Review

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PDE5 inhibitors: breaking new grounds in the treatment of COVID-19

https://doi.org/10.1515/dmdi-2023-0011
Received March 29, 2023; accepted July 30, 2023;
published online August 24, 2023

Abstract

Introduction: Despite the ever-increasing occurrences of the coronavirus disease (COVID-19) cases around the world, very few medications have been validated in the clinical trials to combat COVID-19. Although several vaccines have been developed in the past quarter, the time elapsed between deployment and administration remains a major impediment.

Content: Repurposing of pre-approved drugs, such as phosphodiesterase 5 (PDE5) inhibitors, could be a game-changer while lessening the burden on the current healthcare system. Repurposing and developing phosphodiesterase 5 (PDE5) inhibitors could extrapolate their utility to combat the SARS-CoV-2 infection, and potentially aid in the management of the symptoms associated with its newer variants such as BF.7, BQ.1, BQ.1.1, XBB.1.5, and XBB.1.16.

Summary: Administration of PDE5 inhibitors via the oral and intravenous route demonstrates other potential off-label benefits, including anti-apoptotic, anti-inflammatory, antioxidant, and immunomodulatory effects, by intercepting several pathways. These effects can not only be of clinical importance in mild-to-moderate, but also moderate-to-severe SARS-CoV-2 infections. This article explores the various mechanisms by which PDE5 inhibitors alleviates the symptoms associated with COVID-19 as well as well as highlights recent studies and findings.

Outlook: These benefits of PDE5 inhibitors make it a potential drug in the physicians' armamentarium in alleviating symptoms associated with SARS-CoV-2 infection. However, adequate clinical studies must be instituted to eliminate any untoward adverse events.

Keywords: COVID-19; delta; omicron; phosphodiesterase 5 inhibitors; SARS-CoV-2; sildenafil; tadalafil

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Introduction

A new coronavirus strain was reported in December 2019 by the Chinese Centre for Disease Control and Prevention (CDC) that demonstrated a high transmission potential in humans [1, 2]. This etiological agent was determined to be the causal agent of the COVID-19 pandemic and was later flagged as severe acute respiratory Syndrome Coronavirus-2 (SARS-CoV-2). This strain is a subset of the Coronaviridae family and bears similarities to the zoonotic SARS-CoV [1, 3, 4]. As of January 2022, global COVID-19 statistics have estimated 310 million cases with approximately 5.5 million deaths. Thus, the high mortality rate poses a threat to the mental and physical health of individuals, substantially affecting the quality of life (QoL) [1, 2]. The detailed morphology, transmission, and pathogenesis of SARS-CoV-2 infection have been elucidated in numerous reviews and are beyond the scope of this review. Several modalities have been proposed for the treatment of SARS-CoV-2 infections. These interventions

include antimalarial [5–8], antiviral [9–11], dietary supplements [12–15], corticosteroids [16–21], and convalescent plasma [22–27], to name a few. However, due to the lack of supporting evidence, no treatment intervention is curative for the clinical manifestations linked to SARS-CoV-2 infection [28–30]. Although progress toward the development of a novel drug and/or vaccine is promising, the time factor is of paramount importance. Thus, the repurposing of the pre-existing approved molecule(s) could be a respite in the already overburdened healthcare and pharmaceutical system [30]. Additionally, several novel techniques have been used for the early detection of SARS-CoV-2 at lower viral loads, including real-time quantitative reverse transcription-polymerase chain reaction (RT-PCR), and carbon nanotube-based detection for point-of-care detection [31]. However, at present there is no gold standard for the detection and/or treatment of SARS-CoV-2 infections. This article aims to paint a clinical landscape of various phosphodiesterase-5 (PDE5) inhibitors, as well as to explore their potential in the management of symptoms associated with SARS-CoV-2 infections. Additionally, the article would summarize the mechanistic pathways that have been intercepted following the administration of these drugs.

Transmission and pathophysiology of SARS-CoV-2 infection

SARS-CoV-2 is transmitted primarily through respiratory droplets, often through contact with the patient. However, evidence also supports its potential transmission via contaminated and unsanitized surfaces. Although SARS-CoV-2 can spread through aerosols, its mechanism needs to be elucidated further [32]. Recent studies have reported that approximately 48–62 % of transmission occurs through pre-symptomatic carriers [33]. Additionally, hospital-based studies have reported that the most prevalent signs and symptoms of SARS-CoV-2 infection are ageusia, anosmia, diarrhea, dyspnoea, fatigue, fever, headache, myalgia, nausea, non-productive cough, rhinorrhoea, and vomiting [32, 34]. Upon laboratory analysis, the significant anomalies noted in the hospitalized patients included elevated levels of inflammatory markers such as C-reactive protein, erythrocyte sedimentation rate (ESR), ferritin, interleukin-1, interleukin-6, and tumor necrosis factor-α. Additionally, abnormal coagulation parameters include elevated D-dimer levels, extended prothrombin time, low fibrinogen levels, lymphopenia, and thrombocytopenia [35]. A growing body of evidence from radiographic analysis of SARS-CoV-2 infected individuals has demonstrated bilateral infiltrates predominantly in the lower lobe. Furthermore, chest computed tomography (CT) often highlights peripheral, bilateral, and lower lobe ground-glass opacities (GGO) and/or consolidation [32]. Furthermore, acute liver injury, characterized by elevated levels of alanine transaminase, aspartate transaminase, and bilirubin; cardiac injury; increased troponin levels; acute heart failure; myocarditis; and dysrhythmias were the most frequent adverse effects of SARS-CoV-2. In addition, prothrombic coagulopathy further culminating in venous and arterial thromboembolism has been observed in admitted patients [32, 34, 36–40]. Furthermore, cytokine storm and macrophage activation syndrome are rare clinical manifestations of SARS-CoV-2 in critically affected individuals [32]. These pathways could potentially reflect the etiopathology of SARS-CoV-2 infection, while elucidating avenues for the development and/or repurposing of novel drugs.

Introduction to PDE-5 inhibitors

Phosphodiesterase-5 is an intrinsic part of the Nitric Oxide/soluble Guanylyl Cyclase/cyclic Guanylate Monophosphate pathway. The phosphodiesterase-5 enzyme has been associated with the hydrolysis of cGMP into 5′GMP [41, 42]. Phosphodiesterase-5 (PDE-5) inhibitors are a class of drugs that inhibit phosphodiesterase-5, which is present in the smooth muscle cells of the vessels. These medications intercept the PDE-5 enzyme and subsequently prevent cGMP degradation. Interception of the NO/sGC/cGMP pathway and prevention of cGMP hydrolysis enhance the effect of cGMP in the body. These effects include lower intracellular calcium levels, vasodilation, increased penile blood flow, and [30, 43]. Currently, the United States Food and Drug Administration has approved four oral PDE-5 inhibitors: avanafil (Stendra), sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra), owing to their good therapeutic efficacy and manageable side effects [44, 45]. Other PDE-5 drugs that are commercially available without FDA approval include Lodenafil, Mirodenafil, and Udenafil [46]. From the biopharmaceutical perspective, sildenafil citrate was first introduced in 1998. It demonstrated its maximum plasma concentration time (Tmax) at 60 min on an empty stomach, followed by an action lasting 4–6 h. Subsequently, vardenafil and tadalafil hydrochloride were approved by the US FDA in 2003. Vardenafil hydrochloride exhibited a Tmax of 60 min on an empty stomach, followed by an effect lasting up to 7 h. However, Tadalafil experimentally showed a Tmax of 120 min regardless of an empty stomach, and a sustained effect of approximately 36 h post-administration. Furthermore, avanafil was approved in 2012, with a Tmax of approximately 30–45 min

after administration on an empty stomach [30, 47]. Currently, the well-demonstrated indications of PDE-5 inhibitors include treatment of Erectile Dysfunction (ED) [48, 49], premature ejaculation associated with ED [50, 51], and penile rehabilitation after radical prostatectomy [52], idiopathic pulmonary hypertension [53, 54], angina [55, 56], high altitude illness [57, 58], and lower urinary tract infections [59, 60]. However, its therapeutic utility has also been extrapolated to investigate its utility in stroke [61–63], heart failure [64, 65], peripheral arterial disease (PAD) [53, 66, 67], and diabetic nephropathy [68–70].

Repurposing PDE-5 inhibitors in COVID-19

Owing to their high tolerance, safety profile, and ease of drug administration, oral PDE-5 drugs have become an appealing area for identifying new potential avenues for treatment other than their currently known indications [30, 71–74]. However, the high rates of attrition, associated costs, and regulatory rigmarole impede the discovery and development of novel therapeutic molecules that can be developed by modifying the chemical structures of the parent molecule. Thus, the reuse of old established and pre-approved drugs as a treatment modality for diseases has become an appealing proposition, primarily owing to its safety profile. This process of drug repositioning or drug repurposing could result in both the low cost of drug and formulation development, as well as a shorter timeframe for development [75], which is of paramount importance amid the COVID-19 pandemic. Various data-driven, in silico, and experimental approaches have been proposed for repurposing pre-approved and/or commercially marketed drugs. Repurposing various drugs in the phosphodiesterase-5 inhibitor superclass could be a game-changer for alleviating symptoms and managing SARS-CoV-2 infections [76]. Multiple mechanisms have been studied to modulate the Angiotensin II (Ang II) and NO signaling pathways. Angiotensin II regulates the expression and synthesis of NO through its effect on NO synthase [30]. Subsequently, NO follows a negative feedback mechanism, thereby downregulating Ang II type I (AT1) receptor. Furthermore, there is an intertwined mechanism of Ang II and NO signaling [30, 77]. Thus, through the NO/sGC/cGMP pathway, PDE5 inhibitors are indicated for the alleviation of intrapulmonary vasoconstriction, which is the result of the downregulation of the AT1 receptor, caused by the binding of SARS-CoV-2-ACE2 to the bronchial epithelium, alveoli, and vascular endothelium [78, 79]. The clinical approval of nasal nitric oxide (NO) by the US FDA as an intervention in treating interstitial pulmonary fibrosis linked to COVID-19, along with the profound expression of PDE5 in lung tissue, corroborated the speculation of the role of PDE5 in COVID-19 [80, 81]. Generally, it has been found that SARS-CoV-2 infected patients develop life-threatening illnesses that necessitate inpatient management, and in more severe cases, admission to critical care facilities. Frequent adverse reactions of SARS-CoV-2 infection include thromboembolism, which is mainly caused by excessive platelet aggregation after activation of the NO/cGMP/PDE5 pathway [82, 83]. A study by Mario et al. exhibited an exceedingly high amount of nitric oxide, after COVID-19 diagnosis, which ultimately induced the NO/cGMP pathway [84]. Thus, acute lung failure in most cases may not be driven by the onset of acute respiratory distress syndrome but instead by microvascular thrombotic events in the pulmonary vasculature, which appear to be in a vicious cycle. While the NO/cGMP pathway could ensure NO-associated tissue protection, its dysregulation via both the iNOS and eNOS pathways could result in a well-documented pro-inflammatory cascade, often as a consequence of oxidative stress [65]. Physiological activity of eNOS is driven in part by AMPK, a three-subunit serine-threonine protein kinase [85]. Although the inhibitory effect of AMPK on iNOS potentially reduces inflammation, the former plays a role in the generation of a lengthy anti-inflammatory axis, AMPK/eNOS/NO/cGMP [80]. A recent study underscores the role of PDE-5 inhibitors, especially sildenafil, in downregulating inactive AMPK and iNOS in individuals diagnosed with cerebellar demyelination [86]. Furthermore, previous studies have shown that most coronaviruses produce polyproteins, and SARS-CoV-2 is no exception. These polyproteins are then processed by viral proteases to produce functional proteins, mainly $3CL^{pro}$, which further aids viral replication [80]. This hypothesis was corroborated by a study in which patients diagnosed with SARS were treated with protease inhibitors in 2004. This study demonstrated that the use of protease inhibitors resulted in a much lower mortality rate (2.4 % compared to 28.8 %) [87]. This was further strengthened in a study conducted by Jin et al., who underscored the crystal structure of SARS-CoV-2 $3CL^{pro}$ [88]. Another recent study reported the calculation of inhibitors for SARS-CoV-2 $3CL^{pro}$ and spike protein as prospective therapies against COVID-19 infection. These calculations have been corroborated by the high docking scores (less than −8.5 kcal/mol) of various PDE5 inhibitors such as sildenafil, tadalafil, and vardenafil, which are potent inhibitors of the SARS-CoV-2 $3CL^{pro}$ protease [89, 90]. Several studies have underscored the various aspects of PDE5 inhibitors as potential treatment modalities in the fight against COVID-19. These studies were conducted as follows:

Pulmonary and systemic indications of PDE5 inhibitors

(1) PDE5 inhibitors bring about the selective degradation of cGMP, which has anti-inflammatory activity [91]. It does so by increasing the expression of the anti-inflammatory cytokine, IL-10. This has led researchers to believe that PDE4 inhibitors can be used to regulate the pro-inflammatory and anti-inflammatory balance in the early stages of COVID-19 pneumonia patients [92]. PDE4 also has antiviral and bronchodilator effects, making it an effective choice for the treatment of inflammatory symptoms of COVID-19 [93].

(2) Inhibition of PDE5 was also found to inhibit COVID-19 in the expression of angiotensin-converting enzyme-2 (ACE2). A decrease in ACE2 surface expression is observed in patients, which ultimately leads to vasoconstriction [94]. Therefore, oral drug therapy that improves NO activity in the intrapulmonary vasculature is a preferable treatment option for COVID-19 [95].

(3) PDE5 inhibition aids in increasing cGMP, which prolongs its vasodilating effects in the pulmonary vasculature and significantly decreases the mean pulmonary vascular resistance [96, 97]. Since evidence has been found that COVID-19 infection may lead to pulmonary hypertension or right ventricular dysfunction, PDE5 inhibitors would be of most benefit to these patients, as modulation of NO availability has the potential to counteract the adverse effects of pulmonary microangiopathy [98].

(4) In the lungs, PDE5 is predominantly expressed in vascular smooth muscles and airways, where it acts as a pulmonary vasodilator and inhibitor of vascular hypertrophy [99–101]. In addition to airway relaxation, it alleviates oxidative stress [102–104]. Several studies have concluded that PDE5 inhibitors can modulate alterations associated with ARDS in procoagulant and thrombotic events in the pulmonary arteries [105]. Reduction in acute hypoxic pulmonary vasoconstriction and hypertrophy of the right ventricle are observed as therapeutic benefits of sildenafil [106].

(5) Sildenafil citrate is a PDE5 inhibitor that has recently been used in the treatment of pulmonary arterial hypertension and idiopathic pulmonary fibrosis, primarily to prevent or block the progression of fibrosis [107]. Tadalafil is a selective PDE5 inhibitor, with an IC50 of 5 nM [108]. Researchers have suggested that it may be useful in the fight against fibrosis and improve tissue fibrosis, and can be prescribed as a once-daily drug treatment for discharged patients with COVID-19 [109].

(6) Sildenafil citrate is a well-known FDA-approved vasodilator [sildenafil citrate (Viagra)] and was shown to be useful in treating pulmonary arterial hypertension in 2005 at an oral dose of 5 or 20 mg three times a day, or 2.5 mg or 10 mg as an intravenous bolus [Sildenafil citrate (Revatio)]. It inhibits the breakdown of cGMP by binding to phosphodiesterase-binding sites and therefore influences platelet activation, T cell proliferation, and proinflammatory cytokine production. This enables it to exhibit anti-inflammatory, antioxidant, vasodilatory, and other abilities [110].

(7) Sildenafil administration results in a significant reduction in fibrinogen, TNF-α, hsCRP, and hsIL-6, independent of their baseline values, and has been shown to have a favorable effect on the inflammatory activation of erectile dysfunction [111].

(8) Inhibition of PDE5 with sildenafil significantly reduces cardiac dysfunction, ERS-induced apoptosis, and endoplasmic reticulum stress (ERS) in cardiomyocytes after ischemia or reperfusion injury by decreasing the expression of phosphoprotein kinases such as ER kinase [112].

(9) Gudmundsdóttir et al. stated in their study that the use of sildenafil citrate aids NO-mediated inhibition of platelet aggregation by the cGMP pathway and that PDE5 inhibitors potentially possess antiplatelet activity [113].

(10) Sildenafil was found to have an inhibitory effect on xanthine oxidase (XO), resulting in a decrease in the production of free oxygen radicals, which play an important role in vascular injuries [114]. The decrease in free radical formation was found to be the result of PDE5 inhibitors acting as antioxidants [115].

(11) Several studies have suggested a role for cGMP pathogenesis in cell apoptosis and survival [116]. Puzzo et al. demonstrated the use of sildenafil citrate to inhibit the expression of apoptotic molecules [117]. Choi et al. demonstrated the anti-apoptotic effects of sildenafil by inducing iNOS and eNOS [118]. Therefore, the modulation of the expression of these factors leads to cell death or survival.

(12) A recent study by Sarkar et al. suggests that sildenafil, which acts by inhibiting cyclic guanosine monophosphate (cGMP) breakdown by binding to the phosphodiesterase binding site, can aid vasodilation, an effect of nitric oxide that induces smooth muscle relaxation [119, 120]. A pilot study was to evaluate the effectiveness and acceptability of sildenafil tablets in their citric form at a dose of 0.1 g/day for 14 days to combat COVID-19 [121].

(13) Sepsis-induced kidney and lung damage can be prevented or treated with PDE5 inhibitors because of their

ability to maintain an oxidant-antioxidant balance [122]. Sildenafil was also found to decrease markers of systemic inflammation and increase TNFR1 levels in septic mice [123].

(14) Experimental studies in animal models have also been reported to be successful in cases of direct and indirect lung injuries. Sildenafil has numerous therapeutic implications, such as suppression of pro-inflammatory mediator release, decreased cell leakage in the lungs [124], and improved cardiac output without compromising oxygenation status [125], etc. Sildenafil has also been proven to be an effective treatment for ALI caused due to scald burns in murine models, where it significantly reduced lung inflammation and oxidative stress and increased antioxidant capacity [126]. Using dual PDE inhibitors has been shown to be beneficial. The dual use of the PDE4/PDE5 inhibitor LASSBio596 maintained lung mechanics, TNF-α release, and increased collagen fiber content induced by intratracheal LPS [127].

(15) The researchers opined that the thromboembolic complications observed in COVID-19 patients can be traced back to dysregulation of iNOS. The consequent inflammatory cascade can be eliminated by activation of eNOS aided by the prescription of PDE5 inhibitors, which enhance the AMPK/eNOS/NO/cGMP pathway, which helps thwart thromboembolism in patients [65, 128].

(16) Recent studies have suggested that PDE5 inhibitors, especially vardenafil, help decrease the activation of transforming growth factor- β1 (TGF- β1) and aggregation of the extracellular matrix (ECM), thus inhibiting the progression into pulmonary fibrosis [129]. An *in vivo* study conducted by Bourne et al. on a bleomycin mouse model concluded that vardenafil substantially decreased ECM production. However, a significant synergistic therapeutic outcome was observed upon co-administration of nintedanib [130].

(17) COVID-19 has been observed to activate the host inflammatory response, and this progressive endothelial thrombotic inflammatory syndrome ultimately leads to fatal complications such as pulmonary failure. PDE5 Inhibitors, such as tadalafil, are used as vasodilators and are administered once daily to improve tissue angiogenesis and prevent vascular endothelial sclerosis in patients [109]. Complications vary depending on the severity of infection, and given the pharmacology of PDE5I, these drugs are used as early complementary drugs in the treatment of COVID-19 [131]. The use of PDE5 Inhibitors has also been proposed to relieve acute respiratory distress syndrome and to reduce pulmonary hypertension as a synergistic treatment for COVID-19 [20].

(18) Another study by Mokry et al. evaluated the effect of administering the PDE5 inhibitor tadalafil (1 mg/kg body weight) on experimentally induced allergic inflammation in guinea pig models. The study reported that tadalafil administration reduced specific airway resistance after histamine nebulization. The latter study also demonstrated a marked decrease in the *in vitro* airway reactivity to cumulative doses of acetylcholine and histamine in both tracheal and lung tissue strips [103]. This could prevent allergy and inflammation resulting from eosinophil infiltration, potentially leading to ARDS.

(19) The selectivity of tadalafil to PDE5 or PDE6 [108] substantially improves vascularization in lung tissues. Furthermore, owing to the long-acting nature of the drug, the administration of tadalafil once a day could be a potential method for combating lung fibrosis [109].

(20) Clinical trials are being conducted to test the efficacy of oral sildenafil in treating perfusion abnormalities in COVID-19 patients, as SARS-CoV-2 has been observed to cause hypoperfusion in the lung parenchyma, resulting in ventilation-perfusion mismatch. No statistical differences were found in oxygenation parameters in patients after being subjected to sildenafil treatment; however, patients were observed to have a reduced hospitalization duration and initiation of invasive mechanical ventilation (IMV). Therefore, sildenafil could potentially play major therapeutic roles in patients with specific perfusion patterns on sCTA [132].

(21) Recent research suggests that selective and non-selective PDE inhibitors could prove to be a potential intervention in the treatment of acute respiratory distress syndrome (ARDS) [133], which primarily causes COVID-19 fatalities as illustrated in Figure 1. These PDE5 inhibitors facilitate contraction and remodeling of smooth muscles of the airways and vasculature. They also participate in platelet function, neuronal conduction, and inflammatory and oxidative stress [133].

(22) Various PDE5 Inhibitors, such as sildenafil, tadalafil, and the nonselective inhibitor dipyridamole, can potentially be used as treatment options for chronic obstructive pulmonary disease and asthma [134]. The anti-inflammatory effect of PDE5 is mediated by inhibition of neutrophils and macrophages [135].

(23) Dipyridamole, a non-specific PDE5 inhibitor, can assist in managing SARS-CoV-2 infection due to its antiplatelet action, which aids in the mitigation of ALI and expresses antiviral and anti-inflammatory abilities [136]. The relationship between the effect of PDE5 Inhibitors on platelets and that of PDE4I on lymphocytes helps prevent COVID-19-induced coagulopathy. DIP attenuates hypercoagulopathy-induced complications [137].

The administration of antiplatelet agents such as DIP or aspirin in the early onset of COVID-19 may help reduce the severity of ARDS [138], and sildenafil possesses significant antiplatelet activity [82].

(24) The enzyme hemeoxygenase-1 (HO-1) and its reaction products are anti-apoptotic molecules that protect against inflammation and apoptosis and possess antiviral properties that aid in inhibiting viral growth in cells. HO-1 enzyme expression is induced by PDE5 inhibitors via the sGC-cGMP pathway [30].

(25) According to a study conducted by Horn et al., patients suffering from PHT are at an increased risk of COVID complications such as cardiovascular and acute respiratory distress syndrome [ARDS] [139]. Another recent study suggested that renin-angiotensin system (RAS) functionality is reduced by PDE5 Inhibitors by restricting renal renin secretion [140]. It is involved in acute kidney injury (AKI) and acute liver injury (ALI) in COVID-induced ARDS due to high levels of angiotensin-2. NO suppresses ALI by reducing fibrin deposition and lung inflammation [141]. Therefore, PDE5 Inhibitors can be used as a preventive option for common AngII-induced COVID complications [142, 143].

(26) According to multiple studies conducted in animal models, PDE5 Inhibitors can improve immunity in mice. These results further suggested that sildenafil has sex-specific immunoregulatory properties [144]. In a multiple sclerosis model of experimental autoimmune encephalomyelitis, it was found that the administration of sildenafil reduced the infiltration of cells in the white matter of the spinal cord of mice [145]. Another study concluded that sildenafil prolonged the survival of tumor-bearing mice by improving antitumor immunity [146, 147].

(27) Recently, patients with COVID-19 have been reported to exhibit perfusion anomalies. A study initiated by Andre's Bello National University sought to test the effect of sildenafil on two relevant prognostic parameters: alveolo-arterial gradient and arterial oxygenation [Clinical Trial identifier: NCT04489446]. Another ongoing clinical trial funded by Tongji Hospital, China, intends to test the entry rate into the critical stage and the remission of the disease and to measure the time of entry into the critical stage by evaluating the therapeutic effects of sildenafil at a dose of 100 mg/day for 14 days [Clinical Trials Identifier: NCT04304313].

Clinical investigation on PDE5 inhibitors

Evidence and proposals for the repurposing of PDE5 inhibitors have driven researchers and institutions worldwide to invest in clinical trials to substantiate the utility of PDE5 inhibitors in combating the symptoms affiliated with

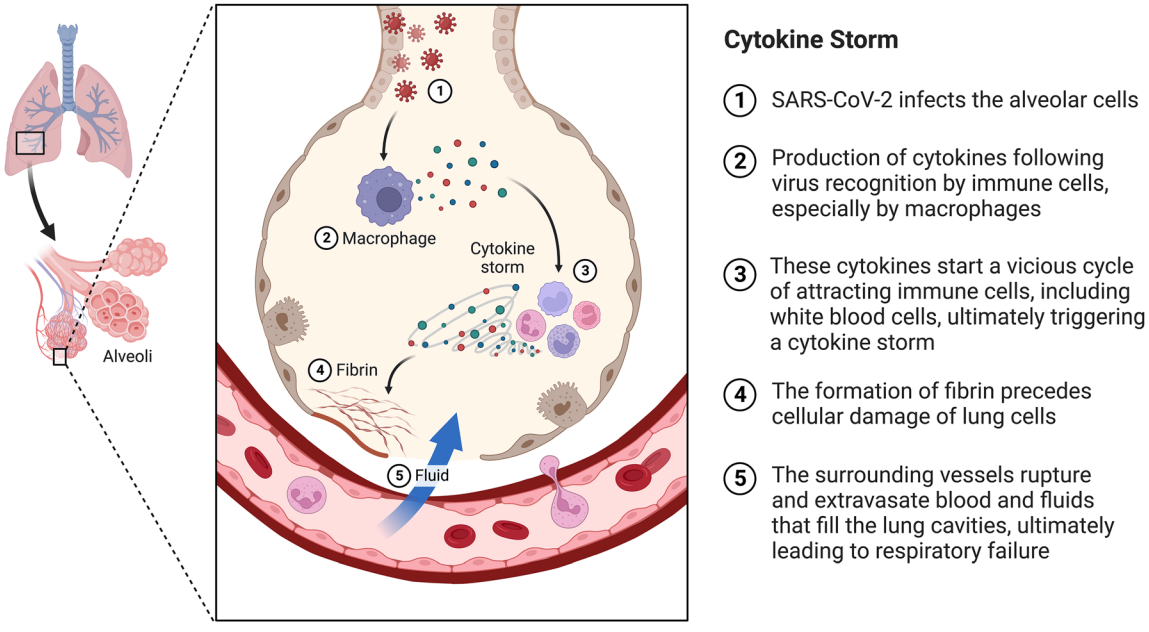

Figure 1: The mechanism of progression of Acute Respiratory Distress Syndrome (ARDS) following SARS-CoV-2 infection.

COVID-19. Therapeutic effects of PDE5 inhibitors in patients suffering from underlying conditions such as diabetes were first observed in a wide scope study, DEDALO, which is the abbreviation of "silDEnafil administration in DiAbetic and dysmetaboLic patients with COVID-19". This study systematically reviews the role of the NO/cGMP/PDE5 pathway in COVID-19 and concludes that sildenafil may be useful in counteracting vascular damage in lung tissue and preventing thromboembolism [79]. The DEDALO project is being conducted as a phase-3 randomized controlled trial, in which diabetic and dysmetabolic men infected with mild to severe COVID-19 will be subjected to sildenafil citrate 60 mg for 8 weeks. This trial aimed to test the effects of oral sildenafil on the disease remission rate. Strong evidence has shown that PDE5 inhibitors can help ease the harmful after-effects of over-stimulating the immune system. Given the positive results of various ongoing clinical trials, PDE5 inhibitors can be a valuable resource for combating COVID-19, given their easy availability and low cost [79]. The study reported that sildenafil administration impeded AT-1 down-regulation, while simultaneously down-regulating the production of pro-inflammatory chemokines from monocytes. Subsequently, this reduces the chances of pulmonary tissue damage, further inhibiting the transformation of endothelial cells into their mesenchymal counterparts. This ultimately prevents thromboembolism from developing and progressing in COVID-19 patients [79]. A multitude of additional clinical trials are also underway to investigate the effectiveness of PDE5 inhibitors in reducing COVID-19-related symptoms. These clinical trials are summarized in Table 1 (obtained from the data available on clinicaltrials.gov).

Conclusion and outlook

Since its first reports, several medications, vaccines, and therapies have been indicated for the treatment and prevention of SARS-CoV-2 infection. Despite the publication of numerous preclinical studies indicating the efficacy of various drugs in alleviating the symptoms associated with COVID-19 infection, the current clinical armamentarium available to physicians in a real-world setting is sheerly limited to a handful of drugs. This is mainly because the proposed drugs and their respective formulations would require adequate real-world evidence that substantiates their affordability, efficacy, biopharmaceutics, and safety profile [30]. In such cases, the repurposing of drugs that have been pre-approved for other indications could be of paramount importance and would help in easing the burden inflicted on the already overburdened healthcare system. PDE5 inhibitors such as sildenafil and vardenafil were initially indicated and validated for the treatment of pulmonary hypertension, cardiovascular anomalies, and later in the treatment of erectile dysfunction. However, their off-label indications include anti-apoptotic, anti-inflammatory, antioxidant, and immunomodulatory effects, and are achieved by the interception of several metabolic and signaling pathways. Recent reports suggest the utility of PDE5 inhibitors in the suppression of Reactive Oxygen Species [148, 149], yielding a pleiotropic effect of the drug in the clinical manifestations associated with the SARS-CoV-2 infection [150] and beyond. These properties could corroborate their utility in the alleviation of symptoms associated with the SARS-CoV-2 infection. Since there are similarities in the clinical manifestations reported in the mild-to-moderate and moderate-to-severe cases of the SARS-CoV-2 infection as well as with different variants, including, BF.7 [151], BQ.1 [151], BQ.1.1 [151], XBB.1.5 [151], and XBB.1.16 [152], these drugs could have a projected potential in these cases. While several *in-vitro* and *in vivo* studies corroborate the efficacy and potential of the subsets of this class in the interception of various signaling pathways involved in precipitating the symptoms of COVID-19, rigorous clinical studies must be conducted to validate their potential in such cases. Furthermore, these studies could be extended to include special populations, such as pediatric, geriatric, comorbid, and smokers [153]. Additionally, with the corroboration of these studies, the potential of these drugs could also be tested in other diseases which may present ARDS, including tomato flu or hand-foot and mouth disease [154], and diseases not presenting ARDS, such as Monkeypox or Mpox [155], and in other untoward future viral outbreaks [156]. Further research on the topic could include the optimization of the delivery vehicle and the administered dose. The delivery and loaded dose could be optimized by the development and characterization of nano-formulations [157], and the dose optimisation could be achieved by novel methods such as 3D printing of dosage forms and use of artificial intelligence and machine learning models [158], including pharmacometric modelling. Since several herbal supplements and phyto-constituents have been indicated for immunomodulation and the treatment of SARS-CoV-2 infection, further research could also employ the use of such simulation models and pharmacovigilance studies at the interface of modern with complementary and alternative medicine systems [159]. In conclusion, although there are various pipelines for emergency approval, the authors opine on the need for more studies, including preclinical and clinical trials, to substantiate their utility as well as shortcomings, if any.

Table 1: Clinical trials investigating the efficacy of PDE5 Inhibitors against COVID-19.

Sr. No.	Title	Status	Condition	Intervention	Characteristics	Population	Locations	NCT identifier
1.	Sildenafil in COVID-19	Completed	– COVID-19 – SARS-CoV-2 infection	– Drug: Sildenafil – Drug: Placebo	A. Study type: Interventional – Allocation: Randomized – Intervention model: Parallel assignment – Masking: Quadruple (participant, care provider, investigator, outcomes assessor) – Primary purpose: Treatment B. Outcome measures: – Arterial oxygenation – Alveolo-arterial gradient – Intensive care unit admission – Non-Invasive mechanical ventilation or requirement of high-flow nasal cannula – Invasive mechanical ventilation – Survival	A. Enrolment: 40	– Hospital naval almirante nef, viña Del Mar, valparaiso, Chile	NCT04489446
2.	A pilot study of sildenafil in COVID-19	Recruiting	– COVID-19	– Drug: Sildenafil citrate tablets	A. Study type: Interventional – Intervention assignment – Treatment B. Outcome measures: – Remission – Respiratory symptom remission – Recover – Rate of biochemical – Undetectable (continuous) – Time for hospitalization	A. Enrolment: 10	– Department and institute of infectious disease, Wuhan, Hubei, China	NCT04304313
3.	The use of tadalafil in confirmed COVID-19 pneumonia	Withdrawn	– COVID-19 – SARS-CoV-2 – ARDS, human	– Drug: Tadalafil pills	A. Study type: Interventional – Allocation: N/A – Intervention assignment: Treatment B. Outcome measures: – Improvement in P:F ratio – Improvement in oxygen saturation – Improvement in partial pressure of oxygen in the bloodstream	A. Enrolment: 0	N/A	NCT04946162

Research ethics: Not applicable.
Informed consent: Not applicable.
Author contributions: Conceptualization, Methodology, Investigation, data collection and Writing-original manuscript: Ryan Varghese, Gargi Digholkar, Jainam Karsiya; Editing and proof reading, Jeenam Shah, Sahil Salvi, Dileep Kumar; Supervision: Rohit Sharma. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Competing interests: The authors state no conflict of interest.
Research funding: None declared.

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