DO CANNABINOIDS HAVE A ROLE IN THE TREATMENT OF RHEUMATIC AND AUTOIMMUNE DISEASES?

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Abstract. In recent decades there has been an increasing scientific research on the therapeutic potential of cannabinoids. Although their use for medicinal purposes dates back from ancient times, the misunderstanding of the mechanisms, by which they affect different organs and systems in the human body and the related side effects limit their introduction into the clinical practice. At this stage, the pathogenetic mechanisms, by which cannabinoids affect such heterogeneous diseases, remain elusive. There is a growing body of evidence that they have anti-inflammatory and antifibrotic effects, take part in the regulation of overactive immune response and has the therapeutic potential to relieve chronic pain. This review presents the physiological and pathophysiological role of the endocannabinoid system, the therapeutic potential of cannabis and synthetic cannabinoid analogues and their application in various rheumatic and autoimmune diseases, as well as considering the possible risks of this type of treatment.

Key words: cannabis, cannabinoids, endocannabinoid system, treatment

INTRODUCTION

The therapeutic potential of cannabis has been the subject of research and heated debate for decades, as it is demonstrated by numerous clinical studies. Along with its benefits, the use of medical marijuana has several adverse events and drug interactions that limit its mass legalization. With the adoption of the Single Convention on Narcotic Drugs by the United Nations, many countries have banned the use and distribution of cannabis due to negative effects on individual and public health [1]. On the other hand, over the years there has been a growing body of investigation in this field concerning the efficacy of cannabinoids in the treatment of chronic pain, insomnia, a broad range of rheumatic, neurologic, neoplastic, endocrine, psychiatric diseases, as well as autoimmune diseases. It is assumed that they can be useful not only for the relief of symptoms but also to determine the favorable outcome of a disease [1]. This review summarizes the data available in the literature related to the therapeutic potential of medical marijuana and its clinical application in various rheumatic and autoimmune diseases, taking into consideration the possible risks of such treatment.

ENDOCANNABINOID SYSTEM OF THE BODY:

Cannabinoids are divided into phytocannabinoids – cannabis plant extracts, synthetic cannabinoids and endocannabinoids. Medical marijuana belongs to the family Cannabaceae, genus Cannabis and contains a group of chemicals – cannabinoids. The most psychotropic cannabinoid is tetrahydrocannabinol (better known as THC). The other cannabinoids are cannabidiol (CBD), delta-8-tetrahydrocannabinol (CBN), cannabicyclol (CBL), cannabichromen (CBH), cannabigerol (CBG), cannabinol (CBT). They have less psychotropic effects than THC, but are related to the overall effect of cannabis on the organism [2]. Endocannabinoids and their receptors are found throughout the body – in the brain, in the cells of the immune system, endocrine glands, connective tissue and internal organs. This system fulfills different functions in different tissues, but the goal is always to maintain a stable internal environment of the body [1,2]. For instance, cannabinoids have the ability to suppress sensory stimuli, slow down the conduction of impulses on afferent sensory neurons, stabilize the nerve cell to prevent excessive firing, as well as blocking the release of proinflammatory cytokines from immune cells at the site of inflammation. Cannabinoids act through three different mechanisms on three different types of cells with one goal – to reduce the pain and injury-related damage [3].

Two separate cannabinoid receptors have been identified: 1. CB1, distributed widely throughout the central nervous system – spinal cord and most structures of the brain – cerebral cortex, hippocampus, hypothalamus, basal ganglia, cerebellum; peripheral
nervous system as well as to a lesser extent found in the gastrointestinal tract, heart, musculoskeletal system, endocrine glands, including the gonads. CB2, expressed primarily in cells and organs of the immune system and to a lesser extent in the nervous system [4, 6]. Many tissues contain both types of receptors leading to different effects upon stimulation [5]. CB1 receptors are related to many types of CNS affecting diseases, including a number of neurodegenerative ones, such as Huntington’s disease, multiple sclerosis (MS) and Alzheimer’s disease (AD) [4]. CB2 receptors play a significant role in inflammatory processes and regulation of the immune system, reduce chronic inflammatory and neuropathic pain while avoiding the adverse psychotropic side effects that can accompany CB1-receptor signaling [7] (table 1).

### Table 1. Cannabinoids in the treatment of different diseases and pathological conditions, probable mechanism of action and therapeutic effects

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Probable mechanism of action</th>
<th>Therapeutic effects</th>
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<tr>
<td>Rheumatoid arthritis</td>
<td>CB2 receptor agonists [14, 15]</td>
<td>Analgesic, anti-inflammatory and immunomodulatory effect [14, 15]</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>CB1 agonists [46]</td>
<td>Analgesic and sleep-enhancing effect [28, 29]</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>CB1, CB2, GRP55 and PPAR-gamma agonists [31]</td>
<td>Analgesic, anti-inflammatory effect, Chondroprotective effect [30, 31]</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>CB2 agonists [35]</td>
<td>Promoters of bone formation and inhibitors of bone resorption [32, 33, 34]</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>CB2 agonists inhibitors of the production of key proinflammatory cytokines by T-cells [22, 23]</td>
<td>Anti-inflammatory and immunomodulatory effect [22, 23]</td>
</tr>
<tr>
<td>Progressive systemic sclerosis</td>
<td>CB2 and PPAR-gamma agonists inhibitors of the release of growth factors responsible for the collagen synthesis [19, 19]</td>
<td>Anti-inflammatory and anti-fibrotic effect [18, 19]</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>CB1 and CB2 receptor agonists [4]</td>
<td>Anti-inflammatory, Immunomodulatory, Analgesic, antipsasmyolytic and neuroprotective effect [4, 5]</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>CB1 agonists mainly and to a lesser extent CB2 agonists [42, 43]</td>
<td>Neuroprotective effect and effect on motor disorders [42, 43]</td>
</tr>
<tr>
<td>Chronic pain</td>
<td>CB1 and CB2 agonists [38]</td>
<td>Suppression of the perception of nociceptive stimuli, blocking the transmission of impulses from afferent sensory neurons to the spinal cord and brain; Work synergistically with opioid drugs to relieve chronic pain [3, 38]</td>
</tr>
<tr>
<td>Insomnia</td>
<td>CB1 and CB2 agonists [57]</td>
<td>Accelerating the time needed to get into deep sleep as well as extending its duration [57]</td>
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<tr>
<td>Diabetes</td>
<td>Inhibition of CB1 receptors and activation of CB2 receptors [47]</td>
<td>Improving the function of insulin-producing beta cells in pancreas and increasing insulin sensitivity in peripheral tissues [47]</td>
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<tr>
<td>Glaucoma</td>
<td>CB1 agonists [49]</td>
<td>Reducing high intracocular pressure, Neuroprotective and antioxidant effect [50, 51]</td>
</tr>
<tr>
<td>Neoplastic diseases</td>
<td>CB1/ CB2 depending on the expression of corresponding receptors in tumor cells [55]</td>
<td>Inhibition of cancer cell proliferation, Appetite stimulation, Antiemetic effect in patients on chemotherapy [55]</td>
</tr>
</tbody>
</table>
and macrophages, and inhibits the release of proinflammatory cytokines from immune cells [10]. Thus CB2 activation results in suppression of T-cells and amelioration of the negative impact of autoreactive immune cells [10, 11, 12]. In addition, there is evidence that cannabinoids have the potential to alleviate symptoms of various autoimmune diseases such as rheumatoid arthritis, ulcerative colitis and Crohn’s disease, fibromyalgia, Huntington’s disease, multiple sclerosis and others [13]. For instance, they reduce chronic pain, muscle spasticity and symptoms of inflammation associated with some of these pathological conditions [3, 13].

**IS CANNABIS EFFECTIVE FOR THE TREATMENT OF RHEUMATIC DISEASES?**

Up to now there is limited data to support the use of cannabinoids in rheumatology. They are thought to be particularly useful as the main clinical manifestations of rheumatic diseases are pain and inflammation. Cannabis is known for its analgesic effect due to the ingredient THC. The expanding legalization of medical cannabis and its therapeutic potential could be assessed as a safe opportunity [9, 10].

**Rheumatoid arthritis (RA)**

There is growing evidence suggesting that the endocannabinoid system, in particular the cannabinoid receptor CB2, plays a crucial role in the pathophysiology of RA [14]. This system inhibits synovial inflammation and pannus formation, which causes destruction of the articular cartilage leading to the formation of bone erosions in RA. In particular, specific activation of CB2 receptors can alleviate symptoms and slow the progression of the disease by inhibiting not only the production of autoantibodies, proinflammatory cytokines and metalloproteinases from the inflamed synovial tissue, but also by directly suppressing osteoclast activity [14, 15].

The efficacy and safety of cannabinoids on rheumatoid arthritis-related chronic pain were evaluated in a clinical trial by Blake et al. [16]. In a study of 58 patients, the authors concluded that cannabis possesses a significant analgesic effect without any serious side effects.

Another clinical trial focused on the use of cannabidiol (CBD) gel in rats. The researchers found that CBD gel binds to both CB1 and CB2 receptors leading to reduction in pain and inflammatory symptoms [17].

**Progressive systemic sclerosis**

Systemic sclerosis (SS) is an autoimmune chronic systemic connective tissue disease characterized by fibrosis of the skin and internal organs, microangiopathy, and activation of the immune system with autoantibody production. It is characterized by high morbidity and mortality. There is evidence that medical marijuana has anti-inflammatory and antimicrobial effects. By binding to CB2-receptors and PPAR-gamma receptors expressed on the surface of fibroblasts and immune system cells, cannabinoids inhibit the release of growth factors - transforming growth factor-beta, platelet-growing factor, which are responsible for fibroblast differentiation and increased collagen formation [18, 19]. Lenabasum, a synthetic CB2 and PPAR receptor agonist, provides promising results for the treatment of diffuse cutaneous scleroderma in the second phase of a clinical trial [20]. An improvement in the combined response index for SS was reported, which included a reduction in the modified Rodnan skin score (mRSS), an improvement in the HAQ-DI index, the patient’s and physician’s global assessment of his condition, and FCV% from baseline.

**Dermatomyositis**

Dermatomyositis is an idiopathic inflammatory myopathy with typical skin changes that precede, accompany, or follow muscle involvement with progressive proximal muscle weakness [21]. Cannabinoids, in particular synthetic CBD derivatives, inhibit the production of key proinflammatory cytokines by T-cells - IFN-α, IFN-β, TNF-alpha, which are involved in the pathogenesis of the disease [22]. In recent years, intensive clinical studies have been conducted on the efficacy and safety of ajulemic acid (Lenabasum) in the treatment of dermatomyositis, which provide evidence of subjective and objective control of disease activity without serious adverse reactions [18, 23].

**Psoriatic arthritis**

As for the effects of cannabinoids in patients with Psoriasis and Psoriatic arthritis (PsA), it has been reported that they have an important role in suppressing joint pain by inhibiting the activity of multiple proinflammatory cytokines and angiogenic growth factors. In addition, they can also delay the excessive proliferation of the epidermis and reduce the prevalence and severity of skin psoriasis [24, 25].

**Fibromyalgia (FM)**

Fibromyalgia is a syndrome characterized by chronic, diffuse musculoskeletal pain in the muscle itself or its fascia [26]. Pain accompanied by morning stiffness, fatigue and sleep problems are the main clinical signs of the disease [27]. Research and stud-
ies have demonstrated the effectiveness of cannabis in FM through its analgesic and sleep-enhancing effects [28, 29, 46].

**Osteoarthritis**

Topical administration of cannabinoids in patients with osteoarthritis reduces mechanical pain by inhibiting the activation of nociceptive nerve endings and the conduction of sensory stimuli along the ascending nerve pathways. In addition to their analgesic effect, cannabinoids have anti-inflammatory effects and reduce the onset of secondary synovial inflammation in osteoarthritis [30]. A study – conducted in 2016, found that a wide range of cannabinoid receptors – CB1, CB2, including the less well-known – GRP55 and PPAR, are expressed in chondrocytes of normal and degenerative articular cartilage. It was shown that activation of these receptors by cannabinoids can have a chondroprotective effect and slows the progression of the disease [31].

**Osteoporosis**

There are still no definite data on the efficacy of cannabinoids in increasing bone density and reducing fracture risk. Information from experimental studies and clinical trials is expected to „shed light“ on the exact mechanisms by which medical cannabis affects bone remodeling. The results available to date show that CB2 receptors are expressed in osteoblasts and osteoclasts, stimulate bone formation and inhibit bone resorption [32, 33, 34]. In a study examining women with postmenopausal osteoporosis, Karsak et al. (2005) concluded that polymorphism in the CNR-2 gene, which encodes CB2 receptors, is an important genetic risk factor for osteoporosis [35].

**USE OF CANNABINIDS IN OTHER PATHOLOGICAL CONDITIONS AND DISEASES**

**Chronic pain**

Increasingly, many clinical trials support the use of cannabis to relieve some types of chronic pain, including neuropathic pain and pain due to muscle spasticity [3, 36]. A study conducted at McGill Medical University in Canada included 21 patients, mean age of 45.4 years, with post-surgical and post-traumatic neuropathic pain [37]. Participants in the study received cannabis in four potencies (0%, 2.5%, 6% and 9.4% THC). The results showed less pain, rated at 10 cm Visual Analogue scale (VAS scale), better mood, improvement of sleep and better quality of life in patients taking cannabis.

Cannabinoids are supposed to act on a central and peripheral level by suppressing pain sensitiv-
tion which acts as hallmark feature of the disease [44]. Furthermore, in comparison to Donepezil and Rivastigmine, THC is a significantly stronger inhibitor of amyloid-beta-peptide aggregation. The results of the study elucidate the mechanism by which THC directly influences the pathogenetic processes in Alzheimer’s disease [44]. Another survey in 2017 proved the role of cannabidiol and the use of combined synthetic analogues (THC-CBD) in delaying the course of the disease due to their neuroprotective effect and anti-inflammatory properties [45].

**Diabetes**

Scientists at the Oxford Biomedical Research Center have found that marijuana extract has the ability to regulate blood glucose levels. Preclinical data show that taking cannabis extract twice daily has beneficial effects in diabetes such as improving the function of insulin-producing beta cells in pancreas and increasing insulin sensitivity in peripheral tissues thus reduces serum glucose levels [47].

**Glaucoma**

Several studies in patients with glaucoma published in 1971 show that marijuana can reduce intraocular pressure by nearly 25% [48]. Until the discovery of cannabinoid receptors in the human eye, it was previously suggested that the decrease in intraocular pressure is a result of a decrease in blood pressure caused by marijuana use [48]. To date, the endocannabinoid system plays a far more crucial role in controlling high intraocular pressure as it has neuroprotective and antioxidant effects and can regulate the production and drainage of intraocular fluid [49, 50, 51].

**Neoplastic diseases**

Being in a contact with cancer cells, cannabinoids disrupt many biochemical processes responsible for their survival, inhibit cancer cell proliferation, migration and induce their apoptosis. The antitumor activity of cannabinoids depends on the level of cellular expression of CB1 and CB2 receptors in the different types of cancer. Various researchers have suggested that THC, which binds primarily to CB1 and to a lesser extent to CB2 receptors, can be used as part of the therapeutic approach in breast, prostate and bone cancer [52, 55]. Besides, cannabis is known for its pleotropic effect to stimulate appetite and reduce weight loss in patients with neoplastic disease [54]. Approved by The US Food and Drug Administration (FDA), the synthetic THC derivatives – Dronabinol and Nabilon, are widely used in the prevention of nausea and vomiting caused by cancer chemotherapy [53, 56].

**Insomnia**

Low doses of THC before sleep significantly stabilize the sleep cycle by accelerating the time required to get into deep sleep phase and by increasing the duration of the slow-wave or delta phase [57]. This is essential for eliminating overall stress and maintaining the normal activity of the immune system [57].

**The most common side effects of cannabinoid use:**

1. Drug dependence and tolerance [58, 60, 62].
2. Central nervous system – altered perception (visual, auditory, tactile), memory impairment, loss of coordination, cognitive disorders, difficulties associated with learning and problem solving [60].
3. Mental disorders – hallucinations, delusions [54, 62], anxiety disorders [59].
4. Respiratory system – dyspnea, infections of the lower respiratory tract [65].
5. Gastrointestinal tract – vomiting, diarrhea syndrome [65].
6. Heart effects – the risk of a heart attack is four to five times higher within the first hour after cannabis use [61].
7. Effects of exposure during pregnancy – Prenatal exposure to marijuana can lead to abnormal neuropsychiatric development in the periods of growth, changes in perception of visual stimuli, tremor, attention and memory deficit [63, 64].

**Conclusion**

To date, there are controversial points of view in the scientific society about the use of cannabinoids for medical purposes. Therefore, further intensive clinical trials and results from real practice are needed to critically evaluate the efficacy and safety of cannabis in various fields of medicine which would probably answer many of the questions we face. Clarifying the physiological and pathophysiological role of the endocannabinoid system and finding a balance between benefits and risks is a starting point for future research. At this stage, the pathogenetic mechanisms by which cannabinoids affect such heterogeneous diseases remain elusive. Time, data from clinical trials and daily clinical practice will show whether cannabis will find its place in the comprehensive therapeutic approach in patients with rheumatic and autoimmune diseases.


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