Cannabis and Covid-19: The Endocannabinoid System to the Rescue!

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INTRODUCTION

I'm a Psychiatric Nurse Practitioner specializing in the medical use of Cannabis. My area of expertise has been in treating Post Traumatic Stress Disorder (PTSD) and in 2017 I became the Nurse Practitioner Journal "Author of the Year" for explaining the neurobiological processes involved in PTSD and discussing the role of the endocannabinoid system and Cannabis for treating PTSD. In my clinical experience, I have found Cannabis to be the only medication capable of treating every symptom cluster of PTSD and I have helped thousands of patients reduce or eliminate their need for pharmaceuticals with use of Medical Cannabis and dietary supplements to support endocannabinoid function.

Although I am not an attorney, I do dabble in the law as a hobby. In 2016, I forced the DEA to ease policies designed to block Medical Cannabis research and to finally admit that Cannabis is not a gateway drug, does not cause lung cancer, does not cause psychosis and does not cause cognitive decline with aging. Because the DEA continued to violate the terms of this settlement, I filed a new rescheduling petition and brought a lawsuit to the US Court of Appeals in Washington, DC, which was denied by a panel of George Bush and Donald Trump appointed judges. I appealed to the US Supreme Court in an effort to remove Cannabis from federal control and have it regulated by the States. This petition was the featured "Petition of the Month" by Supreme Court Press in July 2019, just before a Supreme Court stacked with Trump appointed justices denied my petition for rehearing.

I had been working on an appeal to the United Nations and the World Health Organization, hoping I might be able to have Cannabis removed from control under the Single Convention Treaty, which could end prohibition Worldwide. Then SARS Co-V-2 came along demanding a more immediate response. Legal appeals can be excessively time consuming which could place many lives at risk in light of this new disease.

I began studying the use of Cannabis for treating Coronaviruses during the SARS Co-V outbreak in 2002. SARS Co-V-2 now presents us with a challenge that threatens the lives of millions of citizens across the globe. The endocannabinoid system regulates almost every biological process in the human body, including immune function. Cannabis and the endocannabinoid system may offer us our single best chance to save the lives of those who develop Covid-19 as a result of this new virus, until we are able to find a vaccine and/or develop herd immunity.

SARS Co-V-2 is a newly emerging human infectious coronavirus that causes Covid-19 disease. Covid-19 has has been recognized as a pandemic by the World Health Organization and it threatens the lives of million of people (1). It has proven to be very contagious and has quickly spread across the globe. We have had a new major coronavirus epidemic every decade in the twenty-first century and this coronavirus is similar to the coronaviruses that caused the SARS Co-V outbreak in 2002 and the MERS Co-V outbreak in 2012 (2,3). Coronaviruses have become the major pathogens of emerging respiratory disease outbreaks in the World today (4).

There are no vaccines or definitive treatments for Covid-19 because its pathogenesis and proliferation pathways are still not fully understood. Although several companies have been attempting to develop MERS Co-V vaccines since 2012, there are still none available (5,6,7). There is no reason to expect an effective vaccine for SARS Co-V-2 will be available any time soon. Cannabis offers us a potential treatment option that not only may help to save millions of lives among those who develop Covid-19, but it is also safer than any pharmaceutical options that may be available.

At the moment, the therapeutic strategies to deal with the infection are only supportive and prevention aimed at reducing transmission in the community is our best weapon (4). Although those under 20 have have much lower rates of infection and hospitalization, about 20% of those infected with Covid-19 will develop severe symptoms. In the US, rates of hospitalization are high among all age groups over 20 years old, but 80% of deaths have occurred in those over age 65 (8). The mortality rate of Covid-19 worldwide is approximately 2.4% and is caused by multi-organ failure (9). It's clear that new treatment strategies are required in order to save lives until an effective vaccine can be developed.

Evidence suggests that a subgroup of patients with severe Covid-19 develop a virally driven cytokine storm leading to hyperinflammation and mortality. Respiratory failure from acute respiratory distress syndrome (ARDS) is the leading cause of mortality and secondary hemophagocytic lymphohistiocytosis may lead to fatal hypercytokinemia with multiorgan failure. Although immunosuppression is likely to be beneficial, corticosteroids are not routinely recommended and might exacerbate Covid-19-associated lung injury (10).
Rapid development of new treatment strategies for Covid-19 by stabilizing altered immune function, without inhibiting appropriate immune responses is critical. Cannabis has proven to be effective for stabilizing the altered immune functions involved in the pathogenesis of Coronaviruses. Cannabis may help to stop the cytokine storm, thus preventing pneumonia and the complications of pneumonia, offering us a safe and effective treatment for Covid-19.

DISCUSSION

The prognosis of a viral infection is determined by a balance between the rate of viral replication and the ability of the immune system to clear the virus. Innate immunity is critical at the onset of infection and involves interferon (IFN)-γ action, cytokine-mediated signaling, chemotaxis, and complement activity. These processes are triggered at days 0–1 following

infection and decline 3–4 days thereafter. This early innate immune response generates a reduction in viral replication during days 0–3 of infection (11). Type I interferons are essential to limit virus spread associated with early mortality and interferon-γ promotes further virus clearance in astrocytes/microglia and oligodendrocytes, respectively (12).

However, the clinical behavior of a virus may be associated with genetic variants which allow them to effectively evade this early immune response, leading to more severe clinical consequences (11). The immune evasion mechanism of SARS Co-V-2 is likely similar to that of SARS Co-V and MERS Co-V, which inhibit innate immune responses, including type I interferon recognition and signaling (9). These viruses contain proteins that act as an antagonist of type I interferon (α/β), and suppress the JAK-STAT signaling pathway. Deficiencies in these immune-driven antiviral responses result in increased viral replication and dissemination in the host (11). Because of their immune evasion properties, Coronaviruses can efficiently escape host immune detection at the early stage of infection, allowing them to propagate and be spread by asymptomatic individuals (9).

A rapid and effective immune response is essential to limit viral spread and mortality but this anti-viral response needs to be tightly regulated in order to limit immune mediated tissue damage. Inflammation seen in delayed-type hypersensitivity plays a critical protective role against intracellular pathogens (13). By targeting altered immune responses resulting in cytokine storm we may be able to save the lives of many of those who may contract coronavirus, in spite of our best efforts to socially distance ourselves and wash our hands after contact with surfaces (12).

Δ9-Tetrahydrocannabinol (THC) reduces T cell driven inflammation via apoptosis, induction of immunoregulatory cells, regulation of Th cell cytokines, and even epigenetic modifications. THC treatment increases anti-inflammatory cytokines causing a drop in proinflammatory cytokines such as IL-12, IFN-γ, and TNF-α while reducing T cell activation. THC treatment induces Tregs which are known to inhibit both Th1/Th17 lineage differentiation and reduces cytokines associated with Th17 differentiation such as IL-6 and IL-17 (13). THC modulates immune responses through activation of CB2 cannabinoid receptors expressed on immune cells to suppresses lymphocyte proliferation, inflammation, and induce a shift in T cells from Th1 to Th2 by suppressing the expression of pro-inflammatory genes while inducing the expression of anti-inflammatory genes (14).

IL-6 is an important mediator in the host's susceptibility to respiratory infections, playing an important role in both host defense and in the prevention of lung injury from various pathogens. The cellular response to IL-6 is mediated through a Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) signal transduction pathway. Although many viruses attenuate the IL-6-mediated JAK/STAT3 signaling cascade in lung epithelial cells, some viruses prevent TNF-α-induced apoptosis of infected cells until very late in the infection by disrupting IL-6 signal transduction pathways, thereby modifying the expression of several genes needed to maintain lung homeostasis and increasing the host’s susceptibility to injury (15).

STAT3 is a transcription factor which can be activated by cytokines, growth factor receptors, and nonreceptor-like tyrosine kinase. An activated STAT3 translocates into the nucleus and combines with DNA to regulate the expression of target genes involved in cell proliferation, differentiation, apoptosis and metastasis, which plays an important role in viral infection and pathogenesis. Although STAT3 exhibits a proviral function in several viral infections, in some circumstances, including the SARS coronavirus, STAT3 has an antiviral function (16).

IFNγ and TNFα significantly increase levels of multiple inflammatory pathways by increasing levels of CREB, JNK, NF-KB, p38, ERK1/2, Akt, p70S6k, STAT3, and STAT5. Treatment of cytokine-stimulated tissue with CBD suppresses increased secretion of inflammatory mediators. CBD also prevents Anandamide (AEA) uptake and catabolism, which has been shown to down regulate NF-KB and exert anti-inflammatory properties through IL-10. CBD increases Granulocyte-macrophage colony-stimulating factor (GM-CSF) production in the absence of inflammation, but the increased production of GM-CSF due to stimulation by IFNγ and TNFα is inhibited by CBD (17).

GM-CSF has a profound role in regulating the immune response and maintaining immunological tolerance. GM-CSF affects diverse cell types including lung epithelial cells. GM-CSF leads to the recruitment and activation of Janus Kinase-2 (JAK-2) and has also been shown to modulate the properties and functions of the more matured myeloid cells such as granulocytes, macrophages and eosinophils. GM-CSF plays a critical role under inflammatory or immunomodulatory conditions by inducing specialized cell types from precursors or by influencing phenotypes of mature cell populations, thus exerting a profound effect on the state of immune tolerance (18).

Finding appropriate treatment strategies for Covid-19 is critical. The use of corticosteroids may increase the risk of superinfection, prolonged viral replication, and increase the risk of death (19). Hydroxychloroquine is currently being touted as a potential treatment, but although it may may help to reduce the duration of symptoms and viral shedding in COVID-19, it also has serious potential SEs including cardiac failure and has demonstrated limited efficacy (20).

Cannabis use is associated with a potentially beneficial reduction in systemic inflammation and immune activation. Heavy cannabis users show decreased frequencies of intermediate and nonclassical monocyte subsets, and decreased frequencies of interleukin 23 and tumor necrosis factor-α producing antigen presenting cells. Heavy cannabis use is associated with significantly lower frequencies of TNFα+ B cells, thus potentially decreasing viral production by infected cells (21). Phytocannabinoids modulate inflammatory responses by regulating the production of cytokines. In human cells stimulated with polyinosinic-polycytidylic acid to simulate viral infection, CBD elevates the levels of AEA and dose-dependently inhibits release of MCP-2, interleukin-6 (IL-6), IL-8, and tumor necrosis factor-α, with no cytotoxic effect (22).

Preventing progression of Covid-19 to the point of requiring ventilation is critical, but in spite of our best efforts many people will advance to a stage in which they require ventilation. The use of ventilation in treating advanced cases of Covid-19 poses its own set problems and may contribute to the death of those who advance to this stage. Appropriate treatment strategies need to be developed to protect patients at risk for Ischemic-Reperfusion Injuries (IRI). Damage to an organ subjected to ischemia is exacerbated as result of reoxygenation during reperfusion and may be more harmful than the ischemia itself. IRI begins in the presence of oxygen and requires the maintenance and activation of vascular, humoral, and cellular factors. It is caused by the formation of reactive oxygen species (ROS), endothelial cell injury, increased vascular permeability, and the activation of neutrophils and platelets, cytokines, and the complement system. (23)

Reperfusion after a prolonged period of ischemia produces injury to organs by necrosis, apoptosis, and autophagy triggered by an increase in cellular ions, free radicals, and the products of lipid peroxidation (24). The ischemic-reperfusion phenomenon occurs in multiple organs, but unlike other organs, the lung can suffer ischemia without hypoxia because alveolar oxygen helps to maintain aerobic metabolism to prevent hypoxia. Pulmonary IRI induces systemic effects in the liver and heart, and is characterized by neutrophil sequestration and the release of significant amounts of reactive oxygen species into the circulation. The pulmonary system may also suffer consequences from IRI located remotely because a single organ exposed to ischemic-reperfusion can cause inflammatory activation in other organs, leading to the failure of multiple systems. (23)

During reperfusion after a prolonged period of ischemia, the release of massive amounts of free radicals, lipid hydroperoxides, and their derived products causes cellular damage and cell death. However, their release in smaller amounts after limited, less severe ischemic and hypoxic insults can confer some degree of protection to the cells to protect them from subsequent much more severe insults, due to a condition referred to as preconditioning. Small amounts of free radicals induce cellular protection through activation of several signaling pathways to inhibit the opening of mitochondrial permeability transition pores (mPTPs) during reperfusion, conferring cellular protection by activating multiple signaling pathways (24).

Cells also have adaptive mechanisms which can attenuate IRI. Membrane receptors for cannabinoids have been implicated in ischemic conditioning and may help to protect against IRI. Both the Reperfusion Injury Salvage Kinases (RISK) pathway and the Survivor Activating Factor Enhancement (SAFE) kinase pathway have been linked to ischemic conditioning and both pathways are activated during post-conditioning. TNFα can have both deleterious and protective effects during reperfusion, but unlike the other membrane agonists involved in pre- and post-conditioning, TNFα cytoprotection is mediated by activating both janus kinase (JAK) and the activating factor of transcription 3 (STAT-3) kinase, a cellular pathway involved in both pre- and post-conditioning. There appears to be cross-talk between these two cytoprotective pathways and it appears that JAK-STAT might be working parallel to or upstream of the RISK pathway, and that the RISK pathway must be functional for the JAK-STAT pathway to work fully. (24)

Exposure to oxidative stress activates mitogen-activated protein kinases (MAPKs), which help determine cell fate in IRI. Among these kinases, extracellular signal regulated kinase (ERK) inactivation has been implicated in protecting against IRI (Hochhauser). Both pre and post-conditioning with THC induces long lasting changes in ERK/MAPK activity and the downstream proteins BDNF and CREB which may provide safe and effective long-term protection against IRI. THC binds to CB1 and CB2 receptors and acts as both a partial agonist and antagonist at the CB1 receptor (26). THC has been shown to be neuroprotective against carbon monoxide (CO)-induced hypoxia and repeated treatment with THC can protect against chronic insults (27). By activating the endocannabinoid system, we may be able to reduce and/or prevent ischemic injuries (28)

N-acetylcysteine (NAC) may prove to be an important complement to cannabis therapy by reducing the production of Reactive Oxygen Species (ROS), a critical component of preventing IRI. NAC is a mucolytic that can be used for treating congestive and obstructive lung diseases associated with hypersecretion and adult respiratory distress syndrome (ARDS). NAC modulates the activity of inducible nitric oxide synthase, reducing the formation of inflammatory cytokines and inhibiting the action of neutrophils. NAC also acts as a "scavenger" of free radicals by inhibiting oxidative stress and preventing cell damage. The intravenous administration of NAC demonstrates protective properties against lung IRI and the use of NAC immediately after reperfusion potentiates its protective effects (23)

NAC produces profound alterations in endocannabinoid function by altering levels of anandamide (AEA), 2-arachidonoylglycerol (2-AG), palmitoylethanolamide (PEA) and oleoylethanolamide (OEA) (29). N-Acetylcysteine (NAC) acts a scavenger of oxygen radicals and restores intracellular glutathione levels, attenuating reperfusion injury and decreasing inflammation and nitric oxide production (30). NAC in combination with CB1 antagonists prevents AEA and HU210- induced generation of ROS, MAPK activation and cell death, producing cytoprotective and anti-inflammatory effects in IRI (31). Pre-administration of a CB2 receptor agonist prior to reperfusion decreases production of lipid peroxidation, reverses the depleted glutathione, and inhibits the expression of TNF-α and of IL-1β (32).

Although Cannabis provides a critical treatment option for a large number of diseases, the DEA has banned phase 3 clinical trials of cannabis in the United States for decades. However, on August 12, 2016, the DEA settled a rescheduling petition I filed in 2007, forcing them to adopt policies requiring them to stop blocking Medical Cannabis research and to allow more people to grow Cannabis for research purposes. Legally, we should have been actively engaged in Medical Cannabis research long ago. Unfortunately, the Trump administration, via previous attorney General Jeff Sessions and now Bill Barr, has ordered the DEA to continue to violate the law by continuing to ban needed research of this plant. Furthermore, our judicial system has now been stacked with unqualified and incompetent judges appointed by Trump, and forced through in confirmation hearings by Mitch McConnell and his Republican stooges in the Senate.

Our legal system too often serves the prison/industrial complex, the pharmaceutical industry and the ultra rich, rather than defending the Constitution and the citizens of the United States.

Because the DEA had failed to honor the settlement of my first rescheduling petition, I filed a new Rescheduling Petition for Cannabis on May 22, 2017. This led to the resignation of DEA Administrator Chuck Rosenberg, stating he doesn't trust this administration to follow the law. His replacement, Robert Patterson, denied my new rescheduling petition, a decision I appealed. Shortly after I appealed his denial, Patterson also resigned as head of the DEA, stating he doesn't know enough about marijuana to lead the agency.

Prohibition of Cannabis was masterminded by Harry Anslinger, a racist hate monger who demonized drug use, race and music, to criminalize "non-whiteness". He created a massive criminal-industrial complex in the United States, which now incarcerates a higher percentage of its citizens than any other industrialized country in the World. Anslingler was head of the Federal Bureau of Narcotic and Dangerous Drugs for over 3 decades and his legacy of racism and hate has remained the foundation of both US and World drug policy to this day. His influence led to the adoption of the Single Convention Treaty on Narcotic Drugs in 1961 and at the insistence of the United States, Cannabis was placed in the most restrictive status.

Although the World Health Organization has found that Cannabis has medical applications, there has been no action to remove Cannabis from its criminal status. Restrictions against Cannabis go far beyond those for opiates, amphetamines and cocaine. Because Cannabis remains in the most restrictive schedule of the Single Convention Treaty, Medical Cannabis research has been prevented throughout the World. This allows the DEA to argue that the United States must continue to prohibit "marijuana", because it is banned by the United Nations.

The DEA bans legitimate Medical Cannabis research while illegally tampering with witness testimony from the FDA to maintain total prohibition of Cannabis (33). Although prohibition of Cannabis has proven to be a cash cow for the prohibitionists, the lack of appropriate research into Medical Cannabis has cost countless lives, and may now may cost millions more by denying a potentially safe, affordable and effective treatment for Covid-19. Compounding the problem of Covid-19 in the US, is a narcissistic, sociopathic, megalomaniac serving as President who ignores science and demonizes anyone who dares to question his judgement.

Trump has fired everyone in his administration willing to stand up to his delusional rants and/or illegal actions. He eliminated key departments of US government designed to monitor potential pandemics and threats to National security, rolling them under the authority of incompetent toadies he appointed to head those departments. He has created an environment of fear in which his closest medical advisors stand quietly by while he subjects the public to grandiose lies about his medical expertise and how "perfect" his response has been to Covid-19. He denies needed medical equipment to States that don't support him politically and has now cut off funding to the World Health Organization (WHO) in an attempt to shift blame away from his

own incompetence. This at a time when the expert advice the WHO is critical to coordinating a worldwide response to this pandemic. Trump has repeatedly demonstrated that protecting his own fragile ego is more important to him than protecting the lives of millions of World citizens.

He portrays the media as enemies of "The People" while his sycophantic minions threaten reporters and seek to instill fear into anyone who may dare to speak the truth. He promises the rapid development of a safe and effective vaccine for Covid-19 while ignoring the failure to develop vaccines for other coronaviruses in the last 2 decades. He touts unproven treatments with potentially lethal outcomes. He is a pathological liar who is unable to accept responsibility for his own actions and who will blame anyone in an attempt to deflect attention from his own failings.

On the up side, 33 States and the District of Columbia have now legalized access to Medical Cannabis and CBD is legal in nearly every State of the Union. Millions of Americans now have access to high quality Cannabis products. Having access to Cannabis and/or CBD affords people a scientifically based treatment option that is reasonably safe until much needed clinical research can be conducted. Gathering epidemiological data on clinical outcomes for Cannabis users vs non- Cannabis users with Covid-19 may help us identify the best ways to use Cannabis and to aid the development of clinical trials to treat both this and numerous other disorders. A study could be quickly developed to monitor a cohort of a thousand people who test positive for SARS Co-v-2. Ask them if they use Cannabis and if so how often. Then monitor those patients for progression to Covid-19 and assess clinical outcomes between the groups.

CONCLUSION

Covid-19 is an emergent virus currently threatening the lives of millions of people across the globe. There are currently no proven methods of effectively treating this virus and social distancing to prevent spread of the virus is currently considered our best defense. However, Cannabis may offer a safe and effective method of reducing mortality associated with Covid-19. It's time for politicians and bureaucrats across the Globe to take a stand against the unreasonable, arbitrary and capricious actions of US Although Cannabis may occasionally cause mild side effects such as dizziness, anxiety, paranoia, dry mouth, fatigue or weakness, tolerance to most adverse reactions develops rapidly. Due to its low toxicity there has never been a reported case of fatal overdose with Cannabis, making it safe for patients to self titrate. Cannabis is generally well tolerated and has been shown to help regulate immune function. Cannabis may help to prevent the cytokine storm that can ultimately lead to pneumonia, organ failure and death in Covid-19, as well as protecting against Ischemic Reperfusion Injuries associated with ventilation when required.

Unfortunately, ignorant, incompetent, unqualified and cowardly politicians and bureaucrats around the globe continue to prohibit access to this lifesaving medication. Vital research on Medical Cannabis continues to be banned. In the US, neither the US Court of Appeals nor the US Supreme Court have been willing to hold any administration accountable for nearly a century of Cannabis prohibition, which has led to countless millions of deaths. Now we

face a healthcare crisis that may have been largely preventable. Clearly, those within the Trump administration can not be trusted to put the safety of the American People ahead of their own personal agendas.

In the US, Republican legislators blindly support the illegal activity of the Trump administration in favor of enriching themselves. Legislators like Mitch McConnell and Lindsey Graham have repeatedly violated the public trust and must be voted out of office if we hope to see any substantive changes in healthcare policies that place patients ahead CEOs and stock holders. The DEA, FDA, HHS and NIDA must be held accountable for their failures to protect the American People and must be reformed into agencies designed to protect and serve The People instead of blindly supporting failed governmental policies. The World Health Organization must be willing to stand up to decades of bullying by the United States and finally speak truth to power.

The Zika virus taught us that in order to speed up the available vaccine during ongoing outbreak, preclinical studies of SAR-CoV-2 vaccine candidates may need to be performed in parallel with clinical trials (Prompetchara). The same lesson applies to development of novel treatments for Covid-19, including the use of Cannabis. In light of the healthcare crisis we now face, the US Congress needs to legalize the medical use of Cannabis and support immediate access to this medication, while supporting parallel clinical trials of Cannabis to determine how it may best help to save the lives of those stricken by this deadly disease. Numerous States and other Countries have the authority to conduct such research even without federal approval.

In order to move towards this goal the United Nations and World Health Organization must denunciate the Single Convention Treaty and move towards an International legal regime that supports regulation of drug markets, rather prohibition. Drug abuse must be treated as a medical problem rather than legal one. Only by shifting the focus of governments from “further enriching the already rich”, to “creating a better World we can all share”, will we be able to better manage emerging threats to global health and security in the future. We need to accept that what happens to any of us, can happen to all of us. Only by working together can we hope to leave a planet in which our progeny might experience a World better than the one we were born into.

REFERENCES

1. World Health Organization. Coronavirus disease (COVID-19) Pandemic. https://www.who.int/emergencies/diseases/novel-coronavirus-2019

2. Chen W-H, Strych U, Hotez PJ, Bottazzi, ME. The SARS-CoV-2 Vaccine Pipeline: an Overview. Curr Trop Med Rep. 2020 Mar 3 : 1–4.

3. Yang Y, Peng F, Wang R, Guan K, et.al. The deadly coronaviruses: The 2003 SARS pandemic and the 2020 novel coronavirus epidemic in China. J Autoimmun. 2020 Mar.

4. Marco Cascella; Michael Rajnik; Arturo Cuomo; Scott C. Dulebohn; et.al. Features, Evaluation and Treatment Coronavirus (COVID-19). [Updated 2020 Mar 20]. In: StatPearls [Internet].

5. Al-Osail AM and Al-Wazzah MJ. The history and epidemiology of Middle East respiratory syndrome corona virus Multidiscip Respir Med. 2017; 12: 20.

6. Rismanbaf A. Potential Treatments for COVID-19; a Narrative Literature Review. Arch Acad Emerg Med. 2020 Mar 21;8(1):e29.

7. Yong CY, Ong HK, Yeap SK, Ho KL, et.al. Recent Advances in the Vaccine Development Against Middle East Respiratory Syndrome-Coronavirus. Front Microbiol. 2019; 10: 1781.

8. CDC. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) — United States, February 12–March 16, 2020. Weekly / March 27, 2020 / 69(12);343-346. https://www.cdc.gov/mmwr/volumes/69/wr/mm6912e2.htm

9. Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Asian Pac J Allergy Immunol. 2020 Mar;38(1):1-9.

10. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020 Mar 28;395:1033-1034.

11. Delgado-Enciso I, López-Lemus UA, Valcarcel-Gamiño JA, Rodriguez-Sanchez IP, et.al. Dengue virus-1 NS5 genetic variant associated with a severe clinical infection: Possible reduction of the innate immune response by inhibition of interferon type 1 and the Janus kinase-signal transducer and activator of transcription signaling pathway. Int J Mol Med. 2018 Apr;41(4):2263-2269.

12. Savarin C, Bergmann CC. Fine Tuning the Cytokine Storm by IFN and IL-10 Following Neurotropic Coronavirus Encephalomyelitis. Front. Immunology, 2018 Dec 20; 9:3022.

13. Sido JM, Jackson AR, Nagarkatti PS, et.al. Marijuana-derived Δ-9-tetrahydrocannabinol suppresses Th1/Th17 cell-mediated delayed-type hypersensitivity through microRNA regulation. J Mol Med (Berl). 2016 Sep; 94(9): 1039–1051.

14. Yang X, Bam M, Nagarkatti PS, Nagarkatti M. RNA-seq Analysis of Delta -9-Tetrahydrocannabinol-treated T cells Reveals Altered Gene Expression Profiles that Regulate

Immune Response and Cell Proliferation. The Journal of Biological Chemistry, 05 Jun 2016, 291(30):15460-15472.

15. Mitzel DN, Jaramillo RJ, Stout-Delgado H, Senft AP, et.al.Human metapneumovirus inhibits the IL-6-induced JAK/STAT3 signalling cascade in airway epithelium. J Gen Virol. 2014 Jan;95(Pt 1):26-37.

16. Chang Z, Wang Y, Zhou X, Long JE. STAT3 roles in viral infection: antiviral or proviral? Future Virol. 2018 Aug;13(8):557-574.

17. Couch DG, Tasker C, Theophilidou E, Lund JN, O'Sullivan SE. Cannabidiol and palmitoylethanolamide are anti-inflammatory in the acutely inflamed human colon. Clin Sci (Lond). 2017 Oct 25;131(21):2611-2626.

18. Bhattacharya P, Thiruppathi M, Elshabrawy HA, Alharshawi K, et.al. GM-CSF: An Immune Modulatory Cytokine that can Suppress Autoimmunity. Cytokine. 2015 Oct; 75(2): 261–271.

19. Martinez MA. Compounds with therapeutic potential against novel respiratory 2019 coronavirus. Antimicrob Agents Chemother. 2020 Mar 9.

20. Shah S, Das S, Jain A, Misra DP, et.al. A systematic review of the prophylactic role of chloroquine and hydroxychloroquine in Coronavirus Disease-19 (COVID-19). Int J Rheum Dis. 2020 Apr 13. [Epub ahead of print]

21. Manuzak JA, Gott TM, Kirkwood JS, Coronado E, et.al. Heavy Cannabis Use Associated With Reduction in Activated and Inflammatory Immune Cell Frequencies in Antiretroviral Therapy-Treated Human Immunodeficiency Virus-Infected Individuals. Clin Infect Dis. 2018 Jun 1;66(12):1872-1882.

22. Petrosino S, Verde R, Vaia M, Allarà M, et.al. Anti-inflammatory Properties of Cannabidiol, a Nonpsychotropic Cannabinoid, in Experimental Allergic Contact Dermatitis. J Pharmacol Exp Ther. 2018 Jun;365(3):652-663.

23. Ferrari, RS, Andrade CF. Oxidative Stress and Lung Ischemia-Reperfusion Injury. Oxid Med Cell Longev. 2015;

24. Pac-Soo CK, Mathew H, Ma D. Ischaemic conditioning strategies reduce ischaemia/ reperfusion-induced organ injury. Br J Anaesth. 2015 Feb;114(2):204-16.

25. Hochhauser E, Lahat E, Sultan M, Pappo O, et.al. Ultra Low Dose Delta 9-Tetrahydrocannabinol Protects Mouse Liver from Ischemia Reperfusion Injury. Cell Physiol Biochem. 2015;36(5):1971-81.

26. Paronis CA, Nikas SP, Shukla VG, Makriyannis A. Δ(9)-Tetrahydrocannabinol acts as a partial agonist/antagonist in mice. Behav Pharmacol. 2012 Dec;23(8):802-5.

27. Fishbein M, Gov S, Assaf F, Gafni M et.al. Long-term behavioral and biochemical effects of an ultra-low dose of D9 -tetrahydrocannabinol (THC): neuroprotection and ERK signaling Exp Brain Res (2012) 221:437–448.

28. Durst R, Lotan C. The Potential for Clinical Use of Cannabinoids in Treatment of Cardiovascular Diseases. Cardiovascular therapeutics Volume29, Issue1. February 2011, Pages 17-22.

29. Smaga I, Bystrowska B, Gawliński D, Pomierny B, et.al. Antidepressants and Changes in Concentration of Endocannabinoids and N-Acylethanolamines in Rat Brain Structures. Neurotox Res. 2014; 26(2): 190–206.

30. Cilioa MR, and Ferriero DM. Synergistic neuroprotective therapies with hypothermia. Semin Fetal Neonatal Med. 2010 Oct; 15(5): 293–298.

31. Rajesh M, Mukhopadhyay P, Haskó G, Liaudet L, et.al. Cannabinoid-1 receptor activation induces reactive oxygen species-dependent and -independent mitogen-activated protein kinase activation and cell death in human coronary artery endothelial cells. Br J Pharmacol. 2010 Jun; 160(3): 688–700.

32. Bayram S, Parlar A, Arslan SO. The curative effect of cannabinoid 2 receptor agonist on functional failure and disruptive inflammation caused by intestinal ischemia and reperfusion. Fund-am Clin Pharmacol. 2020 Feb;34(1):80-90.

33. 81, Fed. Reg. 156, August 12, 2016 / Proposed Rules, Denial of Petition to Initiate Proceedings to Reschedule Marijuana, page 53767-53845.