CANNABIS SATIVA L. A NATURAL, LOCAL SOURCE OF CANNABINOIDS IN STRENGTHENING HUMAN HEALTH

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Abstract

This article provides a bibliographic synthesis regarding the importance of endocannabinoids from the species Cannabis sativa. Cannabinoids are the most intensively studied group of compounds, particularly because of their wide range of pharmacological effects on humans, including psychotropic activities. Most of the biological properties associated with cannabinoids are related to their interactions with the human endocannabinoid system. Endocannabinoids regulate or modulate a variety of physiological processes, including appetite, pain perception, mood, memory, inflammation, insulin sensitivity, and fat and energy metabolism. CBD (cannabidiol) exhibits anti-anxiety, anti-nausea, anti-arthritis, antipsychotic, anti-inflammatory, and immunomodulatory properties. In preclinical models of central nervous system diseases (such as epilepsy, neurodegenerative diseases, schizophrenia, multiple sclerosis), mood disorders, and central modulation of feeding behavior, CBD has also demonstrated strong antifungal and antibacterial properties, including remarkable efficacy against methicillin-resistant Staphylococcus aureus (MRSA). Additionally, cannabidiol possesses anti-inflammatory and anticancer properties. We believe that Cannabis sativa holds particular interest for cultivation and utilization aimed at enhancing human health.

Key words: *Cannabis sativa*, endocannabinoids, human health

Hemp, *Cannabis sativa* L. is an herbaceous species that belongs to the genus *Cannabis*, family *Cannabaceae*, and is native to Central Asia, used by humans for over 4,000 years. The plant has been utilized in ancient folk medicine for treating or alleviating various diseases (Alexander S., 2016). This fast-growing plant has recently experienced a resurgence of interest due to its multifunctional applications: it is indeed a treasure trove of phytochemicals and a rich source of both cellulose and woody fibers, energy biomass (Tabără V., 2009; Kreuger E. *et al*, 2011; Alexander S.P., 2016; Kraszkiewicz A. *et al*, 2019; Wawro A. *et al*, 2019; Ţîţei V., 2022; Melnic V. *et al*, 2023; Ţîţei V. *et al*, 2023; Visković J. *et al*, 2023).

Cannabinoids are biologically active substances derived from cannabinol. These substances are found naturally in plants from the hemp family. Endogenous cannabinoids are often referred to as anandamides—neurotransmitters with a different chemical structure but a similar impact on the body. The inflorescences and leaves of cannabis contain over 60 different cannabinoids. As the plant develops, cannabidiol (CBD) predominates, which is then converted into tetrahydrocannabinols (THC), and as the plant matures, these break down into cannabinols (CBN). All cannabinoids are fat-soluble substances. When they enter the body, they accumulate in lipid-rich tissues (brain, lungs, internal reproductive organs) and are gradually released into the circulatory system.

Cannabidiol (CBD) is one of the main cannabinoids present in Cannabis sativa. It is found in the inflorescences and leaves of hemp, partially in the form of butyl analogs, cannabidivarin, and cannabidiolic acid. Its maximum concentration is reached before flowering, after which it transforms into tetrahydrocannabinols (THC). Cannabidiols does not have psychotropic properties and can block some of the unpleasant effects of tetrahydrocannabinols (particularly the so-called "paranoia"). Recent experiments have shown that cannabidiol and cannabidiolic acid are responsible for the antibacterial effect of freshly pressed hemp juice, known since ancient times. These substances can effectively suppress a range of microorganisms, including penicillin-resistant staphylococci and other antibiotics. Additionally, there is a very high probability that cannabidiol

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may significantly help with motor disorders, epilepsy, multiple sclerosis, and more. One of the main biologically active substances in the biomass of *Cannabis sativa* L. is cannabinol (CBN). It is found in the inflorescences and leaves of hemp, partially in the form of butyl analogs and cannabivarin. Cannabinol reaches its maximum concentration during seed ripening as tetrahydrocannabinols and its analogs break down. Cannabinol has a moderate psychotropic effect (ten times weaker than tetrahydrocannabinols); products with a dominance of cannabinols are considered low quality (Melnic V. *et al*, 2023).

Scientific interest in cannabinoids arose after the discovery of the main psychoactive component, Δ9-tetrahydrocannabinol. Subsequently, receptors in the brain were identified that interact with cannabinoids, as well as endogenous cannabinoid ligands (EC), along with the enzymes responsible for their synthesis, transport, and degradation, forming the endocannabinoid system (ECS).

Interest in endogenous cannabinoid ligands has steadily increased in recent years, especially after discovering their important role in cognitive functions. They regulate synaptic transmission in the brain, mediate numerous forms of plasticity, and control neuronal energy metabolism. ECs exert their effects through a variety of mechanisms and interactions with neurotransmitters, neurotrophic factors, and neuropeptides.

The main functions of ECs in the brain are retrograde synaptic signaling and neuromodulation, which help maintain cellular homeostasis. There is extensive literature indicating a protective effect of ECS activation in human neurodegenerative diseases and in animal models of cognitive deficits. This analysis examines the evidence demonstrating the effects of cannabinoid medications and ECS activation on cognitive function in normal brains and in neurodegenerative diseases, Alzheimer's disease, and temporal lobe epilepsy (Kichigina V.F., 2021; Shubina L.V., 2015; Bossong M.G. *et al*, 2013).

Anti-Anxiety Effect

The first scientific studies demonstrating that CBD + THC from *Cannabis sativa* has an anti-anxiety effect were conducted in 1982. Experiments on a sample of eight individuals with an average age of 27 highlighted that administration of CBD + THC significantly alleviated anxiety, establishing scientifically that *Cannabis sativa* has an anti-anxiety effect on humans (Zuardi A.W. *et al*, 2006).

Subsequent research revealed that CBD has beneficial effects in cases of social anxiety disorders. Specifically, administration of CBD resulted in a significant reduction in anxiety levels, somatic symptoms, and negative self-evaluation among the participants (Bergamaschi M.M. *et al*, 2011).

In another study, administration of a single 400 mg dose of CBD to individuals suffering from social anxiety disorders contributed to a subjective reduction in anxiety, reduced activity in the left parahippocampal gyrus, hippocampus, and inferior temporal gyrus, and increased activity in the right posterior cingulate gyrus. These results suggest that CBD reduces anxiety in social anxiety disorders and that this is related to its effects on activity in the limbic and paralimbic brain areas (Crippa J.A.S. *et al*, 2011). Research involving the administration of 600 mg of CBD to patients with anxiety demonstrated a trend toward reduced anxiety (fear in patients), showing a distinct effect on neural responses, acting on activation in limbic and paralimbic regions, and contributing to reduced autonomic arousal and subjective anxiety. Additionally, it was established that the anxiolytic action of CBD occurs through modulation of prefrontal-subcortical connectivity via the amygdala and anterior cingulate (Fusar-Poli P. *et al*, 2009).

Anti-Nausea and Vomiting Effect

Nausea and vomiting are among the most distressing symptoms reported by cancer patients undergoing treatment. With currently available treatments, vomiting and especially nausea remain problematic, highlighting the need for alternative therapies. In vitro and in vivo research has demonstrated the efficacy of CBD in managing nausea and vomiting, showing significant potential for evaluation in clinical studies due to its enhanced ability to reduce nausea and/or vomiting (Rock E.M. *et al*, 2021).

Considerable evidence indicates that manipulating the endocannabinoid system regulates nausea and vomiting in humans and other animals. The anti-emetic effect of cannabinoids has been demonstrated in a wide variety of animals capable of vomiting in response to toxic challenges. Animal experiments suggest that cannabinoids may be particularly useful in treating nausea and anticipatory nausea symptoms, which are more difficult to control in chemotherapy patients and are less managed by currently available conventional pharmaceutical agents. The primary non-psychoactive compound in cannabis, cannabidiol (CBD), also suppresses nausea and

vomiting within a limited dosage range. The anti-nausea/anti-emetic effects of CBD may be mediated by the indirect activation of 5-HT1A somatodendritic receptors in the dorsal raphe nucleus; activation of these autoreceptors reduces the release of 5-HT in terminal regions of the forebrain. Preclinical research indicates that cannabinoids, including CBD, may be clinically effective for treating both chemotherapy-induced nausea and vomiting or other therapeutic treatments (Parker L.A. *et al*, 2011).

Anti-Arthritic and Anti-Inflammatory Effect

Arthritis and inflammatory conditions require effective therapies, but conventional medications often have side effects. Recent research has highlighted that essential oil from *Cannabis sativa* administered in models with induced inflammatory conditions (in the ear and paw) resulted in a significant reduction in ear weight in the xylene-induced ear swelling test, indicating a potential inhibition of neutrophil accumulation. In the carrageenan-induced paw inflammation test, it reduced paw volume, suggesting interference with edema formation and leukocyte migration. Additionally, in the paw inflammation test, a decrease in the volume of the contralateral paw was observed, along with restored body weight and reduced levels of C-reactive protein (Kabdy H. *et al*, 2024).

Recent studies indicate that cannabinoids exhibit anti-inflammatory effects by activating cannabinoid receptor type 2 (CB2), which decreases cytokine production and immune cell mobilization. Conversely, activation of cannabinoid receptor type 1 (CB1) on immune cells is pro-inflammatory, while CB1 antagonism provides anti-inflammatory effects by enhancing β2-adrenergic signaling in joints and secondary lymphoid organs. Furthermore, the non-psychoactive cannabinoid cannabidiol (CBD) has demonstrated anti-arthritic effects independent of cannabinoid receptors. In addition to controlling inflammation, cannabinoids reduce pain by activating central and peripheral CB1 receptors, peripheral CB2 receptors, and non-cannabinoid receptor targets sensitive to CBD (Lowin T. *et al*, 2019).

Antipsychotic Action

The primary antipsychotic effects of Cannabis sativa plants are attributed to CBD, which has demonstrated antipsychotic properties in both rodents and rhesus monkeys. Following several individual treatment trials, the first randomized, double-blind, controlled clinical study showed that in acute schizophrenia, cannabidiol exhibits antipsychotic properties comparable to the antipsychotic medication amisulpride, with a superior side effect profile resembling that of a placebo. As the clinical improvement with cannabidiol was significantly associated with increased levels of anandamide, it appears that its antipsychotic action is based on mechanisms related to elevated anandamide concentrations (Rohleder C. *et al,* 2016). Further research involving volunteers indicated that CBD from Cannabis sativa has antipsychotic effects, suggesting that CBD has a pharmacological profile similar to that of atypical antipsychotic medications. Additionally, reports from schizophrenia patients treated with CBD and preliminary findings from a controlled clinical study comparing CBD to an atypical antipsychotic have confirmed that this cannabinoid may serve as a safe and well-tolerated alternative treatment for schizophrenia (Zuardi A.W. *et al,* 2006).

Effects in Metabolic Syndromes

CBD may have beneficial effects for individuals with obesity, impaired glucose and lipid metabolism, hypertension, and non-alcoholic fatty liver disease (NAFLD). It appears that CBD helps maintain insulin sensitivity in adipose tissue and reduces glucose levels, making it a potential target in this type of metabolic disorder, although some research findings are inconclusive. CBD shows promising results in treating various lipid disorders, with some studies demonstrating its positive effects by lowering LDL and increasing HDL levels. Despite their likely efficacy, CBD and its derivatives will probably remain adjunctive treatments rather than primary therapeutic options.
Studies have also shown that CBD has positive effects in patients with hypertension, even though its hypotensive properties are modest. However, CBD may be used to prevent increases in blood pressure, stabilize it, and provide a protective effect on blood vessels. Preclinical studies have indicated that cannabidiol's effects on NAFLD may be potentially beneficial in treating metabolic syndrome and its components (Wiciński M. *et al,* 2023).

Neuropathic Pain

Neuropathic pain is a clinical condition resulting from an identifiable injury or disease of the somatosensory nervous system, which can be caused by certain abnormalities, trauma, or underlying conditions such as stroke or diabetes.

According to WSIB policy, cannabis can be prescribed for cases of neuropathic pain that are refractory to standard pharmaceutical and non-pharmaceutical treatments. An acceptable pharmaceutical treatment must involve at least three first-line and/or second-line medications along with a pharmaceutical cannabinoid.

Numerous systematic reviews have reported the efficacy of medical cannabis preparations (Cannabis sativa) for the treatment of neuropathic pain in general, and particularly in patients with HIV/AIDS. Furthermore, one of these reviews reported the effective use of THC and FAAH inhibitors for neuropathic pain and in cancer chemotherapy. Research indicated that median pain was reduced twice as much (34% compared to 17%) in the cannabis group versus the placebo group. A recent major systematic review reported a reduction in neuropathic pain (odds ratio of 1.37, p-value <0.05) with cannabinoids (combining pharmaceutical and non-pharmaceutical formulations), corresponding to achieving at least a 30% reduction in symptoms. Three recent clinical guidelines have reported strong, reasonable, and consistent evidence for the use of medical cannabis and cannabinoids in treating patients with neuropathic pain.

It is well known that *Cannabis sativa* exhibits pronounced beneficial effects in conditions such as schizophrenia, epilepsy, multiple sclerosis, Parkinson's disease, Alzheimer's disease, dementia, insomnia, diabetes, anorexia, and more (Workplace Safety Insurance Board, 2021).

Antifungal and Antibacterial Effects

Research on five different strains of cannabis has revealed that all cannabis varieties were effective to varying degrees against both Gram-positive and Gram-negative bacteria, as well as against the germination of spores and vegetative growth of pathogenic fungi. These effects were not correlated with the content of major cannabinoids such as CBD or THC, but rather with the presence of a complex terpene profile. The efficacy of the extracts allowed for a reduction in the doses required for a widely used commercial antifungal to prevent fungal spore development (Vozza Berardo M.E. *et al*, 2024).

Other studies indicate that extracts obtained from Cannabis sativa exhibit pronounced effects against Gram-positive bacteria (such as *Staphylococcus aureus, Streptococcus alpha hemolyticus, Streptococcus beta hemolyticus, Enterococcus, Diplococcus pneumoniae, Bacillus subtilis, Bacillus anthracis, Bacillus pumilus, Corynebacterium diphtheriae, Corynebacterium cutis, Erysipelothrix rhusiopathiae, Clostridium perfringens, Mycobacterium tuberculosis, Micrococcus flavus, Listeria monocytogenes, and T. mentagrophytes*), Gram-negative bacteria (such as P. *vulgaris, Bordetella bronchiseptica, Helicobacter pylori*, and *E. coli*), and fungi (such as *Candida albicans, Aspergillus niger, A. parasiticus, and A. oryzae*) (Schofs L. *et al*, 2021).

CONCLUSIONS

The present literature review study highlights the importance of hemp crops, *Cannabis sativa* as a valuable source of endocannabinoids, emphasizing the remarkable therapeutic potential of these compounds for human health. Cannabinoids, particularly CBD (cannabidiol), have demonstrated a wide range of pharmacological effects, including anti-inflammatory, antipsychotic, anticancer, and antibacterial properties. The interactions of cannabinoids with the human endocannabinoid system regulate essential physiological processes, making hemp crops a major resource of interest for research and utilization aimed at improving public health.

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