

# Anti-infection mechanism of phosphodiesterase-5 inhibitors and their roles in coronavirus disease 2019 (Review)

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**Abstract.** Coronavirus disease 2019 (COVID-19) has a variety of impacts on the human body. Severe acute respiratory syndrome coronavirus 2 is the pathogen that causes COVID-19. It invades human tissues through the receptor angiotensin-converting enzyme 2, resulting in an imbalance in the angiotensin II (AngII) level and upregulation of renin-angiotensin system/AngII pathway activity. Furthermore, the binding of AngII to its receptor leads to vasoconstriction, endothelial injury and intravascular thrombosis. In addition, COVID-19 may have adverse effects on male reproductive organs and a marked impact on male reproductive health. Phosphodiesterase-5 inhibitors (PDE5Is) may improve vascular endothelial function, promote testicular and systemic blood circulation and testosterone secretion and enhance epididymal function, as well as sperm maturation and capacitation. PDE5Is may also be of use in the treatment of infectious diseases by enhancing immunity and anti-inflammatory responses and improving vascular endothelial function. Based on the pharmacological mechanism of PDE5Is, they are of unique value in the fight against infectious diseases and may be effective in combination with direct antiviral drugs. The anti-infection mechanisms of PDE5Is and their roles in COVID-19 were reviewed in the present study.

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## 1. Introduction

Coronavirus disease 2019 (COVID-19) is an emerging and rapidly evolving situation, causing an unprecedented continuous impact on survival and daily life worldwide (1). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the pathogen that causes COVID-19 (2). Furthermore, SARS-CoV-2 is mutating, and it appears that numerous vaccines have been developed and are now available. But most vaccines that specifically target the existing SARS-CoV-2 may not be effective against a mutant SARS-CoV-2 (3). In the context of viral infection, the body mainly relies on immune function to eventually eliminate the virus, but treatment for the series of consequences of infection is also essential. Exploration of more effective treatment methods, including comprehensive and combined therapies, is urgently required. Previous studies have indicated that phosphodiesterase-5 inhibitors (PDE5Is) exhibit important anti-infectious disease efficacy and may have multiple mechanisms different from those of direct antiviral therapy. The present study systematically summarized the mechanisms of action and potential combined application value of PDE5Is in the treatment of COVID-19.

## 2. Adverse effects of COVID-19

*Unfavourable impacts of COVID-19 on the respiratory system and general health.* SARS-CoV-2 invades human cells through the receptor angiotensin-converting enzyme 2 (ACE2). During virus entry into host cells, the spike protein on the envelope of SARS-CoV-2 is cleaved into the S1 and S2 subunits. S1 contains a receptor-binding domain (RBD) that directly binds to the peptidase domain (PD) of ACE2 to allow entry into the host cell (4). The peptidase activity of ACE2 is required for SARS-CoV-2 to enter the host cell's cytoplasm. The cleavage of the RBD in the C-terminus of the S1 subunit initiates the interaction with the PD of ACE2 (5). The binding of S1 to the receptor ACE2 triggers the cleavage of ACE2 via a disintegrin and metalloprotease 17 (ADAM17)/tumour necrosis factor (TNF)-converting enzyme in the outer domain. In addition, a transmembrane serine protease (TMPRSS2) cleaves the C-terminal domain of ACE2 and the cleavage of ADAM17 and TMPRSS2 (outer domain and inner domain) promotes effective viral entry (6). This process appears to result in the loss of ACE2 receptor function and systemic release of the S1/ACE2 complex.

ACE receptors are expressed in almost all tissues, while ACE2 is expressed in alveolar epithelial cells and capillary endothelial cells. ACE2 is highly expressed in capillary-rich organs, including the lungs and kidneys, as well as in the intestine and brain (7). ACE regulates the renin-angiotensin-aldosterone system (RAAS). ACE2 balances the harmful effects of the ACE/renin-angiotensin system (RAS) pathway through its downstream ACE2/angiotensin/MAS axis (1-7). The classic activation of angiotensin II (AngII) depends on renin and ACE activity. When the juxtaglomerular apparatus of the afferent glomerular artery is activated, a special protease cleaves prorenin into renin. Renin decomposes angiotensinogen into AngI and ACE catalyses the conversion of AngI into AngII. After AngI is converted into AngII, AngII binds to AngII receptors in the kidneys, adrenal cortex, arterioles and brain. AngII acts on the adrenal cortex and stimulates the release of aldosterone, which leads to the retention of sodium and water, and the binding of AngII to angiotensin II type (AT) receptors leads to vasoconstriction, endothelial damage, intravascular thrombosis and an increased blood volume (8). Moreover, AngII may also effectively induce interleukin (IL)-6 and TNF- $\alpha$  through serine tyrosine kinase, ERK/JNK-MAPK, G protein-coupled receptor activation or corticosteroid receptor interactions (4). AngII is an effective activator of NADPH oxidase, so it is also an inducer of reactive oxygen species. In addition, AngII may activate neutrophils and macrophages to migrate to affected tissues and inhibit the production of nitric oxide (NO), thus promoting vascular injury (9).

ACE2 acts as a ligand through the MAS1 receptor, which is a G protein-coupled receptor. ACE2 is a single carboxypeptidase that is able to cleave AngI into Ang1-9 and AngII into Ang1-7 (10). These two peptides have vasodilating, anti-proliferative and protective effects mediated by activating the MAS/G receptor. The ACE2/Ang1-7/MAS1 axis provides an endogenous reverse regulation in the RAAS to balance the harmful effects of the ACE/AngII/AT1 receptor axis. ACE2 activation may prevent the harmful effects of AngII on cells and organisms, such as cell death, fibrosis, vasoconstriction and thrombosis, that lead to alveolar epithelial injury and respiratory failure (11,12). When SARS-CoV-2 binds to ACE2 and enters pulmonary epithelial cells, the receptor ACE2 is released from the surface of host cells and loses its protective function. The loss of ACE2 activity blocks the production of Ang1-9 and Ang1-7, resulting in an imbalance in the AngII level and the upregulation of RAS/AngII pathway activity. The upregulation of the AngII level leads to vasoconstriction, thrombosis, alveolar epithelial injury and respiratory failure, which eventually leads to the symptoms of COVID-19 in the lungs and even the whole body.

*COVID-19 may have adverse effects on the testes and reproductive system.* Certain studies have examined the expression pattern of ACE2 in adult human testes at the level of single-cell transcriptomes. ACE2 was indicated to be mainly enriched in spermatogonia, Leydig cells and Sertoli cells. Gene ontology analysis suggested that genes related to virus propagation and transmission were highly enriched in ACE2-positive spermatogonia, while the expression of genes related to male gametogenesis was downregulated. ACE2-positive Leydig

and Sertoli cells exhibited increased levels of intercellular junction- and immune-related genes, while the levels of mitochondria- and reproduction-related genes were decreased (13). These results suggested that the human testes are a potential target for SARS-CoV-2. SARS-CoV-2 is likely to bind to the receptor ACE2 on testicular cells, which leads to an imbalance in the AngII level and the upregulation of RAS/AngII pathway activity, resulting in vasoconstriction, thrombosis and activation of the inflammatory system, thus causing damage to testicular cells (14).

A study has reported that SARS-CoV-2 may be detected in the semen of certain patients (15.8%) and that SARS-CoV-2 may persist in the male reproductive system, causing harm to this system (15). In another study, a mild COVID-19 infection was not likely to affect testis and epididymis function, but semen parameters did seem impaired after a moderate infection. There is no evidence of SARS-CoV-2 shedding in semen of recovered men or men with an acute COVID-19 infection after a recovery time of 32.7 days on average (16). In addition, pathological analysis of testicular tissues from patients with COVID-19 revealed obvious damage to the seminiferous tubules, decreased interstitial cell counts, as well as mild lymphocyte infiltration and obviously damage to the testicular parenchyma. Although SARS-CoV-2 was not detected in the testes of the vast majority of autopsy cases (90%) by reverse transcription PCR, there were still certain cases (10%) in which testis autopsy provided evidence of SARS-CoV-2 (17). Therefore, it is likely that COVID-19 may have adverse effects on the male reproductive system.

### 3. PDE5Is and their anti-infection mechanisms

*General.* PDE5Is are drugs that effectively improve erectile function. PDE5Is increase the concentration of cyclic guanosine monophosphate (cGMP) by inhibiting the activity of PDE5, resulting in relaxation of the smooth muscle of the penis, which increases the blood flow of the artery in the cavernous body of the penis and produces an erection (18). In addition, PDE5Is protect and repair the vascular endothelium and improve the blood circulation; therefore, they are used in the treatment of cardiovascular diseases (19). The detailed mechanism of action of PDE5Is is presented in Fig. 1. Compared with other similar drugs that improve vascular endothelial function, such as ACE inhibitors, statins, calcium antagonists and  $\beta$ -receptor blockers, PDE5Is have unique mechanisms to improve vascular endothelial function and numerous advantages, including high effectiveness, more diverse indications, benefits for male reproductive health, as well as only a small number of side effects, which are tolerable. The commonly used PDE5Is include sildenafil, vardenafil and tadalafil.

At present, there is no satisfactory specific drug for COVID-19; thus, it is important to improve systemic immune function in the context of viral infection. Furthermore, it is necessary to effectively intervene in a series of pathophysiological processes and inflammatory products caused by infection, including improvement of local tissue blood circulation disorder, tissue hypoxia, vascular endothelial damage and oxidative stress injury (20). Based on the pharmacological mechanism of action of PDE5Is, these drugs have unique value in the treatment of infectious diseases and may be effective

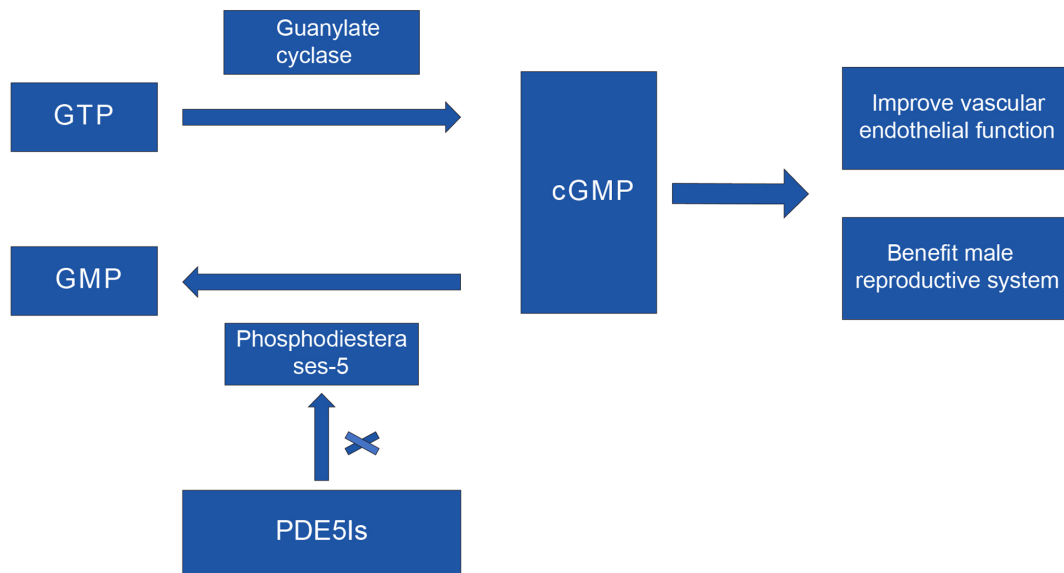


Figure 1. Detailed mechanism of action of PDE5Is. PDE5Is, phosphodiesterase-5 inhibitors; cGMP, cyclic guanosine monophosphate; GTP, guanosine triphosphate.

in combination with direct antiviral drugs. The anti-infection mechanism of PDE5Is in COVID-19 is presented in Fig. 2. The mechanism shown in the Fig. 2 is as follow: COVID-19 can cause adverse effects on human body by reducing immunity, enhancing inflammatory responses and reducing vascular endothelial function. But PDE5Is can synergistically treat COVID-19 by enhancing immunity, reducing inflammatory response and enhancing vascular endothelial function.

*Enhancement of immunity.* PDE5Is are able to enhance immune function. In healthy male mice treated with sildenafil, the percentage of CD4<sup>+</sup> T cells was indicated to be decreased, while the percentage of CD8<sup>+</sup> T cells was increased. It was also observed that the levels of effector memory and central memory T cells were decreased in male mice but increased in female mice. The percentages of activated natural killer (NK) cells and T cells were increased in female mice but decreased in male mice. In addition, sildenafil decreased the level of serum IL-6 and increased the level of IL-2. These results suggest that sildenafil has sex-specific immunoregulatory properties (21). Furthermore, the effects of sildenafil on thymocytes, splenocytes and T cells isolated from the lymph nodes of mice were studied. Oral sildenafil (1 mg/kg) temporarily reduced the percentage of CD4<sup>+</sup>CD8<sup>+</sup> thymocytes and increased that of CD8<sup>+</sup> cells. In lymphocytes isolated from the mesenteric lymph nodes, the percentage of CD19<sup>+</sup> cells was decreased and the percentage of CD3<sup>+</sup> cells was increased 72 h after the last administration (22). Certain studies have indicated that sildenafil increases the production of IL-1 $\beta$  and NO in peritoneal macrophages and the percentage of phagocytes and decreases the percentage of monocytes (23). In a study on experimental autoimmune encephalomyelitis, a multiple sclerosis model, it was determined that sildenafil was able to reduce cell infiltration in the spinal cord and white matter of mice. Sildenafil increased the number of YM-1 cells (which is a marker of the alternative macrophage/microglial M2 phenotype that has neuroprotective and regenerative properties) and the expression of the granzyme B cluster in regulatory T cells (Tregs) (24). In addition, sildenafil

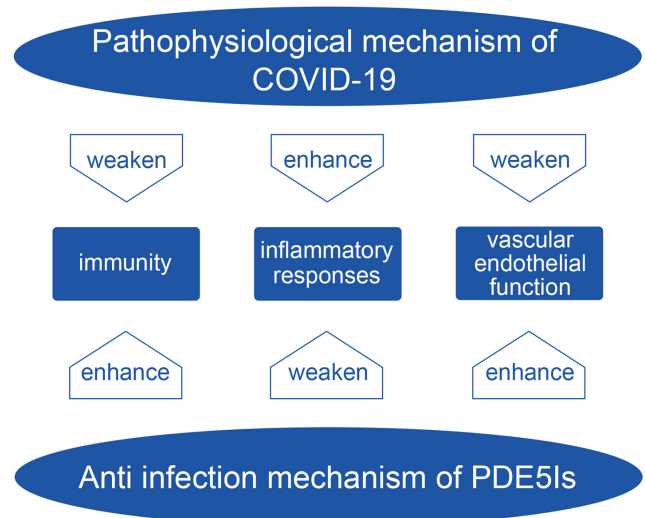


Figure 2. Anti-infection mechanism of PDE5Is in COVID-19. PDE5Is, phosphodiesterase-5 inhibitors; COVID-19, Coronavirus disease 19.

was able to prolong the survival time of tumour-bearing mice by enhancing antitumour immunity, which is achieved by inhibiting CD11b<sup>+</sup>/Gr-1<sup>+</sup> myeloid-derived suppressor cells (MDSCs) and downregulating IL-4 receptor  $\alpha$  expression (25,26).

Certain studies have indicated that sildenafil may significantly reduce the activity of NK cells in the peripheral blood of females with recurrent abortion and endometrial thickness significantly increases after treatment (27). A case of B-cell chronic lymphoblastic leukaemia (B-CLL) treated with sildenafil alone was reported. During the 3.5-year period of treatment with sildenafil (50 mg/week), the lymphocyte count of the patient decreased significantly and sildenafil induced apoptosis in B-CLL cells in a caspase-3-dependent manner (28). In addition, sildenafil may affect angiogenesis, platelet activation, Treg proliferation, proinflammatory cytokines and autoantibodies, thus affecting the innate and adaptive immune systems of experimental animals and patients (29).

*Anti-inflammatory responses.* PDE5Is may also limit inflammatory factor activity and inflammatory responses and have anti-infection effects. It has been reported that F508del-CF mice exhibit a potential inflammatory state characterized by neutrophil infiltration and mouse macrophage inflammatory protein 2 and TNF- $\alpha$  expression. Intraperitoneal administration of vardenafil was indicated to significantly reduce the inflammatory response of F508del-CF mice and decrease macrophage infiltration, macrophage chemokine levels and IL-1 $\beta$  levels. These results suggest that vardenafil may significantly reduce lung inflammation in F508del-CF mice, particularly in terms of macrophage markers (30). Another study indicated that vardenafil is able to reduce the proinflammatory and fibrotic functions of fibroblasts in mice with cystic fibrosis, providing convincing novel support for developing a drug therapy to target the cGMP signalling pathway in cystic fibrosis (31). It has also been reported that tadalafil is able to reduce the levels of malondialdehyde and NO in the kidneys of rats with acute pyelonephritis and enhance the activities of superoxide dismutase (SOD) and catalase. These results suggest that tadalafil may improve the levels of circulating inflammatory cytokines, reverse oxidative dysfunction and ultimately protect the kidneys (32). In addition, in an acute lung injury (ALI) model, sildenafil treatment reduced cell leakage, particularly neutrophil infiltration into the lungs, decreased the release of proinflammatory mediators (TNF- $\alpha$ , IL-8 and IL-6) and the levels of nitrite/nitrate and oxidative damage markers, reduced the formation of pulmonary oedema and improved respiratory parameters. Therefore, sildenafil also has a potential role in the treatment of ALI (33).

In a rat model of bronchopulmonary dysplasia, prophylactic treatment with sildenafil was indicated to significantly increase cGMP levels in the lungs, reduce the pulmonary inflammatory response, fibrin deposition and right ventricular hypertrophy and to stimulate alveolarization (34). In addition, oral administration of tadalafil (1 mg/kg) for 8 weeks was able to significantly improve silica-induced lung injury. The protective effect of tadalafil is related to the inhibition of cytokine expression in inflammation and fibrosis, recovery of the antioxidant capacity and promotion of angiogenesis (35). It has been indicated that in a rat model of lipopolysaccharide-induced sepsis, sildenafil may increase the level of glutathione, reduce the activities of myeloperoxidase (MPO), lipid peroxidase and SOD and to decrease the level of serum TNF- $\alpha$  and the inflammatory score. Therefore, sildenafil has protective effects on the lung and kidney damage caused by sepsis (36). In addition, tadalafil may prevent or slow ureteral inflammation and urothelial degeneration in rats with ureteral obstruction and reduce the expression of  $\alpha$ -smooth muscle actin and transforming growth factor- $\beta$  (37).

T helper 1 (Th1)-type cytokines and chemokines are bioactive mediators in the inflammatory response and the Th1 chemokine C-X-C motif chemokine ligand (CXCL)10 is involved in the occurrence and development of cardiac injury. In diabetic subjects with cardiomyopathy, sildenafil was able to significantly reduce the protein secretion and gene expression of CXCL10 in human cardiomyocytes and reduce the level of CXCL10 in patients (38). Cavernitis is a rare acute infection of the penis. If not treated properly, cavernitis may lead to cavernous abscess formation, fibrosis and subsequent

erectile dysfunction. In a clinical study, two patients with cavernitis were treated with antibiotics and tadalafil and their clinical symptoms improved rapidly. After 3 months of follow-up, the erectile function of the patients was normal and there was no penile scarring. This suggests that tadalafil may have a synergistic effect with antibacterial therapy (39). In addition, the therapeutic effect of vardenafil combined with antibiotics in the treatment of patients with chronic bacterial prostatitis (CBP) was studied. The National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) scale, urinary bacteria and leukocyte counts and the urine flow rate were used to evaluate the therapeutic effect. It was indicated that the combination of antibiotics and vardenafil achieved a significantly improved efficacy in CBP (40). In addition, a study reported that in a patient with a severe chronic foot wound, the wound healed almost completely after treatment with tadalafil (20 mg three times a day) and was stable for 2 years, which unexpectedly revealed a role for tadalafil in chronic wound infection treatment (41).

*Improvement of vascular endothelial function.* PDE5Is relax vascular smooth muscle and improve the local blood circulation. Certain studies have explored the therapeutic effect of sildenafil in the early stage of sepsis. Sildenafil may increase the renal blood flow, decrease pulmonary MPO activity and reduce the levels of plasma creatinine, lactate and creatine kinase. Therefore, sildenafil may be a treatment for early sepsis (42). In addition, the effects of intraperitoneal injection of sildenafil on left colonic anastomosis healing and intra-abdominal adhesion formation were also studied. The healing of an anastomotic stoma in model rats was significantly improved and histopathological results indicated that angiogenesis was increased and intra-abdominal adhesion was significantly reduced (43). Severe endothelial cell injury is the key event in the process of ischaemia-reperfusion (I/R) injury. It was indicated that sildenafil may dilate blood vessels and increase the cGMP level, but was not able to affect the recovery of renal function or I/R injury (44). In addition, sildenafil may prevent early transplantation failure, prolong ischaemic tolerance and improve lung function in pigs with lung I/R injury (45). Furthermore, a study reported that for patients with benign prostatic hyperplasia, 5 mg tadalafil may relax the vascular smooth muscle, improve vascular endothelial function and increase vascular elasticity (46). The effect of sildenafil on the microvascular blood flow in patients with systemic sclerosis secondary to Raynaud's phenomenon (RP) was also explored in one study. The results suggested that sildenafil improved the finger artery blood flow and RP symptoms after 8 weeks of treatment, which indicates that sildenafil is a good choice for the treatment of secondary RP (47).

Studies have also investigated the effect of sildenafil on AngII-dependent hypertension and renal vascular dysfunction. It was indicated that sildenafil is able to lower AngII-dependent hypertension and enhance NO-mediated vasodilation, which is a key regulator of renal haemodynamics in patients with hypertension (48). In addition, there the effects of sildenafil on irisin levels in the heart, liver and kidney tissues were explored and it was evaluated whether sildenafil impacts serum irisin or NO levels in rats with induced experimental myocardial ischaemia. Sildenafil was effective in eliminating

ischaemia and may be the first choice for offsetting the effects of ischaemia in the future (49). Studies have also explored the effects of vardenafil on the systemic endothelial function of diabetic patients with erectile dysfunction. Chronic vardenafil administration was able to significantly improve endothelial parameters in diabetic patients (50). Whether sildenafil is able to improve tissue perfusion and neovascularization and downregulate proinflammatory molecules following limb ischaemia has also been examined. Sildenafil was able to significantly improve tissue perfusion and the inflammatory status after limb ischaemia, which implies that sildenafil potentially has properties related to neovascularization and vascular protection (51). Studies exploring the effects of sildenafil on cerebrovascular function and cerebral metabolism in patients with Alzheimer's disease (AD) have also been performed. After sildenafil administration, the cerebral blood flow and cerebral oxygen metabolism rate of the patients were significantly increased (52). Furthermore, numerous studies have confirmed that sildenafil is able to significantly improve pulmonary hypertension and relax blood vessels (53,54).

#### 4. Roles of PDE5Is in COVID-19

*Combination treatment of COVID-19.* COVID-19 may promote the induction of endothelial inflammation in multiple organs, which is the direct result of SARS-CoV-2 infection and host inflammatory response activation. This progressive endothelial thrombotic inflammatory syndrome involves the microvessels of numerous important organs, leading to multi-organ failure and death; this syndrome is also the mechanism underlying interstitial pneumonia developing into pulmonary failure. As a vasodilator, tadalafil may be administered once a day to improve tissue angiogenesis and anti-fibrotic function, thus blocking or preventing vascular endothelial sclerosis in patients with COVID-19 (55). There is a strong correlation between the severity of infection caused by COVID-19 and the presence of hypertension and numerous studies have demonstrated that hypertension is related to NO. Considering the pharmacology of PDE5Is, these drugs may be used as early complimentary drugs in the treatment of COVID-19 (56). Furthermore, numerous patients with COVID-19 have symptoms of bilateral diffuse alveolar injury and pulmonary oedema, increased levels of proinflammatory mediators and elevated pulmonary capillary pressure. Whether PDE5Is should be included in combination treatments of COVID-19 to facilitate the recovery of patients has also been considered (57). Certain studies have indicated that NO may alleviate lung injury, reduce the concentrations of proinflammatory cytokines and decrease the number of neutrophils entering the lungs. Therefore, PDE5Is may be used to increase the level of NO as part of the treatment of COVID-19 (58). The use of PDE5Is to reduce pulmonary hypertension and relieve the symptoms of acute respiratory distress syndrome and the use of PDE5Is for synergistic treatment of COVID-19 have also been proposed (59).

Therefore, PDE5Is also have important roles in protecting against infectious diseases. PDE5Is may improve the treatment of infectious diseases by enhancing immunity and anti-inflammatory responses and improving vascular endothelial function. In patients with COVID-19, PDE5Is

may be considered as synergistic drugs for combined treatment.

*Multiple beneficial effects for COVID-19.* Various studies have indicated that COVID-19 has potential adverse effects on the male reproductive system (60,61). ACE2 is expressed in the spermatogonia, Leydig cells and Sertoli cells of the testes. SARS-CoV-2 may cause reproductive dysfunction in patients via the ACE2 pathway (62). Certain studies have indicated that patients with COVID-19 have symptoms of viral orchitis and scrotal discomfort, which have a negative impact on male reproductive function and spermatogenesis (63). Certain studies have also summarized the adverse effects of SARS-CoV-2 on male reproductive health, which may lead to testicular damage and male infertility and suggest the theoretical possibility of sexual transmission, as SARS-CoV-2 has been identified in the semen of infected patients. It is also necessary to rehabilitate and monitor the reproductive system of patients with COVID-19 (64,65).

PDE5Is may improve vascular endothelial function, promote the testicular and systemic blood circulation and testosterone secretion and improve epididymal function, sperm maturation and capacitation (66,67). Therefore, in view of the possible damage to the male reproductive system and whole body caused by SARS-CoV-2, PDE5Is may be considered for inclusion in combined therapy to treat COVID-19, which may improve orchitis and sperm quality while enhancing systemic antiviral effects. In general, PDE5Is are safe in clinical practice. The incidence of side effects is low (from 9 to 25%), the symptoms are not serious and most symptoms are tolerable, and PDE5Is may be obtained from a pharmacy with a prescription. The potential side effects of PDE5Is include headache, flushing, dyspepsia, nasal congestion, dizziness, abnormal vision, back pain and myalgia. The absolute contraindication is combined use with nitrates (68). For patients with COVID-19 with damage to male reproductive function or erectile dysfunction, the combined use of PDE5Is may not only help to treat the viral infection but also benefit reproductive function. For patients with COVID-19 without damage to male reproductive function or erectile dysfunction, the combined use of PDE5Is may prevent damage to the male reproductive system.

#### 5. Conclusion

COVID-19 has certain adverse effects on numerous parts of the human body, including the respiratory system and male reproductive system. PDE5Is with a variety of anti-infection mechanisms may become important drugs for combination therapy, particularly in patients with male genital infection, and the combined use of PDE5Is may achieve multiple beneficial effects.

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### Availability of data and materials

Not applicable.

### Authors' contributions

HS, CM and HL were involved in the acquisition, analysis and interpretation of the data. HS and HL also contributed to the design and conception of the study. HS drafted the manuscript. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

Not applicable.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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