MINI-REVIEW ARTICLE

Can Cannabinoids Suppress the Cytokines Cascade in Patients with Coronavirus Disease COVID-19? A Mini-Review

Hanane Zaki1,* and Mohammed Bouachrine1

1Molecular Chemistry and Natural Substances Laboratory, Faculty of Science, Moulay Ismail University of Meknes, Morocco EST Khenifra, Sultan Moulay Sliman University, Khenifra, Morocco

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Abstract: Coronavirus disease-2019 (COVID-19), caused by SARS-CoV-2, started in Wuhan, China in December 2019 and became a global pandemic. According to WHO, more than fourteen million cases were reported and thousands of casualties worldwide (until July 18, 2020). Most of the COVID-19 patients have symptoms such as fever, tiredness, and dry cough. Some people may also experience body aches, nasal congestion, a runny nose, and diarrhea. So far, doctors have been using treatment to relieve symptoms and give patients’ immune systems time to regain control of this virus. Many studies have highlighted the important role of cytokine cascades in the death rate in COVID-19 patients. Therefore, inhibition of this phenomenon has become a very important target in the clinical management of this disease. With this idea, in this mini-review, we will focus on the potential role of cannabinoids in the suppression of cytokines cascades in patients with COVID-19 and their importance in the clinical management of this disease.

Keywords: Cannabinoids, THC, CBD, cytokines, COVID-19, SARS-COV-2.

1. INTRODUCTION

Since the appearance of Severe Acute Respiratory Syndrome (SARS) at the end of February 2003 [1] and Middle East Respiratory Syndrome (MERS) in 2012 [2], the coronavirus family has shown a real threat to human health. Therefore, scientists have warned about the appearance of a virus from the same family, that can be fatal to control. The year 2019 was marked by the appearance of this expected virus SARS-COV-2 (Fig. 1) which causes coronavirus disease 2019 (COVID-19) [3]. The pandemic suspected to originate in Wuhan, China and in seven months it has killed thousands of people and has affected more fourteen million worldwide [4]. There is any treatment or vaccine against this disease, however, the abundance of cases gives a lot of information to physicians and scientists concerning the management and treatment of this disease. There are some strategies requiring validation, like repurposing drugs such as hydroxychloroquine, favipiravir, remdesivir, lopinavir, and ritonavir [5-7]. Wuhan’s doctors described an early clinical management protocol for this disease as follows, the use of early antiviral treatment for timely elimination of pathogens [8], anti-shock and anti-hypoxemia treatment by using glucocorticoids when necessary, suppression of cytokines cascade and oxygen therapy for hypoxemia, [9] also the use of antibiotics to prevent secondary infection. This protocol is described in a handbook published by Hospital, Zhejiang University School of Medicine, China [10]. In this handbook, they emphasized the importance of suppressing cytokines cascades in the clinical management of the COVID-19. Cytokine-mediated inflammation, also described as a cytokine storm, is a characteristic of the Acute Respiratory Distress Syndrome (ARDS) which is noticed in patients with COVID-19 [11]. Clinical studies in patients with COVID-19 have shown high levels of interleukin1β (IL1β), interleukin6 (IL6), interleukin8 (IL8), and tumor necrosis factor-alpha (TNFα) [12]. Other studies have highlighted the importance of cytokines storm suppression in reducing COVID-19 mortality [12-14]. Therefore, cytokine suppression becomes an important target in the clinical management of this disease [15].

Cannabis and cannabinoid-based chemicals (Fig. 2) have become increasingly accepted by the scientific community as pharmacologically active compounds [16]. In addition to their analgesic effect, cannabinoids have an important effect on the immune system and inflammatory responses, they also affect digestive organs, including the pancreas and liver [17]. Furthermore, cannabinoids are antispasmodic, antitumor, appetite-stimulating, anti-emetic, anticonvulsant, sedative, hypnotic, antipsychotic, and antioxidant [18, 19]. Therefore, we will discuss briefly in this mini-review, the potential role of cannabinoids in the suppression of cytokines cascades in patients with COVID-19 and their importance in the clinical management of this disease, after describing how SARS-CoV-2 infect the cells, the host immune responses to SARS-COV-2, and the COVID-19-associated acute respiratory distress syndrome.
**Fig. (1).** The SARS-CoV-2 virion and its proteins: The figure was taken from [43]. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

**Fig. (2).** Structure of the two most studied cannabinoids, (a) THC (b) CBD. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

### 2. SARS-COV-2 CELL INFECTION

SARS-COV-2 infects cells firstly by Fusion, and it binds to ACE2 (the angiotensin-converting enzyme 2) by its Spike glycoprotein (S) (Fig. 1). The spike glycoprotein is initiated by a protease enzyme (TMPRSS2) to complete his entry [20]. This activation by TMPRSS2 as a protease is needed to attach virus spike protein to its human cellular ligand [20, 21]. Secondly, SARS-CoV-2 infects cells by endocytosis, this type of invasion involves different pathways depending on the type of cells and can include Clathrin-mediated endocytosis, caveolae, and a clathrin- and caveolae-independent mechanism involving lipid rafts [22]. Inside the host cell, the viral genome is transcribed and then translated by diverting the cellular machinery to its favor. Therefore, the host cell turns to apoptosis and releases new viral copies that infect other cells [23].

### 3. HOST IMMUNE RESPONSES TO SARS-COV-2

The mechanism of the immune response of the Host-cell against SARS-CoV-2 (Fig. 1) is not yet well understood, but due to the similarity of this virus with SARS-COV and MERS-COV, it has been possible to predict this mechanism [24]. The first line of defense against viral infection is the set of recognition factors; Toll-like-Receptors (TLR) and RIG-I-like receptors which recognize the viral genome. Endosomal sensors TLR7 and TLR 8 detect Single-stranded RNA, and cytosolic sensors RIG-1 and MDA-5 detect double-stranded RNA. Once activated, these sensors recruit the signaling proteins myeloid differentiation primary response 88 (MyD88) and the mitochondrial antiviral-signaling protein (MAVS). This leads directly to transcription factors activation and the release of pro-inflammatory Cytokines [24-27].

The entrance of the virus also activates the NLRP3 inflammasome pathway which recruits the Caspase-1 and leads to the secretion and maturation of inflammatory interleukins (IL-1, IL-6, IL-8, IL-21…) [28, 29] which induces cell pyroptosis. This phenomenon is called Cytokine Release Syndrome and it is the main cause of the deterioration of certain organs in COVID-19 patients [30].
4. COVID-19 -ASSOCIATED ACUTE RESPIRATORY DISTRESS SYNDROME

Acute Respiratory Distress Syndrome (ARDS) is associated with COVID-19 due to the accumulation of inflammatory cytokines which damages the cells [31]. The rapid increase in the number of infected cells and viral copies will induce a severe immune response accompanied by overexpression of cytokines [32, 33]. The immune system that protects us from any external agents can be in the case of SARS-COV-2 a real danger against our organism because it requires strict balanced regulation; the under-expression of cytokines indicates an insufficient immune response. While an overexpression of cytokines causes an immune overreaction which is considered as a danger against the cells [34]. The immune cells arriving to protect the tissues against infection become infected, which creates confusion and anarchy between immune cells [35]. The novel coronavirus forces infected cells to over-react by releasing a huge quantity of cytokines and becoming out of control, which leads to pyroptosis. Also, the uncontrolled release of cytokines forces lymphatic cells to be sent to the tissues, which wastes energy and resources [35-38].

In this case, two types of immune cells can cause enormous damage, neutrophils being one play an important role in the destruction of cells by the release of destructive enzymes. Due to the cytokines storm, a large number of neutrophils arrive at the infected site and destroy thousands of cells, even healthy cells [39]. The second type of cells that lose control is the killer T cells, and in the normal case, these cells force the infected cells to self-destruction and also destroy healthy cells [40]. The more the cytokines are released, the more the immune cells are released, the more healthy tissues are damaged which can induce permanent and irreversible damage in certain organs such as lungs, kidneys, and the digestive system [41, 42]. The destruction of respiratory tissue is the origin of acute respiratory distress syndrome associated with COVID-19.

In most cases, the immune system gradually regains control, clears the infected cells out of the body, and protects the other cells from infection. However, in some cases, the uncontrolled immune response has caused severe symptoms and even death. Reducing the severe inflammatory response caused by the cytokines storm can decrease severe symptoms in some patients with COVID-19 [44, 45], and protect against acute respiratory distress syndrome [46].

5. POTENTIAL ROLE OF CANNABINOIDS IN THE SUPPRESSION OF THE CYTOKINES CASCADE

Cannabinoids (Fig. 2) bind to CB1 and CB2 receptors [47]. CB1 receptors (Fig. 3) are found mainly in neurons [48] while CB2 receptors are found in addition to neurons in other cells like immune cells. The two most studied cannabinoids are THC and CBD (Fig. 2) [49]. THC is analgesic, antispasmodic, antitumor, anti-inflammatory, appetite-stimulating, and anti-emetic. Cannabidiol, which binds to the CB1 and CB2 receptors, is anti-inflammatory, anticonvulsant, sedative, hypnotic, antipsychotic, antioxidant, neuroprotective, and immuno-modulator [18, 19]. The binding of the CB1 or CB2 receptor to its endogenous or exogenous agonists (in this case the cannabinoid) can inhibit the release of intracellular and/or extracellular Ca^{2+} in the cell [50]. Inside the cell, many important intracellular proteins involved in immune-response depend on Ca^{2+} for activation, mainly NLRP3 inflammasome, disturbance of signal transduction via the CB1 or CB2 receptor can alter these pathways [51, 52] and have a profound influence on the ability of viruses to replicate in cells containing this type of receptors [53]. Many other cellular mechanisms in which there is an important involvement of Ca^{2+} are directly influenced by cannabinoids. For example, phospholipase A2, which plays an important role in inflammation [54], Phospholipase C and Phospholipase D1 which are essential in signal transduction and neurotransmission [55, 56], Ca^{2+} Calmodulin which intervenes in adaptive immunity and inflammatory response [57], Calpains which is a Ca^{2+}-dependent protease, it intervenes in cell migration and inflammation and Transglutaminases essential in inflammation, fibrosis, cell cycle and programmed cell death [58]. The common point between all these Ca^{2+} dependent enzymes is that they all play a role in inflammation in the host's responses to viral infection. These pathways can be improved or altered in the presence of cannabinoids.

Fig. (3). Structure of the Human Cannabinoid Receptor CB1 PDB code 5TGZ [59]. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

In the case of COVID-19, with which the inflammation process is associated with immunopathology [60, 61], we believe that treatment with cannabinoids may be beneficial by the inactivation of certain inflammatory mechanisms associated with the production of cytokines, mainly the NLRP3 Inflammasome [62]. By targeting this protein we can decrease cytokines in the early inflammatory response [38] and we will give the immune system time to organize and reduce the damages, which will decrease severe symptoms evident in COVID-19 patients and prevent the acute respiratory distress syndrome (ARDS) [60].

6. OTHER EFFECTS OF CANNABINOIDS

Most of the COVID-19 patients suffer from emotional and psychic stress. Therefore, the antidepressant and anxiolytic properties of these molecules can be exploited [63], the stress and anxiety accompanied during the period of confinement, the economic losses, and social distancing could be attenuated by these molecules. Another important effect
of these molecules which could be important for patients with COVID-19 is the anticoagulant effect. Several studies showed a considerable anticoagulant effect of THC and CBD by the inhibition of thrombin-induced clot formation [64]. Patients with COVID-19 could suffer from many cardiac dysfunctions, including acute myocardial injury and heart failure [65]. Recent studies suggest that anticoagulants decrease mortality in patients with COVID-19 [66, 67]. Cannabinoids may also be an alternative to anti-inflammatory drugs used in the treatment of patients with COVID-19 [68]. Therefore, administering cannabinoids to COVID-19 patients in a clinical study could be very promising.

CONCLUSION

In this paper, we have briefly discussed the biological effects of cannabinoids, and the potential role of these chemicals in the clinical management of COVID-19, by suppressing cytokines cascades in patients with COVID-19. We think that a clinical study in this subject would be very interesting and promising to verify the reliability of these molecules against the COVID-19 disease.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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