

# Cannabinoid

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**Primary Disciplinary Field(s):** Biochemistry, Pharmacology, Neuroscience, Physiology, Immunology

### 1. Core Definition

Cannabinoids constitute a heterogeneous class of chemical compounds defined by their ability to interact with and modulate the activity of specific cannabinoid receptors, which are integral components of the human and animal endocannabinoid system (ECS). These compounds are fundamentally characterized by their lipid solubility and structural diversity. They are broadly categorized based on their origin into three main groups: **endocannabinoids**, which are biosynthesized naturally within the body; **phytocannabinoids**, which are isolated from plants, primarily *Cannabis sativa*; and **synthetic cannabinoids**, which are artificially engineered in laboratory settings.

The defining pharmacological feature of cannabinoids is their binding affinity for G-protein coupled receptors, specifically the CB1 and CB2 receptors. Through this interaction, cannabinoids elicit a vast array of physiological responses. The ECS, regulated by these compounds, is a pivotal homeostatic mechanism, influencing critical functions across the central and peripheral nervous systems. These functions include the modulation of mood, memory, immune response, pain perception, appetite regulation, and neuroprotection. Consequently, the study of cannabinoids is crucial for understanding normal physiological functioning and for developing therapeutic strategies targeting systemic imbalances and various chronic medical conditions.

### 2. Etymology and Historical Development

The nomenclature "cannabinoid" is derived directly from the cannabis plant, the historical source from which the most famous members of this class were first isolated. The modern scientific exploration of cannabinoids commenced in the mid-20th century. The critical breakthrough occurred in 1964 when Raphael Mechoulam and his research team at the Weizmann Institute of Science successfully isolated and determined the chemical structure of **delta-9-tetrahydrocannabinol ( $\Delta^9$ -THC)**. This discovery was revolutionary, identifying the primary psychoactive component of cannabis and initiating systematic research into the plant's pharmacological profile.

Following the characterization of  $\Delta^9$ -THC, the scientific focus shifted to deciphering its mechanism of action within the body. This effort culminated in the cloning of the first specific binding site, the **CB1** receptor, in 1990 by Allyn Howlett and colleagues, followed by the discovery of the **CB2** receptor in 1993. The identification of these dedicated receptors strongly implied the existence of

an intrinsic signaling system within the body--the ECS--that naturally interacted with cannabinoid-like ligands.

The existence of this endogenous system was confirmed shortly thereafter by the discovery of the first endogenous cannabinoids, or endocannabinoids. In 1992, Mechoulam's group isolated **Anandamide** (N-arachidonylethanolamine), deriving its name from the Sanskrit word for "bliss." This was quickly followed by the identification of the second major endocannabinoid, **2-arachidonoylglycerol (2-AG)**, in 1995. These landmark discoveries solidified the understanding of cannabinoids as ligands for a complex, ubiquitous biological system essential for maintaining cellular and systemic homeostasis, thereby establishing the field as a cornerstone of modern biomedical research.

### 3. Key Characteristics and Receptor Systems

Cannabinoids are structurally diverse lipid-based compounds that exert their effects primarily through modulation of the CB1 and CB2 receptor system. They are classified into three distinct categories based on their biochemical origin, each possessing unique pharmacological properties, synthesis pathways, and metabolic fates.

**Endocannabinoids (eCBs):** These are endogenous, lipid-derived, on-demand retrograde neurotransmitters. The most studied examples are **Anandamide (AEA)** and **2-AG**. Unlike classical neurotransmitters, eCBs are synthesized from membrane phospholipids only when needed and are rapidly inactivated near the site of action by specific enzymes. Fatty acid amide hydrolase (FAAH) degrades AEA, while monoacylglycerol lipase (MAGL) metabolizes 2-AG. This rapid synthesis and degradation ensures highly localized and transient signaling, critical for functions such as synaptic plasticity and stress modulation.

**Phytocannabinoids:** These compounds are naturally produced by the *Cannabis sativa* plant, with over 100 distinct variants identified. The two most prominent members are  **$\Delta^9$ -THC**, which is responsible for the plant's characteristic psychoactive effects and possesses analgesic and antiemetic properties; and **cannabidiol (CBD)**, which is non-psychoactive and exhibits significant therapeutic potential, including anti-inflammatory, anxiolytic, and anticonvulsant effects. Other notable phytocannabinoids include cannabitol (CBN), cannabigerol (CBG), and cannabichromene (CBC).

**Synthetic Cannabinoids:** Created artificially, these compounds were initially developed as research tools to probe the ECS but have also been manufactured illicitly for recreational use. Medically relevant synthetic cannabinoids (e.g., dronabinol and nabilone) are used to treat chemotherapy-induced nausea. However, unregulated synthetic compounds (e.g., JWH-018) often possess extremely high affinity for cannabinoid receptors, leading to unpredictable, potent, and sometimes dangerous effects, posing serious public health concerns.

The primary mechanism of action for all cannabinoid classes is agonism or antagonism at the two established G-protein coupled cannabinoid receptors, which are differentially distributed throughout the body.

**CB1 Receptors:** These are among the most densely populated G-protein coupled receptors in the **Central Nervous System (CNS)**, concentrating in regions vital for executive function (cortex), memory (hippocampus), reward (ventral striatum), and motor control (basal ganglia). Their presence in peripheral tissues--including the liver, adipose tissue, gastrointestinal tract, and lungs--indicates their widespread involvement in metabolic and regulatory processes outside the brain.

**CB2 Receptors:** These receptors are predominantly expressed in cells and tissues of the **immune system**, such as T-lymphocytes, B-lymphocytes, macrophages, and microglial cells in the CNS. Their activation is primarily linked to immunomodulation and the suppression of inflammation. Since CB2 receptors are generally not associated with psychoactive pathways, they are considered a major target for developing anti-inflammatory and pain therapies without the central nervous system side effects common to CB1 agonists.

#### 4. Significance and Impact

The significance of cannabinoids stems from their integral role in regulating the ECS, which functions as a master regulatory system essential for maintaining nearly all aspects of mammalian physiological homeostasis. This profound and pervasive influence makes the study of cannabinoid pharmacology indispensable for understanding health, disease progression, and the development of next-generation pharmacological treatments.

Within the CNS, cannabinoid signaling, largely mediated by CB1 receptors, modulates a wide spectrum of neurological processes. Cannabinoids critically influence **synaptic plasticity**, thereby affecting memory formation and learning. They are deeply involved in **mood regulation**, impacting anxiety levels, stress resilience, and depressive behaviors. Furthermore, their powerful ability to modulate neurotransmitter release in ascending and descending pain pathways positions them as significant agents in **pain perception and analgesia**. The ECS also contributes to essential functions such as appetite stimulation, neuroprotection against excitotoxicity, and the regulation of sleep-wake cycles.

Beyond neurological functions, cannabinoids exhibit substantial effects peripherally. Activation of CB2 receptors drives significant **anti-inflammatory and immunomodulatory responses**, offering therapeutic avenues for chronic inflammation, autoimmune disorders, and neuroinflammatory diseases. Cannabinoids also regulate **metabolism and energy balance**, famously stimulating appetite (the "munchies" associated with THC) and influencing lipid and glucose metabolism. The burgeoning therapeutic landscape includes the use of cannabinoid-based medications for intractable conditions such as drug-resistant epilepsy, multiple sclerosis-related spasticity, chronic

neuropathic pain, and chemotherapy-induced nausea and vomiting.

## 5. Debates and Criticisms

Despite rapid advances in cannabinoid science and pharmacology, the field remains fraught with significant regulatory, safety, and ethical debates. A primary concern is the fragmented **regulatory status** of cannabis and its derivatives globally. While specific cannabinoids, such as purified CBD and certain synthetic THC analogues, have achieved pharmaceutical approval, the plant itself often remains highly restricted, severely limiting large-scale, standardized clinical research and therapeutic access. This regulatory inconsistency fosters an environment where non-standardized products are widespread, leading to challenges in consistent dosing, quality control, and ensuring patients receive reliable information.

Central to the medical debate are concerns regarding the **safety profile and long-term health consequences** of cannabinoid use, particularly those containing high levels of psychoactive  $\Delta^9$ -THC. While CBD is generally safe and well-tolerated, THC can cause acute impairments in cognitive function, motor coordination, and perception, and may precipitate anxiety or transient psychotic episodes in vulnerable populations. Critically, chronic use, particularly initiating during adolescence when the brain is still developing, has been linked to potential risks for mental health disorders and neurodevelopmental changes. Therefore, establishing a clear, evidence-based understanding of the precise risk-benefit ratio for various cannabinoid delivery methods and potencies remains a priority for clinicians and policymakers.

Finally, the scientific complexity of the plant itself presents challenges. The hypothesized "**entourage effect**"--the synergistic interaction between multiple phytocannabinoids, terpenes, and flavonoids--is often cited but remains poorly understood and difficult to isolate for scientific study. Ethically, the debate encompasses equitable access to cannabinoid therapies, mitigating the risks associated with potential misuse and dependence, particularly for high-potency recreational products, and managing the associated societal costs. Addressing these multifaceted challenges requires sustained, rigorous scientific investigation and the implementation of clear, globally aligned regulatory frameworks.

## Further Reading

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