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Therapeutic Opportunities and Potential Risks of Cannabinoids in relation to COVID-19

Introduction

The global outbreak of coronavirus-2019 (COVID-19, caused by variants of the SAR-CoV-2 virus) has caused significant disruptions in almost all aspects of life in countries around the world. These impacts occurred when the medicinal potential of cannabis was already undergoing extensive examination,[1] [2] naturally prompting interest in potential applications to COVID-19. The current review examines the current state of the evidence concerning the medical opportunities for COVID-19 prevention and treatment, as well as potential risks for individuals using cannabis from COVID-19. The scope is deliberately focused on this narrow scope, rather than broader epidemiological questions about changes in cannabis use during the pandemic.

Methods

Searches were conducted on Pub Med and Google Scholar at the end of March, 2022, using the following terms: "cannabis," "marijuana," "COVID" and "coronavirus." Articles in English or available in translation into English, that were conducted on cannabis and COVID-19 or a COVID-19 proxy were reviewed. In total, 37 articles were obtained that described the therapeutic potential of cannabis for the prevention or treatment of COVID-19 (also referred to as SARS-CoV-2) and 14 discussing negative COVID-19 outcomes that may be associated with cannabis use.

I. Therapeutic Opportunities

a) Commentaries and reviews

A number of commentaries and review articles have been published discussing the potential to use cannabinoids, such as on cannabidiol (CBD), cannabidiolic acid (CBDA), cannabigerolic acid (CBGA), β-Caryophyllene (CBP), and cannabivarin (CVN), for the prevention or treatment of COVID-19. Although a few are based on anecdotal evidence [3] or clinical trials of other medical conditions, [4] [5] [6] [7] [8] [9] most of these reviews have focused upon preclinical findings to argue that cannabinoids may be helpful in one or both of two ways:

1) reducing the attachment and replication of the SAR-CoV-2 virus; [10] [11] [12] [13] [14]

2) preventing or ameliorating lung damage by moderating the release of cytokines, such as interleukins (IL, e.g., IL-6, IL-8, IL-1β, IL-18), tumor necrosis factor alpha (TNFα), and cyclooxygenase-2 (COX2), as well as enzymes such as angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2). [15] [16] [17] [18] [19]

With one exception, [5] most reviews call for more research before trying to use cannabis for COVID-19 prevention or treatment. The current situation may be similar to that witnessed for hydroxychloroquine, i.e., time is needed for sufficient evidence emerges to separate speculation from evidence. [20] [21] [22] [23] As noted by Brown et al., for some cannabinoids, replicating *in vitro* results in large-scale clinical trials may be unlikely because of their high cost and short half-life. [24] Regulatory agencies should consider whether unscrupulous companies promote misleading claims for cannabis (particularly CBD) among an anxious and vulnerable population. [25] [26]

b) *In vitro* research

As summarized in Table 1, 12 *in vitro* studies have been conducted focusing upon the ability of cannabinoids to reduce COVID infectivity and ameliorate cytokine release.

Table 1: *in vitro* studies (n=12) on cannabinoids and COVID-19

Reference	Publication Type/ Methodology	Summary
Anil SM et al [27]	Study of CBD and CBG compounds using alveolar epithelial cell line.	Although cannabis solutions appeared to reduce secretion of inflammatory cytokines, there was an increase in macrophage-secreted IL-6 and IL-8. For present, should avoid using cannabis for COVID treatment.
Chatow L et al [28]	Study of terpene-based formulations, with or without CBD, on human lung fibroblast cells.	Pretreatment of cells reduced viral (H CoV-2292, a less virulent COVID strain) attachment and/or entry.
Chen et al [29]	Study using single-cell RNA sequencing of bronchoalveolar lavage fluid samples from 10 healthy donors, 6 severe COVID-19 patients, and 3 mild recovered patients.	Compared to healthy controls, ACE2 and TMPRSS2 expressions were significantly high in COVID-19 patients. The authors propose that when COVID-19 infects lung epithelium, it alters the communication patterns with the immune system and promotes a dysregulated host immune response.
Corpetti et al. [30]	Study of the effect of CBD on epithelial cells exposed to SARS-CoV-2 spike protein.	CBD reduced all study proinflammatory marker, including ACE2, and inhibited a number of cytokines (IL-6, IL-1β, TNFα, IL-18). Based on these findings, the authors conclude that *in vitro*, CBD is a powerful inhibitor of spike protein enterotoxicity.
Erukainure OL, et al [31]	Molecular docking analysis of effects of phytocannabinoids.	Suggests phytocannabinoids may interact with codon mRNAs of proteins involved in the replication, translation, assembly and release of COVID-19.
Kovalchuk A et al [32]	Study of 7 cannabis extracts on 3D artificial epidermis cells and lung fibroblast cell lines.	For 5 of the 7 extracts, down-regulation was observed of inflammatory cytokines such as COX2, TNFα, IL-6, CCL, etc. However, caution must be used as 1 extract had deleterious effects.
Nguyen LC et al[33]	Preprint of an article describing a) a study of human lung carcinoma cells pretreated with CBD, and b) a chart review of patients at the University of Chicago Medical Center.	In the *in vitro* study, CBD inhibited viral gene expression and reversed some effects of the SARS-CoV-2 on host gene transcription. In the review of charts of 93,000 patients, those who took CBD had a lower rate of testing positive for COVID-19.
Santos S et al [34]	Study of 6 CBD and terpene formulations in 4 cell lines	The formulations appeared to reduce infectivity of a B.1.1.7 strain of SARS-CoV-2. Two of the formulation appeared to modulate cytokine release, suggesting a role in COVID treatment. Calls for

Reference	Publication Type/ Methodology	Summary
		more research on the topic.
Sarkar I et al [35]	Molecular docking and simulation studies to focus on effect of CBD and CVN on proteins damaged in COVID-19.	CBD and CVN can bind to central nervous system proteins such as ACE2, IL-6, transmembrane serine protease and NRP1 and downregulate them. There is a potential that CBD and CVN could be beneficial in treating post-COVID symptoms.
Van Breeman RB et al [36]	Affinity selection-mass spectrometry was used to study cannabinoid ligands to the SARS-CoV-2 spike protein in a human epithelial cell model.	CBGA and CBDA prevented infection of the cell line by two variants of pseudo-virus with the COVID-19 spike protein. These findings suggest there may be a role for cannabinoids to prevent as well as treat COVID-19 infections.
Wang B et al [37]	Study of CBD and various cannabis extracts using human cell lines.	High-CBD extracts modulated ACE2 and TMPRSS2 expression and, through the AKT signaling pathway, the induction of a variety of inflammatory mediators (COX2, IL-6, IL-8). This suggests a potential for using CBD extracts in COVID-19 treatment.
Wang B et al [38]	Studty using artificial 3D human oral, airway and intestinal tissues.	Authors identified 13 high CBD extracts that down-regulated ACE2 protein levels; in addition, some downregulated TMPRSS2. Further, larger studies are needed to validate these findings.

These studies tend to focus on three main pathways.

1) Effects on the attachment of the COVID-19 spike proteins:

A number of studies have proposed that cannabis extracts, particularly those high in CBD, may down-regulate cell receptors that play roles in the attachment, entry into cells, and/or replication of the COVID virus. Five studies appear to support this hypothesis:

- A study of terpene-based formulations with or without CBD showed pretreatment reduced attachment and/or entry of a less virile COVID strain (H CoV-2292) into human lung fibroblast cells. [28]
- Reduced infectivity was also observed in another study of human lung carcinoma cells. [33]
- Molecular docking analysis found evidence that phytocannabinoids may interact with codon mRNAs of proteins involving in the replication, translation, assembly and release of COVID-19, suggesting a potential role in prevention. [31]
- A study of 6 CBD and terpene formulations in 4 cell lines showed reductions in the infectivity of a B.1.1.6 strain of SARS-CoV-2. [34]
- A study using affinity selection-mass spectrometry found CBDA and CBGA prevented infection of a human epithelial cell line by two variants of a COVID-pseudo cell line. [36]

2) Modulating the inflammatory response:

The release of cytokines such as IL-6, COX2, and TNFα in reaction to an infection can result in acute lung injury and is a key concern in the management of COVID-19 patients. [39] There is evidence that inflammation in COVID-19 may also be associated with changes in the levels of ACE2 and TMPRSS2.[40] As described by Khodadadi et al., research on other viral respiratory infections suggest CBD may have a variety of immunomodulatory and anti-inflammatory effects that mitigate cytokine storms and/or ACE2 and TMPRSS2 expression. [41] This potential has been the focus of several studies:

- A study of a cannabis extract containing CBD, CBG, tetrahydrocannabivarin (THCV) and multiple terpenes found that it reduced IL-6, IL-8 and C-C Motif Chemokine Ligands (CCLS) 2 and 7 in an alveolar epithelial cell line. However, the authors recommend caution before adopting cannabis as a treatment option, as an increase of macrophage-secreted IL-6 and IL-8 can occur that could, in theory, lead to a worsening of the "cytokine storm" in patients with severe disease. [27]
- Santos et al. tested CBD and terpene formulations in 4 cell lines found that 2 modulated cytokine release. [34]
- In a study of 7 cannabis extracts, 5 of them down-regulated inflammatory cytokines in 3D artificial epidermis and lung fibroblast cell lines. However, the authors caution that one of the formulations had deleterious effects. [32]
- Two studies using 3D artificial cell lines found that high-CBD extracts modulated ACE2 and TMPRSS2 expression and, through the AKT signaling pathway, the induction of a variety of inflammatory cytokines, such as COX2, IL-6 and IL-8. [37] [38]

3) Effects on peroxisome proliferator-activated receptors (PPAR):

Cannabinoids may bind to and activate PPAR gamma (PPARγ), a receptor that (among other functions) may mediate inflammatory effects. [30] [42]

In summary, many of these preclinical studies showed encouraging results, but several also noted that results could vary between formulations, with some having either no effect or negative effects. [27] [32] [34] Viability of translation into humans remains unclear.

c) <u>Clinical studies</u>

As noted in Table 1, in addition to an *in vitro* study of human lung carcinoma cells, Nguyen et al. conducted a chart review of patients enrolled in the National COVID Cohort Collaborative. Of 1,212 patients with a record of taking CBD for a seizure-related condition, 6.2% (75 patients) had a record of COVID; this was lower than the 25% observed for the overall study population (n=5,681,382) or the 14% for those with a prior seizure-type condition (n=302,460). Likewise, when a sample was extracted of those with seizure conditions who were taking CBD (active group, n=531) and a matched sample without CBD (matched controls, n=531), the proportions who tested positive was much lower in the active than the control group (4.9% vs. 9.0%, p=.011).[33]

The sole RCT that was available was a small study involving COVID patients (49 treatment and 42 placebo controls) recruited from 2 hospitals in Brazil. It found CBD was well tolerated but had no effect on time to disease resolution. [43]

II. Risks/Complications

Table 2 summarizes the 14 articles that discussed COVID-19 risks or complications for individuals using cannabis. Methodologies used in these studies varied: 3 used surveys, 3 genomic analyses, 2 case studies, 2 narrative reviews/commentaries, 2 web analytics, 1 retrospective cohort study and 1 *in vitro* study. It should be noted that in the genomic studies, the proxy for current cannabis use is genetic vulnerability (as defined by the researchers) for cannabis use disorder (CUD).

Table 2: COVID-19-related risks or complications among cannabis users

Reference	Publication Type/Methodology	Summary
Abarno CN et al [44]	Survey (point prevalence) of 727 psychology students at a single Louisiana university	Cannabis users (n=184) reported significantly great COVID-related functional impairment compared to non-users (n=543), even after controlling for sex, difficulty with emotional regulation, and COVID-related distress. Admits that the cross-sectional design makes it impossible to establish temporal (causal) relationship.
Archie SR et al [45]	Review of 9 case studies of COVID patients documenting neurological symptoms	Theorizes that cannabis could increase risk of neurology effects because of observed relationship between cannabis and stroke, structural and functional changes in the brain, and cognitive and behavioural distress. Discusses the mechanism by which coronaviruses can increase inflammatory factors that are associated with a greater risk of stroke; however, none of the case studies examined provide information on cannabis use.
Hatoum AS et al. [46]	Preprint of meta-analysis of genome databases for those with CUD (n=14,080 vs. 343,726) and those hospitalized with COVID-19 (n=9,373, controls=1,197,256).	A genetic vulnerability to COVID-19 was correlated with a genetic liability of CUD, even after controlling for related risk factors and covariates. In this study, CUD is considered moderately (50-60%) heritable risk, with an associated increased risk of respiratory disease. As a result, suggests caution when proposing to use cannabis to help prevent COVID.
Ismail et al [47]	Retrospective cohort study of 993 mild COVID-19 cases treated by public health system in a Brazilian city.	Cannabis use did not have a significant relationship with the development of COVID or number or type of symptoms reported.
Janmohamed K et al. [48]	Structural topic modeling to map temporal (August 1, 2019 – April 21, 2020) trends in approximately 200,000 web domains discussing vaping.	Compared to the pre-COVID period (defined as prior to December 31, 2019), during COVID there was a surge in discussions about claims that CBD could be beneficial for COVID prevention and treatment. Over time, but to a lesser extent, discussions also emerged about the potential risks of CBD vaping.

Reference	Publication Type/Methodology	Summary
Merianos AL et al [49]	Survey (point prevalence) of students at 4 American colleges (n=800).	52% (n=416) of e-cigarette users concurrently used cannabis. Concurrent used were 3.52 times more likely to report COVID symptoms than sole e-cigarette users, and were 1.85 times more likely to report a COVID diagnosis.
Monnig MA et al [50]	Web survey of self-reported adherence to CDC COVID guidelines among 1,084 youth 18 and older living in 5 New England (American) states.	There was no effect on adherence to guidelines among those who reported cannabis, e-cigarette or stimulant use, which there was significantly lower adherence among those reporting daily opioid or alcohol use. However, only 5.7% of participants reported daily and 4.5% nondaily cannabis use.
Pirnia B et al [51]	Case report of a patient with chronic hyperemesis syndrome (CHS).	Because some symptoms of CHS are similar to some of COVID-19, clinicians must be careful in making their diagnoses.
Rosoff DB et al [52]	Genetic data from >1.7 million Europeans used to conduct single- and multi-variable Mendelian randomization studies.	Genetic liability for smoking demonstrated a strong association with risk of COVID-19 requiring hospitalization. There was an association in single-variable Mendelian randomization (MR) between cannabis use and a COVID-19 diagnosis, but this relationship was not significant in multivariable MR or MRs for CUD.
Sivaraman V et al [53]	In vitro study of K. pneumoniae in mice exposed to alcohol and/or endocannabinoid.	Cannabinoid-exposed mice had more serious disease than mock-infected control animals, including increase inflammatory cytokine levels and clinical signs of disease. Mice doubly-exposed displayed the highest levels of inflammatory proteins.
Spechler PA et al [54]	Subset of Tulsa 1000 survey study who had completed a COVID-19 vaccination questionnaire; compared 45 who lifetime use of cannabis was $\geq$10 to 45 for whom it was <10 times (light users).	Vaccine willingness did not differ between the 2 groups. Within the more frequent cannabis use group (n=45), there was a negative correlation between frequency of cannabis use and willingness to receive a vaccine.

There is evidence in animal models that smoking cannabis may increase inflammatory processes in the lungs. [53] In one study of patient records, the risk of respiratory disease was elevated not only in those who smoked tobacco but those who had a diagnosis of CUD and/or at least two urine drug screens positive for cannabinoids.[55] Because of findings such as this, it has been theorized that cannabis users may be more vulnerable to COVID-19 infection. **Error! Bookmark not defined.** However, differences in how cannabis is consumed (e.g., smoking, vaping or edibles), may complicate our understanding.

Studies specific to COVID have had mixed results. A recent study of American youth 18-24 who vape found no significant relationship between cannabis vaping and either asthma or other respiratory symptoms. [56] Likewise, a retrospective cohort study of 993 mild COVID-19 cases in Brazil reported no significant relationship between cannabis use and the development of COVID or number or type of symptoms reported. [47] However, a survey of 800 American college studies found that 52% of e-cigarette users concurrently used cannabis. Concurrent tobacco and cannabis users were 3.5 times more likely to report COVID symptoms and 1.85 times more likely to report a COVID diagnosis than sole e-cigarette users. [49]

Two brief publications discussed the fact that what may appear to be symptoms of COVID may actually be cannabinoid hyperemesis syndrome. **Error! Bookmark not defined.** [51]

COVID-19 has been shown to be associated with neurological symptoms. [57] The mechanism by which these occur is still being defined but may be changes in ACE2 expression and elevated cytokine levels.[58] Although in most patients such symptoms resolve, there is evidence suggesting involvement of the central nervous system (CNS) is associated with a poor prognosis and disease worsening. [59] Archie et al. make the point that even prior to the COVID-19 pandemic, relationships had already been observed between cannabis and structural and functional changes in the brain; on this basis they argue that cannabis might increase the neurological risk of COVID patients. [45] However, the case reports they reviewed did not provide information on cannabis use so no direct evidence was offered to support that claim.

Functional (but not neurological) impairment in the activities of everyday life because of COVID has been detected among university students who are cannabis users (n=184) compared to those who do not (n=543). This type of impairment persisted even after controlling for sex, difficulty with emotional regulation, and COVID-related distress, but the cross-sectional design of the study made it impossible to establish temporal or causal relationships. [44]

Three studies have used genomic risk to examine the relationship between COVID and cannabis, one a meta-analysis of data from 20 datasets and two by another team using data from >1.7 million Europeans. [46] **Error! Bookmark not defined.** [52] In the first, CUD is described as a moderately (50-60%) heritable risk associated with not only respiratory disease but COVID-19. [46] The other two studies found a strong association between genetically-predicted lifetime smoking and increased risk for COVID-19 hospitalization but little evidence of a relationship between genetically-predicted liability for CUD and COVID-19. **Error! Bookmark not defined.** [52]

Three studies have examined the relationship between cannabis use and COVID attitudes or behaviours. A small, questionnaire-based study comparing 45 light cannabis users (defined as <10 occasions) to 45 more frequent users found no differences in vaccine willingness. Within the frequent cannabis use group there appeared to be a negative correlation between frequency of cannabis use and vaccine willingness, but due to the small number of cases (n=45), this finding should be interpreted with caution. [54] In a larger study of 1,084 American youth living on the east coast, the use of cannabis, e-cigarettes or stimulants had no effect on self-reported adherence to public health COVID-19 guidelines. [50] A structural topic analysis of vaping-focused web domains found that during COVID, there was a surge in discussion on vaping CBD as a possible treatment and, to a lesser extent, as a potential risk. The authors note that such discussions about the beneficial effects of CBD may have been amplified by marketing activities of CBD and vaping retailers. [48]

Conclusions

The emergence of COVID-19 and the world-wide pandemic has resulted in a surge of interest in the potential of cannabinoids for prevention or treatments. To date, there is *in vitro* research using human and animal cell lines that show some cannabinoids, particularly formulations relatively high in CBD, may be able

to reduce COVID infectivity and damaging inflammatory reactions. However, no human trial has been conducted that provides evidence of medical benefit of cannabinoids for COVID-19. Randomized controlled trials (similar to those conducted to test the COVID-19 vaccines) would be needed before cannabinoids can be seriously considered for use in ameliorating the current pandemic.

If cannabinoids are beneficial in preventing or treating COVID-19, it might be expected that cannabis users would be at reduced risk of contracting the disease, or being ill enough to require hospitalization. To date, evidence on the relationship between cannabis use and COVID-19 is limited. At this point, there is no consensus on whether cannabis (whether smoked or vaped) substantially increases the risk of contracting COVID or disease severity. Large-scale genomic studies have produced conflicting results, with one group reporting a genetic liability for CUD increases the risk of respiratory diseases, including COVID, but another group finding no evidence of such a relationship. Likewise, there is no consensus on whether cannabis use can be correlated to COVID-19 attitudes and behaviours (e.g., compliance with public health guidelines).

In summary, our current state of knowledge about the health risks and benefits of cannabis in relation to COVID-19 can best be described as nascent. Promotion of cannabis products for preventing or treating COVID-19 is not warranted based on the existing evidence. Although promising preclinical observations have been reported, this work requires translation into human trials to test the hypothesis that medical cannabis may be useful in the clinical management of COVID-19.

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