REVIEW

Fenofibrate for COVID-19 and related complications as an approach to improve treatment outcomes: the missed key for Holy Grail

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Abstract

Introduction Fenofibrate is an agonist of peroxisome proliferator activated receptor alpha (PPAR-α), that possesses anti-inflammatory, antioxidant, and anti-thrombotic properties. Fenofibrate is effective against a variety of viral infections and different inflammatory disorders. Therefore, the aim of critical review was to overview the potential role of fenofibrate in the pathogenesis of SARS-CoV-2 and related complications.

Results By destabilizing SARS-CoV-2 spike protein and preventing it from binding angiotensin-converting enzyme 2 (ACE2), a receptor for SARS-CoV-2 entry, fenofibrate can reduce SARS-CoV-2 entry in human cells Fenofibrate also suppresses inflammatory signaling pathways, which decreases SARS-CoV-2 infection-related inflammatory alterations. In conclusion, fenofibrate anti-inflammatory, antioxidant, and antithrombotic capabilities may help to minimize the inflammatory and thrombotic consequences associated with SARSCoV-2 infection. Through attenuating the interaction between SARS-CoV-2 and ACE2, fenofibrate can directly reduce the risk of SARS-CoV-2 infection.

Conclusions As a result, fenofibrate could be a potential treatment approach for COVID-19 control.

Keywords Fenofibrate · COVID-19 · SARS-CoV-2 · Angiotensin-converting enzyme 2

Introduction

Fenofibrate, a phenoxy-isobutyric acid derivative (Fig. 1), is metabolized to fenofibric acid, an active metabolite that activates the peroxisome proliferator-activated receptor alpha (PPAR-α) [1].

Fenofibrate stimulates lipoprotein lipase (LP) through activating PPAR-α and inhibiting apoprotein C-III, which inhibits LP activity [1]. Furthermore, fenofibrate causes lipolysis and lowers triglycerides by converting small low-density lipoprotein (LDL) particles into large particles with a higher affinity for cholesterol receptors, resulting in rapid catabolism of these large particles. The expression

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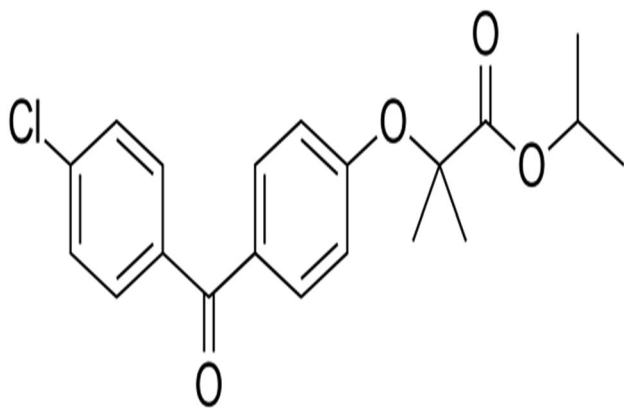
Fig. 1 Chemical structure of fenofibrate

of apolipoprotein A-I, A-II, and high-density lipoprotein (HDL) increases when PPAR-α is activated [1, 2]. Overall, fenofibrate lowers cholesterol, triglycerides, LDL, VLDL, and apoprotein B while increasing HDL levels.

In 1974, fenofibrate was synthesized for the first time, and it was first used in medicine in 1975 in France [3]. It can improve glycemic indices in patients with type 2 diabetes mellitus (T2DM) by improving fasting chylomicronemia [4]. It is also used to treat hypertriglyceridemia and mixed dyslipidemia. In T2DM patients, it also lowers diabetic retinopathy and microvascular problems [4]. Fenofibrate also lowers serum uric acid and is used as a supplementary in the treatment of gout [5]. Rhabdomyolysis, pancreatitis, gallstones, and toxic epidermal necrolysis are the most prevalent side effects of fenofibrate [6]. Fenofibrate additionally exhibits pleiotropic effects, such as anti-inflammatory, antioxidant, anti-atherogenic, and antiviral characteristics [7]. As a result, the aim of this critical review was to give an overview of the possible function of fenofibrate in the pathogenesis of SARS-CoV-2 and its consequences.

Fenofibrate and viral infections

Fenofibrate has antiviral activity, and it has been shown to be effective and reduce mortality in a mouse model of Japanese encephalitis [8]. Fenofibrate reduced mortality in mice with Japanese encephalitis by 80% by inhibiting viral-induced microglial activation and the release of pro-inflammatory cytokines [14].

Similarly, fibrate suppresses influenza virus replication and could be an effective antiviral medication alone or in conjunction with antivirals in the scenario of an influenza pandemic [9]. Fenofibrate 45 mg/kg was found to be effective in lowering induced influenza A virus infection in mice, with a 30% reduction in mortality when compared to simvastatin, which had no effect on infection outcome [9]. In HIV-positive patients with hypertriglyceridemia, fenofibrate also

inhibits lipid oxidation [10]. Fenofibrate and other PPAR-agonists have been shown to reduce the risk of HIV-1 brain infection by reducing the breakdown of the blood–brain barrier (BBB) caused by elevated matrix metalloproteinase (MMP) levels in HIV-1 infection [11]. Interestingly, PPAR-α inhibits HIV-1-induced neuroinflammation by inhibiting the pro-inflammatory response [12].

In addition, fenofibrate reduces release of hepatitis E virus (HEV) via raising intracellular cholesterol, with subsequent enhancement of lysosomal degradation [13]. Statins, which lower intracellular cholesterol, increase HEV release and infectivity [13]. Activation of PPAR-α, on the other hand, promotes herpes virus replication, suppresses interferon type I production, and causes the creation of reactive oxygen species (ROS) [15]. Following activation of the stimulator of interferon, the activated PPAR-α suppresses the cytoplasmic sensing pathway, impairing the immunological response to herpes virus infection [15]. Herpes virus can also boost PPAR-α expression by encoding a protein that targets these receptors [16]. These findings imply that PPAR-α agonists like fenofibrate suppress the immune system and may increase the risk of herpes virus infection. As a result, there are various debates on whether fenofibrate's antiviral activity is beneficial or harmful.

Fenofibrate and anti-inflammatory effects

It has been reported that fenofibrate has anti-inflammatory effects through inhibition expression of induced nitric oxide synthase (iNOS), cyclooxygenase 2 (COX2), and matrix metalloproteinase 9 (MMP9) in experiment rats with traumatic brain injury [17]. Fenofibrate reduces the level of inflammatory biomarkers including C-reactive protein (CRP), soluble CD40, IL-6, and monocyte chemoattractant protein 1(MCP-1) independent of changes in lipid profiles [18]. As well, fenofibrate has anti-thrombotic effects by decreasing thrombin-anti-thrombin complex and generated thrombin at site of vascular injury [18]. Fenofibrate promotes anti-inflammatory actions in patients with metabolic syndrome by inducing anti-inflammatory adiponectin, according to a clinical trial involving 50 patients with dyslipidemia treated with the drug [19].

The anti-inflammatory effects of PPAR-α agonists are through induction of an inhibitory protein called inhibitory kappa B (IκB) which inhibits nuclear factor kappa B (NF-κB) [20]. Therefore, fenofibrate through activation of PPAR-α blocks NF-κB-mediated releases of tumor necrosis factor alpha (TNF-α) [21]. Fenofibrate also reduces TNF-expression and release via an adiponectin-dependent mechanism [22]. Fenofibrate improves endothelial dysfunction (ED) in patients with dyslipidemia by stimulating the release of adiponectin, according to Koh et al. [22]. Fenofibrate

does, in fact, increase the expression of the anti-inflammatory cytokine IL-10 [23].

Of interest, fenofibrate stimulates PPAR-α in immune cells such as macrophages and lymphocytes, causing the release of IL-10 to be stimulated while IL-17 and interferon gamma (INF-γ) are suppressed [24]. Moreover, fenofibrate also suppresses the expression of the chemokines CCL20, CXCL10, and CCL2 [24]. In virtue of its anti-inflammatory effects, fenofibrate is effective against aggressive rheumatoid arthritis in rats [25]. Likewise, a previous pilot study demonstrated that fenofibrate was effective in the management of erosive osteoarthritis through inhibition of pro-inflammatory cytokines and adipokines [26]. Furthermore, fenofibrate plays a critical role in resolution of neuroinflammation through modulation of pro-inflammatory cytokines and oxylipins from activated astrocytes [27]. These observations indicated that fenofibrate has potent anti-inflammatory effects and could be effective in different inflammatory disorders (Fig. 2).

Fenofibrate and COVID-19

The existing coronavirus 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has sparked a worldwide pandemic [28]. Uninterrupted SARS-CoV-2 cytopathic injury and release of pro-inflammatory cytokines can induce development of acute respiratory distress syndrome (ARDS) [29]. Due to high expression of angiotensin-converting enzyme 2 (ACE2), a receptor for SARS-CoV-2 entrance, SARS-CoV-2
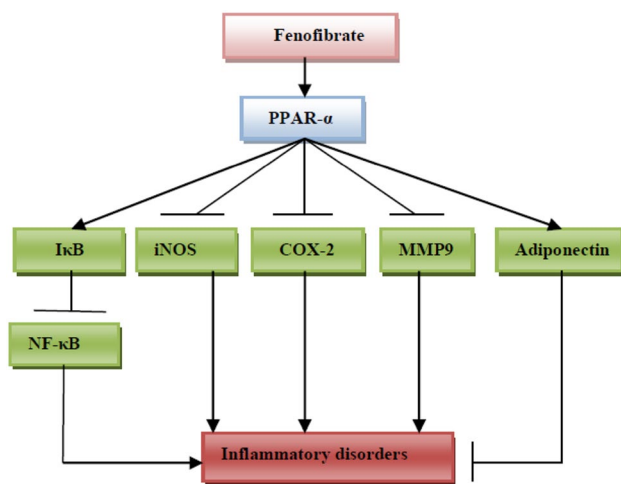

Fig. 2 Anti-inflammatory effects of fenofibrate: fenofibrate, through activation of peroxisome proliferator-activated receptor alpha (PPAR-α), inhibits inducible nitric oxide synthase (iNOS), cyclooxygenase 2 (COX2), matrix metalloproteinase 9 (MMP9), and activates release of adiponectin and inhibitory kappa B (IκB), causing a reduction of inflammatory disorders

preferentially damages lung alveolar type II pneumocyte cells in COVID-19 [30]. The majority of COVID-19 patients are asymptomatic or have only minor respiratory symptoms. Despite this, a small percentage of COVID-19 patients experienced severe respiratory problems as a result of the progression of acute lung injury (ALI) and/or ARDS [31].

Hyperinflammation and the development of a cytokine storm as a result of an excessive immune response against SARS-CoV-2 are the main causes of COVID-19-induced complications [32]. As a result, anti-inflammatory and immunosuppressive drugs may be effective in the treatment of SARS-CoV-2-induced immunological dysregulation and over-activation [33, 34]. Fenofibrate's anti-inflammatory and immuno-regulatory properties may actually be useful in the battle against SARS-CoV-2 infection.

Various in vitro investigations conducted during the COVID-19 era revealed that fenofibrate was beneficial against SARS-CoV-2 infection. Fenofibrate, by destabilizing SARS-CoV-2 spike protein and preventing it from binding ACE2, can lower SARS-CoV-2 in human cells by 70%. Fenofibrate also prevents the accumulation of sphingolipid, which is required for SARS-CoV-2 replication [35, 36]. Fenofibrate, but not fenofibric acid, inhibits ACE2 dimerization and prevents it from engaging the SARS-CoV-2 receptor binding domain in an in vitro investigation [37]. Buschard discovered that the glycosphingolipid sulfatide (3-O-sulfogalactosylceramide), a key component of sphingomyelin, inhibits viral entry across the cell membrane, including SARS-CoV-2 [38]. Sulfatide levels were shown to be low in hypertension and metabolic syndrome patients, but greater in children [39, 40]. Fenofibrate increases sulfatide glycosphingolipid levels, which may reduce SARS-CoV-2 infectivity [38]. Since vitamin K stimulates sulfatide biosynthesis in the brain, the vitamin K antagonist warfarin impairs brain sulfatide [41]. Sulfatide, on the other hand, may have a role in the pathogenesis of autoimmunity by acting as a possible ligand for L and P-selectin and up-regulating the expression of chemokine co-receptors (CXCR4) on neutrophils [42]. In an experimental investigation, sulfatide stimulates the replication of influenza A virus and hepatitis C virus (HCV) [43, 44]. As a result, the role of fenofibrate-mediated sulfatide in the prevention of SARS-CoV-2 should be reconsidered.

Of interest, SARS-CoV-2 triggers expression of cholesterol and lipogenesis in bronchial epithelial cells causing lipotoxicity [45]. Therefore, lipid-lowering activity of fenofibrate can inhibit accumulation of lipid in bronchial epithelial cells and associated inflammation [46]. Remarkably, PPAR-α is highly expressed in alveolar epithelial cells of the lung which conducted in fatty acid oxidation and promoting pulmonary function [47]. It has been shown that expression of alveolar PPAR-α was reduced by 60% in response to lung inflammation and high circulating TNF-α with subsequent

disruption of alveolar fatty acid oxidation [48]. Delayer-Orthez et al. reported that mice with deficiency of PPAR-α were susceptible for severe pulmonary inflammation in response to lipopolysaccharide (LPS)-induced inflammation [49]. Therefore, reduction in the expression of PPAR-α may increase for development of pulmonary inflammation and ALI/ARDS in COVID-19 [47].

PPAR-α also controls endothelial function, namely the fate of progenitor cells and colony-forming cells [50]. Disruption of endothelial function by SARS-CoV-2 with production of endothelial dysfunction (ED) may diminish PPAR-α expression in endothelial cells, leading to the establishment of a cytokine storm [51]. In COVID-19, these alterations impair pulmonary vascular responsiveness, resulting in a disruption of the alveolar–capillary barrier, contributing in ventilation–perfusion mismatches and hypoxemia [52]. Furthermore, SARS-CoV-2 can cause ED by inducing apoptosis in endothelial cells, lowering anti-thrombotic activity and causing diffuse pulmonary microthrombosis [53]. As a result, SARS-CoV-2-induced ED impairs expression of endothelial PPA-α with the spread of systemic inflammation. As a result, PPAR-α agonists such as fenofibrate may be beneficial against COVID-19 by reducing ED and pulmonary inflammation while also diminishing metabolic disorders.

Mechanism of fenofibrate against COVID-19

SARS-CoV-2 infection triggers activation of toll-like receptor 4 (TLR4) with release of pro-inflammatory cytokines such as TNF-α and IL-6 mainly in patients with cardio-metabolic disorders [54]. Activation of TLR4 induces activation of NF-κB and release of pro-inflammatory cytokines [54]. Over-activation of TLR4 attenuates expression of PPAR-α with intensification release of pro-inflammatory cytokines [55]. Of interest, oleoylethanolamide, a bioactive lipid, stimulates PPAR-α which initiates a cascade of events which decreases the inflammatory response and reactions [56].

TLR4/NF-κB axis is highly activated in SARS-CoV-2 infection and linked with development of hyperinflammation, cytokine storm, and multi-organ injury [57]. In LPS-stimulated vascular smooth muscle cells, fenofibrate suppresses TLR4 expression while increasing PPAR-α activity [58]. Furthermore, fenofibrate inhibits NF-κB expression and thereby protects the outer blood retinal barrier [59]. In recent studies, activation of the TLR4/NF-κB axis has been linked to lung inflammation and ALI [60]. As a result, fenofibrate may be beneficial against ALI through modulating the TLR4/NF-κB axis. Fenofibrate, according to Zhuo et al., can attenuate ALI in mice caused by intestinal ischemia by ameliorating intestinal and lung damage through anti-ischemic, anti-inflammatory, and antioxidant characteristics [61]. These findings suggested that fenofibrate could be a

virtuous candidate for treating COVID-19 patients who have hyperinflammation and are at high risk of developing ALI.

Indeed, SARS-CoV-2 infection triggers activation of nod-like receptor pyrin 3 (NLRP3) inflammasome with subsequent stimulation of immune cells, TLR4/NF-κB axis and pro-inflammatory cytokine release [62]. These changes linked NLRP3 inflammasome activation with development of cytokine storm and sever systemic inflammation. Thus, inhibitors of NLRP3 inflammasome could be beneficial against immune over-activation-induced hyperinflammation and development of cytokine storm in COVID-19 [62]. Of note, fenofibrate had ability to mitigate diabetic retinopathy by inhibiting activation of NLRP3 inflammasome in mice with experimental diabetes [63]. In a similar way, Liu et al. illustrated that fenofibrate enhances expression of nuclear erythroid-related factor 2 (Nrf2) which is the main regulator of oxidative defense, by which it decreases the risk of oxidative stress-induced neuroinflammation and retinal injury [63]. Nrf2 is activated by oxidative stress and plays a critical role in the regulation of oxidative stress and inflammation by antioxidant and anti-inflammatory properties [64]. Nrf2 is inhibited during SARS-CoV-2 infection leading to oxidative and inflammatory disorders [64]. Taken together, fenofibrate through inhibition of NLRP3 inflammasome and activation of Nrf2 may reduce the oxidative and inflammatory disorders in COVID-19.

Furthermore, in SARS-CoV-2 infection, activation of the inflammatory p38 mitogen-activated protein kinase (p38MAPK) signaling pathway is associated with viral replication, ALI, and severe cardiac damage [65]. SARS-CoV-2 infection can induce overexpression of p38MAPK, resulting in ED, vasoconstriction, and thrombosis [65]. In COVID-19, p38MAPK inhibitors are trialed in patients with severe SARS-CoV-2 infection. Concerning the potential effect of fenofibrate on the expression of p38MAPK, Hou et al. demonstrated that PPAR-α agonists like fenofibrate had nephroprotective effect in hypertensive rats via suppression the activity of p38MAPK [66]. Likewise, fenofibrate decreases cardiovascular-associated inflammatory changes by modulation the effect of activated T cells in releasing pro-inflammatory cytokines through inhibition of p38MAPK [67]. In this sense, fenofibrate through suppression of activated p38MAPK could be beneficial against SARS-CoV-2 infection by inhibiting p38MAPK-dependent inflammatory disorders.

Likewise, mechanistic target of rapamycin (mTOR) which is member of protein kinases senses cellular regulatory signals to control autophagy, organelle biogenesis, and expression of inflammatory genes [68]. As well, mTOR pathway is triggered during SARS-CoV-2 infection for transcription and translation of SARS-CoV-2 mRNA [69]. Inhibition of mTOR signaling pathway may reduce viral replication and might be a latent therapeutic option against COVID-19

[69]. It has been shown that fenofibrate inhibits activated mTOR pathway with induction of apoptosis of cancer cells in human prostate [70]. Similarly, fenofibrate can attenuate cardiac hypertrophy via inhibition of mTOR pathway [71]. Taken together, fenofibrate through inhibition of mTOR pathway may decrease severity of SARS-CoV-2 infection.

Furthermore, advanced glycation end product (AGE) is intricate in the pathogenies of SARS-CoV-2 infection; however, soluble RAGE (sRAGE) reflects the underlying AGE in COVID-19 [71]. Lim and colleagues reported that sRAGE serum level is regarded as a biomarker and indicator for COVID-19 severity, mortality, and the need for assist ventilation [72]. An observational-cohort study comprised 164 COVID-19 patients revealed that sRAGE serum level was increased in patients with COVID-19 pneumonia and correlated with disease severity [72]. Suppression formation of AGE in COVID-19 may attenuate the pathogenesis of SARS-CoV-2 infection and associated inflammations. Interestingly, fenofibrate inhibits activity of polyol pathway with subsequent reduction of AGE, oxidative stress, and release of inflammatory cytokines [73]. Fenofibrate also suppress activity of vascular endothelial growth factor (VEGF) in patients with diabetic retinopathy [73]. VEGF is regarded as key factor in the development of ALI and ARDS through induction of vascular permeability. VEGF serum levels were illustrated to be higher in patients with severe COVID-19 compared with the mild one [74, 75]. SARS-CoV-2 infection-induced down-regulation of ACE2 is considered as the main cause for overexpression of VEGF. Thus, fenofibrate can decrease COVID-19 severity via inhibiting the activity of AGE and VEGF.

In addition, lipid-lowering drug statins have pleiotropic effects; however, its outcome on the circulating adiponectin was contentious, and diverse studies accuse statins of decreasing the adiponectin level [76, 77]. Nevertheless, a meta-analysis demonstrated that statins increase adiponectin level through intonation of inflammatory cytokines [77]. Into the bargain, fenofibrate improves circulating adiponectin which has potent anti-inflammatory effects [22]. Of note, ACE2 has perilous role in the regulation of adiponectin production; ACE2 and Ang1-7 reduce epicardial adipose tissue-mediated inflammation via up-regulation expression of adiponectin [78]. As well, fosinopril attenuates liver fibrosis by up-regulating adiponectin through ACE2/Ang1-7 expression [78, 79]. Therefore; dysregulation of renin–angiotensin system (RAS) in COVID-19 could be the possible cause of low adiponectin level. Therefore, fenofibrate through induction production and release of adiponectin could explain its beneficial effect against SARS-CoV-2.

Fascinatingly, fenofibrate improves ED by suppressing production of endothelin-1 (ET-1), increases synthesis of endothelial NO production and inhibition of vascular inflammation [80]. Fenofibrate increases synthesis of tetrahydrobiopterin which is necessary for activation of eNOS and NO production with regulation of vascular reactivity [81]. Besides, ED is regarded as a hallmark of COVID-19 and mainly predominates in the SARS-CoV-2 infection. ED is associated with thrombosis, ALI/ARDS, and multi-organ injury [82]. Lee et al. reported that fenofibrate had anti-platelet and anti-thrombotic properties. The anti-platelet effect is mediated by inhibition of thromboxane A2, COX1, and mobilization of cytosolic calcium [83]. As well, fenofibrate reduces thrombin-activatable fibrinolysis inhibitor thereby decreasing the risk of thrombosis in patients with metabolic syndrome [84]. Thrombosis and platelet hyper-activation are linked with COVID-19 severity [85]. Therefore, fenofibrate through modulation of ED, thrombosis, and platelet hyper-activation can reduce COVID-19 severity.

Overall, fenofibrate seems to be of a great benefit against pathogenesis of SARS-CoV-2 infection and COVID-19 severity by its anti-inflammatory, antioxidant, and anti-thrombotic activities (Fig. 3).

Moreover, Feher et al. illustrated that fenofibrate inhibits replication of SARS-CoV-2 in human lung epithelial cells [86]. As well, fenofibrate attenuates SARS-CoV-2-induced up-regulation of lipogenesis and glycolysis with subsequent suppression of metabolic footprint for viral replication [87]. However, the other drugs such as metformin, rosiglitazone, and empagliflozin which have impacts on the lipogenesis and glycolysis did not affect viral replications [87]. Furthermore, laboratory findings have been suggested as modes of action of fenofibrate against SARS-CoV-2 infection [87]. A cohort-observational study involved 477,803 COVID-19 patients; 596 on fenofibrate therapy for at least 3 months compared to 2980 on non-fibrate therapy showed that there was no difference in 28-day mortality and survival rate [86]. These findings suggest that in vitro positive effects of fenofibrate are not correlated with in vivo effects. Thus, randomized clinical trials are recommended to confirm the modifying effect of fenofibrate on the pathogenesis of SARS-CoV-2 infection and clinical outcomes in COVID-19 patients.

Concerning the risk of drug-drug interactions between fenofibrate and drugs used in the management of COVID-19, fenofibrate interacts with several drugs like statins, bile acid sequestrants, cyclosporine, and warfarin [88]. Interestingly, there is no significant interaction between fenofibrate and remdesivir, which is commonly used in the management of severely affected COVID-19 patients [89]. Thus, fenofibrate seems to be an active drug together with anti-SARS-CoV-2 agents in the management of COVID-19.

The present review had several limitations, including the scarcity of clinical and preclinical studies concerning the role of fenofibrate in the management of COVID-19. However, this critical review discusses the potential role of the

Fig. 3 Mechanism of fenofibrate against SARS-CoV-2 infection: SARS-CoV-2 induces activation of signaling pathways including toll-like receptor 4 (TLR4), nuclear factor kappa B (NF-κB), mechanistic target of rapamycin (mTOR), nod-like receptor pyrin 3 (NLRP3) inflammasome, advanced glycation end product (AGE), p38 mitogen-activated protein kinase (p38MAPK), and vascular endothelial growth factor (VEGF) with subsequent development of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)
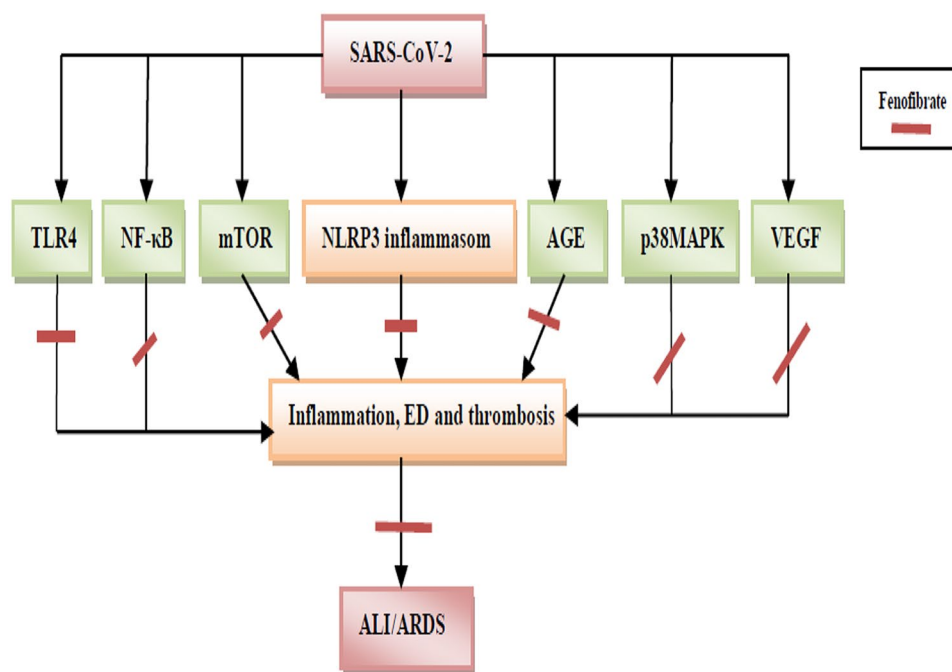
anti-inflammatory, antioxidant, and anti-thrombotic properties of fenofibrate against COVID-19.

Conclusion

Fenofibrate is a PPAR-α agonist that has anti-inflammatory, antioxidant, and anti-thrombotic properties through modulation of inflammatory signaling pathway, oxidative stress, and platelet activation. Fenofibrate through these properties may reduce SARS-CoV-2 infection-associated inflammatory and thrombotic complications. It can directly reduce the risk of SARS-CoV-2 infection through attenuation of the interaction between SARS-CoV-2 and ACE2. Therefore, fenofibrate could be a novel therapeutic option in the management of COVID-19. Thus, experimental, preclinical, and clinical studies are recommended to confirm the possible role of fenofibrate against COVID-19.

Declarations

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