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Cannabis Addiction and COVID-19 Protocols: Are Safety and Efficacy Issues Questionable?

Mohamed Raslan[1], Eslam M. S.[2], Sara A. R.[3], Nagwa A. Sabri[4*]

[1]Member of Clinical Research and Bio Analysis Department, Drug Research Centre, Cairo, Egypt, ORCID ID: https://orcid.org/0000-0003-1039-9230
[2]Drug Research Centre, Cairo, Egypt
[3]Clinical Researcher, Drug Research Centre, Cairo, Egypt
[4]Ph.D., Professor of Clinical Pharmacy Department, Ain Shams University, Cairo, Egypt,ORCID ID: https://orcid.org/0000-0002-2611-4853

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***Corresponding author:** Nagwa A. Sabri Ph.D.
Professor of Clinical Pharmacy Department, Ain Shams University, Cairo, Egypt

Abstract

***Background*:** COVID-19 is one of the emerged pandemics that threaten the globe. On the other hand, cannabis smoking is considered one of the risk factors for increased incidence of lung infection, and hence covid-19 infection. ***Aim*:** Investigation of potential interactions between covid-19 therapeutic agents and cannabis addiction associated with changes in both or either of therapeutic safety and efficacy. Besides, the effect of cannabis smoking addiction on covid-19 incidence and severity. ***Discussion*:** Different studies indicated the effect of cannabis components on the metabolic rate by induction or inhibition of several metabolic pathways. Different drugs used in covid-19 management are either substrates or inhibitors for those metabolic pathways. The final result could be a bidirectional interaction between tetrahydrocannabinol, cannabidiol and those drugs used in COVID-19 management. Side effects of elevated levels of both tetrahydrocannabinol, cannabidiol, or drug therapeutic agents may occur. Studies showed that cannabis smoking is acting as a risk factor for elevated incidence for pulmonary tract infection and so covid-19 infection. ***Conclusion*:** Caution should be taken in consideration, and addiction screening for COVID-19 patients should be performed before starting therapeutic regimen to avoid any possible undesirable effects during treatment and to predict patients response to therapeutic measures applied and disease severity.

Keywords: COVID-19, Tetrahydrocannabinol, Cannabidiol, Interactions, Sofosbuvir.

INTRODUCTION

Corona virus Disease (COVID-19) has appeared as a rapidly spreading infective disease all over the globe. It is caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) occurring mainly via large respiratory droplets, regardless of the fact that the probability of other transmission routes cannot be ruled out, as the virus has been found in feces and urine of affected individuals [1].

Smoking cannabis is definitely damaging to the lung tissues. Evidence found that smoking cannabis produces chronic bronchitis and harm the cell linings of respiratory tract, besides, destroying the cells that help eliminate dust and pathogens. This could justify why smoking cannabis gives rise to symptoms like phlegm production, chronic cough, wheeze and acute bronchitis. Additionally, it may lead to a higher risk of respiratory infections among people who smoke of cannabis. This can be evidenced by including much more respiratory healthcare visits of frequent cannabis smokers than non-smokers [2-4].

Conversely, recent researches have shown that, cannabis smoking is related to increase in respiratory forced vital capacity (FVC). Also, studies showed absence of chronic airflow obstruction with cannabis smokers. This may be attributed to its acute anti-inflammatory, immune-modulatory and bronchodilator effect [5].

Cannabis smokers may be more prone to infection as well as deterioration of their clinical situation due to covid-19 disease. This can be described by the action of the psychoactive substance on the

nervous system and not on the immunity, as well as the way of use of this substance, and the smokers behaviour [6].

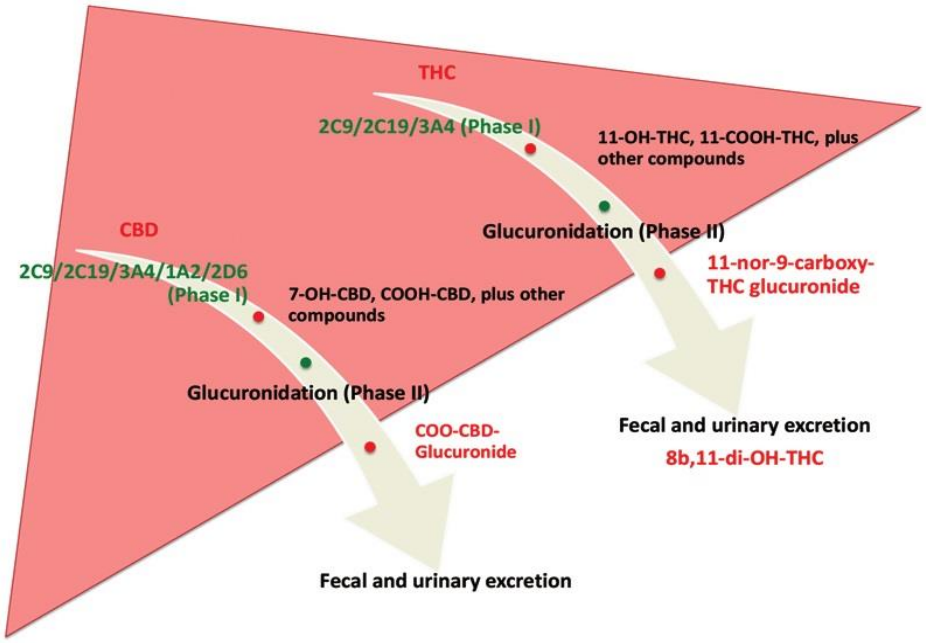

Figure 1: Schematic diagram representing Hepatic metabolic pathways phase I and phase II of Tetrahydrocannabinol (THC) and Cannabidiol (CBD) and their metabolic fate [7]

Figure (1) shows a diagram representing phase I and phase II metabolic pathway of THC and CBD via CYPs to different intermediates that undergoes glucuronide conjugation producing the in active glucuronide during phase II metabolic process. THC and CBD conjugates are excreted via fecal or urinary excretion route.

Hydrolytic pathway biotransformation is the main metabolic route of endocannabinoid. Phytocannabinoids are extensively metabolized by CYP450 enzymes. Enzymes CYP2C9, 2C19, and 3A4 accelerate most phytocannabinoid hydroxylation. Besides, CYP450 enzymes represents a major metabolic pathway for both synthetic cannabinoids used for therapeutic purposes and in-vitro experiments showed that cannabidiol is the most powerful inhibitor of CYP450 metabolic enzymes [8].

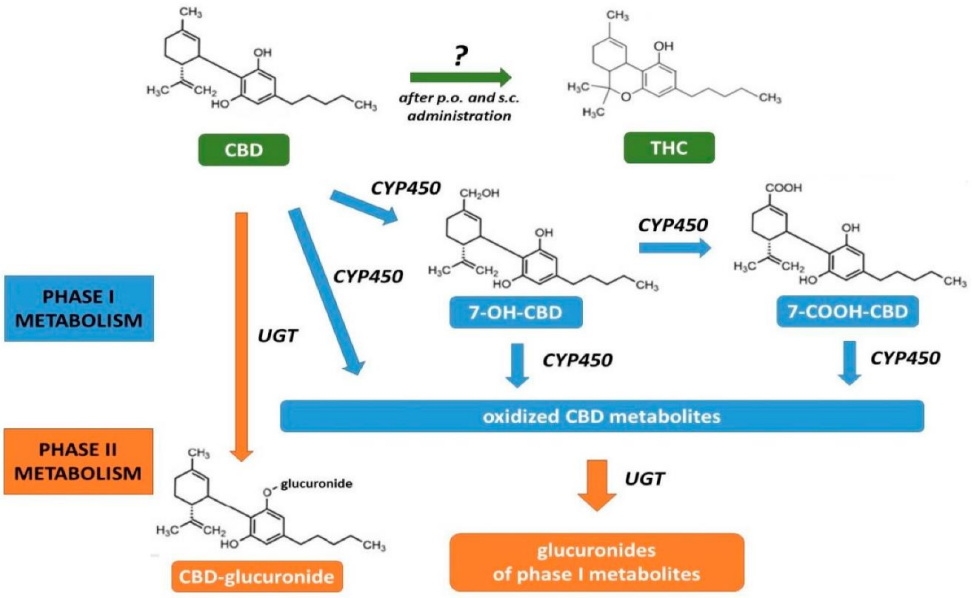

Figure 2: Schematic diagram representing different Hepatic metabolic pathways Phase I and Phase II of Cannabidiol (CBD) supported with their chemical structures [9]

Figure (2) shows a schematic diagram presenting phase I and phase II metabolic pathway of CBD to different active and inactive forms. The metabolic pathway via CYPs includes many intermediates that undergoes glucuronide conjugation producing the in active glucuronides of phase I metabolites. Furthermore, CBD is directly undergoes glucuronide conjugation via UGT producing CBD-glucuronide in active metabolite.

A study investigated the inhibition effects of tetrahydrocannabinol, cannabidiol and cannabinol on cytochrome P450 / 3A enzymes activity, where, cannabidiol showed to be the most potent CYP3A4 and CYP3A5 inhibitor (IC_{50}=11.7 and 1.65 µM, respectively). Tetrahydrocannabinol, cannabidiol, and cannabinol inhibited activity to a comparable extent in CYP3A7 (IC_{50}=23-31 µM) [10].

It was indicated that cannabinoids present in marijuana have been shown to significantly affect (inhibit or induce) the activity of several CYP450 isoenzymes. *In-vitro, in-vivo, and clinical findings suggest potential interactions of marijuana components with CYP3A, 1A, 2C9, 2A6, and 2B6* [11]. Additionally, investigations showed that plant-derived cannabinoids contribute in decreasing P-glycoprotein (P-gp) expression [12].

In general, increased risk for diarrhea, headache, somnolence, dizziness, infection, and liver injury were identified to occur in many pharmaceutical products which are candidates for management of COVID-19 and are well-known side effects of tetrahydrocannabinol and cannabidiol [13, 14].

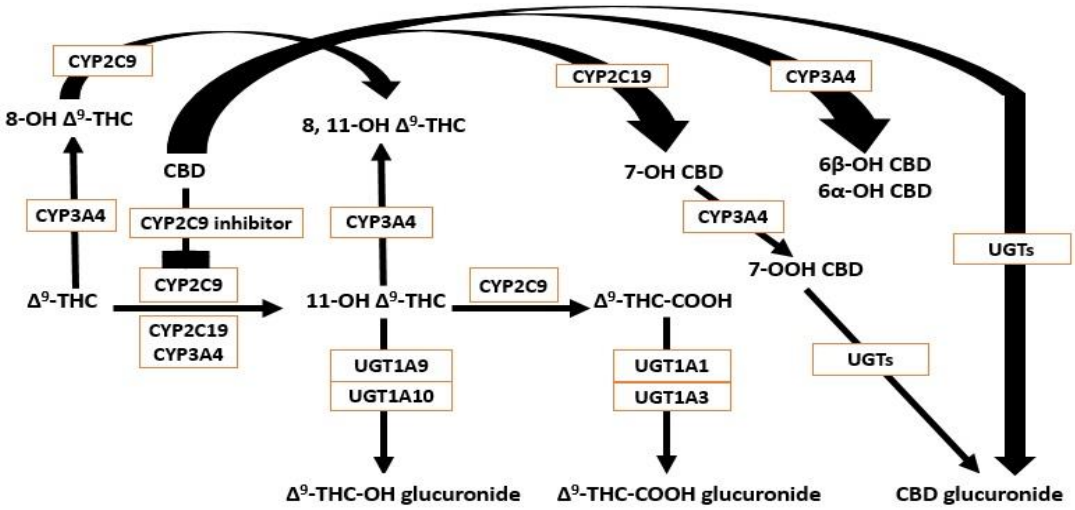

Figure 3: Schematic diagram representing different Hepatic metabolic pathways of Tetrahydrocannabinol (Δ^9-THC) and Cannabidiol (CBD) ([15] with modifications)

The metabolic process of Δ^9-THC and CBD through CYPs and glucuronide conjugation to different active and inactive forms is clear in figure (3), where, the metabolic pathway via different CYPs includes many active intermediates like 11-OH Δ^9-THC, 7-OH CBD, and 7-OOH CBD. The final metabolic fate as shown is through different glucuronide conjugation UGTs producing in actives like Δ^9-THC-OH glucuronide and CBD glucuronide.

DISCUSSION

The different potential interactions, which might affect both efficacy and safety of administered drugs, between the medications included in the management protocol of COVID-19 and cannabis will be discussed hereunder:

Lopinavir/Ritonavir

Lopinavir/ritonavir is approved for the treatment of HIV-1 infection in children, adolescents, and adults when used jointly with other antiretroviral drugs. Lopinavir/ritonavir is linked with typically tolerable gastrointestinal side effects, as well as hypercholesterolaemia and hypertriglyceridaemia, that may necessitate the addition of lipid-lowering medications to minimize coronary heart disease risks [16].

A combination of lopinavir and ritonavir was showed good therapeutic efficacy against SARS-CoV. Lopinavir and ritonavir could bind effectively to (SARS-CoV $3CL^{pro}$) SARS-CoV 3C-like protease. According to conducted studies, both anti-HIV medicines reacted effectively with SARS-CoV-2 $3CL^{pro}$ active sites [17].

When compared to lopinavir, ritonavir had a slightly larger number of atomic contacts, a little better binding efficiency, and a slightly higher number of crucial binding residues, which corresponded to a somewhat reduced water accessibility at the $3CL^{pro}$ active site. Furthermore, only ritonavir could establish

two hydrogen bonds with the N142 and G143 oxyanion hole residues. Dispersion, electrostatics, and charge transfer interactions all played key roles in drug binding. The findings showed how repurposed anti-HIV medicines may be utilized to confront COVID-19 [17].

It was reported that cannabis use is associated with increased antiretroviral treatment (ART) related side effects indicating possible occurrence of CYP450 inhibitory effects [18].

Another study reported that high plasma levels of tetrahydrocannabinol were associated *with decreased plasma concentrations of protease inhibitors therapy [19]. This decreased plasma bioavailability* is found to be in agreement with CYP450 inducing effect that were reported in cannabinoid treated mouse [20].

Tetrahydrocannabinol (THC) is metabolized by CYP3A4 and 2C9 enzymes to active metabolites [21], *a study showed that antiretroviral drugs don't have an effect on THC pharmacokinetics* [22].

Azithromycin

Azithromycin is an antibiotic belonging to azalide group, which is a kind of macrolide antibiotic. It is produced from erythromycin by incorporating into the lactone ring a methyl-substituted nitrogen atom, creating 15-membered lactone ring. It inhibits bacterial growth by interfering with protein synthesis [23].

It binds to the 50S component of the bacterial ribosome, preventing mRNA translation. Azithromycin is used to treat bacterial infections, most commonly those that cause middle ear infections, pneumonia, typhoid, bronchitis, strep throat, and sinusitis. It has largely been utilized in recent years to prevent bacterial infections in newborns and individuals with weakened immune systems. It's also effective against sexually transmitted diseases including nongonococcal urethritis, chlamydia, and cervicitis [23].

In an in-vitro and clinical context, azithromycin had a synergistic antiviral activity against SARS-CoV-2 when coupled with HCQ. Azithromycin alone has a substantial antiviral impact on SARS-CoV-2. The mechanisms of AZM's antiviral action support broad-spectrum antiviral activity [24].

The antibiotic azithromycin appears to inhibit viral entrance into cells. Furthermore, it can boost the immune response to viruses through a variety of mechanisms. Azithromycin stimulates the synthesis of type I and III interferons (particularly interferon-β and interferon-λ), as well as, virus-recognition genes such as MDA5 and RIG-I. These systems are generally implicated in the innate response to infectious pathogens, including SARS-CoV-2 [24].

Azithromycin is well-known antibiotic that is used in conjunction with hydroxychloroquine in management of COVID-19 patients. *Azithromycin showed to have a potential antiviral activity [21] and excreted unchanged in the bile through both MRP2 (encoded by ABCC2 gene) and ABCB1 transporters* [25, 26].

Possible pharmacokinetic interactions can occur with tetrahydrocannabinol, cannabidiol and azithromycin due to downregulation of P-glycoprotein transporters [27] *leading to elevated levels of azithromycin and increased risk for diarrhea* [27].

Tocilizumab

Tocilizumab (TCZ) is a monoclonal antibody that act as interleukin-6 receptor antagonist which is primarily used in treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis (pJIA), and systemic juvenile idiopathic arthritis (sJIA) [28].

In the European Union, TCZ is now approved for use in treatment of adult patients with moderate to severely active rheumatoid arthritis (RA), children over the age of 2 with polyarticular juvenile idiopathic arthritis, or children over the age of 2 with systemic juvenile idiopathic arthritis. Also it has been investigated as a therapy for systemic lupus erythematosus, Crohn's disease, Takayasu arteritis (TA), giant cell arteritis (GCA), polymyalgia rheumatica (PMR), and refractory adult-onset arthritis but no licenses in these indications have been approved [28].

Interleukin-6 (IL-6) is generated in response to tissue damage and many types of infections, and it aids host defence by activating immune responses and stimulating acute phase reactions. Tocilizumab has been developed because IL-6 is important in the pathophysiology of several inflammatory disorders, including infectious inflammations linked with tissue fibrosis [29].

The cytokine environment promotes the generation of inflammatory cytokines such as IL-6 by inflammatory monocytes. According to the findings, substantial numbers of inflammatory cells infiltrate the lungs of COVID-19 patients. This mechanism may be responsible for immunological damage, resulting in lung functioning injuries and rapid death [29].

Tocilizumab acts against interlukin-6 receptor (anti-IL-6) that may contribute to the mitigation of cytokine storm syndrome [27].

Tetrahydrocannabinol (THC) and cannabidiol (CBD) cause inhibition of CYP3A4, CYP1A2, and CYP2C9. Also, CBD can lead to CYP2B6 and CYP2C19 inhibition and THC inhibits CYP2D6, thus,

co-administration of tocilizumab with CBD may potentiate the risk of infections [27].

Sofosbuvir

Sofosbuvir, with its significant suppression of hepatitis C virus multiplication, good safety profile, and fewer medication interactions, has ushered in a new age of hepatitis C treatment. International guidelines now recommend sofosbuvir-based regimens as first-line treatments for people with chronic hepatitis C (CHC). Sofosbuvir with ribavirin and ledipasvir/sofosbuvir are very effective and safe in CHC patients aged 3-17 years old, indicating that they can fulfil the unmet medical requirements of adolescents and children with CHC in China [30].

SARS, MERS, and SARS-CoV-2 coronaviruses, like HCV and the flaviviridae, are positive-sense single-strand RNA viruses with a replication mechanism that requires an RNA-dependent RNA polymerase (RdRp). Sofosbuvir may be able to firmly bind to SARS-CoV-2 RdRp. In a recent in silico (preliminary) investigation, sequence analysis and homology modelling were utilized to construct a novel SARS-nCoV RdRp model, which was subsequently targeted by anti-polymerase medicines such as the authorized medications Sofosbuvir and Ribavirin. The docking scores showed that sofosbuvir, ribavirin and remdisivir might be effective antiviral medicines against the novel coronavirus [31].

Sofosbuvir is RNA-dependent RNA polymerase (RdRp) inhibitor used in treatment of hepatitis C [32] and may inhibit SARS-CoV-2 RdRp [33].

Sofosbuvir is a drug transporter substrate of P glycoprotein and breast cancer resistance protein [34]. *Possible pharmacokinetic interactions can occur resulting in possible bidirectional elevation of tetrahydrocannabinol, cannabidiol or sofosbuvir levels. In addition, cannabidiol could increase diarrhea, fatigue, and headache* [27].

Chloroquine/ hydroxychloroquine

Chloroquine (CQ) is used as a prophylaxis and cure from malaria and amebiasis. On the other hand, hydroxychloroquine (HCQ) is a less toxic metabolite of chloroquine, and it is used in treatment of juvenile idiopathic arthritis, systemic lupus erythematosus, rheumatoid arthritis, and Sjogren's syndrome. Moreover, chloroquine has a long history of usage in the treatment of Plasmodium vivax, ovale, malariae, and falciparum malaria in areas where P. falciparum has not evolved resistance to it (mainly in North Africa). It is also useful in the treatment of amebiasis, particularly extra-intestinal amebiasis. Patient can start 500 mg CQ phosphate once a week from 2 weeks before to 8 weeks after travel to an endemic location for malaria prevention in adults [35].

As previously stated, HCQ relieves rheumatic diseases. It is also useful in the treatment and prevention of malaria. Adults should begin 400 mg HCQ once a week 2 weeks before and 8 weeks after travelling to an endemic location for malaria prevention [35].

The mechanism of action in the potential antiviral role against SARS-CoV-2 includes interference in the endocytic pathway, sialic acid receptor blockade, restriction of pH-mediated spike (S) protein cleavage at the ACE2 binding site, and prevention of cytokine storm [36].

Are antimalarial agents with anti-inflammatory, immunomodulatory, and antiviral activities, acting by inhibition of viral entry and host immunomodulatory effects [37]. THC, CBD are inhibitors of CYP3A4, CYP2D6, and CYP2C8 *causing an elevated levels of chloroquine and hydroxychloroquine.* Moreover, *cannabidiol could increase risk of diarrhea and headache* [30].

Dexamethasone

Dexamethasone has a wide range of medical applications. Dexamethasone showed to be effective in the treatment of acute exacerbations of multiple sclerosis, allergies, cerebral edoema, inflammation, and shock. Dexamethasone has helped patients with diseases such as asthma, atopic and contact dermatitis, and medication hypersensitivity responses. Dexamethasone has been proven to be effective as a test for Cushing syndrome in endocrinology [38].

Dexamethasone is a strong glucocorticoid with little to no mineralocorticoid action. The body responds to dexamethasone in a number of ways. It acts by inhibiting neutrophil migration and reducing lymphocyte colony growth. The capillary membrane also gets less porous. Lysosomal membranes have become more stable [38].

Dexamethasone's major anti-inflammatory action is to suppress a pro-inflammatory gene in COVID-19 that encodes for cytokines, chemokines, cell adhesion molecules (CAM), and the acute inflammatory response [39].

Dexamethasone corticosteroid used to treat aggravations of multiple sclerosis allergies cerebral edema inflammation shock and other conditions. *Patients with conditions such as asthma, atopic and contact dermatitis, and drug hypersensitivity reactions have got benefit from the use of dexamethasone* [40]. Dexamethasone (DEX) is extensively metabolized to 6-hydroxyDEX by CYP3A4 enzyme [41]. *Tetrahydrocannabinol; cannabidiol are strong inhibitors for CYP450 enzymes and could elevate dexamethasone blood levels.*

Cannabidiol could increase risk of headache. Co-administration of dexamethasone may potentiate the risk of infections. *It was found that cannabidiol demonstrated antagonism in some anti-inflammatory in-vivo models with dexamethasone* [27].

Darunavir/Cobicistat

Guidelines indicate that darunavir (an HIV protease inhibitor) can be co-administered with low-dose ritonavir (800/100 mg once day) in conjunction with other antiretrovirals for HIV patients who do not have darunavir resistance-associated mutations. Cobicistat is an antiretroviral medication that works similarly to ritonavir in increasing plasma drug levels of darunavir and other antiretrovirals. Cobicistat showed much higher selectivity toward cytochrome P450 3A than ritonavir that does not induce enzyme activity [42].

Darunavir and lopinavir are both HIV-1 protease inhibitors that work in a similar way to prevent HIV replication. Darunavir would act as potent inhibitor of the main protease (M^{pro}) against COVID-19 [43].

Cobicistat is a CYP3A4 enzyme inhibitor with no inhibitory activity on HIV [41] and tetrahydrocannabinol is metabolized primarily by CYP2C9 and CYP3A4, thus, *administration of Darunavir / Cobicistat could potentially increase tetrahydrocannabinol levels and increase its side effects* [45].

Table (1) represent a summary for the seven previously mentioned therapeutic agents in the review (Lopinavir/Ritonavir, Azithromycin, Tocilizumab, Sofosbuvir, Chloroquine/ hydroxychloroquine, Dexamethasone, Darunavir/Cobicistat). In this summary we highlighted the original therapeutic use of the drug, why this drug is a candidate for use in covid-19 therapeutic protocols, and what are the potential interactions of THC and CBD with those therapeutic agents.

Table 1: Therapeutic use, Pharmacological Effect and Potential Interaction with Tetrahydrocannabinol, and cannabidiol of the therapeutic agents used for Management of COVID-19

Drug(s)	Original therapeutic use	Pharmacological effect making it candidate for use in covid-19 protocols	Potential interaction with THC and CBD
Lopinavir/ Ritonavir	An antiretroviral for HIV treatment	Could bind effectively to (SARS-CoV $3CL^{pro}$) SARS-CoV 3C-like protease	Cannabis use is associated with increased antiretroviral treatment related side effects indicating possible occurrence of CYP450 inhibitory effects
Azithromycin	Treatment of bacterial infections, most commonly those that cause middle ear infections, pneumonia, typhoid, bronchitis, strep throat, and sinusitis	Synergistic antiviral activity against SARS-CoV-2 when coupled with HCQ Stimulates the synthesis of type I and III interferons (particularly interferon-β and interferon-λ), as well as virus-recognition genes such as MDA5 and RIG-I	Downregulation of (P-glycoprotein) transporters leading to elevated levels of azithromycin and increased risk for diarrhea
Tocilizumab	Treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis	Acts against interlukin-6 receptor (anti-IL-6) that may contribute to the mitigation of cytokine storm syndrome	Co-administration of tocilizumab with CBD may potentiate the risk of infections
Sofosbuvir	First-line treatment for people with chronic hepatitis C	Sofosbuvir is RNA-dependent RNA polymerase (RdRp) inhibitor may be able to firmly bind to SARS-CoV-2 RdRp	Possible bidirectional elevation of THC, CBD, or sofosbuvir levels. In addition, CBD could increase diarrhea, fatigue, and headache
Chloroquine/ hydroxychloroquine	Used as anti-malaria and anti-amebiasis. Also used in treatment of juvenile idiopathic arthritis, systemic lupus erythematosus, rheumatoid arthritis, and Sjogren's syndrome	Potential antiviral role against SARS-CoV-2 includes interference in the endocytic pathway, sialic acid receptor blockade, restriction of pH-mediated spike (S) protein cleavage at the ACE2 binding site, and prevention of cytokine storm	THC, CBD cause an elevated levels of chloroquine and hydroxychloroquine. Moreover, cannabidiol could increase risk of diarrhea and headache
Dexamethasone	Treatment of acute exacerbations of multiple sclerosis, allergies, cerebral edoema, inflammation, and shock	Suppress a pro-inflammatory gene in covid-19 that encodes for cytokines, chemokines, cell adhesion molecules, and the acute inflammatory response.	THC; CBD could elevate dexamethasone blood levels It was found that CBD demonstrated antagonism in some anti-inflammatory in-vivo models with dexamethasone
Darunavir/ Cobicistat	An antiretroviral for HIV treatment	Act as potent inhibitor of the main protease (M^{pro})	Administration of Darunavir / Cobicistat could potentially increase THC levels and increase its side effects.

Association of Cannabis Addiction and Incidence and severity of COVID-19

During the COVID-19 disease outbreak, psychoactive substances use, such as tobacco, cannabis and cocaine, showed to increase the risk of influenza contamination and was associated with a poorer clinical prognosis, due to deteriorating health condition [46].

A study showed that patients with recent use of psychoactive substances *were at significantly higher risk (approximately five times) of developing COVID-19* compared to patients without a recent substance use disorder [47].

Studies indicated that deleterious cardiac and respiratory consequences of cannabis smoking and tobacco smoking have certain similarities. Although there is a difference in active ingredients between marijuana and tobacco, and the different smoking modes, cannabis compounds are kept in the body for longer periods of time. Marijuana also may contain other harmful substances such as tar which has been related to the progression of pulmonary emphysema, lung cancer, and bronchitis. All this may contribute to higher incidence and severity of covid-19 [48, 49].

Some studies have found a slight decrease in specific airway conductance in relation to cannabis, possibly reflecting endoscopic evidence of bronchial mucosa edema among regular marijuana smokers. Tetrahydrocannabinol's immunosuppressive effects increase the potential for higher risk of pneumonia. Several clinical study have shown pneumothorax and bullous pulmonary illness in people who smoke cannabis [50, 51].

Previous studies showed that high mortality rates, heart disease, metabolic syndromes and changes in the immune system are associated with long-term cannabis use. Besides, using cannabis can cause or increase psychological disorders (mainly psychotic symptoms). Aggressive emotional and behavioral responses, such as worry, depressed mood, loneliness, anxiety, insomnia, anger and aggressive behavior were reported during the disease outbreak [52-54].

CONCLUSION

It is highly recommended to undergo screening of COVID-19 patients for cannabis addiction which might have a potential interactions with drugs included in treatment of COVID-19. This might lead to exaggeration or reduction of drugs effect and /or incidence of side and adverse events. From the review it can be concluded that most of the drugs used in management of COVID-19 showed possible interactions with THC, and CBD and especial attention should be given to those drugs which modulate immune system in order to avoid possible risks of infection. Special care should be taken to those cannabis smokers individuals as they are more vulnerable to respiratory tract infections and incidence of COVID-19.

RECOMMENDATION

It is recommended that practical researches for accurate investigation of these theoretically approved interactions, some of which might be serious, should be performed and detection of their clinical presentation effect on COVID-19 patients.

Conflict of Interest Statement: No conflict of interest declared.

Author Contribution Statement

N.A.S contributed to the conception and design of the work. **M.A.R** contributed to the analysis and interpretation of the data. **E.M.S** wrote the manuscript. **N.A.S, and S.A.R** contributed to the drafting and revision of the manuscript.
All authors have read and approved the final manuscript.

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