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Cannabis in the Time of Coronavirus Disease 2019: The Yin and Yang of the Endocannabinoid System in Immunocompetence

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Editor's Note: For those whose response to COVID-19 includes exploring beyond vaccines, conventional pharmaceuticals, and the watchful or healthy waiting until such tools might arrive, interest in cannabinoids has been high - and controversial. It has already stimulated one journal, the Liebert Cannabis and Cannabinoid Research, to issue a call for papers on COVID-19. The unique place of cannabis in the culture seems to always mark the herb with an exponential asterisk whenever basketed with the other natural health strategies that are both widely used, and as broadly derided. In this invited commentary, *JACM* Editorial Board member Michelle Sexton, ND starts by describing the multiple immune modulating effects associated with the herb. The University of California San Diego Assistant Adjunct Professor in Anesthesiology then asks: ''Given these effects, can phytocannabinoids be either helpful, or harmful for immune competency, in the context of the current COVID-19 pandemic?'' A skilled edge-walker, Sexton lets the research fall where it may in wending a path through this evidentiary maze. —*John Weeks, Editor-in-Chief*, JACM

The endogenous cannabinoid signaling system (ECS) is a highly conserved, ubiquitous, pleiotropic biochemical system known as a gatekeeper in immune homeostasis.[1] A multitude of ECS-mediated immunosuppressive effects have been demonstrated to date, including inhibition of immune cell proliferation, migration and antibody production, induction of apoptosis, and cytokine suppression (via downregulation of immunoregulatory genes). Given these effects, are phytocannabinoids helpful or harmful for immune competency in the context of the current coronavirus disease 2019 (COVID-19) pandemic?

The plant cannabinoid delta9-tetrahydrocannabinol (THC) mimics the actions of endogenous cannabinoids (ECB) as a nonselective partial agonist (higher affinity than ECBs) at cannabinoid receptors 1 and 2 (CB_1 and CB_2). Both receptors are expressed on immune cells, with CB_2 exclusively expressed in human immune cells and tissues. Agonism of these receptors on immune cells has been shown to reduce the production and secretion of inflammatory mediators.[2] Cannabidiol (CBD) acts as a negative allosteric modulator with very low affinity at both cannabinoid receptors. CBD has also been shown to be immunosuppressive through diverse (non-ECS-mediated) mechanisms.[3] The dietary sesquiterpenoid beta-caryophyllene, found in *Cannabis* and other plants, and alkylamides in *Echinacea purpurea* activate the CB_2 receptor (Ki: 100 and 60 nM affinity, respectively).[4,5]

Generally speaking, the role of CB_2 is underexplored relative to the role of CB_1, particularly with regard to acute, innate immune responses. Activation of CB_2 is associated with intracellular pathways that tone down immune responses. Because of this, CB_2 agonists may hold promise as therapeutic agents in autoimmune diseases by suppression of antibody production through T-cell mechanisms.[6]

The innate immune response is nonspecific, intended to prevent the spread of infection through chemical and cellular mechanisms. Toll-like receptors (TLR), expressed on the surface of macrophage and dendritic cells, recognize commonly conserved pathogen-associated molecular patterns. Upon recognition, a pro-inflammatory signaling cascade (via cytokine release) is triggered that eventually dictates lymphocyte involvement (adaptive immunity). Cytokine release is mediated by several pathways known to be affected by the ECS: NF-κB, MAPK, and JAK-STAT.[7]

Cannabinoids have been shown to inhibit cytokine production in monocyte cell cultures and in animal models of acute infection, primarily through inhibition of TLR4-induced activation. This has also been demonstrated in human subjects who smoke cannabis, indicating that cannabinoids may impair TLR-induced immune activation.[8–10] Further, THC has been shown via CB_2 to inhibit the macrophage co-stimulatory signaling required for T-cell activation, thus impairing the adaptive immune response (antibody production and immune memory).[6] Early investigations suggested a TH1 to TH2 shift by cannabinoids, but this has not been replicated in humans with multiple sclerosis—a condition that would benefit from this shift.[10]

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Table 1. A Sample of Completed and Recruiting Trials of CBD for Therapeutic Purposes to Demonstrate the Range of Therapeutic Dosing

Sample of completed trials with CBD (from search in PubMed)

CBD dose	*Condition*	*Author, year*	*Size of study*	*Type of study*
5–50 mg/kg[a]	Treatment-resistant epilepsy	Szaflarski et al., 2018[18]	$N=72$ (child) $N=60$ (adult)	Open label
600 mg/day, fixed dose	Schizophrenia	Boggs et al., 2018[19]	$N=36$	Randomized, placebo controlled, parallel group, fixed dose
600 mg, single dose	Public-speaking anxiety model	Bergamaschi et al., 2011[20]	$N=12$	Double blind, placebo controlled
200 mg, q.i.d.	Schizophrenia	Leweke et al., 2012[21]	$N=33$	Double blind, randomized, parallel group
Up to 20 mg/kg/day	Dravet syndrome	Devinsky et al., 2017[22]	$N=34$	Double blind, placebo controlled
1000 mg/day	Schizophrenia	McGuire et al., 2018[23]	$N=43$ (T) $N=45$ (C)	Double blind, randomized, placebo controlled, parallel group
Up to 50 mg/kg/day	Severe, intractable, childhood-onset, treatment-resistant epilepsy	Devinsky et al., 2016[24]	$N=162$ (safety and tolerability) $N=137$ (efficacy)	Open label
20 mg/kg/day	Lennox–Gastaut syndrome	Thiele et al., 2018[25]	$N=86$ (T) $N=85$ (C)	Randomized, double blind, placebo controlled (Phase III)
10 or 20 mg/kg/day	Drop seizure in Lennox–Gastaut syndrome	Devinsky et al., 2018[26]	$N=225$	Double blind, placebo controlled
20 mg/kg	Drug-resistant seizure in Dravet syndrome	Devinsky et al., 2017[22]	$N=120$	Double blind, placebo controlled
75 or 300 mg/day	Parkinson's disease	Chagas et al., 2014[27]	$N=119$	Double blind, placebo controlled
Single ascending dose from 1500 to 6000 mg; multiple dose 750 or 1500 mg; 1500 mg single dose	Healthy subjects	Taylor et al., 2019[28]	$N=6$–12 per arm	Phase I open label
50–150 mg b.i.d.	Chronic pain in kidney transplant patients	Cunetti et al., 2018[29]	$N=7$	Open-label
750, 1500, or 4500 mg dose compared to alprazolam and dronabinal	Healthy recreational polydrug users	Schoedel, 2018[30]	$N=43$	Single dose, randomized, double blind, double dummy, placebo and active controlled crossover design
600 mg	High risk of clinic psychosis	Battacharyya et al., 2018[31]	$N=33$	Single dose, parallel group, double blind placebo controlled

Sample of trials listed on ClinicalTrials.gov (currently recruiting), N = *43*

Dose	*Condition*	*Preliminary investigator*	*Size of study*	*Type of study*
Starting at 25 mg/b.i.d. and increasing to 150 mg/b.i.d.	Steroid-sparing effects in stable autoimmune hepatitis[b]	Stero Biotechs Ltd.	$N=15$	Open label, Phase II
Starting at 25 mg/b.i.d. and increasing to 150 mg/b.i.d.	Steroid-sparing effects in Crohn's disease[b]	Stero Biotechs Ltd.	$N=28$	Open label, Phase IIa, randomized, crossover, placebo controlled
Sublingual, 10 mg/t.i.d. (30 mg/day)	Anxiety	Stacey Gruber, MD	$N=16$	Phase I: open label; Phase II: placebo controlled

(*continued*)

TABLE 1. (CONTINUED)

Sample of trials listed on ClinicalTrials.gov (currently recruiting), N = *43*

Dose	*Condition*	*Preliminary investigator*	*Size of study*	*Type of study*
150–300 mg/day	Bipolar	Márcia Kauer-Sant'Anna, MD, PhD	*N* = 100	Double blind, randomized, placebo controlled
600 mg/day	Alcohol use disorder in patients with PTSD	Charles Marmar, MD	*N* = 48	Double blind, randomized, parallel
2.5–5 mg/kg up to 20 mg/kg/day (in divided doses)	Gastropareisis and functional Dyspepsia	Michael Camilleri, MD	*N* = 96	Randomized, double blind, parallel design
20–40 mg/kg/day	Prader–Willi syndrome	Ahmed Elkashef, MD	*N* = 66	Open label (safety trial)
20 mg/kg/day	Chronic back pain	Jodi Gilman	*N* = 20	Open label
400 or 800 mg/day	Cocaine addiction		*N* = 110	Randomized, parallel design, placebo controlled
Up to 2.5 mg/kg/day	Motor symptoms in Parkinson's disease	Maureen Leehey	N = 60	Parallel design, double blind, randomized controlled trial
3, 6, or 9 mg/kg/day	Autism spectrum disorder	Francisco Castellanos, MD	*N* = 30	Open label, single group, Phase II study
75, 150, or 300 mg (p.o.) b.i.d.	Graft-versus-host disease	Ram Ron, MD	*N* = 36	Open label
300 mg/day	Post-traumatic stress disorder	Michael J. Telch, PhD	*N* = 120	Randomized

[a]Most patients were treated with 20–30 mg/kg/day using an upward titration model.
[b]Studies for anti-inflammatory effects.
T, treatment; C, control.

A systems-based analysis of the ECS biologic network revealed that tumor necrosis factor alpha (TNF-α) is one of the major nodes, or units connecting to other signaling units, in the network. Using data published from 2003 to 2013, investigators built a database of elements (including protein receptors, ECB, and other ligands) with connections to the two primary ECBs: AEA and 2AG. Calculations of node connectivity revealed TNF-α to be one of the eight most highly connected nodes in the ECS system topology. TNF-α is a pleiotropic cytokine that has a pivotal role as the master regulator in the pro-inflammatory cytokine cascade (primarily via the NF-κB pathway) by activating macrophage cells. Thus, TNF-α is crucial for promoting the acute phase reaction in immune cells and has been shown to have a central role in ECS signaling.[11]

Overall, these immunomodulatory effects warrant further exploration of the ECS either for treating chronic inflammation/autoimmune diseases or for potential impacts on healthy host immunocompetence.

There has been some media hype about *Cannabis* for ''treating'' the COVID-19-associated cytokine storm, a fatal immune dysregulation during the course of disease. While there is a paucity of human data on acute viral infections and cannabinoids, *in vitro* and *in vivo* studies shed some light on their role in immune suppression in viral influenza illness.

For example, mice infected with attenuated influenza A were administered intraperitoneal (IP) THC (75 mg/kg; wild type vs. $CB_{1/2}$ knockout). The percentage of CD4+ (but not CD8+) cells increased, while the percentage of natural killer (NK) cells decreased, in bronchoalveolar lavage fluid of wild-type mice but not knockout mice. Also, THC significantly suppressed interleukin (IL)-17-producing NK cells (needed to target and kill infected lung epithelial cells) in the wild-type mice. Further, THC suppressed the ability of macrophages and dendritic cells to migrate into the lungs. This effect was only observed in wild-type mice. Functionally, THC also attenuated interferon gamma production, which is a critical lymphocytic cytokine in immune responses to viral infections. Cannabinoids may be a therapeutic strategy in certain chronic viral infections (that invade the central nervous system), but other viral studies have shown increased viral replication and disease pathology.[12]

These data illustrate how cell populations necessary for a healthy immune response are affected by THC in a $CB_{1/2}$-dependent manner, impairing migration of antigen-presenting cells to the lungs, subsequent cytokine production, and antigen presentation needed for T-cell responses for healthy adaptive immunocompetence. Collectively, suppression of host immunity against influenza was demonstrated in this mouse model, although it should be noted that the dose of THC was administered IP at a supraphysiologic dose.

Similar to tobacco smoking, chronic cannabis smoking can lead to long-term effects of increased cough, sputum production, and wheeze, along with airway disease such as

chronic bronchitis and decline in lung function. Additionally, data from healthy, adult-use cannabis smokers demonstrated a global reduction in cytokine production.[8–10] Further, the use of vape pens (vaporization devices with concentrated cannabis) may pose an even greater risk through concentration, adulteration, or contamination of the extracts. The concentration of cannabinoids and terpenes can be increased by 3.2- to 4-fold and 2.7- to 8.9-fold, respectively (depending on extraction process and terpene structure), and this concentrated form may also contribute to respiratory symptoms and dysfunction.[13] Avoidance of smoking cannabis and vaping of concentrates is particularly relevant for pulmonary health in light of COVID-19. These administration methods may diminish the respiratory system's efficacy in responding to infection and thereby increase the risk of rapid progression to hypoxemia.

Cannabis has a long history of relatively safe use as a botanical medicine, with therapeutic benefit achievable at doses below the threshold for intoxication. THC dosing for recreational use versus therapeutic use can be widely divergent. Cannabinoids are known to have bi-phasic effects, and higher doses are commonly associated with adverse events.[8,14]

A recent survey of health care professionals specializing in cannabinoid medicine reported 44.7% recommend 6–10 mg/day of THC for chronic pain, fibromyalgia, arthritis, sleep disorders, anorexia, and other conditions—an average dose of 2–3.3 mg per dose (t.i.d.).[15] This dose is significantly less than recreational dosing and miniscule compared to 75 mg/kg (used in the aforementioned mouse study).[16] This translates to a human equivalent dose of 360 mg for a 60 kg individual. Clearly, THC dose is a critical factor in assessing clinical impact.

CBD, primarily from hemp-based products, is also being touted as a potential treatment for COVID-19. CBD has been shown to have anti-inflammatory effects, as demonstrated in an animal model of collagen-induced arthritis, by suppressing lymphocyte and macrophage functions.[17] Without high-quality evidence in humans, however, effective anti-inflammatory doses for CBD are unknown. Based on effective doses of CBD in the existing clinical literature, an anti-inflammatory dose is likely to be quite high, and not approximated in most of the hemp-based products currently marketed. Table 1 presents a sample of completed and recruiting clinical trials of CBD for various therapeutic purposes (referenced from a search in clinicaltrials.gov), showing the range of what is considered to be therapeutic dosing. (Only two trials for anti-inflammatory effects were identified.) Because CBD is principally available as an unregulated dietary supplement ingredient, it is difficult for patients and their doctors to know exactly what is contained in the products they are purchasing.[15]

In summary, there are dichotomous effects of phytocannabinoids on immunocompetence. On the one hand, targeting the ECS for anti-inflammatory benefits in chronic inflammatory/autoimmune disease in humans may be a possibility, although effective dosing has not yet been documented. On the other hand, detrimental effects in the setting of acute infection may also be a possibility, although dosing guidelines to avoid immunosuppression in humans has not been documented.

When interacting with patients on the topic of cannabis use, respiratory and immune health education on mode of administration and dosing is critical. A harm-reduction approach for individuals smoking cannabis would be substituting orally administered products at low doses ($\leq$5 mg THC suggested)[15] or using vaporized dried flower material (to avoid byproducts of combustion). For patients using low-dose oral products, it appears likely that clinically significant immunosuppression is not a risk. However, this should still be on health care professionals' radar. An individualized approach to assessing the patient, including respiratory and cardiovascular health or existing immunocompromise (e.g., cancer patients, use of biologic drugs), should guide the health care provider. Reduced innate defense is being considered as a driving feature of COVID-19, and to be clear, no data suggest that THC or CBD is a proven therapeutic intervention for treating COVID-19.

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References

1. Olah A, Szekanecz Z, Biro T. Targeting cannabinoid signaling in the immune system: ''High''-ly exciting questions, possibilities, and challenges. Front Immunol 2017;8:1487.
2. Sexton M, Silvestroni A, Moller T, et al. Differential migratory properties of monocytes isolated from human subjects naive and non-naive to cannabis. Inflammopharmacology 2013;21:253–259.
3. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. Br J Pharmacol 2008;153:199–215.
4. Gertsch J, Leonti M, Raduner S, et al. Beta-caryophyllene is a dietary cannabinoid. Proc Natl Acad Sci U S A 2008;105:9099–9104.
5. Raduner S, Majewska A, Chen J-Z, et al. Alkylamides from Echinacea are a new class of cannabinomimetics. Cannabinoid type 2 receptor-dependent and -independent immunomodulatory effects. J Biol Chem 2006;281:14192–14206.
6. Chuchawankul S, Shima M, Buckley NE, et al. Role of cannabinoid receptors in inhibiting macrophage costimulatory activity. Int Immunopharmacol 2004;4:265–278.
7. Tahamtan A, Tavakoli-Yaraki M, Rygiel TP, et al. Effects of cannabinoids and their receptors on viral infections. J Med Virol 2016;88:1–12.
8. McCoy KL. Interaction between cannabinoid system and Toll-like receptors controls inflammation. Mediators Inflamm 2016;2016:5831315.

9. Pacifici R, Zuccaro P, Pichini S, et al. Modulation of the immune system in cannabis users. JAMA 2003;289: 1929–1931.
10. Sexton M, Cudaback E, Abdullah RA, et al. Cannabis use by individuals with multiple sclerosis: effects on specific immune parameters. Inflammopharmacology 2014;22: 295–303.
11. Bernabo N, Barboni B, Maccarrone M. Systems biology analysis of the endocannabinoid system reveals a scale-free network with distinct roles for anandamide and 2-arachidonoylglycerol. OMICS 2013;17:646–654.
12. Reiss CS. Cannabinoids and viral infections. Pharmaceuticals (Basel) 2010;3:1873–1886.
13. Sexton M, Shelton K, Haley P, et al. Evaluation of cannabinoid and terpenoid content: cannabis flower compared to supercritical CO_2 concentrate. Planta Med 2018; 84:234–241.
14. Randall K, Hayward K. Emergent medical illnesses related to cannabis use. Mo Med 2019;116:226–228.
15. Corroon J, Sexton M, Bradley R. Indications and administration practices amongst medical cannabis healthcare providers: a cross-sectional survey. BMC Fam Pract 2019; 20:174.
16. Cash MC, Cunnane K, Fan C, et al. Mapping cannabis potency in medical and recreational programs in the United States. PLoS One 2020;15:e0230167.
17. Klein TW, Cabral GA. Cannabinoid-induced immune suppression and modulation of antigen-presenting cells. J Neuroimmune Pharmacol 2006;1:50–64.
18. Szaflarski, JP, Bebin EM, Comi AM, et al. Long-term safety and treatment effects of cannabidiol in children and adults with treatment-resistant epilepsies: Expanded access program results. Epilepsia 2018;59:1540–1548.
19. Boggs DL, Surti T, Gupta A, et al. The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia a randomized placebo controlled trial. Psychopharmacology (Berl) 2018;235:1923–1932.
20. Bergamaschi MM, Queiroz RH, Chagas MH, et al. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naive social phobia patients. Neuropsychopharmacology 2011;36:1219–1226.
21. Leweke FM, Piomelli D, Pahlisch F, et al. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. Transl Psychiatry 2012;2:e94.
22. Devinsky O, Cross JH, and Wright S, et al. Trial of Cannabidiol for drug-resistant seizures in the Dravet syndrome. N Engl J Med, 2017;377:699–700.
23. McGuire P, Robson P, Cubala WJ, et al. Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: a multicenter randomized controlled trial. Am J Psychiatry 2018; 75:225–231.
24. Devinsky O, Marsh E, Friedman D, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. Lancet Neurol 2016;15:270–8.
25. Thiele EA, Marsh ED, French JA, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2018;391:1085–1096.
26. Devinsky O, Patel AD, Cross JH, et al. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. N Engl J Med 2018;378:1888–1897.
27. Chagas MH, Zuardi AW, Tumas V, et al. Effects of cannabidiol in the treatment of patients with Parkinson's disease: an exploratory double-blind trial. J Psychopharmacol 2014;28:1088–1098.
28. Taylor L, Gidal B, Blakey G, et al. A phase I, randomized, double-blind, placebo-controlled, single ascending dose, multiple dose, and food effect trial of the safety, tolerability and pharmacokinetics of highly purified cannabidiol in healthy subjects. CNS Drugs 2018;32:1053–1067.
29. Cunetti L, Manzo L, Peyraube R, et al. Chronic pain treatment with cannabidiol in kidney transplant patients in Uruguay. Transplant Proc 2018;50:461–464.
30. Schoedel KA, Szeto I, Setnik B, et al. Abuse potential assessment of cannabidiol (CBD) in recreational polydrug users: A randomized, double-blind, controlled trial. Epilepsy Behav 2018;88:162–171.
31. Bhattacharyya S, Wilson R, Appiah-Kusi E, et al. Effect of cannabidiol on medial temporal, midbrain, and striatal dysfunction in people at clinical high risk of psychosis: a randomized clinical trial. JAMA Psychiatry 2018;75:1107–1117.

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