

Phytocannabinoids: Unlocking the Therapeutic Potential

Gogula Priya, Chinthaginjala Haranath*, Donnepati Pradeep Sai, Konda Sai Megha, Sugur Samhitha, Vallapureddy Vasanthi, Kopparapu Maddi Venkata Ramu, Talapula Santhosh Kumar, Lingadahalli Bilwa Malini, Kotra Mounika

Department of Pharmaceutics, Raghavendra Institute of Pharmaceutical Education and Research (RIPER)-Autonomous, Ananthapuramu, Andhra Pradesh, INDIA.

ABSTRACT

Cannabis sativa is the primary source of phytocannabinoids, which are meroterpenoids with a resorcinol core that are also present in other plant species such as *Helichrysum* and *Echinacea*. There are over more than 100 phytocannabinoids known to exist, delta-9-tetrahydrocannabinol (Δ^9 -THC), Cannabidiol (CBD) and Cannabigerol (CBG) are the most commonly used. Based on lead structures, these compounds are categorized into eleven major chemical classes. The effects of phytocannabinoids on endocannabinoid systems in the human brain occur primarily through cannabinoid receptors CB1 and CB2. CB1 receptors are predominantly located in the central nervous system, whereas CB2 receptors are predominantly located in the immune system. The entourage effect is a therapeutic effect produced by the combination of phytocannabinoid and endocannabinoid. Hydrodistillation, hydrodynamic extraction, pressurized hot water extraction, enzyme-assisted extraction, focused ultrasound extraction, Soxhlet extraction, dynamic maceration, supercritical fluid extraction, ultrasound-assisted extraction and freeze-drying are among the methods applied to extract phytocannabinoids from plant material. Each method possesses advantages in terms of active component preservation, yield, and selectivity. Phytocannabinoids are weakly soluble in water but highly lipophilic and therefore exhibit less oral bioavailability. They are extensively metabolized in the liver mainly by cytochrome P450 enzymes and quickly spread into organs with good vascularization. The administration route influences bioavailability and absorption. Drugs like Sativex for multiple sclerosis and Epidiolex for epilepsy have been approved in several countries. In India, use and production of *Cannabis sativa* are illegal under the Narcotic Drugs and Psychotropic Substances Act, 1985, except for research or certain plant parts like bhang.

Keywords: Bioavailability, *Cannabis sativa*, Endocannabinoid, Phytocannabinoid.

Correspondence:

Dr. Chinthaginjala Haranath

Professor and Head, Department of Pharmaceutics, Raghavendra Institute of Pharmaceutical Education and Research (RIPER)-Autonomous, Ananthapuramu-515721, Andhra Pradesh, INDIA.
Email: haranathriper@gmail.com

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INTRODUCTION

Phytocannabinoid is a term for meroterpenoids that contain a resorcinol core and are generally congruently surrounded by an isoprenyl, alkyl, or aralkyl para-positioned side chain (Gulck & Moller, 2020). *Cannabis sativa* is also the main source of phytocannabinoids, which are a class of plant secondary metabolites which can also be found in the plants *Echinacea purpurea*, *Echinacea angustifolia*, *Echinacea pallida*, *Acmella oleracea*, *Helichrysum umbraculigerum*, and *Radula marginata*. (Govindarajan *et al.*, 2023). The human and animal endocannabinoid systems are able to interact with phytocannabinoids derived from the plant. Over 100 phytocannabinoids present in plants of cannabis, the three most prominent ones are CBD, CBG, and delta-9-THC (Rezende *et*

al., 2023). The "lead" compound is employed to identify each of the eleven chemical classes into which phytocannabinoids are conventionally divided: Δ^8 -trans-tetrahydrocannabinol (Δ^8 -THC), a number of phytocannabinoids, Cannabichromene (CBC), Cannabidiol (CBD), Cannabielsoin (CBE), Cannabigerol (CBG), cannabicyclol (CBL), Cannabinol (CBN), Cannabinodiol (CBND), and Cannabitrinol (CBT) (Blebea *et al.*, 2024). Cannabinoids can be identified in three categories. First, endocannabinoids are compounds that are naturally occurring within plants. Second, synthetic cannabinoids are chemicals that can produce effects of cannabinoids but are chemically synthesized. Lastly, phytocannabinoids are compounds that are naturally occurring within plants (Rathod & Agrawal, 2024). Cannabinoid receptors (CBx) are members of the endocannabinoid system, and these are the receptors which the human brain interacts with phytocannabinoids. The endocannabinoid system, or more specifically the endogenous cannabinergic system, was biologically observed through preliminary research based on the potential medical benefits of *C. sativa* (Morales & Reggio, 2017). Furthermore, studies have confirmed that the central nervous system expresses CB2 receptors. Other receptor channels



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are associated with ECS signaling in addition to CB1 and CB2 receptors (Martinez Ramirez *et al.*, 2023). GPR55 and GPR18 are specifically linked to phytocannabinoid modulation, while staying in the GPCR domain. Controlling a number of biological processes requires the ECS, a complex signaling system (Farrelly *et al.*, 2021). On the basis of their relationship with the cannabinoid receptors (CB1 and CB2), phytocannabinoids pharmacological modulation presents a viable therapeutic option due to the intricate relationships and functions within the ECS. Terpenes and phytocannabinoids synergistically contribute to an effect referred to as the "entourage effect" where the summation effect of these two products is more than the sum of the contributions of each individually (Russo *et al.*, 2011). The Biopharmaceutics Classification System classifies these phytocannabinoids as class II drugs because of its very poor intestinal absorption (Reddy *et al.*, 2023). Furthermore, because of their high lipophilicity, the medications can be swiftly transported to the liver, where a range of Cytochrome P450 (CYP) complex enzymes primarily breakdown them (Zendulka *et al.*, 2016). Cannabis use in India is currently governed by the Narcotic Drugs and Psychotropic Substances Act (NDPS) of 1985, which forbids its production, sale, and possession in the forms of ganja (flowering or fruiting tops), hashish (liquid), and charas (resin), but not in the form of bhang (i.e. leaves or seeds).

Search Strategy

A comprehensive literature search was conducted to identify relevant studies on the medicinal value of phytocannabinoids from *Cannabis sativa* and related plants. Electronic databases including PubMed, Scopus, Web of Science, and Google Scholar were systematically searched from inception to latest.

Soxhlet Extraction

A filter bag holding roughly 15 g of the substance was weighed inside the cylindrical section of the Soxhlet apparatus. The solvent was then heated to 180 mL to produce a reflux. The solvent was extracted for 240 min at a temperature higher than its boiling point, and then it was extracted using a vacuum rotavapor at 40°C. Until it was analyzed, the extract was kept at -20°C in the freezer. Ethanol yielded the highest amounts of cannabinoids in a study that compared different kinds of organic solvents for cannabis extractions using the Soxhlet apparatus (Dussy *et al.*, 2005).

Supercritical Fluid Extraction (SFE)

The extractor utilized a water bath to keep the temperature constant while containing around 15 g of powdered sample material. A high-pressure pump was then used to add the CO₂ from the pressurized tank to the extractor and keep the flow to the extractor constant at 2.5 mL/min. The extract was collected from the extractor and sample tube at 15°C and room pressure. It took 180 min to complete the extraction, and was kept in a freezer

at -20°C until the analysis. CO₂ is a strongly adjustable solvent that can be used to extract unique compounds from plants at different pressures and temperatures, unlike butane or alcohol (Anwar *et al.*, 2013).

Hydrodistillation

The hydro-distillation process was performed with 30 g samples of entire flowers. A 1000 mL round-bottom flask was filled with each sample, and then 600 mL of Milli-Q water is added. Once on a heating mantle, the sample was connected to a distilling apparatus. After bringing the samples to a boil, a total of 60 min being cooled to a medium temperature. Out of the discharge valve, oil was extracted from the distillation apparatus's return tube and placed in a 20 mL scintillation vial. To remove any remaining water, the oil was filtered through a glass pipette lined with a loosely packed layer of glass wool (Szalata *et al.*, 2022).

Hydrodynamic extraction system

As the first hydrodynamic extraction system in the world, PhytoXTM maximizes plant utilization, lowers processing costs, and boosts yields by processing whole, fresh, undried cannabis plants. It processes uses hydrodynamic forces and ultrasonication to directly dissolve down fresh cannabis flower after it has been frozen. This generates a nanoemulsion in an aqueous phase containing all of the terpenes, cannabinoids, and other oils present in the cannabis plant. Centrifugal separation converts the nanoemulsion into an efficient and highly bioavailable cannabis extract, which is then dried and vacuum-distilled at ambient temperature (Malabadi *et al.*, 2024).

Pressurised hot water Extraction (PLE)

Supercritical water can serve as an effective solvent in SFE, providing solvating power comparable to methanol and ethanol, although it requires very high temperature and pressure to remain supercritical. This method shows strong selectivity for extracting CBD over THC and CBN. The extraction sequence includes solute desorption, solvent penetration into the plant matrix, solute transfer into the solvent, and movement of the extract to the collection vial, similar to accelerated solvent extraction. In cannabis processing, PLE is typically performed at 100°C and 40 bar for about 15 min with n-hexane, but because Δ⁹-THCA has low solubility in n-hexane, both methanol and n-hexane extract Δ⁹-THC and CBN efficiently while failing to extract Δ⁹-THCA. Pressurized Hot Water Extraction (PHWE), essentially PLE using hot water, is particularly suitable for producing CBD-rich extracts while suppressing THC and CBN levels (Rozanc *et al.*, 2021).

Focused Ultrasound Extraction (FUSE)

In order to extract phytocannabinoids from herbal cannabis, the FUSE method uses a mixture of cyclohexane and isopropanol at a 1:1 (v/v) ratio and at ice-cold temperature, which can also prevent degradation of the compounds and loss of the solvent.

The extracts are centrifuged and filtered through a 0.45 μm nylon filter after extraction. Overall, the FUSE method shows slightly greater extraction efficiency than subcritical SFE based on the recovery of Δ^9 -THC, CBD, and CBN. FUSE can recover approximately 80% of phytocannabinoids in the first extraction, less than 40% from the third extraction of pure supercritical CO_2 , and 90% if co-solvent is used for initial extraction. However, sample preparation for the laboratory analysis with flowers utilized the SFE method because it separates the terpenes from the phytocannabinoids, which minimizes matrix effects (Stefkov *et al.*, 2022).

CHARACTERIZATION

GC- Based methods

The sensitivity, speed, reproducibility, and robustness of phytocannabinoid profiling render it applicable to the use in plant material and biological matrices. For phytocannabinoid profiling purposes, such as for the determination of the 9-THC/CBD ratio and the detection of the principal phytocannabinoids (9-THC, CBD, and CBN), were done using GC methods. Additionally, residual solvent analysis, pesticide screening, and terpene profiling are performed using this analytical platform (Cardenia *et al.*, 2018).

TLC and HPTLC methods

HPTLC techniques are the result of recent developments in TLC. For cannabis profiling, such accurate methods may be superior to both HPLC and GC techniques. These advantages include the capacity to analyze multiple samples at once, which results in lower operating costs and analysis runtime. Because color determination is the basis for qualitative evaluation of cannabinoid presence during HPTLC analysis, analysts frequently make incorrect conclusions. When detecting 9-THC, CBD, CBN, and CBG in cannabis extracts, recent studies using the Sci-Chromus[®] software have introduced a system for naming and standardizing colors that greatly reduces the subjectivity involved in color identification (Fischedick *et al.*, 2009).

Vibrational spectroscopy methods

A combination of Near-Infrared (NIR) Spectroscopy and Multivariate Data Analysis has been used to assess cannabis samples, with the Analytic results generated from NIR showing a very good correlation with UHPLC-UV Analytic Results supporting the use of NIR in the routine assessment of cannabis plant materials and resins. NIR Dispersive Methods have also been developed to differentiate between legal and illegal cannabis by analyzing the phytocannabinoid profile. The structural assignment of cannabis substances using Nuclear Magnetic Resonance (NMR) Methods was much improved over previous methods, as isotopes provide distinct correlation information between chemical shifts and chemical environments as seen in

both 1H-1H COSY and Heteronuclear experiments through HMQC and HMBC. Researchers have all the information needed to create comprehensive 1H and 13C spectra of the most significant cannabis ingredients thanks to instruments including 1H NMR, 13C NMR, 1H-1H COSY NMR, HMQC NMR, and HMBC NMR. Flavonoids, Cannflavin A and Cannflavin B, Δ^9 -THC, Δ^9 -THCA, Δ^8 -THC, CBG, CBN, CBD, and CBDA are among these cannabis components (Choi *et al.*, 2004).

Scanning electron microscopy

The surface morphology can be estimated by using Scanning Electron Microscopy (SEM). Disperse the samples onto polished silicon (100) chips and dry under ambient conditions. To minimize charging effects and improve electrical conductivity, dry the samples and sputter-coat with a 5-6 nm thick iridium layer using a Leica EM ACE600 sputter coater. SEM images can be acquired using an FEI Nova NanoSEM 430 under appropriate accelerating voltage and vacuum conditions (Banerjee *et al.*, 2021).

Attenuated Total Reflectance - Fourier Transform Infrared Spectroscopy

It has been applied for quantifying CBN and CBD using a validated method designed for solid-state phytocannabinoid analysis. The procedure involves identifying characteristic wavelengths by comparing the reference spectra of pure cannabinoids with the spectra of different cannabis cultivars. For CBN, the IR bands at 910-872 cm^{-1} and at 1001 cm^{-1} were identified as unique markers and used for its quantification, while the 1036 cm^{-1} band served as the specific wavelength for CBD determination (Mandrioli *et al.*, 2024).

Microwave ageing

Experimental evaluation of different conditions with respect to microwave oven power (600-1000 W) and treatment time (1-600 sec) has been conducted in order to determine the application of microwaves towards accelerated cannabis ageing. ATR-FTIR measurements are taken every 120 sec. In an open, heat-resistant borosilicate glass vessel, 100 ml of ultrapure water was placed near the sample to provide the humid environment needed to start accelerated ageing protocols (humidity not monitored) (Radoiu *et al.*, 2020).

Antioxidant Assay

Using the DPPH (2,2-Diphenyl-Picryl-Hydrazil) assay, we evaluated extracts based on their capacity to eliminate free radicals. Using 200 μL of the DPPH solution (0.025 g/L) and 10 mL of the extract solution prepared in methanol (at a concentration of 1 mg/mL) was placed into a vial containing a known concentration of pure methanol. A negative control for the assay contained 200 μL of DPPH solution plus 10 μL of methanol. Absorbance readings were taken at the end of an incubation time period of

15 min at room temperature. A blank was utilized as a reference to compare against. A commercially available and standardised antioxidant, ascorbic acid, had been tested in addition to the extracts under these same conditions as well and was tested as well to compare against. Inhibitory activity against DPPH free radicals was calculated in percent to determine antioxidant activity of the extracts (Elayaraja *et al.* 2018).

Cell Viability Assay

In this study, cell viability was evaluated through the use of a cell viability assay. A total of 10,000 cells from each of the different cell lines tested (e.g. THC, CBD, CAN1-7) were seeded in 96-well plates and allowed to attach for 24 hr before treatment. On day 2, the cells were treated with different concentrations of each of the Cannabis extracts (CAN1-7) along with THC and CBD for 48 hr. Following treatment, the cells were treated with MTT reagent for 4 hr at 37°C to determine the amount of viable cell growth and viability after treatment (Blal *et al.*, 2023).

REVIEW OF LITERATURE

Pharmacokinetics

Absorption

The bioavailability of cannabinoids after oral administration is very poor and can range from 6-20% for THC and between 6-19% for CBD. In our setting, the bioavailability was slightly improved compared to other methods of administration. The decreased blood concentrations and AUC can be accounted for in comparison to equivalent doses of CBD (for example: 5 mg), which included a prolonged absorption time as well as comparatively shorter half-life with THC. For human trials, CBD has an oral bioavailability of about 6% and an inhalation bioavailability from 11% to 45% (Hlozek *et al.*, 2017).

Distribution

Cannabinoids are readily distributed out of highly vascularized tissues (i.e., organs) to less vascular tissues over time. Factors that affect this distribution include: body size; body composition; disease states that change the permeability of the blood-tissue barrier. Following prolonged exposure, cannabinoids may be found in fat tissue because of the lipophilic characteristics of cannabinoids. CBD and THC have very large volumes of distributions. For example, after intravenous injection ($V_d\beta$), the volume of distribution was approximately 32 L/kg, while the volume of distribution following inhalation (V_{dss}) was approximately 3.4 L/kg (Lucas *et al.*, 2018).

Metabolism

Cannabis metabolizes differently according to how it is consumed. For example, when taken orally, the THC component will go through a process of first-pass metabolism (a process where drugs

get broken down before entering into the body's circulation) in the liver. In this case, THC gets broken down into 11-OH-THC which is an active metabolite that produces a "high" and then further gets converted to 11COO-THC which is a non-psychoactive version of THC. Approximately 20% of all metabolites created from cannabis use are expelled through urine and over 65% are removed from your body via bowel movements. Of these compounds, 80-90% are cleared within 5 days and the majority are converted to hydroxylated and carboxylated metabolites. In addition to route of consumption, the levels of cannabinoids will vary based on drug/active compound interaction with enzymes. For instance, drugs that induce the CYP3A4 enzyme during liver metabolism are expected to decrease levels of THC and CBD, etc. In contrast, drugs that inhibit CYP3A4 and CYP2C9 will typically raise levels of THC and CBD (Chayasirisobhon, 2020).

Elimination

According to a recently published population pharmacokinetic model, the terminal half-life (approximately 22 hr) of THC is reported as prolonged, while the first-order elimination or rapid distribution phase has a much shorter half-life (approximately 6 min). However, following an "equilibration phase," the rate of elimination begins to show an influence from the redistribution of the drug from the adipose tissue (fat) compartments into the bloodstream. For frequent cannabis users, this process occurs very slowly. Therefore, THC can be detected in their blood ($>1 \mu\text{g l}^{-1}$) for over 24 hr after their last cannabis use (Huestis *et al.*, 2005).

APPLICATIONS

Pain management

The ability of THC to produce analgesia through interactions with targets of CB1, CB2, and Gly receptors allows it to help relieve chronic pain. Pain and inflammation are reduced when the CB2 receptor is activated. Additionally, by acting as an agonist on the capsaicin receptor or vanilloid Transient Receptor Potential-1 (TRPV-1), CBD interacts with the Fatty-Acid Amide Hydrolase enzyme (FAAH), which hydrolyzes anandamide and prevents its absorption (Peng *et al.*, 2022).

Antimicrobial effects

CBD and Δ^9 -THC are effective agents for killing Streptococci and Gram-positive Staphylococci within the low concentration ranges of 1-5 $\mu\text{g/mL}$, while not being effective against Gram-negative bacteria. The resorcinolic core of CBD and Δ^9 -THC does not have any antimicrobial properties in isolation, which means that the antimicrobial properties are associated with the prenyl group (in the case of DCA and GFA) that is present in both substances. The prenyl groups provide a structure that is similar to the bioactive monoterpenoids (Appendino *et al.*, 2008).

Dermatology

In a mouse model, allergic inflammatory skin was increased when CB1 and CB2 were diminished by genetic loss or pharmacologic blockade, while pharmacologic stimulation of CB1 and CB2 or genetic ablation of the endocannabinoid-hydrolyzing enzyme Fatty Acid Amide Hydrolase (FAAH) reduced cutaneous contact hypersensitivity. Topical FAAH inhibitors decrease the inflammatory reaction on Toll-Like Receptor (TLR)-2 by elevating endocannabinoids and subsequently activating CB1 and CB2 in keratinocytes (Gaffal *et al.*, 2013).

Dementia

Phytocannabinoids significantly improved a range of neuropsychiatric symptoms in dementia patients, but other trials found no change. Reduced agitation and aggression, pain management, objective mood, and increased appetite are regularly observed indications of symptomatic benefit (Bahji *et al.*, 2020).

Antioxidant

The antioxidant benefits CBD offers are through either oxidative stress neutralizing free radicals (free radical chain reaction) or converting them into less reactive compounds, so CBD is considered an effective antioxidant and protects cells from oxidative stress damage. CBD's antioxidant properties come from its phenolic compound and the presence of hydroxyl groups on the aromatic ring of the phenolic compound. In addition, through maintaining optimal levels of essential trace mineral (zinc and selenium) CBD can also enhance the activity of antioxidant enzymes (Atalay *et al.*, 2019).

Huntington's disease

Treatment with CBG partially restored the dysregulated genes associated with Huntington's disease in these mice. There was also a moderate improvement in the anti-inflammatory peptide PPAR γ 's changed gene expression (Valdeolivas *et al.*, 2015).

Multiple Sclerosis

MS patients experienced improvement in pain and reduction in spasticity with oromucosal spray containing equal concentrations of THC and CBD. Several human studies have demonstrated that each combination was beneficial in decreasing spasticity in MS patients (Koehler *et al.*, 2014).

Anticancer

The anticancer potential of cannabinoids has been specifically defined with regard to the treatment of liver and pancreatic carcinoma cells with the primary form of cannabinoid, THC. Furthermore, the modulation of p8-induced mechanisms of autophagy appears to be directly associated to THC. Finally, it has been suggested that the anticancer activity of CBD may also involve interactions with numerous types of receptors including GPR55, TRPV1, and TRPM8 (Pagano *et al.*, 2021).

Epilepsy

Patients who have epilepsy are increasingly using cannabis. THC acts as an anticonvulsant in animal models, though it can also be proconvulsant in certain species CBD is the most researched molecule for treating epilepsy. Public interest in CBD-enriched oils has been excited by anecdotal reports of specific children with drug-resistant epilepsy who appear to respond incredibly to them (Onaivi *et al.*, 2020).

Parkinson's disease

CBD was found to have beneficial effects on patients. During the six weeks of oral administration of CBD to study participants, researchers determined that not only did the quality of life improve for PD patients, but also the REM Sleep Behaviour Disorder improved significantly (Jurga *et al.*, 2024).

Alzheimer's Disease

Pathogenesis and development are significantly influenced by A β accumulation and neuroinflammation. When microglial CB2 receptors are stimulated, native A β is removed from human brain tissue sections (Aso & Ferrer, 2016).

Table 1: List of patents for Phytocannabinoids.

Patent number	Description	Year
US 10624872	Apparatuses, methods, and systems for extraction, isolation and conversion of various cannabinoids, and modifications of whole-plant hemp extracts there with	2020
US 10413845	Processes for solvent extraction of cannabinoids, terpenes, and flavonoids from biomass	2019
US 10517911	Manufacturing methods, compositions, and medical applications of orally administered cannabis pharmaceuticals using representative/total/complete cannabis extractions (cannabis infused pills)	2019
US 09937218	Systems and methods for cannabinoid and terpene extraction and purification	2018
US11,241,413B2	Cannabinoid lozenge formulation	2022
US 8,790,719B2	Phytocannabinoids in the treatment of cancer	2014

Table 2: List of Marketed products of Phytocannabinoids.

Product name	Brand name	Formulation	Main phytocannabinoids	Approved country	Use
Epidiolex®	Epidyolex	Oral solution	CBD	US	Seizures
Sativex®	Nabiximols	Oromucosal spray	CBD, THC	UK	MS spasticity, neuropathic pain.
Dronabinol	Marinol syndros	Capsules, oral solution	THC	US	Chemotherapy Anoxeria in AIDS patients And treat nausea and vomiting.
Nabilone	Cesamet	Oral capsule	THC	Canada	Nausea and vomiting caused by cancer chemotherapy, fibromyalgia and movement disorders
Bedrocan	Bedrocan Bedropuur® Bedrolina® Bediol®	Galenic preparation	THC, CBD	Netherlands	Stimulating appetite in anorexic patients, Chronic Neuropathic Pain and Glaucoma.

The patents on phytocannabinoids and marketed products were represented in Tables 1 and 2 respectively.

FUTURE DIRECTIONS

Future research should studies must focus on novel nano-delivery platforms, including liposomes, niosomes, and targeted nanoparticles, to address the limited water solubility and suboptimal oral absorption of phytocannabinoids, thereby improving their pharmacokinetic profiles. Applying Quality by Design (QbD) frameworks alongside tools like Design Expert can refine these systems, achieving optimal particle dimensions, drug loading, and sustained release suited for epilepsy or persistent pain management. Large randomized clinical trials are essential to substantiate benefits in neurodegenerative disorders such as Alzheimer's and Parkinson's, while exploring synergistic entourage effects from combined phytocannabinoid profiles. Enhancing extraction standardization through techniques like supercritical CO₂ methods, coupled with precise analytics including HPTLC, NMR, and cryo-SEM, will promote uniform quality and pave the way for approvals expanding on therapies like Epidiolex and Sativex. Under India's NDPS regulations, academic-industry collaborations could drive targeted research on non-psychoactive compounds like CBD for antimicrobial and anti-inflammatory applications, paving the way for affordable, scalable production. Comprehensive long-term assessments of safety covering CYP450 metabolism and toxicity plus pharmacogenomics will support individualized treatments and broaden therapeutic availability.

CONCLUSION

Phytocannabinoids from *Cannabis sativa* offers significant therapeutic potential, acting mainly through the endocannabinoid system to modulate neurological and immune functions. The quality and consistency of cannabinoid products have increased due to advancements in extraction and analytical methods, and there is clinical evidence that supports their use in treating inflammation, pain, epilepsy, and neurodegenerative diseases. As evidenced by recent U.S. efforts to reschedule cannabis and the explosive growth of the global cannabis market, regulatory environments around the world differ, with changing policies reflecting a growing recognition of their medicinal value. Despite ongoing issues with standardization, bioavailability, and regulatory harmonization, phytocannabinoids are expected to become more important in contemporary medicine as research and technology progress.

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ABBREVIATIONS

CB1: Cannabinoid receptor 1; **CB2:** Cannabinoid receptor 2; **CBx:** Cannabinoid receptors; **Δ⁹THC:** 9-tetrahydrocannabinolic acid; **Δ⁸THC:** 8-trans-tetrahydrocannabinol; **CBDA:** Cannabidiolic acid; **CBC:** Cannabichromene; **CBE:** Cannabielsoin; **CBL:** Cannabicyclol; **CBN:** Cannabinol; **CBND:** Cannabinodiol; **CBT:**

Cannabitol; **GPR55**: G protein-coupled receptor 55; **GPR18**: G protein-coupled receptor 18; **NDPS**: Narcotic Drugs and Psychotropic Substances Act; **SFE**: Supercritical Fluid Extraction; **PHWE**: Pressurized Hot Water Extraction; **PLE**: Pressurised hot water extraction; **FUSE**: Focused Ultrasound Extraction; **GC**: Gas Chromatography; **TLC**: Thin-Layer Chromatography; **HPTLC**: High-Performance Thin-Layer Chromatography; **NIR**: Near-infrared Spectroscopy; **NMR**: Nuclear magnetic resonance; **COSY**: Correlation Spectroscopy; **HMQC**: Heteronuclear Multiple Quantum Coherence; **HMBC**: Heteronuclear Multiple Bond Correlation; **SEM**: Scanning Electron Microscopy; **FIB/SEM**: Focused Ion Beam/Scanning Electron Microscope; **ATR-FTIR**: Attenuated Total Reflectance-Fourier Transform Infrared Spectroscopy; **DPPH**: 2,2-diphenyl-picryl-hydrazil; **MTT**: Methylthiazol Tetrazolium; **AUC**: Area Under the Curve; **CYP**: Cytochrome P450; **Vd_β**: Volume of distribution (beta phase); **Vd_{ss}**: Volume of distribution (steady-state); **TRPV-1**: Transient Receptor Potential Vanilloid-1; **TRPM8**: Transient Receptor Potential Melastatin 8; **FAAH**: Fatty-acid amide hydrolase; **TLR-2**: Toll-like receptor 2; **A β** : Amyloid-beta; **MS**: Multiple Sclerosis; **BCS**: Biopharmaceutics Classification System; **HPLC**: High-Performance Liquid Chromatography; **PPAR γ** : Peroxisome proliferator-activated receptor gamma; **PD**: Parkinson's Disease; **REM**: Rapid Eye Movement; **QbD**: Quality by Design; **AIDS**: Acquired Immunodeficiency Syndrome.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Haranath Chinthaginjala, Conceptualized the work. Haranath Chinthaginjala, Priya Gogula contributed to extraction methods and patents. Donnepati Pradeep Sai, Konda Sai Megha, Sugur Samhitha contributed to characterization aspects. Vallapureddy Vasantha, Kopparapu Maddi Venkata Ramu, Talapula Santhosh Kumar, Lingadahalli Bilwa Malini, Kotra Mounika involved in literature collection, writing the pharmacokinetics and applications. All authors have read and agreed to the final version of the manuscript.

SUMMARY

This review article explores the medicinal value of phytocannabinoids from *Cannabis sativa* and related plants, emphasizing their therapeutic potential through interactions with the endocannabinoid system via CB1 and CB2 receptors. Key phytocannabinoids like Δ^9 -THC, CBD, and CBG are classified into 11 chemical classes, extracted using methods such as Soxhlet, supercritical fluid, and ultrasound-assisted techniques, and characterized by GC, HPTLC, NMR, and SEM. Phytocannabinoids exhibit poor oral bioavailability (6-20%) due to high lipophilicity and first-pass metabolism by cytochrome

P450 enzymes, with rapid distribution to vascularized tissues and prolonged elimination influenced by adipose storage. Applications include pain management, antimicrobial effects, dermatology, dementia, antioxidant activity, Huntington's disease, multiple sclerosis, anticancer properties, epilepsy, Parkinson's, and Alzheimer's, supported by products like Sativex and approved patents.

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