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Review

A Holistic Review of Cannabis and Its Potential Risks and Benefits in Mental Health

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Abstract

Background: The dual nature of cannabis, as both a promising therapeutic tool and a widely used recreational substance with potential risks, raises important societal controversies, including its unclear impacts regarding mental health. This narrative review provides a comprehensive overview of cannabis, addressing (i) its historical context; (ii) its chemical composition and pharmacokinetics; (iii) its pharmacological effects; (iv) its negative impacts on physiological and mental health; (v) its potential use as a drug for the treatment of neurological and psychiatric disorders; (vi) its relationship with the gut microbiome and how this interaction might influence mental functioning; (vii) the pathophysiology, prevalence, comorbidities, and treatment strategies of cannabis use disorder; and (viii) social perspectives on its legalization. Results: Cannabis presents a complex chemical profile and pharmacokinetics that show promise in treating numerous neurological, psychiatric, and psychological conditions. However, its use carries risks, which depend on factors such as compound concentration, dosage, consumption method, frequency of use, and individual vulnerability. Cannabis use disorder seems to be less severe than other substance use disorders, but it still constitutes a significant concern, as its manifestation is not uniform across all users. Conclusions: Cannabis demands a thorough understanding that goes beyond simplistic explanations and prejudices, standing as a plant of substantial clinical significance and highlighting the importance of personalized approaches to its use and increased awareness of how individuals respond to its effects.

Keywords: cannabis; marihuana; marijuana; hemp; mental health; potential risks; therapeutic effects; cannabis use disorder; gut microbiome

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1. Introduction

Cannabis, also known as marihuana, marijuana, or hemp, is a substance derived from the cannabis plant (*Cannabis sativa* L., 1753) that contains more than 100 cannabinoid compounds [1]. Its consumption is widespread worldwide, including cultural, medical, and recreational applications, and has been the subject of extensive research due to its low potential for inducing dependence compared to other drugs, its relatively mild adverse health effects, and its numerous potential therapeutic benefits [2,3]. Moreover, cannabis use disorder (CUD) has been considered a condition in which both the individual and public health implications are less severe than those of other distinct substance use disorders (SUDs), but due to the global prevalence of cannabis use, a notable number of users seek treatment [4].

Beyond its industrial applications as a source of fiber, oil, and bioactive compounds, cannabis has garnered significant scientific interest for its pharmacological potential, including antibacterial properties, anti-inflammatory effects, and therapeutic benefits in several physical diseases (e.g., cancer and glaucoma), neurological diseases (e.g., amyotrophic lateral sclerosis, multiple sclerosis, epilepsy, and Tourette syndrome), neurodegenerative diseases (e.g., Alzheimer's disease, Huntington's disease, and Parkinson's disease), medical conditions (e.g., chronic pain, inflammatory bowel disease, and sleep disturbances), and mental health disorders (e.g., anorexia nervosa, anxiety disorders, and post-traumatic stress disorder [PTSD], SUDs) [1–3]. Conversely, cannabis has also raised considerable concern due to its potential negative effects on mental health. While the exact causal relationship is not fully understood, research has shown an association between cannabis use and the onset or exacerbation of diverse psychiatric conditions, including schizophrenia, bipolar disorder (BD), depression, generalized anxiety disorder, social phobia, and personality disorders. Nevertheless, these associations are complex and influenced by several confounding factors, such as pre-existing mental health conditions, individual vulnerability, age of first use, and frequency of consumption [5]. In addition, studying the potential of cannabis is hindered by factors such as regulatory restrictions, the complexity of its diverse phytocannabinoids, variations in product content, and the lack of standardized formulations and administration routes, all of which complicate efforts to conduct effective placebo-controlled trials and accurately assess its efficacy and safety [3]. This underscores the importance of examining cannabis and its derivatives not only from a pharmacological perspective but also through a broader lens that integrates public health and clinical practice considerations, independent of prohibitionist biases or sociopolitical influences, including alternative pathways that remain underexplored but could significantly mediate its effects, such as the role of microbial products.

The dual nature of cannabis, as both a promising therapeutic tool and a widely used recreational substance with potential risks, raises important societal controversies, including its unclear impacts on mental health. As attitudes toward cannabis continue to evolve, particularly with movements advocating for its legalization in various parts of the world, there is a growing need for research to address the potential benefits and the negative consequences associated with its use, as well as its underlying mechanisms as a substance. In fact, a better understanding of the endocannabinoid system (eCBS) could help clarify the psychoactive outcomes of cannabis and its possible advantages and drawbacks. Ultimately, enhancing our comprehension of the topic is pivotal for developing evidence-based guidelines that not only maximize the medicinal potential of cannabis but also minimize its risks, ensuring that its use is both safe and beneficial in clinical settings. Therefore, building on the expanding body of research into cannabis and its diverse applications, this narrative review provides a comprehensive overview of cannabis as both a substance and a potential therapeutic agent. Specifically, addressing the topic from a holistic perspective with a particular focus on mental health, this review examines the following key aspects of cannabis: (i) its historical context; (ii) its chemical composition and pharmacokinetics, including its cannabinoid constituents and routes of consumption; (iii) its pharmacological effects; (iv) its negative impacts on physiological and mental health; (v) its potential use as a drug for the treatment of neurological and psychiatric disorders; (vi) its relationship with the gut microbiome (GM) and how this interaction might influence mental functioning; (vii) the pathophysiology, prevalence, comorbidities, and treatment strategies of CUD; and (viii) social perspectives on its legalization.

2. Method

The conceptual framework underlying the present review was structured to support a broad, integrative examination of cannabis. Accordingly, the review was intentionally designed to adopt a holistic perspective that would enable the synthesis of heterogeneous lines of evidence within a descriptive framework. A non-systematic narrative approach was deemed the most appropriate, as it allowed the integration of a wide range of literature addressing multiple facets of the subject under study. An extensive search of the scientific literature was conducted using the databases PubMed, Scopus, ResearchGate, and Web of Science. A broad range of keyword combinations was employed, with iterative adjustments to maximize coverage. These combinations were thematically aligned with the core focus of the review and were constructed using Boolean operators to capture variations across terminology and conceptual domains. MeSH terms were employed for the core concepts of "cannabis" and "mental health" to ensure conceptual consistency and retrieval accuracy. Additionally, a wide-ranging set of free-text keywords was used to expand thematic coverage and capture relevant literature. No language restrictions were applied, although only English-language search terms were used. Most of the included articles were published in English, with some in Spanish, and none required the use of translation tools. No temporal restrictions were applied regarding the publication date. However, when the results overlapped between older and more recent studies, priority was given to the latter to ensure the inclusion of the latest available evidence, unless the earlier work provided more comprehensive data or offered greater relevance to the topic under examination. Moreover, given the high number of studies on cannabis-related topics, selection was necessarily constrained to those considered most pertinent and aligned with the specific scope and objectives of the review. In addition to database searches, relevant studies were also identified through screening the reference lists of previously published articles, as well as from literary sources and foundational works within the field. The selection of studies was carried out in two stages. The first stage involved screening titles and abstracts to identify studies with potential relevance to the review. In the second stage, full texts were examined in detail, and only those articles that fulfilled the established criteria and were deemed appropriate were retained for analysis. Both authors independently conducted the screening process at each stage. Studies were included if they examined cannabis-related topics such as its history, chemical constituents, including cannabinoids, routes of administration, pharmacokinetics, biological and pharmacological effects, impacts on physiological and mental health, therapeutic applications in mental health, interactions with the GM and microbial metabolites, addiction potential and treatment, including prevalence and psychiatric comorbidities, and broader social implications related to legalization. Exclusion criteria involved the removal of (i) non-peer-reviewed literature; (ii) conference abstracts; (iii) studies that did not provide sufficient information pertinent to the topic under investigation; (iv) articles focused exclusively on industrial, agricultural, or forensic aspects of cannabis; (v) studies focusing on substances other than cannabis or on SUDs not specific to CUD; and (vi) doctoral dissertations. While no formal risk of bias tool was implemented, given the narrative nature of this review, preference was given to studies employing clearly defined methodologies and appropriate statistical analyses, especially in those addressing the relationship between cannabis use and mental health outcomes, as well as in those addressing the therapeutic potential of cannabis. Studies that failed to meet the inclusion criteria or lacked sufficient relevance were excluded from the review.

3. Historical Context of Cannabis

Cannabis has been feared and praised in different ways over the centuries, depending on the prevailing culture and politics. While the Eastern cultures of Hindustan employed

cannabis as a source of happiness (*vijohia*) and life (*ananda*), the Buddhists used it as a tool for meditation, and in Babylon and Egypt, it was consumed for medicinal purposes or as a means of pleasure. The earliest registrations of the medicinal applications of cannabis appeared in China, where a mixture of wine and herbal extracts, possibly containing cannabis, was used as a general anesthetic in surgery [6]. Ancient Greece also makes references to the use of cannabis in the writings of Homer, who stated that its origin came from Egypt. For his part, Herodotus described how the Scythians, after the burial of a king, prepared small ceremonies in which the participants threw hemp seeds on red-hot stones in order to be "delighted" by the fragrant smoke [6]. In the Roman Empire, the medical use of cannabis was mentioned by several erudites such as Pliny the Elder, Dioscorides, and Galen, who discussed the medicinal implications of the plant, differentiating cultivated cannabis and wild varieties, and indicating both antalgic and anti-inflammatory properties related to this substance. During the 12th century, Saladin gave lessons in honorability to the Templar knights, not only treating the prisoners in an exemplary manner, but also sending doctors to enemy camps in order to cure illnesses. In fact, the virtues of his remedies plunged many Christians into an admiring stupor, and upon returning to Europe, they were the first to defend preparations made from hemp and other drugs with narcotic effects [7]. However, the Inquisition, an institution that exercised its power within a European culture in which positive attitudes towards alcohol predominated, opposed cannabis during the 12th and 13th centuries, since it was thought that it could be a drug associated with witchcraft rituals, as well as with Eastern religions. In addition to religious issues, commercial pretensions led Napoleon to ban hemp at the beginning of the 19th century, although the newly founded American nation witnessed the regular cultivation of various species of this plant [7]. Indeed, cannabis became fully accepted in Western medicine in the late 19th century. For instance, Queen Victoria took this drug for painful menses, while Empress Elisabeth of Austria took it for a cough, and possibly to stimulate the appetite [6]. In the present time, however, global culture manifests itself in a relatively homogenized attitude that has come to be known as the "War on Drugs" [8].

This current situation with cannabis is the result of a prohibitionist perspective built up throughout the 20th century, as opposed to a more tolerant 19th century. For instance, the British Indian Hemp Drugs Commission of 1894 did not consider its moderate use to be sufficiently detrimental to health to warrant restrictive measures against it in their Indian colonies. By this time, the drug was not only serving as an inspiration tool in art, but was also included as a basic ingredient in the Western pharmacopeia. Over time, cannabis was displaced by the discovery of other sedative and analgesic drugs like aspirin [6]. In this regard, replacement of cannabis by synthetic alternative products could happen due to more predictable results in the treatment. The conclusion of the Hemp Drugs Commission coincides in a way with the ancient Chinese medicine hero Shen Nung, in 2737 BC, as noted in the Pen Tsao Ching (1st century AD), which associated habitual consumption of cannabis with cognitive distortions [9]. This legendary figure warned that hemp taken in excess makes one see monsters, and if used for a long time, it can serve to communicate with the spirits and to lighten the body [7].

In the early 20th century, particularly in the United States of America, cannabis was demonized due to social fears and prejudices, with propaganda such as the 1936 film *Reefer Madness* falsely portraying the substance as a cause of violence and moral decay, despite the lack of scientific evidence. There are multiple value judgments as to whether the current prohibition of cannabis is a reaction to the promotion of favored alternatives by the pharmaceutical industry, societal trends towards abstinence or perceived virtue, advancements within the clinical field, concerns over immigration, political and economic interests, social prejudices, or a legacy of disinformation and stigmatization. After World

War I, the United States of America led the first steps towards prohibitionism, which became evident during the World Drug Conventions of Geneva in 1931 and 1936, and later with the Marihuana Tax Act of 1937, just after the failed attempts of the frustrated Dry Law [10]. This stance limited the medical use and research of cannabis, resulting in several years of no scientific progress within the study of this plant. While reports such as LaGuardia's in 1944 did not opt for the prohibitionist stance, this position gradually established itself as the international pattern of attitudes towards drugs, contributing to the illegalization of cannabis even in geographical contexts with a traditional use of this substance. Cannabis was awakened again later, with the psychedelic revolution of the 1960s, during which use increased, especially among young people [11]. Nevertheless, despite the declarations of the 1972 National Commission on Marihuana and Drug Abuse that the harms were not serious enough to justify a criminal law, the Nixon administration implemented it. As a result, the legacy of an "aborted rebellion" became even more prohibitionist [7].

4. Basic Aspects of Cannabis

The effects of cannabis are influenced by a variety of factors, including its composition, the methods of consumption, and the pharmacokinetics of its active compounds. The primary cannabinoids found in cannabis interact with the eCBS, leading to a wide range of physiological and psychological effects. In addition, the route of administration greatly impacts the onset and intensity of these effects, as each method alters how cannabinoids are absorbed and metabolized by the organism. Moreover, the pharmacokinetics of cannabis are also pivotal, as the body's processing of cannabinoids can vary depending on factors such as dosage, individual metabolism, and the specific form of cannabis used.

4.1. Cannabinoid Constituents of Cannabis

About 100 specific cannabinoids have been isolated from *C. sativa* and categorized into different types: cannabichromenes (CBCs), cannabicyclols (CBLs), cannabidiols (CBDs), cannabielsoins (CBEs), cannabigerols (CBGs), cannabinodiols (CBNDs), cannabinols (CBNs), cannabitriols (CBTs), (−)-Δ^9-trans-tetrahydrocannabinols (Δ^9-THCs), (−)-Δ^8-trans-tetrahydrocannabinols (Δ^8-THCs), and the multifarious cannabinoids [12]. Table 1 shows the cannabinoids produced by different biological species and their major relevant bioactivities [12–17].

Table 1. Cannabinoids produced by several biological species and their most relevant bioactivities (according to [12–17]).

Biological Species	Cannabinoids Produced	Bioactivities
Cannabis sativa	Tetrahydrocannabinols (THCs) Cannabidiols (CBDs) Cannabigerols (CBGs) Cannabichromenes (CBCs) Cannabicyclols (CBLs) Cannabielsoins (CBEs) Cannabinols (CBNs) Cannabinodiols (CBNDs) Cannabitriols (CBTs) Miscellaneous cannabinoids	- Analgesic responses, relaxation, dysphoria, tolerance, and dependence. - Antiemetic, antiglaucoma and appetite stimulant. - Sleep disorders and gut inflammation improved. - Anticonvulsive, anti-anxiety, antipsychotic, and antirheumatoid arthritis properties. - Anti-inflammatory, antihyperalgesia, and neuroprotective effects. - Protection against UV and desiccation. - Influence on lipolysis, decreased fasting plasma glucose, and energy balance.

Table 1. *Cont.*

Biological Species	Cannabinoids Produced	Bioactivities
Cannabis sativa	Tetrahydrocannabinols (THCs) Cannabidiols (CBDs) Cannabigerols (CBGs) Cannabichromenes (CBCs) Cannabicyclols (CBLs) Cannabielsoins (CBEs) Cannabinols (CBNs) Cannabinodiols (CBNDs) Cannabitriols (CBTs) Miscellaneous cannabinoids	- Analgesic responses, relaxation, dysphoria, tolerance, and dependence. - Antiemetic, antiglaucoma and appetite stimulant. - Sleep disorders and gut inflammation improved. - Anticonvulsive, anti-anxiety, antipsychotic, and antirheumatoid arthritis properties. - Anti-inflammatory, antihyperalgesia, and neuroprotective effects. - Protection against UV and desiccation. - Influence on lipolysis, decreased fasting plasma glucose, and energy balance.
Rhododendron adamsii *R. anthopogonoides* *R. dauricum* *R. rubiginosum*	Chromane/chromene meroterpenoids (CBC, CBL) Grifolic acid (GFA) Daurichromenic acid (DCA) Confluentin (decarboxylated DCA) Rhododaurichromenic acids A-B Rubiginosins A-G Anthopogochromenes A-B Cannabigerorcynic acids Cannabiorcicyclolic acids	- Bioactivities in the immune system. - Anticancer, antimicrobial, anti-inflammatory, antithrombotic, and antipsychotic activities. - Anti-HIV activity.
Helichrysum umbraculigerum *Glycyrrhiza foetida* *Amorpha fruticosa*	Amorfrutins (bibenzyl cannabionoids)	- Anti-inflammatory effects.
Radula laxiramea *R. marginata* *R. perrotteti*	Perrottetinene (bibenzyl cannabinoid)	- Elicits the tetrad of behaviors: hypothermia, catalepsy, hypolocomotion, and analgesia.
Mycorrhizal fungi: *Albatrellus dispansus* *Cylindrocarpon olidum*	GFA DCA Grifolin and neogrifolin Confluentin Cannabiorcichromenic acids	- Antimicrobial activity (bacteria and fungi). - Anti-inflammatory. - Anti-HIV activity. - Anticancer. - Anti-oxidative properties.

C. sativa mainly produces alkyl-type cannabinoids with a monoterpene isoprenyl moiety and a pentyl side chain [18]. Cannabinoid biosynthetic pathways typically produce acidic cannabinoids (precannabinoids), and further modified cannabinoids are genuine conversion or degradation products that result from cyclization, decarboxylation, and oxidation, or that are established in the course of isolation [19]. These transformations occur due to the poor oxidative stability of alkyl cannabinoids, especially Δ^9-THC [18]. *C. sativa* is the most abundant and productive source of phytocannabinoids, although it is not the unique entity with the capacity for synthesizing this category of bioactive natural products, such as *Rhododendron* spp., *Helichrysum umbraculigerum*, *Glycyrrhiza foetida*, *Amorpha fruticosa*, *Radula* spp., and the mycorrhizal fungi *Albatrellus dispansus* and *Cylindrocarpon olidum*.

4.2. Routes of Consumption

Several studies point out that the prevalence of cannabis consumption and CUD is growing over time, although there is insufficient consensus regarding how to estimate cannabis use [20]. One of the pivotal issues in establishing such measures is identifying the route of administration (e.g., inhalation, oral, topics) [21,22]. There is paucity of empirical research scrutinizing the diverse modes of cannabis administration, and the studies published to the current date are quite limited due they typically examine only one mode of consumption (i.e., mostly inhalation of the substance by combustion), do not assess poly-use, and measure the mode of use at only one point in time [23]. According to Wadsworth et al. [21], Canada and the United States exhibit some of the highest global rates of cannabis use. Within these countries, smoking cannabis is declining, while vaping cannabis is increasingly prevalent among youth and young adults. Although fewer studies have investigated non-smoking routes of cannabis use, it is estimated that approximately one-third of recent cannabis consumers use the substance via alternative modes of administration.

Route of consumption influences the duration, the intensity, and the onset of substance effects and health consequences [24]. Inhalation is the most common way of consumption for cannabis (6–14% THC), hashish (10–20% THC), and budder (82–97% THC). Cannabis can be smoked through a variety of instruments (e.g., blunt, bong, dabbing, hookah, joint, pipe, waterpipe), and also vaporized, a mode in which exposure to toxins and to respiratory harm has been considered to be less compared to smoking, but subjective effects are similar, while pharmacological effects are substantially stronger [25,26]. Therefore, different modes of cannabis use (route of consumption and device used) are related to distinct drug outcomes. For example, smoking cannabis delivers Δ^9-THC to the circulation and to the central nervous system (CNS) more rapidly than oral ingestion, which may have implications in abuse liability [27]. Moreover, smoking blunts has been linked to higher levels of perceived intoxication and of withdrawal than other smoking means [28]; while it has been stated that joints, in turn, seem to produce more plasma THC than blunts [29]. In addition, vaporized cannabis seems to result in higher peak concentrations of THC in blood, compared to equal doses of smoked cannabis [30].

Oral forms of cannabis use include edibles, ingestible oils, and tinctures. Some forms of cannabis, such as edibles and concentrates, contain up to 90% THC [31], and the pharmacokinetics of cannabis are highly variable. In this respect, the onset of action is delayed, with maximum blood levels occurring up to 6 h after ingestion and a half-life of 20 to 30 h [32]. The oral route of administration comprises solids enriched which butter, leaf flour, oil or seeds, legal tablets, and liquids such as fermented rice (chastri), milk (cannabis milk, or cannamilk, or marijuana milk, which should not be confound with hemp milk, because the latter is free from psychotropic effects), butter (cannabutter), oil (cannabic-oil), and yogurt (bhang lassii).

Based on their liposolubility, whole fats have been employed for THC extraction, but the dosage is difficult to estimate, so higher concentrations than estimated can be obtained. Because it is absorbed in the gastrointestinal tract and metabolized in the liver, cannabis effects start 1–3 h after ingestion and last up to 24 h; unlike the inhalation route, where cannabis effects onset is fast and persist for up to 6 h on average [30,33]. Some studies have reported cases of poisoning after the consumption of THC extracted from a milk infusion [33–35]. Symptoms include psychotic episodes and visual distortions ranging from color images to interaction with simple, small figures or cartoons, as well as tachycardia, hypotension, and somnolence. Users of low/moderate doses of cannabis have a higher risk of experiencing a cardiac ischemic episode during the 60 min after consumption [36], due to increased sympathomimetic activity and decreased parasympathomimetic

activity, thereby provoking tachycardia and increasing oxygen consumption, so it may be recommended to be cautious regarding to the doses applied in patients with pre-existing cardiovascular disease or ruptured intracranial aneurysms [36,37]. The use of cannabis milk as a form of recreational cannabis consumption may well develop. As with inhalation, cardiac symptoms are also frequent; however, the oral route develops less tolerance, psychotic symptoms are much more common, and cognitive distortions can be closer to those experienced after the use of LSD or hallucinogenic mushrooms [38].

The topical route of administration, specifically in the form of a cream, has been utilized for the treatment of arthritic pain with differing degrees of success. Other alternative routes, such as lozenges, skin patches, sublingual tablets, or suppositories, have been tried for medical purposes with limitations in attaining standardized results. Additionally, the considerable variation of cannabinoids in each mixture makes it difficult to determine an accurate dosing [39].

5. Pharmacological Effects of Cannabis

Cannabinoids consist of two plant-derived components (phytocannabinoids), the psychoactive molecule Δ^9-THC and the non-psychoactive molecule CBD, which are related to another of internal synthesis, the eCB [40]. The varied and potent effects of numerous phytocannabinoids on human physiology arise from their interaction with endogenous cannabinoid receptors and are influenced by the levels of their endogenous ligands. These receptors and ligands, along with the enzymes and transporters that regulate their metabolism, constitute the eCBS. This system is conserved throughout evolution from coelenterates to humans [41]. Thus, the eCBS comprises two cannabinoid receptors (CB1 and CB2), their endogenous ligands, termed endocannabinoids (eCBs), and at least five anabolic and catabolic enzymes that regulate the availability of these ligands in the tissues [42,43]. The eCBs are arachidonic acid precursors that are derived from cell membrane phospholipids, such as N-arachidonyl-ethanolamide (AEA or anandamide) and 2-arachidonoylglycerol (2-AG), with different affinities for CB1 and CB2 [41,44,45].

Cannabinoid receptors CB1 and CB2 belong to the G protein-coupled receptor (GPCR) family. CB1 is predominantly expressed in the brain, making it the primary mediator of the psychoactive effects of cannabis, while CB2 is mainly expressed in the immune system [46,47]. Both receptors interact with G proteins and regulate various intracellular signaling pathways, including inhibition of adenylyl cyclase activity and calcium channels, modulation of D-type potassium channels, enhancement of mitogen-activated protein kinases phosphorylation, and activation of A-type potassium channels [48–50]. Apart from CB1 and CB2 receptors, endocannabinoids have been shown to influence various other receptors and channels. These include glycine receptors, transient receptor potential channels, and several GPCRs such as GPR 55, GPR18, and GPR119, as well as γ-aminobutyric acid A ($GABA_A$). Furthermore, endocannabinoids also interact with the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ) [41,49].

Dysregulation of eCBS has been related to physiological and neuropsychiatric conditions, such as acute stress, Alzheimer's disease, autism, depression, mastocytosis, cancer, and schizophrenia [51–54]. In addition, the eCBS acts as a link between the brain and the GM, regulating intestinal homeostasis and modulating the stress response [40,55–59]. While the eCBS was originally thought to be restricted to the CNS and associated with the regulation of cognitive processes, memory capacity, motor control, and neurotransmitter release [60], it is currently understood that cannabinoid receptors are also expressed in the immune and reproductive systems, thereby being influenced by these compounds [61–63].

The psychoactive and enteric effects of cannabis are mediated by CB1 and CB2 receptors [64]. CB1 is expressed in the intestinal epithelium, brain, and on activated immune

cells, among other locations [63]. Its activation decreases gastrointestinal motility and gastric acid secretion, but increases feeding and binge-like behavior [65]. CB2 is highly expressed in plasma cells, including macrophages, but poorly expressed in the brain [66]. CB2 activation is involved in modulating intestinal inflammation, in regulating abnormal gut motility, and in limiting visceral sensitivity and pain [67]. In addition, activation of CB2 activation can also lead to significant changes in the immune response, including apoptosis, cytokine suppression, altered T cell differentiation toward T regulatory (Treg) cells, induction of myeloid-derived suppressor cells (MDSCs), and a shift in immune status from a pro-inflammatory (Th1) to an anti-inflammatory (Th2) profile [61,63,68–73]. Thus, the diverse pharmacological effects of cannabinoids result from their complex interaction with multiple receptor systems, leading to widespread modulation of neurological, immune, and gastrointestinal functions. This dynamic signaling underlies both the therapeutic potential and the variable clinical responses observed with cannabis use. Figure 1 presents the enteric effects of cannabis mediated by CB1 and CB2 receptors (modified from [57]).

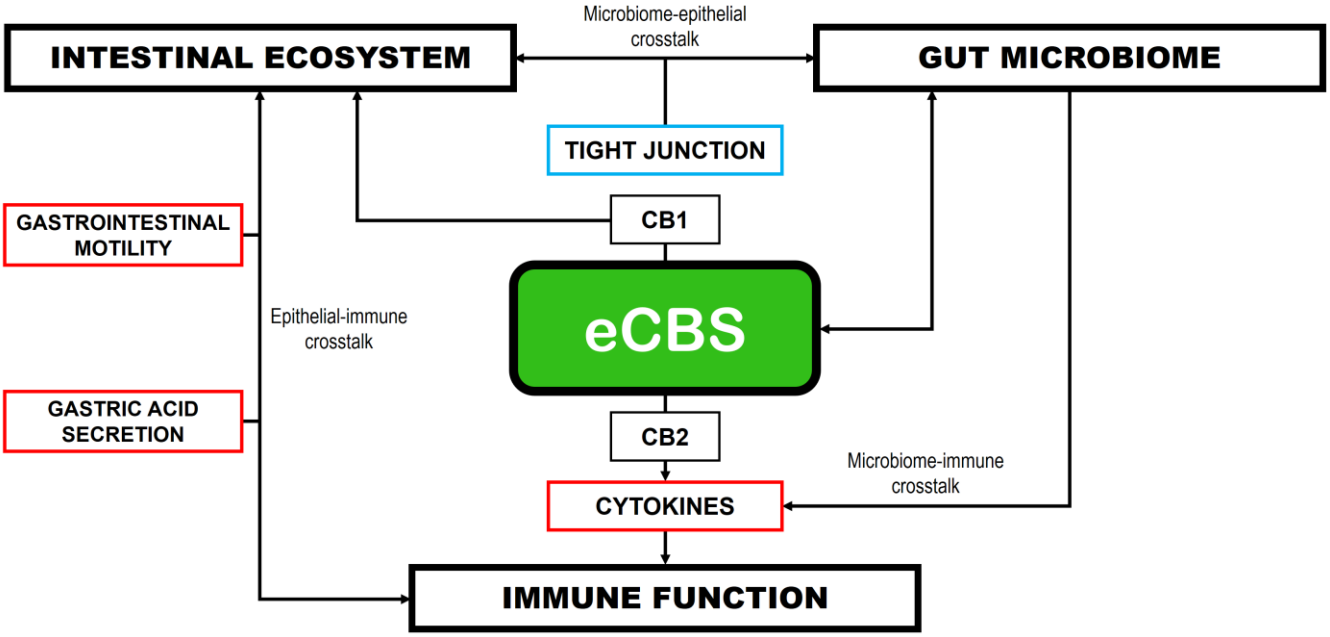

Figure 1. Enteric effects of cannabis mediated by CB1 and CB2 receptors. Rectangles in blue: increase. Rectangles in red: decrease. The eCBS, through both CB1 and CB2 receptors, modulates the complex crosstalk between the epithelium and the immune system, the immune system and the microbiome, and the microbiome and the epithelium. Activation of CB1 exerts a positive regulatory effect on tight junctions, thereby reducing gastrointestinal motility and gastric acid secretion. The eCBS also regulates immune cell function by decreasing cytokine release, primarily through CB2 receptor activation. Notably, the eCBS and the GM exhibit reciprocal interactions.

Cristino et al. [42] proposed the term endocannabinoidome (eCBome) to describe an expanded eCBS that includes several non-eCB long-chain fatty acid amides and esters, including: (i) the congeners of AEA (the N-acyl ethanolamines, NAEs) and 2-AG (the 2-acylglycerols, 2-AcGs); (ii) the N-acyl amino acids; (iii) the acylated neurotransmitters such as the N-acyl dopamines and N-acyl serotonins; and (iv) the primary fatty acid amides. Although these lipid mediators may share biosynthetic or inactivating enzymes with AEA and 2-AG, they do not necessarily share their receptors, which encompass orphan GPCRs, ligand-activated ion channels, and peroxisome proliferator-activated nuclear receptors (PPARs). Di Marzo [74] argued that eCBome explains some of the pharmacological properties of non-THC phytocannabinoids.

Cannabis Pharmacokinetics

The pharmacokinetics of cannabis depend on the formulation and on the route of administration. Inhalation of cannabis rapidly increases the concentration of THC in the bloodstream, peaking within 3 to 10 min, and the bioavailability of THC after inhalation is reported to be 10 to 35%. Oral ingestion results in peak levels within 1 to 2 h, and hepatic metabolism reduces the oral bioavailability of THC by 4 to 12% [75]. After being absorbed into the bloodstream, THC rapidly penetrates fatty and highly vascularized tissues, including the brain and muscles [34]. This initial distribution is followed by a slower phase, during which the compound is redistributed from the adipose tissue, liver, lung, and spleen back into the bloodstream [76,77].

Hepatic metabolism of THC by cytochrome P450 (CYP450) enzymes (CYP3A4, CYP2C19, and CYP2C9) results in the formation of psychoactive 11-hydroxy-THC (11-OH-THC) and 11-carboxy-THC (11-COOH-THC) [78], which reduce oral THC bioavailability [32]. The rate at which the plasma clears can differ based on various factors, including gender and history of use, with a half-life of 18–32 h [79]. The majority of metabolized cannabis is excreted from the body through feces (65%) and urine (20%). Glucuronic acid conjugation increases the solubility of metabolites. Carboxy-THC is typically detected in urine, whereas hydroxy-THC is predominantly found in feces.

The non-psychoactive CBD is hepatically metabolized as well, mainly by the isozymes CYP2C19 and CYP3A4, and also by CYP1A1, CYP1A2, CYP2C9, and CYP2D6 [80]. After hydroxylation to hydroxyl-cannabidiol (7-OH-CBD), there is additional hepatic metabolism followed by fecal excretion, with a lesser extent of elimination of these metabolites through urine [81].

6. Negative Impacts of Cannabis on Physiological and Mental Health

Research has shown that prolonged cannabis use can significantly impact certain physiological and mental functions in humans. Several experimental studies indicate that cannabinoids exhibit immunosuppressive effects [61,69,72,82,83]. On the contrary, increased levels of IL-1ß, IL-6, IL-8, and TNF-α have been found in cannabis users [84]. Therefore, the critical regulatory role of the endocannabinoid system in immunity makes it a promising candidate for medical intervention in cases of immune-related diseases, such as transplantation, autoimmune diseases, infectious diseases, and cancer [82]. Figure 2 shows several negative effects of chronic cannabis use on physiological and mental health through the GM.

6.1. Cannabis Use and Physiological Outcomes

Cannabis use during pregnancy has been linked to numerous adverse effects on the developing fetus [45,85], such as low birth weight in humans, which has been associated with an increased risk of coronary heart disease in later life [86]. Prenatal exposure to cannabis also negatively impacts neurodevelopment, leading to adverse effects on neuropsychiatric health, behavioral patterns, and executive functions [87]. Notably, cannabinoids can pass through the placenta and the blood-brain barrier (BBB), and are also present in breast milk [45,87]. Multiple studies have investigated the impact on neurological development in children. For instance, researchers have found that prenatal exposure to cannabis significantly impairs intelligence by age 6, increases depressive symptoms by age 10, and negatively affects academic performance by age 14 [88–90]. There is also an elevated risk of attention difficulties, cognitive dysfunction, heightened aggression, memory impairment, and psychosis linked to cannabis exposure during pregnancy [87]. However, while cannabinoids are recognized for their suppressive effects on the immune system, no human studies

have been performed to explore whether adverse immunological outcomes arise from in utero exposure.

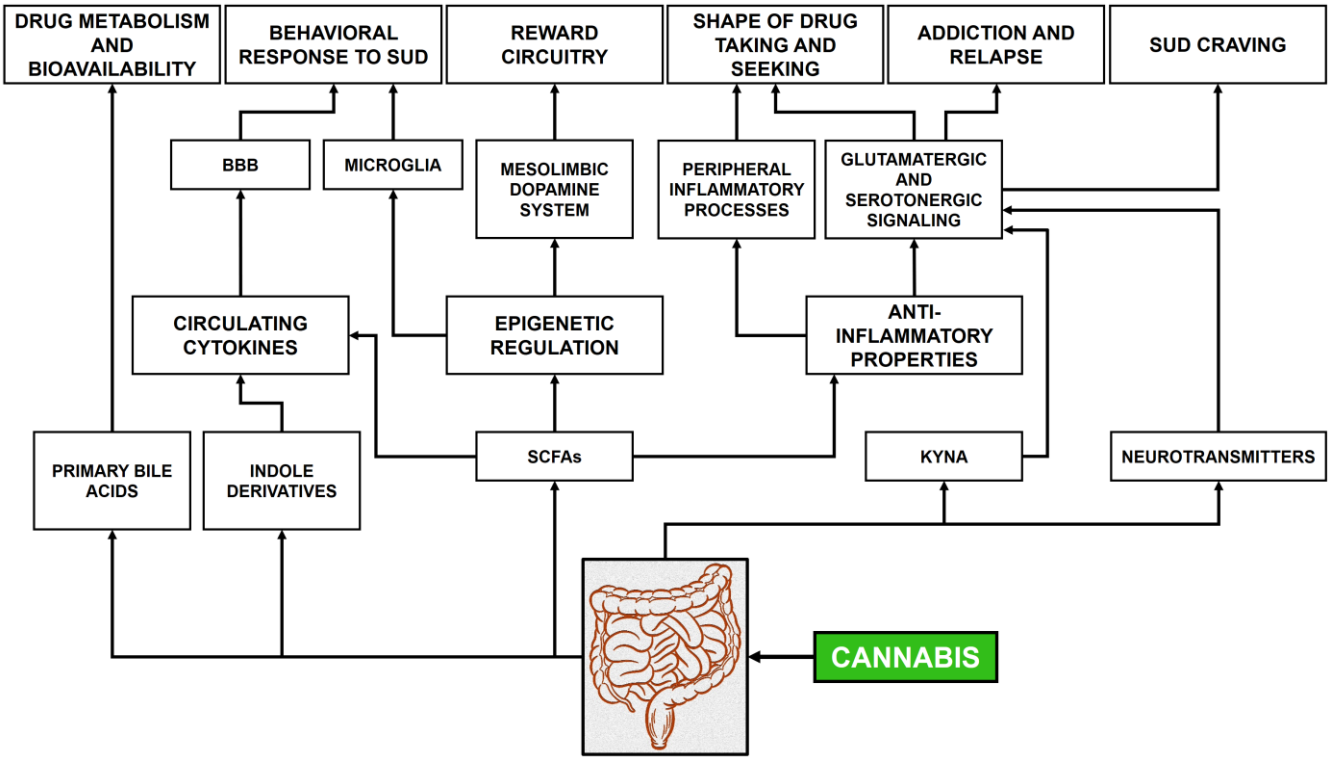

Figure 2. Negative effects of chronic cannabis use on physiological and mental health through the GM. SCFAs: short-chain fatty acids; KYNA: kynurenic acid; BBB: blood–brain barrier; SUD: substance use disorder.

Although regular cannabis use has been associated with physiological benefits, such as inducing mucosal healing in ulcerative colitis patients [91,92], it has also been linked to highly adverse health outcomes. In this regard, Ghasemiesfe et al. [93] reviewed the relationship between cannabis consumption and the risk of several cancers, including lung, head and neck, and genitourinary, concluding that constant cannabis use was linked to the development of testicular germ cell tumors, but the robustness of evidence was weak. Moreover, the evidence associating cannabis with other cancers was also limited.

6.2. Cannabis Use and Mental Health Outcomes

While cannabis and other cannabinoids have been employed to alleviate anxiety, several studies have demonstrated that CB1 receptor activation can produce anxiolytic effects in animals [94], as this activation inhibits the release of GABA or glutamate in postsynaptic neurons, and also blocks calcium channels [95]. More recently, Baral et al. [96] reported that cannabis use in adolescents was linked to cognitive decline, depression, psychosis, the development of attention deficit/hyperactivity disorder (ADHD), and suicide. However, its relationship with anxiety remains unclear.

One of the most extensively studied functions of CB1 is its involvement in food intake regulation following food deprivation, as disruptions or abnormalities in eCB signaling at CB1 receptors may contribute to disorders such as anorexia nervosa (AN) or binge eating disorder (BED) [97]. In healthy individuals, the consumption of palatable foods leads to alterations in peripheral blood levels of eCBs, particularly 2-AG, and/or eCB-like mediators. However, these changes are impaired in individuals with AN or BED [98,99].

Unfortunately, the application of CB1 receptor antagonists as a pharmacological treatment for these disorders has not produced satisfactory outcomes [100].

Cannabis abuse has been linked to an earlier onset of psychosis in genetically predisposed individuals [101], but the role of the CB1 receptor in these conditions remains controversial. Some studies in animal models of schizophrenia have suggested that CB1 receptor activation may be detrimental, while CB1 receptor antagonism could be beneficial [102]. Recent findings suggest a potential involvement of the eCBome in autism spectrum disorder (ASD) [103]. Significantly lower levels of AEA and NAE, but not 2-AG, have been observed in the serum of children with ASD [58,104]. Wu et al. [105] reported that in the valproate-induced autism model, enzyme inhibition mitigated both cognitive and synaptic dysfunction, indicating that reduced AEA and NAE signaling may contribute to some ASD symptoms. Furthermore, alterations in eCB levels have been reported in children with ADHD [106,107]. Some studies have also highlighted changes in the expression of the eCBS in multiple sclerosis (MS), including higher levels of CB1 and CB2 receptors in the MS-affected brain [108].

Although cannabis may have medical applications for several conditions, including epilepsy, MS, Parkinson's disease, arthritis, and anxiety [109], there is evidence suggesting both immediate and long-term harm from its use, particularly with respect to the age of onset and chronic exposure [110]. Table 2 summarizes several empirical human studies on the effects of cannabis use on mental health.

Table 2. Studies on the effects of cannabis use on mental health.

Reference/ Country	Sample Size and Age	Study Design	Summary of Findings
Albertella et al. [111]/Australia	*N* = 162 Age: 15–24 years	Longitudinal	Follow-up analyses showed that the early onset of cannabis use was associated with higher levels of introversive anhedonia in females only.
Bahorik et al. [112]/USA	*N* = 307 Age: >18 years	Longitudinal	Cannabis use led to poorer mental and physical health functioning.
Bechtold et al. [113]/USA	*N* = 506 Mean age: 13.9 years	Longitudinal	Four distinct subgroups of cannabis users were defined. However, these groups did not significantly differ in terms of their physical and mental health outcomes, including anxiety and suicide problems.
Chadi et al. [114]/USA	*N* = 26,821 Age: 12–18 years	Longitudinal	Cannabis use was associated with depression and suicidality.
Danielsson et al. [115]/Sweden	*N* = 8598 Age: 20–64 years	Longitudinal	No associations were found between cannabis use and the incidence of depression/anxiety or between depression/anxiety and later cannabis use onset.
Feingold et al. [116]/Israel, Canada, and Germany	*N* = 43,093 Age: >18 years	Longitudinal	The findings suggest that cannabis use and CUD are not associated with increased incidence of most anxiety disorders, and inversely, most anxiety disorders are not associated with increased incidence of cannabis use or CUD.

Table 2. *Cont.*

Reference/ Country	Sample Size and Age	Study Design	Summary of Findings
Floyd Campbell [117]/USA	*N* = 240 Age: 18–30 years	Cross-sectional	More than 20% of cannabis users experienced depression, which was higher in African American females compared to White females.
Han et al. [118]/USA	*N* = 281,650 Age: 18–34 years	Longitudinal	CUD was associated with a higher prevalence of past suicide ideation, plan, and attempt. The suicide plan among those with CUD and major depressive episode was higher for women than for men.
Horwood et al. [119]/Australia	*N* = 6900 Age: 12–45 years	Longitudinal	The frequency of cannabis use was significantly associated with increasing depressive symptoms.
Kim et al. [120]/R. Korea	*N* = 234 Mean age: 41.8 years	Longitudinal	Cannabis use negatively affects the long-term clinical outcomes in patients with BD.
Leadbeater et al. [121]/USA	*N* = 36,309 Age: >18 years	Longitudinal	More frequent cannabis use was associated with increased psychotic symptoms, higher depression, and anxiety symptoms. Females exhibited a stronger association between CUD and mental health symptoms.
Levy & Weitzman [122]/USA	*N* = 527 Age: 14–18 years	Cross-sectional	Frequent cannabis use was linked to reports of symptoms of hallucinations, paranoia, or anxiety.
London-Nadeau et al. [123]/USA	*N* = 1538 Age: 13–17 years	Longitudinal	There is a bidirectional relationship between cannabis use and depression/anxiety symptoms in adolescents. Differences were found between heterosexual and LGBTQI participants; the latter showed a stronger association between cannabis use and depression.
Meier et al. [124]/USA	*N* = 506 Age: 15–26 years	Longitudinal	Increases in cumulative years of weekly cannabis use were linked to higher levels of depression symptoms and anxiety/depression problems.
Moitra et al. [125]/USA	*N* = 332 Age: 18–25 years	Longitudinal	A relationship between reductions in cannabis use and reductions in depressive symptoms was found.
Muñoz-Galán et al. [126]/Spain	*N* = 948 Age: 14–18 years	Longitudinal	From the 948 participants who commenced treatment for CUD, almost 20% developed a mental health disorder in the years following the onset of cannabis use.

Table 2. *Cont.*

Reference/ Country	Sample Size and Age	Study Design	Summary of Findings
Otten et al. [127]/The Netherlands	*N* = 1424 Age: 10–11 years	Longitudinal	Cannabis use is associated with an increase in symptoms of anxiety, but only in carriers of the short allele of the 5-HTTLPR genotype (a polymorphism in the promoter region of the serotonin transporter gene).
Patel et al. [128]/United Kingdom	*N* = 2026 Age: 16–25 years	Cross-sectional	Cannabis use reduces response to conventional antipsychotic treatment and increases compulsory hospital admissions.
Phillips et al. [129]/USA	*N* = 300 Age: 18–25 years	Cross-sectional	Among the three psychological factors tested (social anxiety, general anxiety, and depression), only depression was associated with cannabis use.
Rabin et al. [130]/Canada	*N* = 19 Age: 18–55 years	Cross-sectional	Verbal memory and learning improvements in schizophrenic subjects with cannabis abstinence for 28 days were found.
Rabin et al. [131]/Canada	*N* = 19 Age: 8–48 years	Cross-sectional	Short-term (28 days) cannabis abstinence is not associated with improvement in psychotic symptoms, but may be associated with improvement in depressive symptomatology in patients with schizophrenia.
Rasic et al. [132]/Canada	*N* = 976 Age: >16 years	Longitudinal	Illicit drug use, with and without cannabis use, among high school students increases the risk of depression, suicidal ideation, and suicidal attempts. Heavy cannabis use alone predicts depression but not suicidal ideation or attempts.
Richter et al. [133]/USA	*N* = 55,271 Age: 18–62 years	Cross-sectional	Anxiety was associated with a higher prevalence of CUD, while depression showed no significant association.
Sagar et al. [134]/USA	*N* = 12 Mean age: 28.6 years	Longitudinal	No evidence was found of an additive negative impact of BD and cannabis use on cognition.
Schoeler et al. [135]/United Kingdom	*N* = 285 Age: 18–55 years	Longitudinal	Frequent cannabis use during adolescence was a risk factor for later life depression.
Scholes-Balog et al. [136]/Australia	*N* = 927 Age: 15–19 years	Longitudinal	The rates of cannabis use increased with age, and were more common among males than females. Anxiety and depression are the most prevalent cannabis-related harms.
Tull et al. [137]/USA	*N* = 202 Age: 18–60 years	Cross-sectional	Findings suggest that patients with co-occurring PTSD and cannabis dependence may experience alterations in their emotional processing in response to a traumatic cue.

Table 2. *Cont.*

Reference/ Country	Sample Size and Age	Study Design	Summary of Findings
Weinberger et al. [138]/USA	*N* = 204,102 Age: 12–17 years	Cross-sectional	Youth with depression were more than twice as likely to report cannabis use compared to those without depression.
Welsh et al. [139]/USA	*N* = 483 Age: 12–24 years	Longitudinal	Cannabis use was associated with the development of externalizing behavior disorders and with ADHD.
Wilkinson et al. [140]/USA	*N* = 2276 Mean age: 51.7 years	Longitudinal	Initiation of cannabis use after treatment was associated with worse PTSD symptoms and more violent behavior.
Wilkinson et al. [141]/USA	*N* = 9816 Age: 18–32 years	Longitudinal	The frequency of cannabis use increases from adolescence to young adulthood, together with the rise in adolescent depressive symptoms. This association was found to be stronger in women.
Wong et al. [142]/USA	*N* = 73,183 Age: 12–15 years	Cross-sectional	Adolescents with a history of cannabis use showed an association with suicidal ideation or attempts in the previous year.
Zaman et al. [143]/USA	*N* = 483 Age: 12–18 years	Cross-sectional	Among adolescents with CUD, there was a high co-occurrence of alcohol and opioid abuse or dependence. These individuals also experienced significant psychiatric comorbidities.
Zorrilla et al. [144]/Spain	*N* = 1922 Age: 35.3–46.2 years	Longitudinal	BD patients who stopped using cannabis during manic/mixed episodes had similar clinical and functional outcomes to never users.

ADHD: attention deficit/hyperactivity disorder; BD: bipolar disorder; CUD: cannabis use disorder; PTSD: post-traumatic stress disorder.

Several systematic reviews have identified an association between cannabis use among young individuals and the development of depressive symptoms. Knopf et al. [145] reported that adolescent cannabis users were 1.37 times more likely to develop depression than non-users. Similarly, another systematic review found that weekly cannabis users were more likely to develop depression compared to non-users, with the stronger association observed among adolescents [146]. A meta-analysis involving over 650 subjects and 5600 controls revealed that cannabis use was linked to cognitive decline, as evidenced by a two-point decrease in IQ, compared to non-users in the United States [147].

As shown in Table 2, cannabis use is related to an increase in depressive symptoms [114,117–119,121,123–125,129,132,135,136,138,141], suicidal ideation [114,118,142], and anxiety symptoms [121–124,127,133,136]. However, some studies have reported conflicting results, including the lack of an association between cannabis use and depressive or anxiety symptoms [115,116] or even a potential improvement in bipolar symptoms [134]. Moreover, an inverse relationship has been observed between the prevalence of anxiety or depressive symptoms and the age of cannabis initiation, with higher prevalence in adolescents and lower prevalence in emerging adults [115,116]. In addition, contradictory results have been reported regarding the interaction between mental health, cannabis use, and gender. In this regard, only one study found males to be more prone [136], while four studies indicated that females were more vulnerable [111,118,121,141], and another suggested that LGBTQI individuals may be more susceptible [123]. Given these mixed findings, further research us-

ing more robust methodologies is necessary to establish a clear causal relationship between cannabis consumption and mental health outcomes. Nevertheless, based on the studies summarized, it can be stated that consistent risk factors for adverse mental health outcomes related to cannabis use include early age of initiation, frequent or heavy use, female sex, and co-occurring psychiatric conditions such as BD and PTSD, while evidence for potential protective factors remains limited and inconclusive.

7. Cannabinoid Drugs in the Treatment of Mental Health Disorders

The report from the U.S. National Academy of Medicine highlights strong evidence supporting the efficacy of cannabis or cannabinoids in only three areas [22]: (i) alleviating chronic pain in adults; (ii) serving as an antiemetic for chemotherapy-induced nausea and vomiting (CINV); and (iii) improving patient-reported spasticity in MS (via oral cannabinoids). Nevertheless, given the role of the eCBS, there is significant interest in the potential use of cannabinoid-based drugs for the treatment or management of a wide range of neurological, psychiatric, and psychological disorders [148], including anxiety, depression, chronic pain, PSTD, MS, Tourette's syndrome, and various neurodegenerative diseases [149–155]. Despite the growing number of governments allowing whole-plant cannabis consumption for medical purposes, only a few cannabinoid drugs have been rigorously tested for safety and efficacy, and have been approved for use by regulatory agencies, such as the Federal Drug Administration (FDA) and the European Medicines Agency (EMA) [3].

Based on the therapeutic potential of cannabis in humans, several cannabinoid-based formulations have already been approved in various countries, such as dronabinol (Marinol® and Syndros®), nabilone (Cesamet® and Canemes®), rimonabant (Acomplia®), nabiximols (Sativex®), Δ^9-THC and CBD-enriched plant extracts (Epidiolex®, GWP42006®, and Bedrocan®), as well as lesser-used compounds like cannabidivarin (CBDV) and tetrahydrocannabivarin. Dronabinol is an orally administered, synthetically produced form of Δ^9-THC, which has been approved by the FDA and EMA for treating anorexia and weight loss in patients with AIDS and for CINV. This drug is classified as a Schedule III substance, and the most frequently reported side effects include asthenia, heart palpitations, amnesia, and abdominal pain [156]. Nabilone is an orally administered synthetic cannabinoid with similar CB1 receptor properties to Δ^9-THC. This drug has been approved for the treatment of CINV. Due to its psychoactive effects, nabilone is classified as a Schedule II drug. Its side effects are generally mild and include dryness of the mouth, headache, orthostatic hypotension, drowsiness, and euphoria [157]. Rimonabant is a potent synthetic CB1 receptor antagonist that was marketed in Europe for type 2 diabetes, dyslipidemia, and weight management. However, it was withdrawn from the market by the EMA in 2009 due to serious side effects, including nausea, major depression, suicidal ideation, and upper respiratory tract infections [158]. Nabiximols is an oromucosal spray derived from the *C. sativa* plant extract, which predominantly contains Δ^9-THC and CBD in nearly equal amounts. Sativex has been approved in Europe for the treatment of spasticity, with the most commonly reported side effects being blurred vision, constipation, dizziness, fatigue, depression, changes in appetite (either increase or decrease), and vertigo [159]. Cannabidiol (Epidiolex®) is a 98% pure oral CBD solution derived from plants that has been approved for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in pediatric patients. Epidiolex has received approval from both the FDA and EMA [160]. Its side effects include decreased appetite, diarrhea, drowsiness, fatigue, and hepatocellular toxicity [160].

Recent research proposes three hypotheses regarding the role of the eCBS in emotional and behavioral regulation [161]. The first suggests its interaction with the stress response

system, particularly the hypothalamic–pituitary–adrenal (HPA) axis, which modulates behavioral reactions and maintains homeostasis [162]. The second focuses on the integration of sensory perception with behavioral execution, which mitigates maladaptive responses and may protect against psychiatric symptoms [163]. The third posits that promoting proactive coping mechanisms during adversity can foster anxiolytic and antidepressant effects [164]. These hypotheses converge, highlighting the eCBS as a promising therapeutic target for addressing affective dysregulation [165]. Table 3 presents the medical applications of cannabis and its derivatives in several neuropsychiatric disorders.

Table 3. Cannabis and cannabis-derived products in the treatment of several neuropsychiatric disorders.

Neuropsychiatric Disorders	Treatment	Sample and Duration	Outcomes	Ref.
Epilepsy	Artisanal formulations of CBD.	*N* = 209. Age: >19 years. Treatment for 1.1–2.5 years.	With concomitant use of clobazam, 44% of patients had a 50% reduction in seizures upon addition of CBD compared with 33% in the population not treated pharmacologically. The most common reported side effect of CBD was sedation in less than 4% of patients, all of whom were also taking clobazam.	[166]
	CBD-enriched cannabis oil: 1–10 mg/kg/d and 10–20 mg/kg/d. The selected formula contained CBD and THC at a ratio of 20:1 dissolved in olive oil.	*N* = 74. Age: 1–18 years. Treatment for 3–6 months.	CBD treatment yielded a significant positive effect on seizure load, with a significant reduction in seizure frequency. In addition, improvements in behavior and alertness, language, communication, motor skills, and sleep were found. AEs included somnolence, fatigue, gastrointestinal disturbances, and irritability.	[167]
Dravet syndrome	Epidiolex® GWCARE1b: 20 mg/kg/d CBD.	*N* = 120. Age: 1–18 years. Treatment for 14 weeks.	The median reduction in convulsive seizures was 38.9%. AEs occurred often in the CBD group (93%) as well as in the placebo group (75%), most of the AEs were moderate or mild, including somnolence, diarrhea, decreased appetite, and fatigue.	[168]
	Epidiolex® GWPCARE5 with a mean CBD dose of 21 mg/kg/d.	*N* = 264. Age: 2–55 years. Treatment for 274 days.	A sustained convulsive seizure reduction (between 37.5% and 44.3%) was achieved. AEs were common, including diarrhea, pyrexia, decreased appetite, and somnolence.	[169]
	Epidiolex® GWPCARE2: 10 mg/kg/d and 20 mg/kg/d CBD.	*N* = 198. Age: 2–18 years. Treatment for 14 weeks.	Median convulsive seizure reduction was 48.7% in the CBD 10 mg/kg/d group, 45.7% in the 20 mg/kg/d group, and 26.9% in the placebo group. The most common AEs were decreased appetite, diarrhea, somnolence, pyrexia, and fatigue.	[170]

Table 3. *Cont.*

Neuropsychiatric Disorders	Treatment	Sample and Duration	Outcomes	Ref.
Lennox–Gastaut syndrome	Epidiolex® GWPCARE3: 10 mg/kg/d and 20 mg/kg/d CBD.	*N* = 225. Age: 2–55 years. Treatment for 14 weeks.	A significant reduction in drop seizures was found in the 10 mg/kg/d and 20 mg/kg/d groups. AEs frequently occurred in all groups, including somnolence, decreased appetite, and diarrhea.	[171]
	Epidiolex® GWPCARE4: 20 mg/kg oral CBD daily.	*N* = 171. Age 2–55 years. Treatment for 14 weeks.	Significant reduction in drop seizures. AEs occurred often with diarrhea, somnolence, pyrexia, decreased appetite, and vomiting being the most common.	[172]
	Epidiolex® GWPCARE5 with a mean CBD dose of 23 mg/kg/d.	*N* = 366. Age: 2–55 years. Treatment for 38 weeks.	Sustained reduction in seizures (between 47.7% and 57.4%) across all 12-week periods. AEs were common in all groups, including diarrhea, somnolence, and convulsions.	[173]
Alzheimer's disease	Nabilone: 1–2 mg/d.	*N* = 39. Age: >55 years. Treatment for 14 weeks.	Nabilone may be an effective treatment for agitation. However, sedation and cognition should be closely monitored.	[174]
Dementia	Oral THC: 1.5 mg twice daily.	*N* = 18. Mean age: 77 years. Treatment for 12 weeks.	Significant increases in dynamic balance, stride length, and gait velocity after THC administration compared to placebo. AEs included dizziness, somnolence, balance disorders, and falls.	[175]
Parkinson's disease	CBD/THC treatment (dose not reported).	*N* = 15. Mean age: 67.5 years. Treatment for 3 months.	Patients who were already taking a CBD/THC product (*N* = 8) had lower global cognition scores, more non-motor symptoms, and improved pain levels and sleep, as well as reductions in anxiety. A few AEs, including sleepiness, concentration difficulties, and forgetfulness.	[176]
Multiple sclerosis	Oral cannabis extract (CE). 2-week dose titration phase from 5 mg to 25 mg of THC daily and a 10-week maintenance phase.	*N* = 144. Age: 18–64 years. Treatment for 12 weeks.	The rate of relief from muscle stiffness after 12 weeks was almost twice as high with CE as with placebo.	[177]

Table 3. *Cont.*

Neuropsychiatric Disorders	Treatment	Sample and Duration	Outcomes	Ref.
Autism spectrum disorder	Cannabis oil solution at a 20:1 ratio of CBD and THC. Sublingual administration 2 or 3 times/daily with CBD doses started at 1 mg/kg/d and titrated up to 10 mg/kg/d.	*N* = 60. Age: 5–17.5 years (mean age: 11.8 years). Treatment for 2–4 weeks.	Following the cannabis treatment, behavioral outbreaks were improved in 61% of patients. AEs included sleep disturbances (14%), irritability (9%), and loss of appetite (9%).	[178]
	Recommended daily dose of CBD was 16 mg/kg (maximal daily dose 600 mg), and for THC daily dose of 0.8 mg/kg (maximal daily dose of 40 mg).	*N* = 53. Age: 4–22 years. Treatment for 66 days.	Self-injury and rage attacks, hyperactivity symptoms, sleep problems, and anxiety improved. AEs such as somnolence and a change in appetite were mild.	[179]
	Cannabis oil containing 45% olive oil, 30% CBD, and 1.5% THC. 1 sublingual oil drop 3 times per day (15 mg CBD and 0.75 mg THC).	*N* = 188. Mean age: 12.9 years. Treatment for 6 months.	After 6 months of treatment, 30.1% of the patients reported a significant improvement; 23 patients experienced at least one side effect. The most common was restlessness.	[180]
	Standardized CBD-enriched CE (with a CBD to THC ratio of 75/1).	*N* = 15. Age: 6–17 years (mean age: 10 years). Treatment for 5–24 months.	After 6–9 months of treatment, the strongest improvements were reported for seizures, attention deficit/hyperactivity symptoms, sleep disorders, and communication and social interaction deficits. The most frequently reported AEs were drowsiness, psychoactive symptoms, increased appetite, digestive disturbances, dry mouth, and lack of appetite.	[181]
Rett syndrome	Epidyolex®: 100 mg/mL oral solution of CBD (38% patients were treated with CBD, and 50% in combination with clobazam). The median dose at their last follow-up was 15 mg/kg/d.	*N* = 26. Age: 7–32 years. Treatment for 13 months.	CBD reduced the incidence of seizures in 70%. A reduction in agitation or anxiety attacks, and an improvement in spasticity were reported. Only one patient experienced a transitory drooling and somnolence episode at the CBD initiation. Half of the patients showed a reduction in agitation and/or anxiety attacks, and an improvement in spasticity was reported in 40% of patients.	[182]

Table 3. *Cont.*

Neuropsychiatric Disorders	Treatment	Sample and Duration	Outcomes	Ref.
Tourette syndrome	A vaporized single 0.25 g dose of THC (10%), THC/CBD (9%/9%), CBD (13%), and placebo at 2-week intervals.	*N* = 12. Age: 22–54 years. Treatment for 6 weeks.	In terms of tics, there was no statistically significant difference for any of the cannabis products. The main AEs observed were sedation, psychomotor effects, dizziness, cough, burning throat, dry mouth, and feeling cold.	[183]
	Medical cannabis treatment, including THC and CBD.	*N* = 18. Age: 20–50 years. Treatment for 12 weeks.	After 12 weeks of treatment, a significant average reduction of YGTSS and of PUTS was observed. Common side effects were dry mouth, fatigue, and dizziness. Three patients suffered from psychiatric side effects, including worsening of obsessive-compulsive disorder, panic attacks, and anxiety. Six patients reported cognitive side effects regarding time perception, visuospatial disorientation, confusion, slow processing speed, and attention.	[184]
Attention deficit/Hyperactivity disorder	Sativex Oromucosal Spray: THC (2.7 mg) and CBD (2.5 mg).	*N* = 30. Age: 18–55 years. Treatment for 6 weeks.	The treated group showed an improvement in Qb Test scores that approached significance. Nominally significant improvements in attention deficit/hyperactivity symptoms were also found for the treated group compared to the placebo. Concerns about cognitive impairment were alleviated by lower THC formulas.	[185]
	Task-based fMRI data from young adults with and without cannabis use. Go/NoGo behavioral and fMRI data were evaluated for main and interaction effects of disorder diagnosis and cannabis use.	*N* = 73. Age: 21–27 years (mean age: 24.6 years). Treatment for 1 year.	Patients made significantly more commission errors on NoGo trials than controls, and also had less frontoparietal and frontostriatal activity, independent of cannabis use. No main effects of cannabis use on response inhibition or functional brain activation were observed. An interaction of disorder diagnosis and cannabis use was found in the right hippocampus and cerebellar vermis, with increased recruitment of these regions in cannabis-using controls during correct response inhibition.	[186]

Table 3. *Cont.*

Neuropsychiatric Disorders	Treatment	Sample and Duration	Outcomes	Ref.
Bipolar disorder	Both patients received a placebo for the initial 5 days and CBD from the 6th to the 30th day. The initial oral dose of 600 mg reaches 1200 mg/d. From the 6th to the 20th day, the first patient received adjunctive olanzapine (oral dose of 10–15 mg). On day 31, CBD treatment was discontinued and replaced by a placebo for 5 days.	*N* = 2. Age: 35 and 36 years. Treatment for 40 days.	One patient showed improvements in YMRS and BPRS scores while on CBD plus olanzapine, but no additional improvement during CBD monotherapy. The second patient had no symptom improvement with any dose of CBD. CBD appears not to be effective in attenuating mania. No side effects reported.	[187]
Social anxiety disorder	CBD (600 mg).	*N* = 24. Mean age: 24.6 years. Treatment for 1.5 hours before a simulated public speaking test.	Pre-test CBD administration in patients versus placebo resulted in significantly reduced anxiety, cognitive impairment, and discomfort in speech performance, and significantly decreased hyper-alertness in anticipatory speech. CBD and control groups, however, did not differ, reflecting similar response profiles during the public speaking test.	[188]
	CBD (400 mg).	*N* = 10. Age: 20–33 years (mean age: 24.2 years). Treatment for 140 min.	CBD compared to placebo resulted in significantly lower subjective anxiety, and modulated blood flow in the left parahippocampal gyrus, hippocampus, and inferior temporal gyrus, and right posterior cingulate gyrus.	[189]
Anxiety	Oral CBD (600 mg).	*N* = 32. Mean age: 26 years. Treatment for 130 min prior to entering virtual reality.	Immersion in the virtual reality session elicited anxiety as indexed by the BAI, as well as increased cortisol concentration, heart rate, and systolic blood pressure. However, CBD had no impact upon any of these effects, except for a strong trend to increase anxiety. CBD had no effect on persecutory ideation as assayed by the CAPE questionnaire or the SSPS.	[190]
	CBD 25 mg/d in capsules.	*N* = 72. Age: 18–70 years (mean age: 34 years). Treatment for 1 month.	Anxiety scores decreased within the first month of treatment in 57 patients (79.2%) and remained decreased during the study duration.	[191]

Table 3. *Cont.*

Neuropsychiatric Disorders	Treatment	Sample and Duration	Outcomes	Ref.
Post-traumatic stress disorder	Three active concentrations of smoked cannabis (i.e., high THC, 12% THC and <0.05% CBD; high CBD, 11% CBD and 0.50% THC; and THC + CBD, 7.9% THC and 8.1% CBD).	*N* = 80 (stage 1) and *N* = 74 (stage 2). Mean age: 44.9 years. Treatment for 3 weeks in stage 1, and after a 2-week washout period, treatment for 3 weeks in stage 2.	The study did not find a significant difference in symptom severity changes between the active cannabis concentrations and placebo by the end of stage 1. However, THC + CBD and high THC led to decreased depression and social anxiety in stage 2.	[192]
	Oral CBD (22–28 mg/capsule).	*N* = 11. Mean age: 39.9 years. Treatment for 8 weeks.	Ten patients experienced a decrease in symptom severity, as evidenced by a lower PCL-5 score at 8 weeks than at initial baseline.	[193]
	Medical cannabis.	*N* = 80. Age: >18 years. Analyzed retrospectively, CAPS data were collected.	Patients reported a >75% decrease in CAPS scores when they were using cannabis compared to periods when they were not. In addition, the treatment reduced anxiety and improved sleep disturbances.	[194]
	Nabilone tablets treatment (0.5 mg).	*N* = 10. Mean age: 43.6 years. Treatment for 7 weeks.	Reduction in nightmares as measured by the CAPS scores in treated patients.	[195]
Sleep disturbances	CBD (50 mg/d).	*N* = 387. Age: 25–54 years. Treatment for 3–6 months.	CBD use improves general health and well-being, stress, post-workout sore muscles, anxiety, skin conditions, and sleep problems.	[196]
	CBD capsules (25 mg) + liquid (12–24 mg).	*N* = 1. Age: 10 years. Treatment for 5 months with CBD capsules + 1 month with CBD liquid.	SDSC scores decreased over the 5-month period, indicating an increase in sleep quality and quantity.	[197]
	Nabilone (0.5–1.0 mg) compared to amitriptyline (10–20 mg).	*N* = 31. Age: >18 years. Treatment for 2 weeks.	Although sleep was improved by both nabilone and amitriptyline, nabilone was superior to amitriptyline. The most common AEs for nabilone were dizziness, nausea, and dry mouth.	[198]
Pain	Nabiximols: THC (2.7 mg) and CBD (2.5 mg) in sprays. Three doses: low (1–4 sprays), medium (6–10 sprays), or high (11–16 sprays).	*N* = 263. Mean age: 58 years. Treatment for 5 weeks.	Reports of pain relief were significantly greater for nabiximols than placebo overall, especially in the low- and medium-dose groups. There were no other significant group differences. AEs were dose-related, with only the high-dose group reporting a decrease in mood.	[199]

Table 3. *Cont.*

Neuropsychiatric Disorders	Treatment	Sample and Duration	Outcomes	Ref.
	Dronabinol: THC.	*N* = 240. Age: 18–70 years. Treatment for 16 weeks.	The primary endpoint was the change in pain intensity on the 11-point NRS over a 16-week treatment period. Pain intensity during 16-week dronabinol and placebo treatment was reduced by 1.92 and 1.81 points, without a significant difference. AEs: Restlessness, irritability, sleep interference, decreased appetite, and excessive sweating.	[200]
	Inhaling medium dose (3.53%) and low dose (1.29%) of THC.	*N* = 39. Mean age: 50 years. Treatment for 2 h.	Cannabis has analgesic efficacy, with the low dose being as effective as the medium dose for pain relief. Pain relief appears to be maximal after the second dosing at 180 min post-baseline, but the peak effect drops off 1 to 2 h later.	[201]
Fibromyalgia	THC-rich cannabis oil (24.44 mg/mL of THC and 0.51 mg/mL of CBD).	*N* = 17. Mean age: 51.9 years. Treatment for 8 weeks.	After the intervention, the cannabis group presented a significant decrease in FIQ score in comparison with the placebo group. The cannabis group presented significant improvement on the "feel good", "pain", "do work", and "fatigue" scores.	[202]
	Single vapor inhalation of Bedrocan (22.4-mg THC, <1 mg CBD); Bediol (13.4-mg THC, 17.8 mg CBD); Bedrolite (18.4 mg CBD, <1 mg THC).	*N* = 20. Mean age: 39 years. Treatment: mean of 22 inhalations.	None of the treatments had an effect greater than placebo on spontaneous or electrical pain responses, although more subjects receiving Bediol displayed a 30% decrease in pain scores compared to placebo. AEs: deterioration in mood and alertness, sore throat and sour taste, coughed during inhalation, nausea without vomiting.	[203]
Migraine	Inhaled medical cannabis.	*N* = 653. Age: 18–74 years. Treatment: 7441 sessions.	There were significant reductions in headache and migraine ratings after cannabis use (56%). Men reported larger reductions in headache than women, and the use of concentrates was associated with larger reductions in headache than flowers.	[204]
	Dried *Cannabis* flower.	*N* = 582. Treatment: the average user entered 21 sessions (median = 5 sessions) over 125 days (median = 65 days).	Dried *Cannabis* flower may be an effective medication for the treatment of migraine- and headache-related pain, but the effectiveness differs according to characteristics of the *Cannabis* plant, the combustion methods, and the age and gender of the patient.	[205]

Table 3. *Cont.*

Neuropsychiatric Disorders	Treatment	Sample and Duration	Outcomes	Ref.
Schizophrenia	CBD (600–800 mg).	*N* = 42. Treatment over 4 weeks.	Both treatments were effective in reducing PANSS and BPRS scores at each time point. CBD was tolerated better, with fewer side effects reported. Anandamide levels were higher in the CBD group post-treatment.	[206]
	CBD (600 mg).	*N* = 39. Age: 18–50 years. Treatment for 6 weeks.	Both groups showed improvement on PANSS scores, and only the placebo group improved on the MCCB. Similar AEs were noted between the groups, with more sedation evident in the CBD group.	[207]
	CBD (1000 mg).	*N* = 88. Age: 18–65 years. Treatment for 6 weeks.	The CBD group reported lower positive symptom scores (PANSS, CGI-S) and was more likely to be rated as improved and less severely ill than the placebo group. The CBD group also showed improvements in the cognitive domain of motor speed compared to placebo (BACS and GAF scores). Similar AEs were reported between groups.	[208]

AEs: Adverse events; BACS: Brief Assessment of Cognition in Schizophrenia; BAI: Beck's anxiety inventory; BPRS: Brief Psychiatric Rating Scale; CAPE: Community Assessment of Psychic Experiences Questionnaire; CAPS: Clinician Administered Post-traumatic Scale; CGI-S: Clinical Global Impressions and Severity Scale; FIQ: Fibromyalgia Impact Questionnaire; fMRI: Functional Magnetic Resonance Imaging; GAF: Global Assessment of Functioning; MCCB: MATRICS Consensus Cognitive Battery; NRS: Numerical Rating Scale; PANSS: Positive and Negative Syndrome Scale; PCL-5: PTSD Checklist for the DSM-5; PUTS: Premonitory Urge for Tic Scale; SDSC: Sleep Disturbance Scale for Children; SSPS: State Social Paranoia Scale; YGTSS: Yale Global Tic Severity Scale; YMRS: Young Mania Rating Scale.

7.1. Epilepsy and Related Syndromes

Epilepsy is a chronic condition characterized by recurrent seizures, commonly presenting in childhood, and results from an imbalance between neuronal excitation and inhibition in the brain [209]. Cannabinoids have potential neuroprotective properties, as they may reduce inflammatory responses in patients with epilepsy [46]. Clinically, cannabidiol seems to be more effective than smoked whole-plant cannabis in treating epileptic seizures, as case reports and surveys have suggested that smoked cannabis exhibits both pro- and anticonvulsant effects [210]. Several clinical trials have explored its use as an adjunctive therapy for drug-resistant epilepsy [166,167]. Despite significant variability among individuals within each study, these findings were consistent across patients with various underlying causes of their seizures, such as Dravet syndrome and Lennox-Gastaut syndrome [168–173]. Interestingly, cannabidiol demonstrated an improvement in disease symptoms, accompanied by a sustained reduction in convulsive seizures.

7.2. Neurodegenerative Diseases

Neurodegenerative diseases, such as Alzheimer's disease, dementia, Parkinson's disease, and MS, are characterized by progressive demyelination and neuronal loss, leading to debilitating symptoms and a decline in both cognitive and motor functions [211,212]. Interestingly, emerging evidence suggests that cannabis and its derivatives possess neuro-

protective properties. Through their interaction with the eCBS, cannabinoids have shown anti-inflammatory, antioxidant, and anti-excitotoxic effects, which may help counteract the underlying mechanisms of neurodegeneration [211]. In this regard, several clinical trials have investigated the use of cannabis in the treatment of various neurodegenerative diseases [174–177]. Generally, CBD/THC treatments have resulted in lower global cognition scores, more non-motor symptoms, and improvements in pain levels and sleep, as well as in reductions in anxiety [213]. Furthermore, cannabinoids have been shown to interact with CB1 receptors to regulate dopamine and other neurotransmitters in the basal ganglia, which may provide therapeutic benefits to patients with Parkinson's disease [214]. Patients with these diseases have been found to exhibit changes in the expression of CB1 and CB2 receptors, potentially explaining the therapeutic potential of cannabis-derived products [49].

7.3. Neurodevelopmental Disorders

Neurodevelopmental disorders (NDDs) encompass a range of conditions that emerge early in life and interfere with brain development, leading to alterations in cognitive, emotional, and motor functions [215]. Additionally, many patients with NDDs experience comorbidities such as ADHD, anxiety, depression, obsessive-compulsive disorder, and rage attacks [216]. Given the anti-anxiety properties of cannabinoids and their high receptor expression in the striatum, cannabis could serve as a potential therapeutic option for these conditions [217]. For this reason, several clinical trials have focused on the use of cannabis products for the treatment of ASD, Rett syndrome, Tourette syndrome, and ADHD [178–186]. Clinical evidence indicates that early intervention with cannabidiol may offer a promising therapeutic approach for neurodevelopmental disorders such as ASD, ADHD, tic disorders, and intellectual disability [218]. Several proposed mechanisms underlie CBD's effects, including the inhibition of endocannabinoid degradation, modulation of serotoninergic activity, and its anti-inflammatory properties. Increasingly reliable literature highlights the potential of CBD for ameliorating symptoms associated with somatic symptom disorders, as well as psychiatric and neurodevelopmental conditions [219].

7.4. Bipolar Disorder

BD is a chronic mood condition characterized by recurrent episodes of mania, hypomania, and depression. In a study [187] involving only two BD patients, CBD treatment showed limited and inconsistent effects, with one patient improving only during combined CBD and olanzapine therapy and the other showing no benefit. CBD alone did not clearly reduce manic symptoms, although no adverse effects were observed. These preliminary findings suggest that while CBD may have adjunctive potential, its efficacy as a standalone treatment for BD remains uncertain and warrants further comprehensive investigation.

7.5. Anxiety Disorders and Post-Traumatic Stress Disorder

One of the most commonly reported reasons for cannabis use among patients is the treatment of anxiety, particularly with products high in CBD [220,221]. Graczyk et al. [222] highlighted the role of the eCBS in mood modulation and its therapeutic potential in reducing anxiety. In this respect, several trials have assessed the effects derived from the use of cannabinoids for the treatment of anxiety, social anxiety, and PTSD [188–195]. A recent systematic review of twelve studies on anxiety onset found that three studies indicated that cannabis use increased the likelihood of developing anxiety disorders [223]. In addition, high Δ^9-THC cannabis is more likely to induce anxiety symptoms in naïve patients [224]. Therefore, while some cannabinoids may have therapeutic utility in reducing anxiety, caution should be exercised regarding Δ^9-THC, as the relationship between Δ^9-THC and anxiety is still unclear. PTSD arises from extreme emotional events [225]. Several

studies have demonstrated that cannabis use can alleviate global PTSD symptoms, showing a correlation between reduced PTSD severity and cannabis use [226]. Cannabinoids have also been found to be effective in reducing anxiety associated with PTSD, although they do not appear to have the same effect on the depression commonly linked with PTSD and other disorders [227].

7.6. Sleep Disturbances

A common reason reported by individuals for using CBD oil is for sleep improvement [228]. However, there is limited human data supporting the use of CBD for sleep [196–198]. Survey data from individuals using CBD to enhance sleep have shown considerable variability, likely due to differences in content and quality of CBD products available on the market [196]. In contrast, acute Δ^9-THC use has been associated with increased total sleep time, while chronic Δ^9-THC use may lead to sleep disruption (possibly due to tolerance) [229]. Interestingly, withdrawal from Δ^9-THC has been linked to an increase in vivid dreams and sleep disturbances [229]. Taken together, more research is needed to draw definitive conclusions about the effectiveness of cannabinoids in promoting sleep.

7.7. Chronic Pain

One therapeutic area for which medical cannabinoids may hold significant potential is in the relief of chronic pain [230]. Several cannabinoid-based treatments have been utilized for neuropathy, including nabilone, nabiximols, dronabinol, Δ^9-THC, CBD, and mixtures of them (bedrocan, bediol, and bedrolite) [199–203,230]. Nabilone was found to be the most effective treatment, with nabiximols being close behind in efficacy. In contrast, Δ^9-THC (dronabinol) alone has been found to be ineffective for the treatment of neuropathic pain. Interestingly, cannabinoid-induced pain relief tends to be more pronounced in patients with peripheral neuropathic pain compared to those with centrally arising neuropathic pain [230]. Beyond pain relief, the majority of the analyzed trials reported improvement in secondary outcomes, including anxiety, quality of life, sleep, and sensory profiles [230].

7.8. Fibromyalgia

In the case of fibromyalgia, Strand et al. [231] found low-quality evidence supporting short-term pain relief in patients treated with cannabinoid-based therapeutics. There may be positive effects on quality of life measures impacted by this syndrome, such as appetite, libido, mood, and sleep quality. However, these improvements were largely inconsistent across studies. Both THC and CBD have been explored as treatment options for fibromyalgia. Studies have shown that THC positively affects appetite, mood, and pain regulation. In turn, CBD has been shown to possess both anti-inflammatory and pain-relieving properties. THC acts as a partial agonist at the CB1 and CB2 receptors, while CBD is a negative allosteric modulator of the CB1 receptor. In theory, the synergistic effects of both components, when combined, could enhance the potential of cannabis as an anti-nociceptive agent [232]. Nevertheless, antagonistic interactions between THC and CBD may also arise due to their differing properties [231].

7.9. Migraine

Cannabis has been utilized as a therapeutic option for migraine management. In this respect, medical cannabis inhalation has shown promise in reducing headache and migraine severity, with over half of users reporting relief, particularly men and those using concentrates [204]. Similarly, dried cannabis flower may alleviate migraine-related pain, though its effectiveness appears influenced by factors such as strain, consumption method,

and patient demographics [205]. While these findings highlight potential benefits, further controlled studies are needed to clarify optimal use and individual responses.

7.10. Schizophrenia

Schizophrenia constitutes a severe psychiatric disorder marked by a range of cognitive, behavioral, and emotional dysfunctions. Various clinical trials have explored CBD as a treatment for schizophrenia, showing that CBD can reduce symptom severity with a favorable tolerability profile compared to placebo [206–208]. While some studies report improvements in positive symptoms and cognitive domains, results vary, and cognitive benefits are not consistently observed. These findings suggest that CBD holds therapeutic potential as an adjunctive treatment in schizophrenia, but further research is needed to confirm its efficacy and clarify its role alongside existing therapies.

8. Gut Microbiome and Cannabinoids: The Role of Microbial Products

The human GM is composed of a varied microbial community, with a density of approximately 10^{11} to 10^{12} microbial cells per milliliter [233]. The human GM contains multiple microbial taxa, including archaea, bacteria, fungi, protozoa, and viruses, with the Bacteria domain being the most dominant [234,235]. Low archaeal genera are present in the healthy human GM, with *Methanobrevibacter smithii* as the most prevalent species [236]. The most commonly detected eukaryotic microorganisms in the intestinal tract are fungi, such as the genera *Candida* and *Saccharomyces* [237]. These fungi preserve both the ecological and immune balance of the GM [238]. Certain protozoa, such as *Blastocystis*, have been found in the human GM and their presence has been related to a mitigation of gastrointestinal disease [239]. The human virome is mainly composed of bacteriophages [240], and they perform a role within the gut as modulators of the bacteriome [241]. Furthermore, bacteria are the most frequent microorganisms in the human intestine, which are constituted by around 100 species that belong to the following eight phyla: Actinomycetota (synonym Actinobacteria), Bacillota (synonym Firmicutes), Bacteroidota (synonym Bacteroidetes), Campylobacterota, Fusobacteriota (synonym Fusobacteria), Pseudomonadota (synonym Proteobacteria), Thermodesulfobacteriota, and Verrucomicrobiota (synonym Verrucomicrobia) [233,242–244].

The human GM composition can differ functionally and taxonomically based on factors such as host genetics, age, diet, drug administration, and the presence of neuropsychiatric disorders [245–251]. The predominant genera of the human healthy gut bacteriome are *Bacillus*, *Blautia*, *Clostridium*, *Dorea*, *Enterococcus*, *Eubacterium*, *Faecalibacterium*, *Lactobacillus*, *Roseburia*, and *Ruminococcus* (phylum Bacillota); *Bacteroides* and *Prevotella* (phylum Bacteroidota); *Bifidobacterium* (phylum Actinomycetota), and *Escherichia* (phylum Pseudomonadota) [233,235,252]. However, when the homeostatic ecological balance and structure of the microbiome is disrupted occur a gut bacterial dysbiosis [253], which affects the bacterial diversity, their metabolic and immunological functions, and the intestinal permeability [254,255].

8.1. Cannabis Use and Gut Microbiome Dysbiosis

Given that smoking is the primary method of cannabis consumption in humans, few studies have been conducted on the effects of this substance on the GM. Cani et al. [63] found that exogenous cannabinoids and the eCBS regulate the gut microbiota. Chronic treatment of obese rodents with THC resulted in an altered microbiota with an increased Bacillota/Bacteroidota ratio, and a concomitant reduction in obesity [256]. Table 4 presents the effects of cannabinoid use on GM composition, as reported in several studies [257–264].

Table 4. Influence of cannabinoid use on the composition of the GM of humans and mice.

Bacterial Phyla, Families, and Genera	Increased	Decreased	Reference
Clinical studies			
ACTINOMYCETOTA			
Bifidobacterium	X		Vigay et al. [260]
Collinsella		X	Vigay et al. [260]
BACILLOTA			
Peptostreptococcaceae		X	Castonguay-Paradis et al. [257]
Acidaminococcus		X	Fulcher et al. [258]
Anaerostipes		X	Fulcher et al. [258]
Clostridum	X		Fulcher et al. [258]
Coprococcus	X		Vigay et al. [260]
Dialister		X	Fulcher et al. [258]
Dorea		X	Fulcher et al. [258]
Faecalibacterium	X		Vigay et al. [260]
Ruminococcus	X		Fulcher et al. [258]
Solobacterium	X		Fulcher et al. [258]
Veillonella		X	Castonguay-Paradis et al. [257]
BACTEROIDOTA			
Bacteroides	X		Panee et al. [259]
	X		Zhuang et al. [261]
Prevotella		X	Fulcher et al. [258]
		X	Panee et al. [259]
FUSOBACTERIODOTA			
Fusobacterium	X		Fulcher et al. [258]
PSEUDOMONADOTA			
Escherichia/Shigella		X	Vigay et al. [260]
VERRUCOMICROBIOTA			
Akkermansiaceae		X	Castonguay-Paradis et al. [257]
Preclinical studies			
BACILLOTA			
Erysipelotrichaceae		X	Mehrpouya-Bahrami et al. [263]
Lachnospiraceae		X	Mehrpouya-Bahrami et al. [263]
Ruminococcus	X		Mohammed et al. [264]
VERRUCOMICROBIOTA			
Akkermansia	X		Al-Ghezi et al. [262]
	X		Mehrpouya-Bahrami et al. [263]
		X	Mohammed et al. [264]

Vijay et al. [260] reported a positive correlation between the eCBS and bacterial α-diversity, as well as with SCFAs-producing bacteria such as *Bifidobacterium*, *Coprococcus*, and *Faecalibacterium*. Moreover, human dietary interventions involving specific fatty acids were shown to increase eCB levels, which were associated with changes in the gut microbiota, such as increases in *Peptostreptococcaceae*, *Veillonellaceae*, and *Akkermansiaceae* [257]. In a study examining the effects of drugs on the GM during HIV infection, Fulcher et al. [258] found that cannabis use was associated with an increased abundance of the genera *Clostridium*, *Fusobacterium*, *Ruminococcus*, and *Solobacterium*, and with a decreased abundance of the genera *Acidaminococcus*, *Anaerostipes*, *Dialister*, *Dorea*, and *Prevotella*. Cannabis use has also been linked to an increased abundance of *Bacteroides* species in the human GM, a change that may be associated with intestinal inflammation and metabolic disorders [261]. In a

cohort study comparing cannabis users and cannabis non-users, Panee et al. [259] reported a positive correlation with the abundance of *Prevotella* and an inverse correlation with the abundance of *Bacteroides* among participants, with the *Prevotella/Bacteroides* ratio being 13 times higher in the non-users.

In a preclinical study, Al-Ghezi et al. [262] found that chronic THC administration in mice led to changes in the gut microbiota, with an increase in the relative abundance of *A. muciniphila*, a bacterium associated with improved gut barrier function and metabolic health. In addition, a negative association was observed with *Collinsella* and *Escherichia/Shigella*. Mehrpouya-Bahrami et al. [263] found that CB1 antagonism reduced cytokine release, decreased intestinal permeability, and altered the gut microbiota, including an increase in *Akkermansia muciniphila* and a decrease in the abundance of *Lachnospiraceae* and *Erysipelotrichaceae*. THC treatment enhanced the abundance of the beneficial bacterial species *Ruminococcus gnavus*, while reducing the pathogenic species *A. muciniphila* in both the lung and gut [264].

Although these findings highlight interactions between cannabis use, the eCBS, and GM composition, the effects of different cannabis types, doses, and usage patterns on the GM remain unclear. Furthermore, heterogeneity in microbiota analysis methods, such as differences in sequencing technologies and bioinformatics approaches, complicates comparisons across studies. Moreover, the mechanisms linking cannabis-induced changes in the GM with systemic health outcomes are not yet well understood. Therefore, future research should prioritize well-designed longitudinal studies with standardized methodologies to better elucidate these relationships and their potential clinical relevance.

8.2. Intermediate Bacterial Metabolites

SCFAs (e.g., acetic acid, butyric acid, and propionic acid) are bacterial metabolites associated with multiple metabolic, immunological, and neural host functions [265–268]. SCFAs, as well as tryptophol, an indole derivative, regulate host cytokine production; circulating cytokines that can cross the BBB and act on the brain to modulate behavioral responses to SUD [266,269]. In addition, SCFAs have beneficial effects on the host based on their anti-inflammatory properties and their epigenetic regulation of gene expression [265,270]. Inflammation affects the glutamatergic signaling, a key neurotransmitter system in drug addiction and relapse [271]. Moreover, alterations in peripheral inflammatory processes may shape drug-taking and -seeking behaviors in SUD [272–274]. On the other hand, SCFAs can act as histone deacetylase inhibitors, stimulate histone acetyltransferases, and serve as molecular substrates for histone post-translational modifications [275–278], all of which are essential molecules for the normal microglial function [279]. It is well established that the role of microglia is in immune surveillance, but it may also play a neuronal complementary role in regulating the behavioral aspects of SUD [280]. In addition, Walker and Nestler [278] suggested that the mechanisms regulating the behavioral aspects of SUD may involve changes in gene expression in the mesolimbic dopamine system, which is part of the brain's reward circuitry.

The GM may be an alternative pathway for the production of kynurenic acid (KYNA), an endogenous tryptophan metabolite [281]. Decreased levels of KYNA, which modulates glutamatergic neurotransmission, have been correlated with alcohol craving in patients with alcohol use disorder [282]. Similarly, Morales-Puerto et al. [283] have reported that modulation of KYNA metabolism can reduce drug-seeking behavior for several substances, including alcohol, nicotine, cannabis, amphetamines, cocaine, and opioids.

8.3. Signaling Molecules

Bile acids (BAs) are important signaling molecules that influence immune homeostasis, induction of inflammation, and even cell death. The GM regulates the balance between primary and secondary BAs, which are involved in the intestinal absorption of lipids and in energy production [284]. Conditions of bacterial dysbiosis reduce the production of secondary BAs, leading to an overabundance of primary BAs, which can increase the bioavailability of drugs to the host or alter drug metabolism [285,286]. BAs, metabolites produced by the liver and modified by the GM, can establish composites with cannabinoids, leading to their reabsorption and prolonged retention within the organism [287].

The gut bacteriome produces acetylcholine, glutamate, serotonin (5-HT), dopamine, epinephrine, norepinephrine, and GABA [288], which play important roles in the brain as neurotransmitters [289,290]. Bacterial dysbiosis affects the synthesis and regulation of gut neurotransmitters, such as 5-HT [291]. Previously, Ciccocioppo [292] reported that the serotonergic 5-HT system is associated with the appropriate control of overmedication and, therefore, with the maintenance of drug addictive behavior. Later, Müller and Homberg [293] reviewed the role of 5-HT in behaviors of the establishment, transition, and maintenance of drug addiction to alcohol, amphetamine, cannabis, cocaine, MDMA (ecstasy), methamphetamine, morphine/heroin, and nicotine. These authors have identified various drug-specific mechanisms in the 5-HT system, including serotonergic adaptations in the 5-HT system, as well as genetic risk factors for the establishment of controlled drug-using behaviors and for the transition to compulsive drug-using behaviors.

The importance of dopamine signaling in the nucleus accumbens for the reinforcing effects of drugs is well established. In addition, chronic drug exposure, which can lead to addiction, activates glutamatergic-mediated neuroadaptations in dopamine striato-thalamo-cortical and limbic pathways (amygdala and hippocampus) [294]. The GM plays an important role in maintaining adequate dopamine levels, promoting dopamine synthesis, and regulating its degradation [288].

Interestingly, the GM can metabolize drugs, modifying their efficacy and pharmacokinetics, which can alter the magnitude of reward and withdrawal symptoms [295]. Indeed, diverse studies have recognized microbial enzymes with the capacity of metabolizing cannabinoids, resulting in the establishment of active or inactive metabolites [48]. For example, the GM contains the enzyme β-glucuronidase, which is able to deconjugate glucuronide metabolites of THC, thereby releasing the active form of THC back into the circulatory system [296]. The GM can also exert an impact on systemic exposure to cannabinoids by altering the enterohepatic circulation [297]. The ability of the GM to metabolize cannabinoids can pronouncedly influence their bioavailability and therapeutic effects, further underlining the interaction between the GM and cannabis with respect to the modulation of physiological responses [298].

8.4. Neural Pathways

The vagus nerve, which is part of the parasympathetic nervous system, provides an indirect bidirectional communication in the brain-gut axis [299] by receiving and responding to signals from gut bacterial metabolites such as SCFAs [300,301]. In addition, enteroendocrine cells of the gut epithelium transmit signals to the vagus nerve via the liberation of cholecystokinin, glucagon-like peptide-1, peptide YY, and 5-HT [300,302,303]. These interactions between the GM and the enteric nervous system may influence interoceptive signals that are important in SUD and other psychiatric disorders [304,305]. Although the vagus nerve may be important for SUD behavioral responses, the influence of the human GM via the vagal pathway to modulate these behavioral responses has not yet been established [306].

Microglia, resident immune cells in the brain and spinal cord, are mobilized in response to CNS infection or injury and exert protection against many neurodegenerative diseases [307]. Activated microglia promote tissue repair and homeostasis through cytokine release and phagocytosis of cellular debris [308]. However, the current understanding of the mechanisms that regulate microglial functions is not fully understood, especially with regard to the influence of extrinsic factors such as the human GM [309]. The GM regulates the microglia-mediated inflammation response in the CNS through secreted bacterial metabolites and neurotransmitters [310]. During SUD, resident CNS macrophages are activated, and the subsequent TNF-α and IL-1β released by microglia contribute to the pathophysiology of SUD [311]. Therefore, this communication between the microglia and the GM may be considered as an important factor in the mechanism of microglial activation during SUD, as microglial cells depend on a healthy and complex GM for proper development, maturation, and function. For example, translocated bacteria in the gut can release pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, which can further disrupt the intestinal epithelium and impair microglial function [312].

Brain-derived neurotrophic factor (BDNF) appears to be a prominent candidate for determining the role of the GM in drug addiction processes. BDNF is synthesized by both glial and neuronal cells, and also by peripheral immune cells and by the vascular endothelium [313]. BDNF is epigenetically regulated by changes in histone acetylation in cocaine use, and BDNF has also been shown to influence the behavioral effects of opioids [314].

The HPA axis, which constitutes a neuroendocrine system related to stress, produces cortisol in humans. Adequate levels of this glucocorticoid are essential for normal neurodevelopment and neural function, and are also involved in several cognitive processes, such as learning and memory [315]. Evidence suggests that the GM, the HPA axis, and cognitive processes are interconnected through substances (neurotransmitters, hormones, and bacterial metabolites) and various pathways, such as the vagus nerve, immune system, and BBB regulation [316]. Gut dysbiosis resulting from drug use and other factors can affect the host's stress response, the HPA axis activity, and even cognitive health [316]. Stress increases craving and drug-taking behavior, but it is not established whether this stress hormone may rather reduce them by interfering with addiction memory.

9. Cannabis Use Disorder and Its Treatment

An established habit can drive behavior almost automatically, although its acquisition depends on a deliberate search that energizes motivation. In this regard, it is common that the initial reasons for drug use are driven by curiosity and that, after reinforcement, such behavior can become a habit [317]. Repeated consumption can lead to the development of addiction, and this practice is widely spread among the young population, which is negatively affected in terms of their personal and social development.

Although it is commonly noted that there are no withdrawal effects derived from cannabis consumption, it has been argued that CUD can produce withdrawal symptoms comparable to those provoked by other drugs [318]. The DSM-5 includes a cannabis withdrawal syndrome [319], which consists mainly of emotional and behavioral symptoms, including anxiety, agitation, depression, irritability, and also appetite, sleep, and weight disturbances [320]. Less frequent physical symptoms include abdominal pain, shakiness, and sweating [321]. The clinical symptoms of the withdrawal syndrome are associated with increased functional impairment in normal daily activities, and symptoms often appear 2–3 days after cessation of intense cannabis consumption and can last 2–3 weeks [322,323]. However, withdrawal symptoms are strongly associated with relapse, so most abstinent in-

dividuals who experience withdrawal symptoms will use the drug to relieve the symptoms, thereby continuing to use cannabis [324].

Importantly, withdrawal symptoms from cannabis use often coincide with manifestations seen in anxiety and mood disorders, and numerous subjects cite mood fluctuations as a motivation for cannabis use, unaware that using it in a short-term way for symptomatic relief may lead to a long-term withdrawal syndrome [325]. Furthermore, medical cannabis can be considered no different from other medications whose pharmacology results in physiological dependence, including a withdrawal syndrome (e.g., benzodiazepines and opioids), which requires clinical consideration and management. Certainly, this also applies to their propensity for misuse within the context of CUD [326].

9.1. Prevalence of Cannabis Use Disorder

Cannabis continues to be the most frequently used illicit psychoactive substance. Extensive epidemiological studies indicate that approximately 43% of people in the United States of America and Canada report having tried cannabis, with nearly 35% having tried it more than once [327–329]. Cannabis use is highest among adults aged 18–44 years, with just over half reporting use [328]. Consumption among emerging adults (18–24 years) is approximately 33.3%, with daily use at nearly 4% in this age group [328,329]. The increase in the frequency of cannabis use coincides with decreasing risk perceptions of the drug [327]. Recently, Shah et al. [330] reported that, for both sexes together, prevalent cases of CUDs increased steadily from 17.1 million in 1990 to 23.8 million in 2019. The highest age-adjusted incidence was observed in High-Income-North-America (HINA) (121/100,000), followed by Australasia (100/100,000), Oceania (83.97/100,000), and tropical Latin America (69.59/100,000). Globally, age-standardized disability-adjusted life year rate (ASDR) was observed to be higher in HINA, followed by Australasia, and Western Europe. In men, the number of incidences for all ages increased from 1.7 million in 1990 to 2.4 million in 2019. The most significant annual percentage of variation in age-standardized incidence rate (ASIR) was observed in East Asia (22%), with the Middle East and North Africa (MENA) next in line (15%). The 15–24 age group had the highest burden of CUDs.

Prevalence rates for CUD range from 2.9 up to 19%, with approximately 13 million people worldwide meeting criteria [331–333]. Severe lifetime CUD rates are approximately 2%, with rates peaking in emerging adulthood (around age 21 years). Prevalence rates also vary across different sociodemographic groups: among adults aged 18–29 years, with a mean age of onset in the early twenties, married individuals, and those with lower socioeconomic status report higher CUD prevalence rates. Nevertheless, education seems to be mostly unassociated [332]. Curiously, CUD has been linked to comorbidity and disability, which may impact emotional and social functioning [332]. Information on cannabis-related disability is relatively new, as many earlier studies did not include cannabis when examining disease burden, but recent studies show that CUD does not increase mortality as other forms of illicit drug dependence do, and neither is a major contributor to population-level disease burden [334]. Disability may persist even after CUD remission, although the reason for this is not yet clear [335]. In this sense, converging evidence supports that cannabis use for medical purposes is effective, but should be avoided by certain population groups, such as adolescents, individuals with severe mental disorders, and pregnant women [336].

9.2. Common Comorbidities

The main comorbid conditions associated with CUD are anxiety, depression, concomitant substance use, and personality disorders [327,332]. Understanding the relationship between CUD and other conditions can be useful because it can provide further insights

into the course and progression of the comorbid disorder. Different SUDs have been associated with CUD, such as those related to club drugs, heroin, inhalants, pain relievers, stimulants, and other prescription drugs [337]. In this respect, cannabis and stimulant co-use is aimed at balancing the pharmacokinetic effects of each drug [337]. Individuals with CUD are also likely to smoke, reporting in turn higher rates of alcohol use [21,337]. Longitudinal studies have supported a causal relationship between early cannabis use and CUD, other illicit substance use, depressive states, and suicide ideation [338]. Overall, data indicate concurrent use of multiple substances with CUD, even when adjusting for other health and psychiatric factors that were present before or during adolescence [337,338].

Regarding other conditions, personality disorders frequently coexist, with elevated rates of antisocial and borderline personality traits [332]. Anxiety disorders are also associated with CUD, with PTSD having the highest association, followed by general anxiety disorder and panic disorder [21,332]. Converging lines of preclinical, epidemiological, and empirical studies show solid associations between cannabinoids and psychosis. In this sense, the exogenous cannabinoid hypothesis proposes that regular cannabinoid exposure is associated with the development of psychosis [339]. In controlled human laboratory research, the administration of THC and cannabis extract results in heightened positive symptoms like delusions, suspiciousness, and alterations in perception, and also negative symptoms such as blunted affect, cognitive deficits (e.g., attention, learning, and memory processes), psychomotor retardation, and reduced rapport. Some of these symptoms are related to those observed in schizophrenia, including verbal recall impairment with increased "false positives" and "intrusions" [340]. In line with findings from acute intoxication experiments, epidemiological studies also indicate that cannabis consumption increases the risk of developing psychosis [341]. However, more research is needed that integrates epidemiology, neurobiology, and psychopharmacology with specify compounds and strengths to ascertain the extent and mechanisms of a causal effect [341]. Nevertheless, many people who consume cannabis regularly do not develop psychotic disorders, so understanding which subgroups are most at risk for propsychotic effects remains to be elucidated [339].

9.3. Treatment

Some psychosocial and behavioral interventions have shown potential for reducing CUD within 16 months of treatment. However, although pharmacotherapies are highly effective for other SUDs, there are no approved pharmacological treatments for CUD [342]. Evidence demonstrates that the current best psychosocial interventions to diminish cannabis use include the combination of cognitive behavioral therapy (CgBT) and motivational enhancement therapy (MET), in conjunction with contingency management approach, drug education counseling, mindfulness meditation, social support counseling, and relapse prevention [343,344]. The CgBT, MET, relapse prevention, and contingency management produced moderate effect sizes compared to controls at 2–14 weeks follow-up [345]. Combining CgBT or MET with abstinence-oriented contingency management further reduces the frequency of use and severity of cannabis problems than either intervention alone [346–348].

Clinical trials for CUD based on pharmacotherapy have explored agonist-like drugs that target the CB1 receptor (substitution therapies), such as dronabinol, gabapentin, nabiximols, and N-acetylcysteine. These CB1 agonists reduce the severity of cannabis withdrawal symptoms [4,349], and zolpidem and other benzodiazepines (nitrazepam) have been used to treat withdrawal-related sleep disturbances [350,351]. Bahji et al. [352] reviewed other medications and concluded that nabilone, topiramate, and fatty acid amyl hydroxylase inhibitors reduced cannabis use compared to placebo. Dronabinol improved treatment

retention, whereas topiramate worsened treatment retention; gabapentin reduced cannabis craving, while vilazodone worsened craving severity; and finally, buspirone, venlafaxine, and topiramate caused more adverse events, whereas topiramate caused more dropouts due to adverse events.

Interestingly, the anxiolytic, antipsychotic, and neuroprotective effects of CBD may have additional benefits by reducing many of the mental health and cognitive impairments reported in people with regular cannabis use. In addition, some medications for mood, sleep, or craving that reduce withdrawal symptoms have not led to commensurate reductions in the amount of cannabis use or increased the duration of cannabis abstinence [353,354].

Recently, Pinapati et al. [355] have suggested that the links between gut bacteria, CNS, eCBS, and cannabis dependence, which would be an insight to overcome cannabis withdrawal symptoms. In this regard, a protocol to evaluate the therapeutic implications between probiotics (*Lactobacillus acidophilus*, *A. muciniphila*, *Bifidobacterium bifidum*, and *Streptococcus thermophilus*) and Δ^9-THC has been proposed [356]. A subtype of *A. muciniphila* was found to be negatively associated with *Bacteroides* abundance [357], suggesting that there is scope for using this bacterium as a potential nootropic in cannabis addiction. In support of this, *A. muciniphila* has been identified as an effective probiotic against alcohol-induced liver injury and has therapeutic justification in chronic opioid use [358].

10. Social Perspectives on the Legalization of Cannabis

Social norms are particularly relevant regarding cannabis-related behaviors [359]. Indeed, social acceptability and perceptions of risks and benefits, including the active sharing of these beliefs on social networks, are important predictors for the abstinence or consumption of cannabis [360], which at the end can vary in function of factors such as gender or age. Nevertheless, cannabis is, in general terms, perceived as more socially acceptable, less risky, and more beneficial than other drugs, such as tobacco. The fact that potential consumers obtain experience-based information from fellow users about cannabis consumption indicates that there is a need not only for practical advice, but also for much closer scrutiny and regulation of the products based on cannabis within contexts where they are legal, including accurate labeling of the levels of cannabinoids, appropriate doses, and potential side effects [361]. In this respect, given the wide acceptance of cannabis use and the corresponding high proportion of people who believe that this drug is neither harmful nor addictive, serious consideration is required in the regulatory regime accompanying potential legalization [362]. However, it is essential to consider, at the same time, that the legalization of the consumption of this plant could provide multiple benefits to the economy, society, and populations that obtain favorable outcomes from responsible use.

The recent shift in sociopolitical debates and growing liberalization of cannabis use across the globe has raised concern regarding its impact on vulnerable populations, such as pregnant women and adolescents. Epidemiological studies have long demonstrated a relationship between developmental cannabis exposure and later mental health symptoms [363]. This relationship is especially strong in people with particular genetic polymorphisms, suggesting that cannabis use interacts with genotype to increase mental health risk [364]. Seminal animal research directly linked prenatal and adolescent exposure to Δ^9-THC, the major psychoactive component of cannabis, with protracted effects on adult neural systems relevant to psychiatric disorders and SUD [363].

The debate on the legal status of cannabis remains lively due to the heterogeneity of regulations and legislation around the world, ranging from possible legal consumption (The Netherlands) to prison sentences, life sentences, or death penalties for traffic in countries such as Indonesia, the United Arab Emirates, and Saudi Arabia. This variety

of legislation is the result of a complex historical drift resulting from cultural, scientific, and political movements debating the benefits and harms of regular use. Therefore, the legal status of cannabis varies widely across countries and regions; although cannabis is largely illegal at the global level, policies surrounding the use of this substance are becoming steadily liberalized [365]. Reduced penalties for self-use of cannabis, but not distribution, are more widespread worldwide, including in The Netherlands, Portugal, and parts of Australia. Medical legalization is also seen in Peru, Germany, New Zealand, The Netherlands, and across many U.S. states. To date, Canada, Uruguay, and Malta are the only three countries to legalize recreational cannabis use at the national level. Furthermore, individual U.S. states began legalizing recreational cannabis in 2012, with nearly half of U.S. states having legalized recreational cannabis by 2023. There are arguments both for and against recreational cannabis legalization. Common pro-legalization arguments involve increasing regulatory control over product distribution, weakening organized crime, reducing burden and inequality in the criminal justice system, and generating economic benefits such as tax revenues and commercial activity. Moreover, as cannabis obtained from illicit markets is of varying and unknown potency, cannabis legalization may help better regulate the potency and quality of cannabis products [365]. In addition, as states continue to proceed with legalization for both medical and recreational use, certain public health issues have become increasingly relevant, including the effects of acute cannabis intoxication on driving abilities, unintentional ingestion of cannabis products by children, the relationship between cannabis and opioid use, and whether there will be an increase in health problems related to cannabis use, such as dependence/addiction, psychosis, and pulmonary diseases [366].

11. Discussion

The present review was aimed at providing a holistic overview of cannabis, with particular focus on its risks and benefits regarding mental health. Based on the literature examined, it is reasonable to assert that this substance is far less harmful than other drugs of abuse also used in medical settings [367,368] or for recreational purposes [369–373]. However, it should not be considered entirely harmless. This duality highlights the complexity of its impact on individuals, requiring a comprehensive interpretation that extends beyond reductive frameworks. From a mental health perspective, while cannabis has been shown to offer numerous therapeutic benefits, it also presents potential risks. These risks, however, are mainly subject to individual influencing factors that underscore the importance of personalized approaches to cannabis use, as well as the need for individuals to be aware of their own reactions to the substance. Thus, society is faced with a plant of extraordinary clinical significance whose potential disadvantages seem to be balanced given its obvious utility.

The examination of the studies included in this review provides a comprehensive overview of the current state of knowledge on cannabis and serves to guide further investigation and clinical practice. Derived from this examination, several key points can be extracted and highlighted. With respect to adverse mental health outcomes associated with cannabis use, it has been stated that (i) there is a bidirectional relationship between cannabis use and mental health disorders; (ii) cannabis use is linked to increased symptoms of anxiety, depression, and suicidality, especially among adolescents; (iii) genetic factors, such as the 5-HTTLPR genotype, influence the impact of cannabis on anxiety; (iv) reducing cannabis use may lead to improvements in depressive symptoms; (v) early cannabis use is a significant risk factor for mental health issues later in life; (vi) cannabis use can worsen outcomes in individuals with pre-existing mental disorders, such as borderline personality disorder and PTSD; and (vii) CUD frequently co-occurs with other SUD, exacerbating

mental health issues. Despite the observed relationships between cannabis use and various mental health outcomes, it is important to consider the potential limitations inherent in the studies evaluating these associations, including (i) confounding variables, as many studies fail to account for pre-existing mental health conditions; (ii) sample diversity, as the sample populations in some studies were limited in terms of age or cultural background, making it difficult to generalize findings across different demographic groups; (iii) a significant number of studies that were cross-sectional, which limits their ability to establish causal relationships; (iv) self-reporting bias; (v) variable cannabis use patterns; (vi) the influence of genetic and environmental factors; (vi) lack of long-term follow-up; (vii) the varying effects of cannabis use in function of the developmental stage; (viii) substance use co-occurrence; and (xi) mental health assessment limitations, as the tools used varied across studies, which may lead to inconsistencies in the findings.

On the other hand, the potential therapeutic efficacy of cannabis-based treatments in a clinical and mental health context shows a variety of outcomes based on the studies analyzed. These results have been synthesized and simplified to reflect an overview of the observed effects, which ultimately depend on factors such as the type of compound administered, dosage, and sample characteristics. Therefore, the interpretation of these findings should not be taken literally, as they are based on a limited number of studies for each mental health disorder and are subject to the nuances of the specific study designs and variables involved. The findings are summarized as follows: (i) for epilepsy, it was found that treatment led to a significant reduction in seizure frequency and improvements in behavior, motor skills, and sleep, with better outcomes observed when used alongside clobazam; (ii) for Dravet syndrome, treatment resulted in a reduction of convulsive seizures; (iii) for Lennox-Gastaut syndrome, treatment led to a significant reduction in drop seizures; (iv) for Alzheimer's disease, treatment may reduce agitation, although it requires monitoring of sedation and cognition; (v) for dementia, treatment significantly improved dynamic balance and gait velocity; (vi) for Parkinson's disease, treatment improved pain and sleep, and reduced anxiety; (vii) for MS, treatment showed almost double the relief from muscle stiffness compared to placebo; (viii) for ASD, treatment led to improvements in behavioral outbreaks, self-injury, hyperactivity, sleep problems, and anxiety; (ix) for Rett syndrome, treatment reduced seizures and showed improvement in agitation and spasticity; (x) for Tourette syndrome, treatment showed mixed results in reducing tic severity; (xi) for ADHD, treatment showed improvements in ADHD symptoms and task performance, reductions in cognitive impairment, but no significant effects on response inhibition or brain activity; (xii) for BD, treatment showed limited effectiveness in reducing mania symptoms; (xiii) for social anxiety disorder, treatment significantly reduced anxiety, cognitive impairment, discomfort during speech, hyper-alertness in anticipatory speech, and also modulated cerebral blood flow in specific brain regions involved in anxiety processing; (xiv) for anxiety, treatment showed mixed results, with low and daily doses exhibiting higher potential in reducing anxiety symptoms; (xv) for PTSD, treatment showed mixed results, indicating certain potential for improving certain symptoms, such as sleep disturbances, anxiety, social anxiety, and depression; (xvi) for sleep disturbances, treatment was found to improve sleep quality and general well-being; (xvii) for pain, treatment significantly reduced its intensity, demonstrating analgesic efficacy; (xviii) for fibromyalgia, treatment improved symptoms related to pain and fatigue, promoting overall well-being; (xix) for migraine, treatment led to a reduction in headache severity; and (xx) for schizophrenia, treatment demonstrated effectiveness in reducing positive symptoms and improving cognitive performance. Regarding the main side effects found in the cannabis-based treatments, the following have been identified: somnolence, fatigue, gastrointestinal disturbances, irritability, decreased appetite, pyrexia, cognitive disturbances, dizziness, dry mouth, sleep

disturbances, increased appetite, mood deterioration, restlessness, altered mental states, headache, nausea, and agitation. In light of the findings previously presented on the potential utility of cannabis-based drugs for the treatment of mental health conditions, it should be acknowledged that the studies present several potential limitations, including small sample sizes, short treatment durations, high variability in doses and formulations, side effects, inconsistent outcome measures, placebo effects, heterogeneity in patient populations (e.g., age, gender, ethnicity), interactions with comorbid psychiatric disorders, and retrospective nature of some studies. In this respect, these factors may contribute to divergent findings and should be carefully considered in future research, as they represent possible confounders. For instance, developmental differences between adolescents and adults may influence both the pharmacodynamics of cannabis and the vulnerability to psychiatric symptoms, complicating the generalizability of results across age groups. Dosage variability and differences in cannabinoid composition can lead to inconsistent therapeutic effects and side effect profiles, making it difficult to establish standardized treatment protocols. Furthermore, the presence of comorbid conditions such as PTSD or CUD may interact with cannabis effects in complex ways, potentially exacerbating or mitigating psychiatric symptoms and thereby confounding outcome measures. These variables underscore the need for more rigorous, well-controlled studies with carefully defined populations and standardized interventions to clarify the effects of cannabis on mental health outcomes. Thus, progress in research on this controversial yet promising substance is imperative, requiring a greater volume of studies across diverse populations and employing rigorous methodological designs capable of establishing causal relationships.

Medical cannabis exemplifies a significant convergence between ancient herbal remedies and modern pharmacology. This reflects a fascinating historical continuity, demonstrating humanity's inherent reliance on plant-derived compounds. The rich biochemical arsenal belonging to cannabis interacts intrinsically with the human eCBS, which is thought to naturally mediate the effects of such substances. Thus, said "symbiotic" relationship suggests that plant-based drugs may be more than just therapeutic tools; they could be integral to our biological evolution, aligning with the body's natural processes. In this sense, cannabinoids may modulate a wide range of physiological functions. Moreover, cannabis therapeutic use has been documented over millennia, illustrating a deep-seated human affinity for harnessing nature's pharmacopoeia aimed at enhancement and healing effects, which constitutes a fundamental aspect of our evolutionary heritage, extending from ancient knowledge to contemporary science.

Regarding the results of the review on the relationship between cannabis use and the GM, and on how this interaction may influence mental functioning, several key points can be highlighted: (i) exogenous cannabinoids, along with the eCBS, play a role in regulating the GM; (ii) a positive correlation exists between the eCBS and bacterial α-diversity, as well as SCFAs-producing bacteria, such as *Bifidobacterium*, *Coprococcus*, and *Faecalibacterium*; (iii) CB1 antagonism has been shown to reduce cytokine release, intestinal permeability, and alter the microbiota, including an increase in *A. munciniphila*, which is linked to improved gut barrier function; (iv) THC treatment has been shown to enhance beneficial bacteria such as *R. gnavus*, while reducing pathogenic species such as *A. muciniphila* in both lung and gut tissues; (v) cannabis use can induce a potential shift in GM composition, involving *Prevotella*/*Bacteroides* ratios; (vi) SCFAs have anti-inflammatory effects and can epigenetically regulate gene expression, which may be beneficial for reducing inflammation associated with SUD; (vii) alterations in KYNA metabolism have been associated with reduced drug-seeking behavior for various substances, including cannabis; (viii) the GM has the ability to metabolize cannabinoids by producing enzymes that can modify their efficacy and pharmacokinetics; (xix) specific microbial enzymes in the GM, such as β-glucuronidase,

can deconjugate glucuronide metabolites of THC, increasing its bioavailability; and (x) the GM may serve as an alternative pathway for modulating responses in SUD, offering potential avenues for therapeutic interventions in addiction issues, such as CUD.

Without any doubt, CUD presents a compelling area of study, as its severity and prevalence require critical assessment. Current research indicates that while CUD can constitute a significant concern, its manifestation is not uniform across all users. In this respect, the disorder intensity seems to correlate with patterns of use, especially abuse or misuse, and individual vulnerability. For this reason, addressing CUD requires a comprehensive approach that integrates behavioral patterns and individual differences, ensuring that responses to cannabis use are both targeted and proportionate to the actual risk presented. Interestingly, the metabolic processing of cannabinoids may also contribute to individual variability. Δ^9-THCs, Δ^8-THCs, CNBNs, and CBNs undergo microbial hydroxylation, producing mono- and dihydroxylated derivatives [374]. These metabolic alterations could modulate the bioavailability and pharmacokinetics of cannabinoids, potentially influencing the progression and severity of CUD. Moreover, a bidirectional relationship between the GM and SUDs, including CUD, has been highlighted [375]. This interplay not only reflects the impact of chronic substance use on the composition and dynamics of the GM but also suggests that GM dysbiosis may modulate behavioral responses to drugs of abuse. In this context, targeting the GM or its metabolites emerges as a promising avenue for therapeutic intervention in SUDs. Similarly, advances in microbiome research point to the potential use of human microbiota profiles, including those of the oral cavity, gut, and upper respiratory tract, as biomarkers for identifying individuals at increased risk of pathological cannabis use. Importantly, gaining deeper insights into host-microbiome interactions and their genetic underpinnings may be pivotal for understanding the role of the microbiome in addiction vulnerability and for guiding the development of customized treatment approaches [375].

Socially, cannabis legalization and decriminalization have had profound impacts. In regions where this drug has been legalized, there have been several societal advantages, and there have also been concerns about increased accessibility leading to higher rates of use among adolescents. The shift in the legal status of cannabis brings to the fore issues of social justice, particularly in the context of past drug-related incarcerations and their disproportionate impact on marginalized communities. The cultural perception of cannabis is evolving. Formerly stigmatized, it is increasingly seen as a natural remedy or as a safer alternative to other substances like alcohol or opioids. This changing perspective can influence public health policies and individual choices, potentially reducing the stigma associated with its use and encouraging more open discussions about its benefits and risks.

Limited research has explored the underlying mechanisms contributing to disparities in cannabis use between sexual minority and heterosexual young adults. Romm et al. [376] investigated the associations between sexual orientation (heterosexual, gay/lesbian, bisexual) and cannabis use outcomes, alongside perceived risks (e.g., harm, addictiveness) and social norms (e.g., social acceptability, peer use). Bisexual women exhibited increased odds for multiple cannabis use outcomes, whereas lesbian women and gay men showed elevated odds specifically for current use. These findings suggest that cannabis-related perceptions and social norms may serve as key targets for public health interventions aimed at sexual minority young adults. Dyar [377] conducted a review on disparities in cannabis use and CUD among sexual and gender minority populations. The review provided strong evidence that sexual minorities are at higher risk for cannabis use, with particularly elevated rates of CUD among sexual minority women. Evidence supports a concurrent relationship between minority stress and CUD symptoms, with coping motives emerging as a robust mechanism linking minority stress to both cannabis consumption and

CUD. Furthermore, cannabis use norms and contextual factors have also been identified as potential contributors to this elevated risk. These findings underscore the importance of incorporating sexual orientation and gender identity into public health strategies and research on cannabis use. Addressing minority stress, challenging normative contexts, and customizing interventions to the particular experiences of sexual minority populations may be pivotal steps toward reducing disparities in cannabis-related outcomes.

Regarding the implications for practice and research, this review draws attention to several important aspects. Clinically, practitioners should be aware of the bidirectional relationship between cannabis use and mental health disorders in adolescents, a period when cannabis use seems to be associated with increased anxiety, depression, and suicidality. Early initiation, heavy use, and co-occurring psychiatric conditions worsen mental health outcomes, underscoring the need for targeted screening and intervention strategies in these populations. From a research perspective, there remain significant gaps and uncertainties, in part because many existing studies suffer from methodological limitations that restrict causal inferences. Thus, future studies should prioritize longitudinal designs with diverse populations, standardized assessment tools, and longer follow-up periods to clarify causal pathways and identify protective factors. In addition, research into the role of genetic factors, such as the 5-HTTLPR genotype and the interaction between the GM and the eCBS, may reveal novel targets for intervention. Regarding cannabis-based treatments for various neurological and psychiatric conditions, evidence suggests potential benefits for disorders like epilepsy, Parkinson's disease, ASD, and anxiety-related disorders. However, variability in compound types, dosages, and patient characteristics requires cautious interpretation. Moreover, side effects and long-term safety profiles need further elucidation through well-designed clinical trials. The growing societal changes in cannabis legalization underscore the need for public health strategies that balance increased access with prevention of misuse, especially among vulnerable groups. Addressing CUD demands integrated approaches that consider individual behavioral patterns, genetic metabolism, and social determinants. Therefore, actionable clinical steps include early screening, targeted interventions for at-risk populations, and cautious consideration of cannabis-based therapeutics. Future research must overcome current limitations to better understand causality, therapeutic potential, and mechanisms underlying the impact of cannabis on mental health.

As we advance in our understanding of cannabis, it becomes clear that the future of this drug lies in taking advantage of its benefits through carefully strategies that address both individual needs and broader societal impacts. This balanced perspective will be essential for optimizing its role in medicine and for ensuring its responsible use. Therefore, further objective and impartially research should concentrate on the aspects yet not been fully developed regarding cannabis, such as long-term impact on diverse populations, evidence-based guidelines for its use, and detailed mechanisms implicated in therapeutic and adverse effects. This will be pivotal in maximizing its therapeutic benefits while mitigating risks, ultimately guiding the responsible and effective incorporation of cannabis into clinical practice, and even accepting it as a viable drug for recreational consumption.

This review was aimed at providing a holistic, integrative, and innovative overview of the topic investigated. To the best of our knowledge, no previous review has approached cannabis from such diverse perspectives, which contributes to a deeper understanding of this versatile substance. However, this review may present potential limitations, including the lack of a systematic methodology and a quantitative synthesis of data, due to the broad scope and heterogeneity of the studies considered. Another limitation of this review is the absence of a formal grading of the quality or level of evidence. Given its narrative nature, studies were not evaluated using standardized tools for assessing methodological rigor or risk of bias. As a result, comparisons across studies should be interpreted with

caution, and the strength of evidence supporting specific findings may vary. In this regard, many studies vary in sample size and effect size, which may influence the strength of their conclusions. Common limitations, such as cross-sectional designs and reliance on self-reporting, can introduce bias and limit causal interpretations. Therefore, these factors should be considered when interpreting results and underscore the need for more rigorous, longitudinal studies. Furthermore, the conclusions drawn may not capture the full extent of variability across studies.

12. Conclusions

Cannabis has a long history of use for various purposes, with a complex chemical profile and pharmacokinetics that show promise in treating numerous neurological, psychiatric, and psychological conditions. However, its use carries risks, which depend on factors such as compound concentration, dosage, consumption method, frequency of use, and individual characteristics, as not all users exhibit the same level of vulnerability. While CUD may be less severe than other SUDs, it can still lead to adverse consequences. CUD often co-occurs with other SUDs and may exacerbate psychiatric symptoms in vulnerable individuals. In this context, the GM emerges as a potential alternative pathway for modulating responses in SUDs, opening up possibilities for therapeutic interventions in addiction, including CUD.

The dual nature of cannabis underscores the complexity of its effects, demanding a thorough understanding that goes beyond simplistic explanations and prejudices. From a mental health perspective, there is no doubt that cannabis offers notable therapeutic benefits, highlighting the importance of personalized approaches to cannabis use and increased awareness of how individuals respond to this substance. Changing social perceptions of cannabis could influence consumption patterns, creating opportunities to advance public health strategies. Ultimately, cannabis stands as a plant of substantial clinical significance, where its potential risks appear balanced by its clear utility.

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Abbreviations

The following abbreviations are used in this manuscript:

eCBS	Endocannabinoid system
CUD	Cannabis use disorder
SUD	Substance use disorder
CNS	Central nervous system
BBB	Blood–brain barrier
HPA	Hypothalamic–pituitary–adrenal
GM	Gut microbiome
THCs	Tetrahydrocannabinols
Δ^8-THCs	(−)-Δ^8-trans-tetrahydrocannabinols
Δ^9-THCs	(−)-Δ^9-trans-tetrahydrocannabinols

eCBome	Endocannabinoidome
2-AcGs	2-acylglycerols
2-AG	2-arachidonoylglycerol
AEA	N-arachidonyl-ethanolamide
NAEs	N-acyl ethanolamines
CBCs	Cannabichromenes
CBLs	Cannabicyclols
CBDs	Cannabidiols
CBEs	Cannabielsoins
CBGs	Cannabigerols
CBNDs	Cannabinodiols
CBNs	Cannabinols
CBTs	Cannabitriols
BAs	Bile acids
GFA	Grifolic acid
KYNA	Kynurenic acid
DCA	Daurichromenic acid
SCFAs	Short-chain fatty acids
GABA	γ-aminobutyric acid
5-HT	Serotonin
BDNF	Brain-derived neurotrophic factor
GPCR	G protein-coupled receptor
PPARs	Peroxisome proliferator-activated nuclear receptors
AN	Anorexia nervosa
ADHD	Attention-deficit/Hyperactivity disorder
ASD	Autism spectrum disorder
BED	Binge eating disorder
BD	Bipolar disorder
NDDs	Neurodevelopmental disorders
PTSD	Post-traumatic stress disorder
CgBT	Cognitive behavioral therapy
MET	Motivational enhancement therapy

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