Cannabinoids: THC and CBD

Key differences, scientific evidence and regulatory context

THC - PSYCHOACTIVE AND INTOXICATING
A partial agonist of the CB1 and CB2 receptors. It affects perception, memory, appetite and pain processing.

Pertwee, 2008 [2]

CBD – NON INTOXICATING
It has low affinity for CB1/CB2 and acts through several molecular targets. The full mechanism has not yet been clarified.
Peng et al., 2022 [4]; EMA [9]

INTRODUCTION

The *Cannabis sativa L.* plant synthesises more than 100 structurally characterised phytocannabinoids. Two of them remain the principal object of pharmacological research: Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). The isolation, structural determination and partial synthesis of THC were achieved in 1964 by Gaoni and Mechoulam, opening the way for modern research on phytocannabinoids.

The endocannabinoid system constitutes a lipid signalling network mediated by the G protein-coupled receptors CB1 and CB2, their endogenous ligands anandamide and 2-arachidonoylglycerol (2-AG), and the biosynthetic and catabolic enzymes (FAAH, MAGL) that regulate the duration of the signal. CB1 predominates in the central nervous system, where it mediates retrograde synaptic transmission, while CB2 shows a higher density in the compartments of the immune system, without being confined exclusively to them. THC and CBD interact divergently with this system, which explains their pharmacodynamic differences.

THC (Δ9-tetrahydrocannabinol)

Mechanism of action. THC acts mainly as a partial agonist of the CB1 and CB2 receptors. Its effect depends on the distribution and density of the receptors, on the activity of the endocannabinoid system and on the dose. Activation of the CB1 receptors in the central nervous system is associated with the psychoactive and intoxicating effects of THC.

What does the clinical evidence show? The systematic review and meta-analysis by Whiting et al. (2015), which included 79 randomised clinical trials with 6,462 participants, found moderate-quality evidence for the use of cannabinoids in chronic pain and spasticity. For chemotherapy-induced nausea and vomiting, the evidence was assessed as being of low quality.

IMPORTANT QUALIFICATION

This review did not assess isolated THC alone. It included different formulations and products, among them THC preparations, THC/CBD combinations and synthetic cannabinoids. Consequently, the results should not automatically be attributed to THC alone.

Adverse effects. Products containing THC may be associated with dizziness, drowsiness, disturbances of attention and memory, euphoria, anxiety or changes in perception. The risk depends on the dose, the route of administration, the composition of the product and individual characteristics. In the review by Whiting et al., cannabinoids were associated with an increased risk of short-term adverse effects.

Regulatory status. Because of its intoxicating effect and its potential for misuse, THC and the products containing it are subject to special controls in most jurisdictions. In Albania, activities relating to *cannabis* for medical and industrial purposes are regulated by Law no. 61/2023, alongside the specific legislation on narcotic drugs and psychotropic substances.

CBD (cannabidiol)

Mechanism of action. Unlike THC, CBD has a low direct affinity for the CB1 and CB2 receptors and does not produce the characteristic intoxicating effect of THC. The scientific literature describes possible interactions with several molecular targets, including TRPV1, PPARγ, 5-HT1A and GPR55. However, its full pharmacological mechanism has not been definitively clarified; the EMA likewise considers the antiepileptic mechanism of CBD not to be fully understood.

The most consolidated evidence: rare epilepsies. Randomised clinical trials have assessed purified pharmaceutical CBD as an add-on therapy in patients with *Lennox-Gastaut* syndrome and *Dravet* syndrome. In the Lennox-Gastaut trials, the median reduction in drop seizures was approximately 37-44% with CBD, compared with 17-22% with placebo. In the Dravet trials, the reduction in convulsive seizures was approximately 39-49% with CBD, compared with 13-27% with placebo.

WHAT HAS BEEN AUTHORISED IN THE EU?

Epidyolex® is authorised in the European Union for the adjunctive treatment of seizures associated with Lennox-Gastaut or Dravet syndrome in patients aged 2 years and above. It is also authorised as an adjunctive therapy for tuberous sclerosis complex in patients aged 2 years and above. This authorisation refers to a standardised pharmaceutical medicine and cannot be generalised to every commercial product containing CBD.

Other fields of research. CBD is also being studied in fields such as anxiety, sleep, pain and certain neuropsychiatric disorders. However, for these uses the evidence remains heterogeneous and generally less consolidated than for the rare epilepsies covered by the Epidyolex® authorisation. Preliminary results should not be presented as proof of confirmed clinical efficacy.

Safety and monitoring. CBD may cause adverse effects and interactions with other medicines. For the authorised pharmaceutical formulation, drowsiness, decreased appetite, diarrhoea and increased

liver enzymes, among others, have been reported. Therapeutic use requires prescription, a standardised dose and clinical monitoring in accordance with the approved product information.

Regulatory status. The regulatory status of a product containing CBD is not determined by the designation "CBD" alone. It depends on the THC content, the origin of the material, the intended use, the claims made, the product category, for example a medicine, a cosmetic product or a food product, and the legislation of the relevant jurisdiction. For this reason, "non-intoxicating" does not automatically mean *"uncontrolled"* or *"marketable without conditions"*.

KEY DIFFERENCES: THC AND CBD

Characteristic	THC	CBD
Intoxicating effect	Yes	No
Main interaction	Partial agonist of CB1/CB2	Low affinity for CB1/CB2; acts through several targets
Clinical evidence	From various cannabinoid formulations; not isolated THC alone	More consolidated for LGS, Dravet and TSC with a pharmaceutical formulation
Possible effects	Changes in perception, attention, memory and coordination	Drowsiness, diarrhoea, decreased appetite, increased liver enzymes; interactions with medicines
Regulatory treatment	Controlled substance; special requirements	Depends on the THC content, the intended use, the product category and the jurisdiction

LGS: Lennox-Gastaut syndrome; TSC: tuberous sclerosis complex.

"Entourage effect"

The term "entourage effect" was first used by Ben-Shabat et al. in 1998, in the context of interactions between endocannabinoids and related constituents. In 2011, Ethan Russo examined the hypothesis that the plant's phytocannabinoids and terpenes may interact synergistically. Although this hypothesis is of scientific interest, its clinical relevance has not been fully confirmed by large, well-controlled, randomised trials. For this reason, the "entourage effect" should not be presented as a proven therapeutic mechanism.

REGULATORY CONTEXT IN ALBANIA

Research on THC and CBD has scientific and pharmaceutical value, but it does not imply availability for personal consumption in Albania. Under Article 29, point 2, of Law no. 61/2023, by-products and products manufactured in the country are intended solely for export. Article 5 prohibits the sale, distribution, acquisition and consumption, within the territory of the Republic of Albania, of by-products or final products for medical purposes.

The National Agency for *Cannabis* Control supervises, controls and inspects activities in the field of cultivation, processing and production, and monitors the implementation of the legal framework. Technical requirements apply according to the stage and nature of the activity:

- cultivation and primary processing - in accordance with the EU-GACP requirements
- quality control and analysis of dried flower - in accordance with national acts, the applicable methods and, where applicable, the "*Cannabis* flower" monograph 3028 of the European Pharmacopoeia;
- stages constituting pharmaceutical manufacturing - in accordance with the applicable EU-GMP requirements;
- traceability, sampling and laboratory analysis

THC and CBD have different pharmacological and regulatory profiles. Evidence for one constituent, dose or standardised formulation should not be generalised to all *cannabis* products. Quality, composition, traceability and laboratory control are essential to any assessment of safety and compliance.

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