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*Review*

# Endocannabinoid System: Chemical Characteristics and Biological Activity

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**Abstract:** The endocannabinoid system (eCB) began to be studied from the identification of the molecular structures present in the cannabis sativa plant. The ECS is constituted of cannabinoid receptors, endogenous ligands and all the associated enzymatic apparatus responsible for maintaining homeostasis. Several physiological effects of cannabinoids are exerted through interaction with various receptors such as CB1 and CB2 receptors, vanilloid receptors, and the recently discovered [GPCRs (GPR55, GPR3, GPR6, GPR12 and GPR19). Endogenous ligands such anandamide and 2-arachidonoylglycerol might modulate these receptors. eCB has proved to play a critical role in some human diseases and has been extensively studied due to its wide therapeutic potential and because it is a promising target for the development of new drugs. Phytocannabinoids and synthetic cannabinoids have shown varied affinities to eCB, which are relevant to the treatment of various diseases. They may also have potential as lead compounds in the development of cannabinoid-based pharmaceuticals for a variety of diseases. Furthermore, Integrative and Complementary Health Practices (ICHP) appear to influence the endocannabinoid system through modulation. This review will show a description of ECS components and discuss how phytocannabinoids, other exogenous compounds, and PICS may operate the eCB balance.

**Keywords:** Endocannabinoid system; receptor cannabinoid; endocannabinoids ligands; phytocannabinoids; Integrative and Complementary Health Practices

## 1. Introduction

Cannabis sativa has been used for recreational, therapeutic, and other purposes for thousands of years. The plant contains more than 120 terpenes phenolic constituents called phytocannabinoids, including one of the main and most recognized representatives, Δ9-tetrahydrocannabinol, or THC. The molecular structure of Δ9-tetrahydrocannabinol was identified for the first time in 1964, which led to the conclusion of the existence of a cannabinoid receptor and boosted the discovery of the Endocannabinoid System (eCB), largely responsible for the maintenance of body homeostasis and is primarily brain modulatory network. In addition, the importance of the eCB gained prominence during the COVID-19 pandemic not only in the inhibition of SARS-CoV-2 replication but also in different studies that include the use for the treatment of chronic pain and mood disorders [1-4].

The eCB is an active and complex cell signaling network. It involves a combination of cannabinoid receptors, endogenous cannabinoids (endocannabinoids), and the enzymes responsible for the synthesis and degradation of the endocannabinoids. The first

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studies started with the identification of receptors that would be named cannabinoid receptors type 1 or CB1R and type 2 or CB2R [5-8].

Moreover, there was the discovery of endogenous ligands, which enabled enhancing knowledge on new compounds, such as N-arachidonoylethanolamide, the first endocannabinoid molecule to be discovered and which was named "anandamide", a Sanskrit word meaning "bliss" or extreme happiness [9], followed by the identification of 2-arachidonoylglycerol (2-AG) which, together with the enzymes responsible for the synthesis and degradation of these compounds, make up what we know today as the Endocannabinoid System[10].

Until now (October 2022), a PubMed search for scientific journal articles published in all periods available containing the word "Endocannabinoid" revealed 12,272 results, with increased interest in the study and publications since 2000. These numbers illustrate the fast increased financial support in recent years, as well as scientific interest in understanding more about molecular mechanisms in different contexts of clinical ap-plication. This review focuses on recent advances in the understanding of ECS compo-nents and discusses how phytocannabinoids, other exogenous compounds, and Endo-cannabinoid Systems in Health Practices.

## 2. Cannabinoid receptors

The CB1/CB2 cannabinoid receptors are distinguished mainly by the sequence of amino acids in the polypeptide chain and by the distribution in different tissues [11-14] (Figure 01). Pharmacological studies suggest that cannabinoid molecules might act on receptors other than the classic CB1 and CB2 cannabinoid receptors, such as the vanilloid receptors TRPV1, TRPV2, TRPV3, TRPV4, TRPA1, and TRPM8; metabotropic receptors such as GPR55, GPR3, GPR6, GPR12, and GPR19, among other receptors, as well as enzymes and proteins that can change from the interaction with cannabinoids [15-17]. Nowadays, the eCB system has been expanded, and the researchers named it Endocannabinoidome (eCBome), which was suggested to include all components as well as proteins, enzymes, and ligands that are directly or indirectly involved with cannabinoid modulation and which significantly impact upon health. This complex signaling system is deeply involved in the onset, progress symptoms, and disorders; it may provide a future perspective for therapeutic substances to treat different conditions [18-21].

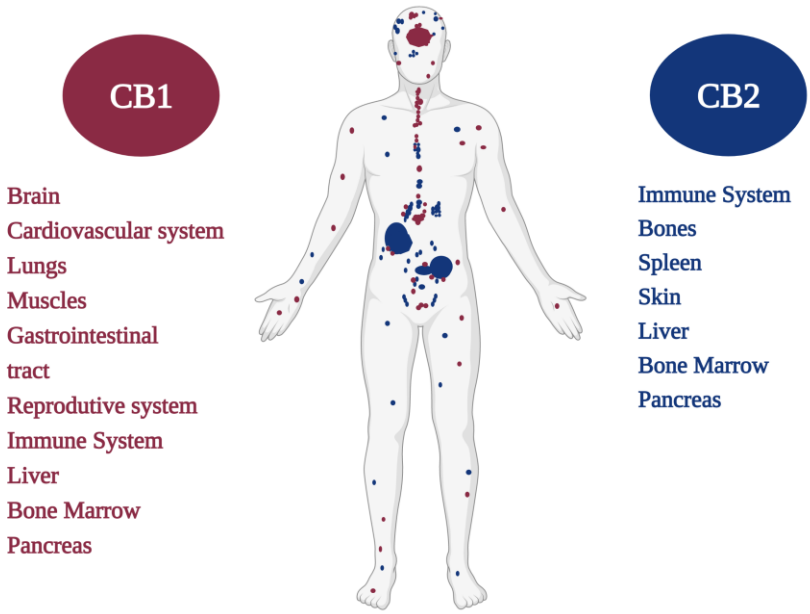

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Figure 01 – CB1 and CB2 cannabinoid receptors and their major distribution in the human body

The phytocannabinoid are molecules such as cannabidiol (CBD) with a wide therapeutic window, possibly due to their ability to target several different receptors. In addition, eCBome plays a role in the microbiota-gut-brain axis, which emerges as an important player in the control of affective and cognitive functions and their pathological changes. However, the molecular and biochemical basis of the interaction and the biological relationship of the new receptor subtypes with the cannabinoid ligands has not been fully elucidated, therefore, further studies need to be explored [22-24].

The type 1 cannabinoid receptor (CB1R) is encoded by the CNR1 gene and was cloned in 1990 by Matsuda et al., with 97-99% amino acid sequence identity between these species). After the receptor cloning, it was possible to design ligand molecules that fit these receptors following the t logic of the key-lock model [5,25-27]. A radioactive tracer synthesized by Pfizer ("CP55, 940") enabled the researchers to begin mapping the locations of cannabinoid receptors in the brain. These receptors have been identified in the CNS and high concentrations in regions responsible for mental and physiological processes such as the hippocampus (memory), cerebral cortex (cognition), cerebellum (motor coordination), basal ganglia (movement), hypothalamus (appetite), the amygdala (emotions). There are fewer cannabinoid receptors, more precisely CB1R, identified in the brainstem, the region that controls breathing and heartbeat, which may explain the fact that there have never been reports of overdose deaths from cannabis use, regardless of the age, its purpose or route of administration [28,29].

In addition to neurons, CB1R is expressed, albeit to a much lesser extent, in astrocytes, oligodendrocytes, and microglia, which has been shown to mediate synaptic transmission [29-31]. Some previous studies have suggested a CB1Rs high expression at presynaptic terminals, modulating retrograde endocannabinoid signaling [32]. However, the existence of CB1Rs in postsynaptic sites is not excluded, such as in functional studies demonstrating autoinhibition in neocortical neurons by endocannabinoids [29]. Studies involving the mapping of the rat brain suggest that the preferred location of CBR1 is in axons and nerve terminals; and its actions are related to the modulation of the release of neurotransmitters such as norepinephrine, dopamine, acetylcholine, glutamate, 5-hydroxytryptamine, γ-aminobutyric acid (GABA), and D-aspartate [33-35].

CB1R can be abundantly expressed in the peripheral nervous system (PNS) as well as in other region of the body [36,37]. In the PNS, CB1R is highly expressed in sympathetic nerve terminals. Furthermore, CB1Rs are observed in the trigeminal ganglion, dorsal root ganglion, and dermal nerve endings of primary sensory neurons, where it regulates the nociception of afferent nerve fibers. In the gastrointestinal tract (GIT), CB1R is expressed both in the enteric nervous system and in non-neuronal cells such as intestinal mucosa, including enteroendocrine cells, immune cells, and enterocytes. CB1Rs can modulate GIT mobility, the secretion of gastric acids, fluids, neurotransmitters, and hormones, as well as the permeability of the intestinal epithelium. The CB1Rs present in the CNS can control appetite in the hypothalamus, regulating energy balance and food intake in the GIT. Interestingly, hepatic CB1R may also participate in the regulation of energy balance and metabolism [29,38,39].

Normally, the CB1R expression in the liver is very low; however, under pathological conditions, CB1R expression in various liver cell-types can be remarkably increased, where CB1R actively contributes to hepatic insulin resistance, fibrosis, and lipogenesis. Likewise, CB1R is upregulated in the cardiovascular system in pathological conditions, promoting disease progression and cardiac dysfunction [37,40-42].

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Oxidative stress, inflammation, and fibrosis have been observed through CB1R activation in cardiomyocytes, vascular endothelial cells, and smooth muscle cells. In addition to the mentioned tissues, CB1R expression has also been reported in adipose tissue, skeletal muscle, bone, skin, eye, reproductive system, and various cancer cell-types. Skeletal muscle and myocardium CB1R are predominantly located in mitochondria (mtCB1R). Activation of mtCB1 receptors may participate in mitochondrial regulation of oxidative activity, probably through relevant enzymes involved in the metabolism of pyruvate, the main substrate for tricarboxylic acid activity [14,43-45].

The type 2 cannabinoid receptor (CB2R) was cloned in 1993 from human promyelocytic leukemia cells of the HL-60 lineage [2], and CB2R was identified in mice, rats, zebrafish, and dogs [46-49]. It has an amino acid sequence that presents around 44% homology with the CB1R receptor amino acid residues. CB2R was found, mainly, in cells of the immune system. The expression levels are higher than CB1R [15,29,50].

CB2R can modulate immune system cells and contribute to the analgesic and/or antinociceptive effects of cannabinoids. The CB2R was identified in the central nervous system. However, some studies showed its presence on the surface of microglia and neurons located in the cerebellum, brainstem, thalamus, striatum, cortex, amygdala, and hippocampus [29,51].

Both receptors belong to the large family of G protein-coupled receptors (GPCRs). They are a family of membrane proteins that have an amino-terminal extracellular domain, seven conserved transmembrane helices, with a characteristic sequence of 20 to 27 amino acid residues with high hydrophobicity, three extracellular and three intracellular loops, in addition to an intracellular carboxylic acid domain terminal [52,53] (Figure 02).

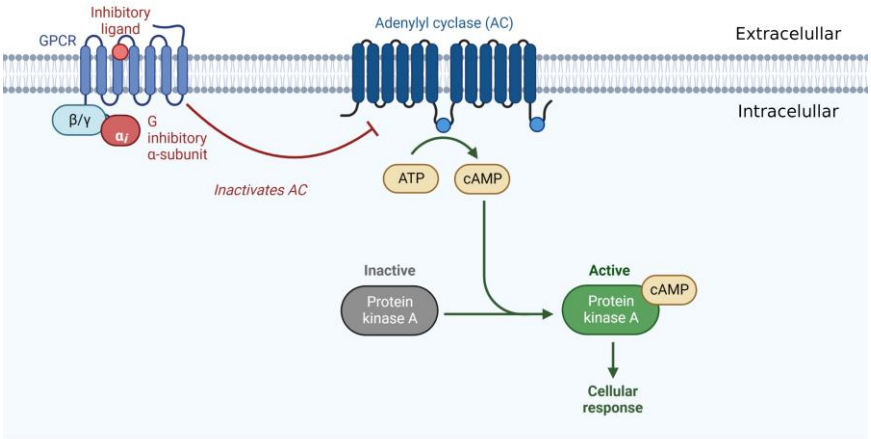


Figure 02 – Illustration of the receptor belonging to the large family of G protein-coupled receptors (GPCRs)

Activation of both cannabinoid receptor types promote the adenylate cyclase inhibition, in various cell types, which occurs through coupling with the Gi/o protein. This action leads to decreasing the levels of cyclic adenosine monophosphate (cAMP) and protein kinase A activity, which may be associated with the nociceptive neurons' sensitization, and proteins that might be related to increased intracellular calcium, inositol triphosphate and diacylglycerols, that are ultimately involved in the modulation of neurotransmitter

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release [54,55]. The CB1R stimulation leads to the activation of mitogen-activated protein kinase (MAPK) signaling pathways, including extracellular signal-regulated kinase 1/2 (ERK1/2), c-Jun N-terminal kinase (JNK), and p38, that are involved in the regulation of cell proliferation, cell cycle control and cell death [29,56] (Figure 03).

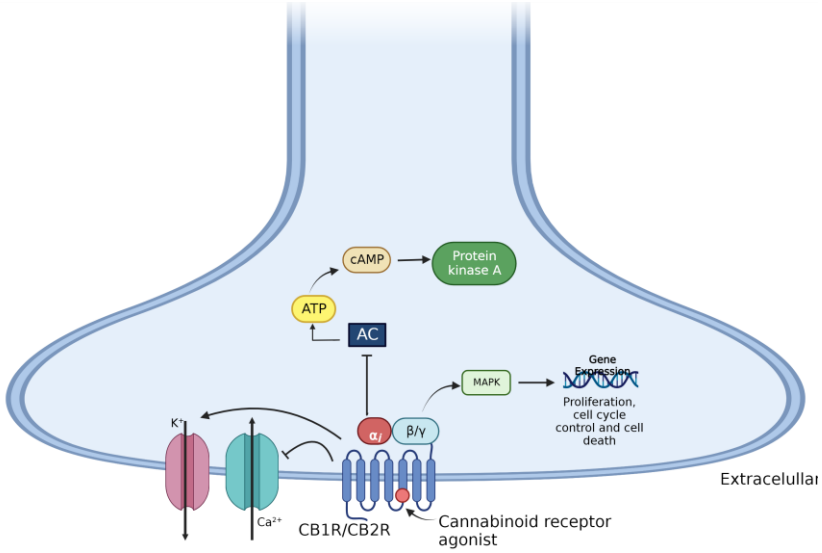


Figure 03. Mechanism of intracellular signaling via activation of CB1 and CB2 cannabinoid receptors. AC-adenylate cyclase, cAMP-cyclic adenosine monophosphate; ATP-adenosine triphosphate; MAPK-mitogen-activated protein kinase; protein kinase A (PKA).

**2. Endocannabinoids: synthesis, release, and metabolism**

With the discovery of cannabinoid receptors, there was an interest to find endogenous ligands that are responsible for their modulation. An evaluation of purified porcine brain fractions led to the identification of a new compound that binds to CB1R. The arachidonylethanolamide, an arachidonic acid derivative in the porcine brain, had its structure characterized and named anandamide (AEA), a word derived from ananda, from Sanskrit, which means extreme happiness [9,55,57-59].

Based on structural elucidation of AEA, other endogenous lipid molecules were identified (Figure 04)and generally called N-acylethanolamines (NAEs) such as 2-arachidonoylglycerol (2-AG), N - oleoylethanolamine (OEA), 2-arachidonyl glyceryl ether (noladin, 2-AGE), virodhamine, N - arachidonoyldopamine (NADA), and N - palmitoylethanolamine (PEA) AEA and 2-AG are the most studied endogenous ligands, however research on endocannabinoids has since evaluated, and additional receptors along with their lipid mediators and signaling pathways continue to be revealed [58,60-63].

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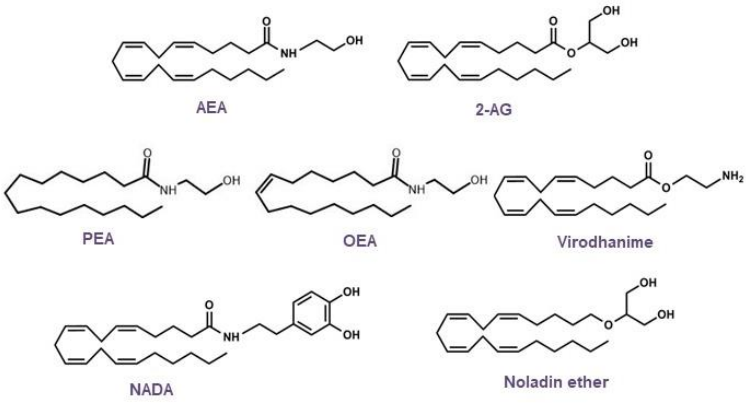


Figure 04. Chemical structures of the main endocannabinoids

Endocannabinoids, unlike classical neurotransmitters, are considered atypical messengers, due to the modulation of information from postsynaptic terminals to presynaptic, a retrograde manner, being responsible for the retrograde signaling mechanism. Endogenous ligands are synthesized on demand or by activity dependent on the cleavage of phospholipid membrane, being immediately released after their biosynthesis to act as pro-homeostatic factors through interaction with the specific receptor [55,64,65].

The synthesis and degradation of endogenous cannabinoid receptor ligands involve different enzymatic reactions. Anandamide biosynthesis occurs through release from membrane phospholipids, which are substrate to Ca2+-dependent or independent N-acyltransferase (NAT or iNAT). The N-arachidonoyl-phosphatidylethanolamine (NArPE) is formed, which and by the action of N-Acyl-phosphatidylethanolamine-specific phospholipase D (NAPE-PLD) is converted to *N* - arachidonoylethanolamine (AEA) [37,66,67].

The 2-AG is formed in a two-step mechanism. Initially, 1,2-diacylglycerol (DAG) is synthesized due to the cleavage of membrane phospholipids by the enzyme phospholipase C (PLC). DAG is subsequently esterified by the enzyme diacylglycerol lipase (DAGL), synthesizing the 2-AG [68,69].

Endogenous cannabinoids become inactive through a cellular reuptake mechanism via membrane transporters (EMT), followed by intracellular degradation through the action of hydrolytic enzymes. Anandamide is metabolized mainly by the fatty acid amide hydrolase enzyme (FAAH), and the 2-AG is asubstrate for monoacylglycerol lipase (MAGL), producing arachidonic acid (AA) and ethanolamine or glycerol, respectively[70,71] (Figure 05).

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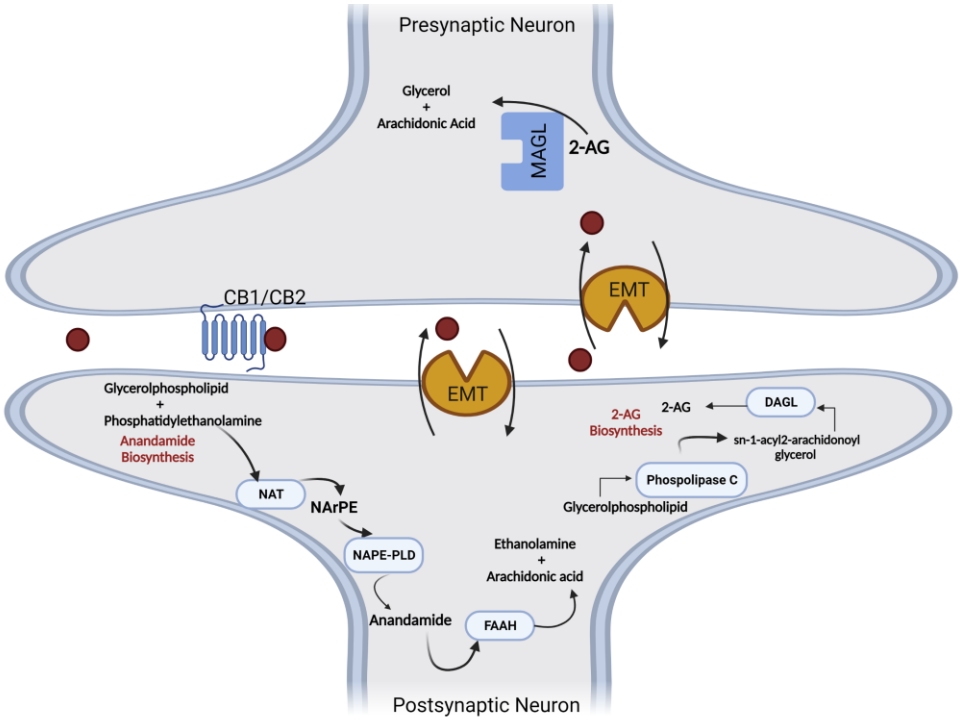


Figure 05. Metabolic pathways involved in the synthesis and degradation of anandamide (5) and 2-arachidonyl glycerol (6). AA- arachidonic acid; 2-AG-2- arachidonylglycerol; DAGL-diacylglycerol lipase; EMT- membrane transporters; FAAH- Fatty acid amide hydrolase ; MAGL- monoacylglycerol lipase; NAPE-PLD- N -arachidonylphosphatidylethanolamine phospholipase D; NArPE- N -acylphosphatidylethanolamine; NAT - N -acyltransferase; PLC-phospholipase C.

Furthermore, AEA and 2-AG may be susceptible to oxidation mechanisms catalyzed by cyclooxygenases (COXs) and lipoxygenases (LOXs), enzymes involved in the oxidative metabolism of arachidonic acid (AA), which can be biotransformed into prostaglandins (PG), eicosanoids and hydroxy-peroxy-anandamide, among other compounds derived from this degradation [37,55].

The endocannabinoid deficiency theory was based on the concept that many brain disorders are associated with a deficiency of neurotransmitters, such as acetylcholine in Alzheimer's disease, dopamine in parkinsonian syndromes, serotonin, and norepinephrine in depression, and that a comparable deficiency in endocannabinoid levels can similarly manifest in certain disorders, which exhibit predictable clinical features as sequelae of this deficiency [72-74].

In 2004, professor and researcher Dr. Ethan Russo and his collaborators proposed Clinical Endocannabinoid Deficiency Syndrome (CDS), suggesting that a lack of endocannabinoids could be the cause of many diseases, such as migraine, a highly complex disease that involves signaling between different areas of the brain and variousneurochemicals transmitters. The exact cause of migraine is not fully understood, although genetic predisposition is considered a primary contributor to its genesis and modulation [72,73]. The possible relationship of migraine with the endocannabinoid system is highlighted by several findings [75,76].

Fibromyalgia was also considered to have a relation with deficiencies in the endocannabinoid system. Fibromyalgia is a disease characterized by acute and chronic widespread musculoskeletal pain throughout the body. This pain is more often accompanied by other conditions such as insomnia, migraines, mood swings, memory problems, irritable bowel syndrome, and chronic fatigue. The presence of characteristic

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painful nodules known as trigger points is notable, being particularly prevalent in the shoulder and neck. Like migraine, fibromyalgia is associated with hyperalgesia, a lowered pain threshold, which is associated with central endocannabinoid hypofunction in the spinal cord. According to Russo and colleagues, the approved drugs for fibromyalgia, duloxetine and milnacipran (serotonin and adrenergic inhibitors) and pregabalin (an anticonvulsant used to treat neuropathic pain) showed little efficacy in treating fibromyalgia compared to cannabis [76-78].

Irritable bowel syndrome (IBS) also known as spastic colon, is a functional disorder characterized by gastrointestinal (GI) pain, spasm, discomfort, and altered bowel movements, predominantly diarrhea. Gastrointestinal tract propulsion, secretion, and inflammation in the gut are modulated by the endocannabinoid system, providing a rationale for the cannabinoids' inclusion as candidates for IBS treatment. Studies observed that increased capsaicin receptor TRPV1-expressing sensory fibers may contribute to visceral hypersensitivity and pain in IBS and provide a new therapeutic target. Cannabidiol could be used for therapeutic interventions due to its effect on vanilloid VR1 receptors; it also enhances anandamide signaling. Its analogues had shown to be potent inhibitors of anandamide cellular uptake [79-84].

Neurodegenerative disorders might lead developing Parkinson's disease (PD) and Alzheimer's disease (AD). Normally they are characterized by cognitive impairment and other neurological defects. Currently, the endocannabinoid system is studied as a drug target in PD and AD, due to the overexpression of endocannabinoid system receptors, which exerted neuroprotection against PD and reduced neuroinflammation in AD. Anandamide increased levels were found in the cerebrospinal fluid of untreated Parkinson's disease (PD) patients, which was suggested to be a possible compensatory mechanism. AD patients with cognitive deficits correlate with cerebral disturbances in sensitive brain areas, largely in the frontal cortex and the hippocampal region, areas that are rich in CB1Rs. The Δ9-THC and CBD showed neuroprotection in PD and AD animal models; however, triggered toxic effects on patients when administered directly. Studies are necessary to evidence the therapeutic efficacy of targeting the endocannabinoid system for neurodegenerative diseases [71,85-87].

## 3. Molecules that modulate the endocannabinoid system

Cannabis, as an herbal medicine, is a complex mixture of several compounds, including cannabinoid phenols, non-cannabinoid phenols (stilbenoids, lignans, spiroindanose, and dihydrophenanthrenes), flavonoids, terpenoids, alcohols, aldehydes, n-alkanes, wax esters, steroids, and alkaloids. Currently, more than 500 different substances have been isolated and reported from the cannabis plant belonging to different classes, among which the class of cannabinoid compounds is the most representative because it has more than 120 identified compounds, such as delta-eight and delta-nine tetrahydrocannabinol Δ 8 -THC and Δ 9 -THC, cannabidiol (CBD) and cannabinol (CBN) (Figure 07). The diverse classes of secondary metabolites are different parts of the plant with a wide range of applications (nutraceuticals, cosmetics, aromatherapy, and pharmacotherapy) that are beneficial to humans. However, in the past, they focused the studies mainly on the two most abundant phytocannabinoids: THC and CBD, which resulted in greater knowledge about their pharmacological activities, increasing interest in the numerous possibilities of medicinal actions of the plant [88-92]

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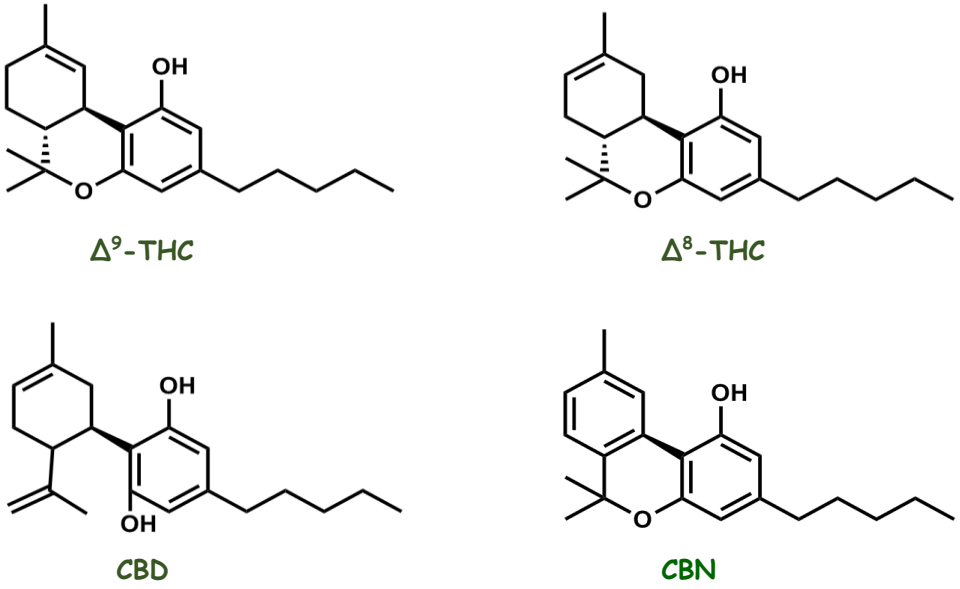


Figure 07. Chemical structure of the main pharmacologically active cannabinoid compounds isolated from Cannabis sativa

The biochemical basis of the pharmacological activity of cannabinoids, however, remained an enigma for many years. The highly lipophilic molecular structure of cannabinoids suggested that they exert their effects by penetrating cell membranes, and they have acted in the central nervous system. Nowadays, there are important insights into the physicochemical properties of cannabinoids. Novel selective ligands for the cannabinoid's receptor can have specific substituents that increase the binding kinetics and decrease side effects [93-97].

**4. Harmonization of the Endocannabinoid System through Integrative and Complementary Health Practices (ICHP)**

Clinical interventions are characterized as integrative and complementary health practices (ICHP) or also known as "complementary and alternative medicine (CAM)" that include various medical and health systems, practices, and products, which are not currently part of conventional medicine. CAM can be classified into three broad groups: "natural products" (dietary and herbal supplements), "mind and body medicine" (meditation, yoga, and acupuncture), and "body-based practices" (massage, spinal manipulation) [98,99].

A rodent study by Chen et al. showed that electroacupuncture promoted antinociceptive activity in animals and increased anandamide levels in skin tissue. It was also found that the antinociceptive effects were attenuated when using AM630, a CB2R antagonist, but not by the CB1R antagonist, AM25 [100]. Furthermore, anandamide increased expression of the CB2R receptors in the skin [101,102]. The CB2R activation in the skin likely stimulates the release of β-endorphin, which then acts on peripheral μ-opioid receptors to inhibit nociception [98]. Furthermore, it was observed that electroacupuncture conferred neuroprotection against cerebral ischemia by stimulating the mobilization of endocannabinoids in the brain and activating CB1 receptors [103,104].

A study by Sadhasivam and colleagues suggests that endocannabinoids may serve as biomarkers after a meditation session. Scores for depression and anxiety decreased significantly from baseline to immediately after four days of the Isha Yoga Bhava Spandana Program. In addition, one day before and one day after withdrawal, blood samples were collected voluntarily for evaluation of endocannabinoids (anandamide, 2-AG, 1-AG, docosatetraenoylethanolamide (DEA), oleoylethanolamide (OLA) and brain-derived neurotrophic factor (BDNF). Analyses suggest that major endocannabinoids, including

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anandamide, 2-AG, 1-AG, DEA, and BDNF, were increased after meditation in >70% of patients (ng/mL) suggesting an important role for these biomarkers in the mechanism underlying meditation [105]. Studies indicate that there is a correlation between acupuncture and the endocannabinoid system through the biological effects shared by both, including analgesia, neuroprotection, and cardiovascular regulation. A better understanding of these intrinsic links between acupuncture and CES may allow the development of new techniques that combine acupuncture with therapeutic agents that target the endocannabinoid lysis signal [106-109].

Another study found that massage and osteopathic manipulation of asymptomatic participants increased serum anandamide levels by 168% compared to pre-treatment levels; there were no changes in 2-arachidonoylglycerol levels. Participants who received SHAM-type manipulation (control) showed no changes [99]. An integrative approach with a combination of acupuncture, massage, yoga, mind-body approaches, and medical *cannabis* can be quite effective. As an example, we have a patient with chronic neuropathic pain showing improvement in the clinical picture when treated this way [110]. The importance of a complex individualized approach is needed, highlighting patient guidance and engagement in integrative modalities and the medicinal use of *cannabis*.

**5. Research perspectives, trends on the Endocannabinoid System**

Since the beginning of scientific research with cannabinoids, with special emphasis on the isolation and identification of phytocannabinoids such as THC, scientists have continued to improve, day after day, the knowledge of pharmacology, biochemistry, and clinical effects of Cannabis. For years the physiological effects of its consumption have been well known, especially the state of euphoria. But what goes on inside our organism, at the molecular level, especially inside the brain to alter consciousness, was still unknown. Then in 1973, US researchers identified receptors in the brain that linked with opiates (derived from Opium). Some scientists expected the discovery of receptors for marijuana to follow soon. However, it was not as easy and fast a task as they wanted. Research by Allyn Howlett and William Devane identified that cannabinoid receptors were in greater abundance in the brain than any other G protein-coupled receptor [109,111-113].

Cannabinoid receptors (CB1R and CB2R), as part of the endocannabinoid system, play a critical role in numerous physiological conditions and human diseases. Therefore, considerable efforts have been made to develop ligands for CB1R and CB2R, resulting in hundreds of phytocannabinoids and synthetics that have shown varied relevant affinities to the treatment of various diseases [7]. However, only a few of these ligands are used clinically. Currently, more detailed structural information for cannabinoid receptors has been revealed thanks to the power of cryo-electron microscopy, which can accelerate the discovery of structure-based substances [114]. At the same time, new peptide-like cannabinoids of animal origin arrived on the scene, with their potential therapeutic effects in vivo on cannabinoid receptors [115,116].

From the point of view of natural products, it is expected that more new cannabinoids will be discovered and predicted as prototypes for promising drugs from different sources and natural species, such as animal venoms that constitute a true pharmacopeia of toxins modulating diverse targets, including ion channels, receptors G protein-coupled, such as CB1 and CB2, with surprising affinity and selectivity [117]. Therefore, it is believed that discovering new cannabinoids from the study of the biodiversity of species that live on planet Earth is a territory still little explored.

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by F.F.D, G.F.B and G.C.M All authors have read and agreed to the published version of the manuscript.

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