Int.J.Curr.Res.Aca.Rev.2026; 14(5): 01-14

EXCELLENT PUBLISHERS

International Journal of Current Research and Academic Review

ISSN: 2347-3215 (Online) Volume 14 Number 5 (May-2026)

Journal homepage: http://www.ijcrar.com

doi: https://doi.org/10.20546/ijcrar.2026.1405.001

Cannabinoid Pharmacology Redefined: Molecular Mechanisms, Therapeutic Frontiers, and Emerging Insights into the Endocannabinoid System

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Abstract

Few areas of contemporary pharmacology have evolved as rapidly as the cannabinoid field. The cloning of cannabinoid receptors CB1 and CB2 in the early 1990s, the discovery of anandamide and 2-arachidonoylglycerol as endogenous ligands, and the characterization of the biosynthetic and degradative enzymes diacylglycerol lipase, N-acyl phosphatidylethanolamine phospholipase D, fatty acid amide hydrolase, and monoacylglycerol lipase have collectively defined the endocannabinoid system (ECS) as a pervasive lipid-signalling network modulating synaptic transmission, immune function, energy homeostasis, and pain. Cryo-electron microscopy structures of agonist-bound CB1 and CB2 receptor–G-protein complexes published since 2016 have illuminated activation conformations, biased agonism, and allosteric pockets, opening new avenues for selective drug design. The non-psychoactive phytocannabinoid cannabidiol has been approved for Dravet syndrome, Lennox–Gastaut syndrome, and tuberous sclerosis complex, validating phytocannabinoid pharmacology at the regulatory level. This review provides an in-depth account of cannabinoid pharmacology with a focus on molecular mechanisms: receptor structure and signalling, endocannabinoid biosynthesis and turnover, the pleiotropic targets of cannabidiol, retrograde synaptic signalling, biased agonism, and allosteric modulation. Therapeutic applications in epilepsy, multiple sclerosis spasticity, chronic pain, chemotherapy-induced nausea, neurodegenerative and psychiatric disorders, and inflammation are reviewed alongside pharmacokinetics, drug–drug interactions, and adverse effects. Newer insights into the endocannabidiome, gut–brain endocannabinoid signalling, genetic polymorphisms of FAAH and CNR1, cannabinoid–microbiome interactions, and the role of CB2 in neuroinflammation are highlighted, and the contemporary drug-development pipeline of peripheral CB1 antagonists, selective CB2 agonists, MAGL/FAAH inhibitors, allosteric modulators, and cannabinoid nanoformulations is discussed.

Article Info

Received: 10 March 2026
Accepted: 22 April 2026
Available Online: 20 May 2026

Keywords

Cannabinoid, Endocannabinoid system, CB1 receptor, CB2 receptor, Cannabidiol, Tetrahydrocannabinol, Pharmacology

Introduction

Cannabis sativa has occupied a contested place in human pharmacopoeia for more than five thousand years, but the modern era of cannabinoid pharmacology was inaugurated only in 1964, when Gaoni and Mechoulam isolated and characterized Δ9-tetrahydrocannabinol (THC) as the principal psychoactive constituent of the plant (Mechoulam *et al.,* 2014). The next pivotal advance came in 1990 with the cloning of the cannabinoid CB1 receptor by Matsuda and colleagues (Matsuda *et al.,* 1990), followed in 1993 by the cloning of the peripheral CB2 receptor (Munro *et al.,* 1993). The subsequent identification of the endogenous lipid ligands N-

arachidonoylethanolamine (anandamide, AEA) (Devane *et al.,* 1992) and 2-arachidonoylglycerol (2-AG), together with their biosynthetic and degradative enzymes, transformed cannabinoid science from a chemistry curiosity into the study of an ubiquitous lipid-signalling network now known as the endocannabinoid system (ECS) (Pacher *et al.,* 2006; Lu and Mackie, 2021).

Three converging developments have reignited contemporary pharmaceutical interest in cannabinoids. First, in 2017–2018 randomized controlled trials demonstrated unequivocal anticonvulsant efficacy of cannabidiol (CBD) in Dravet and Lennox–Gastaut syndromes (Devinsky *et al.,* 2017; Thiele *et al.,* 2018), leading to United States Food and Drug Administration approval of purified CBD (Epidiolex®) as the first plant-derived cannabinoid pharmaceutical for paediatric refractory epilepsy. Approval for seizures associated with tuberous sclerosis complex followed in 2020 (Thiele *et al.,* 2021). Second, cryo-electron microscopy and X-ray crystallographic structures of CB1 and CB2 receptors in complex with agonists, antagonists and signalling G proteins have provided atomic-resolution insight into receptor activation, biased agonism and allosteric modulation (Hua *et al.,* 2016; Hua *et al.,* 2020; Krishna Kumar *et al.,* 2019; Xing *et al.,* 2020). Third, the global rescheduling of cannabis by the United Nations Commission on Narcotic Drugs in December 2020 (removal of cannabis from Schedule IV of the 1961 Single Convention on Narcotic Drugs) and progressive legislative reform in numerous jurisdictions have permitted a marked expansion of clinical investigation.

Despite this momentum, cannabinoid pharmacology remains burdened by its pleiotropic complexity. THC behaves as a partial agonist at CB1 with profound psychoactive consequences, whereas CBD displays low affinity for orthosteric CB1/CB2 binding yet engages at least a dozen molecular targets including transient receptor potential vanilloid 1 (TRPV1), G-protein-coupled receptor 55 (GPR55), peroxisome proliferator-activated receptor gamma (PPARγ), 5-HT1A serotonin receptors, voltage-gated sodium channels, equilibrative nucleoside transporter 1, and the endocannabinoid degradative enzyme fatty acid amide hydrolase (Pertwee, 2008; Ligresti *et al.,* 2016; Mlost *et al.,* 2020). The objective of this review is to provide an in-depth, mechanism-focused account of cannabinoid pharmacology covering the molecular architecture of the ECS, the pharmacology of the principal phytocannabinoids, signal-transduction pathways, therapeutic applications, drug interactions and safety, recent mechanistic insights, and the contemporary drug-development pipeline.

The Endocannabinoid System: Molecular Architecture

The ECS comprises receptors, endogenous lipid ligands (endocannabinoids), and the enzymatic machinery responsible for their biosynthesis and inactivation. Each element is described below in mechanistic detail.

Cannabinoid CB1 receptor: structure, distribution and signalling

The CB1 receptor is a Class A (rhodopsin-like) G-protein-coupled receptor of 472 amino acids encoded by the CNR1 gene on human chromosome 6q14–q15 (Matsuda *et al.,* 1990; Howlett *et al.,* 2002). It is the most abundant GPCR in the mammalian brain, with the highest densities in the substantia nigra, globus pallidus, hippocampus (CA1/CA3 pyramidal cell layer and dentate gyrus), neocortex, basolateral amygdala, and cerebellar molecular layer; densities are notably lower in the brainstem, accounting for the absence of lethal cardiorespiratory depression from CB1 agonist overdose (Mackie, 2008). CB1 is predominantly localized to presynaptic terminals of both glutamatergic and GABAergic neurons, where it controls neurotransmitter release in a retrograde manner (Kano *et al.,* 2009).

Activation of CB1 by agonist binding induces a characteristic outward movement of transmembrane helix 6 that exposes a cytoplasmic G-protein binding crevice. Cryo-electron microscopy of agonist-bound CB1–Gi complexes resolved by Krishna Kumar and colleagues (Krishna Kumar *et al.,* 2019) and Hua and co-workers (Hua *et al.,* 2020) revealed an unusually large orthosteric ligand-binding pocket capable of accommodating diverse cannabinoid scaffolds, and identified a membrane-accessible side channel through which lipophilic ligands enter the receptor laterally from the bilayer—an arrangement that explains the well-known kinetic peculiarities of cannabinoid binding. Downstream of activation, CB1 couples principally to Gαi/o proteins, inhibiting adenylyl cyclase and reducing intracellular cyclic adenosine monophosphate (cAMP) (Howlett *et al.,* 2002). At presynaptic terminals, CB1 activation inhibits N-type (Cav2.2) and P/Q-type (Cav2.1) voltage-gated calcium channels and activates G-protein-coupled inwardly rectifying potassium (GIRK) channels, hyperpolarizing the terminal and reducing

calcium-dependent vesicular neurotransmitter release (Kano *et al.,* 2009). CB1 also activates mitogen-activated protein kinase (MAPK) cascades including ERK1/2, p38, and JNK, recruits β-arrestin-1 and β-arrestin-2, and under certain conditions couples to Gαs and Gαq pathways (Ibsen *et al.,* 2017). This signalling diversity is the substrate for biased agonism, in which different agonists preferentially activate distinct downstream pathways—a concept of growing importance in cannabinoid drug design.

Endocannabinoid-mediated retrograde signalling is the canonical CB1 mechanism in the central nervous system. Postsynaptic depolarization elevates intracellular calcium, which activates diacylglycerol lipase-α (DAGLα) at the postsynaptic membrane; the resulting 2-AG diffuses retrogradely across the synapse, binds presynaptic CB1, and suppresses neurotransmitter release. This mechanism underlies the synaptic phenomena of depolarization-induced suppression of inhibition (DSI), depolarization-induced suppression of excitation (DSE), and several forms of short- and long-term synaptic plasticity (Kano *et al.,* 2009). 2-AG signalling is terminated locally by monoacylglycerol lipase (MAGL) at the presynaptic terminal, with additional contributions from α/β-hydrolase domain-containing protein 6 (ABHD6) and ABHD12.

Cannabinoid CB2 receptor: peripheral and central immune signalling

The CB2 receptor is a 360-amino-acid GPCR encoded by CNR2 on chromosome 1p36, sharing approximately 44% amino acid identity with CB1 overall and 68% within the transmembrane domains (Munro *et al.,* 1993; Howlett *et al.,* 2002). It is predominantly expressed on cells of the immune system—B lymphocytes, natural killer cells, monocytes, macrophages, neutrophils, microglia, and T lymphocytes (in descending order of expression density)—and on tissues with significant immune components including spleen, tonsils, thymus, and gut-associated lymphoid tissue (Galiègue *et al.,* 1995). Although classically described as peripheral, CB2 is also expressed at low levels in the central nervous system, particularly on microglia and on subpopulations of brainstem, hippocampal, and ventral tegmental area neurons, where it has been implicated in synaptic plasticity, reward and neuroinflammatory signalling (Stempel *et al.,* 2016).

Like CB1, CB2 couples primarily to Gαi/o, inhibits adenylyl cyclase, activates MAPK cascades (ERK1/2, p38, JNK) and modulates β-arrestin recruitment. The cryo-EM structure of the agonist-bound human CB2–Gi complex resolved by Xing and colleagues (Xing *et al.,* 2020) revealed a smaller and more constricted orthosteric pocket than CB1, providing the structural basis for ligand selectivity that has long been a goal of cannabinoid medicinal chemistry. Activation of CB2 on immune cells suppresses pro-inflammatory cytokine release (TNF-α, IL-6, IL-12), enhances IL-10 production, inhibits chemotactic migration, modulates phagocytic activity, and shifts T-helper cell polarization toward Th2 phenotypes—effects that underlie the therapeutic rationale for CB2-selective agonists in inflammatory, autoimmune, and neuropathic pain disorders without psychoactive consequences (Bie *et al.,* 2018).

Endogenous ligands: anandamide and 2-arachidonoylglycerol

Two arachidonic acid-derived lipid signalling molecules dominate endocannabinoid pharmacology: anandamide and 2-arachidonoylglycerol. Anandamide, N-arachidonoylethanolamine, was the first endogenous cannabinoid identified, isolated from porcine brain by Devane and colleagues in 1992 (Devane *et al.,* 1992). It is a partial agonist at CB1 (Ki ≈ 89 nM) and a weaker partial agonist at CB2, and additionally acts as a full agonist at TRPV1 channels at higher concentrations. AEA biosynthesis follows a calcium-dependent two-step pathway in which N-acyltransferase (NAT) couples arachidonic acid from phosphatidylcholine to phosphatidylethanolamine to produce N-arachidonoyl phosphatidylethanolamine (NAPE), which is then cleaved to AEA principally by NAPE-specific phospholipase D (NAPE-PLD), with redundant contributions from α/β-hydrolase domain-containing 4 (ABHD4) and glycerophosphodiesterase 1 (Iannotti *et al.,* 2016). AEA degradation occurs principally via fatty acid amide hydrolase (FAAH), a serine hydrolase localized to the endoplasmic reticulum of postsynaptic neurons; genetic deletion of FAAH in mice elevates brain AEA by an order of magnitude and reproduces several behavioural and analgesic phenotypes of CB1 activation (Cravatt *et al.,* 2001).

2-AG, the more abundant endocannabinoid by mass (concentrations 200-fold higher than AEA in brain), behaves as a full agonist at both CB1 and CB2 receptors. Its biosynthesis is calcium- and Gq-coupled-receptor-driven: phospholipase Cβ generates diacylglycerol from phosphatidylinositol bisphosphate, and the sn-1 specific diacylglycerol lipase-α (DAGLα) at postsynaptic

dendritic spines converts DAG to 2-AG (Bisogno *et al.,* 2003). 2-AG is hydrolyzed to arachidonic acid and glycerol predominantly by MAGL (≈85% of brain hydrolytic activity), with smaller contributions from ABHD6 (≈4%) and ABHD12 (≈9%). Pharmacological MAGL inhibition by selective inhibitors such as JZL184 increases brain 2-AG approximately ten-fold and produces robust analgesic, anti-inflammatory and anxiolytic effects in preclinical models (Long *et al.,* 2009).

Beyond AEA and 2-AG, the ECS extends into the so-called 'endocannabidiome'—a broader family of structurally related lipid mediators including N-acylethanolamines (palmitoylethanolamide, oleoylethanolamide), 2-acylglycerols (2-linoleoylglycerol, 2-palmitoylglycerol), N-acyl amino acids, N-acyl dopamines, N-acyl serotonins, and N-acyl taurines, many of which engage non-cannabinoid receptors such as PPARα and GPR119 and contribute to lipid-mediated homeostatic regulation (Iannotti *et al.,* 2016; Di Marzo, 2018).

Non-canonical and putative cannabinoid targets

Several G-protein-coupled receptors and ion channels respond to cannabinoid ligands without being classified as cannabinoid receptors. GPR55, sometimes proposed as a 'CB3' receptor, is activated by lysophosphatidylinositol and certain phytocannabinoids and is antagonized by CBD; it couples to Gα12/13 and Rho kinase signalling and has been implicated in bone remodelling, cancer cell proliferation and nociception (Pertwee *et al.,* 2010). GPR18 and GPR119 respond to endocannabinoid-related N-acylethanolamines. TRPV1 channels are activated by AEA and by CBD at micromolar concentrations and mediate aspects of cannabinoid analgesia and inflammatory signalling. PPARγ is engaged by THC, CBD and AEA and contributes to anti-inflammatory, anti-fibrotic and metabolic actions (Iannotti and Vitale, 2021). 5-HT1A serotonin receptors are partially activated by CBD and contribute to anxiolytic, antidepressant and antipsychotic effects (Mlost *et al.,* 2020). This pleiotropic engagement of multiple targets is the molecular substrate of cannabinoid therapeutic versatility but also of their off-target liabilities and clinical variability.

Phytocannabinoids: Chemistry and Pharmacology

More than 150 phytocannabinoids have been identified in Cannabis sativa, derived biosynthetically from the central precursor cannabigerolic acid (CBGA) (ElSohly *et al.,* 2017). The principal pharmacologically active phytocannabinoids are summarized below.

Δ9-Tetrahydrocannabinol (THC)

THC is the principal psychoactive constituent of cannabis. It behaves as a partial agonist at both CB1 (Ki ≈ 41 nM) and CB2 (Ki ≈ 36 nM) receptors and additionally engages TRPV2 and TRPV4 channels and PPARγ (Pertwee, 2008).

Its CB1-mediated central effects—euphoria, distortion of time perception, anxiolysis at low doses but anxiogenesis at high doses, cognitive impairment, increased appetite, and analgesia—reflect modulation of glutamatergic and GABAergic neurotransmission across cortical, limbic, and basal ganglia circuits (Mackie, 2008). Tolerance to chronic THC develops through CB1 receptor desensitization and downregulation. Approved THC-containing pharmaceuticals include dronabinol (synthetic THC) for AIDS-related anorexia and chemotherapy-induced nausea, and nabilone (a synthetic THC analogue) for refractory chemotherapy-induced emesis. Nabiximols (Sativex®, an oromucosal extract containing approximately equal amounts of THC and CBD) is approved in several jurisdictions for multiple sclerosis spasticity.

Cannabidiol (CBD)

CBD lacks intrinsic psychoactivity and shows low affinity for orthosteric binding at CB1 and CB2 (Ki > 1 μM at both), yet exerts wide-ranging pharmacological effects through engagement of multiple non-canonical targets. CBD is a negative allosteric modulator of CB1, reducing the efficacy and potency of orthosteric agonists such as THC and 2-AG—the molecular basis for its capacity to attenuate THC-induced psychoactive and anxiogenic effects (Laprairie *et al.,* 2015). CBD inhibits FAAH and the equilibrative nucleoside transporter ENT1 (which mediates adenosine reuptake), elevating extracellular AEA and adenosine and producing indirect cannabinoid and anti-inflammatory effects (Carrier *et al.,* 2006).

It antagonizes GPR55, partially agonizes 5-HT1A receptors, activates TRPV1 channels at micromolar concentrations, modulates voltage-gated sodium and T-type calcium channels (contributing to anticonvulsant effects), and acts as a PPARγ agonist (Mlost *et al.,* 2020; Atalay *et al.,* 2020). This pleiotropic profile underlies

CBD's broad therapeutic spectrum spanning epilepsy, anxiety, inflammation, neuroprotection and pain modulation, and accounts for its bell-shaped dose-response curves observed in numerous preclinical and clinical settings (Gallily *et al.,* 2015).

Minor phytocannabinoids and the entourage effect

Cannabigerol (CBG), the decarboxylation product of the parent CBGA, is a weak partial agonist at CB1 and CB2 and an α2-adrenergic and 5-HT1A receptor modulator, with emerging interest in inflammatory bowel disease, glaucoma and neuroprotection. Cannabinol (CBN), an oxidative degradation product of THC, retains weak CB1/CB2 activity and is being investigated for sedative and bone-anabolic effects. Cannabichromene (CBC) is a strong agonist at TRPA1 channels and a CB2 partial agonist with analgesic and anti-inflammatory potential. Δ9-Tetrahydrocannabivarin (THCV) is a CB1 neutral antagonist at low doses and a partial agonist at high doses, with potential antidiabetic and appetite-suppressant applications. Cannabidivarin (CBDV) shares CBD's anticonvulsant pharmacology and is in clinical development for refractory epilepsy and autism spectrum disorder (Morales *et al.,* 2017).

The concept of the 'entourage effect', proposed by Mechoulam and developed by Russo, holds that whole-plant cannabis extracts produce pharmacological effects qualitatively different from any single isolated cannabinoid by virtue of synergistic and modulatory interactions among major cannabinoids, minor cannabinoids, terpenes (myrcene, β-caryophyllene, limonene, linalool, pinene), and flavonoids (Russo, 2011).

β-Caryophyllene, in particular, is a selective CB2 agonist contributing demonstrable anti-inflammatory activity to many cannabis chemovars. While the entourage hypothesis has been criticized for incomplete mechanistic substantiation, growing pharmacological evidence supports terpene–cannabinoid interactions, and the entourage effect remains a central organizing concept in medicinal cannabis formulation (Aizpurua-Olaizola *et al.,* 2016).

Molecular Mechanisms of Cannabinoid Action

The pharmacological actions of cannabinoids reflect integration of multiple signal-transduction events at the receptor, ion-channel, enzyme and transporter levels. The principal mechanisms are described below.

CB1 receptor signalling and presynaptic neuromodulation

CB1 receptor activation by THC or 2-AG initiates Gαi/o-coupled inhibition of adenylyl cyclase, which reduces intracellular cAMP and downstream protein kinase A activity (Howlett *et al.,* 2002). The most pharmacologically consequential downstream events at presynaptic terminals are the βγ-subunit-mediated inhibition of voltage-gated calcium channels (predominantly Cav2.2 and Cav2.1) and activation of GIRK (Kir3) channels (Kano *et al.,* 2009). The net effect is reduced presynaptic calcium influx during action-potential invasion of the terminal, hyperpolarization of the bouton, and consequent reduction in vesicular release of glutamate, GABA, dopamine, acetylcholine, noradrenaline, serotonin and several neuropeptides—an output that is non-selective with respect to neurotransmitter identity but anatomically specific to those terminals expressing CB1 (Marsicano and Lutz, 2006; Cohen *et al.,* 2019). CB1 simultaneously activates MAPK cascades (ERK1/2, p38 and JNK), phosphatidylinositol 3-kinase/Akt signalling, and recruits β-arrestin-1 and β-arrestin-2, the latter coupling to receptor desensitization, internalization and clathrin-mediated endocytosis underlying the tolerance observed with chronic exposure (Ibsen *et al.,* 2017).

Retrograde endocannabinoid signalling represents one of the most thoroughly characterized examples of unconventional synaptic communication. At inhibitory synapses, postsynaptic depolarization elevates intracellular calcium and activates DAGLα localized to dendritic spines; the resulting 2-AG diffuses across the synaptic cleft, binds presynaptic CB1, and suppresses GABA release for several seconds (depolarization-induced suppression of inhibition, DSI). The analogous phenomenon at excitatory synapses is DSE. These processes underlie multiple forms of short- and long-term synaptic plasticity, including long-term depression at corticostriatal, hippocampal and cerebellar synapses, and are essential to motor learning, fear extinction and working memory (Kano *et al.,* 2009). Disruption of this signalling architecture is implicated in addiction, anxiety disorders, post-traumatic stress and several neurodevelopmental conditions.

CB2 receptor signalling in immune cells and neuroinflammation

CB2 receptor activation similarly inhibits adenylyl cyclase via Gαi/o, with concomitant MAPK activation.

In immune cells the dominant functional output is anti-inflammatory: reduced release of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-12), reduced expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), enhanced IL-10 secretion, and inhibition of leukocyte chemotaxis and adhesion (Bie *et al.,* 2018). On macrophages and microglia, CB2 activation promotes a shift from the pro-inflammatory M1 phenotype toward the anti-inflammatory and tissue-repair M2 phenotype. In experimental autoimmune encephalomyelitis, sepsis, ischaemia-reperfusion injury, neurodegeneration and chronic pain models, selective CB2 agonists confer reproducible protection without psychoactive consequences, establishing CB2 as an exceptionally attractive therapeutic target that has nonetheless proved challenging to translate to the clinic owing to species differences in CB2 pharmacology and the receptor's complex constitutive activity. Newer mechanistic insights point to important roles for neuronal CB2 in regulating hippocampal excitability and reward-related dopaminergic signalling (Stempel *et al.,* 2016).

Pleiotropic mechanisms of cannabidiol

CBD is mechanistically the most complex phytocannabinoid. Its negative allosteric modulation of CB1 (Laprairie *et al.,* 2015) shifts orthosteric agonist concentration–response curves rightward and reduces maximal efficacy, providing the molecular basis for CBD's well-documented attenuation of THC-induced psychoactive, anxiogenic and tachycardic effects—a pharmacodynamic interaction exploited clinically in fixed-ratio THC:CBD preparations. CBD inhibits FAAH and the equilibrative nucleoside transporter ENT1, increasing extracellular AEA and adenosine respectively; the resulting indirect CB1/CB2 activation and adenosine A1/A2A receptor engagement contribute to anti-inflammatory, anxiolytic and cardioprotective actions (Carrier *et al.,* 2006). CBD antagonizes GPR55, an action implicated in its anticonvulsant and anti-cancer effects. CBD is a partial agonist at 5-HT1A serotonin receptors, contributing to anxiolytic, antidepressant and antipsychotic effects (Mlost *et al.,* 2020). At higher concentrations CBD activates TRPV1 and TRPV2 channels, and it inhibits TRPM8.

Two mechanisms underlie CBD's anticonvulsant action validated in randomized trials (Devinsky *et al.,* 2017; Thiele *et al.,* 2018, 2021). First, CBD inhibits GPR55-mediated calcium signalling in hippocampal pyramidal neurons, suppressing seizure-promoting glutamatergic excitability. Second, CBD inhibits the equilibrative nucleoside transporter, elevating extracellular adenosine and activating inhibitory A1 receptors. Additional contributions arise from inhibition of voltage-gated sodium channels (Nav1.1–1.7), inhibition of T-type calcium channels, and modulation of GABA-A receptor positive allosteric activity. CBD is additionally a potent direct antioxidant and PPARγ agonist, accounting for its anti-inflammatory, neuroprotective and antifibrotic effects in a wide range of experimental models (Booz, 2011; Atalay *et al.,* 2020; Petrosino *et al.,* 2018).

Biased agonism and allosteric modulation

Cryo-electron microscopy of CB1 and CB2 in complex with diverse agonists has revealed that different ligands stabilize distinct receptor conformations that preferentially engage subsets of downstream effectors—a phenomenon termed biased agonism or functional selectivity. For CB1, agonists biased toward G-protein signalling versus β-arrestin recruitment produce qualitatively different in vivo profiles, and pharmacologically distinct pathways may be selectively targeted to dissociate analgesia, tolerance, dependence and adverse effects (Ibsen *et al.,* 2017; Hua *et al.,* 2020). Allosteric modulators offer a complementary strategy: positive allosteric modulators (PAMs) such as ZCZ-011 and GAT211 amplify endocannabinoid tone and produce analgesia without classical CB1 agonist side effects, whereas negative allosteric modulators (NAMs) such as ORG27569 and CBD itself reduce orthosteric agonist efficacy. These mechanisms have re-energized cannabinoid drug discovery after the 2008 withdrawal of the orthosteric CB1 inverse agonist rimonabant for psychiatric adverse effects.

Therapeutic Applications

Cannabinoid therapeutics span an unusually broad range of indications reflecting the wide anatomical and functional distribution of the ECS. Evidence quality varies markedly across indications, and only a small subset of applications has been validated by rigorous randomized controlled trials.

Refractory paediatric epilepsy

The most rigorously evidenced contemporary application of cannabinoids is paediatric refractory epilepsy. In the GWPCARE1 randomized double-blind placebo-controlled trial, purified CBD at 20 mg/kg/day reduced convulsive seizure frequency in Dravet syndrome by 38.9% compared with 13.3% with placebo over 14

weeks (Devinsky *et al.,* 2017). In the GWPCARE4 trial of Lennox–Gastaut syndrome, CBD reduced drop seizure frequency by approximately 42–44% (Thiele *et al.,* 2018). The GWPCARE6 trial subsequently established CBD efficacy in tuberous sclerosis complex (Thiele *et al.,* 2021). These trials supported FDA approval of Epidiolex® for these three indications (FDA, 2018) and constitute the first regulatory approvals of a plant-derived cannabinoid for paediatric neurological disease. The mechanism is principally attributed to GPR55 antagonism, adenosine reuptake inhibition, voltage-gated sodium channel modulation, and indirect inhibition of glutamatergic transmission as detailed above.

Chronic and neuropathic pain

Cannabinoids modulate pain at multiple anatomical levels: peripheral nociceptive terminals (via CB1 and CB2 on sensory neurons and immune cells), spinal cord (CB1-mediated inhibition of substance P and glutamate release in the dorsal horn), and supraspinal sites including periaqueductal grey and rostral ventromedial medulla. A 2015 JAMA systematic review of 28 randomized trials found moderate-quality evidence supporting cannabinoid efficacy for chronic neuropathic pain and cancer pain, with effect sizes comparable to gabapentinoids (Whiting *et al.,* 2015). Nabiximols (Sativex®) is approved in over 25 jurisdictions for moderate-to-severe multiple sclerosis spasticity and refractory cancer pain. CBD-rich preparations show modest efficacy in chronic non-cancer pain with a more favourable adverse-effect profile than THC-rich products (Mlost *et al.,* 2020; Bilbao and Spanagel, 2022). The 2018 IASP task force on cannabinoids and pain concluded that the overall quality of evidence supports limited clinical use in carefully selected patients refractory to first-line analgesics.

Chemotherapy-induced nausea, vomiting and appetite stimulation

The CB1-mediated antiemetic action of cannabinoids arises from inhibition of glutamate release in the nucleus tractus solitarius and area postrema, combined with 5-HT3 receptor antagonism. Dronabinol (oral synthetic THC) and nabilone (a synthetic THC analogue) are approved for chemotherapy-induced nausea and vomiting refractory to first-line 5-HT3 antagonists. Dronabinol is additionally approved for AIDS-related anorexia. Newer cannabinoid CB1 inverse agonists targeting peripheral receptors are being investigated for obesity and metabolic syndrome (Di Marzo, 2018).

Multiple sclerosis spasticity and neurodegenerative disease

Nabiximols reduces multiple sclerosis spasticity in approximately 40–50% of patients refractory to conventional therapy, with effects attributed to CB1-mediated reduction of glutamatergic and noradrenergic drive to spinal motor circuits and CB2-mediated anti-inflammatory effects on infiltrating immune cells (Whiting *et al.,* 2015).

In Alzheimer's disease, preclinical data implicate CB1, CB2 and ECS modulation in amyloid-β clearance, microglial activation and tau phosphorylation; small clinical studies of dronabinol and nabilone for agitation in dementia have shown encouraging signals. In Parkinson's disease, CB1 modulation of basal ganglia circuits provides a mechanistic rationale for cannabinoid effects on dyskinesia, although controlled trial evidence remains limited.

In Huntington's disease, loss of striatal CB1 expression is among the earliest molecular changes, and CBD has been investigated as a neuroprotectant. Notably, low-dose chronic THC has been shown to reverse age-related cognitive decline in aged mice through CB1-dependent restoration of hippocampal gene expression and synaptic plasticity (Bilkei-Gorzo *et al.,* 2017), supporting interest in cannabinoid pharmacology of cognitive ageing.

Anxiety, post-traumatic stress and psychiatric disorders

CBD exhibits anxiolytic effects in humans at doses of 300–600 mg, demonstrated in social anxiety provocation tests and small-scale randomized trials, mediated by 5-HT1A partial agonism, indirect FAAH-mediated AEA elevation, and TRPV1 modulation (Mlost *et al.,* 2020).

Anandamide dysregulation has been documented in patients with post-traumatic stress disorder (Hauer *et al.,* 2013), and the endocannabinoid system regulates fear extinction circuits in the basolateral amygdala and infralimbic prefrontal cortex—providing a mechanistic basis for cannabinoid-augmented exposure therapy in PTSD (Hill *et al.,* 2010).

Open-label and small randomized studies of CBD-rich cannabis preparations in autism spectrum disorder have shown reductions in disruptive behaviour, hyperactivity and self-injury (Aran *et al.,* 2019), and pivotal trials of CBD and cannabidivarin in autism are ongoing.

Inflammatory bowel disease, oncology and emerging indications

The ECS regulates intestinal motility, secretion, visceral sensation, epithelial permeability, and mucosal immunity; CB1 and CB2 receptors are expressed throughout the enteric nervous system and on gut-associated immune cells (Cuddihey *et al.,* 2022). Cannabinoids attenuate experimental colitis through CB2-mediated suppression of cytokine release and CB1-mediated restoration of epithelial barrier integrity, and small clinical studies of THC- and CBD-rich preparations have shown symptom benefit in Crohn's disease and ulcerative colitis, although effects on mucosal healing remain modest. In oncology, preclinical evidence demonstrates direct antiproliferative and pro-apoptotic effects of THC and CBD across multiple tumour cell lines through CB1/CB2-mediated ceramide accumulation and induction of autophagy; clinical translation remains limited to symptomatic management (cancer-related pain, nausea, anorexia, sleep) pending adequately powered randomized trials. Glaucoma, post-traumatic stress disorder, opioid use disorder, and inflammatory skin disease are among the active investigational indications (Bilbao and Spanagel, 2022).

Pharmacokinetics and Drug Interactions

Cannabinoids are highly lipophilic small molecules with complex pharmacokinetic profiles. Inhaled THC and CBD show rapid systemic absorption (Tmax 5–10 minutes) with bioavailability of 10–35%, while oral cannabinoids exhibit erratic absorption and extensive first-pass metabolism reducing bioavailability to 6–20% for THC and approximately 6–15% for CBD (Millar *et al.,* 2018). Both compounds undergo extensive hepatic metabolism: THC is hydroxylated by CYP2C9 to 11-hydroxy-THC (a metabolite of comparable psychoactivity that contributes substantially to the prolonged effects of oral cannabis) and further oxidized to 11-nor-9-carboxy-THC; CBD is metabolized primarily by CYP3A4 and CYP2C19 to 7-hydroxy-CBD and 6-hydroxy-CBD. Owing to their lipophilicity, cannabinoids distribute extensively into adipose tissue with terminal half-lives of 1–3 days for occasional users and up to 5–13 days for chronic users.

Cannabinoid pharmacokinetic interactions are clinically significant. CBD is a moderately potent inhibitor of CYP3A4, CYP2C19, CYP2C9 and CYP2D6 and a substrate and inducer of CYP1A2, producing reciprocal interactions with numerous co-administered drugs. The CBD–clobazam interaction is the best characterized: CBD inhibits CYP2C19 metabolism of N-desmethylclobazam, the active clobazam metabolite, raising its plasma concentrations by 3- to 10-fold and accounting for a substantial portion of the seizure benefit (and sedation risk) attributed to CBD in clinical trials. Other clinically relevant interactions include increased plasma levels of warfarin (CYP2C9 inhibition), tacrolimus and other calcineurin inhibitors (CYP3A4 inhibition), tricyclic antidepressants, certain antiretrovirals, valproate (with risk of hepatotoxicity), and topiramate (Millar *et al.,* 2018; Bilbao and Spanagel, 2022). THC is metabolized by CYP2C9 and CYP3A4 and is itself a moderate inhibitor of CYP2C9, with potential interactions affecting warfarin and oral hypoglycaemic agents.

Adverse Effects and Safety Profile

Cannabinoid adverse effects partition along the CB1 axis. THC and synthetic CB1 agonists produce dose-dependent cognitive impairment (working memory, attention, executive function), sedation, tachycardia, postural hypotension, dry mouth, conjunctival injection, and—at higher doses or in susceptible individuals—anxiety, dysphoria, paranoia, and frank psychosis. Heavy chronic cannabis use during adolescence is associated with an increased risk of schizophrenia spectrum disorders, particularly in carriers of certain catechol-O-methyltransferase and AKT1 polymorphisms, although causality remains contested. Cannabis use disorder occurs in approximately 9% of ever-users, rising to 17% among those who initiate in adolescence and 25–50% among daily users (Kalant, 2004). Driving while acutely impaired by THC is associated with roughly a doubling of motor vehicle crash risk. Cannabinoid hyperemesis syndrome—a paradoxical cyclic vomiting disorder of chronic heavy cannabis users—has emerged as a recognized clinical entity since the early 2000s.

CBD has a substantially more favourable adverse-effect profile. The principal CBD-related concerns are dose-dependent transaminase elevations (occurring in approximately 5–20% of patients in epilepsy trials at 20 mg/kg/day, particularly when co-administered with valproate), diarrhoea, somnolence, decreased appetite, and the drug interactions described above (Devinsky *et al.,* 2017; Thiele *et al.,* 2018). The 2018 World Health Organization Expert Committee on Drug Dependence concluded that pure CBD has no abuse potential and an acceptable safety profile. Inadvertent contamination with THC, synthetic cannabinoids, pesticides, heavy metals or

mycotoxins remains a concern for unregulated CBD products available outside the medical channel.

Emerging Insights (2020–2025)

Cannabinoid research has accelerated substantially in the past five years. Several developments warrant particular attention.

Structural biology of cannabinoid receptors

The cryo-electron microscopy revolution has yielded high-resolution structures of CB1 and CB2 receptors in inactive, agonist-bound, antagonist-bound and G-protein-complexed conformations (Hua *et al.,* 2016; Hua *et al.,* 2020; Krishna Kumar *et al.,* 2019; Xing *et al.,* 2020).

These structures have revealed the membrane-accessible lateral entry portal through which lipophilic cannabinoids access the orthosteric pocket, the conformational rearrangement of transmembrane helix 6 during activation, the structural basis for CB1 versus CB2 ligand selectivity, and previously uncharacterized allosteric sites. Computational docking informed by these structures has accelerated the design of selective CB2 agonists, peripherally restricted CB1 antagonists, biased ligands and allosteric modulators—a pharmacological renaissance that is reshaping cannabinoid medicinal chemistry.

The endocannabidiome and lipid-mediator pharmacology

The lipid mediators that signal through or alongside the cannabinoid receptors extend far beyond AEA and 2-AG. The endocannabidiome encompasses more than 200 N-acylethanolamines, monoacylglycerols, N-acyl amino acids, N-acyl serotonins, N-acyl taurines, N-acyl dopamines, and 2-acylglycerols, many of which engage non-CB1/CB2 receptors including PPARα, PPARγ, GPR55, GPR119, TRPV1 and TRPA1 (Iannotti *et al.,* 2016; Di Marzo, 2018; Iannotti and Vitale, 2021).

Palmitoylethanolamide has emerged as an anti-inflammatory and analgesic agent acting through PPARα and entourage potentiation of AEA, and oleoylethanolamide has gained interest as an appetite regulator and metabolic mediator. The expansion of the lipid mediator landscape is driving renewed interest in indirect ECS modulators that elevate endogenous endocannabidiome lipids rather than activating receptors directly.

Gut–brain endocannabinoid axis and the microbiome

The intestinal ECS is densely expressed throughout the enteric nervous system, intestinal epithelium and gut-associated lymphoid tissue, and is now recognized as a bidirectional interface between the gastrointestinal microbiome and the central nervous system (Cuddihey *et al.,* 2022). Specific commensal bacteria including Akkermansia muciniphila and Lactobacillus species modulate intestinal endocannabinoid tone, and gut-derived endocannabinoids in turn influence systemic immunometabolic signalling. Germ-free animals show altered brain endocannabinoid levels and behavioural phenotypes that are corrected by microbial colonization, establishing a microbiome–endocannabinoid–brain axis with implications for obesity, irritable bowel syndrome, anxiety, depression and neurodevelopmental disorders.

Genetic polymorphisms and personalized cannabinoid pharmacology

Common functional polymorphisms in genes encoding ECS components shape interindividual variability in cannabinoid response. The C385A variant of FAAH (encoding a less stable enzyme with reduced AEA hydrolytic activity) is associated with elevated AEA, altered fear extinction, attenuated anxiety, and modified cannabis use trajectories. Polymorphisms in CNR1 (encoding CB1) influence pain sensitivity, susceptibility to cannabis dependence, and antiemetic response to THC. CYP2C9*3 and CYP2C19*2 alleles alter THC and CBD metabolism, respectively. Pharmacogenomic stratification of cannabinoid response is an emerging clinical objective, particularly relevant to paediatric epilepsy and chronic pain (Bilbao and Spanagel, 2022).

Neuroinflammation, CB2 and cognitive ageing

CB2 receptors on microglia are increasingly recognized as critical regulators of neuroinflammatory tone. CB2 activation suppresses NLRP3 inflammasome assembly, modulates microglial phenotype, and reduces neuroinflammation in models of Alzheimer's disease, Parkinson's disease, multiple sclerosis, and ischaemic stroke. The remarkable finding that chronic low-dose THC restores age-related cognitive decline in mice through CB1-dependent reversal of hippocampal transcriptional changes (Bilkei-Gorzo *et al.,* 2017) has opened a new dimension to cannabinoid pharmacology and is being investigated in early clinical trials of cannabinoids for mild cognitive impairment. The brain endocannabinoid system is itself age-regulated, with

declines in CB1 expression and AEA tone observed in ageing brain that may contribute to neurodegenerative vulnerability.

Future Perspectives and Drug Development Pipeline

Several distinct streams of cannabinoid drug development are now advancing toward the clinic.

Selective CB2 agonists

Highly CB2-selective full agonists are advancing for inflammatory pain, neuropathic pain, inflammatory bowel disease and atopic dermatitis, with the promise of cannabinoid-mediated efficacy without CB1-mediated psychoactivity.

Compounds such as olorinab (APD371) have entered clinical trials for visceral pain in inflammatory bowel disease and irritable bowel syndrome (Bie *et al.,* 2018).

Peripherally restricted CB1 antagonists for metabolic disease

Following the 2008 withdrawal of the centrally penetrant CB1 inverse agonist rimonabant for psychiatric adverse events, the development pipeline has refocused on peripherally restricted CB1 antagonists that retain metabolic efficacy (insulin sensitization, hepatic lipid clearance, body-weight reduction) without crossing the blood–brain barrier.

Several such compounds have shown favourable preclinical and early clinical profiles for non-alcoholic steatohepatitis, type 2 diabetes and diabetic nephropathy (Di Marzo, 2018).

FAAH and MAGL inhibitors

Inhibition of endocannabinoid degradation enzymes offers an attractive route to elevate endogenous AEA or 2-AG selectively at sites of physiological demand, theoretically reducing tonic, system-wide cannabinoid receptor activation. Development of FAAH inhibitors was complicated by the catastrophic 2016 Phase I trial of BIA 10-2474 (which produced fatal neurotoxicity attributed to off-target serine hydrolase inhibition rather than FAAH biology), but newer, highly selective FAAH inhibitors and selective MAGL inhibitors (notably lu AG06466/ABX-1431 for Tourette syndrome and neuropathic pain) are now advancing through clinical development (Long *et al.,* 2009; Di Marzo, 2018).

Allosteric modulators and biased ligands

Positive and negative allosteric modulators of CB1 and CB2 retain only contextual activity—amplifying or attenuating responses to endogenous agonists at sites of physiological endocannabinoid release—and therefore promise improved therapeutic windows compared with orthosteric agonists. Biased agonists that selectively engage G-protein over β-arrestin pathways (or vice versa) may dissociate analgesia from tolerance and dependence. These pharmacological concepts have been substantially enabled by the cryo-EM-derived structural understanding of cannabinoid receptor conformational landscapes (Hua *et al.,* 2020; Ibsen *et al.,* 2017).

Cannabinoid nanoformulations and novel delivery

The low and erratic oral bioavailability of cannabinoids has motivated extensive development of nano-emulsions, self-emulsifying drug delivery systems, polymeric nanoparticles, solid lipid nanoparticles, and cyclodextrin inclusion complexes. Several nano-CBD formulations have demonstrated 4- to 6-fold increases in oral bioavailability, more rapid onset, and more predictable plasma levels than conventional oil-based preparations, and are entering late-stage clinical development for pain, anxiety and inflammatory indications.

In conclusion, Cannabinoid pharmacology has progressed in three decades from the discovery of two cannabinoid receptors and two endogenous ligands to a sophisticated understanding of a brain-wide and body-wide lipid-signalling system whose dysregulation contributes to disorders as diverse as epilepsy, neuropathic pain, multiple sclerosis spasticity, anxiety, neurodegeneration, inflammatory bowel disease and metabolic syndrome. Atomic-resolution structural biology of CB1 and CB2 receptors, the cataloguing of an expanded endocannabidiome of bioactive lipids, and the demonstration of clinically meaningful efficacy of cannabidiol in paediatric refractory epilepsy have together validated cannabinoid pharmacology as a mature pharmaceutical discipline. Significant challenges nonetheless remain: optimizing therapeutic indices through receptor-selective, biased, or allosteric ligands; managing pharmacokinetic interactions through enzyme-aware co-prescribing; navigating heterogeneous regulatory and policy landscapes; and translating preclinical findings in CB2-mediated neuroinflammation, microbiome–endocannabinoid signalling and cannabinoid pharmacology of ageing into clinical practice. The next decade of cannabinoid pharmacology

will be defined by the precision targeting of ECS components for indications where conventional pharmacotherapy has failed.

Acknowledgements

The authors gratefully acknowledge the Department of Pharmacology, Malla Reddy College of Pharmacy, for institutional support and access to scientific databases used in the preparation of this review.

Conflict of Interest

The authors declare no financial or non-financial conflicts of interest related to the subject matter of this manuscript.

Ethical Approval

This review article is based exclusively on previously published literature and does not involve any new studies on human participants or animals performed by the authors. Ethical approval and informed consent are therefore not applicable.

Funding

No external funding was received for the preparation of this review article.

Author Contributions

Both authors contributed to conceptualization, literature review, manuscript drafting, and critical revision. Both authors have read and approved the final version of the manuscript.

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How to cite this article:

Kallem Srihasini and Manisha R. L. 2026. Cannabinoid Pharmacology Redefined: Molecular Mechanisms, Therapeutic Frontiers, and Emerging Insights into the Endocannabinoid System. *Int.J.Curr.Res.Aca.Rev.* 14(5), 01-14. doi: https://doi.org/10.20546/ijcrar.2026.1405.001