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Review

Beneficial Effects of Cannabis Sativa Extract on Oxidative Stress

Selim Soydan[1], Begüm Arda[1], İlknur Altuntaş[1], Oytun Erbaş[1]

ABSTRACT

Cannabis sativa L. subspecies *sativa* is a subspecies of the genus Cannabis (Cannabaceae), also known as industrial hemp. It is a herbaceous and double-jawed plant. Tetrahydrocannabinol (THC), a psychoactive compound found in cannabis plants, and the non-psychoactive cannabidiol (CBD) are essential compounds in industry and medicine. These compounds are very similar to endocannabinoids, which are found in the human body. As a result, both compounds have the potential to interact with the body's endocannabinoid system. They exhibit chemical activity in areas affected by oxidative stress, such as the cardiovascular system, muscle development, liver and lung function, reproductive function, metabolism, neurological activities, and cell aging. Since the human body's free radical and antioxidant levels are destabilized, antioxidants fail to neutralize free radicals, resulting in oxidative damage, i.e. a stress effect. This balance in the body can be influenced by compounds like THC and CBD acting on cellular receptors. Thus, the occurrence of various diseases is observed. This review examined the effect of the active substances in the cannabis plant on oxidative stress and the diseases that develop as a result of this stressful situation.

Keywords: Cannabinoid, endocannabinoid, hemp, oxidative stress, tetrahydrocannabinol

Cannabis has been widely used in some cultures and health for many years, particularly in India and China, and it plays an important role in spasticity and the treatment of most pains in modern medicine.[1] Cannabidiol (CBD) and tetrahydrocannabinol (THC) are the two most commonly studied cannabinoid class substances in terms of structural form.[2] Cannabinoid delta-9-tetrahydrocannabinol (Δ9-THC) has the most potent psychoactive effects. CBD, on the other hand, has no effect on the central nervous system (CNS), making it a non-psychoactive compound.[3]

Cannabinoid receptors control ongoing physiological events like mood, memory, and appetite. They activate a group of cellular receptors known as type 1 (CB1) and type 2 (CB2) in the body via these receptors.[4] Because of their chemical function, cannabinoid receptors form an endocannabinoid system (ECS) with endogenous cannabinoids. Endocannabinoids are neuromodulator system that is important in the development of the CNS, in response to environmental and endogenous types of attacks, and in synaptic plasticity.[5] The ECS is a specific molecular system that regulates homeostasis stability. Furthermore, it has become a more common pharmacotherapy target in recent years. Endocannabinoids, which are the amid, ether, and ester forms of long-chain polyunsaturated fatty acids (PUFA), can continue to function as the primary cannabinoid receptor ligands with these properties.[6] Secondary metabolites and phytochemicals can interact with ECS. This condition has been discovered in a variety of plants. Cannabinoids are extremely important for both animals and plants. They are involved in the active regulation of pathological and physiological functions.[7] Tetrahydrocannabinol is a partial agonist of the cannabinoid receptors CB1 and CB2. CB1 receptors are mostly found in the CNS, whereas CB2 receptors are more prevalent in the immune system. THC, which has an easy absorption feature, is easily absorbed, and due to its lipophilic structure,

[1]ERBAS Institute of Experimental Medicine, Illinois, USA & Gebze, Turkey

Correspondence: Selim Soydan. Institute of Experimental Medicine, 41470 Gebze-Kocaeli, Türkiye.

E-mail: selotrak@gmail.com

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can cross the blood-brain barrier.[4] CB1 receptors have been shown to regulate ongoing conditions such as high glutamate production and subsequent oxidative stress, both of which can harm neurons and lead to neurodegeneration.[8] Cannabinoids thus specifically interact with CB1 structures, protecting cortical neurons from ischemic damage.[9] Tetrahydrocannabinol and its analogs have been shown to reduce glutamate toxicity by activating cannabinoid receptors and decreasing calcium flow through voltage-sensitive calcium channel cavities.[10] However, while many cannabinoids have been shown to have neuroprotective effects in various models of neurotoxicity, the mechanisms are not fully understood. The most important thing that is currently being understood is how the positive feedback produced by the ECS via receptors in response to oxidative stress will produce results in various situations.[11]

Oxidative stress is defined as an imbalance in the interaction between the production of reactive oxygen species (ROS) and the antioxidant-mediated defense mechanism, which results in optimal cleaning of the biological system at the appropriate time. This process produces a large number of free radicals.[12] Maintaining ROS within the appropriate amount of cells is important in maintaining the proliferation of signal and redox balance at the standard level in the context of some physiological conditions.[13] Working with ECS receptors to treat cannabinoids' effects on oxidative stress and diseases directly linked to oxidative stress has increased its use as a causative agent in research.[11] Cannabidiol's therapeutic potential in neurodegenerative diseases was investigated, with oxidative stress and associated inflammation coming in second. Since CBD is frequently studied, one of its applications in this field is for the therapeutic effect in the case of diabetes and its complications in human and animal studies.[6] Oxidative stress is generally described as an imbalance between antioxidants and oxidants in which oxidant activity exceeds antioxidants' ability to neutralize oxidants, resulting in the activation of pathological pathways and cellular damage.[14] This stress is caused by exposure to reactive oxygen intermediates, which can damage nucleic acids, cell membranes, and proteins.[15]

Differentiation of antioxidant levels results in a change in compounds that can be corrected while the antioxidant's overall capacity is unaffected. Exogenous antioxidants can reduce the level or intake of endogenous antioxidants without affecting the cell's "total antioxidant potential".[16] When exposed to various harmful stimuli, the body's continuous production of large amounts of active molecules, such as reactive nitrogen species (RNS) and ROS, is referred to as oxidative stress.[17] Oxidants, in general, are collectively referred to as ROS, molecules containing oxygen with more reactive properties than the oxygen molecules found in the air. This point is met by molecules with biological properties such as hydrogen peroxide, hydroxyl radicals, perhydroxyl radicals, and superoxide anion radicals. Furthermore, ROS include peroxynitrite, nitrous anhydride, nitric oxide (NO), nitrogen dioxide, nitrosoperoxycarbonate, and nitroxyl anion. These structures, however, are more commonly referred to as RNS.[18,19]

Reactive oxygen species are clasified into two categories: aggressive and less reactive, based on the fact that the molecules mentioned are ROS and the properties they exhibit. Many species with low reactive properties are produced in small quantities by aerobic metabolism, which is normally functioning. Furthermore, the cell damage is repaired on a regular basis. However, even less reactive ones, such as superoxide structure, can be easily transformed into aggressive radical species that cause extensive cellular damage via oxido-reduction reactions with other redox cycle compounds or transition metals in certain cases.[20,21]

The amount of ROS fluctuates within a range determined by the synchronized operation of elimination and production systems under normal conditions. The antioxidant system in living things is complex and multi-level, and it works effectively to destroy ROS or reduce its negative effects.[22] This system performs the extinguishing process through a series of neutralization and cleaning stages without having a negative metabolic effect or causing any destruction.[23] If the ROS is at a decisive level, it returns to the beginning of the stress induction in a short period of time, and if the metabolism has sufficient resources in the face of response, this is referred to as "acute oxidative stress". However, sometimes ROS levels do not return to the initial interval, but at a slightly higher point it is stable, or only if the stable state present under normal conditions expands the ROS line range and the stress event does not continue over a long period of time in the resulting situation, this stress can be called "chronic oxidative stress." As previously stated, live organisms in normal conditions maintain a specific range of ROS levels. The system, which provides various production-oriented activities of

ROS by the system, elimination, and prevention systems, provides homeostasis.[24,25]

In humans, oxidative stress interacts with diseases in a variety of ways. Stress can occur as a secondary reaction to a pre-existing disease condition, or it can be the primary cause of the disease on its own.[26] Although not all neurodegenerative disorders have all of the same traits, there is one crucial condition that runs along the disease's spectrum and plays a critical function. There is a growing knowledge that there is an increase in the interaction between a neuro-inflammatory component and oxidative stress in the long run. Increased research on nitrite oxide, a second common messenger in the inflammatory signaling system, has recently had a significant impact on the meaning of neurodegeneration.[27] It is well recognized that there are convincing processes involving anomalies in the mitochondrial region, metabolic incompatibility, and the function of oxidative stress that occurs, particularly in Alzheimer's disease (AD).[28] The fact that both diseases have hereditary traits makes it easier to do research on oxidative stress expansions of ancestral origin.[29-31] Evidence for oxidative stress in AD is consistent with the condition's abnormally high levels of redox-capable active metals, particularly iron, in the affected parts of the brain. In this regard, it is thought that an excess of redox-active metal compounds is at least largely responsible for the oxidative damage seen in polyunsaturated lipids, DNA/RNA, and proteins in AD.[32-34]

Furthermore, oxidative stress, which is on the rise with obesity and diabetes, plays a major role in hepatocarcinogenesis. Since oxidative stress causes genetic instability and genomic damage that leads to mutations, these mutations frequently play essential roles in carcinogenesis.[35,36] All of this evidence implies that ROS's cumulative damage contributes to a wide range of disorders.[37] Because of the wide range of disorders associated with oxidative stress, several treatments were investigated, particularly in neurodegenerative diseases. Cannabinoids, which are present in the Cannabis sativa plant and are the subject of this article, are chemicals that have essential receptors for controlling oxidative stress changes. Since cannabinoids have therapeutic efficacy in many neuronal and inflammatory diseases, it is known that cannabinoids can affect the signaling mechanism of oxidative stress, which is a feature of peripheral immune and inflammatory responses.[38]

EFFECT OF CANNABINOIDS ON ALZHEIMER'S DISEASE

Alzheimer's disease is the most common kind of dementia in the world and is caused by a neurodegenerative disorder. This disease causes cognitive impairment and memory loss in patients.[39,40]

The presence of senile plaques in the pathogenic way of β-amyloid (Aβ), a peptide of approximately 1-42 amino acids derived from abnormal processing of the transmembrane structure of amyloid precursor protein, characterizes AD brain. This disease causes cognitive impairment and memory loss in patients.[34,41] Furthermore, among the degenerative features of AD, neurofibrillary balls, the hippocampus, and cerebral cortical circumference all play crucial roles.[42,43] In the event of sporadic AD, the creation and advancement of senile plaques do not correspond to the growth of tau pathology.[44] Tau and Aβ incorrectly folded proteins impair brain activity by increasing their hazardous function or causing the normal function to be lost. As a result, it influences the loss of neuronal organization induced by synaptic dysfunction and neuronal death.[45]

Exacerbation of the AD process is also linked to neuroinflammatory processes and oxidative stress, both of which are well-known.[46] The oxidative stress that occurs in the condition is a significant element in the pathophysiology of AD.[47] There is a growing body of data indicating oxidative stress and AD are associated with progressive cerebrovascular abnormalities. Cerebrovascular dysfunction and neurodegeneration are not mutually exclusive. However, both of the current situations can have an impact on cognition at distinct levels. Furthermore, therapies including antioxidants have a wide range of therapeutic effects under these settings. Cerebrovascular integrity is crucial to the proper conditional metabolism and perfusion of the brain in AD, and stress, which plays an active role, is often characterized by vascular dysfunction. However, mitochondrial dysfunction can coexist with a variety of other alterations in the pathophysiology of AD, such as synaptic protein degradation and increased production of ROS.[48]

It may take years to progress from the early stages of the neurodegenerative process to more advanced symptomatic stages. Unfortunately, once dementia symptoms appear, the disease's course accelerates and has unfavorable consequences.[49] As a result, multiple data indicate that targeting the endocannabinoid system and stimulating the ECS contributes to the

parallel control of certain early pathogenic processes. These data show that they have received a lot of attention in recent years.[50] Since CB1 receptors that play an active role in the ECS are primarily expressed in the nervous system (cerebellum, basal ganglia, hypothalamus, hippocampus, and dorsal horn), CB1 receptors are thought to regulate processes such as oxidative stress, which can produce a large amount of glutamate and then damage neurons, resulting in neurodegeneration.[51-54]

Furthermore, in vivo and in vitro studies demonstrate that cannabis chemicals derived from Cannabis sativa enhance neuroprocessing against Aβ. Some endocannabinoids are administered directly to cell cultures, while others are made more available through reuptake inhibitors in the ECS. As a result, it boosts the viability of neurons following exposure to various types of toxic Aβ and can help to minimize Aβ-induced memory impairment.[55-58] Cannabinoids, on the other hand, demonstrate their mechanisms by interacting with other cannabinoid receptors in the brain, such as G protein-coupled receptor 55 (GPR55) and transient receptor potential vanilloid-1 (TRPV1) channels, alpha and gamma receptors that can be activated by the peroxisome proliferator, and non-cannabinoid receptors. As a result, a partial mechanism of action against problems that may cause oxidative stress has been discovered.[59]

EFFECT OF CANNABINOIDS ON DIABETES MELLITUS

Diabetes mellitus (DM) is a metabolic condition characterized by hyperglycemia and inadequate endogenous insulin secretion or action. This chronic disease has a deleterious impact on numerous metabolic networks. Uncontrolled DM conditions can cause macrovascular and microvascular complications affecting functional and even structural changes in tissues, as well as unfortunately even organ failure.[60,61]

Pathogenesis, on the other hand, mostly includes decreased insulin content or sensitivity, beta-cell malfunction or oxidative stress, mitochondrial dysfunction, inflammation, and apoptosis in general.[62-64] Although various research has been conducted to shed light on the basic molecular pathways behind the formation and development of all of these problems, their etiology remains unknown.[65] Increased oxidative stress, on the other hand, is widely regarded as a contributor to the development and progression of diabetes and its consequences. Diabetes can be associated with an increased free radical generation or decreased antioxidant defenses in a variety of ways.[60,66]

In type 1 diabetes, experimental evidence points to the effect of ROS on the function of damaged beta cells produced by cytokines, autoimmune responses, and inflammatory proteins.[67,68] Experiment investigations that enhance stress through de novo free radical formation and suppression of antioxidant defense systems, on the other hand, indicate the resultant hyperglycemia.[69,70]

During the progression of type 2 diabetes, levels of the lipid complex decline, making body cells more susceptible to lipid peroxidation.[71,72] Polyunsaturated fatty acids are classified as extra susceptible to free radicals due to the presence of multi-structured linkages in the cell membrane.[73] Lipid hydroperoxides (LHP) are the lipids listed. These are toxic-properties lipid radicals that take on the manufacturing of fatty acids by stimulating the production of oxidative stress.[74] Since CB1 and CB2 receptors are specified in endocrine cells, numerous research have focused on the role of these cannabinoid receptors in regulating glucose homeostasis and insulin production. The ECS established by these receptors is known to regulate energy balance and nutrition intake. The CB1 receptor stimulates hepatic lipogenesis considerably. It also increases skeletal muscle breakdown, which activates defective oxidative metabolism at the mitochondrial level via oxidative phosphorylation.[75-77] As a result, ECS is defined as "part of a specialized phenotype selected to make the most of periods of excess and to manage with food scarcity".[78] According to research, the CB2 receptor is found in cells of the human pancreas. Calcium enters ß-cells more easily when CB2 is activated with an agonist. It also results in the previously described insulin release. This is one of the most essential variables in the creation of anti-diabetic medications.[79]

Furthermore, Δ9-THC, another cannabinoid receptor agonist, is employed in a variety of additional applications, including antiemetic, antipyretic drugs, hunger stimulants, analgesics, and many others. THC, on the other hand, is thought to protect against oxidative damage by preventing the generation of ROS.[80]

In conclusion, the effects of cannabinoids on oxidative stress in cannabis plants, which are widely used in the world, are neurodegenerative and metabolic. It has been discovered that receptor interactions can influence a variety of pathways in this

setting. It is said that cannabinoids work in tandem with the human body's ECS, serving as specialized stress inhibitors at degenerative or complex stages. Although it is not a cure, mechanisms of action may play an important role in the prevention of AD and DM in the future. Cannabinoid receptors can trigger ß-amyloid-induced senile plaques, which, along with the system of ROS, are the outcome of this tremendous effect of oxidative stress destructiveness caused by aberrant peptide structures in AD. CB1 receptors, in particular, have been identified to limit excessive glutamate synthesis and provide neuroprotection through collaborating with the ECS. The receptor connections of distinct cannabinoid receptors for oxidative stress were examined in DM evaluations. Increasing CB1 receptor lipogenesis, facilitating calcium entrance into CB2 receptor cells, and reducing ROS of THC can lead to oxidative stress therapy techniques.

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