

# The potential of cannabidiol in the COVID-19 pandemic: a hypothesis letter

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## Abstract

Identifying candidate drugs effective in the new coronavirus disease 2019 (Covid-19) is crucial, pending a vaccine against SARS-CoV2. We suggest the hypothesis that Cannabidiol (CBD), a non-psychotropic phytocannabinoid, has the potential to limit the severity and progression of the disease for several reasons: 1) High-CBD Cannabis Sativa extracts are able to downregulate the expression of the two key receptors for SARS-CoV2 in several models of human epithelia 2) CBD exerts a wide range of immunomodulatory and anti-inflammatory effects and it can mitigate the uncontrolled cytokine production featuring Acute Lung Injury 3) Being a PPAR $\gamma$  agonist, it can display a direct antiviral activity 4) PPAR $\gamma$  agonists are regulators of fibroblast/myofibroblast activation and can inhibit the development of pulmonary fibrosis, thus ameliorating lung function in recovered patients. We hope our hypothesis, corroborated by several preclinical evidence, will inspire further targeted studies to test CBD as a support drug against the COVID-19 pandemic.

## Dear editor,

An aberrant release of cytokines and proinflammatory molecules is closely related to lung injury, multiorgan failure and ultimately poor prognosis in the new Severe Acute Respiratory Syndrome - Coronavirus - 2 (SARS-CoV2) pandemic [1].

Such uncontrolled release of cytokines, namely interleukin (IL)-1 $\beta$ , IL-6, monocyte chemoattractant protein (MCP)-1, paralleled with the decreased natural killer cells may result in the so-called 'cytokine storm'. Immune dysregulation, rather than viremia levels *per se*, has been related to the massive proinflammatory cytokine secretion by alveolar macrophages, and subsequent CD4<sup>+</sup> and CD8<sup>+</sup> T cell dysfunction observed in SARS-CoV infection [2]. Hence, until specific vaccines become available, the use of antiviral agents alone may not be sufficient to stop the cytokine storm and respiratory distress in severely-ill patients. In the attempt of reducing their overall mortality, it is therefore essential to identify new therapeutics able of mitigating the cytokine storm [3]. Nonetheless, redundancies within the complex cytokine network still represent a major obstacle to monoclonal antibodies therapies. The ideal drug candidate should be already in use for other indications, have a favorable safety profile and a multitargeted action, able to synergistically mitigate the cytokine storm, acting as an immunomodulatory rather than an immunosuppressant drug.

In a recent paper, high-cannabidiol (CBD) Cannabis Sativa extracts have been reported to downregulate Angiotensin-converting enzyme 2 (ACE2) and Transmembrane Serine Protease 2 (TMPRSS2) receptors, crucial viral gateways in oral, lung and intestinal epithelia constituting important routes of SARS-CoV2 invasion [4]. By downregulating ACE2 and TMPRSS2 receptors, CBD could be used to prevent SARS-CoV2 entry into susceptible hosts but most importantly, it could reduce the bioavailability of ACE2 receptors in infected tissues, thus limiting the progression of the disease. These newly described effects pair with its well-described immunomodulatory activities, making of CBD a promising candidate drug.

Non-psychoactive phytocannabinoid CBD is indeed considered one of the most interesting emerging molecules in the field of pharmacology, since it exerts a wide range of therapeutic effects, ranging from anticonvulsive, sedative, hypnotic, antipsychotic, anti-cancer, anti-inflammatory and neuroprotective activities [5]. Lacking of the unwanted psychotropic effects of marijuana derivatives, CBD has little binding affinity to cannabinoid receptors (acting as allosteric modulator of cannabinoid CB1 receptors) and a favorable safety profile in humans [6,7]. CBD acts as a powerful antioxidant acting at various receptor sites, including peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ), 5-hydroxytryptamine (5HT)-1A, Adenosine A2, transient receptor potential (TRP) channels receptors to directly or indirectly display a wide range of anti-inflammatory and immunomodulatory effects. A complete review of CBD receptor targets is beyond the purpose of the present article and the readers are invited refer to more extensive review on this subject [5].

Such pleiotropic pharmacological activity has been tested in various pathological conditions, including respiratory diseases resembling COVID19-induced respiratory distress. Acute Lung injury (ALI) refers to a characteristic form of parenchymal lung disease, featured by bilateral pulmonary infiltrates, alveolar-capillary vasculitis with neutrophil infiltration and proinflammatory cytokines release, comparable to COVID19. By acting at adenosine A2 receptor site, CBD caused a marked amelioration of the pulmonary function [8,9] as a consequence of the significantly decreased lung resistance and elastance due to the reduction of leukocyte migration into the lung, accompanied to a marked inhibition of both pro-inflammatory cytokines (TNF $\alpha$  and IL-6) and chemokines (MCP-1 and MIP-2) released [8,9].

Although limited to interesting preclinical studies, scattered evidence also points towards a possible use of CBD in viral infections. Indeed, several plant-derived compounds have evolved to display antiviral activity, including many phenol-based compounds, such as terpenoids.

CBD and other cannabinoids exert their activity through the interaction with the nuclear peroxisome proliferator-activated receptors (PPARs) [10]. The PPARs belong to the family of nuclear hormone receptors and their activity is regulated by steroids and lipid metabolites. Three different PPAR isoforms (PPAR $\alpha$ , PPAR $\beta$ , also called  $\delta$ , and PPAR $\gamma$ ) have been identified and they have been described to regulate the expression of genes related to lipid and glucose homeostasis and inflammatory responses.

PPAR $\gamma$  agonism in resident alveolar macrophages significantly limits pulmonary inflammation and promotes host recovery following respiratory viral infections [11]. As it has been demonstrated during acute pneumonia, alveolar macrophage largely express PPAR $\gamma$ . Such increase has been also detected in pathological conditions similar to COVID-19 infection, such as Middle East Respiratory Syndrome (MERS) [12]. PPAR $\gamma$  activation is also responsible for the control of cytokine over-secretion with consequent amelioration of the tissue damage. It is therefore likely that in addition to directly determining an improvement in lung dynamics, CBD could significantly counteract the onset of the cytokine storm from resident macrophages. Interestingly, prophylactic or therapeutic administration of PPAR $\gamma$  agonists led to reduction of morbidity and mortality during influenza A virus infection [13].

Moreover, PPAR $\gamma$  agonists may directly inhibit viral replication by different human viruses such as Human Immunodeficiency Virus, Respiratory syncytial virus, Hepatitis B Virus and Hepatitis C Virus [14,15]. Noteworthy, these experimental evidences are corroborated by recent study showing a *direct* antiviral against HCV in vitro [16].

Recent reports show that a subset of COVID-19 survivors can develop post-infectious sequelae with persistently impaired lung function and pulmonary fibrosis [17]. PPAR- $\gamma$  receptors represent a potential therapeutic

tic target in fibrotic lung diseases, given their ability of regulating fibroblast/myofibroblast activation and collagen secretion in murine models [18]. Notably, CBD has been shown to reduce pulmonary inflammation and fibrosis in animal models of asthma [19].

It is therefore conceivable to speculate that, being a PPAR- $\gamma$  receptor agonist, CBD can potentially limit the onset of late-onset pulmonary fibrosis in COVID19-recovered patients.

Although CBD is a relatively safe molecule for humans and different trials have been conducted [20] or are ongoing, especially in the field of neurological disorders therapy; there are currently no evidences about the efficacy and relative toxicity of CBD in COVID19.

Even if CBD was (incorrectly in our opinion) considered as a mere therapeutic supplement, there is still lack of data regarding the relative toxicity profile in co-administration with other drugs in the current anti-COVID19 protocols. A possible strategy would be testing CBD therapeutic potential in COVID19 patients, according to a precautionary principle, at an early stage of the disease or alternatively, to evaluate its effectiveness in COVID-19 recovered patients.

The COVID19 pandemic is testing the planet. The off-label use of readily available therapeutics able to limit the severity of the disease must be scrupulously scrutinized, pending a vaccine against SARS-CoV2. In keeping with this, we consider CBD a promise candidate drug to bet on, based on the encouraging preclinical studies and its relative safety profile in humans (**figure 1**). Further evidence will be needed to confirm its beneficial activities and turn CBD into a useful addition to the treatment of COVID-19.

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## FIGURES LEGENDS

**Figure 1.** The potential of cannabidiol in SARS-CoV2 infection.

