Could Oral Phosphodiesterase 5 Inhibitors Have a Potential Adjuvant Role in Combating COVID-19 Infection?

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ABSTRACT

Introduction: The recent global outbreak of coronavirus disease 2019 (COVID-19) has become a pandemic with a lot of sufferers. Excessive inflammation, exaggerated immune response, with ultimate apoptosis contribute to COVID-19 pathology that progress to acute lung acute respiratory distress.

Objective: To shed a light on the likely benefits of the oral phosphodiesterase 5 (PDE5) inhibitor adjuvant role in combating COVID-19 infection.

Methods: A literature review was performed in the PubMed/Medline database, Scopus, Cochrane Library, EMBASE, Academic Search Complete, Google Scholar, and CINAHL databases using the keywords COVID-19; phosphodiesterase-5 inhibitors; cytokine storm; respiratory distress.

Results: Despite the worsening trends of COVID-19, still no drugs are validated to have significant clinical efficacy in the treatment of patients with COVID-19 in large-scale studies. While the progress toward a curative agent and/or vaccine is certainly hopeful, the principal limiting factor in such public health emergencies is always the time. Therefore, a preexisting licensed therapeutic(s) might offer a reprieve to the healthcare systems operating at the edge of capacity. In this context, the innovation of oral PDE5 inhibitors with their valuable effects on erection have provided a breakthrough in the treatment of erectile dysfunction and opened new fields of clinical application for this class of drugs. Oral PDE5 inhibitors have been demonstrated to possess many beneficial useful additional implications with acknowledged anti-inflammatory, antioxidant, immune response regulation, and antiapoptotic properties. These properties have been elucidated through the nitric oxide/soluble guanylyl cyclase/cyclic guanylate monophosphate pathway in addition to the emerged hemeoxygenase-1 enzyme as well as hydrogen sulfide pathways. These properties could support repurposing oral PDE5 inhibitors' potential adjuvant use in targeting different aspects of COVID-19 infection.

Conclusion: Oral PDE5 inhibitors retain several acknowledged off-labeled useful implications with anti-inflammatory, antioxidant, immune response regulation, and antiapoptotic properties. These properties may support repurposing oral PDE5 inhibitors' potential adjuvant use in the protocols combating COVID-19 manifestations. **Mostafa T. Could Oral Phosphodiesterase 5 Inhibitors Have a Potential Adjuvant Role in Combating Coronavirus Disease 2019 Infection? Sex Med Rev 2021;9:15–22.**

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Key Words: COVID-19; PDE5 Inhibitors; Sildenafil; Tadalafil; Vardenafil; SARS-CoV-2

INTRODUCTION

Since December 2019, a series of global health concern pneumonia cases were reported in Wuhan, Hubei Province, China with coronavirus disease 2019 (COVID-19) with substantial mortalities. The etiological agent of COVID-19 has been confirmed as a novel coronavirus, now known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1,2] Coronaviruses have large (~30-kb) single-stranded, positive-sense RNA genomes that are divided into a 5′ two-thirds and a 3′ third. The first two-thirds code for 2 large polyproteins that are proteolytically cleaved into non-structural proteins essential for the production of new viral genetic material. The rest codes for its structural proteins and carry the accessory genes that produce virions and alter the host response.[3,4] Asymptomatic or minimally symptomatic infection with COVID-19 can result in silent transmission to large numbers of people, resulting in an extension of the disease with an overall increase in its morbidity and mortality.

Currently, no treatment for SARS-CoV-2 is approved because of the lack of evidence, although several protocols have been

presented such as antiviral therapy, corticosteroid therapy, vitamins, antimalarial, and so on. However, there is still a lack of precise treatment(s) for the harsh COVID-19 manifestations.[5,6] Although the progress toward a curative agent and/or vaccine is certainly hopeful, the principal limiting factor in this public health emergency is always the time factor. Therefore a preexisting licensed molecule(s) might offer a reprieve to healthcare systems operating at the edge of capacity.

Currently, oral phosphodiesterase 5 (PDE5) inhibitors, acting on the nitric oxide/soluble guanylyl cyclase/cyclic guanylate monophosphate (NO/sGC/cGMP) pathway, represent the first-line therapy for erectile dysfunction with good responses.[7,8] Specifically, PDE5 hydrolyzes cGMP into 5'GMP by blocking cGMP hydrolysis, potentiates the effects of cGMP, resulting in decreased intracellular calcium, penile smooth muscle relaxation, and vasodilatation with increased penile blood flow.[9] Currently, 4 oral PDE5 inhibitors are approved by the U.S. Food and Drug Administration (sildenafil [Viagra], vardenafil [Levitra], tadalafil [Cialis], and avanafil [Stendra]) with good efficacy and tolerable adverse effects.[10,11]

Sildenafil citrate was released in 1998, has a maximal plasma concentration (Tmax) at 60 min on an empty stomach, and acts for 4—6 hours. Vardenafil hydrochloride was approved in 2003, has a Tmax of 60 min on an empty stomach, and acts for up to 7 hours. Tadalafil was approved in 2003, has a Tmax of 120 min with/without an empty stomach, and acts up to 36 hours. Later on, avanafil was approved in 2012 and has a Tmax of 30—45 min on an empty stomach.[12] These drugs are available in different doses; sildenafil citrate 25, 50, 100 mg; tadalafil 2.5, 5, 10, 20 mg; vardenafil hydrochloride 2.5, 5, 10, 20 mg; and avanafil 50, 100, 200 mg.

The high tolerability of oral PDE5 inhibitors, ease of administration, and its safety margin (except if combined with nitrates) have made these molecules an attractive tool to explore their physiological functions, beyond its immediate prescribed indications, with collateral benefits for a multitude of useful implications beyond erection.[13—16]

This article sheds a light on the likely benefits of the adjuvant use of oral PDE5 inhibitors in the protocols combating COVID-19 virus infection.

METHODS

A literature review has been performed in the PubMed/Medline database, Scopus, Cochrane Library, EMBASE, Academic Search Complete, Google Scholar, and CINAHL databases to search articles published from inception to August 2020 using the terms COVID-19; phosphodiesterase-5 inhibitors; sildenafil; tadalafil; vardenafil; avanafil; cytokine storm; respiratory distress.

COVID-19 Pathophysiology

Many researchers focused their attention on the specific protein that allows the COVID-19 virus to infect human cells, namely the angiotensin-converting enzyme 2 (ACE$_2$) receptor.

This receptor provides the entry point for the virus to hook into a wide range of non-immune cells, such as respiratory and intestinal epithelial cells, endothelial cells, renal tubules, cerebral neurons, and immune cells, such as alveolar monocytes/macrophages.[17] In this context, oral epithelial cells and other respiratory tract areas have an extensive expression of ACE$_2$, explaining their susceptibility to viral entry.[18—20] Then, the virus spreads into the lower respiratory tract (the lungs) where epithelial cells, in particular type II pneumocytes, express ACE$_2$.[20] Infection in the lungs, and especially damage of the alveoli, has been raised to be the primary cause of morbidity in COVID-19.[21]

Common reported symptoms of COVID-19 are fever, cough, myalgia, headache, diarrhea, dyspnea, pneumonia, and in some cases acute respiratory distress syndrome. Besides, most of the infected cases experience significant decreases in hemoglobin, neutrophil counts, and significant increases in serum ferritin, erythrocyte sedimentation rate, C-reactive protein, albumin, and lactate dehydrogenase. The oxygen-carrying capacity of the erythrocytes would, therefore, be compromised exacerbating the difficulties experienced by these patients in maintaining a sufficient partial pressure of oxygen in their alveoli.[22,23]

In this framework, in susceptible patients, the lung cells exhibit intense inflammation because of its inability to exchange carbon dioxide and oxygen frequently resulting in ground-glass—like images and respiratory distress.[24] In addition, apoptosis of the endothelial cells damages the pulmonary microvascular and alveolar epithelial cells causing vascular leakage and alveolar edema that ultimately leads to hypoxia and multiple organ failure.[25]

Certain patients experience severe inflammation and cytokine storm, with overwhelming immune activation that attacks the host. This cytokine storm includes several proinflammatory cytokines (Interleukin [IL]-1β, IL-2, IL-6, IL 7, IL-8, IL-10, granulocyte-macrophage colony-stimulating factor, and reactive oxygen species) and chemokines (C-C Motif Chemokine Ligand (CCL) 2, CCL-5, interferon gamma—induced protein 10, macrophage inflammatory protein (MCP1), MIP1A (monocyte chemoattractant protein), and CCL3 contribute to the occurrence of acute respiratory distress syndrome).[25—28] The accumulated mononuclear macrophages receive activating signals through the interferon alfa/beta receptors on their surface to produce more monocyte chemoattractants (CCL2, CCL7, and CCL12) with additional accumulation of mononuclear macrophages. In turn, these macrophages produce higher levels of the proinflammatory cytokines (tumor necrosis factor [TNF], -6, IL1-β, and inducible NOS), that induce T cell apoptosis, which hinders viral clearance.[29] Such rapid viral replication and vigorous proinflammatory cytokine/chemokine response induces apoptosis in the lung epithelial and endothelial cells through mechanisms involving Fas-Fas ligand or TNF-related apoptosis-inducing ligand death receptor 5.[30]

Rational of Oral PDE5 Inhibitor Role

Oral PDE5 inhibitors have been demonstrated to exhibit several favorable effects and implications that might justify their

ability for targeting multiple aspects in combating COVID-19 pathologic manifestations (Figure 1).

Counteracting the Angiotensin II—Mediated Downregulation of Angiotensin II Type I Receptor

Angiotensin II (Ang II) and NO signaling pathways have been reported to mutually regulate each other by multiple mechanisms. Ang II is recognized to regulate the expression of NO synthase and NO production, where NO downregulates the Ang II type I (AT1) receptor. Besides, the downstream effectors of both Ang II and NO signaling pathways also interact with each other with a feedback mechanism.[31] PDE5 inhibitors were suggested to inhibit the intrapulmonary vasoconstriction caused by AT1 receptor downregulation owing to SARS-CoV-2-ACE2 binding alveolar cells, bronchial epithelium, and vascular endothelium through the NO/sGC/cGMP pathway.[32,33]

The endogenous mammalian peptide AngII is hypothesized to prevent infection from SARS-CoV-2 in multiple ways: (i) it normally binds to ACE_2 during its degradation and hydrolysis into angiotensin-$(1-7)$[34] competing with the SARS-CoV-2 for the ACE_2 receptor; (ii) the binding of Ang II to the AT1 receptor has been revealed to cause internalization and downregulation of ACE_2 through an extracellular signal—regulated kinase 1/2 and p38 MAP kinase pathway;[35,36] and (iii) Ang II has been shown to cause AT1 receptor-dependent destruction of ACE_2 through ubiquitination and transport into lysosomes. The competitive inhibition, downregulation, internalization, and then degradation of ACE_2 decrease the intensity of viral infection by interfering with host cell entry of the virus.[37]

Lately, Qiao et al[38] reported their calculations on the inhibitors for the SARS-CoV-2 3CL protease and the spike protein for the potential treatment of COVID-19. These authors showed that the most potent promising inhibitors of the SARS-CoV-2 3CL protease include saquinavir, tadalafil, rivaroxaban, sildenafil, dasatinib, vardenafil, and montelukast owing to their high docking scores (<-8.5 kcal/mol).

Pulmonary Implications

1. PDE5 inhibitors appear to be particularly appropriate in treating pulmonary diseases because PDE5 is expressed in high levels in the lung tissue and is highly specific for hydrolysis of cGMP.[39]
2. Sildenafil citrate and tadalafil received approval by the U.S. Food Drug Administration and the European Medicines Agency in 2005 and 2009, respectively, for treating pulmonary arterial hypertension functional classes (FC) II and III indication of patients with WHO-functional class and a class IIa indication in patients with WHO-functional class IV (men, women, newborn).[40] Improved endothelial function, as well as prevention of impaired arterial relaxation, is the mechanism that explain the favorable effects of PDE5 inhibitors in these patients.[41,42] Sildenafil citrate use has been

verified to exhibit protective effects in pulmonary arterial hypertension cases by suppressing multiple cytokines involved in the neutrophil and mononuclear cell recruitment including cytokine-induced neutrophil chemoattractant-1, cytokine-induced neutrophil chemoattractant-$2\alpha/\beta$, tissue inhibitor of metalloproteinase-1, IL-1α, lipopolysaccharide-induced CXC chemokine, monokine induced by interferon gamma, macrophage inflammatory protein-1α, and macrophage inflammatory protein-3α. Besides, sildenafil use has been demonstrated to reduce extracellular signal—regulated kinase 1/2 and p38 MAPK activation with enhanced activation of the cytoprotective Akt pathway.[43,44]

3. In cases of acute lung injury, the positive effects of sildenafil use result from inhibiting the proliferation of regulatory T cells and the production of proinflammatory cytokines, autoantibodies, and modulating platelet activation, angiogenesis, pulmonary vasoreactivity.[45]
4. Sildenafil use has been validated to reduce the leak of neutrophils into the lung, the release of proinflammatory mediators TNF-α, IL-8 and IL-6, level of nitrite/nitrate, markers of oxidative stress (3-nitrotyrosine and malondialdehyde), lung edema, protein content in the bronchoalveolar lavage fluid, apoptosis of epithelial cells with ultimate improve in the respiratory parameters.[46]
5. In chronic obstructive pulmonary disease, sildenafil use has been reported to improve pulmonary hemodynamics by inhibiting hypoxic vasoconstriction and facilitating the weaning of these patients from the ventilators owing to improved respiratory parameters.[47]
6. In hypoxic conditions, sildenafil use was shown to increase the exercise capacity in acute normobaric hypoxia by improving arterial oxygenation.[48] In their work, Gibbs[49] associated sildenafil use with ameliorated hypoxic pulmonary vasoconstriction with increased exercise capacity and stroke volume. In addition, Watanabe et al[50] pointed out that sildenafil use decreases pulmonary vascular resistance and improves dyspnea in patients with interstitial pneumonia. In their work, Gammella et al[51] revealed that sildenafil and erythropoietin treatments protect endothelial cells in hypoxic states, whereas Czövek et al[52] reported that sildenafil use prevents the hyperoxia-induced development of bronchial hyperreactivity by preserving the normal end-expiratory lung volume and inhibiting airway inflammation.
6. Although hydrogen sulfide (H_2S) was reported as an endogenous inhibitor of PDE activity,[53] sildenafil use has been demonstrated to promote remarkably intracellular H_2S production that controls proliferation in the pulmonary arterial smooth muscle cells by inducing vasodilation and reducing oxidative stress and inflammation.[54,55] Besides, the protein levels of the enzymes cystathionine γ-lyase and cystathionine-β-synthase and the intracellular concentration of calcium were also increased.
7. Prophylactic treatment with an optimal dose of sildenafil citrate was demonstrated to significantly increase lung cGMP
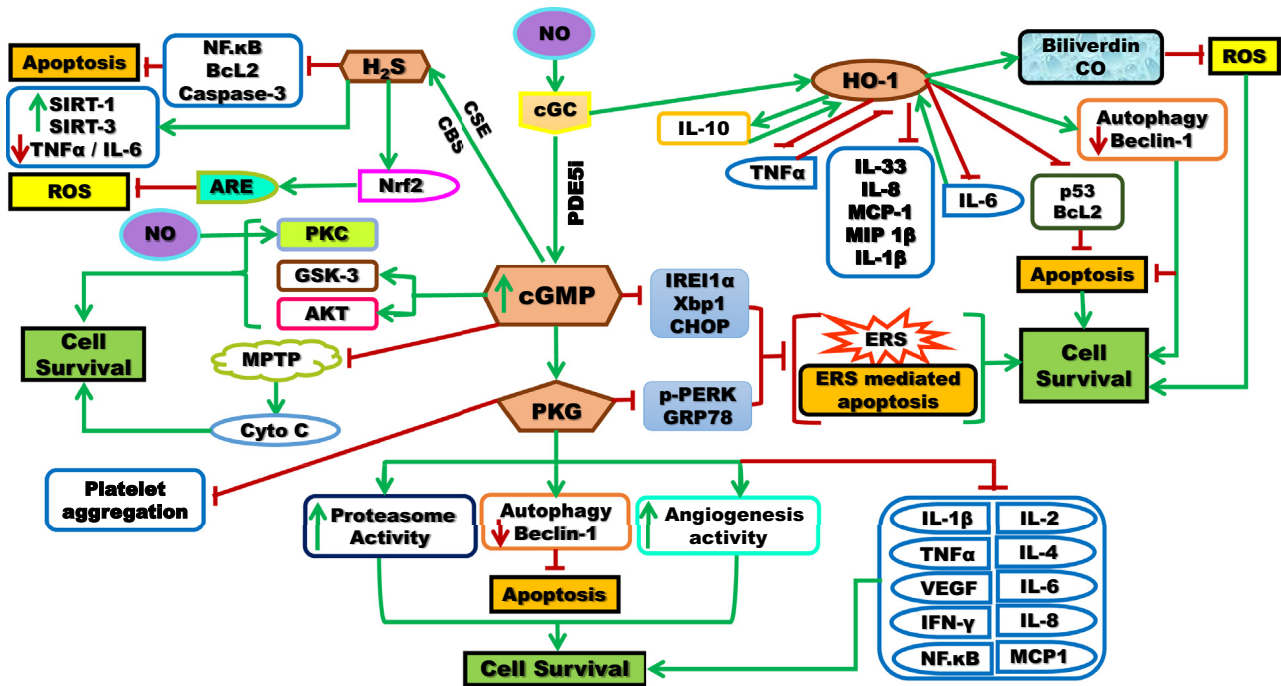
Figure 1. Schematic representation of the signaling pathways involved in the mechanism of actions of PDE5i that act by inhibiting PDE5, the cGMP degrading enzyme, leading to increased intracellular cGMP that acts by activating many kinases, customarily PKG, but it also triggers the activation of PKC/Akt and GSK-3, PKC can be activated by NO, in a cGMP-independent manner. cGMP inhibits MPTP formation and Cyto C release. cGMP activation can, alone/through PKG, suppress the function of molecules associated with ERS and thus prevents ERS and ERS-mediated apoptosis. Besides, PKG stimulates proteasome activity, autophagy and increases angiogenesis resulting in the inhibition of cellular apoptosis and promotion of cell survival. The PKG pathway inhibits many cytokines, and inflammatory mediators leading to cell survival. PDE5i could induce HO-1 expression through Nrf2. HO-1 enzyme has the affinity to inhibit cytokine and chemokine responses such as IL-1β, IL-8, IL-33, MCP-1, MIP-1β, and apoptotic markers. The pro-inflammatory chemokine IL-6 upregulates HO-1, which in turn inhibits IL-6 to limit the inflammatory responses. There is a positive feedback loop between HO-1 and IL-10 (anti-inflammatory) and a negative feedback loop between HO-1 and TNF-α (pro-inflammatory). HO-1 enzyme also produces biliverdin, CO that antagonizes ROS and stimulates autophagy that antagonizes apoptosis with the ultimate cell survival. In addition, PDE5i induces H$_2$S production, stimulated by CSE and CBS enzymes, with an affinity to inhibit inflammatory mediators (TNF-α, IL-6), apoptotic markers (NF.kB, Bcl2, caspase-3) and antagonizes ROS with the ultimate cell survival. Akt = protein kinase B; ARE = antioxidant responsive element; Bcl2 = B-cell lymphoma 2; cGMP = cyclic guanosine monophosphate; CHOP = C/EBP homologous protein; Co = carbon monoxide; CSE = cystathionine gamma-lyase; ERS = endoplasmic reticulum stress; GRP78 = glucose-regulated protein 78; GSK-3 = glycogen synthase kinase-3; H$_2$S = hydrogen sulfide; HO-1 = hemeoxygenase-1; IFN-γ = interferon gamma; IL = interleukin; IREI 1α = inositol-requiring enzyme 1α; MCP-1 = monocyte chemoattractant protein-1; MIP 1β = macrophage inflammatory protein 1-β; MPTP = mitochondrial permeability transition pore; NF-κB = nuclear factor-kappa B; NO = nitric oxide; Nrf2 = nuclear factor (erythrocyte-derived 2)-like 2; PDE5i = phosphodiesterase-5 inhibitors; PKC = protein kinase C; PKG = protein kinase G; p-PERK = phosphoprotein kinase-like ER kinase; ROS = reactive oxygen species; Sirt = sirtuin; TNFα = tumor necrosis factor-alpha; VEGF = vascular endothelial growth factor; Xbp1 = X-box binding protein 1. Figure 1 is available in color online at www.smr.jsexmed.org.

levels, prolongs median survival, and reduces fibrin deposition, total protein content in bronchoalveolar lavage fluid, inflammation, and septum thickness.[56]

Anti-inflammatory and Cellular Implications

1. PDE5 inhibitors target the enzyme PDE5 responsible for the selective degradation of cGMP leading to increased intracellular cGMP. cGMP possesses intense anti-inflammatory effects by reducing the expression of the proinflammatory cytokines IL-1β and TNF-α and increasing the expression of the anti-inflammatory cytokine IL-10.[57] In this context, Dalamaga et al[58] raised the role of PDE4 inhibition and cyclic

adenosine monophosphate in attenuating the cytokine storm in COVID-19, through the upstream inhibition of proinflammatory molecules, particularly TNF-α, and in regulating the proinflammatory/anti-inflammatory balance. These authors believed that selective PDE4 inhibitors may represent a promising option for the early phase of COVID-19 pneumonia before the cytokine storm and severe multiorgan dysfunction take place. Besides, Seirafianpour et al[59] raised many confirmatory data on proper efficacy of pentoxifylline, a methyl-xanthine derivative that inhibits PDE4, on controlling COVID-19 and its consequences with antiviral, anti-inflammatory, antioxidative, immune-modulatory, bronchodilator, and respiratory supportive effects.

2. PDE5 inhibitors have been demonstrated to be a highly protective agent in preventing lung and kidney damage owing to induced sepsis by the maintenance of the oxidant-antioxidant status and decreased TNF-α.[60] It has been reported that increased bioavailability of cGMP is beneficial in ameliorating the inflammation associated with intense sepsis.[61]

3. The PDE5 inhibitor sildenafil has been observed to produce a significant sustained reduction of fibrinogen, high-sensitivity C-reactive protein, high-sensitivity IL-6, TNF-α independent of their baseline values.[62]

4. Pieces of evidence pointed to the participation of cGMP-dependent protein kinase in the complex cellular signaling pathways related to cell survival/apoptosis.[63] In their work, Choi et al[64] advocated that the PDE5 inhibitor sildenafil citrate has antiapoptotic effects by induction of iNOS, eNOS, and decreased BCL2-associated X protein/Bcl2 ratio. In addition, Puzzo et al[65] showed that sildenafil citrate use can inhibit the expression of apoptotic molecules such as; caspase-3 (proapoptotic factor), BCL2-associated X protein (an apoptotic factor), and $p38$ mitogen-activated protein kinases. Collectively, Duarte-Silva and Peixoto[66] pointed out that sildenafil citrate use inhibits apoptosis by 2 interconnected mechanisms directly by modulating caspase expression (through extrinsic and intrinsic pathways) and indirectly by modulating the expression of molecules elaborated in cell death and/or cell survival.

5. PDE5 inhibition by sildenafil was reported to suppress both the endoplasmic reticulum stress (ERS) and ERS-induced apoptosis by decreasing X-Box binding protein 1 expression, phosphoprotein kinase-like ER kinase, and 78-kDa glucose-regulated protein in a protein kinase—dependent manner.[67]

6. PDE5 inhibitors had been reported to induce hemeoxygenase-1 (HO-1) enzyme expression through the sGC-cGMP pathway.[68,69] HO-1 enzyme catalyzes the rate-limiting step in the oxidative degradation of heme to biliverdin and CO, which share many properties with NO, including activation of sGC signal transduction, gene regulation.[70,71] HO-1 enzyme or its reaction products as CO are effective inducible antioxidants and antiapoptotic molecules that protect against inflammation, cleavage of adhesion proteins E-cadherin, and apoptosis by constraining both p53 and Bcl2.[72] Besides, HO-1 has been reported to have antiviral activity by inhibiting viral growth.[73,74]

7. PDE5 inhibitors behave as antioxidants by inhibiting the free radical formation supporting antioxidant redox systems.[75] It was demonstrated that the protective effect of sildenafil intake on the epithelial cells is a consequence of xanthine oxidase inhibition with decreased free oxygen radical production.[76]

8. NO inhibits platelet aggregation primarily via a cGMP-dependent process.[77,78] In their study, Gudmundsdóttir et al[79] determined that sildenafil citrate use potentiates NO-mediated inhibition of platelet aggregation through blockade of cGMP metabolism and that PDE5 inhibitors may have imperative antiplatelet actions.

DISCUSSION

Since the outbreak of the novel COVID-19, the medical research community is in a race to find a cure for that pandemic with unprecedented worldwide respectful research efforts to control the infection and save the lives of severely infected patients. Therefore, in these urgent circumstances, exploring the beneficial repurposing effects of some drugs even being off label (for uses other than what it was approved for) might be of potential help worldwide and a realistic solution.[80] Therefore, the selection of a molecule(s) backed by years of safety margin, widespread use, and affordability may offer the opportunity to prevent/treat infection and its disabling complications that ensue. Several options, such as tocilizumab,[81] hydroxychloroquine and ivermectin,[82] PDE-4 inhibition,[58,59] combined interferon beta-1b, lopinavir-ritonavir, and ribavirin,[83] were raised to manage such pandemic. In addition, camostat mesylate, remdesivir, favipiravir, baricitinib, convalescent plasma, and humanized monoclonal antibodies were suggested as therapeutics for the potential treatment of SARS-CoV-2.[84]

In this context, oral selective PDE5 inhibitors drugs possess extensive clinical support backed by a solid mechanistic scientific rationale based on their ability to target multiple aspects of the underlying disease processes that make COVID-19 so deadly. Therefore, PDE5 inhibitors are worthy repurposing candidates to be thought of on the likely benefits of their adjuvant use in the protocols aimed to combat COVID-19 infection based on the aforementioned rationales. Fortunately, the available PDE5 inhibitors have many existing flexible doses, forms (oral tablets, oral dispersible tablets, and so on), and regimens (daily or on demand) that could be assessed by the health authorities.

CONCLUSION

Optimal real-world repurposing requires a track record of safety, affordability, and access for drug candidates. Oral PDE5 inhibitors retain many beneficial acknowledged useful off-labeled implications with its anti-inflammatory, antioxidant, immune response regulation, as well as antiapoptotic properties. These aforementioned properties may support repurposing oral PDE5 inhibitors' potential adjuvant use in the protocols combating COVID-19 manifestation especially along with the respiratory affection. Besides, it should be highlighted that the main stakeholder in the management of any illness is the patient and not any particular special interest group, political party, or pharmaceutical manufacturer.

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Taymour Mostafa: Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing.

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