Open Access Research Journal of
Biology and Pharmacy
Journals home page: https://oarjbp.com/
ISSN: 2782-9979 (Online)

(REVIEW ARTICLE)

Efficacy of utilizing cannabidiol in reduction of inflammation and autoimmunity manifestation

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Open Access Research Journal of Biology and Pharmacy, 2022, 04(01), 040–047

Publication history: Received on 22 December 2021; revised on 31 January 2022; accepted on 02 Februay 2022

Article DOI: https://doi.org/10.53022/oarjbp.2022.4.1.0020

Abstract

This article reviews recent research on cannabinoids that mediate anti-inflammatory effects through cannabinoid receptors. Inflammation is involved in many of the diseases. Chronic inflammation can be caused by cancer, autoimmune disorders, and untreated infections. Some factors like smoking, obesity, or stress may also be caused by chronic inflammation. Early researchers show that Cannabidiol (CBD) has a significant role in reducing inflammation. Cannabis sativa is most commonly used for its medicinal and anti-inflammatory properties. This article focuses primarily on using cannabinoids as a new class of anti-inflammatory agents against specific autoimmune diseases and inflammatory responses caused by cell-mediated immune compounds or activated T cells.

Keywords: Medicinal Cannabis; Inflammation; Autoimmunity; Therapeutic potential

1. Introduction

Cannabis sativa is a flowering plant that is originated in central Asia. It is commonly known as skunk, hashish, or marijuana, hashish, it has been used for several years for its therapeutic effects, like antipyretic and anti-inflammatory properties. Cannabis sativa has an essential use for medical purposes [1]. Cannabis strains display over 500 compounds: flavonoids, phytocannabinoids, and terpenes. Nearly 80 cannabis compounds are called cannabinoids. Structurally, cannabinoids are compounds of the 21 carbon atoms of cannabis and related compounds and their metabolites [2, 3]. The utilization of cannabinoids for medical purposes has been one of the practical approaches to pharmacotherapy in recent years.

There are two compounds in this plant that are more important than others. [4] Δ9-tetrahydrocannabinol (THC) is the primary psychoactive ingredient, and another important cannabinoid showing various molecular and clinically beneficial properties is Cannabidiol (CBD). Based on the results of many studies, CBD can be anticancer, antioxidant, immunosuppressive effects, antidiabetic, multiple sclerosis attenuating [5]. The World Health Organization (WHO) has reported that CBD does not indicate potential human abuse or addiction.

In 1990, cannabinoids (CB1 and CB2) receptors were discovered, and after those cannabinoids, pharmacology has been making significant advances. After identifying the cannabinoid receptors and their endogenous ligands, sufficient conditions have been provided to assess the pharmacological effects of cannabinoids.

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Arachidonic acid metabolites have been shown to have similar properties to cannabis Sativa compounds, so these metabolites are called endocannabinoids. These endogenous cannabinoids act as natural ligands for cannabinoid receptors and create a vital lipid signaling system called the endocannabinoid system. The endogenous cannabinoid system is an essential biological regulatory system and is very well conserved from lower invertebrates to higher mammals [7]. Endogenous cannabinoids are anandamide (AEA), N-arachidonoylethanolamine, norazin ether, 2-arachidonoylglycerol (2-AG), N-arachidonoyldopamine, and virodhamine.

It is well known that CB1 and CB2 are Gi / or heterotrimeric protein-coupled receptors and are expressed in both the peripheral and central nervous systems. However, CB1 expression is predominant in the CNS, especially in the presynaptic nerve, and CB2 is predominantly expressed in immune cells.

A healthy situation was provided to evaluate the pharmacological effects of cannabinoids after identifying cannabinoid receptors and their endogenous ligands.

Cannabidiol is a non-toxic cannabinoid found in the cannabinoid Sativa. However, CBD, a psychoactive component of tetrahydrocannabinol, does not directly affect cannabinoid receptors such as CB1 and CB2 but enhances the effects of agonist receptors and exhibits allosteric function. Cannabinoid receptors and their ligands play an essential role in analyzing the efficacy of cannabinoids [2, 4, 5]. Typically, the cannabidiol 1 and 2 receptors are associated with heterotrimeric Gi/o proteins, and both of them exert their activity in the central and periphery nervous system. However, CB1 is expressed primarily in the CNS, especially in the presynaptic nerves, and CB2 is expressed mainly in the immune system [5, 6].

The arachidonic acid metabolite has properties similar to those found in Cannabis sativa. These metabolites are also known as endocannabinoids. These endogenous cannabinoids contribute to critical lipid signaling systems because they bind to naturally occurring cannabinoid receptor ligands. This endogenous cannabinoid system is a viable biological system highly maintained by low to high levels of animals [7].

As the inflammation results from the body's natural protective response when it gets injured. So, there are two types of inflammation:

- Acute inflammation: caused by an injury, infection, or illness. The immune system releases immune cells to the affected area to protect from redness and swelling.
- Chronic inflammation: refers to a delayed inflammatory response of the body. When inflammation remains for a long time, it may damage the tissues and organs due to the higher production of free radicals [8].

Recently, a survey has shown that CBD has a significant role in reducing inflammation and decreasing the damaging effects of free radicals. For example, CBD has been proved to be specifically effective in dealing with several types of pain. This activity is also effective as an anti-inflammatory, much as an over-the-counter anti-inflammatory drug is used for typical aches and pains [9]. Recent studies have also proven a significant anti-inflammatory response from synthetic cannabinoids (212-2, 940, WIN55, and CP55).

Both WIN55, 212-2 and CP55, 940 have IL-8 and IL-6 stimulation cytokines from IL-1β-stimulated rheumatoid fibroblast-like synoviocytes (FLS) via a non-CB1 / CB2 mediation mechanism [10].

During the current COVID-19 crisis, researchers have shown that CBD can help reduce inflammation. The results of a study examining more than 600 different cannabis Sativa CBD extracts in a 3D human model show that CBD can regulate ACE2 and TMPRSS2 levels and reduce viral load. Another group of scientists, in order to comparison of a standard phytocannabinoids agent with the effects of cannabinoids, extracted a CBD, CBG, and THCV-containing fraction of a C. Tested in vitro with Sativa strains. The team's findings show that these products reduce the secretion of the inflammatory cytokines IL-6, IL-8, CCL2, and CCL7 from the A549 alveolar epithelial cell line induced by the polarization of the KG1 macrophage cell line. It has been shown that it may increase phagocytosis. In this way, inflammation is reduced with the help of CBD, CBG, and THCV-containing fractions. Indeed, they confirmed the ACE2-reducing activity of cannabis-derived products [9].

2. Discussion

2.1. CBD and Autoimmunity

The immune system is a delicate balancing act that requires more research to understand better the mechanism by which it works. Foods and herbs that affect the immune system are ideal for autoimmune diseases. Cannabis therapy and dietary changes appear cheaper, safer, and perhaps more effective than drugs to combat autoimmune diseases [5,6].

Cannabinoid therapy can help people with autoimmune diseases by reducing systemic inflammation with few or no side effects. Preclinical data showed that cannabinoids could attenuate the autoimmune inflammatory response. In an animal model of multiple sclerosis, CBD reduced transcription of genes that promote inflammation [2, 6, 9].

2.2. Pathophysiology and effects in the immunity system

Adaptogen herbs and Cannabis are known to have immunomodulatory properties. They act as regulatory tools to balance the over-or under-reactive immune system. However, distinguishing between "immune stimulation" and "immune regulation" can be challenging to decipher. It is generally believed that people with autoimmunity do not want to take anything that boosts the immune system, but this causes controversy among professionals [7,8].

Inflammation is the leading cause of many illnesses, and autoimmunity is no exception. Extensive research has been conducted on the anti-inflammatory properties of the other components of Cannabis, CBD, and THC. If the inflammatory response is regulated, the chances of an autoimmune attack are reduced. Further research is needed to study the specific role of cannabinoids in autoimmune diseases [6, 8].

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Incorporating a carboxy group and substituting the n-pentyl sidechain with a 1,1-dimethyl heptyl group in the CBD arrangement culminated in the anti-inflammatory component HU-320. The same modifications were made to D8 -THC, resulting in ajulemic acid (HU239), a molecule containing potent anti-inflammatory properties that displayed apparent CB1 activity in certain preclinical studies. An accurately captured synthesis of ajulemic acid, on the other hand, recently yielded a compound that was essentially free of CB1 activity but also had anti-inflammatory properties. HU-320, the same as HU-239, could not have a cannabimimetic mechanism in vivo, although it did have anti-inflammatory therapeutic consequences in a collagen-induced arthritis template in mice. It suppressed the increase in serum TNF-a concentrations after an LPS challenge and blocked the synthesis of TNF-a by mouse macrophages and ROIs through RAW 264.7 cells in vitro [1-9].

Al-Ghezi studied the function of the gut microbiota to reduce the clinical manifestations of cannabinoid-induced paralysis and inflammation in a mouse model of M.S. called experimental autoimmune encephalomyelitis (EAE) [10-13]. Treatment with THC + CBD reduced the symptoms of EAE, reduced inflammatory cytokines such as IL-17 and IFN-, and increased the production of anti-inflammatory cytokines such as IL-10 and TGF-βEAE mice. Degrading bacterial strains such as Akkermansia muciniphila (A. muc) were significantly reduced after THC + CBD therapy, according to the sequencing of 16S rRNA on bacterial DNA isolated from the intestine. THC + CBD-mediated changes in the microbiome play an important role in lowering EAE, according to fecal mass transfer (FMT) studies. LPS biosynthesis, a central ingredient of gram-negative bacteria like A. muc, was shown to be enhanced in EAE mice, which would have been supported by elevated amounts of LPS in the brain.

In contrast, THC + CBD therapy altered this pattern. In comparison to naive or disease controls, EAE mice administered with THC + CBD had considerably higher concentrations of small chain fatty acids, including butyric, isovaleric, as well as valeric acids. Overall, the findings indicate that cannabinoids can help reduce EAE symptoms and suppress neuroinflammation by eliminating microbial dysbiosis and developing a healthier gut [14].

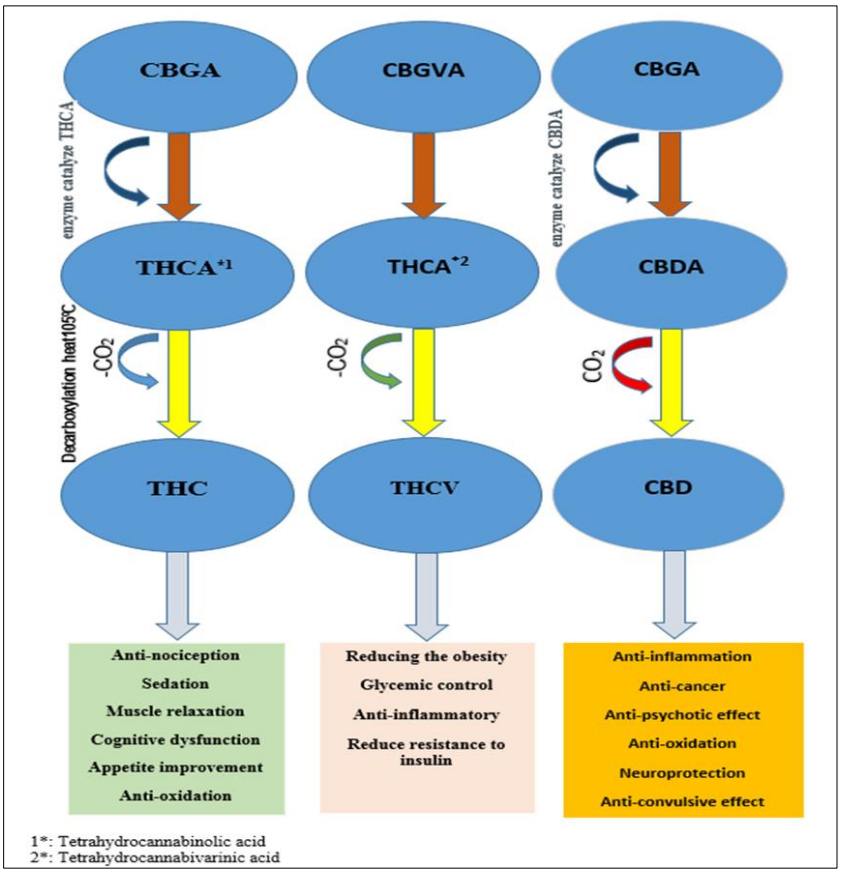

Figure 1 Some of the most important Phytocannabinoid and their effects

Most studies showing the correlation between the use of Cannabis or cannabinoids and their effects on the human immune system are immunology of one or more people with human immunodeficiency virus (HIV) or viral hepatitis C (HCV). For example, in HIV patients exposed to Cannabis, these studies show a low number of immunological endpoints, most important of which are certain types of T cells (CD4 + and CD8 + The number of T cells) circulation. Limited studies provide little information about the effects of cannabis use on the entire immune system of HIV patients. At the same time, other studies have shown the effect of Cannabis on the immune endpoints of healthy people or their susceptibility to infections [15, 16].

Despite all the concerns about Cannabis, the effectiveness of cannabinoids as analgesics, anti-inflammatory agents, multiple sclerosis (M.S.), antiepileptic and anticancer agents cannot be ruled out. They effectively relieve pain, depression, anxiety, sleep disorders, and cardiovascular disorders: appetite stimulation and reverse weight loss in AIDS and chemotherapy. There are still many mysteries about cannabis [16]. Therefore, cannabinoids can be immunosuppressive and antifibrotic agents in treating autoimmune diseases.

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Since research shows that worldwide cannabis use is significant, research on the medicinal properties of Cannabis is indecisive. Recent studies have shown that cannabis derivatives such as Cannabidiol (CBD) and delta-9-tetrahydrocannabinol (delta-9-THC) are primarily involved in many neurotransmitter systems such as the serotonergic, dopaminergic systems, glutamatergic, and noradrenergic systems, which are responsible for recreational and medical properties of Cannabis [2]. Among cannabis removes, THC is the main psychoactive compound because of its lipophilic construction, which permits the atom to cross the blood-cerebrum obstruction [18].

In a system of acute lung injury, prophylactic CBD therapy was reported to suppress inflammation (ALI). CBD is an integral part of lung immunity, as well as elastance, leukocyte migration into the lung, involvement of myeloperoxidase in lung tissue, total protein, and pro-inflammatory cytokines (TNF and IL-6) or chemokines (MCP-1 and MIP-2), according to a study by Burstein (2015), in bronchial alveolar lavage supernatant. CBD is successful in preventing inflammatory respiratory illness [19,20].

2.3. The interaction of medicinal Cannabis and the immune system

The interaction between cannabis activity and immune response was noticed by Kagen et al., [21], whose goal was to determine the part of cannabis use in influencing Aspergillus sensitization. It has been useful to determine that cannabis users have a high risk of fungal infection due to increased immunological lung diseases [22,23]. Cannabinoids and synthetic plant derivatives play the role of immunosuppressive conditions and anti-inflammatory. Their activities are autonomous of cannabinoid receptors and cause the reticence of pro-inflammatory cytokines created by macrophages and lymphocytes. Cannabinoid receptor one and Endocannabinoids may act as regulators of hypotension caused by inflammation, while CB2-binding cannabinoids may decrease vascular inflammation. The immune system is activated to produce macrophages and lymphocytes to alter their cannabinoid receptor expression. The endocannabinoid-mediated effects on the macrophages and immune system show that the endocannabinoid system is principally involved in the host's inflammatory response [24].

Most studies showing the effects of cannabinoids or Cannabis or their use on the human immune system are one or more immunology in people with hepatitis C virus (HCV) or immunodeficiency virus human (HIV). Limited studies provide little information about the effects of cannabis use on the entire immune system of HIV-infected persons. At the same time, other studies have shown the effect of Cannabis on the immune endpoints of healthy people or their susceptibility to infections.

These analyzes focused chiefly on the effects of cannabis use on mingling cytokines, primarily inflammatory cytokines, in healthy persons. Since the immune system plays a vital role in the fight and defense of disease, this article provides evidence of possible connections between cannabis use and immune function and the possibilities among cannabis use and disease susceptibility [25,26].

The anti-inflammatory effects of cannabinoids, which are Cannabis components, are well identified; however, the processes behind these are unknown. The major psychotropic cannabinoid, Δ-9-tetrahydrocannabinol (THC), and the major non-psychotropic cannabinoid, cannabidiol (CBD), are autoimmune-mediated inflammatory diseases, including multiple sclerosis. Significantly reduces the Th17 phenotype, which is thought to rise (Kozela. et al., 2013). Reconstitution of MOG35-55-specific encephalitis-induced T cells (cells that cause experimental autoimmune encephalitis in mice) into the presence of bladder antigen-presenting cells significantly improved IL-17 synthesis and release. The cannabinoids CBD and THC blocked the synthesis and secretion of that kind of cytokine in either a dose-dependent manner (at 0.1–5 M). Furthermore, IL-6 mRNA, including protein, a central factor in Th17 induction, was reduced. Raised concentrations of the anti-inflammatory cytokine IL-10 were also seen after CBD therapy. Not affected TNF and IFN quantities by CBD or THC, which was surprising. The CB1, CB2, PPAR, 5-HT1A, and TRPV1 receptors do not have to suppress the IL-17 secretion by such cannabinoids. Kozela et al. (2013) found that cannabinoids peculiarly modulate the autoimmune cytokine milieu, suppressing the pathogenic IL-17 and IL-6 cytokines while growing the production of the anti-inflammatory cytokine IL-10 [27]. In addition, CBD has proven its effectiveness with the new COVID-19. When the virus invades the host cell, it is identified by pattern recognition receptors (PRRs) such as TLR7 and TLR8. Receptors are expressed by epithelial and local cells of the innate immune response. After binding to the ligand, PRR is an interferon type I and -III antiviral interferon and a variety of types with the help of adapter proteins that stimulate downward transcription factors, including interferon regulatory factor (IRF), AP-1, and NF-κB. Chemokine. These chemokines attract more congenital responsive cells and give rise to chemokines such as MC-1, IP-10, and MIG. These chemokines can attract lymphocytes and lead to the recognition of viral antigens supplied by dendritic cells [21-23].

Reports from various studies have shown that Sars-Cov-2 can infect type I and -II lung cells and has an excellent ability to replicate in lung tissue. In addition, the 2019 coronavirus reduces the IFN-I and IFN-III responses and the induction of some pro-inflammatory chemokines, IL-1B, IL-6, TNF, and IL1RA, and is a cytokine required for cell mobilization immunity [21-24]. A dysfunctional immune response that cannot prevent the virus from multiplying or killing infected cells results in severe inflammatory reactions and severe acute respiratory distress syndrome (ARDS) cytokine storms and systemic consequences [28-30].

3. Cannabinoids Limitations

Cannabis is known to have some side effects due to its widespread receptor distribution. A systematic study [23] reported 8371 adverse events associated with the medical use of cannabinoids, 23 RCTs reported 4779, and 8 observational studies reported 3592. Patients receiving cannabinoid therapy had twice the incidence of serious adverse events compared to the control group. Respiratory (16.5%), gastrointestinal (16.5%), and nervous system (15.2%) disorders are the most frequently reported serious adverse events category assigned to cannabinoids and are of the nervous system. Disorders (30%) were reported most frequently in controls.

Events considered serious side effects were: pneumonia, dyspnea, lower respiratory tract infections, pleural effusion, and pulmonary embolism. Moreover, it can cause vomiting, diarrhea, gastroenteritis, abdominal pain, constipation, duodenal ulcer, recurrence of multiple sclerosis, convulsions. Fifteen deaths were reported in cannabinoid users, compared with three in the control group, but these results were not statistically significant [23]. The incidence of non-serious adverse events was significantly higher in subjects assigned to cannabinoid therapy than in controls, and dizziness was the most frequent non-serious adverse event among participants exposed to cannabinoids. Knowledge of CBD doses and plasma levels and how they relate to immune regulation is still limited.

Some of these limitations are planned for CBD over the next few years and may be revealed in many clinical trials that are associated with the immune effects of CBD. In addition to the need for further data on CBD administration and pharmacokinetics, this extensive summary of the immune and inflammatory effects of CBD revealed some data gaps to be filled. First, identifying the receptors on which CBD acts in the immune system remains important. An essential part of this question is whether CBD-induced FAAH inhibition produces anandamide metabolites that bind to various receptors and mediate some of the immunosuppressive or anti-inflammatory effects of CBD. In addition to the observation that some of the effects of CBD may be attenuated by PPAR-c antagonists, CBD-mediated production of 92-98, anandamide, activate (not yet identified) metabolism of PPAR. May promote subsequent production of things-NS. Another important decision needed for much of the receptor research is to identify the cell type in which the receptors that mediate the effects of CBD are expressed. Some cell types have little data, especially B cells and dendritic cells. Some established targets on T cells have not been extensively studied even in the extensive literature on CBD-T cells. Limited data are investigating the effects of CBD on various subgroups of T cells. Therefore, there needs to be an up-to-date knowledge gap identified. Summary of major studies on the effects of CBD on the immune response of humans and veterinarians, these include well-controlled studies that take into account differences in routes of administration, doses, and pharmacokinetic [23-27].

4. Conclusion

The purpose of this article is to look at the use and effects of Cannabis on inflammatory responses. The main remarks are: among cannabis users and healthy people, cannabinoids reduce the inflammatory response, thereby reducing the immune response, leading to a higher risk of infections; among patients with multiple sclerosis, cannabinoids reduce the effect on inflammatory markers. Therefore, the administration of cannabinoids has an inhibitory effect on immune cells, and endocannabinoids can stimulate the immune system. Thus, both in vivo and in vitro, it has been demonstrated that cannabinoid receptors are involved in maintaining the immune system through their immune-modulatory properties. CBD has recently become a significant research subject, despite being found several years ago. Many informative studies on its biological functions indicate potential therapeutic implementations. Its anti-inflammatory properties have been shown in several clinical studies. Investigational colitis, arthritis triggered by collagen, neuroinflammation produced by b-amyloid, neutrophil chemotaxis, hepatic ischemia-reperfusion (I/R) damage, autoimmune encephalomyelitis, severe pulmonary, among others are only a few instances. This and other questions must be investigated in human clinical experiments with an eye toward therapeutic uses. CBD's lack of psychotropic consequences and other side effects gives it a significant benefit over certain cannabinoids. Another field where more research is needed is the development of synthetic analogs, which are more potent than CBD and have a good therapeutic ratio.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

The manuscript has not been submitted to more than one journal for consideration. The manuscript has not been published previously (partly or in full) unless the new work concerns an expansion of previous work; there is no transparency on the re-use of material to avoid the hint of text-recycling ("self-plagiarism").

Funding

This study was not funded by any organization or institution or any research grant company. Statement of human and animal rights. This article does not contain studies with human participants that have been performed by the Authors.

Author's contributions

Sh.G. and F.M. verified the analytical methods. M.D. encouraged F.M. to investigate and, P.D. and Sh.G. supervised the findings of this work. All authors discussed the results and contributed to the final manuscript.

Availability of data and materials

Data sharing does not apply to this article as no data sets were generated or analyzed during the current study.

References

[1] Fouad AA, Albuali WH, Al-Mulhim AS, et al. Cardioprotective effect of cannabidiol in rats exposed to doxorubicin toxicity. Environ. Toxicol. Pharmacol.2013; 36: 347–57.

[2] Schlicker E, Kathmann M. Modulation of transmitter release via presynaptic cannabinoid receptors. Trends Pharmacol Sci. 2001Nov; 22(11): 565–72.

[3] Mechoulam R. Marihuana chemistry. Science. 1970; 168(3936): 1159–66.

[4] ElSohly MA, Radwan MM, Gul W, Chandra S, Galal A. Phytochemistry of Cannabis sativa L. Prog. Chem. Org. Nat. Prod. 2017; 103:1–36.

[5] Sonego AB, et al. Cannabidiol prevents haloperidol-induced vacuous chewing movements and inflammatory changes in mice via PPARgamma receptors. Brain Behav. Immun. 2018; 74: 241–251.

[6] Mackie K. Cannabinoid receptors as therapeutic targets. Annu Rev Pharmacol Toxicol. 2006; 46: 101–122.

[7] Stefano GB, Liu Y, Goligorsky MS. Cannabinoid receptors are coupled to nitric oxide release in invertebrate immunocytes, microglia, and human monocytes. J Biol Chem. 1996; 271: 19238–19242.

[8] Atalay S, Jarocka-Karpowicz I, Skrzydlewska E.Antioxidative and Anti-Inflammatory Properties of Cannabidiol.Antioxidants. 2019; 9: 21.

[9] Booz GW. Cannabidiol as an emergent therapeutic strategy for lessening the impact of inflammation on oxidative stress. Free radical biology & medicine. 2011; 51: 1054–61.

[10] Selvi E, Lorenzini S, Garcia-Gonzalez E, et al. Inhibitory effect of synthetic cannabinoids on cytokine production in rheumatoid fibroblast-like synoviocytes. Clin Exp Rheumatol. 2008; 26: 574–581.

[11] Moazzami B, Chaichian S, Kasaeian A, Djalalinia S, Akhlaghdoust M, Eslami M, Broumand B. Metabolic risk factors and risk of Covid-19: A systematic review and meta-analysis. PloS one. 15 Dec 2020; 15(12): e0243600.

[12] Zenewicz LA, Abraham C, Flavell RA, Cho JH. Unraveling the genetics of autoimmunity. Cell. 2010; 140(6): 791–797.

[13] Burstein S. Cannabidiol (CBD) and its analogs: a review of their effects on inflammation. Bioorganic & medicinal chemistry. 1 Apr 2015; 23(7): 1377-85.

[14] Al-Ghezi ZZ, Busbee PB, Alghetaa H, Nagarkatti PS, Nagarkatti M. Combination of cannabinoids, delta-9-tetrahydrocannabinol (THC) and Cannabidiol (CBD), mitigates experimental autoimmune encephalomyelitis (EAE) by altering the gut microbiome. Brain, behavior, and immunity. 21 Nov 019; 82: 25-35.

[15] Kagen SL, Kurup VP, Sohnle PG, Fink JN. Marijuana smoking and fungal sensitization. J Allergy Clin Immunol. Apr 1983; 71(4): 389–93.

[16] Roth MD, Whittaker K, Salehi K, Tashkin DP, Baldwin GC. Mechanisms for impaired effector function in alveolar macrophages from marijuana and cocaine smokers. J Neuroimmunol. Feb 2004; 147(1–2): 82–6.

[17] Geiotek A, Ambroziewicz E, Jastrza˛bA, et al. Rutin, and ascorbic acid cooperation in antioxidant and antiapoptotice_ect on human skin keratinocytes and fibroblasts exposed to UVA and UVB radiation. Arch. Dermatol. Res. 2019; 311: 203–19.

[18] Brunet L, Moodie EEM, Rollet K, Cooper C, Walmsley S, Potter M, Klein MB. Marijuana smoking does not accelerate the progression of liver disease in HIV-hepatitis C coinfection: A longitudinal cohort analysis. Clinical Infectious Diseases. 2013; 57(5): 663–670.

[19] Bach J-F. The effect of infections on susceptibility to autoimmune and allergic diseases. The New England Journal of Medicine. 2002; 347(12): 911–920.

[20] Kozela E, Juknat A, Kaushansky N, Rimmerman N, Ben-Nun A, Vogel Z. Cannabinoids decrease the th17 inflammatory autoimmune phenotype. Journal of Neuroimmune Pharmacology. Dec 2013; 8(5): 1265-76.

[21] Tavakolpour S, Kheiry F, Mirsafaei HS, Akhlaghdoust M. The possible role of interleukin-35 and its therapeutic potential in pemphigus. International immunopharmacology. 1 Jan 2017; 42: 11-7.

[22] Velasco G, Sánchez C, Guzmán M. Anticancer mechanisms of can- nabinoids. Current Oncology. 2016; 23: S23-S32.

[23] Sonego AB, et al. Cannabidiol prevents haloperidol-induced vacuous chewing movements and inflammatory changes in mice via PPARgamma receptors. Brain Behav. Immun. 2018; 74: 241–251.

[24] Elbaz M, Nasser MW, Ravi J, et al. Modulation of the tumor microenvironment and inhibition of EGF/EGFR pathway: Novel anti-tumor mechanisms of cannabidiol in breast cancer. Molecular oncology. 2015; 9: 906-919.

[25] Appendino G, Gibbons S, Giana A, et al. Antibacterial cannabinoids from Cannabis sativa: a structure-activity study. J Nat Prod. 2008; 71: 1427-1430.

[26] Stanley CP, Hind WH, Tufarelli C, O'Sullivan SE. Cannabidiol causes endothelium-dependent vasorelaxation of human mesenteric arteries via CB1 activation. Cardiovasc Res. 2015; 107: 568-578.

[27] Campos AC, Fogaça MV, Scarante FF, et al. Plastic and neuroprotective mechanisms involved in the therapeutic effects of cannabidiol in psychiatric disorders. Front Pharmacol. 2017; 8: 269.

[28] García-Arencibia M, González S, de Lago E, Ramos JA, Mechoulam R, Fernández-Ruiz J. Evaluation of the neuroprotec- tive effect of cannabinoids in a rat model of Parkinson's disease: importance of antioxidant and cannabinoid receptor-independent properties. Brain Res. 2007; 1134: 162-170.

[29] ElSohly MA, Radwan MM, Gul W, Chandra S, Galal A. Phytochemistry of Cannabis sativa L. Prog. Chem. Org. Nat. Prod. 2017; 103: 1–36.