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Cannabidiol: mechanisms of action and potential therapeutic applications

Kanabidiol: mechanismy jeho účinku a potenciální terapeutické využití

Bachelor’s thesis

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V Praze, 10. 12. 2024

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ABSTRACT

The primary objective is to create a comprehensive overview of the latest findings about CBD, including its origin, chemical properties, mechanism of action in the human body, pharmacology, and, most importantly, its potential therapeutic applications. This overview is based on research from reliable scientific sources and presents relevant findings. It demonstrates that CBD is a well-known, naturally occurring, lipid-soluble, and biologically available compound that interacts with the human body via the endocannabinoid system, which is widespread throughout the body, particularly in the nervous and immune systems. This interaction affects various physiological processes and pathological conditions through cellular signaling pathways involved in critical processes such as gene transcription and enzyme production. These pathways influence cell functions like growth, survival, immune responses, proliferation, migration, apoptosis, and inflammation. As a result, CBD has shown efficacy as a treatment for a wide range of conditions, including pain, inflammation, immune diseases, neurological and neurodegenerative disorders, psychiatric conditions, and diseases of the digestive tract and metabolism. It also demonstrates potential in treating cardiovascular conditions, skin and bone diseases, severe bacterial and viral infections, and even cancer. Many clinical studies report impressive results, often showing effectiveness comparable to or surpassing traditional treatment methods. This positions CBD as a promising, versatile therapeutic option for further research and clinical application.

Key words: Cannabidiol, CB1 and CB2 receptors, nervous system, immune system

ABSTRAKT

Hlavním cílem je vytvořit komplexní přehled nejnovějších zjištění o CBD, včetně jeho původu, chemických vlastností, mechanismu účinku v lidském těle, farmakologie a, co je nejdůležitější, jeho potenciálních terapeutických aplikací. Tento přehled je založen na výzkumu spolehlivých vědeckých zdrojů a prezentuje relevantní nálezy. Ukazuje, že CBD je dobře známá, přirozeně se vyskytující, lipidická, rozpustná a biologicky dostupná sloučenina, která interaguje s lidským tělem prostřednictvím endokanabinoidního systému, jenž je rozšířen po celém těle, především v nervovém a imunitním systému. Tato interakce ovlivňuje různé fyziologické procesy a patologické stavy prostřednictvím buněčných signálních drah, které se podílejí na klíčových procesech, jako je transkripce genů a produkce enzymů. Tyto dráhy ovlivňují buněčné funkce, jako je růst, přežití, imunitní odpovědi, proliferace, migrace, apoptóza a zánět. V důsledku toho se CBD ukázalo jako účinné při léčbě širokého spektra stavů, včetně bolesti, zánětu, autoimunitních onemocnění, neurologických a neurodegenerativních poruch, psychiatrických stavů a onemocnění trávicího traktu a metabolismu. Také vykazuje potenciál v léčbě kardiovaskulárních onemocnění, kožních a kostních onemocnění, závažných bakteriálních a virových infekcí, a dokonce i rakoviny. Mnohé klinické studie hlásí působivé výsledky, často ukazující účinnost srovnatelnou s nebo převyšující tradiční metody léčby. To řadí CBD mezi slibné, všestranné terapeutické možnosti pro další výzkum a klinické aplikace.

Klíčová slova: Kanabidiol, CB1 a CB2 receptory, nervový systém, imunitní systém

CONTENT

1 INTRODUCTION

For thousands of years, *Cannabis sativa L.* has been cultivated and utilized by humans in various aspects of life, particularly in industrial and medicinal fields. As scientific advancements have progressed, more detailed research has become possible, leading to the study of individual compounds found in the plant. Among these, cannabidiol (CBD) has garnered significant attention. CBD is the second most abundant compound in *Cannabis sativa L.*, a plant commonly cultivated across different cultures, particularly in Western societies. While cannabinoids, including CBD, are widely used for medicinal purposes, the plant has also been associated with both legal and illicit psychoactive effects. Historically grown at home, *Cannabis sativa L.* is now part of industrial-scale production, giving rise to a wide range of products containing cannabinoids, including CBD. These products are primarily marketed for healthcare purposes, such as disease prevention or treatment of non-severe conditions. However, many of these products are not subject to stringent regulation, leading to uncertainty regarding their actual content. Additionally, public awareness about CBD, its mechanisms of action, and therapeutic uses remains limited. Reliable scientific information is not always effectively communicated or accessible to the public. This has resulted in the proliferation of misleading statements and misconceptions about CBD in public discourse, creating confusion. Despite an abundance of scientific literature—thousands of papers are published on this topic each year—the sheer volume of information can overwhelm the general public. Moreover, the scientific presentation of these findings is often difficult for non-specialists to understand. The primary goal of this work is to create a comprehensive overview of the latest findings about CBD. This includes elucidating its origin, chemical properties, mechanism of action in the human body via the endocannabinoid system, pharmacology, and especially its potential therapeutic applications. By consolidating and summarizing current knowledge, this work aims to provide clarity on CBD, address public misconceptions, and establish a foundation for future research in this field.

2 CANNABIDIOL

2.1 ORIGIN

Cannabidiol (CBD) is not a recent discovery, having been identified over 80 years ago. It was first isolated in 1940 from the extract of Minnesota wild hemp. Researchers used raw material from the tops of female *Cannabis sativa* flowers to obtain a substance called "red oil" through ethanol distillation. After further processing, they isolated a compound, bis-3,5-dinitrobenzoate, with the molecular formula $C_{21}H_{30}O_2$, which was named cannabidiol (CBD) (Adams et al., 1940). However, CBD was not the first cannabinoid to be isolated. An earlier compound, cannabinol (CBN), with the molecular formula $C_{21}H_{26}O_2$, had been extracted from Indian hemp resin in 1899. Like CBD, this substance was obtained as "red oil" via distillation (Wood et al., 1899). Following the identification of CBD and CBN, researchers hypothesized the existence of additional related compounds. It wasn't long before another now-famous cannabinoid, tetrahydrocannabinol (THC), was discovered. THC, with the same molecular formula as CBD ($C_{21}H_{30}O_2$), was identified shortly thereafter, and the chemical structures of all three compounds—CBD, CBN, and THC—were elucidated and published in 1964 (Gaoni et al., 1964).

2.1.1 Cannabidiol and other cannabinoids

All three compounds—CBD, THC, and CBN—along with many other related substances, are collectively referred to as cannabinoids. These compounds represent a large group of naturally occurring substances found in *Cannabis sativa*, a plant species first classified by Carl Linnaeus in 1753. At the time, Linnaeus considered it the only species within the genus (Linnaeus, 1753). This classification remained widely accepted until 2000, when McPartland proposed three additional species: *Cannabis indica*, *Cannabis afghanica*, and *Cannabis ruderalis* (McPartland et al., 2000). Later, in 2005, Hillig suggested a more detailed classification comprising seven distinct taxa (Hillig, 2005). Despite these taxonomic updates, most sources continue to refer to all cannabis plants as *Cannabis sativa L.*, with specific strains differentiated by unique names that reflect their genetic or phenotypic traits (Flores-Sanchez et al., 2008). According to the latest research, approximately 120 cannabinoids have been isolated and characterized. This group includes the original compounds, their derivatives, and various transformation products, which are categorized into several cannabinoid classes based on their structural types. Although these cannabinoids occur naturally, many have also been synthesized in laboratories. Today, most known natural cannabinoids are available in synthetic form, enabling broader study and use (Mechoulam et al., 2014).

Table 1 Classification of known cannabinoids to 11 general classes

(ElSohly et al 2017)

Chemical class	2005	2015
Δ^9-THC type	9	23
Δ^8-THC type	2	5
CBG type	8	16
CBC type	6	9
CBD type	7	7
CBND type	2	2
CBE type	5	5
CBL type	3	3
CBN type	7	11
CBT type	9	9
Miscellaneous types	14	30
Total cannabinoids	72	120

2.1.2 Biosynthesis of natural cannabinoids – phytocannabinoids

All natural cannabinoids which occur in *Cannabis sativa L.* plants are commonly called as phytocannabinoids and the most accountable amount of the these compounds are located in glandular tissues called trichomes but these are also distributed in other parts of the plants (Turner et al 1978) while the concentration varies depending on the specific tissue but also on other factors as stage of the life cycle, different gender or specific variety of the plant (Kushima et al 1980). However, the content and ratio of phytocannabinoids in plants are not dependent only on genetics respectively internal factors but also on growing conditions respectively external factors as light, temperature, humidity, air whereas the most important factor seems to be light in sense of light intensity, light spectrum and photoperiod (Magagnini et al 2018). Phytocannabinoids are group of chemicals which are terpene-phenolic compounds with 21 carbons, and they are closely related to the terpenes (Radwan et al 2021). Terpenes and terpenoids commonly called as isoprenoids are the most abundant group of natural compounds with over 30 000 derivatives whereas terpenoids have many biological functions so they have huge therapeutical potential. Biosynthesis of all terpenoids with cannabinoids included has two main precursors isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP) which are both dependent on two different pathways. The first one is pathway of cytosolic mevalonate, and the second one is pathway of plastidial deoxy-xylulose. Both pathways produce IPP which is isomerized to DMAPP (Eisenreich et al 1998) and when IPP and DMAPP are then condensed geranyl pyrophosphate (GPP) is formed (Luthra's et al 1999). GPP is the first of two crucial precursors in cannabinoid biosynthesis where the second one is olivetol acid (OA) produced in polyketide pathway where hexanoyl-CoA and malonyl-CoA are condensed by polyketide synthase (PKS) and olivetolic acid cyclase (OAC) to form OA (Gagne et al 2012). The first product of cannabinoid biosynthesis is cannabigerolic acid (CBGA) which is formed by condensation of GPP and OA (Shoyama et al 1975). These CBGA precursors are condensed by enzyme geranyl pyrophosphate olivetolic geranyl transferase (GOT) when olivetol acid is alkylated by GPP. Also, it has been discovered that GPP could be isomerized to neryl pyrophosphate (NPP) which then also condensates with olivetolic acid by GOT and then form cannabienerolic acid (CBNA), an isomer of CBGA (Fellermeier et al 1998). CBGA is main cannabinoid acid which is common precursor for other cannabinoid acids as cannabidiolic acid (CBDA), delta 9 thetrahydrocannabinolic acid (delta 9-THCA) and cannabichromenic acid (CBCA), whereas each of this reactions are proceeded by unique oxydocyclases (Flores-Sanchez et al 2008). Another cannabinoid acids as cannabicyclol acid (CBLA), cannabinol acid (CBNA) and cannabielsoin acid (CBEA) are produced by non-enzymatic reactions from already mentioned major cannabinoid acids as CBCA, THCA and CBDA. These reactions are driven by effect of oxygen, light, or heat. Particularly CBLA is produced when CBCA is irradiated, production of CBNA occurs when THCA is oxidized and finally CBEA is formed from CBDA mostly by oxidation or irradiation in presence of oxygen (Hanuš et al 2016) (Fig. 1).

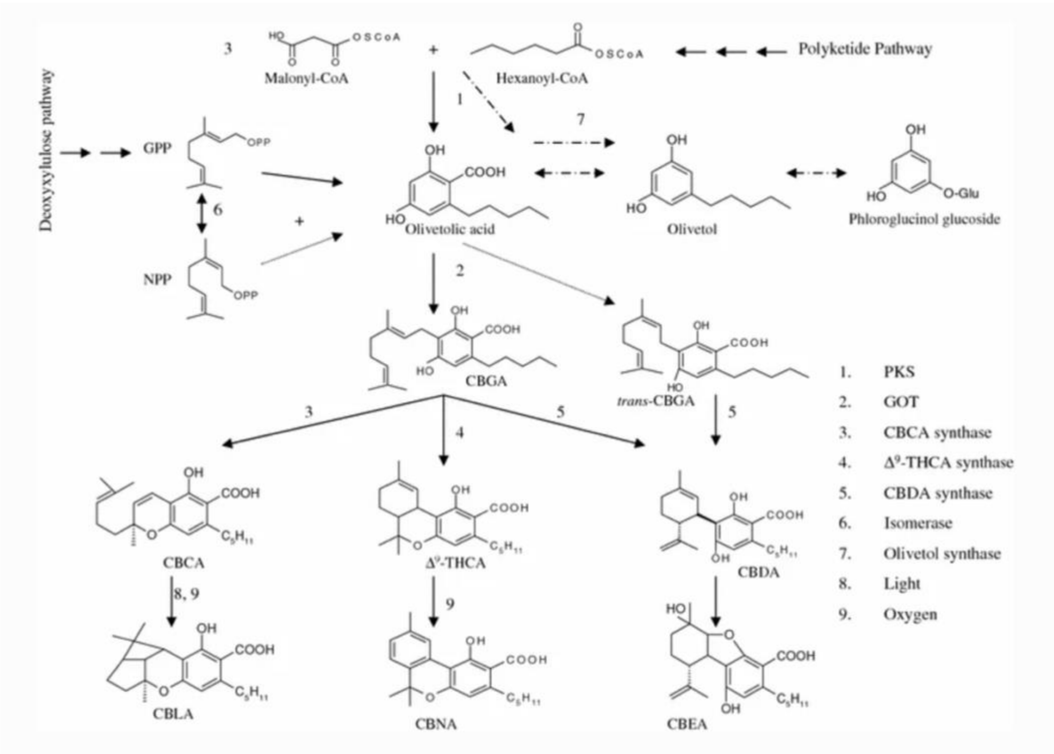

Fig. 1 Cannabinoid biosynthesis – general pathways.

(Flores-Sanchez et al 2008)

2.1.3 Phytocannabinoid decarboxylation – acidic and neutral cannabinoids

All of mentioned cannabinoid acids are on the end of mentioned enzymatic pathways and they are considered as final product of the plant metabolism, but all of these acidic cannabinoids have also their neutral versions which are structural analogues of these acidic versions, and they are produced by releasing of carbon dioxide thus loosing of carboxylic acid in process of decarboxylation. Both versions, acidic and neutral are commonly called as cannabinoids but more precise designation is pre-cannabinoids for acidic versions and cannabinoids in case of their decarboxylation to neutral versions. Even though decarboxylation is common reaction in organic chemistry and there are thousands described examples in literature, most of them are enzymatic or synthetic since they need to be catalyzed while decarboxylation of acidic cannabinoids is considered as non-enzymatic reaction what makes it unique. Also, unlike other general decarboxylation reactions where the carboxylic acid group is replaced by carbon, nitrogen, phosphorous, sulphur or halogen, during decarboxylation of cannabinoid acids it is replaced by hydrogen atom. However, decarboxylation of cannabinoid acids is considered as thermal reaction with heat as source of energy. Decarboxylation of cannabinoid acids in plant material can occur in different situations including processes of growing, harvesting, storage or consumption (Filer 2022).

2.1.4 Other cannabinoid groups – synthetic cannabinoids and endocannabinoids

All natural cannabinoids found in *Cannabis sativa L.* plants are commonly referred to as phytocannabinoids. The majority of these compounds are concentrated in glandular tissues known as trichomes, although they are also present in other parts of the plant (Turner et al., 1978). The concentration of phytocannabinoids varies depending on specific tissues, as well as factors such as the plant's life cycle stage, gender, and variety (Kushima et al., 1980). However, the content and ratio of phytocannabinoids are influenced not only by genetic and internal factors but also by environmental conditions, such as light, temperature, humidity, and air quality. Among these, light—specifically light intensity, spectrum, and photoperiod—appears to be the most critical factor (Magagnini et al., 2018). Phytocannabinoids are terpene-phenolic compounds containing 21 carbon atoms and are closely related to terpenes (Radwan et al., 2021). Terpenes and terpenoids, also known as isoprenoids, form the largest group of natural compounds, with over 30,000 derivatives. Terpenoids have many biological functions and considerable therapeutic potential. The biosynthesis of all terpenoids, including cannabinoids, is dependent on two main precursors: isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP), which are produced via two distinct pathways. The first is the cytosolic mevalonate pathway, while the second is the plastidial deoxy-xylulose pathway. Both pathways generate IPP, which is then isomerized to DMAPP (Eisenreich et al., 1998). When IPP and

DMAPP condense, they form geranyl pyrophosphate (GPP) (Luthra et al., 1999), the first of two crucial precursors in cannabinoid biosynthesis. The second precursor is olivetolic acid (OA), which is synthesized through the polyketide pathway. In this process, hexanoyl-CoA and malonyl-CoA are condensed by polyketide synthase (PKS) and olivetolic acid cyclase (OAC) to form OA (Gagne et al., 2012). The first product of cannabinoid biosynthesis is cannabigerolic acid (CBGA), which forms when GPP and OA condense (Shoyama et al., 1975). CBGA serves as the common precursor for other cannabinoid acids, such as cannabidiolic acid (CBDA), delta-9-tetrahydrocannabinolic acid (Δ9-THCA), and cannabichromenic acid (CBCA), with each of these reactions being facilitated by specific oxydocyclases (Flores-Sanchez et al., 2008). Other cannabinoid acids, such as cannabicyclol acid (CBLA), cannabinol acid (CBNA), and cannabielsoin acid (CBEA), are produced through non-enzymatic reactions from the major cannabinoid acids. These reactions are triggered by oxygen, light, or heat. Specifically, CBLA is produced when CBCA is irradiated, CBNA forms when THCA is oxidized, and CBEA is generated from CBDA, primarily through oxidation or irradiation in the presence of oxygen (Hanuš et al., 2016).

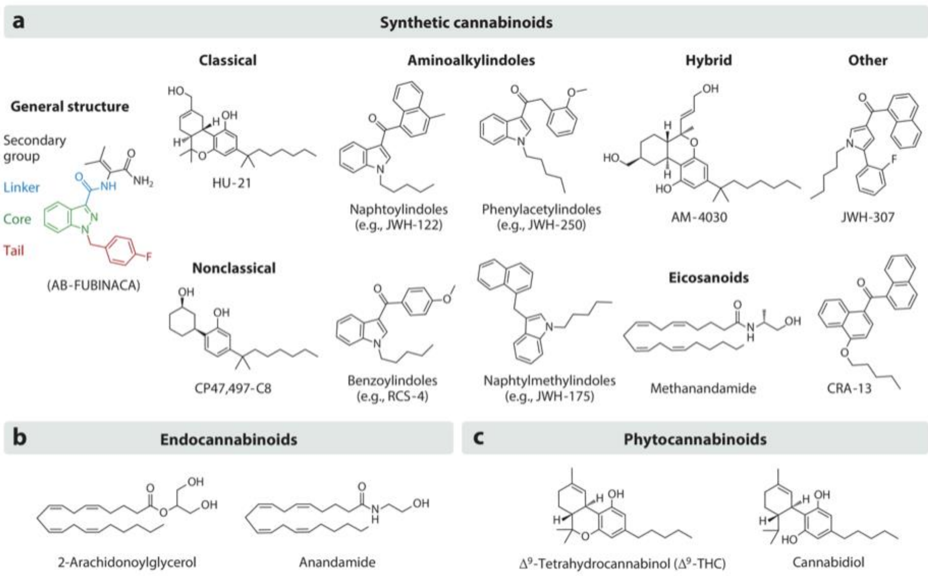

Fig. 2 – General groups of cannabinoids classified according to their origin and their structure

(Roque-Bravo et al 2023)

2.2 CHEMICAL PROPETIEIS OF CANNABIDIOL

2.2.1 Molecule and its activity

CBD (cannabidiol) is classified as a terpenophenolic molecule with a molecular weight of 314.464 g/mol. It consists of 21 carbon atoms, with the chemical formula $C_{21}H_{30}O_2$. The formal IUPAC name for CBD is 2-[(1R,6R)-3-methyl-6-prop-1-en-2-ylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol. The CBD molecule comprises several distinct parts: a cyclohexene ring attached to a phenol ring, with a side pentyl chain. The cyclohexene ring is almost perpendicular to the phenol ring. Additionally, the side chains can be found in three forms—n-propyl, n-butyl, and methyl (Fig. 3).

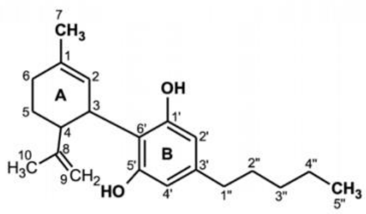

Fig. 3 CBD molecular structure A – cyclohexene ring, B – phenol ring (Atalay et al 2019).

Each of the three general parts of the CBD molecule influences its chemical activity. Specifically, the methyl group bound at the C1 position of the cyclohexene ring, the hydroxyl groups attached at the C1’ and C5’ positions of the phenol ring, and the pentyl side chain bound at the C3’ position all play important roles (Fig. 3). It has also been discovered that the CBD molecule can bind to amino acids such as tyrosine, threonine, glutamine, and glutamic acid through the hydroxyl groups on the phenol ring, forming hydrogen bonds. More intriguingly, it has been found that the CBD molecule exhibits antioxidative effects, primarily through its phenol group (Atalay et al., 2019).

2.2.2 Isomers

CBD exists in two enantiomeric forms: (-)CBD, which is the natural form, and (+)CBD, the synthetic form. Both enantiomers, along with their derivatives, are biologically active in the human body by binding to specific cell receptors, but they do so in different ways. Some of these enantiomers act as agonists, while others function as antagonists at particular receptors. Additionally, each enantiomer exhibits varying levels of affinity for these receptors (Hanuš et al., 2005).

2.2.3 Derivatives

CBD has seven naturally occurring derivatives, all of which possess the absolute (-) trans (1R,6R) configuration. These derivatives include cannabidiolic acid (CBDA-C5), (-)cannabidiol (CBD-C5), cannabidiol monomethyl ether (CBDM-C5), cannabidiol-C4 (CBD-C4), cannabidivarinic acid (CBDVA-C3), (-)cannabidivarin (CBDV-C3), and cannabidiorcol (CBD-C1) (Table 2) (ElSohly et al., 2005).

Table 2 – CBD natural derivatives

(ElSohly et al 2005)

Compound	R^1	R^2	R^3
cannabidiolic acid (CBDA-C_5)	COOH	n-C_5H_{11}	H
(–)-cannabidiol (CBD-C_5)	H	n-C_5H_{11}	H
cannabidiol monomethyl ether (CBDM-C_5)	H	n-C_5H_{11}	Me
Cannabidiol-C_4 (CBD-C_4)	H	n-C_4H_9	H
cannabidivarinic acid (CBDVA-C_3)	COOH	n-C_3H_7	H
(–)-cannabidivarin (CBDV-C_3)	H	n-C_3H_7	H
cannabidiorcol (CBD-C_1)	H	CH_3	H

2.2.4 Reactions

The activity of the CBD molecule has been studied under various conditions, such as acidic and basic environments, as well as oxidative conditions and irradiation exposure. It has been observed that under acidic conditions, CBD's open structure undergoes cyclization to form a ring structure, which then converts into Δ9-THC, followed by isomerization to Δ8-THC and Δ8-iso-THC (Gaoni et al., 1966). This led to the conclusion that CBD could be transformed into THC under the acidic conditions of the gastrointestinal tract after oral administration. However, it has been shown that this transformation does not occur, even at high doses (Nahler et al., 2017). In basic conditions, CBD (naturally Δ1-CBD) isomerizes to Δ6-CBD, but no other CBD forms arise in these conditions (Srebnik et al., 1984). Δ6-CBD has shown effects similar to THC in animal studies, though no conclusive evidence has been found to confirm these observations (Mechoulam et al., 2002). Regarding oxidation, it has been demonstrated that in basic conditions with oxygen present, CBD undergoes oxidation to form a para-quinone structure, now known as HU-331 (Kogan et al., 2004). This quinone exhibits significant potential as a cancer treatment, acting as an inhibitor of DNA topoisomerase II without generating reactive oxygen species (ROS), unlike traditional anthracycline cancer drugs, which produce ROS and cause undesirable side effects. HU-331 does not share these negative effects (Kogan et al., 2007). When exposed to irradiation, particularly from a 450 W lamp in methanol solution, CBD forms several products, including THC, iso-THC, reduced CBD, and cyclohexyl CBD, confirming its photoreactivity and suggesting its instability under light exposure (Mechoulam et al., 2002).

3 MECHANISMS OF ACTION

3.1 ENDOCANNABINOID SYSTEM

The endocannabinoid system (ECS) is an endogenous system with neuromodulatory activity that plays a crucial role in various processes within the central nervous system (CNS), such as neuronal development, synaptic plasticity, and responses to both endogenous and exogenous stimuli. The ECS is primarily composed of cannabinoid receptors and endocannabinoids, but it also includes specific enzymes responsible for their synthesis and degradation. The main receptors involved in the ECS are G-protein-coupled receptors (GPCRs), particularly cannabinoid receptors 1 (CB1) and 2 (CB2). Additionally, receptor channels such as transient receptor potential (TRP) channels, including TRPV1, and peroxisome proliferator-activated receptors (PPARs), such as PPAR alpha and PPAR gamma, are also involved. The primary endocannabinoids (eCBs) are anandamide (AEA) and 2-arachidonoyl-glycerol (2-AG), though other eCBs like virodhamine and 2-arachidonoyl-glycerol ether have also been identified, albeit less studied or discovered. These endocannabinoids are synthesized on demand from their precursors, which are located in the lipid cell membrane. They undergo a series of rapid enzymatic reactions before being released into the extracellular space, distinguishing them from neurotransmitters, which are synthesized in advance and stored in synaptic vesicles (Lu et al., 2016).

3.1.1 Cannabinoid receptors

There are two primary types of cannabinoid receptors, CB1 and CB2, each with different isoforms. CB1 has two isoforms, while CB2 has one. These receptor isoforms, along with their basic forms, are expressed at varying levels and combinations across different tissues. The CB1 receptor is most abundant in the central nervous system (CNS), particularly in areas such as the hippocampus, basal ganglia, cerebellum, and olfactory bulb. It is also expressed in the cerebral cortex, septum, hypothalamus, amygdala, brainstem, and dorsal horn of the spinal cord, albeit at lower levels in the thalamus and ventral horn of the spinal cord (Zou et al. 2018). The CB1 receptor is predominantly located in presynaptic neurons, though it can also be found on postsynaptic neurons, nearby astrocytes, and in glial cells like microglia and oligodendrocytes (Castillo et al. 2012). Furthermore, the receptor is not limited to the plasma membrane but is also present in intracellular structures, including endosomes, lysosomes, the endoplasmic reticulum, and mitochondria, where it helps regulate cellular respiration and calcium release (Zou et al. 2018). While CB1 receptors are primarily associated with the CNS, they are also present in the peripheral nervous system (PNS) and sensory neurons, where they play a role in pain pathways. Additionally, CB1 receptors are found in the autonomic nervous system, contributing to the regulation of vital functions (Howlett et al. 2002). Beyond the CNS and PNS, CB1 receptors are expressed in various peripheral tissues and organs, such as the cardiovascular system, gastrointestinal tract, liver, muscles, bones, skin, and reproductive system. Although CB2 receptors are present in these tissues, their expression is typically lower than that of CB1 receptors. The signaling of CB1 and CB2 receptors can be cooperative or competitive, meaning that the effects of one receptor may be enhanced or attenuated by the other (Maccarrone et al. 2015). CB2 receptors are primarily expressed in immune system cells, particularly in mature B cells and macrophages, and are also found in lymphoid tissues such as the tonsils, thymus, spleen, pancreas, and bone marrow. These receptors play an essential role in hematopoiesis, and while CB1 is expressed in these tissues, its levels are significantly lower than CB2. The presence of CB2 receptors in immune cells, such as monocytes, macrophages, and mast cells (myeloid lineage), and B- and T-lymphoid cells (lymphoid lineage), varies depending on the differentiation and activation state of the cells (Howlett et al. 2002). Activation of CB2 receptors modulates immune responses, often by inhibiting cell functions such as migration and pro-inflammatory cytokine production (Maccarrone et al. 2015). In the CNS, CB2 receptors are found in glial cells, where they help regulate neuroinflammation. Activation of CB2 receptors can reduce neuroinflammatory signaling and promote glial cell recovery (Bie et al. 2018). Interestingly, CB1 and CB2 receptors can form heteromers, which exhibit bidirectional cross-antagonism, meaning the binding of an antagonist to one receptor can block the effect of an agonist binding to the other receptor. These heteromers can also cause negative cross-talk through agonist coactivation (Callén et al. 2012). Both CB1 and CB2 receptors are G-protein coupled receptors (GPCRs), and their activation leads to signaling via G proteins. This signaling influences several critical cellular pathways, including ion channel regulation (e.g., potassium and calcium channels), the adenylate cyclase/cAMP/PKA pathway, the PI3K/Akt pathway, and the ERK, MAPK, and JNK pathways. These pathways regulate processes like enzyme activation, gene expression, cell growth, survival, and immune responses (Howlett et al. 2002; Peyravian et al. 2020; Rapaka et al. 2021).

3.1.2 Non-cannabinoid receptors

In addition to cannabinoid receptors, there are other non-cannabinoid receptors that bind various endocannabinoids, phytocannabinoids, or synthetic cannabinoids. These receptors primarily belong to different types of G-protein coupled receptors (GPCRs). For example, GPR55 is a classical GPCR found mainly in the human brain and liver. It is especially abundant in brain regions such as the hippocampus, forebrain, cortex, and cerebellum, where it plays a role in neural development, sensory neuron function, pain sensitivity reduction, and stress-induced anxiety. It is also involved in regulating neuroinflammation and the production of pro-inflammatory cytokines (Shi et al. 2017; Marichal-Cancinoa et al. 2017). Another GPCR is GPR119, found primarily in pancreatic β-cells, where it helps regulate glucose-dependent insulin secretion, thereby influencing glucose homeostasis (Chu et al. 2007). GPR18, also a GPCR, is found across various tissues and cell types, such as in the spleen, thymus, lymph nodes, bone marrow, and reproductive organs. In particular, it is abundant in myogenic cells, where it aids in reducing inflammation and promoting muscle tissue regeneration. GPR18 is also present in microglia in the CNS, playing an immunoregulatory role alongside CB2 receptors (Reyes-Resina et al. 2018; Morales et al. 2020; Dort et al. 2023). Other GPCRs like GPR3, GPR6, and GPR12 are expressed in the CNS, particularly in the cortex, hypothalamus, hippocampus, and amygdala, as well as in peripheral organs such as the heart, lungs, liver, spleen, kidneys, muscles, and reproductive organs. While their specific physiological and pathological roles are still under investigation, they are thought to be involved in various processes (Laun et al. 2019). Beyond GPCRs, there are also non-cannabinoid receptors like transient receptor potential (TRP) channels and peroxisome proliferator-activated receptors (PPARs) (Muller et al. 2019; Iannotti et al. 2021). TRP channels, including TRPV1, TRPV2, TRPV3, TRPV4, TRPM8, and TRPA1, are involved in regulating various sensory processes, such as temperature, pressure, acid-base balance, and the perception of pain, vision, smell, and taste. These channels are confirmed to bind cannabinoids, although more may be discovered in the future (Muller et al. 2019). PPARs, including PPARα, PPARγ, and PPARβ/δ, are nuclear receptors activated directly by cannabinoids or indirectly through various receptors and enzymes. These receptors regulate gene expression, affecting cellular processes like metabolism, differentiation, and immune responses. PPARs also participate in cross-talk with other receptors like CB receptors and TRP channels (Iannotti et al. 2021).

3.1.3 Endocannabinoids synthesis and degradation

The main endocannabinoids (eCBs), anandamide (AEA) and 2-arachidonoyl glycerol (2-AG), are both synthesized from membrane phospholipids, a process primarily triggered by an increase in intracellular calcium. This increase is mainly mediated by voltage-gated calcium channels (VGCC), and the synthesis and degradation of these eCBs involve distinct enzymatic pathways. The synthesis of AEA from its precursor, N-arachidonoyl phosphatidyl ethanol (NAPE), is predominantly calcium-induced. This activates enzymes such as NAPE-phospholipase D (PLD) and phospholipase A2 (PLA2), although other enzymes also play a role. In contrast, the synthesis of 2-AG, derived from arachidonoyl-containing phosphatidylinositol bisphosphate (PIP2), is also calcium-dependent, but it is mediated through the activation of phospholipase C beta (PLCβ) and diacylglycerol lipase alpha (DAGLα) pathways. This process can also be induced by G-protein activation (particularly via mGluR1/5 and mAchR M1/M3). On the other hand, the degradation of eCBs is an intracellular process, with AEA being degraded by enzymes such as fatty acid amide hydrolase (FAAH) and cyclooxygenase-2 (COX-2), while 2-AG is broken down by monoacylglycerol lipase (MAGL) and other hydrolases (ABHD6/ABHD12). Notably, FAAH is primarily found in postsynaptic neurons, while MAGL is located in presynaptic neurons, meaning that the degradation of AEA and 2-AG occurs on opposite sides of the synapse. Inhibitors of

FAAH and MAGL have been identified, and these could slow the degradation of eCBs, potentially extending their effects through receptor interaction. This presents a promising avenue for therapeutic applications. Additionally, 2-AG is involved in lipid metabolic pathways, as it is a key source of arachidonic acid, which is further converted into pro-inflammatory prostaglandins, highlighting its role beyond the endocannabinoid system (ECS). Similarly, AEA degradation via COX-2 leads to the production of prostamides, which have ECS-independent effects (Lu et al 2016; Winters et al 2021).

3.1.4 Endocannabinoid Signaling

The general model of endocannabinoid (eCB) signaling (Fig. 4) involves the synaptic cleft, where two neurons, along with astrocytes and microglia, are present. The main eCBs, particularly AEA and 2-AG, are synthesized postsynaptically through various mechanisms already discussed, and then released into the synaptic cleft. These molecules cross the cleft and bind to CB1 receptors on the presynaptic membrane, mediating the inhibition of neurotransmitter release through retrograde suppression. Simultaneously, the released eCBs can bind to receptors on the membranes of astrocytes, promoting an increase in intracellular calcium levels. This calcium influx mediates the release of gliotransmitters, which in turn modulate neurotransmitter transmission across the synaptic cleft. Furthermore, these eCBs may also activate CB2 receptors on microglia, which are involved in regulating cytokine release. Some CB1 receptors are also present in the mitochondrial membrane of neurons and astrocytes, playing a crucial role in cellular energetics. In addition to CB1 and CB2 receptors, eCBs, especially AEA, also bind to the TRPV1 receptor, influencing the internalization of glutamate receptors into the cell membrane (Scheyer et al., 2023).

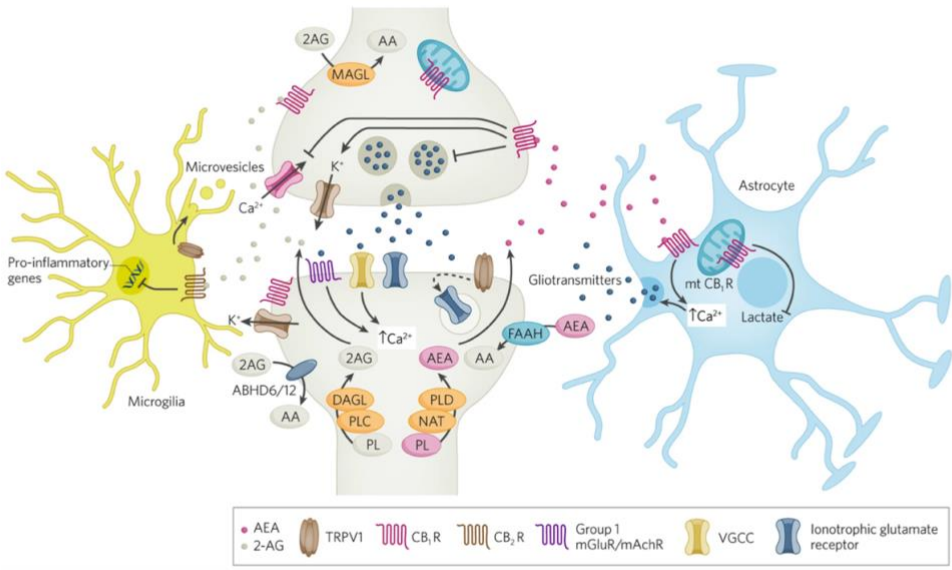

Fig. 4 General model of endocannabinoid signaling

(Scheyer et al 2023)

3.2 PHARMACOLOGY OF CANNABIDIOL

3.2.1 BIOAVAILABILITY

The bioavailability of CBD is largely influenced by its chemical structure, which determines how the body absorbs and utilizes the compound. CBD is a relatively large, lipophilic molecule with a long hydrocarbon chain attached to a phenyl group, making it both lipophilic and hydrophobic. This characteristic impacts its transport and absorption within the body. After CBD is absorbed into the bloodstream, it binds to plasma proteins, such as albumin and lipoproteins, which help transport it throughout the body. Inside the cell, CBD is transported from the membrane to inner structures like the endoplasmic reticulum via intracellular carriers known as fatty acid-binding proteins (FABPs). Due to its lipophilic nature, CBD is often stored in adipose tissue, which can reduce its bioavailability. However, CBD can cross the blood-brain barrier, allowing it to reach the central nervous system (CNS) without being significantly bound to P-glycoprotein, which would otherwise prevent accumulation and potential toxicity in the brain. Several factors related to CBD's chemical properties affect its bioavailability, such as its stability, solubility, permeability, and metabolism. The method of administration plays a crucial role in determining the extent of CBD's absorption. Various administration routes are available, including inhalation (smoke or vapor), oral, sublingual, dermal, transdermal, topical, subcutaneous, intramuscular, intraperitoneal, and rectal routes (Hossain et al., 2023). Inhalation, either via smoke or vapor, results in a rapid onset of action, with distribution occurring within 5 to 10 minutes and a steady state lasting 3 to 5 hours. It has a high bioavailability range of 11–45%, but its short half-life makes it less prolonged compared to other methods. Vaporization is considered safer than smoking due to the lack of combustion and its associated toxic byproducts. Oral and sublingual administration, while common, present slower distribution times: oral administration takes 30 to 120 minutes to take effect and has a bioavailability of 9–13% due to first-pass metabolism. In contrast, sublingual administration avoids first-pass metabolism, improving bioavailability to between 12 and 35%. Intranasal administration also has fast distribution (around 10 minutes) and higher bioavailability (34–46%) (Palrasu et al., 2022; Hossain et al., 2023). Interestingly, studies have shown that taking CBD with a high-fat meal can increase its bioavailability by up to four times (Perucca et al., 2020). Dermal and transdermal routes of administration, which target the skin, have low bioavailability (1–10%) due to CBD's accumulation in the upper layers of the skin (Hossain et al., 2023). Topical administration, especially for ocular surface applications, typically has local effects on inflammation, without significant systemic absorption (Rebibo et al., 2022). Subcutaneous administration, via injection into the adipose tissue, results in slow, sustained release over 28 days (Shilo-Benjamini et al., 2022). This slow release has been similarly observed with CBD nanocrystals injected into muscle tissue, where bioavailability increased more than sevenfold compared to standard oral administration (Fu et al., 2022). Intraperitoneal administration of CBD polymer nanoparticles has shown rapid release of around 80% within the first 90 minutes, with full release within 96 hours (Fraguas-Sánchez et al., 2020). Emerging methods are focused on improving CBD's bioavailability, mainly by enhancing its solubility for more efficient absorption. Innovations include lipid-based carriers, such as vesicles, liposomes, and self-emulsifying drug delivery systems (SEDDS), as well as polymer-based delivery using biodegradable polymers like poly-lactic-co-glycolic acid (PLGA) and poly-ε-caprolactone (PCL). Additionally, solid-based delivery systems, such as CBD nanocrystals and CBD conjugates, are being explored to further improve bioavailability (Hossain et al., 2023).

3.2.2 Pharmacokinetic

"CBD is metabolized and excreted from the human body both in its unchanged form and as various metabolites, which are eliminated through the excretory and digestive systems, primarily via urine and feces. The transformation of CBD into its metabolites occurs mainly in the liver, through two general phases. In phase I, CBD undergoes metabolic transformation by isoenzymes of the cytochrome P450 (CYP) family, including CYP1A1, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5, with CYP2C19 and CYP3A4 being the predominant enzymes involved in CBD metabolism. This phase results in a variety of metabolites, with the primary ones being 7-carboxy-cannabidiol (7-COOH-CBD) and 7-hydroxy-cannabidiol (7-OH-CBD). These metabolites, along with unchanged CBD, then proceed to phase II, where glucuronidation is the main process for further transformation. It is also important to note that CBD not only undergoes metabolic transformation via CYP enzymes but also influences their activity by inducing their expression or inhibiting their function. As a result, CBD can affect the metabolism of other substances in the human body (Kicman et al., 2020)."

3.2.3 Pharmacodynamics

CBD has been shown to function as a potent antagonist to CB1 and CB2 receptors, which are widely distributed across various tissues and cell types throughout the human body. Despite its low affinity for these receptors, CBD's antagonistic activity is notably effective due to its high interaction potential even at low concentrations. This antagonism is often described as inverse agonism of a noncompetitive nature (Thomas et al., 2007; Pertwee, 2008). Additionally, CBD acts as a negative allosteric modulator of cannabinoid receptors, particularly CB1, and also CB2, while simultaneously serving as a partial agonist for CB2 (Laprairie et al., 2015; Martínez-Pinilla et al., 2017; Tham et al., 2019). Moreover, CBD can indirectly affect these receptors by inhibiting FAAH, the enzyme responsible for the degradation of the natural ligand AEA. CBD also interacts with several other G-protein-coupled receptors (GPCRs). For example, it functions as a partial agonist of GPR18, an antagonist at GPR55 (Ligresti et al., 2016), and an inverse agonist at GPR3, GPR6, and GPR12 (Laun et al., 2019), thus exerting antagonistic effects across various GPCRs. Notably, CBD does not uniformly affect all receptors. It acts as a positive allosteric modulator of glycine receptors, particularly α1, α1β, and α3. There is also evidence suggesting that CBD has agonist activity at 5-HT1A receptors and possibly at α1 adrenergic and D2 dopamine receptors, although this evidence remains inconclusive. Furthermore, CBD activates certain TRP channels, such as TRPV1, TRPV2, and TRPA1, while inhibiting TRPM8. It also activates PPARγ receptors. In addition to receptor modulation, CBD can inhibit the reuptake of neurotransmitters such as adenosine, dopamine, and glutamate, while also reducing nitric oxide (NO) production and reactive oxygen species (ROS) production. Interestingly, in cancer cells, CBD induces increased ROS production, leading to cytotoxicity and apoptosis (Ligresti et al., 2016). Lastly, CBD demonstrates strong anti-inflammatory effects through the inhibition of cytokine and chemokine production (Yndart et al., 2023).

3.3.4 Toxicity

Like all substances used as medications, cannabidiol (CBD) has potential adverse effects and toxicity, making it a critical focus of research for its therapeutic applications (Huestis et al., 2019). CBD exhibits a wide range of pharmacological benefits, including anxiolytic, antipsychotic, antiemetic, and anti-inflammatory properties. However, its associated adverse effects, especially during therapeutic use, are not yet fully understood, and both *in vitro* and *in vivo* studies are ongoing to assess its safety at various dosages. Some studies suggest that CBD is non-toxic to non-transformed cells and does not significantly impact essential physiological functions such as body temperature, heart rate, blood pressure, gastrointestinal transit, or nutrient absorption. Additionally, it does not appear to impair psychomotor skills or psychological functions and does not induce catalepsy. Even long-term, high-dose use of CBD has generally been well-tolerated with minimal severe side effects. However, other studies raise concerns, indicating that CBD may inhibit drug metabolism in the liver and suppress the activity of drug transporters like P-glycoprotein. It may also influence cell viability and fertility. For instance, in trials where CBD was used to treat epilepsy or psychosis, observed adverse effects included changes in appetite and weight, diarrhea, and fatigue. Despite these findings, these effects are often considered less severe compared to those of conventional treatments. CBD's interactions with other drugs are particularly noteworthy. It inhibits several cytochrome P450 (CYP) enzymes, which are crucial for metabolizing many medications, leading to drug accumulation and potential toxicity. This includes interactions with antiepileptics such as clobazam, stiripentol, and valproate; antidepressants like selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants; antipsychotics; beta-blockers; opioids; and common substances like acetaminophen and alcohol. For example, inhibition of CYP enzymes by CBD can result in the accumulation of clobazam, causing excessive sedation, or warfarin, leading to an increased risk of bleeding. Interestingly, CBD exhibits a protective effect against some adverse outcomes associated with tetrahydrocannabinol (THC). While it inhibits heroin metabolism, its effect on morphine metabolism is less clear. CBD’s interaction with commonly used substances, such as acetaminophen, can exacerbate liver toxicity, sometimes with severe consequences, highlighting the need for further research into its safety profile and drug-to-drug interactions (Balachandran et al., 2021).

4 POTENTIAL THERAPEUTIC APPLICATIONS

4.1 THERAPEUTIC APPLICATIONS

CBD has been shown to exert various biological effects on healthy human cells. These include a dose-dependent decrease in cell viability, as well as reduced proliferation and migration. Additionally, CBD can induce apoptosis, but this occurs only at higher doses. Other notable effects involve its anti-inflammatory properties, primarily through the suppression of pro-inflammatory cytokine production, which can occur across a broad dosage range. Furthermore, CBD modulates the production of reactive oxygen species (ROS); at low doses, it suppresses ROS production, while at high doses, it enhances ROS levels, potentially causing cellular oxidative stress and resulting in cytotoxic effects. These dose-dependent biological effects must be carefully considered to ensure the proper therapeutic use of CBD (Pagano et al., 2020).

4.1.1 Pain, Inflammation and immune system disorders

One significant area of research on the therapeutic potential of CBD is its application in pain and inflammation management. Numerous studies have highlighted its analgesic and anti-inflammatory properties across various types of pain, including neuropathic, inflammatory, arthritis-related, incision-induced, and myofascial pain, among others. In these cases, CBD has been shown to reduce pain, hyperalgesia, and allodynia, as well as modulate pro-inflammatory and anti-inflammatory cytokines depending on the type of condition. The effectiveness of CBD is highly dependent on its dosage and method of administration (Mlost et al., 2020). In neuropathic pain studies, significant pain reduction was observed. For example, transdermal application of CBD oil in patients with peripheral neuropathic pain led to a marked decrease in intense, sharp pain, and sensations such as coldness and itchiness, without adverse effects (Xu et al., 2020). Similarly, in myofascial pain studies, transdermal CBD application reduced pain intensity significantly, again with no reported side effects (Nitecka-Buchta et al., 2019). A case study involving transdermal CBD cream for chronic back pain reported a noticeable decrease in pain and sensitivity within hours of application, with complete pain elimination after several weeks in one patient. These findings suggest CBD’s potential as a safer alternative to opioid treatments for neuropathic and radicular pain (Eskander et al., 2020). CBD has also been explored as a complementary treatment alongside opioids. In chronic pain patients, co-administration of CBD with opioids improved pain management outcomes and allowed over half of the participants to reduce or eliminate opioid usage altogether (Capano et al., 2020). Beyond pain management, CBD has demonstrated anti-inflammatory properties by suppressing pro-inflammatory cytokines and their receptors, transcription factors, and signaling molecules, particularly in T-cell lines. Significant effects on cytokines like IL-6, IL-10, and IL-17 have been identified, along with the induction of transcripts responsible for anti-inflammatory activity. Additionally, CBD has been shown to modulate oxidative stress mediators, with its effects varying based on dosage, reducing oxidative stress at low doses and inducing cytotoxicity at high doses (Kozela et al., 2016). The first human study on CBD's anti-inflammatory effects confirmed its ability to inhibit pro-inflammatory cytokines like TNF. Cells treated with soluble CBD powder and exposed to bacterial polysaccharides showed reduced inflammatory responses (Hobbs et al., 2020). Another study investigating CBD's role in cytokine release syndrome (CRS) revealed that it could significantly reduce systemic and renal inflammation, suppressing the cytokine storm often associated with cardiac and renal injury in severe infections like sepsis (Maayah et al., 2024). Similarly, CBD decreased cytokine production in acute human colon inflammation (Couch et al., 2017) and expedited mucositis recovery in chemotherapy-induced inflammation (Cuba et al., 2020). CBD's immunosuppressive effects have also been studied, particularly in reducing the incidence of graft-versus-host disease. Patients treated with CBD alongside standard treatments like cyclosporine and methotrexate showed significantly reduced disease occurrence over time (Yeshurun et al., 2015). The immunosuppressive activity is closely related to CBD's ability to downregulate pro-inflammatory cytokines and immune responses, suggesting its potential in autoimmune disease treatments (Peyravian et al., 2020). Other studies have examined CBD's effects on hypersensitivity reactions, revealing its capacity to suppress T-cell and macrophage activity, including the expression of IFN-gamma and TNF-alpha, thus mitigating hypersensitivity symptoms (Liu et al., 2010). CBD also demonstrated potential in airway disorders linked to allergies by inhibiting mast cell degranulation and airway smooth muscle contractions at specific concentrations (Dudášová et al., 2013). Lastly, CBD has been shown to interact with the apelinergic system, increasing apelin levels and reducing symptoms of acute respiratory distress syndrome (ARDS). This suggests its potential for treating inflammatory conditions associated with ARDS, such as COVID-19, by modulating immune responses (Salles et al., 2020).

4.1.2 Neurological disorders, neurodegenerative diseases and Psychiatric disorders

CBD is also considered an intriguing option for the treatment of neurological disorders due to its ability to target a broad spectrum of mechanisms in the central nervous system. It has demonstrated various effects, including neuroprotective, antiepileptic, analgesic, sedative, anxiolytic, antidepressant, and antipsychotic properties. These effects arise from CBD's capacity to regulate pain perception, inflammation, and oxidative processes, making it a potential therapeutic option for neurological conditions such as epilepsy, neurodegenerative diseases like multiple sclerosis, Parkinson's disease, and Alzheimer's disease, as well as psychiatric disorders like anxiety, depression, and schizophrenia (Singh et al., 2023). In epilepsy treatment, several studies have demonstrated the efficacy and safety of CBD. One study highlighted CBD's ability to improve resting-state functional connectivity linked to treatment-resistant epilepsy. After several weeks of treatment with purified CBD, patients experienced a 70% average reduction in seizures, along with positive behavioral changes and normalized functional connectivity (Nenert et al., 2020). Another study involving patients with epileptic spasms showed that oral CBD solutions led to significant cognitive and behavioral improvements in one-third of participants, with fatigue being the only reported adverse effect (Herlopian et al., 2020). Similarly, research on patients with developmental and epileptic encephalopathy reported that almost half experienced a greater than 50% reduction in seizure frequency, while some adverse effects, such as reduced appetite and fatigue, were noted (Pietrafusa et al., 2019). For multiple sclerosis (MS), studies suggest that CBD may reduce neurobehavioral symptoms, inflammation, demyelination, and axonal damage. For example, CBD treatment in a mouse model of experimental autoimmune encephalomyelitis (EAE) showed suppression of inflammatory cytokines and reduced axonal damage (Rahimi et al., 2015). In a single-case study on amyotrophic lateral sclerosis (ALS), co-treatment with CBD and riluzole alleviated symptoms like limb dysfunction and dysphagia, though disease progression resumed after treatment ceased, suggesting CBD may slow ALS progression (Nahler et al., 2017). In Alzheimer's disease (AD), CBD has shown promise due to its neuroprotective, anti-inflammatory, and antioxidant properties. Animal studies indicate that CBD reduces neuroinflammation, promotes neurogenesis, and reverses cognitive deficits (Watt et al., 2017). Additionally, a study on human patients reported improvements in behavioral symptoms like anxiety, agitation, and hallucinations, with minimal adverse effects (Velayudhan et al., 2024). In Parkinson's disease (PD), CBD treatment has yielded mixed results. While one study showed no significant changes in statistical measures, another reported improved motor and emotional function, with mild adverse effects like diarrhea and fatigue (Chagas et al., 2014; Leehey et al., 2020). CBD's antipsychotic properties have been explored in patients at high risk of psychosis, where it modulated brain activity related to emotional and fear processing, supporting its potential as a psychosis treatment (Davies et al., 2020). In schizophrenic patients, CBD treatment was as effective as amisulpride in improving clinical symptoms but had fewer adverse effects, suggesting its value in psychosis management (Leweke et al., 2012). For psychiatric disorders like anxiety and depression, CBD has shown efficacy. In a study on social anxiety disorder, CBD reduced symptoms of anxiety and cognitive impairment, restoring patients' responses to a normal state after a single dose (Bergamaschi et al., 2011). Similarly, in patients with depression, studies in animal models linked CBD's antidepressant effects to increased serotonin and glutamate levels, likely through 5-HT1A receptor modulation (Linge et al., 2016). Single-case studies also highlight CBD's effectiveness in managing major depressive disorders and associated symptoms (Berger et al., 2020; Laczkovics et al., 2021). CBD has been explored for other psychiatric and neurological conditions. For post-traumatic stress disorder (PTSD), patients treated with CBD alongside standard therapies reported reduced symptom severity and improved sleep, with no significant side effects (Elms et al., 2019). CBD has also been tested in children with autism spectrum disorders (ASD), demonstrating reductions in aggression, hyperactivity, sleep disturbances, and anxiety, with only mild adverse effects such as somnolence (Barchel et al., 2019).

4.1.3 Digestive system and metabolic disorders

The anti-inflammatory effects of CBD have been demonstrated across a wide spectrum of animal studies. One study conducted on mice showed that CBD could prevent liver inflammation and mitigate acute hepatitis associated with severe liver injury. This effect is attributed to CBD's activation of myeloid-derived suppressor cells (MDSCs), including neutrophils and monocytes, which suppress T-cell proliferation and their inflammatory response, likely mediated via the TRPV1 receptor. Interestingly, the study highlighted that monocytes were primarily responsible for immunosuppression when MDSCs were present in a 2:1 ratio of monocytes to neutrophils, suggesting CBD as a potential therapeutic option for acute hepatitis (Hegde et al., 2011). Another study on metabolic processes revealed a positive impact on lipid metabolism disorders. Healthy men who received CBD treatment for several weeks experienced significant improvements in HDL cholesterol levels. Additionally, they reported psychological benefits, including reduced stress, better sleep quality, and enhanced overall life satisfaction (Lopez et al., 2020). CBD's effects on metabolic disorders have also been observed in diabetes-focused studies. One study noted a significant reduction in diabetes incidence in non-obese diabetic mice. This was linked to CBD's anti-inflammatory properties, specifically its suppression of cytokine production through the inhibition of Th1 and Th2 cell activation, which in turn prevented insulitis in pancreatic islets, a key factor in diabetes onset (Weiss et al., 2006). Further research explored the impact of sustained obesity, characterized by the accumulation of bioactive lipid derivatives in tissues such as skeletal muscle, on metabolic disorders driven by insulin resistance. CBD treatment was found to reduce intramuscular ceramide production, restore sphingolipid derivative levels, and improve insulin signaling in skeletal muscle. These effects were accompanied by enhanced glucose oxidative metabolism and glycogen restoration, underscoring CBD's potential in managing obesity-related metabolic dysfunctions (Bielawiec et al., 2020).

4.1.4 Cardiovascular diseases

CBD has shown impressive results in the treatment of diabetes, and similar positive outcomes have been observed in cases of diabetic cardiomyopathy. CBD treatment has led to improvements in both diastolic and systolic myocardial performance, along with the attenuation of fibrotic processes. Additionally, it reduced inflammation, oxidative stress, and cell death. These results were observed in both mice and human primary cardiomyocytes, suggesting that CBD could be a promising therapeutic option for cardiovascular diseases (Rajesh et al., 2010). Another study demonstrated CBD's ability to decrease the severity of acute myocardial infarction (AMI). When cardiac occlusion was induced, followed by reperfusion, CBD administered intravenously in double doses resulted in a reduction of AMI size and facilitated ventricular restoration. This effect was attributed to CBD's ability to reduce cardiac leukocyte infiltration, decrease myocellular apoptosis, promote cell wall thickening, and enhance blood flow by alleviating myocardial obstruction (Feng et al., 2015). CBD has also shown cardiovascular benefits in a study focused on reducing the increased blood pressure caused by stress. CBD treatment in several healthy men significantly reduced blood pressure both at rest and in response to stress stimuli, along with a decrease in heart rate. This suggests that CBD could be an alternative treatment for high blood pressure (Jadoon et al., 2017). In a similar study, CBD treatment led to dose-dependent vasorelaxation in both human pulmonary arteries and rat mesenteric arteries. This effect was mediated through several non-cannabinoid receptors in the pulmonary endothelium (Baranowska-Kuczko et al., 2020). A study on healthy men also revealed that short-term CBD treatment could reduce arterial stiffness and increase the internal diameter of the carotid artery, improving endothelial function and resulting in a reduction of blood pressure. Based on these findings, CBD has been suggested as a potential treatment for cardiovascular diseases (Sultan et al., 2020).

4.1.5 Skin and bone disease

It has also been proven that CBD regulates the proliferation and growth of cutaneous cells. In human sebocytes, CBD influences glucose and lipid metabolism through the TRPV4 receptor, as well as the ERK1/2 and MAPK signaling pathways, leading to the inhibition of lipogenesis. Additionally, CBD modulates inflammation via the A2a adenosine receptor and the NF-κB signaling pathway. The ability of CBD to enhance lipostatic and anti-inflammatory activity makes it a potential therapeutic option for treating acne vulgaris (Oláh et al., 2014). Due to its anti-inflammatory and analgesic effects, CBD has also shown promise as a treatment for severe skin diseases such as epidermolysis bullosa. In a case study with several pediatric patients suffering from this condition, CBD, applied topically to affected areas, resulted in faster healing of recurrent wounds, a reduction in blistering, and pain relief. In one case, this treatment even led to the complete reduction of opioid use (Chelliah et al., 2018). The effect of CBD on bone regeneration has also been studied. It has been shown that CBD positively influences regeneration by enhancing the expression of proteins that regulate osteoblast differentiation and activating cell mobility. Additionally, CBD promotes calcium deposition and mineralization (Kang et al., 2020). CBD has also demonstrated effectiveness in the treatment of rheumatoid arthritis, as it increases intracellular calcium levels, leading to reduced cell viability and proliferation in rheumatoid arthritis synovial fibroblasts (RASF) during inflammatory conditions. This effect is largely attributed to the activation of the TRPA1 receptor and the opening of the mitochondrial permeability transition pore (mPTP), which ultimately causes calcium overload and induces cell death. The anti-inflammatory and analgesic effects of CBD in the treatment of rheumatoid arthritis have been further confirmed, although the exact mechanisms remain unclear (Lowin et al., 2020).

4.1.6 Infection treatment

CBD is also considered a potential additional treatment for bacterial infections caused by both gram-negative and gram-positive bacteria, though it acts in different ways for each. In the case of gram-negative bacteria, such as *E. coli*, CBD has been shown to inhibit the release of bacterial membrane vesicles, which are responsible for pathogen-host interactions. This mechanism is considered a general cause of antibiotic resistance. However, this effect has not been observed in gram-positive bacteria like *S. aureus*. On the other hand, in the case of gram-positive bacteria, CBD has demonstrated a different effect. When CBD was co-administered with bacitracin (BAC), its antibacterial effect was significantly potentiated through cell wall targeting, resulting in impaired cell division and membrane irregularities. This effect was not observed in gram-negative bacteria. In summary, CBD still appears to be an effective treatment option, particularly when co-administered with selected antibiotics to enhance their effectiveness or to help suppress resistance (Kosgodage et al. 2019; Wassmann et al. 2020). The effect of CBD on viral infections has also been studied, and it has been shown to have antiviral properties, suggesting its potential as a treatment. This effect was demonstrated in a study involving Zika virus and other viruses. Infected cells treated with non-cytotoxic concentrations of CBD showed a decrease in cholesterol, which impacted the replication of Zika and other viruses. Additionally, CBD-treated cells induced IFN-β production, which regulates viral replication. Thus, CBD has been suggested as a potential treatment for various viral infections and considered a possible therapeutic option during situations like the COVID-19 pandemic (Marquez et al. 2024).

4.1.7 Cancer treatment

There is increasing evidence showing the positive effects of CBD in cancer treatment due to its ability to act as a tumor inhibitor. In one study involving brain tumors, particularly glioblastoma grade IV, a disease with fatal consequences, high doses of CBD were used as an additional treatment to the usual regimen, including maximal resection followed by radiotherapy and chemotherapy. The results were impressive, as the standard prognosis for this diagnosis is around 15 months of survival. However, all patients in the study, except one, were alive at the time of publication, with an average survival time of 22 months, ranging from 7 to 47 months (Likar et al. 2019). Another remarkable outcome was observed in a case study of a man diagnosed with lung cancer, specifically adenocarcinoma, who rejected standard treatment (radiotherapy and chemotherapy) and instead opted for CBD treatment. He self-administered daily low doses of CBD oil for several months, which resulted in almost complete resolution of the tumor mass, with only small residues remaining in the lungs and lymph nodes, and the condition was reported as stable (Sulé-Suso et al. 2019). One of the mechanisms through which CBD affects cancer is by inhibiting angiogenesis, which is crucial in the process of tumorigenesis. In one study, the application of CBD resulted in the inhibition of migration, invasion, and sprouting of human umbilical vein endothelial cells, as well as the inhibition of angiogenesis itself (Solinas et al. 2012). Another important mechanism involved in tumorigenesis is cell proliferation. A study showed that CBD directly induces cell differentiation and subsequent autophagy of tumorigenic cell populations, such as glioma stem-like cells, thereby inhibiting the proliferation process. This autophagy effect appears to be mediated via TRPV2 receptor activation and the PI3K/AKT signaling pathway (Nabissi et al. 2015). CBD has also been shown to cause cytotoxic effects in cancer cells, as it participates in the production of reactive oxygen species (ROS), leading to oxidative stress in the cells and promoting cell apoptosis and tumor necrosis (Cerretani et al. 2020). In summary, CBD has been shown to have anti-proliferative and pro-apoptotic effects in various types of cancer. These effects are based on CBD's ability to regulate several critical cell mechanisms and functions, such as arresting the cell cycle, inducing autophagy, and inhibiting cell migration and invasion. These cellular effects are also accompanied by modifications to the tumor microenvironment, involving the modulation of mesenchymal cells and immune cell activity. All of these effects are mediated by various types of receptors and channels, involving multiple signaling pathways depending on the specific tumor type (Seltzer et al. 2020).

5 CONCLUSION

Cannabidiol (CBD) is a well-known compound that has been studied for over 80 years from various perspectives, including its chemical properties and effects on the human body. The primary goal of this research has been to evaluate its efficacy in treating a wide range of human diseases compared to other treatment options. CBD is widely available because it is naturally synthesized in *Cannabis sativa L.*, alongside other phenolic compounds known as phytocannabinoids. Its natural production levels depend on various internal and external factors. While CBD predominantly occurs in its acidic form, its neutral, decarboxylated version is also naturally produced in smaller amounts. This non-enzymatic conversion is heat-driven, making it easy to achieve. CBD is an organic molecule with two isomers—natural and synthetic—and several natural derivatives. It is reactive under acidic and basic conditions, as well as in the presence of oxygen or exposure to radiation. In the human body, CBD primarily interacts with the endocannabinoid system, which includes cannabinoid and non-cannabinoid receptors, along with endocannabinoids acting as ligands. These components are widely distributed across various organs, tissues, and cell types, particularly in the nervous and immune systems. CBD influences numerous physiological processes and pathological states through cellular signaling pathways. These include critical processes such as gene transcription and enzyme production, which regulate cell functions like growth, survival, immune responses, proliferation, migration, apoptosis, and inflammation. The bioavailability of CBD depends on its lipidic chemical nature and is influenced by several factors, particularly the mode of administration. It is metabolized predominantly in the liver by specific enzymes into various metabolites, which are excreted along with partially unchanged CBD via the excretory and digestive systems. Although CBD is not toxic and does not cause severe adverse effects, it can slow the metabolism of certain drugs. CBD has demonstrated numerous biological effects, such as reducing cell viability, suppressing proliferation and migration, inducing apoptosis, and modulating cytokine production. Specifically, it reduces pro-inflammatory cytokines and enhances anti-inflammatory cytokines. It also regulates the production of reactive oxygen species (ROS), which it can either suppress or enhance depending on the context. These properties make CBD effective in treating a broad spectrum of diseases, including pain, inflammation, immune disorders, neurological and neurodegenerative conditions, psychiatric disorders, metabolic and digestive diseases, cardiovascular conditions, skin and bone diseases, severe bacterial and viral infections, and even cancer. Although most clinical studies have been conducted on animals, many human studies have shown impressive results. CBD has demonstrated effectiveness comparable to or surpassing traditional treatment approaches, positioning it as a promising and versatile therapeutic option. Further research and expanded clinical applications are warranted to maximize its potential.

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