

Original Article



Medical Applications and Misuse Potential of Cannabis: Pharmacological Mechanisms, Therapeutic Benefits, and Clinical Challenges

Fernand Catherine Ferdinica ^{1†}, Rengasamy Rishikesh ^{1†}, Bhagavathi Sundaram Sivamaruthi^{2,3*},
Fairen Angelin Jayakumar¹, Durairaj Ragu Varman ^{*1}

¹ School of Biomedical Sciences, Sri Balaji Vidyapeeth (Deemed to be University), Puducherry.

² Office of Research Administration and Faculty of Pharmacy, Chiang Mai University, Chiang Mai 50200, Thailand.

³ Innovation Centre for Holistic Health, Nutraceuticals, and Cosmeceuticals, Faculty of Pharmacy, Chiang Mai University, Chiang Mai 50200, Thailand.

† Equal First Author Contribution

* Correspondence to: Durairaj Ragu Varman, School of Biomedical Sciences, Sri Balaji Vidyapeeth (Deemed to be University), Puducherry-607 402, India.

ORCID: <https://orcid.org/0000-0002-9409-9456>. Email: raguvarmand@sbms.sbv.ac.in and raguvarma@gmail.com

Citation of this article: Ferdinica F. C., Rishikesh R., Sivamaruthi B. S., Jayakumar F. A., Varman D. R., Medical Applications and Misuse Potential of Cannabis: Pharmacological Mechanisms, Therapeutic Benefits, and Clinical Challenges. Nat Cell Sci 2026;4(4):e00020. doi: 10.61474/ncs.2026.00020.

Abstract

Cannabis, also called *Cannabis sativa*, is widely used both recreationally and medicinally for pain relief, gastrointestinal issues, mental health conditions, and seizures. However, despite its medical uses, it is often abused for its psychoactive effects. Its primary active compounds, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), impact the body differently by mainly interacting with the endocannabinoid system. THC acts as a partial agonist at cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2) receptor, producing the psychoactive effects of cannabis and influencing dopamine-related reward pathways, and neuroplasticity. CBD, unlike THC, does not cause intoxication and offers anti-inflammatory, anxiety-relieving, anticonvulsant, and neuroprotective benefits through complex mechanisms involving both receptor-dependent and independent pathways. Cannabis-based therapies and THC–CBD blends provide health benefits for conditions such as chronic pain, multiple sclerosis (MS) -related spasticity, nausea from chemotherapy, complex epilepsy, and some gastrointestinal issues by affecting inflammation and gut movement. As these treatments become more popular, concerns about misuse, tolerance, withdrawal symptoms, and cannabis use disorder (CUD) increase, especially among adolescents. Activation of CB1 receptors by THC can influence neuronal growth factors and synaptic plasticity. Adjusting dosage primarily by lowering THC and increasing CBD can reduce psychoactive and cardiovascular risks. Recent research backs new pharmacological and behavioural approaches for cannabis withdrawal and CUD, but standardized guidelines are still limited. This review highlights recent findings influence cannabis's medicinal benefits and potential risks. A thorough evaluation of these benefits and risks is essential for informed clinical decisions, responsible prescribing, and evidence-based public health policies.

Key words

Cannabis; Tetrahydrocannabinol; Cannabidiol; Endocannabinoid System; Cannabis Use Disorder; Chronic Pain; Epilepsy; Multiple Sclerosis; Neuroplasticity; Adolescents.

Introduction and Background:

Cannabis (*Cannabis sativa* L.) has transitioned from a historically utilized botanical remedy to a scientifically investigated therapeutic agent in modern medicine. Historical documentation indicates that cannabis was used in ancient Chinese and Indian medicine for analgesia, anti-inflammatory purposes, and neuropsychiatric conditions before being incorporated into Western medical practice in the 19th century.^{1,2}

Nevertheless, the decline in its medical use during the early 20th century was due to variability in plant composition and the lack of standardized pharmacological data.³ However, recent progress in phytochemistry and receptor pharmacology has renewed scientific interest in exploring its clinical potential.⁴

Understanding how cannabis interacts with the body became possible after discovering the endocannabinoid system

Published online: October 15, 2026



Copyright © 2026 Author(s). This is an Open Access article distributed under the terms of the [Creative Commons Attribution-NonCommercial 4.0 International License](https://creativecommons.org/licenses/by-nc/4.0/) (CC BY-NC 4.0), permitting all non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

(ECS).⁵ This system includes naturally produced molecules like anandamide and 2-arachidonoylglycerol, along with cannabinoid receptor type 1 (CB1); cannabinoid receptor type 2 and enzymes that break down these ligands. CB1 receptors are mainly located in the central nervous system and regulate neurotransmitter release. In contrast, CB2 receptors are mostly found in immune and peripheral tissues, where they affect inflammation and immune cell movement.⁶⁻⁷ This neuromodulatory system plays a crucial role in maintaining balance in vital functions such as pain perception, appetite, mood, and neuroimmune responses.⁸ More than 100 phytocannabinoids have been identified so far, with THC and CBD being the most thoroughly studied.^{4,7} THC functions as a partial agonist at CB1 receptors, influencing presynaptic neurotransmitter release and modulating the dopaminergic reward pathway, which accounts for its pain-relieving and psychoactive effects.⁵⁻⁶ Conversely, CBD has minimal direct activity at CB1 receptors but engages with several molecular targets, including transient receptor potential channels and serotonergic systems. These interactions help explain its anti-inflammatory, anticonvulsant, anxiolytic, and possible neuroprotective effects.^{4,7} Over the past twenty years, the legalization of medicinal cannabis in various regions has made it more accessible to patients and facilitated more comprehensive research on its effectiveness as a treatment. Evidence mapping of systematic reviews suggests possible benefits for conditions like chronic pain, spasticity due to multiple sclerosis, chemotherapy-induced nausea and vomiting, epilepsy, and some neuropsychiatric disorders.⁸⁻⁹ However, variations in study design and methodological issues weaken these findings.¹⁰ A thorough scoping review of systematic studies yielded inconclusive results, showing only slight improvements in some pain-related conditions, along with common reports of minor negative effects and generally moderate-to-low quality evidence.¹¹ These findings underscore the need for well-designed randomized controlled trials (RCTs) and standardized outcome measures.³

Although cannabis has therapeutic potential, it is still the most commonly used illegal drug globally, with increasing use among adolescents and young adults.^{3,12} The coexistence of medical approval and recreational use raises concerns for public health. Cardiovascular problems are particularly significant, as cannabis has been associated with tachycardia, temporary blood pressure spikes, and potential ischemic events, especially in at-risk groups.¹³ Neuropsychiatric risks encompass anxiety, psychosis in susceptible individuals, and the onset of cannabis use disorder (CUD).⁵ Research continues to explore the dependence potential of cannabis. While CUD has been well-studied in recreational users, applying these findings to medical settings demands caution. Key differences such as dosing accuracy, cannabinoid makeup (especially THC:CBD ratios), methods of ad-

ministration, and professional care set medical use apart from recreational use.^{1,9} However, high THC exposure and regular use still pose risks for developing tolerance, withdrawal symptoms, and problematic consumption patterns.¹ Recent studies are examining the impact of cannabinoids on health problems linked to metabolism, inflammation, and cancer. Altering CB1 receptor activity has been linked to metabolic issues and fatty liver disease.¹⁴ Meanwhile, research is ongoing into targeting CB2 receptors for their potential to induce cancer cell death via receptor-mediated apoptosis.¹⁵ Preclinical studies further demonstrate modulation of inflammatory and oxidative pathways through ECS signalling.^{4,7} Although these results are preliminary, they underscore the expanding translational potential of cannabinoid research. Overall, current evidence shows that cannabis is a pharmacologically complex substance with proven therapeutic benefits in certain clinical contexts, while also carrying measurable neuropsychiatric, cardiovascular, and dependence risks. As legalization grows and prescribing rises, clinicians should carefully assess the benefit–risk balance of cannabis therapies based on evidence.^{1,13}

Relevant peer-reviewed literature was reviewed to provide an overview of the pharmacological mechanisms, therapeutic benefits, and potential risks of cannabis and cannabinoid-based medicines. This review aims to synthesize current knowledge on the pharmacological mechanisms, therapeutic uses, safety issues, and misuse risks of cannabis and cannabinoid medicines within a clinically relevant and translational context.

Pharmacology of Cannabis and the Endocannabinoid System

Cannabis-derived compounds primarily affect the endocannabinoid system (ECS), a highly conserved neuromodulatory network that regulates synaptic transmission, immune responses, metabolic balance, and neuroplasticity.¹⁶⁻¹⁷ The ECS comprises endogenous ligands—primarily anandamide and 2-arachidonoylglycerol (2-AG)—along with their biosynthesis and degradation enzymes, and two main G-protein-coupled receptors: CB1 and CB2.¹⁸ Discovering this system has offered a mechanistic foundation for understanding the therapeutic effects and side effects of phytocannabinoids. Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most important phytocannabinoids in clinical practice. THC acts as a partial agonist at CB1 and CB2 receptors.¹⁹ CB1 receptors are predominantly found in the central nervous system, especially in the cerebral cortex, hippocampus, amygdala, basal ganglia, and cerebellum.²⁰ Their presynaptic location allows them to regulate neurotransmitter release by inhibiting adenylate cyclase, blocking voltage-gated calcium channels, and activating inwardly rectifying potassium channels.²¹⁻²² These actions result in a reduction in the re-

lease of both excitatory and inhibitory neurotransmitters, including glutamate, GABA, dopamine, serotonin, and acetylcholine.²³

This presynaptic modulation explains THC's dual effects on cognition, motor coordination, reward processing, and emotional regulation. In the hippocampus, activating CB1 receptors affects long-term potentiation and synaptic plasticity, potentially causing short-term memory problems observed with acute cannabis use.²⁴ In mesolimbic pathways, THC-triggered CB1 activation boosts dopamine signalling in the nucleus accumbens (NAc), strengthening reward signals and increasing the risk of misuse.²⁵⁻²⁶ Over time, especially with prolonged use, these neuroadaptive changes can lead to receptor downregulation and changes in synaptic responses, establishing the biological foundation for tolerance and dependence.²⁷ CB2 receptors are primarily located in immune cells, peripheral tissues, and microglia within the central nervous system.²⁸ Activating them influences cytokine release, immune cell movement, and inflammatory pathways.²⁹ Evidence from preclinical studies indicates that targeting CB2 receptors could reduce neuroinflammation and oxidative stress, which are linked to neurodegenerative diseases and chronic inflammation.³⁰ Notably, activating CB2 does not cause psychoactive effects, making it a promising therapeutic option with fewer neuropsychiatric risks. Unlike THC, cannabidiol (CBD) exhibits only a weak affinity for CB1 and CB2 receptors. It acts as a versatile modulator, affecting multiple molecular pathways, including transient receptor potential vanilloid 1 (TRPV1) channels, 5-HT1A receptors, PPAR- γ , and adenosine systems.³¹⁻³² Additionally, CBD indirectly enhances endocannabinoid signalling by inhibiting fatty acid amide hydrolase (FAAH), thereby increasing anandamide levels.³³ This indirect effect explains its calming, anticonvulsant, and anti-inflammatory properties without causing intoxication. Clinically, THC and CBD differ markedly: THC activates CB1 receptors, offering pain relief and anti-nausea benefits, but it may also lead to cognitive impairments, anxiety, increased heart rate, and psychoactive effects.³⁴ Heart rate and blood pressure spikes are linked to CB1 activation in autonomic control centres.³⁵ On the other hand, CBD, which does not cause intoxication and interacts with a wider range of receptors, is being explored as a treatment for epilepsy, anxiety, and inflammatory diseases, thanks to its safer profile.³⁶

Recent studies demonstrate that phytocannabinoids affect intracellular signalling pathways like mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), and nuclear factor kappa B (NF- κ B), which play roles in cell survival, apoptosis, and oxidative stress response.³⁷⁻³⁸ These downstream effects suggest that cannabinoids impact both synaptic neurotransmission and overall

cellular homeostasis regulation. Cannabis compounds have complex pharmacokinetics. THC, which is highly lipophilic, rapidly accumulates in fat tissues and remains in the body for an extended period.³⁹ Its active metabolite, 11-hydroxy-THC, greatly influences psychoactive effects, especially with oral consumption.⁸ Bioavailability varies with the method of use such as inhalation versus oral ingestion significantly impacting how soon, how long, and how strongly effects occur.³⁹ This variability in pharmacokinetics makes it difficult to set standard doses in clinical practice. Chronic stimulation of CB1 receptors often causes desensitization and downregulation of these receptors, which plays a role in developing tolerance.⁴⁰ Neuroadaptive changes in glutamatergic and dopaminergic pathways might explain withdrawal symptoms like irritability, sleep issues, and mood changes.⁴¹ These mechanistic insights are important for clinicians assessing the long-term use of therapeutic cannabis.

In summary, cannabis pharmacology involves a complex interaction between receptor-based neuromodulation, immune system signalling, intracellular pathway control, and variability in pharmacokinetics. THC primarily produces psychoactive and pain-relieving effects by partially activating CB1 receptors, while CBD influences multiple targets with little direct activation of CB1 receptors. Grasping these different pharmacodynamic and pharmacokinetic mechanisms is crucial for enhancing therapeutic use, reducing side effects, and preventing misuse.

Therapeutic Applications of Cannabis.

Over the past twenty years, the scientific re-examination of the therapeutic potential of cannabis has expanded, driven by increased insights into the endocannabinoid system (ECS) and easier access to standardized cannabinoid products. Phyto cannabinoids, primarily delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), interact with CB1 and CB2 receptors as well as various non-cannabinoid targets, affecting neurotransmission, inflammatory processes, immune responses, and cellular balance. Although evidence varies between indications, certain clinical applications have shown consistent benefits in controlled settings.

Chronic Pain Management: Chronic pain, particularly neuropathic pain, is a major focus of research and a primary reason for using medical cannabis. The endocannabinoid system (ECS) plays a crucial role in managing nociceptive signals across the peripheral, spinal, and brain regions. CB1 receptors are widely found in the thalamus, dorsal horn of the spinal cord, periaqueductal gray, and other pain-related brain regions. Activation of presynaptic CB1 receptors reduces calcium influx, thereby decreasing the release of excitatory neurotransmitters such as glutamate and substance P, which helps lower central sensitization. CB2 receptors, mainly expressed on immune cells and microglia, regulate the release

of inflammatory cytokines and help reduce neuroinflammation.²⁸⁻²⁹ Systematic reviews and meta-analyses show that cannabinoid-based treatments can produce modest yet meaningful reductions in neuropathic pain, especially in cases resistant to other therapies. A thorough meta-analysis published in *Journal of the American Medical Association (JAMA)* observed slight reductions in pain severity but also identified a higher risk of side effects such as dizziness and drowsiness. Randomized controlled trials using nabiximols and inhaled cannabis demonstrated significant pain reduction compared to placebo in peripheral neuropathy and multiple sclerosis-related neuropathic pain. Recent controlled studies indicate possible opioid-sparing effects, though comprehensive, long-term RCT data are still limited. Healthcare providers should consider cannabis-based medicines as adjunct options for select patients with neuropathic pain unresponsive to first-line therapies, with careful monitoring for psychiatric issues, cognitive effects, and dependence potential.

Multiple Sclerosis and Spasticity: Multiple sclerosis (MS) frequently leads to chronic spasticity, which significantly impacts quality of life. The presence of cannabinoid receptors in regions like the basal ganglia, cerebellum, and spinal cord offers a molecular foundation for neuromodulating muscle tone. When THC activates CB1 receptors, it decreases excitatory neurotransmission and enhances inhibitory GABA signalling, thereby helping to reduce spastic muscle activity.²² Standardized oromucosal sprays containing balanced THC and CBD ratios have demonstrated advantages for patients with moderate to severe MS who do not respond to conventional antispasmodic therapies. These sprays help reduce spasticity levels and have been shown to improve associated discomfort and sleep issues. Importantly, tolerance to psychoactive effects frequently emerges with consistent dose, although neuropsychiatric monitoring is crucial. Recent pharmacological studies indicate that CBD may mitigate THC-induced anxiety and cognitive deficits while maintaining antispastic properties. Nonetheless, enduring disease-modifying effects have yet to be determined, and treatment continues to be symptomatic rather than curative.

Chemotherapy-Induced Nausea and Vomiting: Cannabinoids have traditionally been used to reduce nausea and vomiting from chemotherapy-induced nausea and vomiting (CINV). THC mainly provides antiemetic effects by activating CB1 receptors in the dorsal vagal complex and nucleus tractus solitarius of the brainstem, key areas responsible for controlling emetic signals.¹⁹ Cannabinoids also affect the release of serotonin by interacting with pathways that are regulated by 5-HT₃. Synthetic cannabinoids like dronabinol and nabilone have been shown to work as second-line treatments for patients who don't respond to standard antiemetic treatments. While modern 5-HT₃ antagonists and neurokinin-1 in-

hibitors are considered first-line treatments, cannabis may be an option for patients who do not respond to these options. Side effects like sedation and dysphoria are dose-dependent and usually reversible once treatment and dysphoria, are dose-dependent and typically reversible upon cessation.

Epilepsy: The most robust recent evidence favours using pure CBD for managing persistent epileptic conditions. CBD does not have the same psychoactive effects as THC. Instead, it works as an anticonvulsant in several ways, such as by changing the balance of calcium in cells, blocking voltage-gated sodium channels, reducing inflammation, and indirectly increasing endocannabinoid tone.³⁶ Extensive, placebo-controlled randomized controlled trials (RCTs) have shown considerable reduction in seizures in juvenile patients with severe epileptic syndromes. Recent neurobiological findings indicate that CBD may mitigate excitotoxicity and neuroinflammation—pathophysiological mechanisms associated with epileptogenesis. Monitoring liver enzymes is essential when administering CBD alongside other antiepileptic drugs because of potential pharmacokinetic interactions.

Gastrointestinal and Inflammatory Disorders: The ECS shows high levels of expression in the gastrointestinal system, where it controls motility, secretion, epithelial integrity, and immune responses. CB1 receptors affect enteric neuron signalling and smooth muscle function, while CB2 receptors regulate inflammatory cell migration and cytokine release. Cannabinoids may help treat inflammatory bowel disease (IBD), functional gastrointestinal disorders, and appetite issues. They can lower pro-inflammatory substances such as tumor necrosis factor-alpha and interleukins, and support the health of the epithelial barrier. However, systematic reviews show inconsistent results in clinical outcomes and a lack of high-quality RCTs. Evidence shows some relief of symptoms, especially stomach pain and hunger, but there are no substantial decreases in inflammatory markers. Recent preclinical research suggests that regulating CB1 could offer liver-protective and metabolic advantages in non-alcoholic fatty liver disease (NAFLD), pointing to wider metabolic impacts of cannabinoid signalling. Human clinical validation of cannabis is still in progress. While cannabis possesses biological mechanisms that may treat certain conditions, and some clinical data support its use for pain, spasticity, refractory epilepsy, and chemotherapy-induced nausea, its benefits must be weighed against possible risks to the brain, mind, and heart. The quality of current evidence is inconsistent, highlighting the importance of large, well-controlled trials that use standardized formulations and include long-term follow-up. Achieving optimal therapeutic results with minimal side effects necessitates a precision-focused strategy. This involves assessing the cannabinoid ratio, dosage, administration method, and the patient's individual risk factors.

Cannabis Use Disorder

Neurobiological Mechanisms Underlying CUD

Cannabis Use Disorder (CUD) involves problematic cannabis consumption that leads to considerable impairment or distress. This includes symptoms such as loss of control, ongoing cravings, tolerance, withdrawal symptoms, and continued use despite negative consequences. Although cannabis is often seen as less addictive than opioids or stimulants, evidence indicates that approximately 9–10% of lifetime users develop CUD. This risk rises to nearly 17% if use starts during adolescence and reaches 25–30% among daily users [34,42]. The growing potency of Δ^9 -tetrahydrocannabinol (THC) in contemporary cannabis products and the expansion of legalized markets have renewed clinical attention toward understanding the neurobiological basis, health implications, and treatment strategies for CUD.^{43–44}

The pathophysiology of CUD is primarily mediated through THC-induced modulation of the endocannabinoid system (ECS). THC acts as a partial agonist at CB1 receptors, mainly found in areas such as the prefrontal cortex, hippocampus, amygdala, basal ganglia, and cerebellum.¹⁶ Activation of these receptors decreases presynaptic neurotransmitter release via Gi/o protein pathways, affecting glutamate and GABA signalling.²¹ This neuromodulation influences synaptic plasticity and plays a role in reward-related neural circuits. Acute THC exposure increases dopamine release in the mesolimbic pathway, especially in the VTA and NAc.²⁶ This dopamine boost explains the reinforcing and pleasurable effects of cannabis. Over time, continued THC use causes the brain to undergo neuroadaptive changes. It causes CB1 receptor desensitization and downregulation mainly in cortical and limbic regions, impacting dopaminergic activity.²⁷ Neuroimaging shows a decrease in CB1 receptor availability in dependent users, which can partially recover after extended abstinence.²⁷ These changes cause increased tolerance, lower reward sensitivity, and compulsive consumption.³⁴ Additionally, long-term cannabis use can alter brain structure and function, especially in regions involved in executive functioning and impulse control. Impaired communication between the prefrontal cortex and limbic system can hinder decision-making and heighten the likelihood of ongoing substance use. Recent molecular studies suggest that epigenetic changes in genes related to synaptic transmission and stress response might influence relapse vulnerability. Recent comprehensive reviews of cannabis pharmacology reveal that dependency risk is mainly affected by THC concentration, how often it is used, and the cannabinoid composition, especially the THC to cannabidiol (CBD) ratio.^{45–46} CBD seems to modify some psychoactive and anxiety-related effects of THC, which may reduce its potential for abuse, although clinical evidence is still in early stages.

Clinical Features and Withdrawal Syndrome

CUD presents itself with varying degrees of severity. Core features include unsuccessful efforts to reduce use, persistent cravings, neglect of work or social responsibilities, and continued consumption despite awareness of psychological or physical harm. Cannabis intoxication typically involves euphoria, changed perception, and relaxation; however, prolonged heavy use can also cause anxiety, mood swings, cognitive difficulties, and reduced motivation.^{34,42} Cannabis withdrawal syndrome is now an acknowledged medical condition.⁴⁷ Symptoms typically begin 24 to 72 hours after cessation, peak within the first week, and may persist for two weeks or longer in heavy users. Common signs are irritability, anxiety, dysphoria, trouble sleeping (especially vivid nightmares and sleeplessness), loss of appetite, restlessness, and physical discomfort.^{47–48} Cannabis withdrawal is usually less severe medically than withdrawal from alcohol or opioids; however, its psychological effects can greatly disrupt functioning and cause relapse. On a neurobiological level, withdrawal involves decreased endocannabinoid activity and diminished CB1 receptor signalling due to long-term receptor downregulation.²⁷ This decrease hampers the body's ability to regulate mood, appetite, and sleep normally. The severity of withdrawal symptoms is closely related to how often and how intensely cannabis is used.⁴⁸ Modern high-potency cannabis products might lead to more severe withdrawal symptoms than older formulations.⁴³

Risk Factors and Vulnerable Populations

Adolescence is a crucial and sensitive period characterized by increased CB1 receptor levels in the developing brain's cortex and subcortex.^{49–50} Exposure to THC during this time can disrupt essential neurodevelopmental processes like synaptic pruning and myelination.^{34,51} Research shows that early cannabis use heightens the risk of developing psychiatric disorders later on, especially in those with genetic vulnerabilities.^{46,52} People with cannabis use disorder (CUD) often face mental health issues such as anxiety, depression, and ADHD.^{42,53} Although some use cannabis as a form of self-medication, long-term use can worsen these symptoms. Overall, early THC exposure may disrupt brain development and heighten the risk of psychiatric problems in the future. People with CUD often face issues such as anxiety, depression, and ADHD.⁴² While some may use cannabis as a way to self-medicate, prolonged use might worsen underlying mental health problems.⁵³ The relationship is complex, involving two-way interactions between stress response systems and the endocannabinoid system.⁵⁴

Treatment Strategies and Public Health and Clinical Implications

Currently, there are no officially approved medications for Cannabis Use Disorder (CUD), so psychosocial interventions remain the primary treatment. Evidence-based therapies such as Cognitive Behavioral Therapy (CBT), Motivational

Enhancement Therapy (MET), and Contingency Management (CM) are central to treatment.^{47,55} CBT focuses on identifying unhealthy thought patterns, enhancing coping skills, and developing relapse prevention techniques. Meanwhile, MET focuses on resolving ambivalence and increasing motivation for behavioural change. Contingency Management employs structured reinforcement techniques to promote abstinence and adherence to treatment. Although combining these methods yields better results than using them alone, relapse rates remain significantly high. This underscores the persistent and cyclical nature of substance use disorders and the necessity for additional therapeutic options.⁵⁵ Current research continues to investigate pharmacological treatments aimed at the neurobiological roots of dependence and withdrawal. For example, cannabinoid agonist replacement therapy, like nabiximols, is being studied as a harm-reduction strategy to reduce withdrawal symptoms and prevent illegal cannabis use by sustaining CB1 receptor activation.^{48,56} Glutamatergic modulators like N-acetylcysteine are being studied for their ability to reestablish synaptic balance within reward pathways through regulation of extracellular glutamate.^{57,58} Research continues on serotonergic and noradrenergic medications to control mood swings and anxiety during withdrawal.⁵⁹ Moreover, cannabidiol (CBD) is gaining attention for its potential to decrease cue-triggered cravings, anxiety, and relapse risk, although comprehensive trials are scarce and its effectiveness is not yet confirmed.^{43,60} Recent reviews of cannabis treatments and dependence emphasize that dose control, cannabinoid composition, and administration method are key factors affecting abuse potential.^{45,34} This underscores the importance of precise prescribing and individualized risk assessment. From a wider clinical and public health standpoint, increasing access to high-potency THC products calls for careful attention.^{44,61} Modern cannabis products often have higher THC concentrations than those previously studied, which can heighten reinforcing effects, withdrawal issues, and mental health risks.⁵² Screening for problematic use should be standard in primary care and mental health check-ups, especially for teenagers, young adults, and those with existing psychiatric conditions.⁵² Educating users about THC potency, proper dosage, risks of overuse, and potential cognitive and psychiatric dangers is crucial, whether for recreational or medical use.³⁴ While supervised medical cannabis use varies from non-medical use in purpose, dosage, and oversight, the risk of dependence remains significant.⁴² Strategies like standardized dosing, opting for lower-THC or balanced THC:CBD products, careful patient screening, ongoing reassessment of benefits, and structured follow-up can help lessen misuse risks. Nonetheless, there is still limited long-term data on dependence risks related to prescribed cannabis.^{62,63} As legal-

ization and commercialization expand, it is essential to integrate evidence-based behavioural treatments with comprehensive pharmacological research and innovative public health strategies to reduce harm and promote legitimate therapeutic applications.⁶⁴

Conclusion

Cannabis holds a unique and evolving role in contemporary medicine, balancing its pharmacological advantages with possible risks. Its main active compounds impact the endocannabinoid system, a neural network essential for pain control, immune response, metabolism, and neurobehavioral processes. The two main phytocannabinoids, THC and CBD, operate differently but can work synergistically. THC partially stimulates CB1 receptors in the brain, aiding in pain relief, nausea reduction, spasticity control, and appetite stimulation. In contrast, CBD provides therapeutic benefits without causing a high by interacting with various receptors. For example, it can modulate serotonin, vanilloid, and inflammatory pathways, producing anticonvulsant, anxiolytic, and anti-inflammatory effects. While cannabis-based medications are used in treatment, clinicians must be cautious about their safety, how they work, their production, and their effects, which vary among individuals. THC's psychoactive effects can impair executive functions, attention, and psychomotor skills, especially in teenagers and individuals with mental health issues. Long-term use may cause neuroadaptive changes, which could lead to tolerance, dependence, and cannabis use disorder. While the effects on cardiovascular health, cognition, and mental well-being vary, they all highlight the need for careful prescribing and ongoing monitoring. Medically, therapeutic cannabis should be seen as a targeted treatment for specific evidence-supported conditions, not as a universal remedy. Research shows modest benefits for conditions like neuropathic pain, spasticity due to multiple sclerosis, hard-to-control epilepsy, and chemotherapy-related nausea. Extended use can result in neuroadaptive changes, which may lead to tolerance, dependence, and cannabis use disorder. Although effects on cardiovascular health, cognition, and mental well-being differ in presentation, they all highlight the need for careful prescribing and ongoing supervision. From a medical standpoint, therapeutic cannabis should be considered a targeted treatment for specific conditions supported by evidence, rather than a universal remedy. Current research shows modest benefits for issues such as neuropathic pain, spasticity from multiple sclerosis, difficult-to-control epilepsy, and chemotherapy-related nausea. Nonetheless, variations in product formulations and study designs hinder definitive conclusions. The lack of standardized dosing protocols and long-term safety data emphasizes the necessity for well-conducted RCTs and comprehensive phar-

macovigilance systems. Clinical decision-making should include a personalized evaluation of risks and benefits, taking into account comorbidities, concurrent medications, age, psychiatric history, and potential for misuse. To achieve the best patient outcomes with minimal harm, it is crucial for doctors, pharmacists, and mental health specialists to work together. Additionally, continuous education for patients about realistic expectations, possible side effects, and how to differentiate between medical and non-medical use is vital. As

regulations around the world continue to change, the demand for high-quality translational and clinical research increases. Future research should focus on standardized formulations, accurate cannabinoid ratios, long-term outcome evaluations, and understanding mechanisms. Adopting an evidence-based, balanced strategy helps promote responsible use of cannabis's therapeutic benefits, protect public health, and tackle problems associated with overuse and dependence.

Pharmacology of Cannabis and Endocannabinoid System

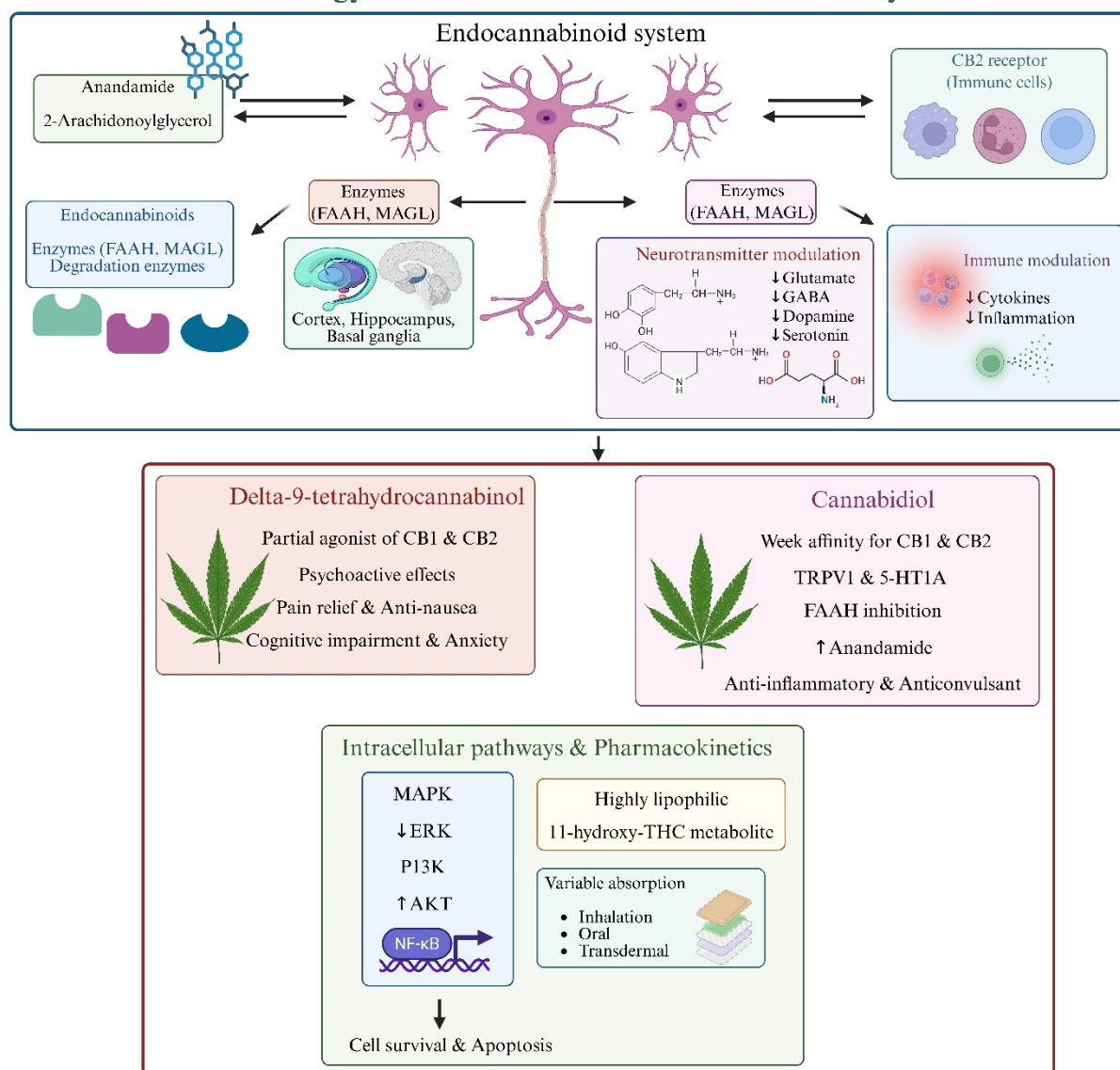


Figure 1: Mechanistic Overview of the Endocannabinoid System and Cannabinoid Actions.

This illustration depicts the endocannabinoid system (ECS) and how THC and CBD function as medicines. The ECS comprises endogenous ligands such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG), along with their metabolic enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), and cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2). CB1 receptors, mainly located in the central nervous system, regulate neurotransmitter release before it reaches the synapse, enabling THC to induce its hallucinogenic, analgesic, and antiemetic effects. Continuous activation of

CB1 may lead to tolerance and dependence. CB2 receptors, found mainly in immune cells and microglia, control cytokine release and inflammation without producing intoxication. THC partially activates both CB1 and CB2 receptors, whereas CBD does not bind directly but influences other targets such as transient receptor potential vanilloid 1 (TRPV1), 5-HT1A receptors, and inhibits FAAH. Differences in pharmacokinetics and downstream signaling pathways like mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), and nuclear factor kappa B (NF- κ B) also influence how these medications work. (Figure created with BioRender.com)

Abbreviations

2-AG – 2-Arachidonoylglycerol
 5-HT1A – 5-Hydroxytryptamine 1A receptor
 5-HT3 – 5-Hydroxytryptamine 3 receptor
 AEA – Anandamide
 ADHD – Attention-Deficit/Hyperactivity Disorder
 Akt – Protein kinase B
 CB1 – Cannabinoid receptor type 1
 CB2 – Cannabinoid receptor type 2
 CBD – Cannabidiol
 CBT – Cognitive Behavioral Therapy
 CM – Contingency Management
 CINV – Chemotherapy-Induced Nausea and Vomiting
 CNS – Central Nervous System
 CUD – Cannabis Use Disorder
 ECS – Endocannabinoid System
 ERK – Extracellular Signal-Regulated Kinase
 FAAH – Fatty Acid Amide Hydrolase
 GABA – Gamma-Aminobutyric Acid
 Gi/o – Inhibitory G-protein subtype
 IBD – Inflammatory Bowel Disease
 LTP – Long-Term Potentiation
 MAGL – Monoacylglycerol Lipase
 MAPK – Mitogen-Activated Protein Kinase
 MET – Motivational Enhancement Therapy
 MS – Multiple Sclerosis
 NAc – Nucleus Accumbens
 NAFLD – Non-Alcoholic Fatty Liver Disease
 NF- κ B – Nuclear Factor kappa B
 PI3K – Phosphoinositide 3-Kinase
 PPAR- γ – Peroxisome Proliferator-Activated Receptor
 Gamma
 RCT – Randomized Controlled Trial
 THC – Δ 9-Tetrahydrocannabinol
 TRPV1 – Transient Receptor Potential Vanilloid 1
 USPSTF – United States Preventive Services Task Force
 VTA – Ventral Tegmental Area

Funding: This review received no external funding.

Data Availability Statement: No new data were created or analysed in this review.

Conflicts of Interest: The author declares no conflicts of interest.

Acknowledgement: The authors thank Dr. Balanehru Subramanian for his encouragement and Sri Balaji Vidyapeeth for support.

Author contributions

Durairaj Ragu Varman -Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. Catherine Ferdinica. F, Rishikesh Rengasamy - Writing – original draft. Bhagavathi Sundaram Sivamaruthi-Writing – review & editing. Fairen Angelin Jayakumar – Writing – review & editing.

AI Disclosure Statement: During the preparation of this manuscript, the authors used Grammarly and ChatGPT for language editing, grammar improvement, summarization, and idea clarification. After its use, the authors thoroughly reviewed, verified, and revised all AI-assisted content to ensure accuracy and originality. The content of the manuscript was not generated by the AI tools. The authors take full responsibility for the integrity and final content of the published article.

References

- [1] Schlag AK, Hindocha C, Zafar R, Nutt DJ, Curran HV: Cannabis based medicines and cannabis dependence: A critical review of issues and evidence. *J Psychopharmacol.* 2021 Jul;35(7):773-785. doi: 10.1177/0269881120986393. Epub 2021 Feb 17. PMID: 33593117.
- [2] Legare CA, Raup-Konsavage WM, Vrana KE: Therapeutic Potential of Cannabis, Cannabidiol, and Cannabinoid-Based Pharmaceuticals. *Pharmacology.* 2022;107(3-4):131-149. doi: 10.1159/000521683. Epub 2022 Jan 28. PMID: 35093949.
- [3] Bridgeman MB, Abazia DT: Medicinal Cannabis: History, Pharmacology, And Implications for the Acute Care Setting. *P T.* 2017 Mar;42(3):180-188. PMID: 28250701.
- [4] Leinen ZJ, Mohan R, Premadasa LS, Acharya A, Mohan M, Byrreddy SN: Therapeutic Potential of Cannabis: A Comprehensive Review of Current and Future Applications. *Biomedicine.* 2023 Sep 25;11(10):2630. doi: 10.3390/biomedicine11102630. PMID: 37893004.
- [5] Garcia-Romeu A, Kersgaard B, Addy PH: Clinical applications of hallucinogens: A review. *Exp Clin Psychopharmacol.* 2016 Aug;24(4):229-68. doi: 10.1037/pha0000084. PMID: 27454674.
- [6] Śmiarowska M, Białecka M, Machoy-Mokrzyńska A: Cannabis and cannabinoids: pharmacology and therapeutic potential. *Neurol Neurochir Pol.* 2022;56(1):4-13. doi: 10.5603/PJNNS.a2022.0015. Epub 2022 Feb 8. PMID: 35133644.
- [7] Blebea NM, Pricopie AI, Vlad RA, Hancu G: Phytocannabinoids: Exploring Pharmacological Profiles and Their Impact

- on Therapeutical Use. *Int J Mol Sci*. 2024 Apr 10;25(8):4204. doi: 10.3390/ijms25084204. PMID: 38673788.
- [8] Grotenhermen F, Müller-Vahl K: The therapeutic potential of cannabis and cannabinoids. *Dtsch Arztebl Int*. 2012 Jul;109(29-30):495-501. doi: 10.3238/arztebl.2012.0495. Epub 2012 Jul 23. PMID: 23008748.
- [9] Mouhamed Y, Vishnyakov A, Qorri B, Sami M, Frank SS, Nowierski C et al.: Therapeutic potential of medicinal marijuana: an educational primer for health care professionals. *Drug Healthc Patient Saf*. 2018 Jun 11;10:45-66. doi: 10.2147/DHPS.S158592. PMID: 29928146.
- [10] Montero-Oleas N, Arevalo-Rodríguez I, Nuñez-González S, Viteri-García A, Simancas-Racines D. Therapeutic use of cannabis and cannabinoids: an evidence mapping and appraisal of systematic reviews. *BMC Complement Med Ther*. 2020 Jan 15;20(1):12. doi: 10.1186/s12906-019-2803-2. PMID: 32020875.
- [11] Pratt M, Stevens A, Thuku M, Butler C, Skidmore B, Wieland LS et al.: Benefits and harms of medical cannabis: a scoping review of systematic reviews. *Syst Rev*. 2019 Dec 10;8(1):320. doi: 10.1186/s13643-019-1243-x. PMID: 31823819.
- [12] Hasan KM. Cannabis Unveiled: An Exploration of Marijuana's History, Active Compounds, Effects, Benefits, and Risks on Human Health. *Subst Abuse*. 2023 Jun 20;17:11782218231182553. doi: 10.1177/11782218231182553. PMID: 37359105.
- [13] Page RL 2nd, Allen LA, Kloner RA, Carriker CR, Martel C, Morris AA, Piano MR et al.; American Heart Association Clinical Pharmacology Committee and Heart Failure and Transplantation Committee of the Council on Clinical Cardiology; Council on Basic Cardiovascular Sciences; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; Council on Lifestyle and Cardiometabolic Health; and Council on Quality of Care and Outcomes Research. Medical Marijuana, Recreational Cannabis, and Cardiovascular Health: A Scientific Statement From the American Heart Association. *Circulation*. 2020 Sep 8;142(10):e131-e152. doi: 10.1161/CIR.0000000000000883. Epub 2020 Aug 5. PMID: 32752884.
- [14] Degraeve V, Vega Joubert MB, Filippa C, Ingaramo P, Torregiani L, Caro YS et al.: Effects of five cannabis oils with different CBD: THC ratios and terpenes on hypertension, dyslipidemia, hepatic steatosis, oxidative stress, and CB1 receptor in an experimental model. *J Cannabis Res*. 2025 Jul 14;7(1):46. doi: 10.1186/s42238-025-00286-8. PMID: 40660358.
- [15] Alghamdi SS, Albahlal HN, Aloumi DE, Bin Saqyah S, Alsubait A, Alamre J et al.: Revealing the therapeutic potential of synthetic cannabinoids: a systematic review of cannabinoid receptor binding dynamics and their implications for cancer therapy. *J Cannabis Res*. 2025 Jun 7;7(1):33. doi: 10.1186/s42238-025-00289-5. PMID: 40483537.
- [16] Lu HC, Mackie K: An Introduction to the Endogenous Cannabinoid System. *Bio Psychiatry*. 2016 Apr 1;79(7):516-25. doi: 10.1016/j.biopsych.2015.07.028. Epub 2015 Oct 30. PMID: 26698193.
- [17] Zou S, Kumar U: Cannabinoid Receptors and the Endocannabinoid System: Signaling and Function in the Central Nervous System. *Int J Mol Sci*. 2018 Mar 13;19(3):833. doi: 10.3390/ijms19030833. PMID: 29533978.
- [18] Kendall DA, Yudowski GA: Cannabinoid Receptors in the Central Nervous System: Their Signalling and Roles in Disease. *Front Cell Neurosci*. 2017 Jan 4;10:294. doi: 10.3389/fncel.2016.00294. PMID: 28101004.
- [19] Pertwee RG: The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. *Br J Pharmacol*. 2008 Jan;153(2):199-215. doi: 10.1038/sj.bjp.0707442. Epub 2007 Sep 10. PMID: 17828291.
- [20] Herkenham M, Lynn AB, Johnson MR, Melvin LS, de Costa BR, Rice KC: Characterization and localization of cannabinoid receptors in rat brain: a quantitative in vitro autoradiographic study. *J Neurosci*. 1991 Feb;11(2):563-83. doi: 10.1523/JNEUROSCI.11-02-00563.1991. PMID: 1992016.
- [21] Howlett AC, Breivogel CS, Childers SR, Deadwyler SA, Hampson RE, Porrino LJ: Cannabinoid physiology and pharmacology: 30 years of progress. *Neuropharmacology*. 2004;47 Suppl 1:345-58. doi: 10.1016/j.neuropharm.2004.07.030. PMID: 15464149.
- [22] Castillo PE, Younts TJ, Chávez AE, Hashimoto-dani Y: Endocannabinoid signaling and synaptic function. *Neuron*. 2012 Oct 4;76(1):70-81. doi: 10.1016/j.neuron.2012.09.020. PMID: 23040807.
- [23] Katona I, Freund TF: Multiple functions of endocannabinoid signalling in the brain. *Annu Rev Neurosci*. 2012;35:529-58. doi: 10.1146/annurev-neuro-062111-150420. Epub 2012 Apr 17. PMID: 22524785.
- [24] Hampson RE, Deadwyler SA: Cannabinoids reveal the necessity of hippocampal neural encoding for short-term memory in rats. *J Neurosci*. 2000 Dec 1;20(23):8932-42. doi: 10.1523/JNEUROSCI.20-23-08932.2000. PMID: 11102504.
- [25] Tanda G, Pontieri FE, Di Chiara G: Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common mu1 opioid receptor mechanism. *Science*. 1997 Jun 27;276(5321):2048-50. doi: 10.1126/science.276.5321.2048. PMID: 9197269.
- [26] Bossong MG, van Berckel BN, Boellaard R, Zuurman L, Schuit RC, Windhorst AD: Delta 9-tetrahydrocannabinol induces dopamine release in the human striatum. *Neuropsychopharmacology*. 2009 Feb;34(3):759-66. doi: 10.1038/npp.2008.138. Epub 2008 Aug 27. PMID: 18754005.
- [27] Hirvonen J, Goodwin RS, Li CT, Terry GE, Zoghbi SS, Morse C et al.: Reversible and regionally selective downregulation of brain cannabinoid CB1 receptors in chronic daily cannabis smokers. *Mol Psychiatry*. 2012 Jun;17(6):642-9. doi: 10.1038/mp.2011.82. Epub 2011 Jul 12. PMID: 21747398.

- [28] Atwood BK, Mackie K: CB2: a cannabinoid receptor with an identity crisis. *Br J Pharmacol*. 2010 Jun;160(3):467-79. doi: 10.1111/j.1476-5381.2010.00729.x. PMID: 20590558.
- [29] Turcotte C, Blanchet MR, Laviolette M, Flamand N: The CB₂ receptor and its role as a regulator of inflammation. *Cell Mol Life Sci*. 2016 Dec;73(23):4449-4470. doi: 10.1007/s00018-016-2300-4. Epub 2016 Jul 11. PMID: 27402121.
- [30] Fernández-Ruiz J, Romero J, Velasco G, Tolón RM, Ramos JA, Guzmán M: Cannabinoid CB2 receptor: a new target for controlling neural cell survival? *Trends Pharmacol Sci*. 2007 Jan;28(1):39-45. doi: 10.1016/j.tips.2006.11.001. Epub 2006 Dec 1. PMID: 17141334.
- [31] Ibeas Bih C, Chen T, Nunn AV, Bazelot M, Dallas M, Whalley BJ: Molecular Targets of Cannabidiol in Neurological Disorders. *Neurotherapeutics*. 2015 Oct;12(4):699-730. doi: 10.1007/s13311-015-0377-3. PMID: 26264914.
- [32] Campos AC, Ferreira FR, Guimarães FS: Cannabidiol blocks long-lasting behavioral consequences of predator threat stress: possible involvement of 5HT_{1A} receptors. *J Psychiatr Res*. 2012 Nov;46(11):1501-10. doi: 10.1016/j.jpsychires.2012.08.012. Epub 2012 Sep 11. PMID: 22979992.
- [33] Bisogno T, Hanus L, De Petrocellis L, Tchilibon S, Ponde DE, Brandi L: Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *Br J Pharmacol*. 2001 Oct;134(4):845-52. doi: 10.1038/sj.bjp.0704327. PMID: 11606325.
- [34] Volkow ND, Compton WM, Weiss SR: Adverse health effects of marijuana use. *N Engl J Med*. 2014 Aug 28;371(9):879. doi: 10.1056/NEJMc1407928. PMID: 25162899.
- [35] Pacher P, Bátkai S, Kunos G: The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacol Rev*. 2006 Sep;58(3):389-462. doi: 10.1124/pr.58.3.2. PMID: 16968947.
- [36] Devinsky O, Cross JH, Wright S: Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. *N Engl J Med*. 2017 Aug 17;377(7):699-700. doi: 10.1056/NEJMc1708349. PMID: 28813226.
- [37] Cudaback E, Marrs W, Moeller T, Stella N: The expression level of CB1 and CB2 receptors determines their efficacy at inducing apoptosis in astrocytomas. *PLoS One*. 2010 Jan 14;5(1):e8702. doi: 10.1371/journal.pone.0008702. PMID: 20090845.
- [38] Sarfaraz S, Afaq F, Adhami VM, Malik A, Mukhtar H: Cannabinoid receptor agonist-induced apoptosis of human prostate cancer cells LNCaP proceeds through sustained activation of ERK1/2 leading to G1 cell cycle arrest. *J Biol Chem*. 2006 Dec 22;281(51):39480-91. doi: 10.1074/jbc.M603495200. Epub 2006 Oct 26. PMID: 17068343.
- [39] Huestis MA: Human cannabinoid pharmacokinetics. *Chem Biodivers*. 2007 Aug;4(8):1770-804. doi: 10.1002/cbdv.200790152. PMID: 17712819.
- [40] Sim-Selley LJ: Regulation of cannabinoid CB1 receptors in the central nervous system by chronic cannabinoids. *Crit Rev Neurobiol*. 2003;15(2):91-119. doi: 10.1615/critrevneurobiol.v15.i2.10. PMID: 14977366.
- [41] Budney AJ, Hughes JR, Moore BA, Vandrey R: Review of the validity and significance of cannabis withdrawal syndrome. *Am J Psychiatry*. 2004 Nov;161(11):1967-77. doi: 10.1176/appi.ajp.161.11.1967. PMID: 15514394.
- [42] Hasin DS, Saha TD, Kerridge BT, Goldstein RB, Chou SP, Zhang H et al.: Prevalence of Marijuana Use Disorders in the United States Between 2001-2002 and 2012-2013. *JAMA Psychiatry*. 2015 Dec;72(12):1235-42. doi: 10.1001/jamapsychiatry.2015.1858. PMID: 26502112.
- [43] Freeman TP, Hindocha C, Baio G, Shaban NDC, Thomas EM, Astbury D, et al.: Cannabidiol for the treatment of cannabis use disorder: a phase 2a, double-blind, placebo-controlled, randomised, adaptive Bayesian trial. *Lancet Psychiatry*. 2020 Oct;7(10):865-874. doi: 10.1016/S2215-0366(20)30290-X. Epub 2020 Jul 28. PMID: 32735782.
- [44] ElSohly MA, Mehmedic Z, Foster S, Gon C, Chandra S, Church JC: Changes in Cannabis Potency Over the Last 2 Decades (1995-2014): Analysis of Current Data in the United States. *Biol Psychiatry*. 2016 Apr 1;79(7):613-9. doi: 10.1016/j.biopsych.2016.01.004. Epub 2016 Jan 19. PMID: 26903403.
- [45] Freeman TP, Winstock AR: Examining the profile of high-potency cannabis and its association with severity of cannabis dependence. *Psychol Med*. 2015 Nov;45(15):3181-9. doi: 10.1017/S0033291715001178. Epub 2015 Jul 27. PMID: 26213314.
- [46] Murray RM, Englund A, Abi-Dargham A, Lewis DA, Di Forti M, Davies C et al.: Cannabis-associated psychosis: Neural substrate and clinical impact. *Neuropharmacology*. 2017 Sep 15;124:89-104. doi: 10.1016/j.neuropharm.2017.06.018. Epub 2017 Jun 17. PMID: 28634109.
- [47] Budney AJ, Roffman R, Stephens RS, Walker D: Marijuana dependence and its treatment. *Addict Sci Clin Pract*. 2007 Dec;4(1):4-16. doi: 10.1151/ascp07414. PMID: 18292704.
- [48] Allsop DJ, Copeland J, Lintzeris N, Dunlop AJ, Montebello M, Sadler C et al.: Nabiximols as an agonist replacement therapy during cannabis withdrawal: a randomized clinical trial. *JAMA Psychiatry*. 2014 Mar;71(3):281-91. doi: 10.1001/jamapsychiatry.2013.3947. PMID: 24430917.
- [49] Lubman DI, Cheetham A, Yücel M: Cannabis and adolescent brain development. *Pharmacol Ther*. 2015 Apr;148:1-16. doi: 10.1016/j.pharmthera.2014.11.009. Epub 2014 Nov 20. PMID: 25460036.
- [50] Renard J, Krebs MO, Le Pen G, Jay TM: Long-term consequences of adolescent cannabinoid exposure in adult psychopathology. *Front Neurosci*. 2014 Nov 10;8:361. doi: 10.3389/fnins.2014.00361. PMID: 25426017.

- [51] Thomson H, Labuschagne I, Greenwood LM, Robinson E, Sehl H, Suo C et al.: Is resting-state functional connectivity altered in regular cannabis users? A systematic review of the literature. *Psychopharmacology (Berl)*. 2022 May;239(5): 1191-1209. doi: 10.1007/s00213-021-05938-0. Epub 2021 Aug 20. PMID: 34415377.
- [52] Di Forti M, Quattrone D, Freeman TP, Tripoli G, Gayer-Anderson C, Quigley H et al.: The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. *Lancet Psychiatry*. 2019 May;6(5):427-436. doi: 10.1016/S2215-0366(19)30048-3. Epub 2019 Mar 19. PMID: 30902669.
- [53] Gobbi G, Atkin T, Zytynski T, Wang S, Askari S, Boruff J, et al.: Association of Cannabis Use in Adolescence and Risk of Depression, Anxiety, and Suicidality in Young Adulthood: A Systematic Review and Meta-analysis. *JAMA Psychiatry*. 2019 Apr 1;76(4):426-434. doi: 10.1001/jamapsychiatry.2018.4500. Erratum in: *JAMA Psychiatry*. 2019 Apr 1;76(4):447. doi: 10.1001/jamapsychiatry.2019.0464. PMID: 30758486; PMCID: PMC6450286.
- [54] Hill MN, McLaughlin RJ, Pan B, Fitzgerald ML, Roberts CJ, Lee TT et al: Recruitment of prefrontal cortical endocannabinoid signaling by glucocorticoids contributes to termination of the stress response. *J Neurosci*. 2011 Jul 20;31(29):10506-15. doi: 10.1523/JNEUROSCI.0496-11.2011. PMID: 21775596.
- [55] Gates PJ, Sabioni P, Copeland J, Le Foll B, Gowing L: Psychosocial interventions for cannabis use disorder. *Cochrane Database Syst Rev*. 2016 May 5;2016(5):CD005336. doi: 10.1002/14651858.CD005336.pub4. PMID: 27149547.
- [56] Lintzeris N, Bhardwaj A, Mills L, Dunlop A, Copeland J, McGregor I et al.: Nabiximols for the Treatment of Cannabis Dependence: A Randomized Clinical Trial. *JAMA Intern Med*. 2019 Sep 1;179(9):1242-1253. doi: 10.1001/jamainternmed.2019.1993. Erratum in: *JAMA Intern Med*. 2023 Dec 1;183(12):1414. doi: 10.1001/jamainternmed.2023.5348. PMID: 31305874.
- [57] Gray KM, Carpenter MJ, Baker NL, DeSantis SM, Kryway E, Hartwell KJ, et al.: A double-blind randomized controlled trial of N-acetylcysteine in cannabis-dependent adolescents. *Am J Psychiatry*. 2012 Aug;169(8):805-12. doi: 10.1176/appi.ajp.2012.12010055. Erratum in: *Am J Psychiatry*. 2012 Aug 1;169(8):869. PMID: 22706327.
- [58] McClure EA, Gipson CD, Malcolm RJ, Kalivas PW, Gray KM: Potential role of N-acetylcysteine in the management of substance use disorders. *CNS Drugs*. 2014 Feb;28(2):95-106. doi: 10.1007/s40263-014-0142-x. PMID: 24442756.
- [59] Haney M, Cooper ZD, Bedi G, Vosburg SK, Comer SD, Foltin RW: Nabilone decreases marijuana withdrawal and a laboratory measure of marijuana relapse. *Neuropsychopharmacology*. 2013 Jul;38(8):1557-65. doi: 10.1038/npp.2013.54. Epub 2013 Feb 26. PMID: 23443718.
- [60] Hurd YL, Spriggs S, Alishayev J, Winkel G, Gurgov K, Kudrich C et al.: Cannabidiol for the Reduction of Cue-Induced Craving and Anxiety in Drug-Abstinent Individuals with Heroin Use Disorder: A Double-Blind Randomized Placebo-Controlled Trial. *Am J Psychiatry*. 2019 Nov 1;176(11):911-922. doi: 10.1176/appi.ajp.2019.18101191. Epub 2019 May 21. Erratum in: *Am J Psychiatry*. 2020 Jul 1;177(7):641. doi: 10.1176/appi.ajp.2020.18101191correction. PMID: 31109198.
- [61] Chandra S, Radwan MM, Majumdar CG, Church JC, Freeman TP, ElSohly MA: New trends in cannabis potency in USA and Europe during the last decade (2008-2017). *Eur Arch Psychiatry Clin Neurosci*. 2019 Feb;269(1):5-15. doi: 10.1007/s00406-019-00983-5. Epub 2019 Jan 22. Erratum in: *Eur Arch Psychiatry Clin Neurosci*. 2019 Dec;269(8):997. doi: 10.1007/s00406-019-01020-1. PMID: 30671616.
- [62] Campeny E, López-Pelayo H, Nutt D, Blithikioti C, Oliveras C, Nuño L at al.: The blind men and the elephant: Systematic review of systematic reviews of cannabis use related health harms. *Eur Neuropsychopharmacol*. 2020 Apr;33:1-35. doi: 10.1016/j.euroneuro.2020.02.003. Epub 2020 Mar 9. PMID: 32165103.
- [63] US Preventive Services Task Force; Krist AH, Davidson KW, Mangione CM, Barry MJ, Cabana M, Caughey AB et al.: Screening for Unhealthy Drug Use: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2020 Jun 9;323(22):2301-2309. doi: 10.1001/jama.2020.8020. PMID: 32515821.
- [64] Hall W, Stjepanović D, Caulkins J, Lynskey M, Leung J, Campbell G, Degenhardt L: Public health implications of legalising the production and sale of cannabis for medicinal and recreational use. *Lancet*. 2019 Oct 26;394(10208):1580-1590. doi: 10.1016/S0140-6736(19)31789-1. Epub 2019 Oct 23. PMID: 31657733.