Cannabis and inflammation.

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Abstract

Inflammation and oxidative stress are involved in many diseases. Chronic inflammation may be caused by autoimmune disorders, untreated infections, or illnesses, and often plays a role in conditions such as asthma, cancer, and diabetes. Factors such as smoking, obesity, or stress may also contribute to chronic inflammation. Emerging research now demonstrates that cannabidiol (CBD) has significant potential in terms of limiting inflammation and downstream effects in terms of free radicals as well.

Keywords: Cannabidiol, Autoimmune disorders, Untreated infections, Illnesses.

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Introduction

Inflammation occurs as a natural protective response when the body is harmed. There are two types of inflammation: Acute and chronic

Acute inflammation: occurs following an injury, infection, or illness. The immune system unleashes immune cells to the affected area to protect it, causing redness and swelling.

Chronic inflammation: refers to a prolonged inflammatory response in the body. When inflammation lingers, it can detrimentally impact tissues and organs due to the increased production of free radicals, which results in oxidative stress, an imbalance between antioxidants and free radicals.

It is certainly clear that our most pervasive chronic conditions share a common feature in terms of their underlying cause. Whether coronary artery disease, hypertension, diabetes, depression, rheumatoid arthritis, or even Alzheimer's disease, what current medical literature reveals is the powerful role that inflammation plays in these and other common conditions [1].

Ultimately, the main issue with higher levels of inflammation that manifests as damage to tissue is the fact that when inflammation has been turned on, it increases the production of damaging free radicals, a situation we call oxidative stress. When oxidative stress is running rampant, damage occurs to our proteins, and fat, and even our DNA.

Unlike THC, CBD is a non-psychotropic derivative of the plant. Recently, research has demonstrated that CBD has wide ranging activity in terms of reducing inflammation and the damaging effects of free radicals. Specifically, CBD modulates the function of the immune system. CBD, for example, has been demonstrated to be specifically effective in dealing with various types of pain [2]. This activity is also thought to represent a manifestation of CBD working as an anti-inflammatory much as over the counter anti-inflammatory medications are used for typical aches and pains.

Further, many of the health-related issues associated with obesity are a consequence of increased inflammation. CBD is being explored extensively in relation to obesity in hopes of reducing some of these important health consequences.

Inflammation and oxidative stress are intimately involved in the genesis of many human diseases. Unraveling that relationship therapeutically has proven challenging, in part because inflammation and oxidative stress "feed off" each other. However, CBD would seem to be a promising starting point for further drug development given its anti-oxidant and anti-inflammatory actions on immune cell [3].

The research in terms of medical application of CBD is expanding dramatically, and with good reason. As a natural, plant derived anti-inflammatory, CBD joins other familiar players in this arena like turmeric which is derived from curcumin, as well as ginger and many others. Moving forward, it is almost certain that CBD research will continue to expand, and likely validate it's efficacy across a wide spectrum of health issues [4].

Cannabis has Anti-Inflammatory Capacity

Cannabis sativa, commonly known as marijuana, has been used for several years for its medicinal effects, including antipyretic and analgesic properties. Approximately 80 cannabis constituents, termed cannabinoids, naturally occur as 21 carbon atom compounds of cannabis and analogues of such compounds and their metabolites [5].

Marijuana-derived cannabinoids

It is related compounds have been tested for the treatment of various diseases, ranging from cancer to glaucoma. Recently, these drugs have been reported to have immunomodulatory effects, so their potential for the treatment of chronic inflammatory diseases is being evaluated. Marijuana-derived cannabinoids function by binding several subtypes of cannabinoid receptor in the brain and other organs. In addition, the body produces endocannabinoids that also function through binding these receptors. Compounds that are chemically related to cannabinoids have also been shown to function by binding other types of receptor, such as the NMDA (N-methyl-D-aspartate) receptor and the peroxisome-proliferative-activated

receptor-γ (PPAR-γ), or by influencing other cellular components, [6] such as lipid rafts. Cannabinoids and endocannabinoids regulate some of the inflammatory aspects of brain injury, through both cannabinoid-receptor-mediated and non-cannabinoid-receptor-mediated mechanisms. It is possible that these drugs reduce brain oedema and other aspects of neuroinflammation by inhibiting NMDA receptors, by functioning as antioxidants and by reducing the levels of pro-inflammatory cytokines in the brain [7]. Cannabinoids regulate the tissue response to inflammation in the colon, and it is possible that this regulation occurs on two levels: the first, involving the smooth-muscle response to pro-inflammatory mediators, thereby affecting gastrointestinal transit time; and the second, involving the direct suppression of pro-inflammatory-mediator production.

Plant-derived cannabinoids and synthetic derivatives are anti-inflammatory and immunosuppressive in animal models of arthritis. The mechanisms of action seem to be independent of cannabinoid receptors and cause suppression of pro-inflammatory cytokines that are produced by lymphocytes and macrophages. Endocannabinoids and cannabinoid receptor 1 (CB1) might function as regulators of inflammation-induced hypotension, whereas cannabinoids that bind CB2 might attenuate vascular inflammation. Cannabinoid-based drugs that do not function by interacting with cannabinoid receptors decrease the symptoms of septic shock, which might result from the ability of these drugs to inhibit pro-inflammatory-cytokine production. Immune activation causes lymphocytes and macrophages to produce endocannabinoids and to alter their expression of cannabinoid receptors. These effects and endocannabinoid-mediated effects on immune-cell migration and cytokine production indicate that the endocannabinoid system is involved in the host inflammatory response [8,9].

Methods

Approximately 200 terpenes have been identified in the cannabis plant so far. Each plant strain is made up of a unique combination of these terpenes, which affects the different tastes, smells, and effects.

Different strains: While there are too many terpenes and their diverse effects to list here, a few of the most popular are as follows:

Limonene: Limonene has a citrusy smell. It has potential anti-carcinogenic properties, among many other benefits.

Myrcene: This is the most prevalent terpene in cannabis varieties and is thought to increase the psychoactive effects of THC. It can also be used as an antiseptic and anti-inflammatory.

Linalool: Linalool, a terpene with citrusy lavender smell, has tranquilizing effects and can help those with psychosis.

Caryophyllene: This terpene has a smell reminiscent of black pepper and is being studied for potential benefits in diabetes reduction and autoimmune disorders.

Alpha Bisabolol: This terpene is also found in chamomile, and also has a floral flavor and scent.

Borneol: Borneol smells similar to camphor and mint and can potentially help reduce fatigue and stress.

Delta-3 Carene: This terpene has a piney scent and has been found in 80 different strains in 162 cannabis plants.

Eucalyptol: Eucalyptol, predictably, smells like eucalyptus. Only small levels of this terpene are found in cannabis.

Nerolidol: This terpene smells like tree bark and has potential as a sleep aid.

Pinene: Pinene, like delta-3 carene, smells like pine. It is mostly found in citrus fruits and pine woods and has medical potential as an expectorant.

Discussion

Cannabinoids and related compounds have been shown to either suppress or increase the production of pro-inflammatory cytokines such as tumour-necrosis factor, interleukin-1β (IL-1β) and IL-6 in both patients and animal models, indicating that these drugs can modulate pro-inflammatory mediators. Depending on the model system, the effects of these drugs do not always depend on their interaction with cannabinoid receptors. Cannabinoids bias the immune response away from T helper 1 (TH1)-cell responses, by mechanisms that involve cannabinoid receptors. It is possible that signalling through these receptors, expressed by T cells, B cells or antigen-presenting cells, suppresses the expression of TH1-cell-promoting cytokines and increases the expression of TH2-cell-promoting cytokines [10].

The major psychoactive component of marijuana is Delta-9-tetrahydrocannabinoid (THC), which has been widely studied. Studies have shown that THC affects growth, development and reproductive activity [11] Studies in mice have shown that THC suppresses antibody formation against sheep red blood cells and causes changes in cytokine production. *In vitro* studies, however, have shown that THC may suppress or enhance (depending on dosage) the production of various cytokines such as IL-1, IL-6 and TNFα by leukocytic cells.

Cannabidiol (CBD) is present in most cannabis preparations (hashish, marijuana, ganja) in higher concentrations than THC. Cannabidiol was, first isolated in 1940 by Todd and Adams. Its structure was elucidated by Mechoulam and Shvo in 1963. Its absolute stereochemistry was determined in 1967 [12]. The synthesis of cannabidiol in its racemic form and its natural form were reported in the 1960's [13].

Cannabidiol has no psychotropic (cannabimimetic activity) and does not bind either the brain or the peripheral receptors, CB1 and CB2 respectively. Cannabidiol has, however, been observed to have anticonvulsant effects. Cannabidiol has also been effective in animal models predictive of antipsychotic activity, and has been found to have antipsychotic effects in the, case of schizophreniaÇ(Psychopharmacol) [14].

CBD has a wide spectrum of biological activity, including antioxidant and anti-inflammatory activity, which is why its activity in the prevention and treatment of diseases whose development is associated with redox imbalance and inflammation has been tested [15].

Based on the current research results, the possibility of using CBD for the treatment of diabetes, diabetes-related cardiomyopathy, cardiovascular diseases (including stroke, arrhythmia, atherosclerosis, and hypertension), cancer, arthritis, anxiety, psychosis, epilepsy, neurodegenerative disease (i.e., Alzheimer's) and skin disease is being considered [16].

CBD also reduces reactive oxygen species (ROS) production by chelating transition metal ions involved in the Fenton reaction to form extremely reactive hydroxyl radicals. In addition to the direct reduction of oxidant levels, CBD also modifies the redox balance by changing the level and activity of antioxidants. CBD antioxidant activity begins at the level of protein transcription by activating the redox-sensitive transcription factor referred to as the nuclear erythroid 2-related factor (Nrf2), which is responsible for the transcription of cytoprotective genes, including antioxidant genes [17]. It is known that under oxidative conditions, alterations in enzymatic activity may be caused by oxidative modifications of proteins, mainly aromatic and sulfur amino acids.

CBD also supports the action of antioxidant enzymes by preventing a reduction in the levels of microelements (e.g., Zink or Selenium), which are usually lowered in pathological conditions. These elements are necessary for the biological activity of some proteins, especially enzymes such as superoxide dismutase or glutathione peroxidase [18].

By lowering ROS levels, CBD also protects non-enzymatic antioxidants, preventing their oxidation, as in the case of GSH in the myocardial tissue of mice with diabetic cardiomyopathy [19]. An increase in GSH levels after CBD treatment was also observed in mouse microglia cells [20]. This is of great practical importance because GSH cooperates with other low molecular weight compounds in antioxidant action, mainly with vitamins such as A, E, and C CBD exhibits much more antioxidant activity (30%–50%) than alpha-tocopherol or vitamin C [21].

The result of an imbalance between oxidants and antioxidants is oxidative stress, the consequences of which are oxidative modifications of lipids, nucleic acids, and proteins. This results in changes in the structure of the above molecules and, as a result, disrupts their molecular interactions and signal transduction pathways (Figure 1) [22,23].

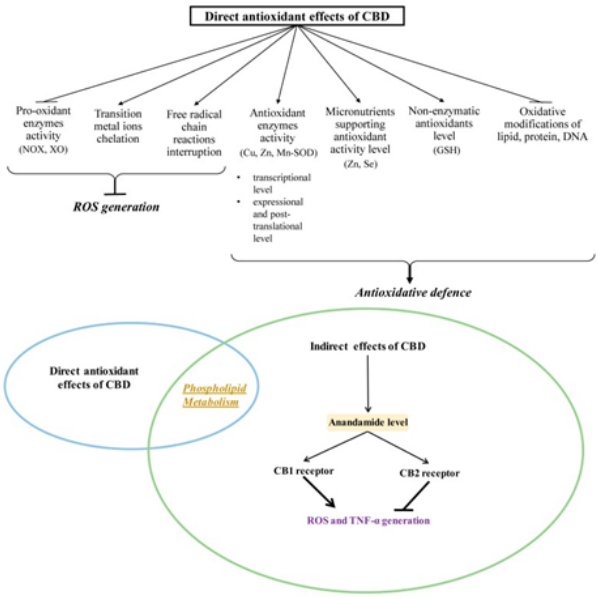

Figure 1. *Direct antioxidant effects of CBD.*

Oxidative modifications play an important role in the functioning of redox-sensitive transcription factors (including Nrf2 and the nuclear factor kappa B (NFkappaB). As a consequence, oxidative modifications play a role in the regulation of pathological conditions characterized by redox imbalances and inflammation, such as cancer, inflammatory diseases, and neurodegenerative diseases. In this situation, one of the most important processes is lipid peroxidation, which results in the oxidation of polyunsaturated fatty acids (PUFA), such as arachidonic, linoleic, linolenic, eicosapentaenoic, and docosahexaenoic acids [21].

One of the most noticeable CBD antioxidant effects is the reduction in lipid and protein Modifications. CBD supplementation has been found to reduce lipid peroxidation, as measured by MDA levels, in mouse hippocampal (HT22) neuronal cells depleted of oxygen and glucose under reperfusion conditions.

Additionally, CBD caused a reduction in the level of PUFA cyclization products, such as isoprostanes, in the cortex of transgenic mice with Alzheimer's disease [3]. Thus, CBD protects lipids and proteins against oxidative damage by modulating the level of oxidative stress, which participates in cell signaling pathways. Several interactions with relevance to the immune system and oxidative stress exist. Despite having low affinity for CB1 and CB2 receptors, CBD has been shown to antagonize the actions of cannabinoid CB1/CB2 receptor agonists in the low nanomolar range, consistent with non-competitive inhibition. CBD acts as an inhibitor of fatty acid amide hydrolase (FAAH), the major enzyme for endocannabinoid breakdown. Because FAAH activity correlates with gastrointestinal mobility, CBD may have utility in treating intestinal hypermotility associated with certain inflammatory diseases of the bowel. CBD may thus be of benefit in treating neueodegenerative diseases associated with

hyperactivation of microglial, as well as retinal neuroinflammation seen in such conditions as uveitis, diabetic retinopathy, age-related macular degeneration, and glaucoma. CBD may have therapeutic utility in treating diabetic complications and atherosclerosis. CBD might be useful therapeutically to counter the increased risk of depression in diseases associated with immune activation and inflammation, which often lead to decreased tryptophan, the precursor of serotonin [20].

Cannabinoids have been shown to exert anti-inflammatory activities in various *in vivo* and *in vitro* experimental models as well as ameliorate various inflammatory degenerative diseases. However, the mechanisms of these effects are not completely understood. Using the BV-2 mouse microglial cell line and lipopolysaccharide (LPS) to induce an inflammatory response a study investigated the signaling pathways engaged in the anti-inflammatory effects of cannabinoids as well as their influence on the expression of several genes known to be involved in inflammation. It has been found that the two major cannabinoids present in marijuana (THC) and cannabidiol (CBD), decrease the production and release of proinflammatory cytokines, including interleukin- 1beta, interleukin-6, and interferon (IFN)beta, from LPS-activated microglial cells. The cannabinoid anti-inflammatory action does not seem to involve the CB1 and CB2 cannabinoid receptors or the abn-CBD-sensitive receptors. In addition, it is found that THC and CBD act through different, although partially overlapping, mechanisms. CBD, but not THC, reduces the activity of the NF-kappaB pathway, a primary pathway regulating the expression of pro inflammatory genes. Moreover, CBD, but not THC, up-regulates the activation of the STAT3 transcription factor, an element of homeostatic mechanism(s) inducing anti-inflammatory events. Following CBD treatment, but less so with THC, it is observed a decreased level ofmRNA for the Socs3 gene, a main negative regulator of STATs and particularly of STAT3. However, both CBD and THC decreased the activation of the LPS-induced STAT1 transcription factor, a key player in IFN beta-dependent proinflammatory processes. In summary, these observations show that CBD and THC vary in their effects on the anti-inflammatory pathways, including the NF-kappaB and IFNbeta-dependent pathways [15].

Preliminary studies

It is showed that cannabidiol inhibited PBQ-induced writhing in mice when given orally at doses up to 10 mg/kg. Cannabidiol was also shown to reduce TPA-induced erythema, which is dependent upon prostaglandin release, in mice when applied topically [18].

In an *in vitro* study, it is demonstrated that THC and cannabidiol inhibited nitric oxide (NO) produced by mouse peritoneal macrophages activated by LPS and IFNγ. Studies *in vitro* the effects of THC and cannabidiol on secretions of IL-1, IL-2, IL-6, TNFα and IFNγ by human leukocytes following activation by mitrogen, found that both cannabinoids in low concentrations increase IFNγ production, whereas in high concentrations (5-24 μg/ml) completely blocked IFNγ synthesis, and cannabidiol decreased both IL-1 and TNFα production and did not affect IL-2 secretion. Cannabinoids may be used to treat inflammatory diseases, such as rheumatoid arthritis and Crohn's disease. Inflammatory diseases involve the complex interaction between several components such as Interleukins (IL-1, IL-6 and IL-8), TNF-α and various mediators such as nitric oxide, ROI and PGE2.

Preferably the cannabinoid is used as an anti-inflammatory agent against inflammatory diseases, especially rheumatoid arthritis or Crohn's Disease, sarcoidosis, asthma, Alzheimer's disease, multiple sclerosis, Psoriasis, ulcerative colitis, osteoarthritis or spondyloarthropathy (erg. ankylosing spondylitis). Anti-inflammatory action of Cannabis sativa may be due in part to the non-psychotropic constituent cannabidiol (and presumably also to its acidic metabolite) [17].

Cannabinoids may be used separately or as mixtures of two or more cannabinoids. They may be combined with one or more pharmaceutically acceptable compounds such as carriers. As a general proposition, the total pharmaceutically effective amount of cannabinoid administered will be in the range of 1 μg/kg/day to 50 mg/kg/day of patient body weight, preferably 2.5 to 10 mg/kg/day especially 5 mg/kg/day. (https://patents.google.com/patent/US6410588B1/en)

Surely one of the most important elements of cannabis are terpenes. Terpenes are fragrant oils produced alongside CBD, THC, and other cannabinoids. They account for the distinctive smell and flavors of your cannabis. Some include pine, mint, berry, and citrus. Without terpenes cannabis would have very little taste or odor. Cannabis terpenes evolved for the cannabis plant to draw pollinators and repel predators. Weather, climate, maturation, age, soil type, and fertilizer use all help to determine which terpenes will develop. Thanks to the wide variety of factors, over 200 terpenes have been noted to date.

Structurally there is little in common between THC and the endocannabinoids. The plant cannabinoids are terpenophenols, while the endocannabinoids are fatty acid derivatives. Yet, pharmacologically they have much in common. Both THC and anandamide cause a typical tetrad of physiological effects: hypothermia, hypomotility, antinociception and catalepsy [6].

Terpenes bind to receptors in the brain. By doing so, they work to either activate or inhibit the effects of other compounds found in the cannabis plant. They also reduce the side effects of chemotherapy, provide antiparasitic benefits, and are powerful anti-inflammatories. The different Cannabis chemotypes showed distinct compositions of terpenoids. The terpenoid-rich essential oils exert anti-inflammatory and antinociceptive activities *in vitro* and *in vivo*, which vary according to their composition. Their effects seem to act independent of TNFα. None of the essential oils was as effective as purified CBD. In contrast to CBD that exerts prolonged immunosuppression and might be used in chronic inflammation, the terpenoids showed only a transient immunosuppression and might thus be used to relieve acute inflammation.

Some terpenes balance the less-desirable psychoactive and physiological effects of cannabis and provide therapeutic qualities not found in products that only contain CBD. One such terpenoid (a terpene that has been dried and cured and therefore undergone chemical modification) is beta-caryophyllene, or BCP. Cannabis contains a large amount of BCP, as do some food plants, legal herbs, and spices such as black pepper. It exists in some leafy green vegetables as well and acts essentially like a non-psychoactive anti-inflammatory [11].

The FDA has recognized terpenes and terpenoids as safe, though more research is necessary before professionals can adequately predict how cannabis terpenes can be used to treat various health conditions. Cannabinoid terpenoid interactions have been shown to be effective treatment for inflammation, addiction, depression, anxiety, epilepsy, bacterial and fungal infections, and general pain.

Conclusion

Over the years there has been extensive research looking at how increasing the availability of antioxidants might help to protect our bodies against these damaging free radicals. But recognizing that the upstream instigator of this problem, to a significant degree, is inflammation, allows us to redirect our targeting in order to protect our body's tissues. Scientists described not only the complexities and challenges posed by trying to specifically target oxidative stress in a variety of disease states, but also the potential benefits of using CBD to accomplish this goal.

References

1. Atalay S, Jarocka-Karpowicz I, Skrzydlewska E. Antioxidative and Anti-Inflammatory Properties of Cannabidiol. Antioxidants. 2019;9:21.
2. 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.
3. Cheng D, Low JK, Logge W, et al. Chronic cannabidiol treatment improves social and object recognition in double transgenic APPswe/PS1DE9 mice. Psychopharmacology. 2014;231:3009–17.
4. Formukong EA, Evans AT, Evans FJ. Analgesic and antiinflammatory activity of constituents of Cannabis sativa L. Inflammation. 1988;12:361-71.
5. 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.
6. Fride E, Mechoulam R. Pharmacological activity of the cannabinoid agonist anandamide, a brain constituent. Eur J Pharmacol. 1993;231:313–4.
7. Gallily R, Yekhtin Z, Hanuš LO. The Anti-Inflammatory Properties of Terpenoids from Cannabis. Cannabis and cannabinoid research. 2018;3:282–90.
8. Gaschler MM, Stockwell BR. Lipid peroxidation in cell death. Biochem. Biophys. Res. Commun. 2017;482:419–25.
9. Geiotek A, Ambroziewicz E, Jastrza¸b A, et al. Rutin and ascorbic acid cooperation in antioxidant and antiapoptotic e_ect on human skin keratinocytes and fibroblasts exposed to UVA and UVB radiation. Arch. Dermatol. Res. 2019;311:203–19.
10. Gertsch J, Leonti M, Raduner S, et al. Beta-caryophyllene is a dietary cannabinoid. Proceedings of the National Academy of Sciences of the United States of America. 2008;105:9099–104.
11. Hammell DC, Zhang LP, Ma F, et al. Transdermal cannabidiol reduces inflammation and pain-related behaviours in a rat model of arthritis. Eur. J. Pain. 2016;20:936–48.
12. I_and K, Grotenhermen F. An Update on Safety and Side E_ects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies. Cannabis Cannabinoid Res. 2017;2:139–54.
13. Jastrza¸b A, Ge¸gotek A, Skrzydlewska E. Cannabidiol Regulates the Expression of Keratinocyte Proteins Involved in the Inflammation Process through Transcriptional Regulation. 2019;8:827.
14. Klein T. Cannabinoid-based drugs as anti-inflammatory therapeutics. Nat Rev Immunol 2005;5:400–11.
15. Kozela E, Pietr M, Juknat A, et al. Cannabinoids Delta(9)-tetrahydrocannabinol and cannabidiol differentially inhibit the lipopolysaccharide-activated NF-kappaB and interferon-beta/STAT proinflammatory pathways in BV-2 microglial cells. J Biol Chem. 2010;285:1616-26.
16. Mechoulam R, Sumariwalla PF, Feldmann M, et al. Cannabinoids in Models of Chronic Inflammatory Conditions. Phytochem Rev. 2005;4:11–8.
17. Mechoulam R. Marijuana Chemistry, Metabolism and Clinical effects, Academic Press, New York. 1973;1-99.
18. Marihuana, Pharmacological Aspects of Drug Dependence, Springer Verlag. 1996;83-15.
19. Rajesh M, Mukhopadhyay P, Bátkai S, et al. Cannabidiol attenuates cardiac dysfunction, oxidative stress, fibrosis, and inflammatory and cell death signaling pathways in diabetic cardiomyopathy. J. Am. Coll. Cardiol. 2010;56:2115–25.
20. Sun S, Hu F, Wu J, et al. Cannabidiol attenuatesOGD/R-induced damage by enhancing mitochondrial bioenergetics and modulating glucose metabolism via pentose-phosphate pathway in hippocampal neurons. Redox Biol. 2017;11:577-85.
21. Thoppil RJ, Bishayee A. Terpenoids as potential chemopreventive and therapeutic agents in liver cancer. World journal of hepatology. 2011;3:228–49.
22. Watzl. Drugs of Abuse, Immunity and Immunodeficiency, Plenum Press, New York. 1991;63-70.
23. Wu HY, Goble K, Mecha M, et al. Cannabidiol-induced apoptosis in murine microglial cells through lipid raft. Glia. 2012;60:1182–1190.

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