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Review

Cannabinoid Type-2 Receptor Agonist, JWH133 May Be a Possible Candidate for Targeting Infection, Inflammation, and Immunity in COVID-19

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Abstract: The COVID-19 pandemic, caused by SARS-CoV-2, is a deadly disease affecting millions due to the non-availability of drugs and vaccines. The majority of COVID-19 drugs have been repurposed based on antiviral, immunomodulatory, and antibiotic potential. The pathogenesis and advanced complications with infection involve the immune-inflammatory cascade. Therefore, a therapeutic strategy could reduce infectivity, inflammation, and immune modulation. In recent years, modulating the endocannabinoid system, particularly activation of the cannabinoid type 2 (CB2) receptor is a promising therapeutic target for modulation of immune-inflammatory responses. JWH133, a selective, full functional agonist of the CB2 receptor, has been extensively studied for its potent anti-inflammatory, antiviral, and immunomodulatory properties. JWH133 modulates numerous signaling pathways and inhibits inflammatory mediators, including cytokines, chemokines, adhesion molecules, prostanoids, and eicosanoids. In this study, we propose that JWH133 could be a promising candidate for targeting infection, immunity, and inflammation in COVID-19, due to its pharmacological and molecular mechanisms in numerous preclinical efficacy and safety studies, along with its immunomodulatory, anti-inflammatory, organoprotective, and antiviral properties. Thus, JWH133 should be investigated in preclinical and clinical studies for its potential as an agent or adjuvant with other agents for its effect on viremia, infectivity, immune modulation, resolution of inflammation, reduction in severity, and progression of complications in COVID-19. JWH133 is devoid of psychotropic effects due to CB2 receptor selectivity, has negligible toxicity, good bioavailability and druggable properties, including pharmacokinetic and physicochemical effects. We believe that JWH133 could be a promising drug and may inspire further studies for an evidence-based approach against COVID-19.

Keywords: cannabinoids; CB2 receptors; COVID-19; immunomodulators; inflammation; JWH133; SARS-CoV-2

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1. Introduction

Coronavirus disease-2019 (COVID-19), a pandemic and public health emergency caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a deadly disease that is affecting millions of people all over the world because of the non-availability of specific drugs or vaccines [1]. Currently, numerous efforts are underway to discover and develop preventive and therapeutic agents for SARS-CoV-2 infections [2]. Despite availability of the vaccines for COVID-19, identifying candidate drugs which could be effective for therapeutic management of COVID-19 is crucial. The majority of the drugs used in COVID-19 have been repurposed based on antiviral, antibiotic, anti-inflammatory, or immunomodulatory activities [3]. Considering the emergence of COVID-19-related mortality, effective medications are needed to improve patient prognosis and to stem the spread of the virus [3]. Among the numerous therapeutic avenues to be explored, the endocannabinoid system (ECS), which physiologically regulates innate and adaptive immunity, inflammation, pain, and oxidative stress [4] represents an important strategy for therapeutic targeting of hyperimmune-inflammatory responses during COVID-19.

The ECS typically consists of two receptors, cannabinoid receptor type 1 (CB1R) and 2 (CB2R), their endogenous ligands (endocannabinoids) and metabolic enzymes, as well as nonclassical targets of cannabinoids (e.g., transient receptor potential (TRP) channels and peroxisome proliferator-activated receptors) that are major players in the immune system and control a wide variety of diseases involving immune-inflammatory states [5]. The ECS is one of the newest drug targets receiving attention and has an excellent reputation due to the emergence of many successful drugs in the clinic in the past few years [6–8]. In the ECS, the CB2R is a G-protein-coupled receptor (GPCR) that, upon activation, regulates immune responses and inflammatory pathways; therefore, CB2R agonists have received enormous interest for possible therapeutic applications owing to their beneficial immunomodulatory, anti-inflammatory, and antioxidant roles, with the absence of psychotropic effects attributable to CB1R activation [9,10].

To date, numerous cannabinoid ligands have been classified as classical, non-classical, aminoalkylindoles, and eicosanoids that have been synthesized. Among the numerous CB2R ligands, JWH133, which was first synthesized by Huffman et al. (2010), has received enormous attention in experimental studies investigating CB2R-dependent pharmacological mechanisms and therapeutic potential [11]. Since its synthesis, it has been shown to be one of the most studied CB2R full functional agonist that exhibits high affinity and approximately 200-fold more selectivity towards CB2R than CB1R. This emerging ligand shows a wide range of therapeutic effects, including cardioprotective, hepatoprotective, neuroprotective, nephroprotective, anticonvulsive, antipsychotic, anticancer, anti-oxidant, anti-inflammatory, immunomodulatory, and antiviral, mediating selective activation of CB2R mimicking as full agonist.

Since the emergence of COVID-19, several drugs, including remdesivir, lopinavir, ritonavir, interferon-β, ribavirin, chloroquine/hydroxychloroquine, azithromycin, tocilizumab, and ivermectin, have appeared as promising therapeutics for COVID-19 [12]. From a pharmacological perspective, these drugs have the potential to either block the virus from entering host cells or prevent viral replication, and attenuate hyperimmune and hyperinflammatory states to prevent the disease progression and complications [3]. The utilization of these drugs in COVID-19 is mostly empirical, based on clinical experience of their therapeutic benefits in the management of previous SARS, Middle East respiratory syndrome, and Ebola virus epidemics.

In principle, immune responses and the resultant inflammatory process are imperative for the abolition of viremia, but this may significantly influence pathogenesis of SARS-CoV-2 and contribute to the signs and symptoms of COVID-19 [13]. In SARS-CoV infections, the use of antiviral agents alone is insufficient to prevent a cytokine storm and related complications in critically ill patients because immune dysregulation with hyperinflammatory conditions lead to complications, worsening, and poor prognosis rather than control of

viremia [14]. To reduce morbidity and mortality, it is important to repurpose old drugs and to identify novel agents capable of attenuating a cytokine storm [15].

Current research efforts are ongoing across pharmaceutical, biotechnological, and academic studies for the discovery of novel drugs, as well as vaccines for SARS-CoV-2 [15]. COVID-19 pathogenesis involves hyperfunctioning of immunoregulatory cells (B cells, natural killer (NK) cells, $CD4^+$ T cells, and $CD8^+$ T cells) in defensive responses to the pathogen [16]. Subsequently, a hyperimmune status induces hyperinflammatory conditions by overproduction and release of cytokines, termed a cytokine storm, which determines the intensity of symptoms, mortality rate, progression, and worsening of the disease, mainly the pulmonary system, and causes extrapulmonary complications and multi-organ failure [17]. COVID-19 pathogenesis and complications involve the immune-inflammatory cascade; therefore, the available approaches emphasize this cascade to reduce inflammation and immune modulation [13,16].

Considering the pharmacological effects, molecular mechanisms, and therapeutic potential of JWH133, we reasonably hypothesize that JWH133 could be useful in COVID-19 because of its notable immunomodulatory, anti-inflammatory, and antiviral properties. Recently, CB2R has been suggested as a potential therapeutic target for regulating the immune-inflammatory axis in COVID-19 [18]. Our proposition is to scientifically contemplate the therapeutic perspective and prospect of JWH133 on infection, immunity, and inflammation with a potential use in COVID-19 to curb severity and progression, as well as poor prognosis. In this article, we discuss the possible prophylactic and treatment mechanisms of JWH133 in COVID-19. Much of the information presented is based on data derived from previously published studies reporting the immunomodulatory, anti-inflammatory, and antimicrobial properties of JWH133.

The roles of cannabinoids are well explored for their antiviral, anti-inflammatory, and immunomodulatory properties [8,19,20] and gaining attention for their candidature for potential in COVID-19 [21]. It has become apparent that agents that have antiviral, anti-inflammatory and immunomodulatory properties altogether could be important in context of COVID-19 to target the trinity of infection, inflammation and immunity. Many of the compounds showed targeting of SARS-CoV-2 using bioinformatics tools, such as in silico analysis, molecular docking, or molecular farming to enhance the production of recombinant proteins including vaccines and antibodies [22,23]. To tackle SARS-CoV-2, the identification of viral protease appears a striking therapeutic target to limit the replication of SARS-CoV-2 and many of the compounds are being investigated for their potential to target replication by inhibiting viral components, such as M^{pro} ($3CL^{pro}$), PL^{pro} and spike proteins [22,23]. Identifying candidate compounds, that have selectivity against viral components and prevent viral entry, as well as improve immunity and attenuate inflammatory factors in host cells, could be more important in context to SARS-CoV-2 infections. In the present article scientifically contemplates the therapeutic prospects of JWH133 in SARS-CoV-2 infection.

In this review, we perform molecular docking studies on JWH133 for the viral and host targets and found that M^{pro} appear to be a one of the important targets, we also elaborated the potential of JWH133 in SARS-CoV-2 infection integrating with previous findings, particularly regarding its immunomodulatory, anti-inflammatory, and antiviral properties.

2. Molecular Docking of JWH133 for its Activity on M^{pro}

Molecular docking is a powerful technique used to check the binding orientation of ligand into the active site of the target protein. The crystal structure of SARS-CoV-2 main protease (SARS-CoV-2 M^{pro} was retrieved from Protein Data Bank (PDB—available at http://www.rcsb.org) using the PDB code: 6LU7 [24], (Berman et al., 2015). Dock Prep tool of UCSF Chimera program was used to prepare receptor molecule [25]. During preparation, binding ligand, hetatoms, and the solvents were removed while the hydrogen atoms were added to the structure. The structure of JWH133 was searched and retrieved

from PubChem database (CID: 6918505) [26]. The ligand structure was prepared in chimera by adding hydrogen atoms and charges.

The ligand binding residues in the structure of SARS-CoV-2 M^{pro} was designated to dock JWH133 using the Autodock Vina chimera plugin [27]. The best-docked ligand pose was selected for further analysis. Energy minimization of the docked complex was performed in Chimera using the energy minimization program [25]. A protein-ligand complex was processed and optimized in the free maestro program to refine molecular interactions [28] (Schrödinger, 2018). The molecular 2D interaction image was also generated using the ligand-receptor interaction module of the maestro package (Schrödinger, 2018). The non-covalent interactions were calculated at cutoff radius of 2.50 Å.

Docking of JWH133 into the active site of SARS-CoV-2 M^{pro} generated several binding poses. The best binding pose with docking energy −6.0 Kcal/mol was selected for molar interaction analysis. Molecular interaction analysis results revealed that JWH133 formed hydrophobic contact with Cys44, Met49, Pro52, Tyr54, Phe140, Leu141, and Met 165 of the target protein (Figure 1). His41, Asn142, Ser144, His163, His164, His172, and Gln189 were involved in polar contacts with target protein (Figure 1). These residues are the key residues, which play an important role in ligand binding. In a recent study, the importance of similar binding pattern of doxycycline, minocycline, lopinavir, oseltamivir, and ritonavir with SARS-CoV-2 M^{pro} have been highlighted [23,29].

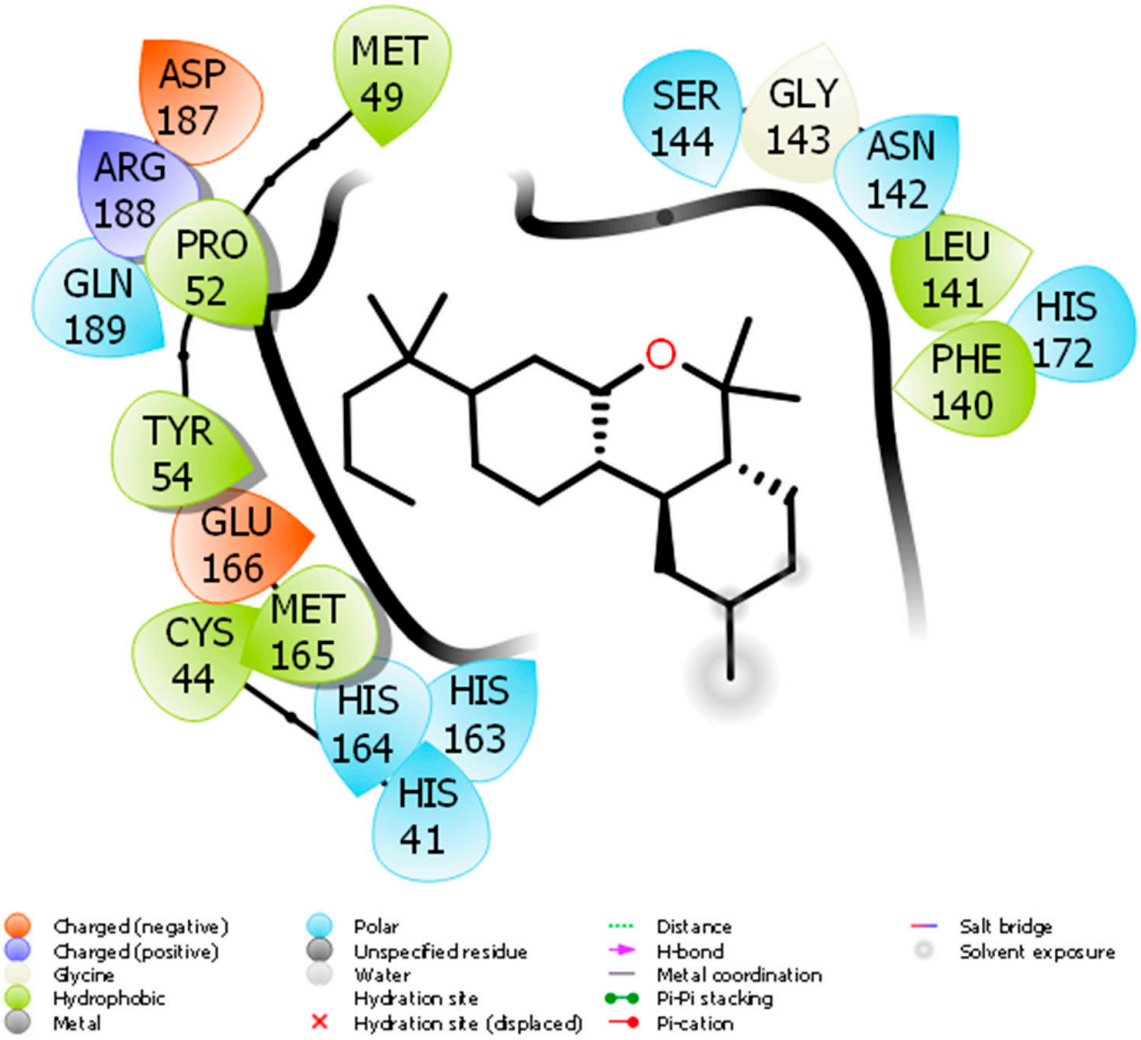

Figure 1. The molecular interaction between SARS-CoV-2 M^{pro} and JWH133.

Based on the role of CB2R in immune-inflammatory mechanisms, the antiviral and agonist properties of JWH133 on CB2R, we hypothesized that JWH133 may be a potentially novel candidate to limit the severity and progression of COVID-19 by modulating infection, immunity, and inflammation. A scheme of the effect of JWH133 mediating CB2 receptor activation on the infection, inflammation, and immunity in context of SARS-CoV-2 is presented in Figure 2.

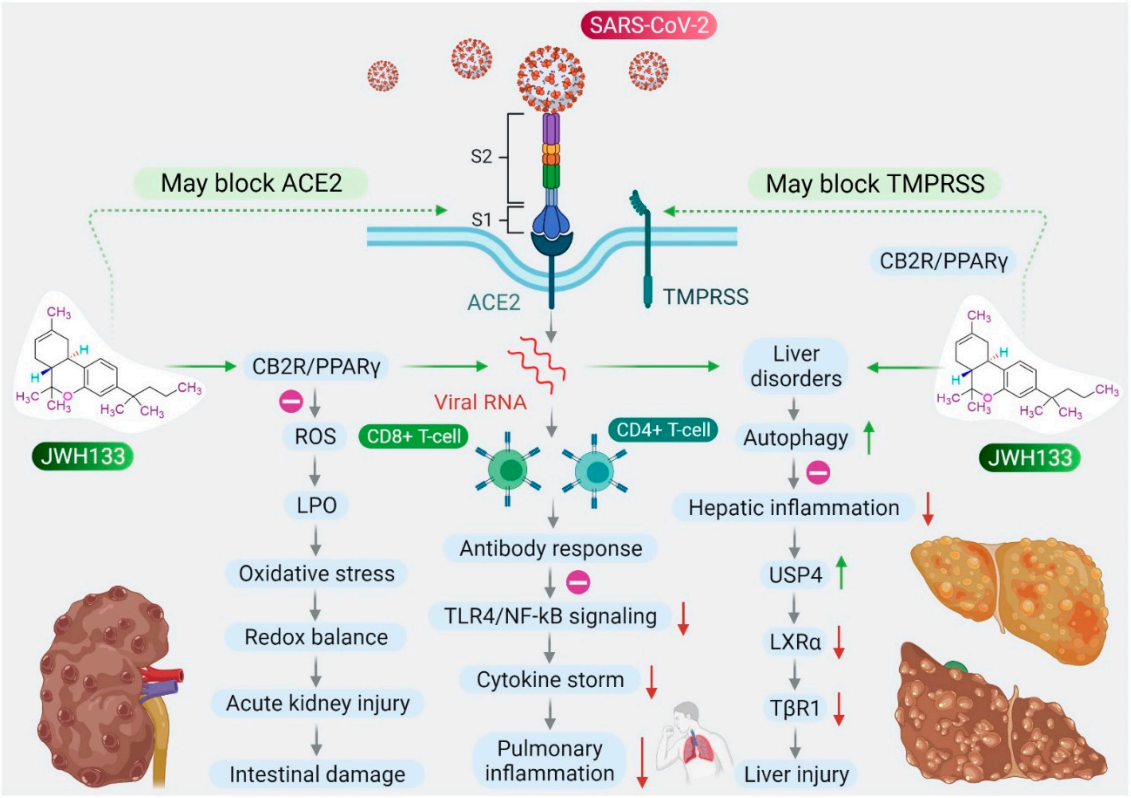

Figure 2. Proposed scheme of potential and mechanisms of JWH133 on immunity, infection, and inflammation against SARS-CoV-2.

3. CB2 Receptors Mediated Anti-Inflammatory Activity of JWH133

The clinical manifestations of SARS-CoV-2 infections range from mild to severe, with widespread participation of the lungs, beginning from pneumonia to acute respiratory distress syndrome (ARDS), as well as acute injury to the liver, heart, intestine, coagulopathy, thrombosis, and neurological manifestations that may lead to sepsis and multi-organ failure with poor prognosis [30,31]. Widespread alveolar damage, along with progressive lung dysfunction, leads to respiratory failure that may cause fatalities [32]. Fatalities are higher in elderly people with cardiometabolic diseases, cancer, patients who are immunocompromised, or with comorbidities of diabetes or cardiometabolic diseases [33]. COVID-19 also causes interstitial lymphopenia, lymphocyte infiltration, and T cell hyperactivation in the lungs and blood [30,31].

CB2Rs are largely expressed in macrophages and participate in the inflammatory process mainly by regulating proinflammatory factors, including cytokines, chemokines, adhesion molecules, and the polarization of macrophages, a key regulator of the M1/M2 pathway of inflammation [34,35]. Activation of CB2R produces anti-inflammatory action by inhibiting leukocyte recruitment, reducing the synthesis and release of proinflammatory cytokines, such as interleukin (IL)-6, IL-18, monocyte chemoattractant protein 1, and reactive oxygen species (ROS) [7]. CB2R primarily couples with Gi/o proteins upon activation, resulting in inhibition of adenylyl cyclase agonism, further activating the 5′ AMP-activated protein kinase (AMPK) pathways that result in reduced anabolic reactions, which, in turn,

promote oxidative phosphorylation and exert anti-inflammatory effects [7,36]. Several studies have demonstrated the anti-inflammatory activities of JWH133 in inflammatory models, including lipopolysaccharide (LPS)-induced macrophages, monocytes, and eosinophils by inhibiting proinflammatory cytokines, inflammatory enzymes, such as inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX)-2, and production of nitric oxide (NO) and prostaglandin E2 [37–39].

Patients with COVID-19 mainly present with acute respiratory distress causing acute lung injuries characterized by neutrophil infiltration, vasculitis, and secretion of proinflammatory cytokines, particularly a massive increase in IL-6, which is related to the severity of the disease pathology, poor prognosis, and death [40,41]. Elevated IL-6 levels have also been demonstrated to contribute to acute lung injury (ALI) in murine models [42], similar to those observed in patients with ARDS and COVID-19; thus, inhibition of IL-6 appears to mitigate ALI [42,43]. A few of the potent inhibitors of IL-6 are tocilizumab and sarilumab; these drugs have gained attention in the inhibition of the cytokine storm in COVID-19, but possess numerous adverse effects, such as liver damage, thrombocytopenia, leukopenia, serious infections, gastrointestinal perforations, hypertension, skin reactions, and anaphylaxis [44]. Macrophages present in the human lung express CB2R, which, upon activation, significantly inhibits LPS-induced production of vascular endothelial growth factor-A and C, angiopoietins, and IL-6 secretion [45]. In addition to IL-6, the NOD-like receptor protein 3 (NLRP3) inflammasome is a mediator of the cytokine storm, and, thereby, clinical and pathological manifestations of patients infected with COVID-19 [46]. Recently, JWH133 has been found to exert protective effects in experimental models of ALI by activating CB2R [37,38]. JWH133 significantly inhibits proinflammatory cytokines, including IL-6, and improves levels of antioxidants, mediating the inhibition of inflammasomes [39], the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathway [37] and the mitogen-activated protein kinase (MAPK)/c-Jun N-terminal kinase (JNK) and nuclear factor-kappa B (NF-κB) pathways [38].

Some patients that have recovered from COVID-19 are reported to have progressive post-infection consequences with persistent lung dysfunction and fibrosis, a life-threatening disease [47]. Pulmonary fibrosis begins with microinjury, resulting in inflammation and over-activation of repair mechanisms following activation of fibroblasts. CB2R present in fibroblasts plays a role in fibrosis, and many studies have demonstrated that activating CB2R exerts anti-inflammatory and antifibrotic effects [48–50]. Notably, JWH133, via activation of CB2R, prevents lung fibrosis and reduces fibroblast proliferation, along with suppression of autoantibodies [48]. By activating CB2R, JWH133 also inhibits hyperemia, hyperplasia of type II pneumocytes, interstitial fibrosis and salvaged lungs, reduced fibrotic markers, collagen deposition, decreased levels of the profibrotic cytokine transforming growth factor (TGF)-β1, and mitigated activation of the TGF-β1/mothers against decapentaplegic homolog 2 pathway [49,50].

Additionally, JWH133, mediating CB2R-dependent anti-inflammatory action mitigates neurogenic pulmonary edema developed following subarachnoid hemorrhage, as evidenced by lung permeability, leukocyte trafficking, and preserved tight junctions [51]. Based on the therapeutic and preventive effects of JWH133 in experimental models of ALI, drug-induced lung injuries, inflammation, and fibrosis, as well as airway hyperresponsiveness and cough centers, it is conceivable to speculate that JWH133 may have the potential to curb ALI in COVID-19. It may also limit late-onset pulmonary fibrosis in recovered patients or may be useful in patients with compromised pulmonary function. However, further proof of concept studies is needed for conclusive evidence.

In extrapulmonary manifestations of COVID-19, cardiac injury also occurs in patients with a critical illness [52]. Patients with cardiovascular disorders, such as ischemic heart disease, hypertension, and hyperlipidemia are also at a greater risk of disease severity and death [52]. Systemic infections and inflammation may cause acute thrombosis by activating platelets, vasoconstriction of the coronary artery, hypoxemia, enhanced sympathetic tone, altered heart rate, coagulation pattern, and impaired endothelium [53]. JWH133, by

activating CB2R, suppresses rostral ventrolateral medulla neuroinflammation associated with hypertension by reducing blood pressure, heart rate, renal sympathetic nerve activity, and proinflammatory cytokines in spontaneously hypertensive rats [54]. JWH133 has been shown to be cardioprotective in acute myocardial injury in numerous experimental models; the protective effects are mediated by CB2R activation and inhibition of inflammasome activation [39], downregulation of receptor interacting protein 1 (RIP1)/RIP3/mixed lineage kinase domain like pseudokinase (MLKL)-mediated necroptosis [55], inhibition of cardiomyocyte hypertrophy through AMPK-endothelial NOS signaling [56], increasing extracellular signal-regulated kinase 1/2 (ERK1/2) phosphorylation and inhibiting mitochondrial permeability transition pore opening [57], suppression of Na^+/Ca^{2+} exchanger current [58], and upregulation of integrins CD18/CD11b (Mac-1) on human neutrophils in tumor necrosis factor (TNF)-α-induced chemotaxis [59]. JWH133 also exerts vasodilatory and positive inotropic effects in spontaneously beating Langendorff-perfused rat hearts [60]. Additionally, JWH133 mitigates antipsychotic drug-induced cardiotoxicity by enhancing RIP3, MLKL, and the phosphorylation of MLKL [61], suppressing proinflammatory mediators and fibrotic markers, and improving survival rate [62].

In patients with COVID-19, cardiovascular complications are aggravated by the high incidence of venous and arterial thrombosis and coagulopathy involving platelet activation, the formation of platelet-monocyte aggregates, complement activation, increases in lipoproteins, endothelial dysfunction, stasis, hypoxia, and overexpression of tissue factors following a cytokine storm or capillary leak syndrome, in reference to thrombosis [63,64]. CB2Rs are widely expressed in hematopoietic and endothelial cells and regulate endothelial inflammation, chemotaxis, adhesion of inflammatory cells to the stimulated endothelium, and the resultant secretion of proinflammatory molecules [65,66]. The activation of CB2R attenuates inflammatory responses, including activation of endothelial cells, adhesion, and migration of immune cells, a common accompaniment of atherosclerosis and restenosis [67]. JWH133 inhibits inflammation and vascular remodeling by attenuating cell proliferation, intima and media formation, macrophage infiltration, and reducing numbers of nuclei and proliferating cells in the intima [68]. Reduced CB2R levels are found in asymptomatic patients with atherosclerosis [69]. JWH133 decreases matrix metallopeptidase 9 (MMP-9) levels in the aortic root, plaque formation in the carotid artery, and with human neutrophils, reduces TNF-α-induced ERK1/2 phosphorylation [69]. Additionally, JWH133 protects against neuroinflammation by activating CB2R enhanced trans endothelial resistance and tight junction proteins by inhibiting proinflammatory mediators, including adhesion molecules [70].

In patients with COVID-19, liver injury or dysfunction is a common issue due to the virus itself or other concurrent conditions, such as hepatotoxicity from the drugs, mainly antipyretics or immunomodulators used in COVID-19 management, or the presence and progression of chronic liver diseases, coexisting systemic inflammation, acute respiratory distress associated hypoxia, and multi-organ failure [71]. SARS-CoV-2 virus causes liver injury via many methods, including cytopathic effects via angiotensin-converting enzyme 2 (ACE2) receptors and immune-mediated hyperinflammatory state caused by cytokine storm. Numerous studies reported the incidence of impaired liver function ranging from 10.5% to 69% in patients with COVID-19 with rise in liver enzymes; alanine amino transaminase (ALT) and aspartate amino transaminase (AST), with a more specific increase in AST [3,5,11–13].

Patients with COVID-19 with a pre-existing liver disease or liver impairment are prone to show poorer prognosis. CB2R regulates innate immunity and is a critical mediator in liver diseases by exerting anti-inflammatory and antifibrogenic effects [72,73]. Polymorphisms in the CB2R gene following liver dysfunction in obese children suggest the role and importance of CB2R in liver diseases [74]. Numerous studies demonstrated hepatoprotective effects of JWH133 against acute liver injury or failure [75–77], septic liver [78], liver ischemia-reperfusion (I/R) injury [79], liver fibrosis [72,73], steatosis [75], ascites, and peritonitis [80] mediating activation of CB2R.

Hepatoprotective mechanisms include inhibition of hepatic inflammation by inducing autophagy [81], activating heme oxygenase-1, promoting an M1 to M2 shift in macrophages, and regulating microRNAs targeting Toll-like receptor 4 (TLR4) [76], inhibiting $CD4^+$ T cell recruitment in I/R-induced injury in the liver [82], suppressing proinflammatory effects of IL-17 and its production by Th17 lymphocytes mediating a signal transducer and activator of transcription 5 (STAT5)-dependent mechanism, along with restoring IL-22 production [73], inhibiting COX, NOS, and vascular endothelial growth factor [83] reducing inflammatory cell infiltration, lipid peroxidation, restoring oxidant/antioxidant balance and levels of proinflammatory mediators [79], and the promotion of liver regeneration. JWH133 also ameliorates portal hypertension, the severity of portosystemic collaterals and mesenteric angiogenesis, intrahepatic angiogenesis, and fibrosis in cirrhotic rats [83,84].

Furthermore, JWH133 also showed to attenuate ascites and peritonitis, and inhibits inflammation and oxidative stress in cirrhosis [80]. JWH133 showed protective effects in an experimental model of acute liver injury by inhibiting ubiquitin-specific peptidase 4 (USP4), deubiquitylating TGF-β receptor 1 (TβRI), downstream of CB2 microRNA 27b, which has been identified as an inhibitor of USP4 and TβRI in hepatocytes [85].

In patients with COVID-19, acute kidney injury includes direct virus-induced tubular or glomerular injury, as well as sepsis-associated injury or thrombotic disease as complications in a significant number of severely affected patients [86]. Interestingly, JWH133 has been shown to be protective in experimental models of acute kidney injury by inhibiting pro-inflammatory cytokines, chemokines, and apoptosis [87], and salvaging kidneys [88] mediated by activation of CB2R.

Intestinal inflammation and diarrhea also occur as a complication in patients with COVID-19 due to SARS-CoV-2-mediated reduction in mucosal angiotensin-converting enzyme 2 following entry, resulting in elevated angiotensin levels and increased TNF-α and tryptophan deficiency [89]. Cannabinoid ligands have roles in inflammation, secretion, and motility, as the ECS regulates the physiology and pathophysiology of the intestine, including motility, secretion, integrity, and immunity, as well as satiety and emesis [90]. Normally, neutrophils are not present in the intestinal mucosa, but during acute inflammation they quickly infiltrate the mucosa to control the pathogen or combat inflammation [91]. If the inflammation does not resolve quickly, neutrophil infiltration leads to massive damage to the intestine. Numerous studies have demonstrated that the cannabinoid system plays an important role in intestinal inflammation induced by the synthesis or release of proinflammatory cytokines following overactivation of immune cells [92–95].

The role of CB2R has been well demonstrated in intestinal inflammation, pain, and immunity [92]. JWH133 attenuates intestinal inflammation by enhancing apoptosis of activated T cells, decreasing the numbers of activated T cells, and inhibiting the induction of neutrophils, mast cells, and NK cells at the sites of inflammation [93]. Additionally, JWH133 also corrects motility impairment in LPS-induced septic ileus by decreasing myoelectrical activity and preventing delay of gastrointestinal transit, along with inhibition of inflammation [94]. JWH133, by activating CB2R in the enteric nervous system, attenuates LPS-induced increases in intestinal contractility [95], neurogenic intestinal inflammation [96], and suggests uses in individuals experiencing diarrhea-predominant inflammatory bowel [97]. CB2R activation also attenuates intestinal ischemia-reperfusion injury by inhibiting proinflammatory cytokines and restoring the oxidant/antioxidant balance.

Patients with COVID-19 also have stroke as a complication, and as a common accompaniment with atherosclerosis, hypertension, and atrial fibrillation [98]. The pathogenesis of stroke involves endothelial dysfunction, hypercoagulopathy, microvascular thrombosis, vasculitis, hypoxia, hemodynamic and cardiac dysfunction, and systemic inflammation following a cytokine storm [98]. In a thrombin-induced in vitro and in vivo rat model and collagenase-induced germinal matrix hemorrhage in rats, JWH133 ameliorates neuroinflammation, brain edema, neuronal degeneration, microglial accumulation, and levels

of phosphorylated ERK proteins [99], and protects the blood-brain barrier by reducing extravasation, activities of MMP-9 and -12, and the number of microglia in rats [100].

Additionally, COVID-19 may influence mental well-being and adversely impact immune functioning [101]. Psychosocial issues, such as stress, anxiety, and depression are believed to increase susceptibility to viral upper respiratory infections [102]. Psychological distress is linked to immune-inflammatory responses and suggests that psychoneuroimmunity is important in COVID-19 infection [102]. JWH133 has been shown to be beneficial in relieving stress, anxiety, and depression [103,104]. Stress exposure causes excitotoxicity and neuroinflammation, which contributes to stress-related neuropathology's, such as depression. Clinically, approximately 30% of patients with stroke develop post-stroke depression. JWH133 shows antidepressant, antistress, and anxiolytic activity in post-stroke depression induced by chronic unpredictable mild stress followed by middle cerebral artery occlusion in rats [103], and in a battery of behavior and stress models [104]. Mechanistically, the pharmacological effects are mediated by CB2R-dependent inhibition of proinflammatory cytokines and inflammatory mediators [104], interactions with the cholinergic system [105] and upregulation of serotonergic receptors, such as 5-hydroxytryptamine receptor 2A (5-HT2A) [106].

Additionally, JWH133 exhibits an antiallodynic effect in a neuropathic pain model induced by retrovirus infection by suppressing neuroinflammation, macrophage activation, and T-cell infiltration via blocking the Janus kinase/STAT3 pathway [107]. JWH133 acts as an analgesic, as it exhibits antihyperalgesic and antinociceptive actions, mainly by mitigating synthesis of proinflammatory molecules and the inhibition of nociception induced by oxidative stress-induced TRPA1 activation, inhibition of vascular permeability and migration of neutrophils, exhibiting systemic and peripheral analgesic-dependent effects on the opioid system [108].

4. CB2 Receptors Mediated Immunomodulatory Activity of JWH133

CB2R is significantly expressed in immunoregulatory cells, including macrophages, B and T cells, and upon activation leads to the subsequent inhibition of cyclic adenosine monophosphate production [109]. CB2R regulates the immune system by controlling immune cell activation through the modulation of T helper cells [110], attenuation of proinflammatory cytokines [111], and NF-κB-mediated apoptosis [112] and found useful in immune-related diseases [113]. CB2R activation has also been shown to mediate immunosuppressive activities of mesenchymal stem cells in immunocompromised conditions [114].

A recent study has demonstrated that JWH133, in combination with dexamethasone, is effective in immune thrombocytopenia purpura (ITP), an autoimmune disease characterized by antibodies against platelets [114]. The combination is effective in mesenchymal stem cells, multipotent cells that have significant roles in immunomodulation and suppress proliferation and activation of both T- and B-lymphocytes, ameliorate apoptotic cell death via B-cell lymphoma 2 signaling, and reinstate the immunomodulatory properties of mesenchymal stem cells derived from patients with ITP [114]. Recently, dexamethasone has been reported to be effective in patients with COVID-19. Thus, JWH133 may reduce the dose of dexamethasone and its adverse effects, along with maintaining its therapeutic effects due to the synergistic combination of dexamethasone and JWH133 [114].

JWH133 prevents the secretion of IL-12p40 and enhances secretion of IL-10 in LPS- or Theiler's virus-activated macrophages, mediating activation of the CB2R-dependent ERK1/2 MAPK pathway [115]. IL-10 and IL-12 both regulate priming of Th1 or Th2 cells in immune responses. IL-12 plays a significant role in innate and adaptive immunity, and differentiates the immune system towards a Th-1 protective response against viral infections. IL-10 plays a role in maintaining the balance of appropriate macrophage responses to LPS by curbing the synthesis and release of IL-12. CB2R activation in cells belonging to macrophage lineages inhibits the induction of a Th-1 immune response, affecting the required immunity to counter a pathogen or inflammatory state [115].

5. CB2 Receptors Mediated Effects of JWH133 on Acute Lung Injury and Airway Activity

ALI in experimental models is akin to acute respiratory distress in COVID-19. ALI is caused by infections, pneumonia, sepsis, acid aspiration, toxic inhalation, and xenobiotics, which are the major causes of a cytokine storm. CB2R stimulation plays a significant role in protecting the lungs in numerous models of ALI, including cecal ligation puncture-induced septic lung injury [116], I/R-induced lung injury and LPS-induced lung injury [37], paraquat-induced ALI [38], and LPS-induced ALI [117]. JWH133, by activating CB2R, shows potent anti-inflammatory effects in LPS-induced ALI mice by reducing leukocyte migration, vascular permeability, and reducing levels of cytokines, chemokines, and adhesion molecules in the lungs and blood, along with salvaging the lungs [117].

JWH133 has been shown to protect against ALI by inhibiting proinflammatory cytokines, MAPKs, and NF-κB activation via activating CB2R [38], as shown in Figure 3. It also reduces neutrophil infiltration and edema, improving histology of the lungs along with PaO2 in arterial blood [38]. JWH133 has also been found to protect against I/R-induced ALI by reducing levels of cytokines, lipid peroxidation, neutrophil infiltration, lung edema, and improving anti-oxidant and lung histology, along with the PaO_2/FiO_2 ratio, mediated by the CB2R-dependent PI3K/Akt pathway [37], as shown in Figure 3. Furthermore, JWH133 exerts an antitussive effect in chronic cough by inhibiting activation of sensory nerves in guinea pig and vagus nerves in humans, and suppresses the cough reflex mediated by CB2R activation [118]. In addition to antitussive activity, JWH133 also mitigates bronchoconstriction via inhibition of pre-junctional neurotransmission, neurogenic airway inflammation, and hyper-reactivity [118,119], as shown in Figure 3.

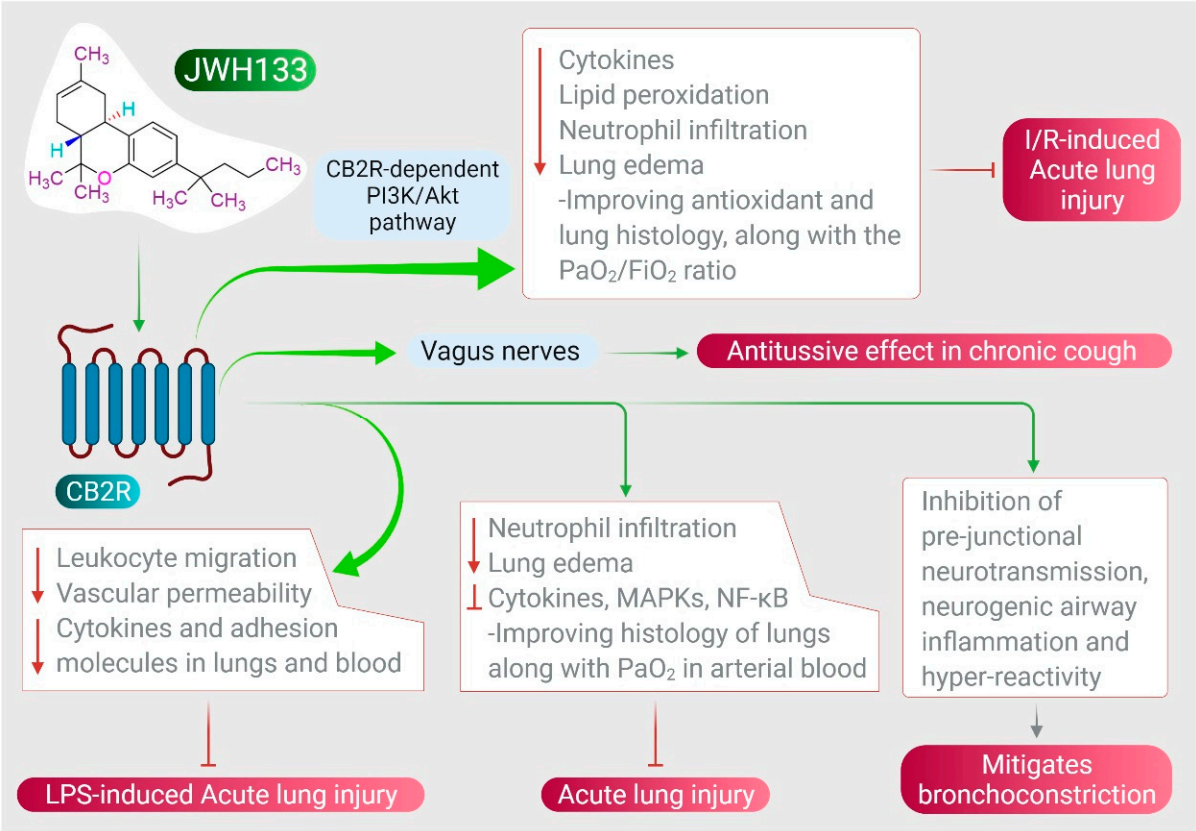

Figure 3. Effect of JWH133 on acute lung injury and airway activity.

Furthermore, at the doses at which cannabinoids produce bronchodilation, JWH133 does not elicit respiratory depression at the central level. CB2R expressed on eosinophils plays a role in lung inflammation mediated by the generation of NO and prostaglandin-

E_2 [120]. CB2R is involved in antigen processing, immune cell differentiation, and macrophage migration, which have all been shown to play a role in airway immunomodulation [121,122].

6. CB2 Receptors Mediated Anti-Inflammatory and Antiviral Activity of JWH133

CB receptors genetically ablated in mice display an enhanced inflammatory response to influenza infection [123,124]. CB2 gene (*CNR2*) polymorphisms also play a role in the immunopathogenesis associated with severe necroinflammation in patients with respiratory syncytial virus (RSV) [125], chronic hepatitis C (HCV) [126], childhood ITP [127], celiac disease [127], and necroinflammation in patients with human immunodeficiency virus (HIV)/HCV co-infection [128].

CB2R activation appears to be a novel therapeutic strategy for immunomodulation to improve RSV-induced lung pathology by inhibiting immunoregulatory cells [125]. Recently, JWH133, by CB2R activation, has been shown to exert anti-inflammatory effects by enhancing the production of IL-10, reducing bronchoalveolar influx, inhibiting the release of interferon-γ and macrophage inflammatory protein-1α, and reducing numbers of neutrophils and monocytes in RSV-induced mice. Further, the inhibitory effect of JWH133 on recruitment of neutrophils at the site of inflammation via activation of p38 is additional indication of its anti-inflammatory effects [129].

CB2R has also been shown to be involved in HIV-associated neuropathogenesis by enhancing migration and altering the expression and compartmentation of the β-chemokine receptor CCR-3, as well as releasing inflammatory factors, including the virus-specified trans-activating protein Tat, which further elicits chemokines, cytokines, and a chemotactic response from microglia [130]. Numerous studies have shown that activation of CB2R exerts pleiotropic effects by ameliorating neuroinflammation via inhibiting replication of HIV-1, reducing microglia migration towards HIV-1 Tat, rescuing neurons and endothelial cells, and suppressing viral infection, as well as associated inflammatory responses [131–134]. CB2R ligands have been shown to suppress replication of HIV-1, rather than interfering with viral entry in microglia [131]. Activation of CB2R significantly suppresses the expression of HIV-1 p24 in microglia and $CD4^+$ T cells in patients infected with HIV-1 [132]. JWH133 also shows significant inhibition of primary $CD4^+$ T cells in HIV-1 infection by inhibiting reorganization and impairing productive infection of C-X-C chemokine receptor type 4-tropic virus [133].

7. CB2 Receptors Mediated Protective Effects of JWH133 in Organ Injuries and Sepsis

Uncontrolled infection and increased inflammatory mediators might cause a systemic inflammatory response and sepsis. CB2R-selective cannabinoids exert potent immunomodulatory and anti-inflammatory effects in the brain, pancreas, intestine, liver, heart, and kidney [34,35]. Activation of CB2R attenuates inflammatory states and oxidative stress in the liver [75–77], lungs [50], heart [39], kidney [87], intestine [93], brain [135], and in sepsis [78] by inhibiting inflammatory cell recruitment, proinflammatory cytokines, and increasing levels of anti-inflammatory cytokines.

In a polymicrobial sepsis model in rats [78], JWH133 shows protective effects on brain, lung, liver and, heart, mediated by CB2R activation [78]. JWH133 decreases proinflammatory cytokines and increases the anti-inflammatory cytokine IL-10 [78]. Sepsis is associated with neuronal damage and cognitive impairment, with the participation of proinflammatory cytokines and oxidative/nitrosative stress [78]. Deregulated immunity and an imbalance between the proinflammatory and anti-inflammatory systems results in multi-organ dysfunction and failure, and consequently may cause death. Acute central nervous system (CNS) injury perturbs the homeostasis of the CNS and immune system and enhances patient susceptibility to infections [136]. JWH133 shows neuroprotective effects in LPS-induced neuroinflammation and endotoxemia by mitigating levels of proinflammatory cytokines, adhesion molecules (vascular cell adhesion protein 1 and E-selectin), and oxidative/nitrosative stress [135]. Based on the role of JWH133 in ameliorating sepsis, JWH133

appears to be a potent candidate for limiting COVID-19 progression and post-infection sequelae, including its impact on the multi-organ system.

Furthermore, JWH133 also shows ROS or free radical scavenging and Fe^{+2} chelating activity against free radicals in numerous in vitro assays, including 2,2-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid, 2,2-diphenyl-1-picryl-hydrazyl-hydrate, ferric reducing antioxidant power, and oxygen radical absorbance capacity, with chelating and reducing power [137,138], promoting mitochondrial biogenesis [139] and improving endogenous antioxidants in vivo in many tissues. JWH133 inhibits oxidative stress, which initiates and contributes to numerous pathways, including inflammasome activation, nuclear factor erythroid 2-related factor 2 (Nrf2)/Kelch-like ECH-associated protein 1 (Keap1), TLR4/high mobility group box 1, MAPK, and sirtuin/PPAR gamma coactivator 1-α (PGC1-α) pathways, leading to the release of inflammatory mediators and cytokines that sustain inflammation, and involving metabolic reprogramming of innate immune cells [77,84,99]. Taken together, JWH133 has been shown to modulate the majority of the signaling pathways that contribute to redox immune-inflammatory signaling those results in organoprotective effects. In addition to the lungs, COVID-19 affects almost all organ systems, including the heart, brain, liver, kidney, intestine, and coagulation system. Thus, the organoprotective effects demonstrated in the in vivo experimental models are encouraging for speculation of the therapeutic benefits of JWH133.

8. Limitations on the Proposed Therapeutic Applications of JWH133

In present manuscript, the possible therapeutic role of JWH133 in COVID-19 has been proposed based on the previously reported potent pharmacological activity of JWH133 against infection, inflammation, and immunity in experimental models of human diseases involving dysregulated immune-inflammatory and redox homeostasis. Many authors proposed the hypotheses that CB2R, an important constituent in endocannabinoid system may play role in maintaining immune system and targeting inflammation and infection [18,21,140]. A recent report suggests that CB2R may play role in targeting the trinity of infection, inflammation and immune dysregulation [18,21]. Given the possible role of CB2R activation in attenuating inflammation, viral replication and favorably modulating immune systems, it has been speculated that JWH133 endowed with CB2 selective agonist property and showing affinity to M^{pro} may be a candidate for further investigation for its possible use in management of COVID-19. There are reports of long-term complications in some patients even after recovery from COVID-19. Thus, given the tissue protective effects and effect on numerous tissue remodeling effects, JWH133 could be a candidate to be investigated for possible use in combating the long-term complications in COVID-19. Taking into consideration the safety of JWH133 and efficacy in various disease models in experimental studies, JWH133 may be a valuable agent to be investigated further in COVID-19. The inhibitory activity on the proteases and other molecular targets should be assessed for specificity, affinity, dose-response, and kinetics in experimental studies. The binding of these compounds limits the availability of the substrate, modifies configuration of active sites, and prevents dimerization, viral entry and, viral replication. The available reports clearly demonstrate that the progression and complications of COVID-19 involves cytokine storm, therefore, cannabinoids activating CB2R may inhibit cytokine storm, coupled with their additional organ-protective effects. However, until now there is no clear evidence available on the antiviral activity of JWH133 on SARS-CoV-2. There are no data available in experimental studies whether JWH133 can protect against COVID-19 or may be useful in treatment of COVID-19. There is paucity of preclinical and clinical data on infection, inflammation, and immunity in context to COVID-19. The recent availability of animal models could be important in evaluating its preclinical efficacy. However, there is lack of clinical data and rigorous pharmacokinetics in humans. Thus, the preclinical evaluation including duration of use and dose to be explored, the safety and interaction with concomitant drugs, as well as the heterogeneity of the target population should be considered before the possible use of JWH133 in therapeutics. Nonetheless, given the

preclinical studies on anti-inflammatory and immunomodulatory properties, there are opportunities for further studies to investigate the possible use in COVID-19. Considering the safety in numerous preclinical studies, further proof of the concept preclinical and translational clinical studies is encouraged to determine the clinical usage and pharmaceutical development of JWH133.

9. Conclusions

Thus, including the immunomodulatory, anti-inflammatory, and antiviral properties of JWH133 and integrating its pharmacological and molecular mechanisms, JWH133 could be a promising therapeutic candidate for COVID-19. The potent anti-inflammatory activity involves multiple pathways, including inhibition of proinflammatory cytokines, chemokines, and adhesion molecules, along with suppression of macrophage infiltration and neutrophil-endothelial cell interactions that inhibit a cytokine storm, which is a major reason for death in patients with COVID-19. JWH133 has potential as an immunomodulatory, as well as a potent anti-oxidant, in improving host cellular immunity against infection; its ability to interfere with virus replication, along with its antibacterial activity, may further help in controlling symptoms and worsening of the disease, secondary infections, complications, progression, and resultant death.

JWH133 appears non-toxic in experimental studies with no abuse potential and possesses numerous characteristics that make it an attractive therapeutic candidate to explore immunomodulatory, anti-inflammatory, and antiviral activities within the context of COVID-19. Furthermore, the drug likeliness properties, pharmacological actions, and molecular mechanisms provide a rationale for the evaluation of JWH133 as a plausible therapeutic candidate against COVID-19. However, it is important to highlight that none of the above studies have demonstrated the effect of JWH133 in COVID-19, due to the lack of a preclinical COVID-19 infected animal model to perform preclinical evaluations and to distinguish whether candidate compounds may become effective drugs. Nevertheless, previous studies have shown efficacy in limiting infection, inflammation, and immunity, which reasonably suggests JWH133 may be a potential candidate for further evaluation in COVID-19.

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Abbreviations

5-HT2A	5-hydroxytryptamine receptor 2A
ACE-2	Angiotensin-converting enzyme 2
ALI	Acute lung injury
ALT	Alanine amino transaminase
ARDS	Acute respiratory distress syndrome
AST	Aspartate amino transaminase
CB1R	Cannabinoid receptor type 1
CB2R	Cannabinoid receptor type 1
CNS	Central nervous system
COVID-19	Coronavirus disease-2019
COX-2	Cyclooxygenase-2
ECS	Endocannabinoid system
ERK1/2	Extracellular signal-regulated kinase $\frac{1}{2}$
GPCR	G-protein-coupled receptor
HCV	Chronic hepatitis C
IL	Interleukin
iNOS	Inducible nitric oxide synthase
ITP	Immune thrombocytopenia purpura
LPS	Lipopolysaccharide
MAPK/JNK	Mitogen-activated protein kinase/c-Jun N-terminal kinase
MLKL	Mixed lineage kinase domain like pseudo kinase
NF-κB	Nuclear factor-kappa B
NK cells	Natural killer cells
NLRP#	NOD-like receptor protein 3
NO	Nitric oxide
NRF2/Keap1	Nuclear factor erythroid 2-related factor 2/Kelch-like ECH-associated protein
PGCV1-α	PPAR gamma coactivator 1-α
PI3K/Akt	Phosphoinositide 3-kinase/protein kinase B
RIP	Receptor interacting protein
RSV	Respiratory syncytial virus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
STAT-5	Signal transducer and activator of transcription 5
TGF	Transforming growth factor
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor
TRP	Transient receptor potential
USP4	Ubiquitin-specific peptidase 4

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