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Letter to the Editor: Possible Drug–Drug Interactions Between Cannabinoids and Candidate COVID-19 Drugs

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Introduction

Cannabinoid preparations are available across the globe as regulatory agency-approved medicines, through medical cannabis programs, and as hemp-derived products. Many regions, including most provinces in Canada, have designated cannabis businesses as "essential" services during the coronavirus disease 2019 (COVID-19) pandemic, and sales of cannabis remain strong in an otherwise economically challenging time. In light of the potential increased use of cannabis and a recent surge in research to rapidly identify medications to treat COVID-19, it is critical to delineate possible pharmacokinetic (PK) and pharmacodynamic (PD) drug–drug interactions (DDIs) between cannabinoids and such experimental medications. Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are lipophilic, highly protein bound, have a large volume of distribution, a long half-life, bioaccumulate, and share common metabolic pathways within the cytochrome P450 (CYP450) family (e.g., 3A4, 2C9, and 2C19), drug transporters (e.g., breast cancer resistance protein), and plasma protein-binding substrates. Both THC and CBD have been shown to have clinically significant PK (e.g., warfarin and clobazam)[1,2] and PD interactions (e.g., valproic acid).[2] The severity of some cannabinoid DDIs, such as potential hepatocellular injury and sedation,[2,3] further highlights the importance of early identification of possible interactions between cannabinoids and medications that may be used to treat COVID-19.

Methods

Pharmaceutical candidates for COVID-19 were identified through reviews[4] and clinicaltrials.gov, Google, and PubMed searches using keywords: (COVID-19, COVID-2) research, drug, investigational product, and clinical trial. The initial search was conducted during March 24–26, 2020 and was updated on August 06, 2020. COVID-19 drug candidates were considered relevant if there was a published mechanism, planned or ongoing clinical trial, and/or off-label use (vaccines and contraindicated medications were excluded). Package inserts, product monographs, and drug submissions were collected from regulatory bodies (U.S. Food and Drug Administration [FDA], Ministry of Health of the Russian Federation, Pharmaceuticals and Medical Devices Agency [PMDA, Japan]) and reviewed to identify PK (i.e., interaction with CYP450s, drug transporters, or protein binding) or PD (i.e., side effects and additive drug effects) sources of DDIs. If not available in regulatory documents, PK and PD sources of DDIs were identified using PubMed searches (keywords: [name of drug], DDI, CYP450, transporter, protein binding, side effect, and adverse effect). DDIs between relevant COVID-19 drug candidates and CBD and THC were identified as "possible" (overlapping sources of DDIs) or "unlikely" (no overlapping sources of DDIs).

Results

Of the 28 identified existing or novel pharmaceutical candidates for COVID-19 treatment, 12 (i.e., bevacizumab, brilacidin, convalescent plasma, favipiravir, galidesivir [BCX4430], griffithsin, intravenous immunoglobulin, niclosamide, REGN3048, remdesivir, vitamin C, and XueBiJing) had unknown or unlikely DDIs due to either unidentified or unrelated metabolic, transporter, or protein-binding pathways. Ten candidates were found to possibly result in DDIs through CYP interaction, five through drug transporter interactions, six through protein binding, and 15 that may cause PD DDIs, including exacerbate side effect profiles (see Table 1). Increased risk for diarrhea, headache, dizziness, somnolence, infection, and liver injury

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Table 1. COVID-19 Investigational Agents with Possible Pharmacokinetic or Pharmacodynamic Cannabinoid Interactions

Investigational agents	Description of agent	Current COVID-19 research	Possible pharmacokinetic interaction(s)	Possible pharmacodynamic interaction(s)
Anakinra	IL-1 receptor antagonist used to treat RA	May mitigate CSS. Clinical trial planned.	Unlikely	CBD: Coadministration of immuno- or myelosuppressive agents may potentiate the risk of infections.
Arbidol (umifenovir)	Non-nucleoside antiviral drug approved in Russia and China for the treatment of influenza	S protein/ACE2 membrane fusion inhibitor. Preliminary clinical trial completed.	↑ THC; ↑ CBD: CYP3A4, plasma protein binding	Unknown
Azithromycin	Antibiotic used in conjunction with hydroxychloroquine	Potential antiviral activity. Previously studied in an RCT co-administered with hydroxychloroquine.	THC; CBD: P-gp transporters	CBD: Could increase risk for diarrhea
Baricitinib	JAK inhibitor approved for the treatment of RA	Predicted to reduce viral entry and may mitigate inflammation. Clinical trial initiated in Italy.	↑ THC; ↑ CBD: CYP3A4, CYP1A2, CYP2C9 ↑ CBD: CYP2C8, CYP2C19, CYP2B6 ↑ THC: CYP2D6	CBD: Possible overlapping increased effect on TNF, may increase chance of serious infections, malignancy, or thrombosis.
Chloroquine/ hydroxychloroquine	Antimalarial agent with multimodal anti-inflammatory, immunomodulatory, antiviral, and zinc ionophore activities	Inhibit viral entry and host immunomodulatory effects. Clinical trials completed and ongoing.	↑ THC; ↑ CBD: CYP3A4 ↑ THC: CYP2D6 ↑ CBD: CYP2C8	CBD: Could increase diarrhea and/or headache risk
Darunavir/cobicistat	HIV-1 protease inhibitor	$3CL^{pro}$ inhibitor. Clinical trial ongoing.	↑ THC; ↑ CBD: CYP3A4, plasma protein binding, P-gp and BCRP transporters	CBD: Could increase diarrhea and/or headache
Disulfiram	Supportive treatment for alcoholism, which blocks alcohol oxidation through acetaldehyde dehydrogenase inhibition	PL^{pro} inhibitor of MERS-CoV and SARS-CoV-1	↑ THC; CBD: CYP3A4, CYP2C9	THC; CBD: Could increase risk for sedation
Dexamethasone	Corticosteroid used to treat rheumatic, dermatological, allergic, gastrointestinal, respiratory, neoplastic, and other conditions	Recommended for use in COVID-19 patients with severe respiratory symptoms from the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial.	↑ THC; ↑ CBD: CYP3A4, plasma protein binding	CBD: Could increase risk of headache. Coadministration of immuno- or myelosuppressive agents may potentiate the risk of infections. Demonstrated antagonism in some anti-inflammatory *in vivo* models with dexamethasone. THC: Could increase euphoria.
Eculizumab	Monoclonal antibody that targets complement protein C5; inhibits cleavage to C5a and C5b.	May mitigate CSS and/or mitigate lung damage. Clinical trial ongoing.	Unlikely	CBD: Could increase risk of headache
Lopinavir/ritonavir	HIV-1 protease inhibitors. Ritonavir is a potent CYP3A4 inhibitor that "boosts" plasma lopinavir concentrations.	$3CL^{pro}$ inhibitor. Preliminary clinical trial completed.	↑ THC; ↑ CBD: CYP3A4, plasma protein binding, P-gp and BCRP transporters	CBD: Could increase diarrhea, fatigue, and/or headache risk. THC: Could increase dizziness.
Nelfinavir	HIV-1 protease inhibitor	May inhibit SARS-CoV-2 replication	↑ THC; ↑ CBD: CYP3A4, plasma protein binding, P-gp and BCRP transporters ↑ CBD: CYP2C19	CBD: Could increase diarrhea and/or headache risk
Nitazoxanide	Broad-spectrum anti-infective and antiviral agent	Antiviral activity against MERS-CoV and SARS-CoV-2, and potential host immunomodulatory effects. Ongoing clinical trial.	↑ THC; ↑ CBD: plasma protein binding	CBD: Could increase headache
Sarilumab	Human monoclonal antibody against IL-6R approved for the treatment of RA	May mitigate CSS. Clinical trial planned.	↓ THC; ↓ CBD: CYP450 induction by investigational agent could alter cannabinoid plasma levels	CBD: Possible risk of liver injury as both drugs increase ALT. Coadministration of immuno- or myelosuppressive agents may potentiate the risk of infections.
Sofosbuvir	RdRp inhibitor used to treat hepatitis C	May inhibit SARS-CoV-2 RdRp	↑ THC; ↑ CBD: P-gp and BCRP transporters	CBD: Could increase diarrhea, fatigue, and/or headache
Tocilizumab	Human monoclonal antibody against IL-6R approved for the treatment of RA and CSS after CAR T-cell therapy	May mitigate CSS. Preliminary clinical trial completed.	↑ THC; ↑ CBD: CYP3A4, CYP1A2, CYP2C9 ↑ CBD: CYP2B6, CYP2C19 ↑ THC: CYP2D6	CBD: Coadministration of immuno- or myelosuppressive agents may potentiate the risk of infections.
TZLS-501	A novel human monoclonal antibody against IL-6R	May mitigate CSS. Clinical trial planned.	Unknown	CBD: Coadministration of immuno- or myelosuppressive agents may potentiate the risk of infections.

$3CL^{pro}$, 3-chymotrypsin-like cysteine protease; ALT, alanine aminotransferase; BCRP, breast cancer resistance protein; CAR, chimeric antigen receptor; CBD, cannabidiol; COVID-19, coronavirus disease 2019; CSS, cytokine storm syndrome; CYP450, cytochrome P450; FDA, Food and Drug Administration; HIV-1, human immunodeficiency virus-1; IL-1, interleukin-1; IL-6, interleukin-6; JAK, Janus kinase; MERS-CoV, Middle East respiratory syndrome coronavirus; P-gp, P-glycoprotein; PL^{pro}, papain-like protease; RA, rheumatoid arthritis; RCT, randomized controlled trial; RdRp, RNA-dependent RNA polymerase; SARS, severe acute respiratory syndrome; SARS-CoV-1, SARS coronavirus 1; SARS-CoV-2, SARS coronavirus 2; THC, delta-9-tetrahydrocannabinol; TNF, tumor necrosis factor; ↑, potential for bidirectional increase in investigational agent and cannabinoid, ↓ potential for bidirectional decrease in investigational agent and cannabinoid.

were identified in many pharmaceutical candidates for COVID-19 and are known side effects of THC and/or CBD.[2,3]

Discussion

The majority of candidate drugs under examination for COVID-19 treatment could have DDIs with THC and/or CBD. Although, to our knowledge, there are no case reports on such DDIs, physicians treating patients with COVID-19 and/or those patients enrolled in clinical trials of candidate drugs should assess for cannabis/cannabinoid use and monitor physiological responses to COVID-19 that could be influenced by cannabis/cannabinoid use (e.g., potentiation of side effects, changes in exposure of candidate drugs, and/or levels of cytokines[5,6]). Although concomitant binding of THC/CBD and candidate drugs for COVID-19 to plasma proteins, transporters, or metabolism do not necessarily produce a clinical effect, the importance of cannabinoid screening is highlighted by the common use of cannabis/cannabinoids for conditions that may function as risk factors for COVID-19 complications or mortality (e.g., human immunodeficiency virus and autoimmune disorders such as multiple sclerosis). The importance of closely monitoring physiological responses to COVID-19 (e.g., cytokines) is supported by research that has identified increased infection potential and immunosuppressive effects associated with CBD[2,7]; concomitant administration of immunosuppressants may further reduce levels of their intended cytokine target(s). Although more research is needed, these additive effects could result in primary and/or secondary infections. In addition, a recent *in vitro* study demonstrated that CBD can antagonize some dexamethasone effects, overriding the anti-inflammatory potential of steroids when used in combination.[8] Until *a priori* research determines whether (and to what extent) successful COVID-19 treatments interact with cannabis/cannabinoids, it seems prudent to assess current cannabis/cannabinoid use among suspected or confirmed COVID-19 patients and consider additional monitoring in the event that modified treatment approaches are needed to avoid unwanted DDIs.

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Abbreviations Used

3CL^{pro} = 3-chymotrypsin-like cysteine protease
ALT = alanine aminotransferase
BCRP = breast cancer resistance protein
CAR = chimeric antigen receptor
CBD = cannabidiol
COVID-19 = coronavirus disease 2019
CSS = cytokine storm syndrome
CYP450 = cytochrome P450
DDI = drug–drug interaction
FDA = Food and Drug Administration
HIV-1 = human immunodeficiency virus-1
IL-1 = interleukin-1
IL-6 = interleukin-6
JAK = Janus kinase
MERS-CoV = Middle East respiratory syndrome coronavirus
PD = pharmacodynamic
P-gp = P-glycoprotein
PK = pharmacokinetic
PL^{pro} = papain-like protease
RA = rheumatoid arthritis
RCT = randomized controlled trial
RdRp = RNA-dependent RNA polymerase
SARS = severe acute respiratory syndrome
SARS-CoV-1 = SARS coronavirus 1
SARS-CoV-2 = SARS coronavirus 2
THC = delta-9-tetrahydrocannabinol
TNF = tumor necrosis factor
↑ = potential for bidirectional increase in investigational agent and cannabinoid
↓ = potential for bidirectional decrease in investigational agent and cannabinoid