Let's Look at Cannabis from This Angle: COVID-19

Kenevire Bir de Bu Açıdan Bakalım: COVID-19

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ABSTRACT

Cannabis sativa (Cannabis=hemp) contains cannabinoid-derived main components. Cannabinoids exert biological effects by stimulating cannabinoid receptors distributed throughout the body. Cannabis products affect various systems in the body such as the cardiovascular, respiratory, nervous and immune systems. They show analgesic, antiemetic, anxiolytic, antidepressant, anti-inflammatory, antimicrobial, antihypertensive, antitussive and cardioprotective effects.

COVID-19 affects different organ systems in the body and causes symptoms depending on the mutation, such as dry cough, shortness of breath, nausea, vomiting, loss of appetite and sense of smell. In this article, effectiveness of *C. sativa* and its components on COVID-19 have been evaluated, based on the fact that components or the extracts can affect the whole body due to cannabinoid receptors. Although cannabis and its components have potential beneficial effects for the entry of COVID-19 through the receptors into the body and the symptoms, further studies are needed for their safe use. Appropriate formulation and administration routes should be determined to eliminate the side effects and risk of addiction.

Keywords: *Cannabis sativa*, cannabis, hemp, COVID-19, tetrahydrocannabinol, cannabinoid

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ÖZET

Cannabis sativa (kenevir), kannobinoid türevi ana bileşenler içerir. Kannabinoidler, tüm vücuda dağılmış olan kannabinoid reseptörlerini uyararak biyolojik etkiler gösterir. Kenevir, vücutta kardiyovasküler sistem, bağışıklık sistemi, sinir sistemi ve solunum sistemi gibi birçok sistemi etkiler. Analjezik, antiemetik anksiyolitik, antidepresan, anti-inflamatuvar, antimikrobiyal, antihipertansif, antitüssif ve kardiyoprotektif etkiler gösterir.

COVID-19, vücutta birçok sistemi etkiler ve iştahsızlık, kuru öksürük, nefes darlığı, mide bulantısı ve kusma gibi semptomlara neden olur. Bu makalede, *C. sativa* ve bileşenlerinin de kannabinoid reseptörleri dolayısıyla tüm vücudu etkileyebildiği gerçeğinden yola çıkarak, COVID-19 üzerindeki etkinliği değerlendirilmiştir. Bu amaçla, kenevir ve bileşenlerinin COVID-19'un reseptörler aracılığıyla vücuda girişi ve yol açtığı semptomlar açısından öneme sahip olan reseptörler üzerindeki etkilerinin yanı sıra COVID-19'un neden olduğu semptomlar ve sistemler üzerindeki etkileri incelenmiştir.

Kenevir ve bileşenlerinin, COVID-19 için potansiyel faydalı etkileri olsa da, güvenli kullanımı için ileri çalışmalara ihtiyaç vardır. Yan etkileri ve bağımlılık riskini ortadan kaldırmak için uygun formülasyon ve uygulama yolları belirlenmelidir.

Anahtar Sözcükler: *Cannabis sativa*, kenevir, kendir, COVID-19, tetrahidrokanabinol, kanabinoid

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INTRODUCTION

Cannabis sativa L. belongs to the Cannabaceae family and is known as 'cannabis' or 'hemp'. It possesses more than 500 chemical compounds, about 100 of which are cannabinoids (1). Four major cannabinoid compounds are cannabinol (CBN), cannabidiol (CBD), delta-9-tetrahydrocannabinol (d-9-THC) and delta-8-tetrahydrocannabinol (d-8-THC) (2). Cannabinoids exert their biological effects by stimulating cannabinoid receptors (CB). Since CB1 is the most expressed in the central nervous system, it is associated with psychoactive effects. On the other hand, CB2 receptors are highly expressed in many organs and tissues in the body, as well as in immune cells (3). The d-9-THC is the main psychoactive component, and increases the release of acetylcholine, dopamine and glutamate in the brain by binding to the CB1 receptor. Although d-9-THC, d-8-THC and CBN show different levels of psychoactive properties, CBD does not have psychoactive features (2).

Marijuana is obtained from the dried leaf stems, flowers and seeds of *C. sativa* and is also known as ganja, pot and weed. Marijuana is one of the most widely used recreational drugs but is not legal in all parts of the world (4). It has mostly recreational usage because it creates behavioral effects such as feeling of euphoria, changing time perception and relaxation. Moreover, it is also used for medicinal purposes. *C. sativa* products have effects on the cardiovascular, immune, nervous and respiratory systems: likewise it is used in the treatment of cancer, epilepsy, multiple sclerosis, parkinson, Tourette Syndrome and inflammatory bowel diseases, as well as in the control of appetite, pain, nausea and vomiting (5). The anti-inflammatory properties of cannabinoids, especially CBD, have been determined and their antiviral effects are being investigated. The effect has been shown against viral hepatitis C, HIV, influenza, herpes viruses (6-8).

Scientific studies show that SARS-CoV-2 enters the body through the mouth and nostrils. Unless the immune system blocks it, the virus travels down the windpipe, infecting the lung. It enters pneumocytes in alveoli for replication (9). COVID-19 affects not only the lungs but also diverse systems and organs in the body causing symptoms such as anorexia, diarrhea, dry cough, dyspnea, fatigue, fever, headache, muscle pain, myalgia, nausea, shortness of breath and vomiting (10). In severe cases, acute respiratory distress syndrome, arrhythmia, shock and even death can ocur (11).

In addition to the current vaccine regimens, the search for effective and reliable drugs continues in order to protect against COVID-19 and to treat infected people. The main goals for COVID-19 are to prevent the virus from entering the body and replication, to eliminate the symptoms it causes, and even to eliminate post-COVID-19 discomforts. We hypothesized that *C. sativa* and its components can be used against COVID-19, based on the fact that COVID-19 affects many systems and the CB receptors to which the *C. sativa* components act by binding show a widespread in the body. Moreover, we evaluated *C. sativa* not only in terms of eliminating the symptoms of COVID-19, but also in terms of protection from the virus and it's deactivation. In this context, firstly, the effects of cannabis and its components on receptors, which are important in terms of the entry of COVID-19 into the body and the symptoms it causes, are discussed. The positive effects of cannabis on the symptoms and systems caused by COVID-19 have been examined under separate headings. *In vitro*, *in vivo* and clinical studies with cannabis and its components are presented as a separate table.

Target Receptors for COVID-19 and C. sativa

Angiotensin converting enzyme 2 (ACE2) receptor is determined as the main route for COVID-19 to enter the human body (12,13). ACE2 is mostly found in the lung and intestine, but also in the nasal mucosa, kidney, testicles and gastrointestinal system (14). Due to high ACE2 levels in the lungs, intestines and oral mucosa, these areas are critical for the entry of COVID-19 into the body and its symptoms. ACE2 expression is higher in men, mostly in smokers, and increases with age. These individuals also constitute a higher risk group (15).

Another target for COVID-19 is TMPRSS2 (Transmembrane protease serine 2). Located adjacent to the ACE2 receptor, this receptor is also attacked by the spike proteins of SARS-CoV2 and is important for the entry of the virus into the host. Overexpression of TMPRSS2 has also been associated with post-COVID-19 neurodegenerative disorders (9). Based on these factors, down-regulation of ACE2 and TMPRSS2 levels has been considered as a strategy for COVID-19. Wang et al. examined the effects of 23 *C. sativa* extracts containing different amounts of cannabinoids and terpenes on ACE2 expression using artificial 3D human tissue models of airway, oral and intestinal tissues. *C. sativa* extracts decreased TMPRSS2 and ACE2 levels, but not all extracts were equally effective. Even, some extracts upregulated the levels of the ACE2 gene and protein, that is, had undesired effects. Moreover, the extracts showed different responses in different tissue. For example, an extract upregulated ACE2 expression in EpiOral tissues, while downregulation occurred in the EpiIntestinal and EpiAirway tissues (16). Sarkar et al. conducted an *in silico* study of molecules obtained from *C. sativa*. They worked with 4 proteins that are crucial for both COVID-19's entry into the host cell and post-COVID-19 neurodegenerative symptoms: ACE2, TMPRSS2, NRP1 protein and Interleukin-6 (IL6). The study showed that cannabidiol and cannabivarin from *Cannabis* bind to and regulate these proteins. They recommend *Cannabis* as a treatment option for post-COVID-19 symptoms (17).

IL-6 plays an important role in the pathogenesis of inflammatory disorders and its overexpression in neurons has been reported in COVID-19 (18). Raj et al. investigated the binding of cannobinoids to another target, the SARS-CoV-2 Mpro enzyme, *in silico* and *in vitro*. d-9-THC cannabidiol actively bound to SARS-CoV-2 Mpro and showed a strong antiviral effect from lopinavir, chloroquine, and remdesivir (19).

Inflammation, Cytokines Storm and C. sativa

High plasma proinflammatory cytokine and chemokine levels (e.g. TNF-α, interleukins, IFN-γ) have been detected in COVID-19 patients. Also, cytokine and chemokine levels were found to be higher in patients, who needed to be hospitalized in the intensive care unit compared to those who did not. Cytokine "storm" that occurs as a result of increased hyperinduction of proinflammatory cytokines is involved in the pathogenesis of COVID-19. IL-6 and TNF-α play important role in the formation of cytokine storm. Inhibition of cytokines, specifically TNF-α, IL-6, can eliminate inflammation and cytokine "storm", thus, affecting the outcome of the disease in a positive direction. Beneficial effects of cannabinoids on inflammatory diseases have been demonstrated scientifically. When the CB2 receptors on mast cells are activated, they inhibit the release of pro-inflammatory factors hence demonstrate an anti-inflammatory effect (20). Kovalchuk et al. investigated the anti-inflammatory effects of 7 different *C. sativa* extracts using artificial human 3D skin. *C. sativa* extracts down-regulated cytokines such as COX2, IL-6, TNF-α and pathways related to inflammation and fibrosis. TNF-α and IL-6 inhibition was evident, and this was crucial for COVID-19 targets. Anti-inflammatory activity was observed in 3 extracts at most, while one extract was ineffective. That ineffective extract produced a potentially harmful effect, and this demonstrated the importance of careful cultural selection (18). There are studies in the literature that *C. sativa* and its components modulate inflammation associated diseases and some of these studies are shown in Table 1.

Pain and C. sativa

Cannabis is frequently used as medicine to heal 'pain'. Li et al. investigated the effects of cannabis on instantaneous pain intensity levels in five pain categories using a dataset from the United States (headache related, gastrointestinal, nerve, musculoskeletal, non-specified pain). Whole medicinal female *Cannabis* flower reduced pain more than any other type of product. The average pain reduction was -3.10 points on a 0-10 visual analogue scale ($p < .001$). THC levels demonstrated analgesic effect in all five pain categories. Negative correlation found between CBD levels and relief from gastrointestinal and unspecified pain (21).

C. sativa has been suggested to be ineffective in the treatment of acute pain (22). However, the effects of *C. sativa* and its components on many types of chronic pain such as chronic cancer pain, neuropathic pain and inflammatory pain were investigated. As a result, the mechanism of *C. sativa* analgesia was reported by inhibition of neuromediator release from presynaptic nerve endings, modulation of postsynaptic stimulation, activation of inhibitory pain pathways and reduction of neural inflammation (23). Romero-Sandoval et al. investigated the analgesic effect of inhaled (smoked or vaporized) cannabis and oral cannabinoids. They found that inhaled cannabis was consistently effective for non-cancer chronic pain. On the other hand, they showed that oral cannabinoids ameliorate some aspects of chronic pain or cancer chronic pain and are not effective in abdominal chronic pain, acute postoperative pain or rheumatoid pain (24).

Neuropathic pain occurs as a result of damage to the nervous system. CB1 and CB2 receptors respond to nerve damage by upregulating nerve structures involved in pain generation. The CB2 receptor has been shown to have an important role in modulating glial activation in response to nerve damage (25). An *in vivo* neuropathic pain model study, cannabis extract containing cannabinoid and non-cannabinoid fractions revealed better antinociceptive effect than a single cannabinoid given alone. The study suggested that this effect was mediated through the vanilloid receptors TRPV1 independently of the cannabinoid receptors and that CBD was responsible for the effect (26).

Psychological Symptoms and C. sativa

COVID-19 has spread rapidly all over the world and caused deaths since it appeared at the end of 2019. Pandemic restrictions such as social isolation, quarantine, restriction of social activities and travel, loss of income may result in post-traumatic stress disorder (PTSD) in individuals (27). During the pandemic period, post-traumatic stress disorder (7%-53.8%), depression (14.6%-48.3%), anxiety (6.33%-50.9%), psychological distress (34.43%-38%), and general stress (8.1%-81.9%) were detected in China, Denmark, Iran, Italy, Nepal, Spain, the USA (United States of America) and in Turkey (28). A study conducted in healthcare workers in China found symptoms of anxiety (45%), depression (50%), distress (72%) and insomnia (34%) in individuals who participated to the questionaire (29).

Cannabis use is quite high in patients with post-traumatic stress disorder (PTSD) (30, 31). These individuals most often use cannabis to cope with insomnia as well as anxiety (32). Li et al. examined 1,819 people who completed five thousand eight hundred seventy six cannabis self-administration sessions using application, with the goal of measuring real-time effects of consuming hemp flower for treating symptoms of depression. After all, the vast majority of users reported a decrease in symptom intensity. The avarege symptom intensity reduction was -3.76 on a 0-10 visual analog scale. When cannabinoid levels were examined, the strong independent predictor of symptom relief was THC. CBD levels were generally unrelated to symptom intensity. Some of the users observed negative effects, namely increased depression. On the other hand, antidepressant effects (such as relaxed, feeling happy, optimistic) were observed in the vast majority of users (33). Cuttler et al. also found a 58% reduction in anxiety- stress and a 50% reduction in depression due to cannabis use. The largest changes in depression ratings were associated with higher CBD (>9.5%)/low THC (<5.5%) ratios. The largest changes perceived in stress were associated with high CBD (> 11%) / high THC (> 26.5%) ratios. On the other hand, long-term use has been found to aggravate core symptoms of depression (34).

Hoch et al. examined the efficacy and safety of cannabis-based drugs in patients with mental disorders such as anorexia nervosa, general social anxiety, dementia, cannabis and opioid addiction, psychosis/schizophrenia, post-traumatic stress disorder, attention deficit hyperactivity disorder, and Tourette's disorder in a systematic review. THC and CBD-based drugs given in addition to drug therapy and psychotherapy were effective on various symptoms of mental disorders. On the other hand, although not serious, it had side effects and did not provide remission (35). In untreated patients with social anxiety disorder, a single dose of CBD (600 mg) significantly reduced anxiety during a simulation public speaking (36). Childs et al. showed that healthy young adults' emotional responses to acute psychosocial stressors varied depending on the THC dosage. THC at 7.5 mg dose did not affect performance but reduced negative emotional responses, on the other hand at 12.5 mg of THC adverse effects and impaired performance slightly but significantly increased (37).

Positive Effects of C. sativa and Its Components on Systems

i. Cardiovascular system

CB receptors are located in different parts of the cardiovascular system: circulating blood cells, myocardium, smooth muscle cells, vascular endothelium. In addition, CB1 can affect cardiovascular functions as it is located in the peripheral nervous system, including vagal afferent neurons. Activation of CB1 receptors has been associated with hypotensive effects (38). In addition, cannabinoids produce vascular effects by modulating vasoactive compounds (such as angiotensin II) (39). The higher the THC content of *C. sativa*, the greater the likelihood of CB1-mediated cardiovascular effects (38). THC at low doses reduced atherosclerosis and vascular inflammation and showed cardioprotective effects (40,41). In addition, CBD has been found to have positive effects on autoimmune myocarditis, cardiomyopathy, myocardial infarction and stroke (42-46).

ii. Gastrointestinal system

Cannabis affects many gastrointestinal processes due to the presence of CB1 receptors on submucosal and myenteric nerve cells and CB2 receptors on immune cells in the digestive system. Cannabis modulates immunity and maintains gastrointestinal homeostasis by affecting these receptors. The effects of cannabis and its components on nausea-vomiting, hepatic damage, fatty liver, pancreatic diseases, intestinal diseases have been demonstrated. These effects have been associated with anti-inflammatory, anti-secretory and anti-nociceptive properties (47). The use of cannabis and its components for the treatment of chemotherapy-induced nausea and vomiting has often been investigated (48, 49). Cannabis is used for the treatment of symptoms of inflammatory bowel diseases such as Crohn's, enteritis, ulcerative colitis. Symptoms

reported to improve are abdominal pain, abdominal cramps, joint pain, diarrhoea, nausea, weight loss. These applications have been confirmed by surveys, but few studies have proven medical efficacy (50). Naftali et al. conducted a double-blind, randomized, placebo-controlled study on patients with ulcerative colitis. They gave patients THC-

rich cannabis cigarettes or placebo for 8 weeks. As a result of the study, a significant improvement in quality of life, appetite, general health, libido, concentration and patient satisfaction was observed in the treatment group. But these clinical effects were not directly linked to the anti-inflammatory effect of cannabis (51).

iii. Immune system

CB receptors, especially CB2, are involved in the immune system. CB2 receptors are most commonly expressed on B lymphocytes. It modulates immune responses such as immune cell migration and proliferation (52). Cannabinoids affect the immune system in the following ways: 1- inhibition of cytokines production, 2- suppression of proliferation, 3- apoptosis, 4- induction of T regs (T regulatory cells) (53). Cannabis and cannabinoid-based therapies have been shown to have immunomodulatory properties and their effects in some immune-related diseases (e.g. cancer, multiple skleroz, transplantation) (54). Along with these, cannabis, CB receptors and cannabinoid-based therapies have been shown to have positive effects on the immune response to the vaccine. Transient blockade of the CB2 receptor during vaccination in young and old mice increased intensity and breadth of antigen responses (55).

iv. Respiratory system

As we mentioned earlier, shortness of breath is a common symptom in COVID-19 patients. In a previous study, Pickering et al. examined the effect of cannabis on shortness of breath. Sublingual cannabis extract or placebo were given for 2 days to 5 normal and 4 chronic obstructive pulmonary disease (COPD) having individuals. Shortness of breath simulated. There were no differences in breathlessness visual analog scale and respiratory measures before and after administration of placebo or cannabis to normal and COPD subjects. COPD patients less chose 'air hunger', one of the descriptors of dyspnea, after cannabis administration (56).

COVID-19 can cause ARDS by affecting not only the upper respiratory tract but also the lower respiratory tract and alveoli, in advanced cases. ARDS is defined as a serious inflammatory lung condition. In particular, CBD, one of the components of *C. sativa*, has been shown to reduce inflammation, suppress cytokine storm and have potential effects for ARDS (57,58). In studies, a viral infection-induced ARDS model was created using intranasal polyribocyridylic acid [poly (I: C)]. Khodadadi et al. showed that CBD improves clinical symptoms of ARDS. They suggested that CBD could be protective for ARDS that occurs in COVID-19 by reducing cytokine storm, protecting pulmonary tissues and promoting inflammatory homeostasis (57). Salles et al. showed that CBD not only modifies ARDS symptoms but also increases the expression of apelin, a substrate for ACE2 (58). In another study, CBD-rich fraction from the *C. sativa* strain showed *in vitro* anti-inflammatory activity in COVID-19-associated inflammation in lung epithelial cells. It decreased IL-8 and IL-6 expression in alveolar epithelial cells and increased it in macrophages. This situation revealed the need for further studies (59). Beneficial effects of *C. sativa* and its components in respiratory system disorders due to their anti-inflammatory properties are given in Table 1.

Table 1: Positive effects of *C. sativa* and its components

Activity	Preparation	Administration/ dose	Study Design	Results	Reference
Antinausea Antivomiting	Plant cannabis-based medicine (CBM) containing THC and CBD	Oromucosal spray Each spray: 2.7 mg of THC and 2.5 mg of CBD or placebo Maximum 3 sprays	16 patients suffering from **chemotherapy-induced nausea and vomiting**	CBM added to standard antiemetic therapy, better protection and tolerance than placebo	60
Analgesic	CBD-rich hemp extract gels	Soft gel: 15.7 mg CBD, 0.9 mg cannabidiolic acid, 0.8 mg cannabichrome, 0.5 mg THC, 0.3 mg cannabidivarin, and >1% terpene. 2 soft gels daily 8 weeks	94 patients **with chronic pain using opioids**	Significantly reducing opioid use Improving chronic pain and sleep quality	61
Analgesic	CBD-rich *C. sativa* extract	Extract: 64.5% CBD, 4% THC, <4% of other cannabinoids and minor components	*In vivo* **neuropathic pain** model	Antinociceptive effect mediated by TRPV1 vanilloid receptors	26
Analgesic Antidepressant Antianorexia	Cannabis	50 g of cannabis cigarette per month 3 inhalations 3 months	13 patients with **inflammatory bowel disease**	Improvement in general health, physical pain, depression, weight gain, social functioning and ability to work	62
Analgesic, Antiemetic Anxiolytic	Cannabis	3 months Quality of life (QOL) metrics Between 1-5 score 1= greatly decreased satisfaction, 5= greatly increased satisfaction	35 **cancer patients**	Average score: Nausea and vomiting: 3.63 Pain: 3.53 More general QOL: Lower 3.46 Cost: 3.03	63
Antihypertensive	CBD	10 mg/kg once daily 2 weeks	*In vivo* **hypertensive** rats	Diminished the width of cardiomyocytes in left ventricle Reduced the carbachol-induced vasoconstriction of coronary arteries Failed to diminish cardiac hypertrophy and diastolic stiffness in hypertension Undesirable structural and functional effects in normotensive hearts	64
Antiinflammatory	CBD	5 mg/kg, i.p. CBD 2 days	**Asthma** 21 rats	Decrease in serum TNF-α, IL-4, IL-5, IL-6 and IL-13 levels	65
Antiinflammatory	*C. sativa* extracts	*C. sativa* cultivars	*In vitro*, artificial human 3D skin	Down-regulated cytokines such as COX2, IL-6, TNF-α and pathways related to inflammation and fibrosis	18
Antiinflammatory	CBD	5 mg/kg i.p. CBD Total: 3 doses	*In vivo*, mice, **ARDS** model	Improves clinical symptoms of ARDS Reducing cytokine storm Protecting pulmonary tissues Promoting inflammatory homeostasis	57
Antiinflammatory	CBD	5 mg/kg i.p. CBD 3 days	*In vivo*, mice, **ARDS** model	Modifies ARDS symptoms Increases the expression of apelin	58
Antiinflammatory	*C. sativa* strain	CBD-rich fraction from the *C. sativa* strain	*In vitro*, **COVID19-associated inflammation in lung epithelial cells**	Decreased IL-8 and IL-6 expression in alveolar epithelial cells Increased in macrophages	59
Antimicrobial	*C. sativa* essential oil	Essential oil: THC < 0.2% w/v from hemp varieties 0.2 to 2.0% (v/v)	*In vitro*	Inhibitory effect on some Gram (+), Gram (-) and yeasts	66
Antiinflammatory Antitussive	CBD d-9-THC	Different cannabinoids	*In vivo*, guinea pigs	Inhibited TNF-α–enhanced vagal-induced bronchoconstriction, neutrophil recruitment to the airways, and citric acid–induced cough responses (only d-9-THC)	67
Cardioprotection	THC	Very low dose: 0.002 mg/kg THC	Very low dose THC administered *in vivo* before **myocardial infarction** in mice	Reduced atherosclerosis and vascular inflammation	41
General health	Cannabis cigarettes	THC-rich cannabis cigarettes or placebo cigarettes 8 weeks	32 patients with **ulcerative colitis**	Improvement in quality of life, concentration, general health, appetite, libido, and patient satisfaction	51

DISCUSSION

Several studies have examined the effect of hemp on COVID-19. *C. sativa* and its components down-regulated ACE2 and TMPRSS2 levels. This effect holds promise, because it can prevent the entry and replication of COVID-19 into the cell. Moreover, in the study by Wang et al., some extracts showed the opposite effect (16). On the other hand, most of these studies are preclinical studies therefore, it is not exactly known if it will show the same effect in humans. It is necessary to use the extract in the right composition and doses to display these effects in human body, and therefore further studies are needed. As mentioned in this study, *C. sativa* has antinausea, antivomiting, analgesic, antidepressant, antianorexia, anxiolytic, antitussive, cardioprotective and immunomodulatory effects (Tablo 1). The powerful anti-inflammatory properties of cannabis components have been effective in the treatment of many disorders. Activities are promising for the control of COVID-19 symptoms. The efficacy of *C. sativa* in more for chronic pain and may also benefit post-COVID symptoms.

Although *C. sativa* is a potential drug against COVID-19 and offering beneficial effects, its side effects cannot be ignored. Inhalation of cannabis is not recommended in France as it can promote the onset of coughing, reduce alertness and therefore, increase symptoms of COVID-19 (68). Cannabis consumption may cause acute and chronic side effects depending on the dose and application method. It causes disorders in mental, coordination, perception of time, memory and learning. Mental disorders can be psychosis, depression, anxiety and might result in suicide (69). Cannabis can cause physical as well as behavioral side effects. These physical side effects are usually on the cardiovascular system and respiratory system. There is epidemiological evidence that cannabis smoking is associated with lung disease, increased cardiovascular and respiratory symptoms, chronic bronchitis and chronic obstructive disease, and emphysema (70). Cardiovascular side effects of cannabis have been reported as cannabis arteritis, cardiomyopathy, myocardial infarction, stroke, sudden cardiac death and transient ischemic attack (4). Marijuana smoke contains toxins, irritants and carcinogens found in tobacco smoke. Even, carcinogens such as benzo[a]pyrene, tar are found in higher concentrations in cannabis smoke (71). Therefore, smoking cannabis can cause respiratory diseases and even cancer depend on the dose (71, 72). However, studies investigating the relationship between cannabis consumption and lung diseases are not of sufficient quality. It is clear that cannabis consumption is a risk for developing chronic respiratory symptoms, but there is insufficient evidence to make a definitive explanation (73).

Given the health benefits of cannabis and its medical consumption around the world, it is important to study this plant against COVID-19. As for its side effects and risk of addiction, we believe that these effects can be eliminated with the appropriate formulation and route of administration. The use of CBD, the non-psychoactive component of *C. sativa*, or its higher content in the extract, may be an approach. These side effects, which occur when taken orally, can be ruled out using different routes of administration. For example, its use as a nasal spray or mouthwash can be considered. Considering the high levels of ACE2 in the mouth and nose mucosa and the associations of COVID-19 with ACE2, these routes of administration may be effective for the management of COVID-19.

Conflict of interest

No conflict of interest was declared by the authors.

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