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Inflammopharmacology

REVIEW

A raising dawn of pentoxifylline in management of inflammatory disorders in Covid-19

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Abstract

The existing pandemic viral infection caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) leads to coronavirus disease 2019 (Covid-19). SARS-CoV-2 exploits angiotensin-converting enzyme 2 (ACE2) as an entry-point into affected cells and down-regulation of ACE2 by this virus triggers the release of pro-inflammatory cytokines and up-regulation of angiotensin II. These changes may lead to hypercytokinemia and the development of cytokine storm with the development of acute lung injury and acute respiratory distress syndrome. Different repurposed had been in use in the management of Covid-19, one of these agents is pentoxifylline (PTX) which has anti-inflammatory and antioxidant properties. Therefore, the objective of the present mini-review is to highlight the potential role of PTX in Covid-19 regarding its anti-inflammatory and antioxidant effects. PTX is a non-selective phosphodiesterase inhibitor that increases intracellular cyclic adenosine monophosphate which stimulates protein kinase A and inhibits leukotriene and tumor necrosis factor. PTX has antiviral, anti-inflammatory and immunomodulatory effects, thus it may attenuate SARS-CoV-2-induced hyperinflammation and related complications. As well, PTX can reduce hyper-viscosity and coagulopathy in Covid-19 through increasing red blood cell deformability and inhibition of platelet aggregations. In conclusion, PTX is a non-selective phosphodiesterase drug, that has anti-inflammatory and antioxidant effects thereby can reduce SARS-CoV-2 infection-hyperinflammation and oxidative stress. Besides, PTX improves red blood cells (RBCs) deformability and reduces blood viscosity so can mitigate Covid-19-induced hyper-viscosity and RBCs hyper-aggregation which is linked with the development of coagulopathy. Taken together, PTX seems to be an effective agent against Covid-19 severity.

Keywords Covid-19 · Blood viscosity · Coagulopathy · Pentoxifylline · Hyperinflammation

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Introduction

The existing pandemic viral infection caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) leads to coronavirus disease 2019 (Covid-19) (Al-Kuraishy et al. 2021d). SARS-CoV-2 exploits angiotensin-converting enzyme 2 (ACE2) as an entry-point into the affected cells and down-regulation of ACE2 by this virus triggers the release of pro-inflammatory cytokines and up-regulation of angiotensin II (AngII) (Onohuean et al. 2021). These changes may lead to hypercytokinemia and the development of cytokine storm with the development of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) (Onohuean et al. 2021). The clinical presentation of Covid-19 is asymptomatic or mild symptoms in the majority of cases. However, 5–10% of patients' progress to develop acute and critical complications requested hospitalization and assist ventilation due to the development of severe ALI and ARDS (Al-Kuraishy et al. 2021a; Al-Kuraishy and Al-Gareeb 2021).

Different repurposed had been in use in the management of Covid-19, though none of used drugs produced complete recovery (Al-Kuraishy et al. 2021c). In this sense, anti-inflammatory and antioxidant agents were trialed against SARS-CoV-2 infection in various in silico, experimental and preclinical studies. One of these agents is pentoxifylline (PTX) which has anti-inflammatory and antioxidant properties (Al-Kuraishy et al. 2019).

Therefore, the objective of the present mini-review is to highlight the potential role of PTX in Covid-19 regarding its anti-inflammatory and antioxidant effects.

Pharmacology of pentoxifylline

PTX is a derivative of xanthine (1-5-oxohexyl-3-7-dimethylxanthine) and structurally related to caffeine and theophylline (Fig. 1) (Wikipedia 2014). PTX is synthesized by introducing hexanone to theobromine extracted from cocoa bean alkaloid. PTX acts as a non-selective phosphodiesterase inhibitor (PDEI) that increases intracellular cyclic adenosine monophosphate (cAMP) which stimulates protein kinase A (PKA) and inhibits leukotriene and tumor necrosis factor (TNF) (Hussien et al. 2019). As well, PTX is regarded as an antagonist for adenosine 2 receptor (A2R) (Hussien et al. 2019). PTX reduces activation of innate immunity and release of inflammatory cytokines.

PTX was in the clinical use since 1972 and approved by Food and Drug Administration (FDA) in 1984 (Frampton and Brogden 1995). PTX is indicated in the management of peripheral vascular diseases, arterial disease-induced intermittent claudication, and chronic leg ulcers (Chandan et al. 2018). PTX decreases blood viscosity by reducing fibrinogen plasma levels, increasing red blood cell flexibility, and inhibiting platelet aggregation (Rasyid et al. 2018). It inhibits the activation and adhesion of neutrophils and reduces the formation of free radicals (Rasyid et al. 2018). As well, PTX inhibits fibrotic changes through inhibition of tumor growth factor-beta (TGF-β) connective tissue growth factor (Delanian et al. 2005).

PTX may be effective in treating sarcoidosis by inhibiting TNF-induced granuloma formation (Tong et al. 2003). Besides, it is effective against alcoholic hepatitis (Whitfield et al. 2009) and diabetic neuropathy (Hosseini et al. 2019). As well, different researches suggested that PTX could be effective in treating erectile dysfunction (Law et al. 2020), hearing loss (Lan et al. 2018), Peyronie's disease (Ibrahim et al. 2019), and osteoradionecrosis (Kolokythas et al. 2019).

Common side effects of PTX are palpitation, flushing, headache, and arrhythmias (Chandan et al. 2018). PTX is orally active with low bioavailability (20–30%) due to extensive first-pass metabolism (Chandan et al. 2018). PTX has high plasma protein binding and 45% of it binds the erythrocyte membrane, it is metabolized by liver and excreted by renal route (Rasyid et al. 2018). PTX has short half-life about 1.6 h (Rasyid et al. 2018). PTX toxicity was reported at a dose of 80 mg/kg, leading to hypotension, flushing, and convulsion (Dianey et al. 2021). These findings suggest that PTX is a safe drug and has no serious drug–drug interaction and can be used easily.

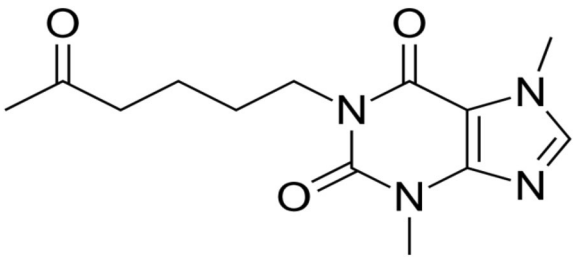

Fig. 1 Chemical of pentoxifylline (Wikipedia 2014)

Pleiotropic effects of pentoxifylline

Anti-inflammatory effects

PTX has potent anti-inflammatory effects by inhibiting the release of pro-inflammatory cytokines and increasing the production of anti-inflammatory cytokines in patients with acute coronary syndrome (ACS) (Fernandes et al. 2008). PTX enhances the anti-inflammatory of steroids and non-steroidal anti-inflammatory drugs for the management of inflammation in rats (Abdel-Salam et al. 2003). A

prospective study comprised 64 patients with ACS treated with PTX 400 mg/day or placebo for 6 months illustrated that PTX reduced interleukin 6, 12 (IL-6, IL-12), and TNF-α with an increment of IL-10 (Fernandes et al. 2008). Dong et al. illustrated that PTX exerts anti-inflammatory effects in rats with cerebral ischemia–reperfusion injury by inhibiting cyclooxygenase 2 (COX2), inducible nitric oxide synthase (iNOS), TNF-α, matrix metalloproteinase 9 (MMP9), caspase-3 and p38 mitogen-activated protein kinase (p38MAPK) (Dong et al. 2018).

Moreover, PTX attenuates the synthesis and release of TNF-α from alveolar macrophages (AMs) and monocytes with suppression expression of IL-2 receptor on the lymphocytes (Marques et al. 1999). Tong et al. observed that PTX reduces the release of cytokine release from lipopolysaccharide (LPS)-induced activated AMs in patients with sarcoidosis (Tong et al. 2003). In a vitro study, AMs were isolated from 14 patients with sarcoidosis, and cultured with PTX or dexamethasone; both PTX and dexamethasone produced similar effects (Tong et al. 2003). Therefore, PTX can replace dexamethasone in the management of sarcoidosis.

Furthermore, PTX inhibits activation and adhesion of T lymphocytes by inhibition of integrins induced by different intracellular signals (González-Amaro et al. 1998). However, PTX can restore the viability of T lymphocytes in hyper-inflammatory conditions (Park et al. 2020). Indeed, PTX has differential effects on the production of cytokines; it increases anti-inflammatory cytokines and reduces releases of pro-inflammatory cytokines (Marcinkiewicz et al. 2000). Similarly, PTX inhibits endotoxin-induced activation of nuclear factor kappa B (NF-κB) with reduction release of pro-inflammatory cytokines in rats through inhibition of A2R and PDE (Ji et al. 2004).

These verdicts suggest that PTX has noteworthy immunological and anti-inflammatory effects through modulation of immune cells and release of inflammatory cytokines (Fig. 2).

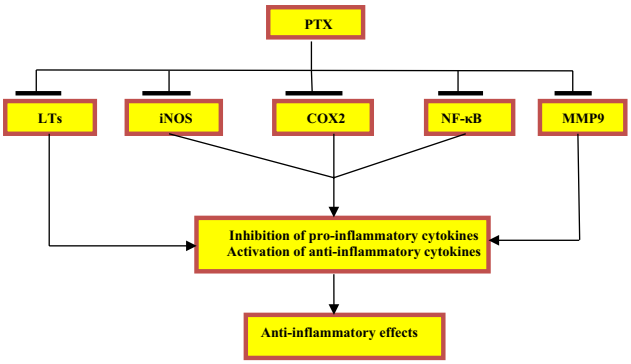

Fig. 2 Anti-inflammatory effects of pentoxifylline (PTX): PTX inhibits activation of leukotrienes (LTs), inducible nitric oxide synthase (iNOS), cyclooxygenase 2 (COX2), nuclear factor kappa B (NF-κB), and matrix metalloproteinase 9 (MMP9) leading to inhibition release of pro-inflammatory cytokines with activation of anti-inflammatory cytokines

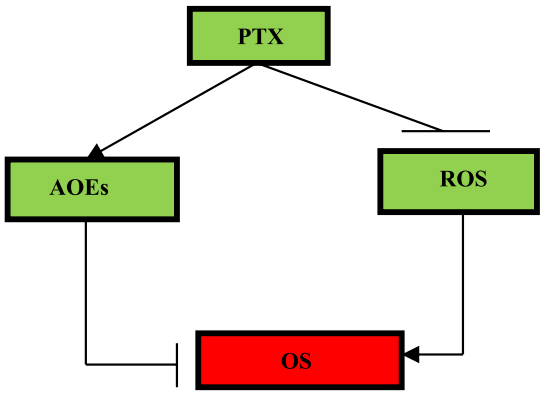

Fig. 3 Antioxidant effects of pentoxifylline (PTX): PTX inhibits the generation of reactive oxygen species (ROS) with activation of antioxidant enzymes (AOEs)

Antioxidant effects

PTX has antioxidant effects by scavenging free radicals and reactive oxygen species (ROS) in patients with cerebrovascular disorders (Horvath et al. 2002). Of interest, PTX had the ability to decrease radiation injury by antioxidant effect; it reduces the activity of myeloperoxidase and malondialdehyde (MDA), with increasing activity of glutathione (Hepgül et al. 2010). Noyan and colleagues demonstrated that PTX exerted an antioxidant effect against experimental short-bowel syndrome by reducing lipid peroxidation as evidenced by the reduction of MDA (Noyan et al. 2003).

Similarly, PTX attenuates oxidative stress-mediated renal injury in rats (Dávila-Esqueda and Martinez-Morales 2004). Moreover, PTX can reduce cardiac oxidative stress by increasing the activity of catalase and superoxide dismutase in rats (Mayyas et al. 2015). As well, PTX decreases oxidative stress in patients with non-alcoholic steatohepatitis (Satapathy et al. 2004). Of note, PTX improves sperm motility in patients with infertility by attenuation of oxidative stress (Oliva et al. 2009). These findings indicated that PTX has antioxidant effects by inhibiting ROS and induction of endogenous antioxidant capacity (Fig. 3).

Antiviral effects

PTX had been reported to be effective to inhibit replication of the Japanese encephalitis virus in a dose-dependent manner both in vitro and in vivo (Sebastian et al. 2009). PTX 100–200 mg/kg protects mice from a lethal dose of the Japanese encephalitis virus (Sebastian et al. 2009). It has been reported that PTX was effective against acute porcine

pneumonia with a reduction of cytokine-induced tissue injury (Myers et al. 2002).

As well, PTX is effective against human immune deficiency virus 1 (HIV-1) by reducing viremia with increasing CD4+ and modulation of inflammatory cytokines (Smith et al. 2007). In addition, PTX inhibits replication of HIV-1 through suppression of TNF-α-mediated long-term repeat-driven expression which is regarded as a vector for this virus (Smith et al. 2007). Therefore, PTX blocks the transduction and replication of HIV-1.

Moreover, PTX inhibits respiratory syncytial virus-induced expression of TNF-α mRNA and TNF-α release (Tao et al. 2001). Remarkably, PTX may increase the risk of enterovirus A71-induced encephalitis by reduction of IL-6, which inversely correlated with the duration of hospitalization in patients with different viral infections (Wang et al. 2017).

Therefore, PTX has broad-spectrum antiviral effects and can reduce associated inflammatory disorders by immunomodulatory effects.

Antithrombotic effects

It has been reported that PTX had antiplatelet and antithrombotic effects and could be an alternative therapy for thromboembolism and vascular vasospasm against ischemia (Bayraktar and Tanyeri-Bayraktar 2021). Similarly, PTX inhibits adenosine-induced platelet aggregation (Timchenko et al. 2019). De-Sanctis et al. (2002) showed that PTX was effective in treating retinal vein thrombosis as compared with placebo in patients with sudden vision loss. As well, PTX inhibits fibrinogen activation, generation of fibrin and platelet hyper-reactivity in patients with disseminated intravascular coagulopathy (DIC) (Ozden et al. 2019). PTX is effective against DIC and coagulopathy in patients with Kassabach–Merit syndrome (Abdul Hadi and Hisham 2011). Indeed, PTX improves the activity of fibrinolytic pathway locally, as PTX increases the activity of streptokinase against the formation of post-operative abdominal adhesions (Jafari-Sabet et al. 2015). Moreover, PTX prevents endotoxic-induced activation of coagulation and fibrinolytic disorders (Levi et al. 1994).

The underlying antithrombotic mechanism of PTX is related to inhibiting the production of fibrinogen and increasing the fibrinolytic pathway in patients with peripheral vascular diseases (Zhang et al. 2004). In addition, PTX attenuates the production and release of platelet-derived growth factors (PDGFs) which engaged with the increase of airway smooth reactivity, vascular smooth contraction, and platelet activation (Shi and Appiah-Kubi 2020). Besides, PTX inhibits platelet activation through increasing cAMP and prostacyclin (Zhang et al. 2004).

Furthermore, red blood cells (RBCs) are involved in thrombosis since quantitative and qualitative abnormalities of RBCs as thalassemia, sickle cell anemia, and polycythemia increase the risk of coagulopathy (Al-Kuraishy and Al-Gareeb 2017; Byrnes and Wolberg 2017). RBCs increase platelets margination with the enhancement of their interaction, accumulation, and adhesion at the subendothelial area (Byrnes and Wolberg 2017). As well, the release of ADP from injured RBCs promotes platelet aggregation by increasing the interaction with P-selectin (Byrnes and Wolberg 2017). Therefore, PTX through inhibition of blood viscosity and enhancement of RBCs deformability may inhibit RBCs induced coagulopathy.

These findings confirm the potential antithrombotic effect of PTX through modulation of coagulation pathway and inhibition of platelet aggregations (Fig. 4).

Anti-acute lung injury

ALI is a common complication in different viral infections including SARS-CoV-2 infection (Onohuean et al. 2021). It has been reported that PTX was effective against ALI in chronic endotoxemia as evident by reduction of intercellular adhesion molecule 1 (ICAM-1) and IL-6 in LPS-induced ALI in rats (Michetti et al. 2003). Sunil et al. demonstrated that PTX can reduce lung toxicity and nitrogen mustard-induced ALI by reduction of oxidative stress and release of pro-inflammatory cytokines as well as expression of COX2

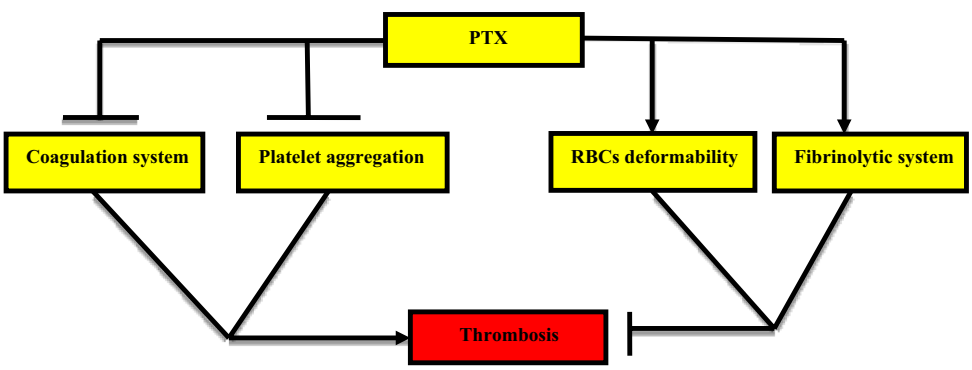

Fig. 4 Antithrombotic mechanism of pentoxifylline (PTX): PTX inhibits coagulation system and platelet aggregations, stimulates red blood cells (RBCs) deformability, and fibrinolytic pathway with subsequent inhibition of thrombosis

and MMP9 on the activated AMs (Sunil et al. 2014). Furthermore, PTX improves gas exchange and reduces lung inflammation in sepsis-induced ALI (Oliveira-Júnior et al. 2006).

The potential mechanism of PTX in the amelioration of ALI could be through modulation of inflammatory cytokines, reduction of oxidative stress and inhibition of ischemic-reperfusion injury (Pawlik et al. 2005). Thus, these observations pointed out that PTX is effective against ALI induced by toxins and chemicals and could be of benefit in the management of ALI.

Potential role of pentoxifylline in Covid-19

Effects on the inflammatory and oxidative burden

In Covid-19, exaggerated immune response and high release of pro-inflammatory cytokines mainly TNF-α and IL-6 are linked with the development of cytokine storm, ALI, ARDS and multi-organ injury (Al-Kuraishy et al. 2022a; b). Therefore, PTX could be effective against Covid-19-induced ALI and ARDS through inhibition of TNF-α and IL-6 (Hendry et al. 2020). As well, PTX attenuates ALI through inhibition of A2R which is linked with induction of inflammatory cascades during ALI (Effendi et al. 2020). Adenosine is released due to cell injury and serves as a mediator of inflammation during SARS-CoV-2 infection (Abouelkhair 2020). Therefore, targeting of the adenosinergic pathway in SARS-CoV-2 infection could reduce Covid-19 severity. Hendry and colleagues proposed that PTX through modulation of inflammatory cytokines and blood viscosity might be a therapeutic option in the management of Covid-19 (Hendry et al. 2020).

Furthermore, phosphodiesterase inhibitors like PTX inhibit the synthesis of leukotriene synthesis by neutrophils through increasing intracellular cAMP (Peters-Golden et al. 2005). Al-kuraishy et al. (2021b) revealed that the leukotriene pathway is activated in Covid-19 and linked with the development of pulmonary and extra-pulmonary complications. As well, PTX decreases the expression of COX2 in the pancreases of diabetic rats (Garcia et al. 2014). Similarly, COX2 is over-activated in Covid-19 causing induction and propagation of inflammatory reactions (Perricone et al. 2020). Thus, PTX could be effective against systemic complications induced by Covid-19 through modulation of the leukotriene pathway.

It has been shown that oxidative stress is augmented in Covid-19 due to the generation of ROS and reduction of endogenous antioxidant capacity leading to endothelial dysfunction (ED) and thrombosis (de Las Heras et al. 2020). Of note, PTX has a potent antioxidant effect (Noyan et al. 2003), therefore, could be effective against Covid-19-induced oxidative stress. Chavarria et al. illustrated that the antioxidant effect of PTX can improve outcomes in Covid-19 patients (Chavarría et al. 2021). A prospective study involved 110 Covid-19 patients treated with standard therapy in conjugation with PTX with several antioxidants showed that PTX added a potential benefit against Covid-19 severity as evident by reduction of IL-6 and c-reactive protein (CRP) (Chavarría et al. 2021).

Of note, sepsis induces neutrophil activation with subsequent release of ROS, and inhibition of nitric oxide (NO) causing an increase in adhesion molecules and platelet aggregation and/or coagulopathy (Kaur et al. 2018). Likewise, lung ischemia is developed due to oxidation caused by the over-activation of iNOS and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Mittal et al. 2014). Delgado-Roche and Mesta (2020) observed that oxidative stress plays a critical role in the induction of ALI/ARDS in SARS-CoV-2 infection through activation of iNOS. However, NO may reduce in severe Covid-19 due to reduction in the synthesis of NO by hypoxia or consumption of NO by ROS (Delgado-Roche and Mesta 2020). PTX can attenuate oxidative stress-induced renal injury by reducing the activity of NADPH oxidase (Ozturk et al. 2019). In addition, PTX reduces inflammatory reactions and oxidative stress by modulation activity of iNOS (de Oliveira Garcia et al. 2015). Therefore, PTX can attenuate SARS-CoV-2 infection-induced oxidative stress via the regulation of activated iNOS and NADPH oxidase.

Indeed, viral infections including SARS-CoV-2 infection-induced oxidative stress trigger the formation of oxidized phospholipids which activate toll-like receptor 4 (TLR4) and NF-κB leading to hyperinflammation-mediated ALI/ARDS (Monji et al. 2020). It was reported that PTX attenuated morphine-induced inflammation by inhibiting the activity of TLR4 in rats (Chehrei et al. 2017). Similarly, PTX mitigated endotoxin-induced release of pro-inflammatory cytokines through suppression of NF-κB activation (Ji et al. 2004). In addition, PTX through inhibition of AMs can inhibit the release of pro-inflammatory cytokines during the development of ALI/ARDS (Tong et al. 2003). Interestingly, the mechanistic target of rapamycin (mTOR) is involved in the induction of autophagy and viral replication including SARS-CoV-2, therefore, inhibition of mTOR might be of therapeutic value in the suppression of viral infection (Karam et al. 2021). It has been shown that PTX inhibits mTOR and autophagy (Hekmat et al. 2020).

Therefore, PTX through inhibition of TLR4, mTOR and NF-κB signaling pathway can reduce the interaction between oxidative stress and inflammatory reaction in Covid-19.

In SARS-CoV-2 infection, nod-like receptor pyrin 3 (NLRP3) inflammasome is activated leading to the activation release of IL-1β and IL-18 from activated macrophages. Activated NLRP3 inflammasome contributes in

the activation of other inflammatory signaling pathways causing the development of cytokine storm and tissue injury (Freeman and Swartz 2020). It has been shown that caffeine; PTX and other phosphodiesterase inhibitors inhibit the expression of NLRP3 inflammasome directly or indirectly by suppression of MAPK and NF-κB (Zhao et al. 2019). As well, oxidative stress and pro-inflammatory cytokines trigger activation and propagation of NLRP3 inflammasome activity in patients with cardiovascular complications (Sharma et al. 2018). In virtue of it antioxidant and anti-inflammatory effects, PTX could be effective against Covid-19 severity through inhibition of NLRP3 inflammasome.

A pilot study comprised 38 patients with severe Covid-19 to study the potential effect of PTX on lymphocyte count and lactate dehydrogenase (LDH) showed that PTX reduced LDH by 29.61% (95% CI 15.11–44.10) and increased in lymphocyte count by 64.25% (95% CI 15.11–83–116.68) (Maldonado et al. 2021). High LDH serum level indicates tissue damage and is correlated with the severity of ALI in SARS-CoV-2 infection (Xiong et al. 2020). Similarly, lymphopenia is regarded as an independent biomarker of Covid-19 severity (Seyit et al. 2021). Monji et al. (2020) observed that PTX therapy could be an effective agent against Covid-19 severity through the improvement of microcirculation and tissue oxygenation by reducing inflammatory/oxidative burden and blood viscosity. Therefore, reduction of LDH serum level and elevation of lymphocyte count following PTX therapy in Covid-19 indicates a promising therapeutic role of PTX against Covid-19 severity.

These findings suggest that PTX could be effective against Covid-19 through modulation of inflammatory and oxidative burden.

Effects on the renin–angiotensin system

Renin–angiotensin system (RAS) has been shown to be dysregulated in Covid-19 due to down-regulation of ACE2 which is necessary for the conversion of vasoconstrictor and pro-inflammatory AngII to vasodilator and anti-inflammatory Ang1-7 (Al-Kuraishy et al. 2020). High circulating AngII level is linked with the development of ALI/ARDS, ED, oxidative stress and release of pro-inflammatory cytokines (Sfera et al. 2020). Therefore, AngII receptor blockers (ARBs) have been shown to be protective against Covid-19 severity through inhibition of vasoconstrictor AngII receptor type 1 (AT1R) (Lopes et al. 2021).

It was reported that PTX inhibits the expression of AT1R without a significant effect on blood pressure (Brie et al. 2016). In clinical trials, PTX had been shown to improve the effect of ARBs in patients with diabetic nephropathy through modulation the effect of AngII (Navarro et al. 2005). In addition, experimental studies demonstrated that PTX inhibits the expression of AT1R mRNA (Guggilam et al. 2008). Navarro et al. demonstrated that PTX modulates the expression of renal ACE through inhibition of pro-inflammatory cytokines in rats (Navarro et al. 2006). Moreover, PTX may attenuate the development of hypertension through the modulation of RAS in rats with induced metabolic syndrome (Azhar and El-Bassossy 2015). In addition, PTX decreases cardiac fibrosis and inflammation in AngII-induced hypertension in rats (Zhang et al. 2016).

Depending on these findings, PTX could be effective against AngII-mediated complications in Covid-19.

Effects on blood viscosity and coagulopathy

It has been shown that blood viscosity and RBC aggregation are increased in Covid-19 patients and linked with risk of thrombosis and life-threatening complications (Nader et al. 2021). A cohort study involved 172 hospitalized Covid-19 patients compared with 38 healthy controls revealed that Covid-19 patients had higher blood viscosity despite of low hematocrit with exaggerated RBC aggregation (Nader et al. 2021). As well, hyper-aggregation of RBCs correlated with thrombosis and extensive lung lesion, and poor clinical outcomes in Covid-19 patients (Nader et al. 2021). Similarly, reduction of RBCs deformability due to structural changes in RBC membrane was confirmed in Covid-19 patients as evidenced by the increased level of schistocytes (Kubánková et al. 2021).

Furthermore, SARS-CoV-2 infection is associated with systemic and pulmonary microthrombosis leading to pulmonary dysfunction and development of ALI/ARDS (Suh et al. 2021). SARS-CoV-2 infection-induced thrombosis is reported to cause acute myocardial injury in about 20% and acute ischemic stroke up to 5% in hospitalized patients (Suh et al. 2021). Down-regulation of ACE2, ED, inflammatory and oxidative stress disorders with platelet hyper-activation could be the possible mechanisms of thrombosis in Covid-19 (Gomez-Mesa et al. 2021). Besides, platelet hyper-activation in SARS-CoV-2 infection contribute to increase factor XII and von Willebrand factor with subsequent spread of procoagulant and pro-inflammatory activities in systemic circulation (Taus et al. 2020).

Of note, PTX has the ability to reduce blood viscosity and coagulopathy by increasing RBCs deformability and inhibition of platelet reactivity respectively (Rasyid et al. 2018; Ozden et al. 2019). Therefore, PTX could be a possible therapeutic modality against Covid-19-induced hyperviscosity and coagulopathy.

Taken together, in virtue of its anti-inflammatory, antioxidant and antithrombotic effects, PTX could be the possible drug in the management of Covid-19 (Fig. 5).

The present review had several limitations including the rareness of clinical studies regarding the role of PTX in Covid-19 and most of the beneficial effects in Covid-19

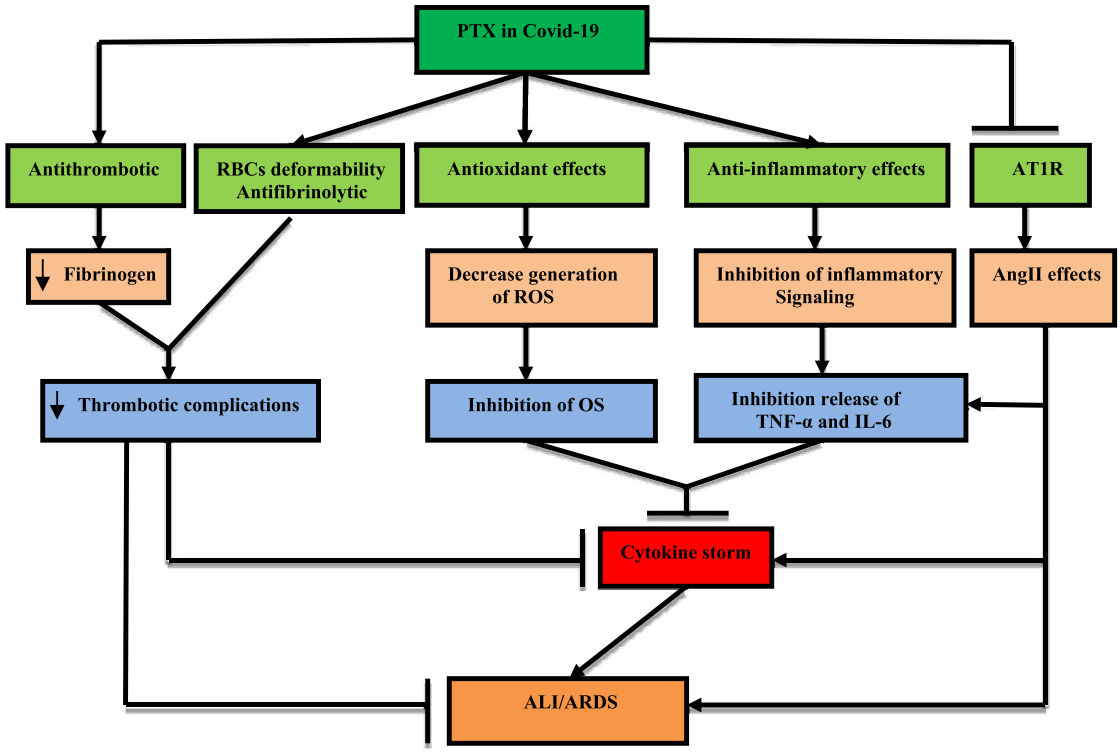

Fig. 5 Role of pentoxifylline (PTX) in Covid-19: PTX inhibits expression of angiotensin 1 receptor (AT1R) with reduction of angiotensin II (AngII)-mediated progression of cytokine storm and development of acute lung injury (ALI)/acute respiratory distress syndrome (ARDS): PTX antioxidant effect reduces the generation of reactive oxygen species (ROS) and the development of oxidative stress (OS). PTX anti-inflammatory effects inhibit release of IL-6 and tumor necrosis factor alpha (TNF-α). PTX through inhibition of fibrinogen, activation of antifibrinolytic and RBCs deformability inhibits thrombosis

were speculative. However, this review highlighted the most important effects of PTX in Covid-19. This review recommends future studies to confirm the possible role of PTX in the management of Covid-19.

Anti-SARS-CoV-2 activity of pentoxifylline

The anti-SARS-CoV-2 activity of PTX has not been evaluated and tested in both in vitro and vivo studies, though its activity was tested against various viral infections (Assimakopoulos et al. 2020). As SARS-CoV-2 infection continues to cause global upheaval, researchers, and scientists are in racing and competing to find and discover optimal animal models to study Covid-19 pathogenesis. Of note, SARS-CoV-2 transmission between ferrets and cats could be an integral animal model for SARS-CoV-2 transmission (Lakdawala and Menachery 2020). However, aged and young cynomolgus macaques infected with SARS-CoV-2 failed to develop clinical symptoms of Covid-19 despite of prolong shedding of this virus in the upper and lower respiratory tract. Thus, these animal models show distinct forms regarding SARS-CoV-2 transmission and development of Covid-19 (Lakdawala and Menachery 2020). The main obstacle in for induction of mouse SARS-CoV-2 infection is the lack of suitable receptors to recruit viral infection since mouse ACE2 does not sufficiently bind SARS-CoV-2 spike protein (Wan et al. 2020). As different models for SARS-CoV-2 infection are under investigations and testing phase and some biotech companies bypassed animal model studies and gone to phase I clinical trials. In this state, bypassing of animal studies for testing novel or repurposed drugs in SARS-CoV-2 infection may reduce our knowledge about human clinical outcomes (Deb et al. 2020). Notably, SARS-CoV-2 has high genomic similarity with SARS-CoV (Al-Kuraishy and Al-Gareeb 2021) and PTX was found to be ineffective against replication of SARS-CoV in mice (Hendry et al. 2020). Despites of these limitations, K18-hACE2 transgenic mice that were initially developed for SARS studies are used in a recent study to evaluate therapeutic intervention in treating Covid-19 (Zheng et al. 2021).

Conclusion

PTX is a non-selective phosphodiesterase drug, has anti-inflammatory and antioxidant effects thereby can reduce SARS-CoV-2 infection-hyperinflammation and oxidative

stress. Besides, PTX improves RBCs deformability and reduces blood viscosity so can mitigate Covid-19-induced hyper-viscosity and RBC hyper-aggregation which is linked with the development of coagulopathy. Taken together, PTX seems to be an effective agent against Covid-19 severity. Further preclinical and clinical studies are warranted to confirm these effects in this regard.

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Data availability Not applicable.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical statement This article does not contain any studies with human participants or animals performed by any of the authors.

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