



The role of berberine in Covid-19: potential adjunct therapy

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Abstract

Coronavirus disease 2019 (Covid-19) is a global diastrophic disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Covid-19 leads to inflammatory, immunological, and oxidative changes, by which SARS-CoV-2 leads to endothelial dysfunction (ED), acute lung injury (ALI), acute respiratory distress syndrome (ARDS), and multi-organ failure (MOF). Despite evidence illustrating that some drugs and vaccines effectively manage and prevent Covid-19, complementary herbal medicines are urgently needed to control this pandemic disease. One of the most used herbal medicines is berberine (BBR), which has anti-inflammatory, antioxidant, antiviral, and immune-regulatory effects; thus, BBR may be a prospective candidate against SARS-CoV-2 infection. This review found that BBR has anti-SARS-CoV-2 effects with mitigation of associated inflammatory changes. BBR also reduces the risk of ALI/ARDS in Covid-19 patients by inhibiting the release of pro-inflammatory cytokines and inflammatory signaling pathways. In conclusion, BBR has potent anti-inflammatory, antioxidant, and antiviral effects. Therefore, it can be utilized as a possible anti-SARS-CoV-2 agent. BBR inhibits the proliferation of SARS-CoV-2 and attenuates the associated inflammatory disorders linked by the activation of inflammatory signaling pathways. Indeed, BBR can alleviate ALI/ARDS in patients with severe Covid-19. In this sense, clinical trials and prospective studies are suggested to illustrate the potential role of BBR in treating Covid-19.

Keywords Covid-19 · Inflammatory signaling pathways · Anti-inflammatory · Antioxidant · Antiviral · Immune-regulatory effects

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Background

The current coronavirus disease, SARS-CoV-2, is caused by a novel coronavirus and has global diastrophic effects (Al-Kuraishy et al. 2021a, b, c). Acute respiratory distress syndrome (ARDS) may result from direct SARS-CoV-2 cytopathic damage and the release of pro-inflammatory cytokines (Al-kuraishy et al. 2022). SARS-CoV-2 primarily infects lung alveolar type II pneumocyte cells due to greater expression of angiotensin-converting enzyme 2 (ACE2), a receptor for SARS-CoV-2 binding and entrance (Biswas, Mahmud et al. 2021). Most Covid-19 patients are asymptomatic or have mild respiratory symptoms. However, a small percentage of Covid-19 patients may suffer severe respiratory symptoms because of the development of acute lung injury (ALI) and/or ARDS. SARS-CoV-2 could cause endothelial dysfunction (ED) either directly or indirectly via elevated pro-inflammatory cytokines (Lugnier et al. 2021). Similarly, during SARS-CoV-2 infection, oxidative stress (OS) is generated, leading to ED. Oxidative stress has been found to cause tissue harm during many viral infections, including hepatitis viruses, human immunodeficiency virus-1 (HIV-1), and most RNA viruses, including coronavirus (Ghosh, Mukerjee et al. 2021, Elekhawy and Negm 2022).

Generally, viral infections increase free radical production and decrease endogenous antioxidant capacity through mitochondrial dysfunction. Covid-19-induced cytokine storms and high levels of pro-inflammatory cytokines have also been linked to the production of reactive oxygen species (ROS) (Al-Kuraishy et al. 2021a, b, c). In addition, pro-inflammatory cytokines activate inducible nitric oxide synthase (iNOS), which produces oxidizing peroxy nitrite by reacting with ROS and superoxide ions (Adedara et al. 2018). Hypoxia, tissue ischemia, hypertension, and diabetes mellitus, all of which are frequently associated with Covid-19, are linked to a decrease in cellular antioxidant capacity (Engwa 2018; Elekhawy et al. 2022).

In Covid-19 patients with underlying comorbidities, a reduction in antioxidant capacity may promote OS progression (Karkhanei et al. 2021). Despite evidence illustrating that some drugs and vaccines are efficient in managing and preventing Covid-19, complementary herbal medicines are urgently needed for more control of this pandemic disease. One of the most used herbal medicines is berberine (BBR), and Fig. 1 illustrates its chemical structure.

BBR is quaternary ammonium derived from isoquinoline salts. BBR is an odorless yellow powder with a bitter taste, characterized by high water-soluble with slight solubility in methanol and ethanol (Habtemariam 2020). BBR can easily gain from medicinal plants or by total synthesis.

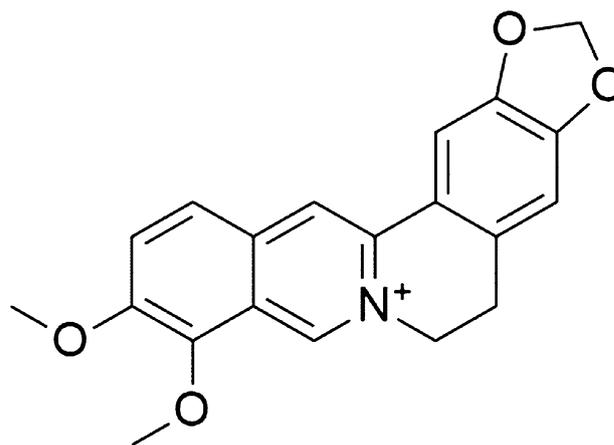


Fig. 1 Chemical structure of berberine

BBR is widely distributed in plants' roots, stems, and rhizomes, including *Papaveraceae*, *Euphorbiaceae*, and *Ranunculaceae*. However, BBR is mainly derived from *Rhizoma coptidis*, a common Chinese herbal medicine utilized to treat diabetes mellitus (DM) and chronic inflammatory disorders since 2000 A.D (Xu et al. 2017).

Herberger and Buchner early discovered BBR in 1830 (Gao et al. 2020), and Hongjing Tao first reported the beneficial effects of BBR in treating DM (Zhang et al. 2014). Furthermore, Indian researchers in 1960 illustrated that BBR salts are promising in treating severe diarrhea, amoebiasis, and cholera (Subbaiah and Amin 1967).

Pharmacology of berberine

Different studies revealed that BBR has important beneficial effects in managing various cardiovascular, metabolic, hematological, neurological, and immunological diseases [Table 1]. BBR has acute effects in managing DM through increasing insulin secretion, activating glycolysis, and inhibiting adipogenesis mediated by adenosine monophosphate protein kinase (AMPK) pathway glycolysis activity (Cicero and Tartagni 2012). Besides, BBR improves peripheral glucose uptake by increasing the expression of glucose transporter 4 (GLUT-4) (Mi et al. 2019). Likewise, BBR stimulates the release of glucagon-like peptide 1 (GLP-1), which through GLP-1, activates AMPK and insulin release (Wang et al. 2021a, b). Indeed, BBR triggers peroxisome proliferator-activated receptor gamma (PPAR- γ), which reduces peripheral insulin resistance (Zhou et al. 2019). Furthermore, BBR has been shown to improve glucose metabolism in the intestine with significant insulin-sensitizing effects (Zhang et al. 2014).

On the other hand, BBR has a potential role in managing various cardiovascular diseases and complications. BBR exerts a protective effect against the development of ED and

Table 1 Pharmacological effects of berberine (BBR)

Ref	Type of the study	Findings
(Zhang, Ren et al. 2008, Li, Li et al. 2014a, b)	Experimental study, 40 rats Experimental study	Administration of 36 mg/kg of BBR effectively attenuated heart failure development BBR prevents the progression of left ventricular hypertrophy caused by pressure overload in rats through inhibition of inflammatory signaling and enhancement of autophagy
(Guo, Chen et al. 2021)	Experimental study, 20 rats	BBR reduces consequent complications of heart failure, like cardiac fibrosis, through upregulation of relaxin expression in the cardiomyocytes
(Huang et al. 2015)	Experimental study, 20 mice	BBR 40 mg/kg reduces the risk of ischemic-reperfusion injury by direct antioxidant effect, inhibition of post-ischemic inflammation, direct coronary vasodilator effect, anti-apoptotic effect, promoting angiogenesis, and suppression of cardiomyocyte autophagy
(Fatehi-Hassanabad, Jafarzadeh et al. 2005)	Experimental study, 30 rats	BBR 0.4 mg/kg IV has hypotensive effects through different mechanisms, including α -1 adrenoceptor antagonist, enhancement of the hypotensive effect of acetylcholine, inhibition of the angiotensin-converting enzyme, and direct vasodilatation effect through activation of K-channel, Ca + 2-channel blocking effect in the cardiomyocytes
(Kong et al. 2004)	In vitro and clinical studies	Oral administration of BBR 1 g/day in 32 hypercholesterolemic patients for 3 months reduced serum cholesterol by 29%, triglycerides by 35%, and LDL cholesterol by 25%
(Wei et al. 2016)	Experimental study, 30 mice	Mice with metabolic syndrome treated with BBR 40–60 mg/kg/day for four weeks experienced significant reductions in the metabolic syndrome criteria
(Ma et al. 2010)	Experimental study, 20 rats	BBR can effectively treat obesity by modulation lipid dysregulation, weight reduction, and decreasing appetite
(Sun et al. 2016)	Experimental study, 30 rats	BBR can reduce body weight by upregulating brain GLP-1, neuropeptide Y, and orexin-A, suppressing the hypothalamic feeding center
(Bäckhed et al. 2007)	Experimental study, 20 mice	BBR-induced AMPK pathway is associated with improved blood glucose and oxidation of fatty acids

atherosclerosis (Ma, Shi et al. 2020). Of interest, this effect of BBR is mediated by modulation of cellular pro-atherogenic events, reduction of oxidative stress by increasing bioavailability of nitric oxide (NO), and suppression of xanthine oxidase (XO) (Hussienet al. 2019). Therefore, BBR, by regulating NO/ROS, may attenuate oxidative stress-induced ED and atherosclerotic complications. Moreover, BBR attenuates cardiac hypertrophy, remodeling, and heart failure development via mitophagy suppression (Abudureyimu et al. 2020). An experimental study by (Zhang, Ren et al. 2008), revealed that administration of BBR 63 mg/day for 4 weeks reduces the development of heart failure by reducing cardiomyocyte Ca^{+2} overload in rats (Zhang, Ren et al. 2008). Similarly, BBR prevents the progression of left ventricular hypertrophy caused by pressure overload in rats through inhibition of inflammatory signaling and enhancement of autophagy (Li et al. 2014a, b). Thus, BBR may reduce consequent complications of heart failure like cardiac fibrosis, which is involved in the induction of cardiac arrhythmia. This effect is mediated by the upregulation of relaxin expression in the cardiomyocytes (Gu et al. 2012). As well, BBR

reduces the risk of ischemic-reperfusion injury by direct antioxidant effect, inhibition of post-ischemic inflammation, direct coronary vasodilator effect, anti-apoptotic effect, promoting angiogenesis and suppression of cardiomyocyte autophagy (Huang et al. 2015). BBR has hypotensive effects through different mechanisms, including α -1 adrenoceptor antagonist, enhancement of the hypotensive effect of acetylcholine, inhibition of the angiotensin-converting enzyme, and direct vasodilatation effect through activation of K-channel, Ca + 2-channel blocking effect in the cardiomyocytes (Fatehi-Hassanabad, Jafarzadeh et al. 2005).

Moreover, BBR improves lipid and glucose metabolism and can be used to manage dyslipidemia, so BBR is regarded as a new lipid-lowering agent (Kong et al. 2004). In addition, BBR controls lipid metabolism via the regulation expression of low-density lipoprotein receptors (LDLRs), extracellular signal-regulated kinases (ERKs), and proprotein convertase subtilisin/kexin type 9 (PCSK9) (Cao et al. 2019). The experimental study illustrated that mice with metabolic syndrome treated with BBR 40–60 mg/kg/day for four weeks experienced significant reductions in metabolic syndrome

criteria. This effect is mainly mediated through the inhibition of hepatic gluconeogenesis and regulation of lipid metabolism via reduction expression of hepatic miR122 and hepatocyte nuclear factor 4 α (Kong et al. 2004; Wei et al. 2016).

Furthermore, BBR can effectively treat obesity by modulation lipid dysregulation, weight reduction, and decreasing appetite by controlling central and peripheral AMPK pathways and serotonin neurotransmission (Ma et al. 2010). BBR can reduce body weight by upregulating brain GLP-1, neuropeptide Y, and orexin-A, suppressing the hypothalamic feeding center (Sun et al. 2016). The anti-obesity effects of BBR are linked with the anti-diabetic effects, as the BBR-induced AMPK pathway is associated with improving blood glucose and oxidation of fatty acids. Prolonged treatment with BBR increases the diversity of gut microbiota. It shifts the bacteria to produce fasting-induced adipose factor, which inhibits lipoprotein lipase activity, a potent regulator of fat mobilization (Bäckhed et al. 2007).

These findings revealed that BBR has wide-spectrum pharmacological effects on the cardiovascular system and substantial modulating effects on the cardio-metabolic profile (Fig. 2).

Anti-inflammatory and antioxidant effects of berberine

BBR has an essential role in controlling different autoimmune disorders due to its anti-inflammatory and immunomodulatory effects (Adeyemi, Afolabi et al. 2022). Herbal medicines, particularly BBR, can potentially target inflammatory processes in DM, cancer, and neurological disorders with anti-inflammatory, immunomodulatory, and antioxidant effects. BBR inhibits the inflammatory process by suppressing the release of tumor necrosis factor- α (TNF- α) and IL-6, matrix metalloproteinases (MMPs), and monocyte chemoattractant protein 1 (MCP-1). BBR also suppresses the expression of cyclooxygenase-2 (COX-2), nuclear factor kappa B (NF- κ B), and mitogen-activated protein kinase (MAPK) (Chen et al. 2008). Based on these findings, BBR

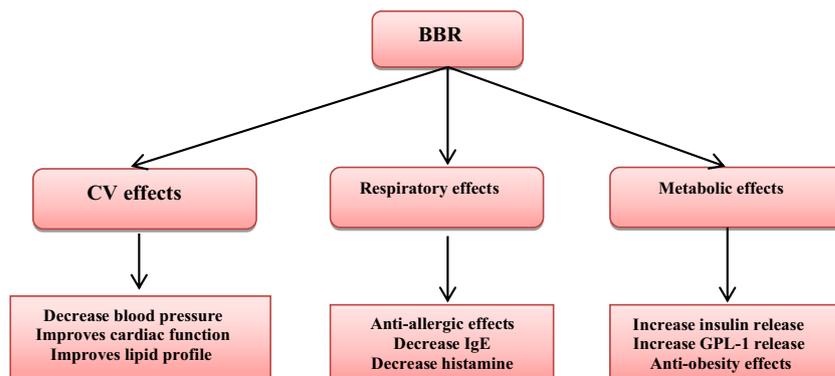
might be an effective agent in managing autoimmune diseases and associated inflammatory disorders (Li, Li et al. 2014a, b).

It has been reported that the abnormal autoreactive response of T helper cells is linked with abnormal production of IL-17 and interferon-gamma (INF- γ) connected with the progression and severity of autoimmune diseases (Liu et al. 2016). Indeed, Th1 and Th2 also recruit other inflammatory cells into injured and inflamed tissues by producing pro-inflammatory cytokines. Various studies showed that BBR could inhibit experimental nephritis by inhibiting proliferation and differentiation of CD4 T cells and down-regulation of Th1. Therefore, in experimental studies, BBR regulates Th1/Th17 immune response with subsequent modulation of INF- γ /Th17 cytokines. The inhibitory effects of BBR on Th1/Th17 cell differentiation are mediated by suppression of transducer and activator of transcription (STAT-3) and Janus kinase (JAK) signaling pathways (Li, Li et al. 2014a, b).

On the other hand, regulatory T cells (Treg) are anti-inflammatory cells that secrete anti-inflammatory cytokines such as IL-10, IL-35, IL-10, and tumor growth factor-beta (TGF- β), thereby inhibiting Th1/Th17 immune response and counterbalance of the inflammatory response (Li et al. 2020a, b). Treg cells are often defective in autoimmune disorders and viral infections (Shimokawa et al. 2020; Wan et al. 2020). BBR improves Treg/Th17 imbalance and attenuates inflammatory response in autoimmune diseases (Shimokawa et al. 2020). Several studies demonstrated that BBR could shift the differentiation of naïve T cells into Treg instead of Th17 cells (Dinesh and Rasool 2019).

In addition, activated macrophages produce several pro-inflammatory cytokines, essential for T cells differentiation into Th1 and Th17 cells (Amoah et al. 2015). Yan et al. found that BBR reduces macrophage activity and releases pro-inflammatory cytokines in experimental colitis mice (Yan, Wang et al. 2012). Similarly, BBR suppresses colonic macrophage infiltration by promoting macrophage apoptosis and inhibition of MAPK and NF- κ B, which are responsible for the activation of macrophages and the release of

Fig. 2 Pharmacological effects of berberine(BBR)



pro-inflammatory cytokines. The macrophages are differentiated into two types during the immunological response, classical M1 and alternative M2 phenotypes. Classical M1 produces pro-inflammatory cytokines, while alternative M2 produces anti-inflammatory cytokines (Mantovani et al. 2013). It has been shown that BBR increases the polarization of macrophages toward alternative M2 phenotype rather than classical M1 phenotype through inhibition of TLR4 and myeloid differentiation primary response 88 (MyD88) (Gong et al. 2019).

Additionally, BBR has potent anti-allergic effects by inhibiting IgE generation, release, and interaction. Therefore, BBR is effective against different allergic diseases like asthma (Yang, Wang et al. 2014). Immunotherapeutic BBR nanomedicine was developed to overcome the low oral bioavailability of BBR. It has been reported that immunotherapeutic BBR has 98–100% protection against peanut-induced severe anaphylaxis in mice through inhibition of histamine from mast cells with induction release of INF- γ (Li, Liu et al. 2022). The net anti-inflammatory effect of BBR is illustrated in (Fig. 3).

BBR has potent antioxidant activity by increasing the antioxidant superoxide dismutase (SOD) enzyme and the AMPK pathway. BBR can also increase mitochondrial uncoupling protein 2 (UCP2), which uncouples and separates ATP from oxidative phosphorylation through modulation of mitochondrial proton outflow (Xu, Shen et al. 2021). BBR attenuates ED by regulating NO/ROS balance in rats with erectile dysfunction (Alorabi et al. 2022). Pei et al. showed that BBR was adept at decreasing oxidized low-density lipoprotein (ox-LDL) and ox-LDL-induced monocyte stimulation by inhibiting the activity of intercellular adhesion molecule 1 (ICAM) and vascular cell adhesion molecule 1 (VCAM-1) (Pei et al. 2019). BBR inhibits vascular inflammation by inhibiting angiotensin II

(AngII)-induced monocytes adhesion to endothelial cells with suppression of expression of MCP-1 and reduction of ROS. Besides, BBR inhibits ROS production by suppressing xanthine oxidase (XO) activity in endothelial cells (Ivanov et al. 2006). Indeed, BBR can scavenge hydroxyl radicals in a dose and concentration-dependent manner. The scavenging ability of BBR is increased significantly at 300–1000 $\mu\text{g/mL}$, close to the effect of Vitamin C (Aoxue and Yijun 2011). Liu et al. demonstrated that BBR derivatives also have antioxidant activity through augmentation of body antioxidant capacity. From these findings, BBR has antioxidant activities that can modulate inflammatory and oxidative stress in different inflammatory and metabolic disorders (Fig. 4).

Antiviral effects of berberine

Different empirical evidence showed that alkaloids from BBR have potent antiviral activity against various viruses [Table 2], including herpes, influenza, respiratory syncytial virus (RSV), and coronaviruses (Warowicka et al.

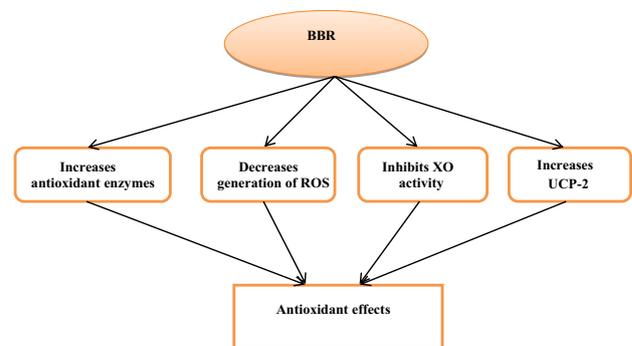


Fig. 4 Antioxidant effects of berberine

Fig. 3 Anti-inflammatory and immunological effects of berberine

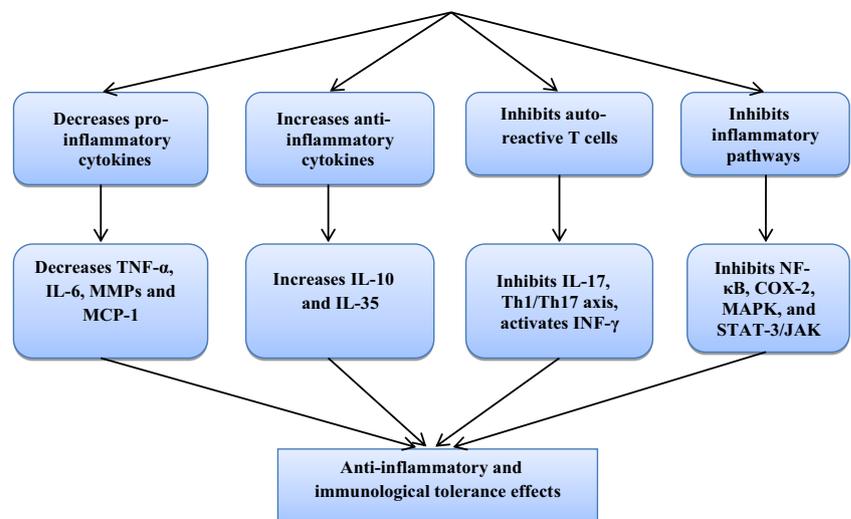


Table 2 Antiviral effects of berberine (BBR)

Ref	Type of the study	Findings
(Warowicka et al. 2020)	Review study	BBR inhibits replications of DNA and RNA viruses
(Hung et al. 2019)	In vitro study	BBR may inhibit the hepatitis C virus (HCV) entry by targeting viral glycoprotein E2, which is responsible for HCV entry
(Srivastava 2018)	In silico study	BBR has antiviral effects against dengue and Zika viruses by blocking the activity of NS5 and NS3 of dengue and Zika viruses, respectively
(Suryavanshi and Kulkarni 2017)	In vitro study	BBR inhibits RNA synthesis and protein assembly and release of SARS-CoV virions. BBR attenuates SARS-CoV-induced NF- κ B activation and release of pro-inflammatory cytokines
(Kim et al. 2016)	In vitro study	BBR inhibits the pathogenesis of the Venezuelan equine encephalitis virus (VEEV) and associated inflammatory reactions
(Mahata et al. 2011)	In vitro study	BBR reduces the proliferation of human papillomavirus (HPV), mainly HPV 16 and HPV18, by inhibiting viral E2, E6, and E7 oncoproteins
(Luganini et al. 2019)	In vitro study	BBR inhibits the replication of herpes viruses by suppressing DNA-dependent RNA polymerase
(Wang et al. 2018)	In vitro study	BBR blocks the replication of picorona viruses like enterovirus 71 and associated inflammatory reactions
(Zha et al. 2010)	In vitro study	Using 20 μ g of BBR resulted in 94% suppression of the reverse transcriptase enzyme in HIV

2020). Hung and colleagues suggested that BBR may inhibit the hepatitis C virus (HCV) entry by targeting viral glycoprotein E2, which is responsible for HCV entry (Hung et al. 2019). Molecular docking confirmed that BBR interacts with HCV glycoprotein E2, so it prevents binding and entry of HCV (Cecil et al. 2011). In addition, BBR displays antiviral effects against dengue and Zika viruses by blocking the activity of NS5 and NS3 of dengue and Zika viruses, respectively (Srivastava 2018). These verdicts indicated that BBR is regarded as a novel viral entry inhibitor, mainly against dengue and Zika viruses.

Furthermore, BBR is effectual against positive sense, enveloped RNA viruses like severe acute respiratory syndrome coronavirus (SARS-CoV) (Marchant et al. 2010). BBR inhibits RNA synthesis and protein assembly and release of SARS-CoV virions. BBR attenuates SARS-CoV-induced NF- κ B activation and release of pro-inflammatory cytokines (Kim et al. 2008; Suryavanshi and Kulkarni 2017). Similarly, BBR reduces the replication of RSV (a negative sense, non-segmental RNA virus) by inhibiting TLR4/ p38MAPK, which is triggered in the early stage of RSV infection. Recently, Tew *et al.* illustrated that BBR inhibits abnormal immunological reactions in RSV infection through suppression release of IL-6 and NF- κ B/ERK/p38MAPK axis (Tew et al. 2020).

Indeed, BBR has potent antiviral effects against the influenza virus, mainly against H1N1, by inhibiting the neuraminidase cytopathogenic effect and associated inflammatory disorders induced by activated NF- κ B/TLR4 (Kim et al. 2016). The inhibitory effects of BBR on the TLR4 pathway may limit intestinal mucosal injury during H1N1 (Li et al.

2015). The anti-inflammatory effects of BBR during viral infections are related to the suppression of activated protein 1 (AP-1) and NF- κ B signaling pathways. NF- κ B and AP-1 are the key transcription factor for regulating gene expression linked with inflammation (Zou et al. 2017). Also, BBR can inhibit MAPK, TLR7 expression, and the release of pro-inflammatory cytokines (Yan et al. 2018).

Furthermore, BBR can inhibit the pathogenesis of the Venezuelan equine encephalitis virus (VEEV) and associated inflammatory reactions by inhibiting signaling pathways and pro-inflammatory cytokines (Kim et al. 2016). Certainly, BBR reduces the proliferation of human papillomavirus (HPV), mainly HPV 16 and HPV18, by inhibiting viral E2, E6, and E7 oncoproteins and host AP-1 (Mahata et al. 2011). BBR inhibits the replication of herpes viruses by suppressing DNA-dependent RNA polymerase and expression of protein E2 with significant down-regulation of the herpes gene (Luganini et al. 2019). Likewise, BBR blocks the replication of corona viruses like enterovirus 71 and links inflammatory reactions by inhibiting autophagy and the Akt signaling pathway (Wang et al. 2018).

BBR and its derivatives have potential effects against human immune deficiency 1(HIV-1) replication and linked inflammatory disorders through inhibition of reverse transcriptase enzyme and modulation expression of IL-6 and ERK signaling. Zha *et al.* observed that using 20 μ g of BBR resulted in 94% suppression of the reverse transcriptase enzyme (Zha et al. 2010). Therefore, BBR has a wide spectrum of antiviral effects through viral entry and proliferation inhibition and suppression of associated inflammatory reactions (**Fig. 5**).

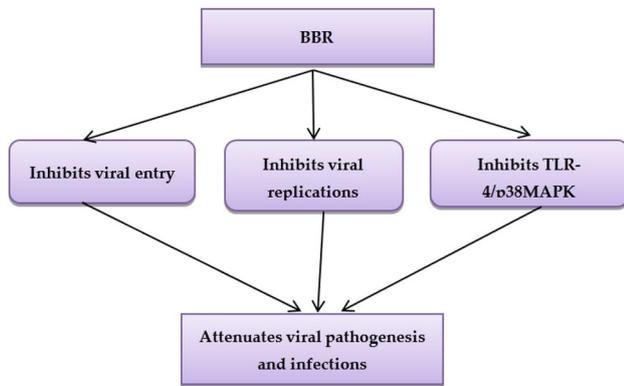


Fig. 5 Antiviral effects of berberine

Antiviral mechanisms of berberine

Viral infection can result in cellular changes and induction of inflammatory signaling pathways, including MAPK and NF- κ B pathways (Zha et al. 2010). Song et al. illustrated that BBR could block virus-induced activation of the NF- κ B pathway with a triggering effect on the I κ B α , an endogenous inhibitor of NF- κ B (Song et al. 2014). Likewise, BBR down-regulates MAPK, which is involved in various viruses' replication and life cycle. MAPK is mainly activated by HCV, Epstein-Barr virus (EBV), RSV, and SARS-CoV-2 infection (Al-Kuraishy et al. 2021a, b, c), leading to noteworthy inflammatory changes via alteration of protein phosphorylation. HIV-1 protein 6 is phosphorylated by MAPK, resulting in the maturation and release of viral particles (Hemonnot et al. 2004; Attallah et al. 2021). Similarly, the chikungunya virus activates MAPK, which is necessary to release progeny virions. Chikungunya virus non-structural protein 2 (nsP2) activates p38 and JNK in host macrophages (Nayak et al. 2019). It has been reported that BBR reduces the pathogenesis of Chikungunya virus infection by inhibiting p38 and JNK, which are concerned with autophagy and the maturation of viral particles (Varghese et al. 2016). Furthermore, different in vitro studies observed that BBR inhibits hepatitis B virus (HBV) infection by inhibiting p38MAPK, which is necessary to maintain this infection. In addition, BBR, through inhibition of p38MAPK, reduces the proliferation and infectivity of HBV infection (Kim et al. 2017). Thus, p38MAPK inhibitors like biphenyl amide might be a potential target in treating HBV infection, inhibiting HBsAg secretion (Kim et al. 2017).

Moreover, BBR can attenuate the severity of viral infection by inhibiting autophagy, an important mechanism engaged with viral replication. Huang et al. observed that EV71 induces autophagy during its replication (Huang et al. 2009). BBR suppresses virus-induced autophagy by inhibiting viral RNA and protein synthesis with inhibition of JNK/

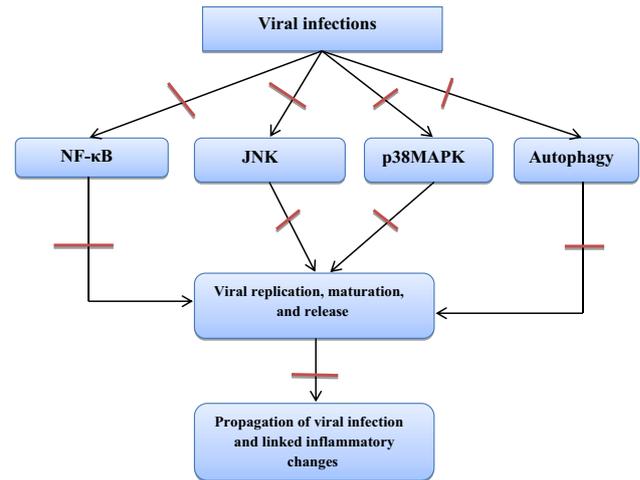


Fig. 6 Antiviral mechanisms of berberine

MER/ERK signaling, which engages with the activation of autophagy (Jin et al. 2017).

Taken together, BBR has potential activity against a broad spectrum of viral infections via inhibition of viral binding and entry with a significant reduction of associated inflammatory disorders. From these findings, BBR could be a novel herbal medicine in managing the recent Covid-19 pandemic. The net antiviral mechanism of BBR is illustrated in Fig. 6.

The potential role of berberine in Covid-19

The potential antiviral and anti-inflammatory properties of BBR make it a possible and novel candidate against SARS-CoV-2 infection (Wang et al. 2021a, b). SARS-CoV-2 infection is linked with the development of hyper-inflammation and hypercytokinemia due to the higher release of pro-inflammatory cytokines. The pathway for this inflammatory condition has been confirmed to be mediated by activation and upregulation of the NF- κ B signaling pathway (Al-Kuraishy et al. 2021a, b, c). A prospective study of 48 Covid-19 patients revealed that the NF- κ B gene and TLR4 are upregulated along with hyper-inflammation (Sohn, Lee et al. 2020). NF- κ B is normally sequestered in the cytoplasm in an inactive form by an endogenous inhibitory protein I κ B. Phosphorylation with subsequent inhibition of I κ B by inflammation induces activation and release of NF- κ B, a hallmark of inflammation (Liu et al. 2017; Alotaibi et al. 2021). BBR has potent inhibitory effects on NF- κ B with activation of I κ B (Song et al. 2014). Thus, BBR may inhibit NF- κ B during SARS-CoV-2 infection and reduce the risk of hyper-inflammation and cytokine storm-induced multi-organ failure (MOF) in patients with severe Covid-19 (Wang et al. 2021a, b).

In Covid-19, SARS-CoV-2 directly activates TLR4, which increases the expression of ACE2 in lung alveolar type II (Aboudounya and Heads 2021). Therefore, activated TLR4 is involved in the pathogenesis of SARS-CoV-2 and associated hyper-inflammation via stimulation of innate immune response. So, TLR4 seems to be a promising target in Covid-19 and using TLR4 antagonists may mitigate SARS-CoV-2-induced ALI/ARDS. BBR inhibits TLR4 in different viral infections (Xu et al. 2017), so it may attenuate SARS-CoV-2-mediated hyper-inflammation and development of ALI/ARDS in Covid-19. Liu et al. illustrated that BBR has protective effects against radiation-induced ALI by inhibiting TGF β -1 and releasing ICAM-1 (Liu et al. 2008). Besides, BBR, through its anti-inflammatory mechanism, reduces the risk of cigarette smoking-mediated ALI (Lin et al. 2013). These findings pointed out the pulmoprotective of BBR and may minimize the risk of ALI in Covid-19 patients.

Indeed, nod-like receptor pyrin 3 (NLRP3) inflammasome is highly activated by SARS-CoV-2, with subsequent release of IL-6 and IL-1 β . NLRP3 inflammasome is either triggered by SARS-CoV-2 or damage-associated molecule patterns (DAMPs) from injured cells. NLRP3 inflammasome is also activated by TLR4 signaling and releases TNF- α . Stimulated NLRP3 inflammasome in Covid-19 and released IL-6 increase the risk for cytokine storm development and MOF progression (Meng et al. 2019; Freeman and Swartz 2020). It has been shown that BBR inhibits NLRP3 inflammasome and pyroptosis in non-alcoholic fatty liver disease (NAFLD) and palmitate-induced NLRP3 inflammasome activation (Zhou et al. 2017; Mai et al. 2020). Thus, BBR, inhibiting NLRP3 inflammasome, may reduce Covid-19 severity.

In addition, p38MAPK is a pro-inflammatory pathway concerned with ALI, and myocardial injury is triggered during SARS-CoV-2 infection due to the down-regulation of ACE2 and elevated AngII. Activation of p38MAPK may occur through direct activation by SARS-CoV-2, resulting in the development of ED, vasoconstriction, and thrombosis (Grimes and Grimes 2020). Sharif-Askari et al. illustrated that SARS-CoV-2 infection reduces corticosteroid sensitivity by stimulating the p38MAPK signaling pathway (Sharif-Askari et al. 2021a, b). BBR inhibits the p38MAPK pro-inflammatory signaling pathway in certain viral infections (Kim et al. 2017), thereby reducing the propagation of associated inflammatory reactions. Cui et al. experimental study revealed that BBR attenuates activation of the p38MAPK pathway in mice with type 1 diabetes mellitus (Cui et al. 2009).

Furthermore, SARS-CoV-2 infection may lead to ED and thrombosis via activation of the p38MAPK pro-inflammatory signaling pathway (Aid, Busman-Sahay et al. 2020). A multicenter prospective cohort study involving 150 Covid-19

from a French tertiary hospital revealed that ARDS in Covid-19 is due to the development of thrombosis. However, despite anticoagulant use, many Covid-19 patients with ARDS develop critical thrombotic complications. Therefore, higher doses of anticoagulants are properly suggested. It has been reported that BBR may prevent thrombosis and assist thrombolysis by streptokinase and urokinase (Aid, Busman-Sahay et al. 2020). A recent in vitro study demonstrated that BBR and its derivative 13-Cys-BBR inhibit inflammation-induced thrombosis (Li et al. 2020a, b). Gao et al. observed that BBR decreases lipopolysaccharide (LPS)-induced activation of tissue factor procoagulant activity (Gao et al. 2014). While Wang et al. showed that BBR directs thrombin inhibitory activity (Wang et al. 2017). These verdicts indicate that BBR may reduce the risk of thrombosis in Covid-19.

In the bargain, SARS-CoV-2 infection increases the risk of thrombosis via augmentation of platelet activation (Al-Kuraishy et al., 2022b). SARS-CoV-2 spike protein binds platelet ACE2, and through activation of p38MAPK, SARS-CoV-2 enhances platelet aggregation with subsequent release of coagulation factors and induction of thrombosis (Zhang et al. 2020). It has been demonstrated that BBR has the anti-platelet effect and can reduce platelet hyper-aggregability in healthy subjects and patients with ischemic stroke via modulation of aldose reductase and NADPH oxidase pathways (Paul et al. 2019). In vitro study revealed that BBR has the ability to inhibit platelet aggregations by inhibiting platelet Ca²⁺ ionophore, adenosine diphosphate (ADP), and arachidonic acid. BBR blocks α 2-adrenoceptors on the platelet membrane, inhibiting ADP release from activated platelets (Huang et al. 2002). In addition, BBR inhibits platelet activations by decreasing P-selectin and thromboxane A2 levels with attenuating fibrinogen binding to platelet glycoprotein receptor (GP IIb/IIIa) and collagen-induced platelet stimulation (Allijn et al. 2016). Chiang and colleagues illustrated that SARS-CoV-2 infection-induced thrombosis is related to the activation of platelets thromboxane A2 and P-selectin (Chiang, Reddy et al. 2020). So, BBR could reduce platelet activation and the risk of thrombosis in Covid-19. Zhang et al. revealed that BBR, in combination with ligustrazine, reduces the risk of coronary micro-embolization through inhibition of platelet activation, von Willebrand factor, endothelin-1 (ET-1), and ICAM-1 (Zhang et al. 2016). Both ICAM-1 and ET-1 are activated during SARS-CoV-2 infection leading to endothelial injury and thrombosis (Sanghavi et al. 2021). In addition, BBR reduces the risk of pulmonary hypertension and pulmonary micro-thrombosis through modulation of the NO signaling pathway (Qiu et al. 2017). These results and findings support the potential role of BBR in preventing and treating SARS-CoV-2-induced thrombosis in critically ill Covid-19 patients.

Furthermore, SARS-CoV-2-induced inflammatory disorders are linked with the activation of COX and LOX inflammatory pathways (Archambault, Zaid et al. 2020). Fatty acid metabolites and activity of both COX and LOX are increased in the lung of Covid-19 patients compared to the healthy controls leading to a lipid storm (Archambault, Zaid et al. 2020). Therefore, inhibition of COX and LOX pathways in Covid-19 may reduce the risk for the development of cytokine and lipid storms (Al-Kuraishy et al. 2022). Recently, BBR inhibits both COX and LOX inflammatory pathways by inhibiting the activity of phospholipase A2 (Jenny and B Kumar 2021). BBR could be a potential candidate against SARS-CoV-2-induced ALL, which is mediated by the activation of COX and LOX inflammatory pathways. Besides, histamine and histamine receptors are upregulated during SARS-CoV-2 infection and linked with the development of cytokine storms (Malone et al. 2021). Therefore, H2-blockers like famotidine potentially manage Covid-19 by mitigating histamine-mediated inflammation (Ennis and Tiligada 2021). Fu et al. observed that BBR inhibits mast cells and histamine release by inhibiting MAPK signaling pathway (Fu et al. 2019). Therefore, BBR could play an important role in mitigating inflammatory disorders in Covid-19 patients via regulating mast cells and histamine release.

Interestingly, autophagy and STAT-3 pathways are activated during Covid-19 leading to apoptosis and hyperinflammation induction through triggering the release of Th1/Th17 cytokines (Fakhri, Nouri et al. 2020). Autophagy is induced by SARS-CoV-2, while the STAT-3 pathway is activated either directly by SARS-CoV-2 or indirectly by associated pro-inflammatory cytokines. The activated STAT-3 pathway promotes lymphopenia, thrombosis, ED, and lung fibrosis (Jafarzadeh et al. 2021). BBR attenuates both autophagy and STAT-3 pathways in different viral infections (Jin et al. 2017). BBR inhibits methotrexate-induced intestinal inflammation by blocking the JAK/STAT-3 signaling pathway (Hassanein et al. 2021).

Remarkably, severe SARS-CoV-2 infection may induce oxidative stress (OS) through ROS generation and the reduction of endogenous antioxidant capacity (Suhail et al. 2020). High AngII due to down-regulation of ACE2 by SARS-CoV-2 may trigger ROS generation and OS induction, which is linked with the pathogenesis of SARS-CoV-2 infection and Covid-19 severity and mortality (Cecchini and Cecchini 2020). It has been shown that SARS-CoV-2 provokes the expression of oxidative genes in a higher manner than other respiratory viruses. Therefore, biomarkers of OS like S100A8 and S100A9 are increased in patients with severe Covid-19 (Sharif-Askari et al. 2021a, b). In this sense, BBR is regarded as potent antioxidant herbal medicine in different OS-related diseases. BBR inhibits ROS generation and increases body antioxidant capacity by activating the

AMPK pathway (Eissa et al. 2018). Besides, BBR reduces the severity of OS by inhibiting the xanthine oxidase (XO) enzyme, which is linked with the generation of ROS in diabetic patients (Pagliaro et al. 2015). XO is upregulated during SARS-CoV-2 infection and might explain the induction of OS in Covid-19, so inhibition of XO by allopurinol may reduce Covid-19 severity (Pratomo, Ariane et al. 2021). Therefore, BBR, by blocking XO activity, may reduce OS injury and Covid-19 severity.

Moreover, the advance glycation end-product and receptor (AGE-RAGE) exerts multiple intracellular signaling via PKC, NADPH oxidase, and MAPK, resulting in the activation of NF- κ B (Serveaux-Dancer, Jabaudon et al. 2019). An AGE-RAGE signaling pathway is activated during SARS-CoV-2 infection; however, soluble RAGE (sRAGE) has a protective role against Covid-19 severity (Yalcin Kehribar et al. 2021). A study involving 23 Covid-19 patients compared to 35 healthy controls illustrated a high sRAGE level in asymptomatic Covid-19 patients (Yalcin Kehribar et al. 2021). The study revealed that BBR therapy reduces AGEs in diabetic patients (Zhang et al. 2019). Thus, BBR, modulation of the AGE-RAGE signaling pathway, may reduce Covid-19 severity.

Overall, BBR may have a protective effect against Covid-19 and related complications. A prospective study involved 18 Covid-19 patients on BBR, and standard treatment compared with 17 Covid-19 controls treated by standard treatment only. This study illustrated that Covid-19 patients on BBR treatment experience low IL-6, TNF- α , and CRP, suggesting the anti-inflammatory role of BBR in Covid-19. Besides, BBR reduces gastrointestinal inflammation and the release of pro-inflammatory cytokines from the injured mucosal epithelium in Covid-19 (Zhang et al. 2021). The optimal BBR dose for anti-inflammation related to SARS-CoV-2 remains unclear, although we based our dose of BBR 900 mg/daily on the effective anti-inflammation dose according to other literature (Zhang et al. 2021). BBR has recently been produced in nanomolecular form with greater oral availability and proposed as Covid-19 therapy. An orally available immunotherapeutic-berberine nanomedicine, named NIT-X, has been developed and has shown significantly increased oral bioavailability of BBR, increased IFN- γ production by CD8+ T cells, and inhibition of mast cell histamine release in vivo, suggesting a protective immune response.

Moreover, the expression of targets, including ACE2, TMPRSS2, IL-1 α , IL-8, IL-6, and CCL-2 in SARS-CoV-2 infected cells, were significantly suppressed by NIT-X. By supporting protective immunity while inhibiting pro-inflammatory cytokines, inhibiting viral infection and replication, inducing apoptosis, and protecting against tissue damage, BBR is a promising candidate for preventing and treating Covid-19 and SARS. Given the high oral

bioavailability and safety of BBR nanomedicine, it may lead to the development of BBR as an orally active therapeutic against Covid-19 and SARS (Wang et al., 2021a, b).

Many clinical trials have been conducted that suggest a wide range of therapeutic applications for BBR. These clinical trials confirmed that using BBR in a dose of 0.6–1.6 g/day did not produce any toxic effects. The effective dose of BBR was 1–2 g/day for different diseases, mainly inflammatory ones (Imenshahidi and Hosseinzadeh 2019, Guo, Chen et al. 2021). Depending on these findings, 1.5 g/day could be effective and safe in Covid-19 patients.

BBR has been shown to inhibit SARS-CoV-2 infectivity by interfering with the binding of SARS-CoV-2 to the ACE2 rather than inhibiting ACE2-driven viral entry (Wu et al. 2020). Similarly, a molecular docking study demonstrated that BBR could inhibit host transmembrane protein serine-type 2 (TMPRSS2), which is implicated in activating SARS-CoV-2 spike protein (Wang et al. 2021a, b). As well, BBR has been proven to block SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), three chymotrypsin protease (3CLpro), and main protease (Mpro); suggesting BBR may inhibit the proliferation of SARS-CoV-2 (Narkhede et al. 2020). These findings indicate that BBR may decrease SARS-CoV-2 pathogenicity by inhibiting viral entry via suppression of ACE2 and TMPRSS2. In addition, BBR may lessen SARS-CoV-2 infectivity by inhibiting the proliferation of SARS-CoV-2. The potential role of BBR in Covid-19 is related to improving the immune response in the early phase of SARS-CoV-2 infection, with suppression of SARS-CoV-2-induced hyper-inflammation in the late phase (Wang et al. 2021a, b). Therefore, BBR could be a preventive and therapeutic agent in Covid-19 by targeting inflammatory signaling pathways with suppression of entry/infectivity of SARS-CoV-2 (Fig. 7). Moreover, BBR can be combined with other anti-SARS-CoV-2 drugs like remdesivir (Pizzorno et al. 2020). The mechanism of action of BBR in the treatment of Covid-19 pneumonia and pulmonary fibrosis is through TNF- α inhibited inflammatory reaction and reduced the activation of fibroblasts. Also, BBR inhibited the synergistic effect between IL-6 and STAT-3, and reduced the inflammatory response. Lastly, BBR inhibits the chemotaxis of CCL-2 to fibroblasts and reduces inflammation (Cao et al. 2019). Further clinical trials and prospective studies are recommended in this field to confirm the potential therapeutic effects of BBR in managing Covid-19.

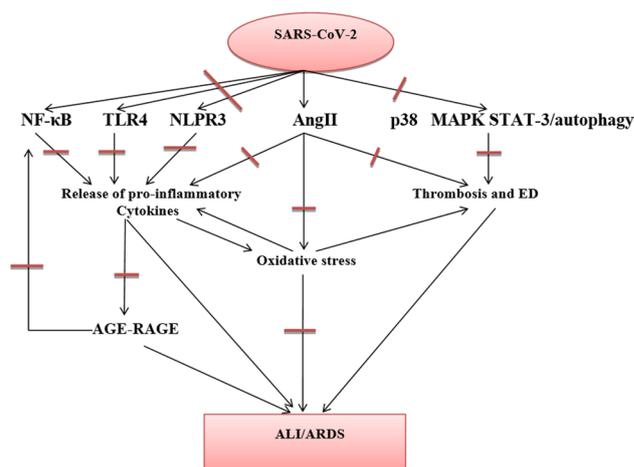


Fig. 7 Anti-SARS-CoV-2 mechanisms of berberine

Conclusion

BBR has potent anti-inflammatory, antioxidant, and antiviral effects. Therefore, it can be used as a possible anti-SARS-CoV-2 agent. BBR inhibits the proliferation of SARS-CoV-2 and attenuates the associated inflammatory disorders linked by the activation of inflammatory signaling pathways. BBR has the ability to inhibit the release of pro-inflammatory cytokines through the inhibition of NF- κ B and p38MAPK signaling pathways, which are highly activated during SARS-CoV-2 infection. Indeed, BBR can mitigate the risk of ALI/ARDS in patients with severe Covid-19. In this sense, clinical trials and prospective studies are suggested to illustrate the potential role of BBR in treating Covid-19.

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Declarations

Conflict of interest The authors declare no conflict of interest.

Informed consent Not applicable.

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