable renal failure [30]. Moreover, in severe cases of Sars-CoV-2 infection, there may be a need for drug interruption due to the presence of hypoxemia and hemodynamic instability, which increases the risk of lactic acidosis [31]. Adverse effects and contraindications have been listed in Chart 1.

The need for unconventional routes for the administration of biguanides is of great clinical importance, as it can direct the drug to the target organ/tissue and decrease possible systemic adverse effects. This is because the MET, after oral ingestion, is unable to be effectively distributed in the lungs [32]. Existing limitations trigger the need for different formulations and administration routes for biguanides. Drug administration systems (micro and nanoparticles, liposomes, niosomes, among others) are very useful to overcome the difficulties associated with conventional pharmaceutical forms. Among the potential advantages are the protection of the active against enzymatic degradation, reduction of side effects, reduction of the need for repetition of doses and alleviation of discomfort generated by the administration of the drug. Additionally, modulation of the release of the active principle(s) in the organism, control of the place where they are released, as well as an increase in the relative bioavailability of the drugs can be obtained [33].

Several studies point out the use of MET in unconventional ways, as in the topical use for the treatment of skin lesions or in the form of suppositories in patients with colorectal adenomas[34]. Experimental studies, in humans and animals, point MET as a promising agent in the treatment and prevention of lung diseases, but which end up having as a barrier the low concentration of the drug in the lungs[32]. Menendez, Quirantes-Piné and Rodríguez-Gallego et al. (2014), address the need for alternative formulations of biguanides related to the site where action is desired, such as inhalation use in lung cancer[35]. Berstein (2018) ratifies the

administration of MET not only by oral route, highlighting the need to take into account its pharmacokinetics, in addition to its different serum and tissue concentrations when used by different routes[34]. In addition, inhibition of mitochondrial complex I by the drug may be useful to reduce oxidative stress and lung injury [36]. Thus, the use of inhaled biguanides to direct its actions may present great pharmacological potential, including for COVID-19.

BIGUANIDES: NEW ANTIVIRAL TOOL?

The search for the antiviral activity of biguanides is not recent. Still in the 60's, the broad spectrum of action of this pharmacological class was already being noticed [8,9]. From several experiments, anti-helmintic, antiviral and antimalarial effects were identified. However, it was found that the high doses necessary for the antiviral activity of the modified biguanides made the clinical use of the compounds known at that time impracticable [8]. In the last decade, several studies have been carried out in order to verify the effect of biguanides in the aid of antiviral therapies, with MET as the main representative. Some of these studies approach the benefits of the drug in the antiviral treatment indirectly, due to its ability to reduce the body's resistance to insulin, which ends up improving body defenses. It was verified that in patients co-infected with HIV and HCV, whose metabolic and/or inflammatory variables were significantly altered, the treatment with MET was well tolerated and significantly increased the sensitivity of peripheral tissues to insulin [37]. Very beneficial effect since viral infections affect glucose metabolism, leading to insulin resistance and development of DM2 in predisposed individuals [38].

By adding MET to alphapeginterferon-2a and ribavirin treatment in individuals with chronic Hepatitis C genotype 1 and insulin resistance, there was an improvement in insulin sensitivity. Additionally, the treatment increased the sustained viral response rate of patients with a good safety profile [39].

A quasi-experimental study selected 138 individuals with chronic hepatitis C who presented insulin resistance and divided three groups: A, treated with interferon and ribavirin; B, plus MET; and C interferon, ribavirin and pioglitazone. After 48 weeks, the sustained viral response was higher in B ($p = 0.003$) [40].

When used in combination with lamivudine or interferon alpha-2b, MET increased inhibition of surface antigen expression and replication of hepatitis B virus, ratifying the possibility of synergism with other antivirals [41].

An in vitro study found that, compared with non-infected control cells, ZIKV infection resulted in decreased AMPK in endothelial cells (dengue and hepatitis C viruses are also known to inhibit AMPK activation). Consequently, ZIKV-infected cells were exposed to AMPK pharmacological activators (such as AICAR) and MET. These compounds did not exert direct antiviral activity nor impaired viral adsorption/entry, but reduced ($p < 0.001$) ZIKV infection. According to the authors, AMPK activation exerts a powerful antiviral response that restricts replication in infected endothelial cells by inhibiting glycolysis induced by ZIKV, an essential source of energy and basic elements for replication. Additionally, this activation enhances the innate antiviral response in ZIKV-infected cells. It is worth noting, however, that the compound AICAR inhibited the replication of ZIKV at a higher rate compared to MET ($p < 0.001$) [42].

The activation of AMPK inhibits the protein kinase mTOR. This effect provoked by biguanides can also bring benefits on antiviral therapies. It was verified that the mitogenic stimulation caused by mTOR accelerates mortality induced by influenza in animals, increasing the susceptibility of alveolar cells type II to infection. Due to the inhibitory property of mTOR, it was suggested the use of biguanides for the treatment of influenza [43].

In order to avoid lactic acidosis, the use of inhaled pharmaceutical forms for treatment has been proposed. However, an important aspect emphasized by the authors regarding this form of administration was that the inhaled MET could require a large amount of powder delivery to the lungs, resulting in reduced complacency, bronchospasm and cough. BUF was pointed out as an adequate substitute, because it has eight times more potency than MET, making possible to reduce the amount of particulate material delivered to the lungs and reducing the occurrence of lactic acidosis as an adverse effect [43].

A study whose objective was to verify drugs with potential to be used in the treatment of pregnant women with COVID-19 cites the use of MET in the therapy directed to the host. This type of therapy aims at activating the body's protective immune response and suppressing the overactive inflammatory response. This method is considered safe and effective, capable of reducing the immunopathology and improving the immune response, in addition to being suitable for pregnant women with the disease [44].

EFFECTS OF BIGUANIDES ON THE IMMUNE SYSTEM

I IMMUNOSTIMULATION

It was suggested that MET may present antagonistic actions according to the pathological state of the submitted organism. In individuals with cancer, it has been shown to activate both the innate and the adaptive immune system. Such immuno-stimulatory effects were able to inhibit the progression of the tumor or even to eradicate it, besides producing an anti-metastatic effect in several animal models [45]. This immuno-stimulatory action was demonstrated in a series of studies chosen for this review and a detailed description of its effects was schematized in Chart 2.

MET has received considerable attention in the field of oncology since 2005, after epidemiological publication highlighting the reduction in the risk of neoplasias. From this, several observational studies corroborate the antineoplastic effects in diabetics, including liver, colorectal, pancreas, and stomach and esophagus cancer [24]. Anisimov (2015), in his meta-analysis, stated that after a single dose of MET, its peak plasma concentration in patients with DMT2 ranged from 4-15μM, and that most in vitro studies used doses of MET between 0.5-50 mM to suppress tumor growth, apparently much more than in humans. However, in vivo studies in several types of rats demonstrated an antitumor effect for several cancers with doses lower than 500 mg/kg, a value that produces plasma concentration equivalent to that produced by the maximum dose in humans (2500 mg/kg), comparing the body surface and weight of mice with 20g and human with 60kg [68].

The mechanisms associated with the benefits of MET against cancer continue to be discussed [20]. The decrease in the production of ATP induced by the drug may be intolerable for cells sensitive to energy stress, and may lead to cell apoptosis [46, 47]. The consequent lower production of ROSs is one of the mechanisms that lead to a lower incidence of cancer, activating AMPK and its related pathways [49]. Pryor and Cabreiro (2015) stated that the protective effects of MET are attenuated by the pharmacological inhibition of AMPK or its absence [24]. MET can also inhibit mTORC1 via Rag GTPase, regardless of the activation of AMPK [47]. MTOR inhibition decreases protein synthesis and growth, inducing cell cycle arrest and apoptosis [25].

There is a hypothesis that the activation of AMPK can also confer resistance against cancer, as it was observed in cells without LKB1 of lung adenocarcinoma, after restoration of AMPK [24, 47]. Pecinova*et al.* (2017) approached that the viability of cancer cells (rho0) without mitochondrial DNA is also affected by MET treatment, which makes the actions related to the respiratory chain questionable [50].

IMMUNOSUPPRESSION

In pathological contexts other than cancer, paradoxically MET can have immunosuppressive effects, both on innate and adaptive immunity [45]. These effects are comprehensive and are schematically illustrated in Chart 2. The study by Diaz et al. (2017) involving obese patients with DMT2 deserves an observation. In it, it was observed that B-cell functions in response to vaccines were recovered and antibody response increased after MET treatment, although the pathological context of DMT2 has exactly the opposite effect to that observed. These effects, although they can be categorized as immuno-stimulators, are due to an anti-inflammatory action of the drug, capable of improving the functions of the B cells [53].

The role of AMPK in inflammation and polarization of macrophages was explored in a study using MET, compound C (an AMPK inhibitor) and AICAR for in vitro intervention. They found that in obese rats, AICAR apparently decreased the percentage of M1 macrophages and increased markedly M2 macrophages, suggesting that activation of AMPK plays a vital role in macrophage polarization [69]. *Chung, Nicol, Cheng et al* demonstrated the blocking of many effects caused by MET in the presence of compound C, suggesting

that activation of AMPK is necessary to decrease pro-inflammatory cytokines, protective effect, decrease levels of nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) [54].

Several studies report the action of MET on inflammatory mediators by reducing mRNA expression levels of inflammatory cytokines TNFα, IL-1α, IL-1β, IL-6, chemokines or by attenuating NF-κB activation [52, 55, 56] (Chart 2). This effect arouses great interest in severe cases of COVID-19, by the elevation of levels of inflammatory markers in the blood (C-reactive protein, ferritin and D-dimers), increase in the neutrophil/lymphocyte ratio and of several inflammatory cytokines and chemokines [70]. Mice with acute respiratory distress syndrome, accumulation of neutrophils and increased levels of inflammatory cytokines showed reduction of these indicators of lung damage after MET treatment (v.o. 50 mg/Kg for 7 days) [71]. Thus, the use of MET as a potential therapeutic tool for COVID-19 is highlighted. However, it is essential to understand, initially, the systemic inflammatory responses induced by SARS-CoV-2 and how these pathways are modulated by the different therapies used today.

MITOCHONDRIAL EFFECTS

Mitochondria are the organelle and key place for understanding the main effects of biguanides, especially of MET [20]. Understanding their capture becomes fundamental to the understanding of their action mechanisms and applications. The MET molecule is positively charged and its capture by the mitochondria depends on the energetic status of this organelle [20, 21, 24, 50]. Lower respiratory activity associated with an increase in membrane potential induced by inhibition of complex I, may help in the capture and accumulation of MET in the mitochondria [21]. Therefore, the concentration may be 100 to 300 times higher within this organelle at a potential between 120 and 150mV, compared to cytosol [20, 50]. Moreover, compared to the extracellular medium, this concentration can be 1000 times higher in the mitochondria [20, 23]. Therefore, milli-molar scales concentrations of MET are achievable, despite micro-molar concentrations of cytoplasm [23]. It is worth noting that its uptake is favored by the action of complex I due to the increase in potential, however, the drug inhibits this complex, decreasing its subsequent uptake [20, 23].

The I complex of the electron transport chain was the first identified target of MET. It is known to have two forms: A (activated) and D (deactivated) [21]. The exact location of the biguanide connection still arouses debate. According to Pecinova et al. (2017), biguanides do not bind to any specific site of dehydrogenesis in the respiratory chain [50]. However, Bridges et al. (2014) concluded that MET is a reversible non-competitive ubiquinone binding site inhibitor. In addition, this compound exhibits greater inhibition in the non-catalytic state of the complex (D) [20]. The possible site of MET in this complex is an amphipathic region at the interface of the hydrophilic and membrane regions, where redox processes initiate proton translocation. MET would keep the complex in an open loop conformation, state D [20, 24]. Matsuzaki and Humphries (2015) observed that 25 mM of MET was able to inhibit 12.1% of the activity of complex I in state A, and about 40% in state D induced by heating, while the same concentration inhibited 44.6% of the activity of complex III-IV, and 59.0% of the activity of NADH oxidase (combination of activities of I-III-IV). Bridges et al. (2014) approached that MET presents a CI50 of 19.4 mM (±1.4) over the bovine heart mitochondrial complex I (Bos taurus) [20]. PHEN at 200 μM is able to inhibit 10% and 35-40% of complex I activity in states A and D, respectively [21]. The main effect of the inhibition of complex I related to MET is the activation of AMPK and its pathways [24, 25]. AMPK favors a cellular catabolic state, regulating several metabolic factors that lead to the restoration of the energy balance [23].

Some effects of MET, including the redox state of the cell, may vary depending on the time or concentration used. While short-term administration has caused little inhibition of complex I activity, long-term is associated with benefits such as reduced oxidative stress and increased antioxidant defenses, resulting in lower incidence of organism damage [58]. Regarding the concentration, a change in the redox state of the mitochondria was observed comparing concentrations of 100 μM and 500 μM. In 500 μM, as observed for retenone, the mitochondria was in a lower NADH/NAD+ state; while in 100 μM, in a more oxidized state [72]. Other effects are described in Chart 2.

CARDIOVASCULAR PROTECTION ASSOCIATED WITH METFORMIN

Sars-Cov-2 can cause or aggravate cardiovascular events in patients with or without comorbidities. A meta-analysis of six Chinese studies, with 1527 patients with COVID-19, reported prevalence of diabetes (9.7%), cardio-cerebrovascular disease (16.4%) and hypertension (17.1%) among the participants. Recent data showed that systemic inflammation and increase of catecholamine caused by COVID-19 can lead to acute atherosclerotic plaque rupture, resulting in acute coronary syndrome. In addition, coagulation cascade deregulation may occur with micro-thrombus formation in terminal organs [73]. In view of this, the important role that MET can play in the treatment and functional recovery of cardio-cerebrovascular diseases, such as stroke and myocardial infarction (MI), conditions present in the severe form of COVID-19 is verified.

Most studies that evaluate the mechanisms of action of MET, when used in stroke, use as a resource the middle cerebral artery occlusion (MCAO) in rats, transitory or permanently. When transient, they usually cause ischemia between 60 and 90 minutes, followed by reperfusion. The daily doses of MET used vary between 10 and 300 mg/kg. It was reported that the moment of administration (pre- or post-stroke), the duration of treatment (acute or chronic) and the degree of activation of AMPK are important factors in physiological responses to the ischemia generated in the brain [74]. MET-induced AMPK activation provides protection against brain ischemia (Chart 2) [62]. There is a lot of discussion about pre-stroke treatment with MET. While the acute treatment three days before the experimental stroke caused more damage from the infarction after 24h of the MCAO because it caused deleterious activation of the AMPK, the treatment for three weeks provided reduction of the acute infarction 24h after the occlusion by reducing this activation [62]. It was observed that these post-ischemic alterations can be mediated by neuronal nitric oxidase (nNOS), since its exclusion abolished the deleterious and beneficial effects presented in each case [62, 74]. It has also been demonstrated that pre-treatment for two weeks with MET provides neuroprotection by activating AMPK. On the other hand, it was observed that the acute pre-treatment 24h before pre-conditioning induced by permanent occlusion of the middle cerebral artery conferred the same effect 24h after ischemia [62]. The divergence in the results may be related to the different MET doses and the ischemia models used. The effects of the treatment in post-stroke are better established, suggesting that there is not only reduction of acute infarction, but also long-term functional recovery. The mechanisms that explain the effect of the drug in post-stroke are described in Chart 2 [62, 63]

The vast majority of studies that evaluated the cardiovascular effects of MET induced MI in rats by occlusion of the left anterior descending artery, causing ischemia (30 to 35 minutes) followed by reperfusion, or through administration of isoproterenol (doses between 25 and 250 mg/kg). One study reported that the drug uses several biochemical pathways to realize its effects. Attenuation of mitochondrial respiratory decoupling in mice treated with MET compared to those treated with saline solution was found. In addition, AMPK has been proven to be an important regulator of myocardial energy balance, activated also in I/R lesions. Activation during reperfusion maintains cardiac viability by limiting apoptosis. Other mechanisms act to minimize cardiovascular damage through nitric oxide (NO) production [64], of adenosine receptor stimulus [64, 65], the suppression of TLR4 signaling [66] and the reduction of cardiac remodeling and neutrophilic activity [67] (Chart 2).

The clinical use of MET to reduce cardiovascular diseases, such as MI and stroke, needs further investigation. A case-control study with patients of MI (n=413), stroke (n=247) and case-control (n=443), in which all used insulin, followed the effect of MET and oral hypoglycemic agents. It was observed that the use of MET compared to non-use provided a lower risk of stroke (OR 0.54; 95%IC, 0.31-0.95), however, the same result was not obtained for MI (OR 0.85; 95%IC, 0.55-1.30) [75]. The clinical benefit of this biguanide was also evaluated at MI, where 380 non-diabetic patients (n=191, MET 500mg twice a day and n=189, placebo), who presented MI with ST segment superstructure submitted to primary percutaneous coronary intervention (PCI), did not obtain improvement in the left ventricle ejection fraction after 4 months of treatment [76]. This same group was analyzed after two years, where it was also found absence of clinical benefits [77]. More promising results are seen in patients who have some pre-established metabolic disorder and who needed an elective PCI without having done previous treatment with the drug. In these, the levels of CK-MB and cardiac troponin I were reduced and, after one year of follow-up, the cardiac events were less frequent [78].

CONCLUSION

Biguanides, especially metformin, have a cardiovascular pharmacological, immunomodulatory, antiviral and antioxidant effect, thus, they are a potential therapeutic tool supporting the treatment of COVID-19. Thus, experimental studies are necessary to confirm its effects in relation to SARS-CoV-2 and the clinical evolution of the disease.

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TABLE AND CHARTS

Table 1. Descriptor strategies used in the search for studies through databases.

Subject	Main descriptors	Combination descriptors (AND)
Hyperglycemia	hyperglycemia, hyperglycemic	coronavirus
Farmacology	biguanides, metformin	absorption, administration, biotransformation, clearance, distri
Mitochondrial effect	mitocondria	biguanides, metformin
Antiviral effect	antiviral	biguanides, buformin, metformin
Imune system	inflamation	biguanides, metformin
	immune system	biguanides, metformin, pharmacology
	cancer, neoplasm	biguanides, metformin
Cardiovascular system	myocardial infarction	biguanides, metformin
	stroke	biguanides, metformin

Chart 1. Summary of the pharmacological aspects of metformin.

PHARMACOLOGICAL PARAMETERS	INFORMATIONS
Absorption and bioavailability	After oral administration is absorbed predominantly by the small intestin
Distribution	Distributed and concentrated mainly in the kidneys, adrenal glands, panc
Biotransformation	MET does not suffer hepatic metabolism.
Excretion	Approximately 30-50% of an oral dose of MET is excreted unchanged in t
Adverse effects	Nausea, vomiting, flatulence, diarrhea and abdominal pain, asthenia, hea
Contraindications	Drug allergy, creatinine clearance above 1.4 mL/min in women and 1.5 m

Source: 26-29. **Subtitle:** REF = reference.

Chart 2. Summary of the pharmacodynamic effects found for biguanides.

	EFFECTS
Immunostimulation	MET: hyperinsulinemia and insulin-related pathways regulation of inflammatory processes — energy stress, which leads to apoptosis of certain cancer cells — of the Warburg effect inhibition of the mTORC1 pathway — caspases 3 and 7 — Bad and Bax expression — of Bcl-2 and Bcl-xl — of VEGF production — of cyclin D1 and E2F1 expression — of fatty acid synthesis in prostate cancer cells anti-folate effect — P53 phosphorylation and its regulator, MDMX (indicating cell cycle arrest — cell resistance of lung adenocarcinoma without LKB1 after AMPK restorat — of ROS production inhibition of tumor growth in obese and pre-diabetic rats — of TGF-β — epithelial-mesenchymal transition regulation of the expression of Notch receptors — viability of rho0 cancer cells (without mitochondrial DNA) — DNA methylation using S-adenosyl-methionine in breast cancer cells — sensitivity to chemotherapy in cancer stem cells — sensitivity to radiation therapy higher sensitivity of MET in cells with high Myc expression in cancer suppress inhibition of M2 macrophage polarization and induction of change from M2 to — the amount of myeloid suppressor cells and their migration to tumors — number of Treg lymphocytes — the amount of memory T lymphocytes
Immunosuppression	MET: inhibition of monocyte differentiation into macrophages — infiltration of monocytes or macrophages in diseased tissues — anti-inflammatory T cells (like Th2, for example) or immunosuppressive (T — inflammatory T cells (such as Th1 or Th17, for example) — of inflammatory cytokine expression and — of anti-inflammatory cytokines inhibition of function and — number of neutrophils improvement in B lymphocyte function and — antibody production — of M1 macrophages and — of M2 macrophages suppression of phosphatase and tensin homolog (PTEN), a tumor suppressor g — expression of messenger RNA from inflammatory cytokines (TNFα, IL-1α, — in the amount of Th2 or Treg lymphocytes and — in the amount and infilt — of autoantibodies in relevant models of autoimmune diseases — in the concentration of components associated with neutrophil extracellular
Autophagy and Longevity	MET: — SIRT3 levels (associated with — biogenesis, mitochondrial function, — sen — reverse transcriptase (hTERT) telomerase activity (associated with — sene — senescence markers: p16, p21, p27 and p53 — the β-oxidation regulatory protein, ACAD10, associated with — nematode

	EFFECTS
Mitochondrial and Associated Effects	— in the expression of FGF21, a mitokine capable of improving the lipid profi PHEN: — autophagy MET, PHEN: — of the activity of mitochondria complex I and, therefore, of oxidative phosp — in the production of ROS by complex I decrease in ROS production by SDH and mGPDH MET: inhibition of mitochondrial glycerophosphate dehydrogenase (mGPDH) inhibition of ATP synthase and succinate dehydrogenase (SDH) activation of AMPK due to energy stress inhibition of acetyl-CoA-carboxylase and — expression of lipogenic genes — gluconeogenesis in hepatocytes — oxidative stress and — antioxidant defenses with long-term therapy improvement of superoxide desmutase levels in patients with DM2
Cardiovascular Effects	MET: protection against cerebral ischemia via nuclear factor related to erythroid 2 (recovery of post-stroke function and ischemia damage improvement of angiogenesis with chronic post-stroke treatment macrophage polarization to M2 with chronic post-stroke treatment — production of nitric oxide (NO) by means of nitric oxide synthase endothel stimulation of the adenosine receptor, increasing its synthesis, decreasing repe inhibition of TLR4 signaling in MI (indicating — of the production of inflamm — cardiac remodeling, neutrophilic activity and myocardial injury in MI with

Source: 20-25, 45-67. **Subtitle:** REF = reference; MET = metformin; PHE = phenformin; — = decrease; — = increase.

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