

CANNABIDIOL AND ITS EFFECTS IN HUMAN

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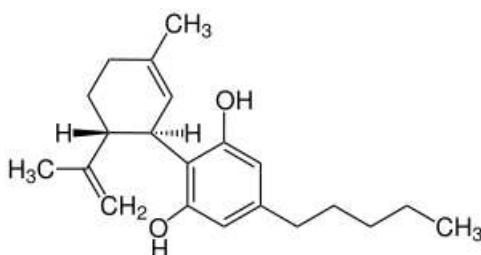
Shevchuk M.M.

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Medical University (Ukraine).**ABSTRACT**

The term "cannabinoids" is used to refer to the secondary metabolites of cannabis contained in hemp, their alteration products and synthetic analogues. At present, the status of cannabinoids as medicinal products is rather controversial. Search for ways of influencing the components of endocannabinoid system is one of the areas of fundamental research in the world pharmacology. Trans-delta-9-tetrahydrocannabinol (Δ^9 -THC) and cannabidiol (CBD) are the most well-known and comprehensively studied cannabinoids. Psychotropic and addictive effects of the plant are attributed to tetrahydrocannabinol. Experimental and some clinical studies have established the effectiveness of antagonists of cannabinoid CB1 receptors as anorectic agents, in the treatment of schizophrenia, alcohol addiction, disorders of cognitive functions and memory, in some neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases, Huntington's chorea and some other diseases. Endogenous cannabinoids are also considered as tissue regulators. At present, there are also clinical and experimental preliminary studies of cannabinoid receptor agonists for such problems as pain, skin lesions of various genesis, neuroprotection, cerebral ischemia, neoplastic neoplasms, rheumatoid arthritis, glaucoma, diseases of the alimentary tract, elevated intracranial pressure, multiple sclerosis, bronchial asthma. Current status of the use of cannabis compounds in global medical practice, and related regulatory issues are currently open. Issues of wider use of active substances in medical practice for certain diseases are under discussion. This requires the development of certain recommendations regarding changes in regulatory approaches in order to ensure access of patients in Ukraine to this group of medicines and biologically active substances. Legalization of medical marijuana is an opportunity to study effects, to create safe and convenient drug dosage forms, and to control this process in the legal context.

KEYWORDS: cannabidiol (CBD), cannabis(hemp), endocannabinoids, endocannabinoid system, legal aspects of CBD use.

Cannabidiol (CBD) is one of more than 113 cannabinoids found in hemp. CBD is the main phytocannabinoid, which share in the plant extract can reach 40%. CBD does not have any psychoactive properties, however along with CBD in hemp we get tetrahydrocannabinol (THC), which has a pronounced psychoactive effect.^[1,2]



Cannabidiol is not on the "List of Narcotics, Psychotropic Substances and Precursors", but this list includes "Cannabis, cannabis resin, cannabis extracts and

tinctures", which may be in conflict with the legal status of cannabidiol.

List of narcotics, psychotropic substances and precursors allows the cultivation of plants of the hemp genus for industrial purposes, with the exception of the production and (or) manufacture of narcotic drugs and psychotropic substances, and is allowed provided that the seeds collected from the varieties of plants whose dried straw contains tetrahydrocannabinol do not exceed 0.08 percent. Modern cultivars of hemp bred for the production of cannabidiol contain a sufficiently small percentage of tetrahydrocannabinol, and can be approved for cultivation in Ukraine.^[4]

Cannabis is illegal, and isolated CBD is legal in most of world. Since CBD is an extract from the hemp plant, its legality is enshrined in many regulations and legislations.^[3] This means that currently, not everyone has the legal right to grow, produce or buy products

containing CBD. Each country has its own laws that are constantly changing regarding the use and synthesis of CBD, each country independently determines the level of legality of products synthesized from marijuana. Synthetic marijuana causes the greatest impact on the body. Spice refers to dried parts of grass treated with narcotic solution, these are smoking mixtures, spice, mixes, "Africa", "feng shui souvenir", JWH, being very dangerous drugs. A synthetic drug is an artificial analogue of cannabis, but much stronger and more dangerous. Spices and other drugs kill more than 10,000 people a year in Ukraine.

EU directives regulate the sale of products containing CBD in most European countries. According to the EU legislation, it is allowed to grow hemp with a THC level in the dry residue of the dry plant with less than 0.2% of weight. Countries are free to interpret the legality, rules and level of punishment according to their current legislation. Toleration of crimes related to the illicit traffic, synthesis and sale of CBD products varies greatly in different European countries, and therefore, the way of CBD law enforcement may change.^[6]

U.S. Federal law states that hemp-derived CBD containing less than 0.3% of THC is legal for growing, transportation and sale in the U.S. Some states have different views and interpretations of CBD and products containing CBD, meaning that each U.S. state has different laws. For example, despite federal approval, CBD is an illegal product in three U.S. states: Nebraska, South Dakota, and Ohio.^[5]

In South America, the CBD products market is rapidly growing. This is due to global changes regarding the dangers of hemp and hemp products. South American countries are beginning to recognize medical benefits cannabis can offer, which is reflected in current legislation on the use of medical marijuana.^[7]

In medicine, some active substances of hemp are used for certain diseases: migraine, neoplasms, pain relief, schizophrenia, disorders of cognitive functions, neurodegenerative diseases. In Ukraine, there is a need for developments of changes in regulatory approaches to ensure patients' access to this group of medications.

Connection of the study with planned scientific research projects

The results of these studies were obtained by the authors during the research project of Danylo Halytskyi Lviv National Medical University (Department of Pathological Anatomy and Forensic Medicine) on "Study of pathomorphological features of diseases of thyroid gland, cardiovascular, digestive, urinary and reproductive systems, and the perinatal period, for improving their morphological diagnosis" (state registration No. 0118U000100. Minutes No. 7 dated 15.04.2015).

INTRODUCTION

Hemp (*Cannabis*) is a genus of herbaceous plants of the hemp family (*Cannabaceae*), which includes several species: cultured hemp (*Cannabis sativa*), Indian hemp (*Cannabis indica*), wild hemp (*Cannabis ruderalis*). Hemp has long been used by humans as food (seed). The main ingredients of hemp seeds include highly digestible protein (20-25%), polyunsaturated fatty acids (PUFA), a large amount of lipids (25-35%) and carbohydrates (20-30%) with high content of insoluble fiber. Hemp seed protein is indicated for human and animal consumption, and consists mainly of high-quality, highly digestible edestin and albumin proteins containing essential amino acids. Hemp seeds are a source of PUFAs, linoleic acid (LA; omega-6) and alpha-linolenic acid (ALA; omega-3), are beneficial and considered to be balanced for human nutrition in the amount of 3:1. Content of LA varies from 64 to 72% of the total fatty acid composition. This range may result from different hemp varieties, cultivation techniques, and processing and storage conditions. These fatty acids must be consumed through food, as they are the basis of proper nutrition, but cannot be synthesized endogenously. Dietary Guidelines suggest that 15–20% of daily calories should come from fat, and about one-third of that fat should be essential fatty acids in the amount of 3:1. Three tablespoons of hemp seed oil can provide the amount necessary to achieve this dietary goal.^[8,35]

Hemp was used as an agricultural crop along with cereals, beans and rice. Stems of these plants contain quite strong fibers, and threads, clothes, shoes, cords, ropes and cables were made of them. Narcotic products were also obtained from hemp raw materials. Hemp originates from Central and Western Asia. Hemp is one of the most traditional psychotropic drugs for humans. Human population has been using hemp long before its first written evidence, so it is difficult to establish the onset. Marijuana and hashish are the most famous forms of the hemp plant. Marijuana is comprised of dried leaves and flowers of the hemp plant. Hashish (Plant resin) is the Arabic name for Indian hemp. Hemp contains various mixtures of structurally active substances, such as cannabinoids, terpenoids, flavonoids, and alkaloids. In particular, the term "cannabinoids" is used to refer to the secondary metabolites of cannabis contained in hemp, their alteration products and synthetic analogues. In total, there are more than 600 different chemical compounds, over 120 of which are unique to this plant.^[8] There are ongoing cannabis and its active compounds debates worldwide regarding the use of cannabis compounds in medical practice, and the issue of its legal regulation remains open. The problem of wider use of active hemp substances for certain diseases in medical practice becomes relevant occasionally. This issue is quite relevant for Ukraine, requiring the development of appropriate recommendations for changing regulatory approaches to ensure access of patients in Ukraine to this group of pharmaceutical products and biologically active substances.^[4]

Aim of the study is to analyze the properties, effects in human, and use in medical practice of hemp (medical cannabis and its active compounds, in particular CBD).

Study Object and Methods

Search and analysis of scientific literature was conducted on the research topic in such databases as PubMed and Google Scholar.

RESULTS AND DISCUSSION

Hemp and its seeds have long been used by people as food, material for various articles, and as raw material for narcotic products. Hemp contains many different substances, the most important of which are phytocannabinoids. Hemp tetrahydrocannabinol reveals the greatest psychotropic effect. In the initial stages, use of marijuana by young people does not cause serious health problems. Long-term use, however, has a negative effect on the development of fetus in pregnant females, on reproductive system, respiratory and cardiovascular systems, mental health and intelligence, mental disorders, loss of motivation and joy in living. Synthetic marijuana causes maximum harm. There are ongoing hemp and its active compounds debates worldwide. The issue of use of hemp compounds in the world medical practice remains unresolved, and its legal regulation remains open by now. As stated above, phytocannabinoids are the most important secondary metabolites of hemp. This group of compounds is found only in hemp, being the chemical substance of this plant which was described in sufficient detail. Trans-delta-9-tetrahydrocannabinol (Δ^9 -THK) and cannabidiol (CBD) are the most well-known and comprehensively studied cannabinoids. Psychotropic and addictive effects of the plant are attributed to tetrahydrocannabinol.^[9] Endocannabinoids (Greek: endo – from the inside + Latin: cannabis – hemp) are a group of biochemical regulators of many physiological processes. Endocannabinoids belong to endogenous lipid molecules acting on the same receptors as the active component of marijuana. Endocannabinoids are formed from phospholipid precursors that are found in cell membranes. They act locally and manifest their effect immediately. The system is activated and inactivated very quickly. Currently, the most comprehensively studied are anandamide and 2-arachidonoylglycerol (2-AG), whose synthesis pathways have been established. 2 types of receptors are described: CB1 and CB2. CB1 receptors are found in the brain structures, including hippocampus, basal ganglia, cortex, cerebellum, hypothalamus, limbic structures, brainstem, adipocytes, and in gastrointestinal tract. CB2 receptors are located on peripheral cells, in particular cells of the immune system.^[10]

CB1 receptor is widely distributed in the body and is coupled to a G protein. In the brain, it mediates most of the behavioral acts of cannabinoid drugs. Signaling events initiated by this receptor include closing of Ca²⁺ channels, opening of K⁺ channels, inhibition of

adenylate cyclase activity, and stimulation of protein kinases. These signaling pathways can modulate synaptic transmission and gene expression in neurons. An important function of cannabinoid receptors is the regulation of GABA formation. In the hippocampus, cannabinoids can modulate plasticity and, accordingly, can influence learning ability and memory. In the amygdaloid complex, inactivation of CB1 receptors causes anxiety-like behavior and certain aggression. In the basal ganglia, cannabinoids modulate motor function, and in the hindbrain, cannabinoid agonists can influence pain perception. It was found that inhibition of GABA release is involved in all these functions. Cannabinoids can also inhibit glutamate release in excitatory synapses in the hippocampus, cerebellum, and other brain regions, affecting the release of other neurotransmitters such as acetylcholine and biogenic amines. Endocannabinoid-dependent long-term depression in the brain may be involved in learning ability and addiction development. During nervous activity, cannabinoids suppress muscle hyperactivity, reduce the release of prolactin, luteinizing hormone, and growth hormone.^[34] Cannabinoids participate in modulation of the inflammatory response by inhibiting the activity of the inducible isoform of NO synthase. Endocannabinoid system modulates the use of food substances by acting in specific mesolimbic regions of the brain. In the hypothalamus, CB1 receptor agonists are the most important link in controlling appetite and absorption of nutritious substances. Both anandamide and 2-AG are capable of stimulating eating behavior. They regulate the processes underlying the enjoyment of food. Endocannabinoid system is also active in peripheral tissues, including adipocytes, hepatocytes, gastrointestinal tract, and skeletal muscles. In general, endocannabinoid system is involved in various physiological functions, many of which relate to post-stress recovery systems and maintenance of homeostatic balance. Cannabinoids are involved in neuroprotection, regulation of motor activity and means of controlling some phases of short-term memory, affect performance of cardiovascular system and respiratory organs, controlling heart rate, blood pressure and bronchial functions. Cannabinoids activate antiproliferative mechanisms in tumor cells, modulate immune and inflammatory responses.^[10,31]

Endocannabinoid system of human body is a general system of physiological post-stress recovery, which normally is inactive. It is temporarily activated in order to return the body's physiological systems to homeostasis. Thus, this system has an effect on metabolism, immunity, appetite, contacts of body cells.^[15] Endocannabinoid system also plays an important role in physical and psychological effects of cannabis in human. They are capable of binding to endocannabinoid ligands and exogenous ligands that are cannabinoids themselves, and to synthetic analogues.^[11] Each receptor responds to a certain type of cannabinoids, but there are also cannabinoids that do not distinguish between these receptors and interact with both. High concentration of

CB1 receptors is noted in areas of the brain associated with human behavior. In particular, these receptors are found in neurons of the hypothalamus and amygdaloid complex, which regulate appetite, manage stress and anxiety, limit nausea, and affect memory and emotional responses.^[11] CB1 receptors also have nerve endings where they reduce susceptibility to pain. This is the main reason for using them for pain relief. CB2 receptors are located on peripheral cells, particularly cells of the immune system. Their activation causes an immune response to inflammation, and this is important for the treatment of many chronic diseases.^[12,13] CB-1 receptor is expressed primarily in the brain (central nervous system, or "CNS"), but also in the lungs, liver, and kidneys. CB-2 receptor is expressed mainly in the immune system and hematopoietic cells, but further research has shown the existence of these receptors in the brain areas.^[18] Increasing evidence suggests that there are new cannabinoid receptors,^[15] being non-CB 1 and non-CB 2, which are expressed in endothelial cells and in the CNS. In 2007, binding of several cannabinoids to the G protein-coupled receptor GPR55 in the brain was described. Cannabinoid receptors are the most numerous in the central nervous system. Endocannabinoids are neurotransmitters by their chemical nature. The first discovered endocannabinoid substance is anandamide, which periodically appears in high concentrations in the nervous system. Chemical structure of tetrahydrocannabinol (THC) in hemp is similar to that of brain anandamide. This similarity allows the body to recognize tetrahydrocannabinol and alter healthy functioning of the brain. Endogenous cannabinoids also act upon areas of the brain that affect pleasure, memory, thinking, concentration, movement, coordination, sensory perception, and time perception. Because of THC's similarity to natural endogenous cannabinoids, it is able to bind to cannabinoid receptor molecules on neurons in these brain areas, and exert an activating effect on them, deranging various mental and physical functions and causing the effects described above.^[12] For example, THC is able to alter functioning of hippocampus and orbitofrontal cortex, those areas of the brain that allow a man to form new experiences and shift the focus of attention from reality. Thought process disorders hindering a person's ability to learn and perform complex activities are the consequences of marijuana use. THC affects healthy functioning of the cerebellum, brainstem nuclei, and basal ganglia, which regulate balance, motor coordination, and reaction time. The results of animal studies and a wealth of human studies suggest that influence of marijuana during the development of nervous system can cause long-term, sometimes even permanent, irreversible changes in the brain.^[13] Cognitive impairments in adult rats exposed to THC in adolescence are associated, in particular, with structural and functional changes in the hippocampus.^[12] According to the results of scientific research, it is suggested that the long-term use of marijuana leads to a decrease in the number of cannabinoid receptors in the brain. This is the result of the brain being overloaded

with active substances of hemp coming from the outside. At the same time, the brain protects itself by reducing the activity of its receptors. Scientists come to the conclusion that performance of mitochondria of neurons containing these receptors is inhibited.^[12] There are medical reports in the scientific literature about cases of heart attacks or myocardial infarctions, strokes and other cardiovascular side effects. In the initial stages of marijuana use by young people, it does not cause health problems. In adults and the elderly people, long-term marijuana use poses greater risks due to increased catecholamine levels, cardiac load, and carboxyhemoglobin levels. Marijuana may be a more common cause of myocardial infarction in the elderly people than it is generally recognized.^[13] Long-term use of marijuana affects the ability to learn and recognize faces, causes a decrease in the volume of gray matter of the brain, which can affect the level of intelligence. Prolonged use of marijuana affects the endocrinal profile of the body, especially in males. Their testosterone synthesis decreases, causing, accordingly, the decrease of sperm motility and libido.^[17,34] Side effects of using cannabis are:

- Psychiatric disorders, depression, nervous crisis, loss of intelligence^[29]
- When used by patients with schizophrenia, their psychic state can be provoked or worsened;
- Anxiety states and panic attacks may occur due to mental problems;
- Loss of motivation, joy in living;
- Hemp has an embryotoxic effect, therefore no amount of cannabis is allowed to use by pregnant females;
- Cannabis harms the reproductive system: it causes menstrual disorders, occurrence of pain in females, and problems with sexual potency and decreased libido in males;
- Possible lung problems, bronchitis, asthma.^[28]

At present, the status of cannabinoids as medicinal products is rather controversial. Search for ways of influencing the components of endocannabinoid system is one of the areas of fundamental research in the world pharmacology. Some drugs containing cannabinoid receptor ligands are used in medical practice. In particular, doctors in the United States prescribe tetrahydrocannabinol per os in order to prevent nausea and vomiting during tumor chemotherapy, and to stimulate appetite in case of significant weight loss in patients with acquired immunodeficiency syndrome. "Nabilone", the synthetic analogue of THC is used in Great Britain as an antiemetic agent. Good tolerance is an important advantage of cannabinoids. Although cannabis products often cause various side effects, the latter rarely require discontinuation of therapy or any treatment. Use of cannabinoid receptor agonists as drugs currently limits their narcogenic potential, ability to deteriorate cognitive functions, including short-term memory, as well as relatively rapid development of tolerance in relation to the most important effects. The last word has not yet been said regarding the optimal

choice of cannabinoids for this or that pathology, as well as the method of their administration and dosage, therapeutic effects and adverse events ratio, drug interaction. Their use causes side effects such as dizziness, drowsiness, inattention and disorders of mental activity.^[18,19,20,21]

Experimental and some clinical studies have established the effectiveness of antagonists of cannabinoid CB1 receptors as anorectic agents, in the treatment of schizophrenia, alcohol addiction, disorders of cognitive functions and memory, in some neurodegenerative diseases: Alzheimer's and Parkinson's diseases, Huntington's chorea. Endogenous cannabinoids are also considered as tissue regulators. At present, there are also clinical and experimental preliminary studies of cannabinoid receptor agonists for such problems as pain, skin lesions of various genesis, neuroprotection, cerebral ischemia, neoplastic neoplasms, rheumatoid arthritis, glaucoma, diseases of the alimentary tract, elevated intracranial pressure, multiple sclerosis, bronchial asthma.^[24,25,26,27] In addition to appetite stimulation and antiemetic activity, CB1 receptor agonists have neuroprotective properties (due to inhibition of glutamate release in the central nervous system). Their effectiveness has been established in motor function disorders (for example, muscular rigidity, tremors), in multiple sclerosis and spinal cord injuries, facial spasms and mental disorders (for example, depression), in Tourette's syndrome, dyskinesias occurring during the treatment of Parkinson's disease. Scientists have reported a pronounced antiepileptic effect of agonists of the endocannabinoid system, especially of cannabidiol. CB1 receptor agonists have a pronounced analgesic activity. Clinical studies suggest that smoking "medical" marijuana significantly relieves the condition of patients with postoperative and neuropathic pain, including patients with HIV-associated peripheral polyneuropathy. Therapeutic benefits are due to sedative, anxiolytic or analgesic effects of these drugs. Agonists of cannabinoid CB2 receptors have anti-inflammatory and immunosuppressive properties. Therefore, cannabis medications are indicated for Crohn's disease and other inflammatory enteropathies. Compounds that do not penetrate the blood-brain barrier could cause pain-relieving effect in inflammatory processes in the absence of side effects due to influence on central nervous system. Current status of the use of cannabis compounds in global medical practice and related regulatory issues are currently open. Issues of wider use of active substances in medical practice for certain diseases are under discussion. This requires the development of certain recommendations regarding changes in regulatory approaches in order to ensure access of patients in Ukraine to this group of medicines and biologically active substances. There are no safe interventions, and pros and cons of any treatment must be assessed. Legalization of medical marijuana is not a license to smoke weed, but an opportunity to create safe and

convenient drug dosage forms, and to control this process within the legal framework.

Cannabis market development prospects

Cannabis is legal in 22 countries of the world. Legalization means the ability to create safe and convenient drug dosage forms, as well as to control this process, but not a legal sale of drugs. Niagara Community College (Ontario, Canada) has started the admission of students for the commercial cannabis production program since September 2018. This is a legitimate stage of the civilization evolution in the context of entry into the market of a new source of raw materials and creation of a business industry. In Ukraine, a non-commercial enterprise, "Ukrainian Technical Hemp" Association was launched, aimed at promoting such line of economic operations as cultivation of hemp in the Ukrainian market.^[4] On April 7, 2021, the Cabinet of Ministers approved using of two new cannabinoid-based medicines in Ukraine. In addition to "Dronabinol", "Nabilone" and "Nabiximols" were also approved. "Nabilone" is a synthetic cannabinoid that mimics the action of THC. "Nabilone" is used to treat side effects of chemotherapy in oncology patients. "Dronabinol" helps in the management of severe anorexia in people with AIDS. "Nabiximols" is a standardized cannabis extract with equal content of THC and cannabidiol, it can be prescribed for the treatment of multiple sclerosis. The three mentioned drugs are on the Restricted Substance List, but cannabis extract and tetrahydrocannabinol, the active pharmaceutical ingredient of these drugs, is still on the list of prohibited substances.

CONCLUSIONS

Long-term use of marijuana leads to a decrease in the number of cannabinoid receptors. Current status of the use of cannabis compounds in global medical practice and related regulatory issues are currently open. Issues of wider use of active substances for certain diseases in medical practice are under discussion. They require the development of certain recommendations for changing regulatory approaches to ensure access of patients in Ukraine to this group of pharmaceutical products and biologically active substances. Legalization of medical marijuana is an opportunity to create safe and convenient drug dosage forms, and to control this process in the legal context.

Directions for future research

Future use of cannabis for the management of various diseases requires study and control of this process within the legal framework.

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