Cannabinoids: Medicine or Poison

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The hemp plant (*Cannabis sativa)* commonly known as Indian hemp belongs to the Cannabinaceae family and is also referred to as marijuana, ganja, pot, hemp or cannabis. It comprises three recognized subspecies: *C. sativa* subspecies sativa (longer and more fibrous, primarily cultivated as industrial hemp), *C. sativa* subspecies indica (shorter and more psychoactive, often referred to as medicinal hemp), and *C. sativa* subspecies ruderalis (wild hemp).[1,2]

The hemp plant contains a wide range of phytochemicals, including amino acids, fatty acids, steroids, phytocannabinoids, terpenes, and phenolic compounds. Their concentrations vary depending on both plant-related factors (e.g., tissue type, subspecies, age) and environmental conditions (e.g., temperature, humidity, light). Among these compounds, Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) have been studied extensively for their pharmacological properties.[1-3]

The medicinal use of cannabis dates back to ancient times. Early Chinese and Indian records describe its hypnotic, analgesic, and anxiolytic properties as early as the pre-Christian era. In Europe and North America, the plant was mainly used for fiber production until the 19th century, when its psychoactive properties were rediscovered. Beyond its role as a recreational drug, cannabis was also employed in the treatment of insomnia, pain, asthma, and several other conditions, including depression.[2-4]

Currently, cannabis is the third-most widely used psychoactive substance worldwide, after alcohol and tobacco. Its narcotic effects, primarily attributed to the high levels of THC, led to prohibitions on production in several countries. However, in recent years, cannabis has regained importance, especially for industrial applications. Meanwhile, medical interest in the plant has increased owing to its diverse pharmacological effects and its impact on multiple physiological systems in the human body.[2]

Debates over the legal, ethical, and social implications of cannabis have persisted for more than a century now. In recent decades, the prescription of cannabinoid-based therapies by physicians has increased worldwide, particularly in the United States, for conditions such as chronic pain and psychiatric disorders.[5]

Cannabinoids exert their effects primarily through cannabinoid receptors, the most abundant G-protein-coupled receptors in humans. Until date, two main receptor subtypes have been identified: CB1 and CB2. CB1 receptors are distributed throughout the central nervous system, particularly in the cortex, basal ganglia, hippocampus, and cerebellum, where they are predominantly localized presynaptically on γ-aminobutyric acid (GABAergic) neurons. The activation of CB1 inhibits adenylate cyclase, thereby reducing cyclic adenosine monophosphate production. Beyond cannabinoid receptors, cannabinoids also interact with other receptors and ion channels via G-protein binding, producing different physiological effects depending on their localization. CB2 receptors, on the other hand, are widely expressed in immune cells, lymphoid tissues, neutrophils, and macrophages. They play a central role in various pathophysiological processes, including inflammation, cancer, and neurodegenerative disorders.[5-8]

The bioavailability of cannabinoids depends largely on the route of administration, with the fastest absorption occurring via inhalation or ingestion. Metabolism primarily involves cytochrome P450 enzymes. Their major pharmacological effects include the following:[8]

- Psychoactive effects such as euphoria and altered sensory perception
- Risk of dependence
- Modulation of cognitive function and appetite
- Both antiepileptic and proepileptic effects
- Analgesic and muscle-relaxant properties
- Anti-inflammatory and antiemetic effects
- Immunomodulatory actions (via CB2 receptors, TRP channels, GPR55, serotonin receptors)
- Inhibition of glutamate release from excitatory neurons and cholinergic neurons, as well as effects on GABAergic interneurons
- Inhibition of voltage-gated Ca^{2+} channels and increased K^{+} channel activity, leading to suppression of presynaptic transmission.

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Available Online Date: • **DOI:** 10.4274/balkanmedj.galenos.2025.2025.290925

Available at www.balkanmedicaljournal.org

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Cite this article as: Karal Y. Cannabinoids: Medicine or Poison. Balkan Med J.;

Several cannabinoid-based products have received regulatory approval for specific indications in limited countries. Dronabinol, a synthetic form of THC, has been approved by the Food and Drug Administration (FDA) for chemotherapy-induced nausea and vomiting, oral mucositis, and as an appetite stimulant in patients with human ımmunodeficiency virus/acquired ımmune deficiency syndrome. Nabilone, another FDA-approved synthetic THC analogue, is prescribed for chemotherapy-induced nausea and vomiting, diabetes-related neuropathic pain, fibromyalgia, rheumatoid arthritis-related pain, spasticity in multiple sclerosis, sleep regulation and refractory epilepsy.[8-13] Despite these therapeutic advances, the long-term safety profile of cannabinoids remains unclear.

Increasing use during childhood and adolescence has raised concerns regarding its effects on brain development. The endocannabinoid system plays crucial roles in neurodevelopment, including synaptic pruning and neural plasticity. Some studies suggest that CBD may be beneficial in treating refractory epilepsy in children and adults. However, significant challenges remain, including limited knowledge of its pharmacodynamics, inconsistent dose-response data, insufficient evidence on monotherapy, lack of seizure-freedom outcomes with long-term use, potential drug-drug interactions, adverse effects, and absence of standardized therapeutic guidelines. Moreover, the variability in formulation and composition across CBD products highlights the importance of distinguishing FDA-approved medications from unregulated preparations.[8,14]

One of the most pressing concerns regarding cannabinoid use is exposure during critical neurodevelopmental periods. Prenatal THC exposure can reduce CB1 receptor expression, leading to abnormal neural connectivity. THC use during adolescence is particularly concerning, as this period is characterized by synaptic pruning and high plasticity in the brain regions associated with emotion and executive function. The disruption of endocannabinoid signaling, particularly in the temporal dynamics of anandamide and 2-arachidonoylglycerol, may underlie these effects. Clinically, adolescent THC use has been associated with increased risk of emotional disorders, particularly among females, and with a higher incidence of schizophrenia in males who initiate heavy use before the age of 18 years.[15] Although most research has focused on THC, CBD exposure during these critical developmental windows also warrants further investigation for potential adverse effects.

Overall, there is a pressing need for further research to clarify the long-term impact of cannabinoids on the developing brain, not only in fetuses but also in adolescents and young adults.

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