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**Review**

**Could cilostazol be beneficial in COVID-19 treatment? Thinking about phosphodiesterase-3 as a therapeutic target**

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**A B S T R A C T**

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19) that has emerged and rapidly spread across the world. The COVID-19 severity is associated to viral pneumonia with additional extrapulmonary complications. Hyperinflammation, dysfunctional immune response and hypercoagulability state are associated to poor prognosis. Therefore, the repositioning of multi-target drugs to control the hyperinflammation represents an important challenge for the scientific community. Cilostazol, a selective phosphodiesterase type-3 inhibitor (PDE-3), is an antiplatelet and vasodilator drug, that presents a range of pleiotropic effects, such as antiapoptotic, anti-inflammatory, antioxidant, and cardioprotective activities. Cilostazol also can inhibit the adenosine uptake, which enhances intracellular cAMP levels. In the lungs, elevated cAMP promotes anti-fibrotic, vasodilator, antiproliferative effects, as well as mitigating inflammatory events. Interestingly, a recent study evaluated antiplatelet FDA-approved drugs through molecular docking-based virtual screening on viral target proteins. This study revealed that cilostazol is a promising drug against COVID-19 by inhibiting both main protease (Mpro) and Spike glycoprotein, reinforcing its use as a promising therapeutic approach for COVID-19. Considering the complexity associated to COVID-19 pathophysiology and observing its main mechanisms, this article raises the hypothesis that cilostazol may act on important targets in development of the disease. This review highlights the importance of drug repurposing to address such an urgent clinical demand safely, effectively and at low cost, reinforcing the main pharmacological actions, to support the hypothesis that a multi-target drug such as cilostazol could play an important role in the treatment of COVID-19.

**1. Introduction**

Since December 2019, the world has faced a major pandemic elicited by Coronavirus disease 2019 (COVID-19). It is a viral respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This infection affects the respiratory, cardiovascular, renal, gastrointestinal system [1]. This outbreak was discovered in December 2019 in Wuhan, China, being highly contagious, it became a pandemic and spread rapidly, affecting millions of individuals worldwide [2]. Despite several studies evaluating therapies such as glucocorticoid, antiviral, antimalarial and antiparasitic, there is no specific and effective treatment yet [3,4]. Studies have reported that the disease severity is related to disorders of coagulation markers such as prothrombin time prolongation, elevated fibrin degradation products, reduced platelet count and especially increased of D-dimer levels [5,6]. These events contribute to coagulopathy activation namely disseminated intravascular coagulation (DIC) which increases the risk of venous thromboembolism [7]. The most severe presentation of COVID-19 is characterized by a hyperinflammation, attributed to excessive and uncontrolled release of pro-inflammatory cytokines, called “cytokine storm” [8]. This inflammatory cascade involves multiple pathways and results in severe organ damage such as acute respiratory distress syndrome (ARDS) [8,9]. The main therapeutic strategies aim to combat the hyperinflammation to prevent multiple organ dysfunction syndrome. To date, only dexamethasone [10] and tocilizumab [11] are recommended for critically ill patients with COVID-19. Therefore, the repositioning of...
multi-target drugs to control the hyperinflammation represents an important challenge for the scientific community.

Cilostazol, a selective phosphodiesterase type-3 inhibitor (PDE-3), is an antiplatelet and vasodilatory drug, clinically used on intermittent claudication treatment and it has been shown to exert vascular protective effects in different ischemic disease [12]. PDE-3 inhibition avoids intracellular 3’-5’-cyclic adenosine monophosphate (cAMP) degradation, mostly in cells that have large amounts of PDE-3, such as platelets, resulting in protein kinase AMPc-dependent (PKA) activation. Cilostazol also can inhibit the adenosine uptake, which enhances intracellular cAMP levels. At the pulmonary level, elevated cAMP is related to anti-inflammatory, vasodilator, antiproliferative effects, as well as to control of inflammatory events. The cAMP modulation plays a crucial role in the lung and bronchial cell maintenance [13,14]. Thus, targeting PDE-3 inhibition for the respiratory diseases treatment is of great interest [15].

Several studies have reported a range of effects associated to cilostazol, such as antiapoptotic [16], anti-inflammatory [17], antioxidant [18] and cardioprotective activities [19]. In recent years, cilostazol has aroused the interest of several scientists due to its pleiotropic actions, including its potential anti-inflammatory effect. Cilostazol is able to prevent nitric oxide and cytokine production in LPS-stimulated microglia [20–22]. It has been also reported to inhibit cytokine expression through direct effect on nuclear factor-κB (NF-κB) activity in RAW264.7 macrophage cells stimulated by different Toll-like receptors (TLRs) ligands [23,24]. In vivo studies have demonstrated that cilostazol suppress neointimal hyperplasia LPS-induced, macrophage infiltration in a rabbit aorta balloon-injury model [25], besides decreasing inflammatory cytokines and mortality in LPS-induced septic shock mice [26]. In isolated platelets, cilostazol can also exerts anti-inflammatory beyond antiplatelet effects through AMP-dependent protein kinase (AMPK) and endothelial nitric oxide synthase (eNOS) activation followed by NF-κB inhibition [17]. Moreover, cilostazol exerts protective effects on vascular and renal bed via NF-κB and cytokines downregulation [27,28]. The potential effects promoted by cilostazol may be useful to prevention of several inflammatory disorders.

Recent studies have demonstrated beneficial effects of cilostazol in patients with pneumonia associated with different pathologies [29], pneumonia in patients with acute cerebral infarction [30] and stroke-associated pneumonia in patients receiving tube feeding [23]. A recent study performed molecular docking-based virtual screening, and it was demonstrated that cilostazol is the most promisor antiplatelet Food and Drug Administration (FDA)-approved drug against COVID-19. Cilostazol played the most favorable binding interaction on viral target protein, main protease (MP30), besides presenting the highest binding affinity on spike glycoprotein (S) when compared to other antiplatelets and other recent inhibitors against COVID-19 such as nelfinavir, umifenovir and darunavir [31].

Whereas the time and cost required to characterize and establish a safe and effective therapy for the treatment of COVID-19 are important limitations, drug repositioning becomes an attractive and fast alternative in this race against time. Based on the pathophysiology of COVID-19, this review describes lots of evidence that support the hypothesis that among all antiplatelet FDA-approved therapies, cilostazol can play an important role as adjuvant treatment of COVID-19 in order to avoid poor prognosis and fatal disclosures.

2. Pathophysiology of COVID-19

In most cases of COVID-19, patients presents mild symptoms as fever, dry cough, shortness of breath, fatigue and diarrhea, but in some cases it progress to severe symptoms as severe respiratory distress, sepsis, coagulation disruption, thromboembolic events which has serious consequences. Elderly age, gender (male) followed by underlying comorbidities (i.e hypertension, obesity, diabetes, cancer) are directly associated with poor prognosis in COVID-19 [32,33]. Lung biopsy analysis of COVID-19 patients in early and late stages, exhibited bilateral diffuse alveolar damage, hyaline membranes, mononuclear cells, macrophages infiltrate and microthrombi in pulmonary vasculature [34]. Recent report has showed that virus can replicate in the lower respiratory tract, developing pneumonia and it progress to ARDS with edema and hypoxemia. The exacerbation of inflammatory process contributes to additional extrapulmonary manifestations as liver, heart and acute kidney failure, sepsis and disseminated intravascular coagulation (DIC) in a few days [6,35]. Regarding to extrapulmonary disturbances, the cardiovascular system is directly damaged. The main cardiovascular disorders observed are cardiac arrhythmias, acute coronary syndromes, heart failure, cardiomyopathy, myocarditis and sudden cardiac arrest [36].

Severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1), Middle East Respiratory Syndrome coronavirus (MERS-CoV) and SARS-CoV-2 belongs to beta-coronaviruses group. SARS-CoV-2 is more genetically similar to SARS-CoV-1, with 82% nucleotide identity, than MERS-CoV, which shares 50% nucleotide identity [37]. The SARS-CoV and MERS-CoV infections share several similarities to SARS-CoV-2 regarding to symptoms, elderly age, risk factors, cardiovascular, lung microthrombi formation and thromboembolic complications [38]. The angiotensin converting enzyme 2 (ACE2), has been recognized as the receptor for SARS-CoV-1 and SARS-CoV-2 syndromes, while the MERS-CoV interacts with dipeptidyl peptidase 4 (DPP4) receptor to enter the host cell. ACE2 is localized on respiratory tract, small intestine, immune cells, arterial smooth muscle, arterial and venous endothelial cells and others, allowing the virus entry [39–41].

Inflammatory process, immunological response and hemostasis are intrinsically associated. Macrophages, dendritic and plasmacytoid dendritic cells, belong to innate immune and, express on their surface pattern recognition receptors (PRR), such as TLRs, NOD-like receptors (NLRs) or RIG-I like receptors (RLRs), which act as sensors in response to various infections, recognizing pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs). They can identify SARS-CoV-2 single stranded viral RNA, inducing gene transcription of type I/III interferons (IFNs), which play a crucial role in early antiviral response in the host cell [6,42]. Moreover, TLRs, NLRs and RLRs can activate downstream signaling effectors, such as adaptor proteins MyD88 and TRAF6, which lead to NF-κB activation, increasing the gene transcription of a range pro-inflammatory cytokines and chemokines including interleukin (IL) 1β, IL-6, tumor necrosis factor-alpha (TNF-α), C-C motif chemokine 2 (CCL2), CCL3, CCL5 (RANTES), CX-C motif chemokine 10 (CXCL10), monocyte chemotactrant protein-1 (MCP-1) and macrophage inflammatory protein 1α (MIP1α) thereby amplifying the recruitment of innate immune response [38,39,43].

In most cases, this initial inflammatory response triggered by TLR and type-1 IFN, leads to cytokine production followed by effective immune response contributing to infection resolution [44]. However, some individuals have a dysfunctional immune response with a delayed or low early antiviral response by type1 IFN, leading to endothelial cells activation by cytokines and viral particles, which contributes to tethering of platelets and expression of adhesion molecules in endothelial surface. Injured endothelial cells expose tissue factor, activating the coagulation cascade with fibrin deposition and blood clotting, leading to pulmonary and systemic damage [35]. All these events are triggered by a phenomenon namely “cytokine storm” which aggravate the inflammatory process with vascular leakage, aberrant monocytes, neutrophils and lymphocytes in the pulmonary alveoli, followed by cell apoptosis, immunosuppression, hyperinflammation, culminating in disease severity [2,45] (Fig. 1).

Inflammatory process can also stimulate the coagulation cascade through polymorphonuclear neutrophils (PMN) which are recruited by activated endothelial cells and then release neutrophil extracellular traps (NETs). NETs release involves the extrusion of neutrophil chromatin webs from its granules in order to eliminate the pathogen in a process termed NETosis [46]. NETs act as a scaffold for thrombus formation, besides bind and activate platelets, amplifying the blood
Serum from severe patients with COVID-19 have presented elevated levels of NETs such as citrullinated histone H3 and myeloperoxidase-DNA and both reflect in poor prognosis. Moreover, serum from COVID-19 patients prompt NET release in control neutrophils, being an in vitro NETosis inducer [48]. The role of NETs in multiple organ damage syndrome and mortality in COVID-19 has been supported. The interplay between platelets and NETs may also be critical on microvascular thrombosis development, inflammatory process and tissue damage observed in COVID-19 [49,50]. Therefore, NETs can be a target for COVID-19 treatment, but further studies are needed to characterize their contribution [50,51].

Several studies have shown that SARS-CoV-2 infection can modify the hemostasis of affected patients and then induce a prothrombotic state [3,5,52–56]. In viral infections such as influenza, the cell damage caused in pulmonary capillaries facilitates the endothelium/platelet interaction, promoting the prothrombotic state and decrease in blood oxygenation [57]. Cameron et al. (2018) have demonstrated that isolated murine and human platelets exposed to hypoxia have an increase of P-selectin and αIIbβ3 integrin expression, suggesting that ischemic conditions alters the platelet phenotype, modifying its activity against several agonists [58]. Hypoxia may also increase the thrombosis risk through modulation of hypoxia-inducible transcription factors expression (HIFs) which accumulates in nucleus and bind to hypoxia-responsive element (HRE), promoting the transcription of genes related to thrombogenic factors and pro-inflammatory mediators, such as IL-1β [59–61].

Platelet count during treatment of COVID-19 may indicate the severity and prognosis of the disease [52]. Furthermore, thrombocytopenia is also associated with threefold enhanced risk to developing the severe form of COVID-19 [5]. In dengue infection, platelets exert a crucial role in immunomodulatory and inflammatory responses through platelet-monocyte aggregate formation and platelet-dependent monocyte activation, leading to increased synthesis and secretion of pro-inflammatory cytokines as IL-1β, IL-6 and MCP-1 [62].

In influenza viral infection, platelets play immunomodulatory effects by TLR7 activation accompanied by α-granules release which increase P-selectin and CD40-L expression, culminating in platelet-neutrophil aggregates. Platelet-TLR7 activation can also release C3 complement system protein from its granules which induce NETs release [63]. Antiplatelet drugs may have beneficial effects against hypercoagulable state on sepsis due their anti-inflammatory properties [64]. The severity of COVID-19 has been associated to hypercoagulability biomarkers, such as prothrombin time prolongation, elevated fibrin degradation products, activated partial thromboplastin time shortened and specially to elevated D-dimer which is highlighted as a prognostic marker [54,56]. Approximately 71.4% of COVID-19 non-survivors presented lethal complications, including DIC according to the criteria of International.
Society for Thrombosis and Hemostasis. DIC may also contribute to development of embolism and extensive pulmonary capillary obstruction, playing a key role in COVID-19 lethality [55]. Interestingly, therapeutic anticoagulants have been used in previous pandemics, such as H1N1 influenza and their use has been associated with a reduction in mortality of COVID-19 patients [65]. These data support that the thrombophrophylaxis can prevent potentially lethal complications, including DIC, thereby reducing the mortality rate [2].

3. Antiplatelet activity of cilostazol

In SARS-CoV-2 infection, the hyperinflammation promoted by inefficient immune response lead to endothelial cell activation and endothelial dysfunction, inducing a prothrombotic profile in which, highlights the interplay between immune system, inflammation, and thrombosis [6]. Hotz and colleagues showed that severe COVID-19 patients present platelet activation, platelet-monocyte aggregates formation, increasing tissue factor expression by monocytes which is correlated to coagulation dysfunction markers as D-dimer. The mechanism seems to be associated with P-selectin and integrin αIIb/β3 signaling, highlighting the key role of platelets on pathophysiology and severity COVID-19 [66]. The increased inflammatory response accompanied by hypercoagulable state in COVID-19 patients, reinforces the importance to investigate the antiplatelet therapy in severe COVID-19 patients [56].

Cilostazol is a potent antiplatelet and vasodilatory drug, its pharmacology is multifaceted, presenting a wide spectrum of pharmacological actions such as anti-inflammatory, antioxidant, antiproliferative and cardioprotective effects. The main mechanism involved in the antiplatelet effect of cilostazol is associated with PDE3 inhibition, increasing intraplatelet cAMP levels, an important second messenger involved in the regulation of platelet activity. Increasing cAMP levels promoted by cilostazol contributes to reversible inhibition of both primary and secondary platelet aggregation induced by several agonists such as ADP, collagen, arachidonic acid and, thrombin [67]. In blood vessels, the increase of cAMP production promoted by cilostazol results in vasodilatory effects [68]. Moreover, cilostazol is able to suppress the expression and release of P-selectin from alpha-granule of platelet-rich plasma and washed platelets from healthy human volunteers [69]. Cilostazol is a drug that exerts not only antiplatelet effect, but also improves endothelial cell function, reducing the platelet-endothelium interaction and thrombotic events [67]. A study performed in health volunteers demonstrated that cilostazol can inhibit platelet aggregation without affect bleeding time [70]. Cilostazol is also able to inhibit both primary and secondary platelet aggregation induced by several agonists [71]. Several clinical studies have reported the antiplatelet effects of cilostazol in the prevention of cerebral infarction [72], peripheral arterial disease [73], critical limb ischemia [74], stroke [75,76] and atherosclerosis [77,78]. In addition to its direct effects on platelets, cilostazol also has effects on hemostasis through independent-cAMP mechanism. In isolated platelets from humans, cilostazol exerts inhibitory effects on platelet-leukocyte interaction through reducing P-selectin expression on the platelet surface [79]. Cilostazol also exerts antiplatelet and anti-inflammatory effects through AMPK activation and NF-κB inhibition in isolated platelets from hypercholesterolemic rats, a cAMP-independent mechanism, highlighting the cilostazol as a multi-target drug [17]. Moreover, in Equid herpes virus type-1 (EHV-1)-induced platelet activation, cilostazol was able to inhibit P-selectin expression on platelets surface, demonstrating a potential effect in reducing EHV-1-induced thrombosis [80]. A prospective and randomized study performed in non-valvular atrial fibrillation patients demonstrated that combined antiplatelet therapy with aspirin and cilostazol significantly reduced coagulation biomarkers levels, such as von Willebrand factor (vWF) and fibrinogen, thus decreasing platelet responsiveness in these patients [81]. The thromboangiitis obliterans (TAO), a peripheral vascular disease caused by immune response, occurs endothelial injury, increase of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) expression and pro-inflammatory cytokines levels. In TAO patients, cilostazol reduced ICAM-1, VCAM-1 mRNA expression and cytokines plasma levels, besides decreasing plasma viscosity, fibrinogen, total cholesterol, and triglycerides levels, demonstrating potential anti-inflammatory, antithrombotic and lipid-lowering effects in these patients [82]. Such preclinical and clinical evidence reinforce the additional anti-inflammatory effect of cilostazol which may be useful in reducing thromboembolic events triggered by hyperinflammation in patients with COVID-19 (Table 1 and 2).

4. Anti-inflammatory and antioxidant effects of cilostazol

Intracellular cAMP levels are fundamental in the modulation of several cellular functions, including the regulation of inflammatory and immune system [83]. PKA activation and NF-κB inhibition, reducing pro-inflammatory genes transcription seem to be one important pathway related to cAMP anti-inflammatory property [15,84]. Inflammation, oxidative stress, and a dysfunctional immune system are linked to severity of COVID-19 infection. Therefore, a therapeutic approach that reduce hyperinflammation and consequently mitigate multiple organ dysfunction syndrome would be useful to COVID-19 treatment. The anti-inflammatory and antioxidant effects of cilostazol have been reported in several studies. In J774 cell lines murine macrophages, cilostazol suppressed cytokines production through direct inhibition of NF-κB and upregulation of PKA/nuclear factor erythroid-related factor 2 (Nrf2), which increase heme oxygenase (HO-1) expression [85]. Interestingly, in cultured proximal tubular epithelial cells, cilostazol showed an increase in Nrf2/HO-1 signaling, demonstrating its important role in adjuvant therapy of metabolic disorder-associated renal injury [86]. In sepsis-induced lung injury, Sirtn1 (SIRT1) inhibited endoplasmic reticulum stress and inflammation [87]. Cilostazol upregulates SIRT1 in various tissues, such as endothelial cells [88], neuronal cells [89] and hepatocytes [90], which contributes to its anti-inflammatory and antioxidant effects.

Recent studies have demonstrated protective effects of cilostazol in animal models of colitis, attributed to its anti-inflammatory action [91–93]. In an animal model of acetic acid-induced colitis, cilostazol exerted an antioxidant and anti-apoptotic anti-inflammatory effect through CAMP/SIRT1 activation, suppressing NF-κB mitogen-activated protein kinases (MAPKs) pathways [94]. In vascular smooth muscle cells (VSMC), cilostazol exerts its anti-inflammatory actions through several mechanisms, such as suppression of the ERK1/2 pathway [95], inhibition of RAGE/ERK/NF-κB signaling [96] and attenuation of Axl signaling and downstream pathways [97]. Moreover, several studies have demonstrated important effects of cilostazol on attenuation of reactive oxygen species (ROS) production, lipid peroxidation, inflammatory cytokines such as IL-6, IL-1β, TNF-α, monocyte chemoattractant protein-1 (MCP-1) and IFN-γ, supporting its antioxidant, anti-inflammatory and immunomodulatory actions [98–100].

High-mobility group box 1 (HMGB1), is a nuclear DNA-binding protein that has been characterized as an inflammatory cytokine release from different tissues, which trigger systemic inflammation, redox state disturbance, NETs release, multi-organ damage and DIC and its release has been correlated with COVID-19 severity [85–87]. In LPS-activated macrophage cells, cilostazol was able to reduce HMGB1 release through AMPK/HO-1 activation, besides decreasing plasminogen activator inhibitor-1 (PAI-1) circulating levels [101,102].

As reported in this review, the worse manifestation of COVID-19 is associated with hyperinflammatory state, culminating in endothelial damage, coagulation cascade activation and multi-organ failure. Given that, the inhibition of PDE3 by cilostazol, as well as its multifaceted pharmacological effects may represent a useful therapy for COVID-19 (Table 1 and 2).
Table 1
A summary of preclinical studies carried out on the potential therapeutic properties of cilostazol against COVID-19.

| Major finding | Experimental design | Results |
|---------------|---------------------|---------|
| Potential drug against SARS-CoV-2 | Molecular docking Screening of antiplatelet FDA-approved drugs | Cilostazol presented the most promising effect against COVID-19 by inhibiting both viral target proteins: main protease (Mpro) and spike glycoprotein (S), compared with other compounds studied, including antivirals anti-COVID-19. [31] |
| Anti-platelet and anti-inflammatory effects | In vitro Platelet rich plasma from horses exposed to EHV-1 | Reduction of platelet activation marker expression (P-selectin) after EHV-1 exposition in cilostazol treated PRP [80]. |
| | Preparation of human platelets and leukocytes | Inhibition of platelet-leucocyte interaction and platelet activation by decrease of P-selectin and integrin α2β3 expression, decrease of ion calcium levels [79]. |
| | In vivo Isolated platelets from hypercholesterolemic wistar rats | Inhibition of platelet aggregation and inflammation by P-selectin and TXB2 inhibition. Increase of cAMP and cGMP levels, increase of eNOS, AMPK-α, pAMPK-α phosphorylation. |
| | Isoproterenol-induced myocardial injury in high-fat-fed rats | Inhibition of platelet aggregation, inflammatory markers, ICAM-1, NF-kB, TNFα, IL-6 and attenuation of oxidative stress by INOS inhibition and GSH increase [16]. |
| Anti-inflammatory and antioxidant effects | In vitro RAW264.7 cells | Anti-inflammatory effect through AMPK/HO-1 pathway activation followed by inhibition of high mobility group box 1 (HMGB1), NF-kB and PAI-1 [101]. |
| | J774 cell line murine macrophages | Cilostazol increase antioxidant enzymes synthesis through Nrf2 and heme oxygenase upregulation [85]. Increase in Nrf2/HO-1 signaling [86]. |
| | Proximal tubular epithelial cells culture Human umbilical vein endothelial cells (HUVECs) | Neuroprotective effect against oxidative stress senescence-induced through eNOS and SIRT1 upregulation [88]. Suppression of NAD(P)H oxidase-dependent superoxide and cytokines formation [110]. |
| | In vivo Rat model of Huntington’s/Parkinson’s disease | Neuroprotective effect through inhibition TLR-4, IL-6, JAK-2/STAT-3/SOCS-3 and activation of IL-10/Akt/GSK-3/CREB signaling pathways (El-Ahbar H, 2018) [155]. |
| | Human synovial macrophages Synovial macrophages from RA patients | Neonartrine effects by Cilostazol down-regulated LPS-stimulated PU.1-linked TLR4 by TLR4/MyD88/NF-kB signaling, reduced TNF-α and IL-1β [114]. |
| | Isolated dendritic cells Human dendritic cells | Inhibition of cytokine production; reduction of IFN-α levels; inhibition of plasmacytoid dendritic cell activation [98]. |
| | Septic mice | Antioxidant effect through reduction of reactive oxygen species levels and prevention of mitochondrial swelling and depolarization [19]. |
| | Cardioprotective effect Cardiac mitochondria treated with H2O2 | Cilostazol attenuated LV diastolic dysfunction, cardiac hypertrophy, cardiac inflammation, inhibited macrophage infiltration and proinflammatory cytokines production and exerted antifibrotic effects [133]. Cardioprotective, anti-inflammatory and antiapoptotic effects by decreasing IL-6, IL-1β and TNF-α levels. Inhibition of apoptotic protein Bax and caspase-3, restoring Bcl-2 levels through activating PPARγ/JAK2/STAT3 pathway [156]. |
5. Immunomodulatory effects of cilostazol

Patients affected by COVID-19 have dysfunctional immune response associated with cytokine storm which results in multi-organ damage [35]. Dendritic cells are important antigen-presenting cells and act as a link between innate and adaptive immune responses [103,104]. Once exposed to infectious agents, dendritic cells express and secrete cytokines expression (IL-1β) in response to infection [116]. The uncontrolled activation of NLRP3 exerts a key role in host immune defenses against fungal, bacterial and viral infections, mediating caspase-1 activation, cytokines secretion and pyroptotic cell death, evoking deleterious consequences, including a dysfunctional immune response against the viral infection and possibly death of the host. Therefore, the direct NLRP3 activation followed by pyroptosis may be a serious side effect which became a problem of great clinical relevance [118]. Patients with adequate immune response are able to clear the viral infection, resulting in recovery. On the other hand, patients with dysfunctional immune response are not able to reduce the viral infection which trigger massive injury in tissues with NLRP3 activation, generating a vicious inflammatory cycle that can result in death [119].

A study performed in human endothelial cells exposed to high free fatty acid (FFA) showed a potential effect of cilostazol on NLRP3 inhibition. The possible mechanism seems to be related to SIRT1 activation

Abbreviations: Akt - protein kinase B; Bel-2 - B-cell lymphoma 2; cAMP - cyclic adenosine monophosphate; cGMP - cyclic guanosine monophosphate; CK - creatine kinase; CK-MB - myocardial creatine kinase; cAMP response element binding protein /CREB; FDA - Food and Drug Administration; GSH – glutathione; GSK-3β - glycogen synthase kinase-3β; HCO – hypercholesterolemic diet; HFD - high fat diet; ICAM - intercellular adhesion molecule; iNOS - inducible nitric oxide synthase; IL-1β - interleukin-1β; IL-23 - interleukin-23; ICAM-1 - intercellular adhesion molecule; iNOS - inducible nitric oxide synthase; Jak-2 - Janus kinase 2; LA - left atrium; LDH - lactate dehydrogenase; LV - left ventricle; MDA – malondialdehyde; NF-κB – Nuclear factor kappa-B; NFκB - nuclear factor erythroid 2-related factor 2; Nurr1 - nuclear receptor related 1; PD – Parkinson’s disease; PAI-1 - plasminogen activator inhibitor-1; PKCα - protein kinase C alpha; RA - rheumatoid arthritis; STAT-3 - signal transducers and activators of transcription 3; SOCS3 - suppressor of cytokine signaling 3; TLR4 - Toll-like receptor 4; TNFα - tumor necrosis factor alpha;

Table 2

A summary of clinical trials carried out on the potential therapeutic properties of cilostazol against COVID-19.

| Major findings | Experimental design/population | Results |
|----------------|--------------------------------|---------|
| Antiplatelet effect | Randomized clinical trial | Reduction of platelet aggregation [70]. |
|                  | Male healthy adults | Reduction of recurrence of cerebral infarction associated with vasodilator and antiplatelet effects of cilostazol [75]. |
|                  | Cerebral infarction patients | Reduction in carotid intima-media thickness when compared to aspirin. Cilostazol has beneficial effects on atherosclerosis through vasodilator and antiplatelet actions [78]. |
|                  | Type 2 diabetes patients | Reduction in left atrium size and left ventricular abnormalities compared to aspirin. Cilostazol has beneficial effects on left ventricular remodeling. |
|                  | Type 2 diabetes patients diagnosed after 30 years | Attenuation of albuminuria through decreasing of E-selectin and VCAM-1 plasma levels. Nephroprotective effect due to its anti-inflammatory action. (Tang et al., 2013). |

Anti-inflammatory effect

| Randomized clinical trial | Reduction of TAO-induced abnormal increase in ICAM-1, VCAM-1 and pro-inflammatory cytokines expression (IL-1β) IL-6 and TNFα in plasma of patients treated with cilostazol [82]. |
|--------------------------|-------------------------------------------------|
| Patients with | Reduction of restenosis rate after coronary stent implantation by downregulation of platelet activation P-selectin-induced, platelet-leukocyte interaction and Mac-1-mediated leukocyte activation (Inoue et al., 2004) [159]. |
| Thromboangiitis obliterans (TAO) | Reduction in inflammatory markers: C-reactive protein and sCD40L and increase of adiponectin levels [159] (Hsieh et al., 2009). |
| Patients with peripheral arterial disease | Cilostazol was able to reduce plasma MMP-9 levels, showing an anti-inflammatory effect [160] (Francis et al., 2013). |
| Artery disease undergoing coronary stenting | Reduction in C-reactive protein levels, total leukocyte count, oxidative status besides decreasing risk of coronary heart disease [161] (Agrawal 2007). |
| Hypertensive type 2 diabetes mellitus patients | Prevention of cardioembolic stroke in patients who received cilostazol compared with patients undergoing to other antiplatelet therapy [134]. |
| Hypertensive type 2 diabetes mellitus patients | Cilostazol was able to reduce oxidative stress through decreasing plasma malondialdehyde levels, as well as increase of reduced glutathione and albumin levels [161] (Agrawal, 2007). |

(continued on next page)
mediate SARS-CoV-2 entry into cardiomyocytes and cause direct cardio-vascular damage [161,162]. NETs play an important and recognized role on inflammation and oxidative response associated to COVID-19 [120]. Cilostazol was able to reduce bronchial hyperresponsiveness to methacholine and presented a bronchodilator effect in elderly patients with asthma [144] and healthy patients [161,162].

Abbreviations: ICAM-1 - intercellular adhesion molecule-1; IL- interleukin; IS- ischemic stroke; sCD40L - soluble CD40 ligand; TF – tube feeding; TNF-a-tumor necrosis factor-alpha; VCAM-1 – vascular adhesion molecule-1.

Table 2 (continued)

| Major findings | Experimental design/ population | Results |
|----------------|----------------------------------|---------|
| Prevention of pneumonia | Retrospective cohort | Decrease in occurrence of pneumonia in patients with acute cerebral infarction. This effect has been associated with the increase of substance P induced by cilostazol, antagonizing swallowing reflex thereby reducing aspiration pneumonia [30]. Cilostazol reduced stroke-associated pneumonia [23]. |
|                       | Randomized clinical trial | Administration of 200 mg/day cilostazol prevent recurrence of cerebral infarction and the onset of pneumonia [143]. Cilostazol was able to reduce bronchial hyperresponsiveness to methacholine and presented a bronchodilator effect in elderly patients with asthma [144] and healthy patients [161,162]. |
| Bronchoprotection | Bronchoprotection | Cilostazol reduced pneumonia incidence probably due to improvement in swallowing function [141]. |

7. Cilostazol as a candidate adjuvant therapy to COVID-19

Cilostazol has been studied in different pathologies due to its potential cardioprotective effects in experimental models and in clinical trials. Its effects may have direct benefits in cardiovascular complications developed by COVID-19. Tawfik et al. (2018) showed in an experimental model of acute cardiac injury induced by isoproterenol an important effect of cilostazol in reducing myocardial markers as CK-MB and CK, in modifying electrocardiographic parameters, in addition to promoting anti-inflammatory and antioxidant effects through modulation of NF-κB and PI3K/Akt/mTOR pathway [116]. In an experimental model of heart failure, cilostazol was able to prevent diastolic dysfunction and hypertension by restoring left ventricular function, reducing inflammatory infiltrate and pro-inflammatory cytokines levels [133]. A multicenter retrospective study of stroke risk in antithrombotic therapy (RESTATE) showed that cilostazol prevents cardioembolic stroke in patients employing antiplatelet therapy. This data suggests a new strategy for the prevention of these occurrences [134]. Zhao et al. (2020) showed that cilostazol was able to suppress atrial remodeling induced by rapid atrial pacing in a dog model of atrial fibrillation (AF), indicating new targets and new strategies for AF management [135]. In myocardial ischemia/reperfusion model in mice, cilostazol has been shown to exert anti-inflammatory and antiapoptotic effects through PPARγ/JAK2/STAT3 activation [136]. Although further studies are still needed to clarify the cilostazol effects, to date, the evidence suggest that cilostazol may have cardioprotective effects in hospitalized patients, who present COVID-19 associated cardiovascular manifestations.

6. Cardioprotective effects of cilostazol

The final stage of COVID-19 is characterized by multi-organ damage which contributes to the development of serious cardiovascular manifestations such as elevation of myocardial damage biomarkers, electrocardiography and echocardiography disorders, arrhythmias, myocarditis, heart failure, acute coronary syndrome, cardiogenic shock and arrest [36,100–103].

Zou et al. (2020) described that more than 7.5% of myocardial cells have positive ACE2 expression. Thus, ACE2 membrane proteins could mediate SARS-CoV-2 entry into cardiomyocytes and cause direct cardiotoxicity [126]. The mechanisms of cardiovascular injury from COVID-19 have not been fully elucidated and it can be associated to direct cardiotoxicity or it can be driven by consequences of “cytokine storm” at cardiovascular system (vascular inflammation, plaque instability, myocardial inflammation, hypercoagulable state). Sepsis and DIC can also be associated to cardiac injury [122–125,127,128].

Patients that present comorbidities such as baseline hypertension, diabetes, coronary heart disease, failure, especially the elderly patients, have an enhanced probability to develop cardiac injury associated to COVID-19. In turn, patients who develop cardiac injury have a worse prognosis, including ICU admission and death [129,130]. Guo et al., (2020) have described a retrospective, single-center case series of 187 patients with COVID-19, where it was found that patients with pre-existing cardiovascular diseases (CVD) have presented more cardiac injury compared with patients without CVD (54.5% vs 13.2%, p < 0.001) [131]. Shi et al. (2020) reported that the mortality rate for hospitalized COVID-19 patients with subsequent evidence of cardiac injury was significantly higher than for those without cardiac injury (51.2% vs. 4.5%; p < 0.001) and, along with ARDS, it represents an independent predictor of death [132]. Arrhythmogenic manifestations were associated to 17% of hospitalized patients with COVID-19 (n = 23 of 138 total), being most prevalent in ICU patients (44%, n = 16) when compared to non-ICU patients (7%, n = 7) [129]. Once the primary pulmonary injury and subsequent cardiovascular complications represent the key pathophysiology of COVID-19, a pharmacological treatment that can play a role in these different targets would be an important strategy.

Cilostazol has been studied in different pathologies due to its potential cardioprotective effects in experimental models and in clinical trials. Its effects may have direct benefits in cardiovascular complications developed by COVID-19. Tawfik et al. (2018) showed in an experimental model of acute cardiac injury induced by isoproterenol an important effect of cilostazol in reducing myocardial markers as CK-MB and CK, in modifying electrocardiographic parameters, in addition to promoting anti-inflammatory and antioxidant effects through modulation of NF-κB and PI3K/Akt/mTOR pathway [116]. In an experimental model of heart failure, cilostazol was able to prevent diastolic dysfunction and hypertension by restoring left ventricular function, reducing inflammatory infiltrate and pro-inflammatory cytokines levels [133].
cerebral infarction patients [141]. Cilostazol treatment has also shown effective in elderly patients with pneumonia [142,143] and asthma [144].

Given the wide distribution of PDEs and their role in the modulation of several cell types and functions, a range of PDE inhibitors have been evaluated for the treatment of COVID-19. In LPS-induced acute lung injury in mice, ZL-n-9, a PDE-4 inhibitor, demonstrated a potential anti-inflammatory effect through reducing pro-inflammatory cytokines levels [145]. Diprydamole, a non-selective PDE inhibitor has been shown antiviral and anti-inflammatory effects with efficacy against RNA viruses [146], besides preventing acute lung injury and fibrosis in heart, liver and kidney [147,148]. A clinical trial demonstrated an important effect of diprydamole in severe COVID-19 patients by decreasing of D-dimer levels, reducing the hypercoagulable state and the multi-organ damage [34]. Sildenafil, a PDE-5 inhibitor, initially approved for erectile dysfunction treatment, also exerts important effects on pulmonary arterial hypertension [149], as well as anti-inflammatory, vasodilator and cardioprotective actions [150-152]. Recently, sildenafil has been investigated in a clinical trial to confirm its therapeutic effects on COVID-19 patients [153].

PDE-3 is associated to many physiological effects in different systems and plays an important role in respiratory diseases such as asthma and chronic obstructive pulmonary disease. COVID-19 infection, primarily affects the lungs and spreads, causing multiple organ failure. It seems reasonable to postulate that phosphodiesterase inhibitors can be an important pharmacological target to COVID-19 treatment [15,154]. In a recent study reported by Abosheasha and colleagues (2020), it was performed molecular docking-based virtual screening of 15 antiplatelet FDA-approved drugs on two main viral target protein of SARS-CoV-2, Mpro and spike glycoprotein, considered as molecular targets to COVID-19 treatment. This study revealed a superiority of cilostazol among all antiplatelets tested, as well as cilostazol was superior when compared to recent described inhibitors to COVID-19 treatment. Cilostazol presented the highest binding interaction with Mpro and spike glycoprotein. These data suggest that cilostazol is a promising drug in the treatment of COVID-19. However, more studies are needed to confirm these findings [31]. This study reinforces the drug repurposing, in order to attend such an urgent clinical demand. This strategy drives the use of drugs with known safety profiles to new patient populations and, in COVID-19 scenario, the cilostazol use may represent a quick and attractive pharmacological approach in this race against time. The pleiotropic actions performed by cilostazol, suggests that it should be explored as a new therapeutic possibility at the complex pathophysiology of COVID-19 [153]. The body of evidence support the PDEs inhibition as a possible therapeutic target in the COVID-19 treatment. Once cilostazol, through PDE-3 inhibition, presents important anti-inflammatory, anti-platelet, immunomodulatory, antioxidant and cardioprotective properties, we do believe that it can play an important role at COVID-19 treatment, especially in the fight to control cytokine storm and the fatal disclosures associated (Fig. 1).

8. Conclusion

COVID-19 is a viral infectious disease mainly manifested as fever and pneumonia. At present, there is not any antiviral therapy or vaccine available to specifically treat COVID-19 and only respiratory supportive therapies and anti-inflammatory drugs remain as the mainstream of treatments for severe cases. Anti-inflammatory drugs are especially important to interrupt cytokine storm phenomenon and all complications associated, even death. All the scientific community is searching for an effective, safe, and already available therapy useful to minimize poor prognosis. The main candidates are anti-inflammatory and antithrombotic drugs in order to minimize the most common complications observed. In a short term, drug repositioning approach may be more appealing and quicker in the fight against COVID-19. In molecular docking study, cilostazol showed its superiority among all antiplatelet drugs by inhibiting both Mpro and spike protein. Moreover, several preclinical and clinical studies have already demonstrated its beneficial properties in different systems damaged by SARS-CoV-2, which reinforce the cilostazol employment as an adjuvant therapy for COVID-19. The potential therapeutic effect of cilostazol as an adjuvant use in the treatment of COVID-19 should be investigated in proof of concept studies, as well as in randomized clinical trials to corroborate its therapeutic use in the future.

CRediT authorship contribution statement

Nadia Alice Vieira Motta: Conceptualization, Writing - original draft, Visualization, Writing - review & editing. Lis Jappour Autran: Conceptualization, Writing - original draft, Visualization. Stephani Correia Brazao: Conceptualization, Writing - original draft, Visualization. Rosane de Oliveira Lopes: Contributed methods, Writing - review & editing. Gabriel Ferreira Lima: Writing - original draft. Fernanda Carla Ferreira de Brito: Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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