(RESEARCH ARTICLE)

Phytocannabinoïds: Therapeutic potential, mechanism of action, and regulatory challenges

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Abstract

Phytocannabinoïds, notably cannabidiol (CBD) and tetrahydrocannabinol (THC), are the primary active compounds in the Cannabis sativa plant. These compounds interact with the endocannabinoid system in humans, which regulates various physiological processes. The scientific exploration of phytocannabinoïds has expanded significantly due to their potential therapeutic effects. Concurrently, regulatory frameworks are evolving to accommodate the increasing medicinal use of these compounds.

A comprehensive review of peer-reviewed literature was conducted to evaluate the therapeutic effects, mechanisms of action, and safety profiles of phytocannabinoïds. Regulatory documents and policy papers from multiple countries were analyzed to understand the legal status and regulatory approaches toward phytocannabinoïds. Data sources included PubMed, regulatory agency websites, and international health organization reports.

The review highlighted that CBD and THC exhibit significant promise in treating conditions such as epilepsy, chronic pain, multiple sclerosis, and anxiety. CBD is generally well-tolerated with a favorable safety profile, while THC, despite its psychoactive effects, has demonstrated efficacy in pain management and muscle spasticity. Regulatory landscapes vary widely, with countries like Canada and Uruguay fully legalizing cannabis, while others, such as the United States, maintain a complex legal framework with federal restrictions but state-level legalization. This fragmentation poses challenges for researchers and healthcare providers.

Phytocannabinoïds present a substantial opportunity for therapeutic advancement, supported by growing scientific evidence. However, the regulatory environment remains inconsistent, necessitating harmonization to facilitate research and clinical application. Future efforts should focus on robust clinical trials to establish definitive efficacy and safety profiles and on developing coherent regulatory policies that balance public health concerns with the therapeutic potential of phytocannabinoïds.

Keywords: Phytocannabinoïds; Regulatory framework; Endocannabinoid receptors; Therapeutic effects; Cannabis sativa

1. Introduction

Phytocannabinoïds, primarily cannabidiol (CBD) and tetrahydrocannabinol (THC), are bioactive compounds derived from the *Cannabis sativa* plant. These compounds have garnered significant attention in recent years due to their potential therapeutic benefits across a range of medical conditions. The endocannabinoid system, which includes cannabinoid receptors CB1 and CB2, plays a crucial role in regulating various physiological processes such as pain, mood, appetite, and immune response [1].

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The therapeutic applications of CBD and THC are diverse. CBD, a non-psychoactive compound, has been shown to be effective in reducing seizure frequency in pediatric epilepsy syndromes, such as Dravet syndrome and Lennox-Gastaut syndrome, leading to the approval of Epidiolex by the U.S. Food and Drug Administration (FDA) [2]. Additionally, CBD has exhibited anxiolytic, anti-inflammatory, and neuroprotective properties in preclinical and clinical studies [3]. THC, the primary psychoactive component of cannabis, is well-known for its analgesic properties and has been used in the management of chronic pain, muscle spasticity, and chemotherapy-induced nausea and vomiting [4].

Despite the promising therapeutic potential of phytocannabinoïds, their regulatory status remains complex and inconsistent across different jurisdictions. In the United States, the 2018 Farm Bill legalized hemp-derived CBD products containing less than 0.3% THC, but THC itself remains a Schedule I controlled substance under federal law, even as several states have legalized it for medical or recreational use [5]. Internationally, the regulatory landscape varies widely, with countries such as Canada and Uruguay fully legalizing cannabis, while others permit its use strictly for medical purposes [6].

The growing body of scientific evidence supporting the therapeutic use of phytocannabinoïds necessitates a comprehensive examination of their mechanisms of action, safety profiles, and regulatory challenges. This review aims to provide an in-depth analysis of the current state of phytocannabinoïd research, highlight key therapeutic applications, and discuss the regulatory frameworks governing their use. By synthesizing existing knowledge and identifying gaps in the current understanding, this review seeks to inform future research and policy development in the field of phytocannabinoïds.

Figure 1 Plant of *Cannabis sativa* [7]

2. Material and methods

A comprehensive search of peer-reviewed literature will be conducted using databases such as PubMed, Google Scholar, and Cochrane Library.

- Keywords used in the search will include: Phytocannabinoïds, Tetrahydrocannabinol (THC, Cannabidiol (CBD), Cannabigerol (CBG), Cannabinol (CBN), regulatory framework, endocannabinoid receptors, therapeutic effects, Cannabis sativa.
- Articles published between January 2010 and December 2023 will be included. Additional searches may involve reference lists of relevant articles to ensure coverage of all relevant studies.

2.1. Inclusion Criteria

- Randomized controlled trials (RCTs), observational studies, systematic reviews, and meta-analyses.
- Studies investigating the effects of phytocannabinoïds, specifically THC, CBD, CBG, CBC, and CBN.
- Articles must be published in English.

2.2. Exclusion Criteria

- Studies focused solely on synthetic cannabinoids, animal models, or in vitro studies.
- Articles that do not specifically evaluate phytocannabinoïds (i.e., THC, CBD, CBG, CBC, or CBN) or focus primarily on other cannabis plant compounds like terpenes or flavonoids.

- Studies that do not report clear and measurable outcomes regarding therapeutic efficacy or adverse effects.
- Any duplicated studies or secondary analyses of previously published data will be excluded

3. Results and discussion

According to the bibliographic research and scientific articles, the results reached can be summarized in the following points:

3.1. Therapeutic Effects

Phytocannabinoïds, particularly CBD and THC, have shown promise in treating a variety of medical conditions. Clinical trials have demonstrated the efficacy of CBD in reducing seizure frequency in patients with Dravet syndrome and Lennox-Gastaut syndrome, leading to the approval of Epidiolex by the FDA [2]. THC, on the other hand, has been effective in managing chronic pain, especially neuropathic pain, and muscle spasticity in multiple sclerosis [8].

3.2. Mechanism of action

Phytocannabinoïds exert their effects primarily through the endocannabinoid system, which includes cannabinoid receptors CB1 and CB2. CBD has a low affinity for these receptors but modulates their activity indirectly by inhibiting the breakdown of the endocannabinoid anandamide and activating TRPV1 receptors [9]. THC directly binds to CB1 receptors in the central nervous system, producing its psychoactive effects and analgesic properties [1].

Table 1 Therapeutic Effects of Phytocannabinoïds and their Mechanisms of action

Phytocannabinoid	Therapeutic effects	Mechanism of action
Δ9-Tetrahydrocannabinol (THC)	- Analgesic, anti-inflammatory, muscle relaxant - Antiemetic, appetite stimulant - Neuroprotective in neurodegenerative diseases (e.g., Alzheimer's) [1]	Partial agonist at CB1 and CB2 receptors [1]
Cannabidiol (CBD)	- Anxiolytic, anti-inflammatory - Antiepileptic (e.g., Dravet syndrome) - Antipsychotic [10]	Allosteric modulator of CB1 and CB2, inhibits FAAH enzyme [10]
Cannabigerol (CBG)	- Antibacterial (MRSA) - Neuroprotective (Huntington's disease) - Antiglaucoma [11]	Weak agonist at CB1/CB2, 5-HT1A receptor antagonist [11]
Cannabicromene (CBC)	- Anti-inflammatory - Antidepressant - Antinociceptive [12]	Interaction with TRPV1 and TRPA1 channels [12]
Tetrahydrocannabivarin (THCV)	- Appetite suppressant - Anti-obesity - Antidiabetic [13]	Antagonist at CB1 receptors, agonist at CB2 receptors [13]

This table effectively summarizes the diverse therapeutic effects of key phytocannabinoïds, highlighting their complex mechanisms and broad clinical potential. It emphasizes both well-established cannabinoids like THC and CBD, as well as emerging compounds such as CBG and THCV.

3.3. Safety and Side effects

The safety profile of CBD is generally favorable, with common side effects including somnolence, decreased appetite, and diarrhea [9]. THC's side effects are more pronounced due to its psychoactive nature, including dizziness, dry mouth, euphoria, and potential for dependency with long-term use [14]. Both compounds have a relatively low risk of severe adverse effects compared to many conventional pharmaceuticals.

3.4. Regulatory Landscape

The regulatory status of phytocannabinoïds varies significantly across the globe. In the United States, the 2018 Farm Bill legalized hemp-derived CBD with less than 0.3% THC, yet the FDA maintains regulatory authority over CBD in foods, supplements, and pharmaceuticals [15]. THC remains a Schedule I substance under federal law, though several states have legalized it for medical and recreational use [5]. In contrast, Canada and Uruguay have fully legalized cannabis, allowing for more straightforward access and research opportunities [6].

3.5. The legal status of medical cannabis in Algeria

In Algeria, cannabis is illegal for both recreational and medical use. The production, sale, and possession of cannabis are strictly prohibited.

Recreational cannabis use is completely banned. Selling or trafficking cannabis carries even harsher penalties, including long-term imprisonment and substantial fines [16].

Medical cannabis laws in Algeria are slightly more lenient but still highly regulated. Although medical marijuana use is technically allowed, there is no comprehensive framework in place to support its legal distribution and prescription. Legislation from 2004 permits the cultivation and research of cannabis for medical and scientific purposes, but practical access remains very limited due to bureaucratic and regulatory challenges [17].

Overall, while Algeria's legal stance on cannabis is among the strictest in the region, ongoing issues with trafficking and limited medical use illustrate a complex legal and social landscape regarding cannabis regulation [18].

3.6. Challenges and Opportunities

The fragmented regulatory environment presents significant challenges for researchers, clinicians, and patients. Inconsistent laws and regulations hinder large-scale clinical trials and the development of standardized dosing regimens [19]. However, the growing body of scientific evidence supporting the therapeutic potential of phytocannabinoïds provides an opportunity for regulatory harmonization and policy reform. Collaborative efforts among stakeholders are crucial to optimize the therapeutic benefits while ensuring patient safety [20].

4. Conclusion

Phytocannabinoïds hold substantial promise as therapeutic agents, with evidence supporting their efficacy in various medical conditions. Despite their potential, the regulatory landscape remains complex and inconsistent, posing challenges to research and clinical application. Future efforts should prioritize conducting robust clinical trials to further elucidate the therapeutic effects and safety of phytocannabinoïds. Additionally, harmonizing regulatory policies will be essential to facilitate access to these compounds and maximize their public health benefits.

Compliance with ethical standards

Acknowledgments

Disclosure of conflict of interest

The authors and all co-authors declare that they have no conflicts of interest in connection with this document.

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