

Cannabis for COVID-19: can cannabinoids quell the cytokine storm?

Emmanuel Shan Onaivi*^{1,2}  & Venkatanarayanan Sharma^{1,2}

¹Department of Biology, College of Science & Health, William Paterson University, Wayne, NJ 07470, USA

²College of Science & Health, William Paterson University, Wayne, NJ 07470, USA

*Author for correspondence: onaivie@wpunj.edu

“Along with many ongoing studies and clinical trials, cannabis and cannabinoid adjunctive treatment in COVID-19 could be of use in countering SARS-CoV-2 infections by quelling the cytokine storm, but require more studies and trials.”

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The recent emergence of SARS coronavirus 2 (SARS-CoV-2) has resulted in the alarming spread of the highly infectious and contagious COVID-19 pandemic that is causing catastrophic damage and affecting health, life and death around the world [1,2]. SARS-CoV-2 has also created a COVID-19 ‘infodemic’ crisis with an overabundance of information and misinformation about the origin of the virus, potential therapies, and whether it was engineered in the laboratory. However, the global pace of SARS-CoV-2 and COVID-19 research is providing rapid and critical advances in comparison to that of the previous SARS-CoV, Middle East respiratory syndrome (MERS) and HIV [1,3,4]. COVID-19 has a protean manifestation, and the cryptic transmission of SARS-CoV-2 is characterized by multiple chains of transmission, unlike the SARS-CoV and MERS-CoV viruses that have been reported to occur mainly through nosocomial transmission [3,4]. There are still many unknowns regarding COVID-19, but there are also important lessons to be gleaned from AIDS that are applicable to the COVID-19 pandemic. They are both zoonotic diseases with different mode of transmission, with no vaccine or cure yet; however, there is an effective antiretroviral therapy for AIDS [5,6]. Furthermore, cannabis and cannabinoids have been proposed and used as adjunctive treatment for AIDS-associated cachexia, and in reduction of disease symptoms [7,8]. The processes of inflammation are important in both the pathogenesis of AIDS and COVID-19 [6,8]. Cannabinoids are effective at suppressing immune and inflammatory functions [7–9], and their potential as an anti-inflammatory treatment in COVID-19 has been suggested [8,9].

As the infection with SARS-CoV-2 causes inflammation due to immune response and a ‘cytokine storm’, resulting in a range of mild to no symptoms all the way to severe and critical COVID-19 induced comorbidity and mortality, this Editorial discusses the potential of the pharmacological immune-modulatory effects of cannabinoids that are constituents of the cannabis plant. It is of importance to determine the effects of cannabis and cannabinoid use by those who have not contracted the disease and those who have contracted COVID-19 and the outcomes.

ECS components as a potential therapeutic target in COVID-19

The physiological effects of cannabis and cannabinoids are mediated through the human endocannabinoid system (ECS), which consists of cannabinoid receptors (CB1R and CB2R and other candidates), endocannabinoids, and their metabolic enzymes [10]. The ECS is widely distributed in almost all human cells and tissues and involved in the regulation of several functions in mammalian physiology and pathology, and as a gatekeeper in immune homeostasis [11,12]. This widespread distribution of the ECS is now being exploited as a potential target for cannabinoid-based therapies in numerous disorders including those associated with inflammation and autoimmune dysregulation. Several studies indicate that cannabis-derived cannabinoids have anti-inflammatory and immunoregulatory properties through the activation of the cannabinoid receptors [13,14]. The role of the ECS

as a key regulator of the immune system was reviewed by Almogi-Hazan and Or, who discussed that the activation of the ECS by cannabis and cannabinoids-based therapeutic regime exerts immune-regulatory properties [14]. This ECS-mediated immunosuppression includes cytokine suppression, inhibition of immune cell proliferation, migration and antibody production, and allows the ECS to exert control of viral pathogenesis [14]. With a seemingly increasing global acceptance for the use of cannabinoid formulations in medicine [10], it has been hypothesized that cannabinoid receptors [8,9,14] could be therapeutic targets in the COVID-19 pandemic. Therefore, it is of interest to determine whether cannabinoids can quell the inflammatory cytokine release by SARS-Cov-2 and reduce the mortality caused by COVID-19.

Quelling the inflammatory cytokine storm in COVID-19

COVID-19 is transmitted by airborne droplets and aerosols, or from fomites into host cells of infected individuals by using the spike protein to bind onto the ACE2R on the surfaces of human cells [4,8]. The respiratory cells are a gateway into the lungs as ground zero, and extend to cells of other organs using ACE2Rs in the throat, heart and blood vessels, kidney, gut, liver and brain [4,8]. Once inside, these cells replicate the virus to produce more SARS-CoV-2, disrupting, provoking and activating immune response. Infected patients may be symptomatic or asymptomatic and the severity of COVID-19 varies with age, genetics, individual exposomes, ethnicity and pre-existing health status [15,16]. As we have learned more about the high transmission rate of SARS-CoV-2, we have seen that variable mild symptoms appear between 2 days and 2 weeks after exposure with fever, cough, fatigue, dyspnea, loss of smell and taste, vomiting and diarrhea [4,8,16], and all dependent on the individual's exposome [2]. Genetic differences in an individual's immune system may also be linked to the severity and progression of COVID-19 [4,16]. The severe and critically ill cases develop acute respiratory distress syndrome, characterized by the body's attempt to defend against the viral invasion with an immune response, with the release of various cytokines such as granulocyte-macrophage colonystimulating factor and IL-6, chemokines and inflammatory mediators [8]. This triggers the inflammatory cytokine storm, perhaps by shifting the Th1 and Th2 cytokines, thereby leading to the cytopathogenic effects that are the cause of mortality in severe to critical COVID-19 patients [6,17,18]. Older men are more susceptible to COVID-19; their higher mortality rate [19] is likely due to estrogen, and some ABO blood groups with group O showing a reduced risk compared with patients with the A blood group [20]. The global scientific and medical community is scrambling to find treatments, investigating for example, the use of convalescent plasma, antiviral drugs such as remdesvir and vaccines, and it is possible that a cure for COVID-19 is already under development. However, experimental treatments and trials for COVID-19 have generated controversy and confusion, one example being the touting of the use of the antimalarial drug hydroxychloroquine.

Several potential strategies include repurposing available medications aimed at reducing the inflammatory storm associated with symptoms of COVID-19 in severe and critically ill patients [17,20,21]. As one of the key causes of mortality in COVID-19 is this inflammatory cytokine storm, anti-inflammatory drugs such as dexamethasone have been shown to reduce deaths [20,21]. What's more, the IL-6 receptor antagonist tocilizumab blocks the COVID-19 inflammatory cytokine storm by reducing symptoms leading to reduced inflammation [21]. This inhibition or blockade of cytokines reduces the need for mechanical ventilation, and also the mortality of patients with severe to critical COVID-19 [17,21]. Given that the cytokine storm plays an important role in the pathogenesis of COVID-19, and the lack of specific treatments, the potential for cannabis and cannabinoids known to regulate inflammatory cytokine production and suppress an overactive immune response has been highlighted [8,9,14,18,22]. Furthermore, ECS signaling on immune system, viral replication and pathogenesis involve several pathways that mediate the release of cytokines/chemokines through NF- κ B, MAPK and JAK-STAT [17,18] or through MNP transcription pathways [6]. Therefore, the essential role that the ECS plays in immunity, and the modulation of inflammatory cytokine storm following activation of cannabinoid receptors by endocannabinoids and phytocannabinoids suggests ECS components are targets for the COVID-19 and AIDS syndemics, as well as in other immune-related disorders [7,8,23]. Specifically, while the CB2 cannabinoid receptor subtype is abundantly localized in immune cells, they are also present in low levels in neurons, and are emerging as a target in limiting excessive inflammation and cytokine storms [8,9].

The neurological manifestations of COVID-19 and AIDS share some molecular pathways [24]. Phytocannabinoids, such as Δ^9 -THC and cannabidiol have been demonstrated to reduce inflammatory cytokine storms [7-9,12-14,22,25]. What's more, the approval by the US FDA for medical use of cannabidiol and Δ^9 -THC [10] supports the hypothesis that cannabinoids could reduce the damage caused by COVID-19 by dousing the inflammatory

cytokine storm provoked by SARS-CoV-2. Thus, the immune-regulatory properties of cannabis and cannabinoid formulations suggest their use in the treatment of immune-related disorders.

The global effort to find therapies and develop vaccines capable of stopping the spread, and end the COVID-19 pandemic is a priority. The response and aftermath of the outbreak of COVID-19 pandemic is and will create a paradigm shift, revealing fault lines and gaping holes explaining the global medical and scientific failures to find cure for the AIDS and COVID-19 syndemics. The possibilities that these diseases will be eliminated, and in order to better prepare for future outbreaks is an ongoing intensive global research effort. If the end game of finding an efficacious vaccine to end the COVID-19 pandemic remains elusive as it has been for AIDS, should we expect COVID-19 to become endemic in the human population, like influenza? Looking forward, the ongoing SARS-CoV-2 pandemic has already been met with an unprecedented response from humanity in an effort to curb it. However, the pandemic has shed light on the lack of fundamental scientific knowledge utilizable in the prevention and treatment of viral infections. Along with many ongoing studies and clinical trials, cannabis and cannabinoid adjunctive treatment in COVID-19 could be of use in countering SARS-CoV-2 infections by quelling the cytokine storm, but require more studies and trials.

Author contributions

The authors contributed equally to this Editorial.

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