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Review

Cannabis sativa L.: A Review on Traditional Uses, Botany, Phytochemistry, and Pharmacological Aspects

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Abstract

Medicinal and aromatic plants have been one of the most important sources of medicine since the dawn of human civilization. Indigenous communities have used products from these plants in different conditions throughout history. *Cannabis sativa* L. is one of the most widely employed herbaceous medicinal plants for textiles, and fibers, in medicine, as a source of food, animal food, animal bedding, and agriculture for seeds. This paper highlights the traditional applications, botany, phytochemistry, and pharmacological properties of *C. sativa*. Extensive database retrieval, such as Google Scholar, Semantic Scholar, ResearchGate, Academia.edu, PubMed, SciFinder, ChemSpider, CNKI, PubFacts was performed using the keywords "Hemp" and "Cannabis," as well as the scientific name of this plant species (*Cannabis sativa*). Besides, reviews of relevant textbooks, documents, and patents were also employed to collect sufficient information. This study revealed numerous pharmacological activities of *C. sativa* that could help with several health issues. Additionally, more than 565 bioactive constituents have been isolated and identified from diverse parts of *C. sativa*. This could help discover potential therapeutic effects and develop new medications to benefit human health.

Keywords: *Cannabis sativa* L.; Botany; Natural products; Phytochemistry; Phytopharmacology; Traditional medicine

Introduction

Cannabis sativa L. (Hemp) is a commonly used herbaceous medicinal plant in agriculture, agrochemistry, beverages, bioenergy, biofuels, building materials, composites, cosmetics, environmental purposes, food industry, furniture, hygiene, medicine, paper, ropes, textiles and tech-textiles [1–10]. Hemp is mainly used in healthcare to relieve pain and treat nervous system diseases [11]. It contains several chemically active compounds, such as cannabinoids, terpenoids, carbohydrates, amides, phenolic compounds, phytosterols, fatty acids, and their esters, flavonoids, and alkaloids [12,13]. *C. sativa* is found beneficial in the therapy of neuralgia, epilepsy, gout, liver, glaucoma, nausea, insanity, insomnia, pain, and rheumatism, among others, with activities mainly on the central nervous system [14-16]. Several pertinent paleobotanical, archeological, and historical evidence of hemp, including seeds, pollen grains, carbonized remains, fibers, phytoliths, cannabinoid chemicals, and trichomes, has been recovered from dated archeological contexts [17]. One of the earliest pieces of Chinese medical literature, Shennong pên Ts'ao Ching, one of the earliest Chinese medical literature, explains *C. sativa* roots as

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a pain treatment, dating back to 2700 BC [18].
C. sativa is widely classified as a "narcotic," a legal term frequently applied arbitrarily. A narcotic is a drug or preparation often related to harsh punishments due to its actual or alleged detrimental properties [19]. Since World War II, hemp has been illegal in Western countries since it is considered a leading substance abused. All pharmacological and non-drug research and development have been forbidden [20]. In recent years, many countries (Canada, Colombia, Germany, Iran, Italy, Netherlands, and Uruguay) have legalized growing and processing hemp varieties containing relatively few psychoactive chemicals (industrial hemp). In Morocco, for example, law No. 13.21 was passed in 2021. This law (No. 13.21) legalizes the cultivation, transformation, and commercialization of cannabis for scientific and medical purposes while stressing the prohibition of its circulation and trafficking for entertainment, hallucinations, and smoking. Consequently, the United Nations Commission on Narcotic Drugs (CND) decided to withdraw *C. sativa* Schedule IV of the 1961 Single Convention on Narcotic Drugs in December 2020, acknowledging hemp's medical and therapeutic benefits [21]. This paper presents an overview of the results found about traditional uses, botany, phytochemical, and pharmacological activities of *C. sativa*.

Methodology

Search strategy

The collected information on botanical description, taxonomy, geographic distribution, traditional use, phytochemical ingredients, pharmacology proprieties, and toxicology effects of *C. sativa* was obtained through literature using various electronic databases and search including PubMed, ScienceDirect, MDPI, Academia.edu, Springer, Google Scholar, ResearchGate, Bentham, Taylor & Francis, Thieme, Scopus, Web of Science, SpringerLink, Wiley Online, Scifnder and to collect, investigate, and summarize all published papers about this medicinal plant. Other literature sources were also utilized, such as books and periodicals from the library. The study was conducted using the terms "*Cannabis sativa* L.", "Lhashish," "Lqennab El Hendi," "Lkif," "Cannabis," "Marijuana," "Hemp," "Canamo," "Sinsemilla," "Chanvre," "Chanvre cultivé," "Marihuana," "Marijuana" and articles published after 1972 were considered.

Inclusion and exclusion criteria

The study for this review was limited to English, French, Spanish and Arabic languages publications since 1972, reporting pharmacological and chemical data, as well as animal research using isolated chemicals, extracts, and essential oils derived from *C. sativa*. About 316 literature papers were reviewed; however, only 200 references were included in this review. The books and resources were chosen based on the subject matter addressed. We did not include papers or literature about other species, cultivation, or anatomical or physiological characteristics of *C. sativa*. The literature on *Cannabis* species taxonomy, distribution, morphological characteristics, ethnobotany, phytochemistry, pharmacology, clinical studies, and toxicity was included.

Data extraction

Three independent reviewers (NC, AA, and BB) collected the data from the included articles into a template created expressly for this purpose using the same methodology as in the screening step. We followed the tool's name and searched for the instrument's original publication to extract the quality assessment tool utilized in each included study. IUPAC names of phytochemicals reported for *C. sativa* were verified using the PubChem database. ChemDraw Pro 8.0 was used to sketch chemical structures. The phytochemical data were categorized according to their constituent types. The pharmacological data table includes a plant part, extract, model type, dose tested, and the outcomes of each investigation.

Botanical description

Cannabis sativa L. is a member of the Cannabaceae family, which includes 12 genera. There are 636 scientific plant names for species ranked on the Plant List (Table 1). There are 102 approved species names among them [22].

Preferred Common Names

The vernacular names used to refer to *Cannabis sativa* L. are as follows (Table 2).

Table 1. Systematic taxonomy of *Cannabis sativa* L.

Taxon	Scientific name
Kingdom	Plantae : Plants
Subkingdom	Tracheobionta: Vascular plants
Superdivision	Spermatophyta: Seed plants
Division	Magnoliophyta: Flowering plants
Class	Magnoliopsida: Dicotyledons
Order	Rosales
Family	Cannabaceae
Genus	*Cannabis*
Species	*Cannabis sativa* L.
Subspecies	• *Cannabis sativa* subsp. *indica* (Lam.) E.Small & Cronquist • *Cannabis sativa* subsp. *intersita* (Soják) Soják [22,23]

Table 2. Vernacular Cannabis names in several languages.

Language	Vernacular Names
Arabic	Lhashish, Lqennab El Hendi, Lkif [24,25]
English	Cannabis, Marijuana, Hemp [26,27]
Spanish	Canamo, Sinsemilla [26,27]
Russian	Konoplya [26,27]
Chinese	Ma fen; Ta ma [27]
Portuguese	Canhamo [27]
French	Cannabis, Chanvre, Chanvre cultivé, Marihuana, Marijuana [24,26,27]

Description

C. sativa is a dioecious annual herbaceous plant of 1-2 meters, pubescent-harsh, with a strong odor whose phenotypic characteristics show considerable variability [28]. Leaves are opposite: petiolate, palmate, with 5-7 lanceolate-acuminate segments, dentate, the upper ones often alternate, and 1-3 pieces. The stem is erect, stiff, and simple [19,29]. The seeds (achenes) are round to nearly lens-shaped, with a round base. Flowers: green, dioecious, in a branching panicle, the females each providing a bract. Male perianth with five equal divisions, five pendulous stamens with terminal anthers, and short filaments [29]. The female perianth is monosepalous, wrapped around the ovary. The fruit is sub-globose, smooth, grown in large, and sometimes sub-spontaneous in various countries [19].

Geographical distribution

C. sativa is among the world's most commonly used industrial herbs [30]. Researchers uncovered fruits in a culinary context, a kitchen midden, with a calibrated radiocarbon age of 8 000 cal BCE [31]. However, tracing the origins of *C. sativa* to a single geographical place is challenging owing to the plant's many species, subspecies, and varieties (Figure 1). The source of *C. sativa* can be found in many diverse areas, depending upon where we draw the line in the phylogenetic tree. Except for Antarctica, *C. sativa* is found almost everywhere on the planet. The hemp plant is indigenous to Central Asia, most likely in the Himalayan foothills [3,32]. *C. sativa* was initially confined to this area; however, it has become more widespread due to man [3]. *C. sativa* is found practically everywhere, bringing about the term "weed."

Legal and regulatory frameworks of *C. sativa* around the world

Many countries have strict prohibitions on *Cannabis* production, marketing, and processing. In Morocco, for example, establishing *Cannabis* cultivation in selected areas (Ketama and Bni Khalid) requires state approval. The prohibition of *Cannabis* first appeared on the international Schedule as a supplement to the 1912 International Opium Convention. Therefore, it was not until the 1961 Single Convention on Narcotic Drugs that *Cannabis* was declared illegal worldwide and put into Schedule I of the treaty [33]. This Schedule includes heroin and places further restrictions on chemicals that are highly addictive, have the potential for abuse and are utilized as precursors for other narcotics [34]. *C. sativa* was also included in Schedule IV of the 1961 Convention, identifying a plant's limited or non-existent medicinal significance. On July 7, 2017, the Act's provisions on varying drug addictions and the reimbursement of drugs, foodstuffs designated for specific nutritional benefits, and therapeutic appliances controlling *Cannabis* production. *Cannabis* control for scientific and therapeutic reasons does not violate treaty obligations if it respects the principles of articles 23 to 28 of the Single Convention. The international debate regarding the regulation of *C. sativa* has intensified in recent years, and more nations have altered their legislation to allow for the plant's medicinal or therapeutic usage. Various governments have established regulations allowing patients to get specific preparations to reduce discomfort, relieve symptoms, or improve their quality of life. Table 3 below summarizes the lawful status of hemp for therapeutic usage around the globe.

Figure 1. Cannabis fields in Tlate Ketama commune, Al Hoceima province, Morocco. Photo taken by Chaachouay, N.

Traditional uses of *C. sativa*

C. sativa is among the first therapeutic, culinary, psychotropic, fiber, and oil-yielding plants discovered since agricultural farming began 10,000 years ago [4,5,54-57]. Hemp plants provide various benefits depending on the species, dose style, and volume. *Cannabis* uses are likewise largely reliant on the extraction procedure. It can be employed in multiple

materials because each plant has different chemical components.

Traditional medicine

C. sativa is commonly used to treat nervous disease and pain [58-62]. It is documented to help manage nausea, neuralgia, cachexia, gout, multiple sclerosis, seizures, cancer, Alzheimer's, rheumatism, insanity, insomnia, and Crohn's disease [4,16,24,63-76]. *Cannabis* extract has been employed in Arabic-Islamic medicine for its antiparasitic, anti-emetic, antipyretic, antitumor, anti-epileptic, anti-inflammatory, antibacterial, carminative, vermifuge, and pain-killing effects [77,78]. *Cannabis* can even be made into an oil or tincture and consumed. Remedies are mainly used in the pharmaceutical industry because of their high concentration of active substances that produce healing results [4,79,80]. They also make dosage adjustments simple, lowering the likelihood of unwanted side effects.

Table 3. *Cannabis* approvals and regulations across the world.

Countries	Possession/Ownership	Transport/Sale	Farming
Argentina	Illegal (not criminal if for personal use and in small quantities)	Illegal	Illegal [35,36]
Austria	Possession of up to 5 grams of *Cannabis* is not criminal.	Illegal	Illegal [37]
Australia	Legal for medical and scientific uses	Illegal	For medicinal and scientific purposes, it is legal [37]
Belgium	Illegal (non-criminal up to 3 grams)	Illegal	Illegal (not criminal if it's a single plant) [37]
Bolivia	Illegal (but not criminal)	Illegal	Illegal [38]
Brazil	Legal (the importation of CBD-based pharmaceuticals, including THC and *Cannabis* flowers, has been legalized)	Illegal	Illegal [39]
Canada	Illegal (legal in medicinal uses)	Illegal	Illegal (small amounts of plants may be allowed) [40]
Chile	Illegal (not criminal)	Illegal (medical uses only)	Legal [36]
Colombia	Personal use is legal up to 22 grams.	Only medical and scientific purposes are permitted.	Personal use is legal up to 22 grams [41]
Costa Rica	Illegal (not criminal)	Illegal	Illegal (not criminal) [35,42]
Croatia	Illegal (non-criminal)	Illegal (therapeutic benefit only).	Illegal [37]
Czech Republic	Illegal (non-criminal, up to 15 grams)	Illegal (up to 15g non-criminal/medical use only)	Illegal (Cultivation of up to 5 small shrubs is illegal/cultivation for medicinal use) [37]
Ecuador	Illegal (not criminal)	Illegal	Illegal [43]
Estonia	Illegal (not criminal)	Illegal	Illegal [35]
Finland	Illegal (medical use only)	Illegal	Illegal [37]
Georgia	Illegal, but possession for private usage is not prohibited	Illegal	Illegal [44]
Germany	Legal for medical use	Legal	Legal [37,39,45]
Greece	Illegal (but using half a gram of cannabis to make one cigarette is not illegal if it is for personal use)	Illegal	Illegal [37]

India	At the federal level, it is prohibited. Some states, including West Bengal, the Northeast, and Orissa, have legalized and permitted *Cannabis* use.	At the federal level, it is prohibited. Some states, including West Bengal, the Northeast, and Orissa, have legalized and permitted *Cannabis* use.	At the federal level, it is prohibited. Some states, including West Bengal, the Northeast, and Orissa, have legalized and permitted *Cannabis* use [39]
Ireland	Legal for medical use	Illegal	Illegal [37]
Malta	Illegal (non-criminal, up to 3.5 grams)	Illegal	Illegal [46]
Mexico	Illegal (not criminal)	Illegal	Illegal (not criminal) [47]
Moldova	Illegal (not criminal)	Illegal	Illegal [48]
Netherlands	Not prohibited 5 grams, for general use or in cafes	Illegal (this law does not apply to coffee shops)	Illegal (Not criminalized for up to 5 plants) [37]
New Zealand	Legal	Legal	Legal [49]
Paraguay	Illegal (not criminal up to 10 grams)	Illegal	Illegal [35]
Peru	Illegal (not criminal up to 8 grams)	Illegal	Illegal [43]
Philippines	Illegal (medical use pending state license)	Illegal	Illegal (for scientific and medical uses only) [42]
Poland	Illegal (legal for medical use only)	Illegal (legal for medical use only)	Illegal [37]
Portugal	illegal (not criminal)	illegal (not criminal)	illegal (not criminal) [37]
Puerto Rico	Illegal (therapeutic benefit only)	Illegal (therapeutic benefit only)	Illegal (therapeutic benefit only) [50]
Russia	Illegal (non-criminal), up to 6 grams	Illegal (not criminal), can transfer up to 6 grams	Illegal (not criminal), can grow up to 20 plants [35,37]
Slovenia	Illegal (not criminal)	Illegal	Cultivation of hemp is not illegal, as farmers can grow it at a certain percentage as per the government's instructions [37]
Spain	Legal (in certain areas only, but illegal in public places (not criminal)) Possession of more than 70/100 grams	Illegal	Legal (only if for personal use) [37]
Switzerland	Illegal (not criminal)	Illegal	Illegal [51]
Turkey	Illegal (therapeutic benefit only)	Illegal	Legal for medical and scientific uses [39]
Ukraine	Illegal (non-criminal possession of up to 5 grams)	Illegal (non-criminal possession of up to 5 grams)	Illegal (not criminal planting up to 10 plants) [52]
United States	At the federal level, it's illegal (but legal in Alaska, California, Colorado, Nevada, and Washington).	It is illegal but legal for medical use	The cultivation of medicinal cannabis is legal in many states [35,41]
US Virgin Islands	Illegal (not criminal), one ounce can be possessed	Illegal	Illegal [53]
Uruguay	Legal	Legal	Legal [36]

Alimentary use

Alimentary use is separated into human and animal categories and food and drink. Traditional drinks containing *Cannabis*, which had healing, psychoactive, or spiritual benefits, were automatically added to the nutrient usage class [5]. *Cannabis* products are becoming more widely recognized as nutritious foods. Seeds are rich in lipids, magnesium, polyunsaturated fatty acids, carbohydrates, insoluble fiber, and protein, making them a popular health food [81]. They can be used in smoothies, salads, and dairy-free milk alternatives [81]. *Cannabis* can be employed to manufacture an oil material to make paints, varnishes, soaps, and cooking oil. The oil derived from hemp seeds and derivatives is used in nutritional supplements, food processing, and animal feed. Furthermore, its nutritional value has improved health outcomes, such as decreased cholesterol and blood pressure [2,4,82].

Hemp Fibers

Cannabis fiber has been used for thousands of years to make textiles, fabrics, ropes, yarns, rugs, and canvas. Unlike other natural fibers such as cotton, nettle, and flax, hemp fiber is very durable. In the stems of *Cannabis*, there are two types of fiber: phloem in the outer stem and xylem in the inner stem. Plants have two vascular systems: phloem tissue, which distributes photosynthetic chemicals from the foliage to other parts of the plant, and xylem tissue, which moves water and solutes from the roots to other parts of the plant. Historically, phloem fiber was commonly used for cordage and textiles; whereas the woody core had little value. However, today, both types of wool are valued at [2,6,12,83-85]. Hemp is also employed in plastics and composites by the automobile and aviation industries as a fiberglass substitute. Hemp fiber was cultivated largely for paper scrolls in ancient China [6]. Hemp paper outperformed tree-based paper's decomposition resistance, strength when wet, and resistance to yellowing [6-8]. Hemp fibers are used for insulation and composites in the automotive, fashion, and furniture sectors, where synthetic fibers are substituted with hemp fiber. Hemp hurdles are also utilized as horticultural mulch. *Cannabis* mulch, like traditional mulch, is often used as a cover application for parks with vegetables, flowers, and even container plants like shrubs.

Other potential applications

Other uses were divided into four subcategories: cosmetic, magico-religious, firewood, and miscellaneous uses [2,6-8]. Only human benefits are included in this category.

Chemical composition of *C. sativa*

Over several decades, the number of phytochemicals isolated or discovered from *C. sativa* has risen. So far, 565 chemicals, including 125 phytocannabinoids, have been discovered in this plant [12,62,86-91]. Cannabinoids are a class of chemicals distinguished by their C21 terpene phenolic backbone [90]. This vocabulary can classify parent cannabinoids, derivatives of cannabinoids, and transformation products [12]. These cannabinoids are further divided into 11 sub-classes, which include: (-)-Δ^{8}-trans-tetrahydrocannabinol (Δ^{8}-THC) (Figure 2), (-)-Δ^{9}-trans-tetrahydrocannabinol (Δ^{9}-THC) (Figure 3), Cannabidiol (CBD) (Figure 4), Cannabichromene (CBC), Cannabinol (CBN), Cannabielsoin (CBE), Cannabicyclol (CBL), Cannabitriol (CBT), Cannabigerol (CBG) (Figure 5), Cannabinodiol (CBND), and miscellaneous-type cannabinoids. In addition to cannabinoids, More than 400 non-cannabinoid compounds have been extracted and determined from the *Cannabis* plant [12,92,93]. These non-cannabinoids are classified into several chemical groups [90,94-96]. The principal non-cannabinoid components are classified into four major classes: non-cannabinoid phenols, alkaloids, terpenes, and flavonoids. Most cannabinoid-related biological features depend on their interactions with the human endocannabinoid system. The endocannabinoid system comprises two G protein-coupled cannabinoid receptors, CB1 and CB2, and two endogenous ligands, anandamide and 2-arachidonoylglycerol [13]. Endocannabinoids are believed to control or regulate several physiological processes, including appetite, pain perception, mood, memory, inflammation, insulin sensitivity, and fat and energy metabolism. THC, the psychoactive decarboxylated form of THCA, is a partial agonist of both CB1 and CB2 receptors but has a greater affinity for the CB1 receptor, which appears to underlie its psychoactive characteristics [97]. On the other hand, THC has been linked to various adverse effects, including anxiety, cholinergic deficiencies, and immunosuppression. CBDA is the most common phytocannabinoid in fiber hemp and the second most common in drug chemotypes (Figure 6). CBD is a promising cannabinoid because it has demonstrated therapeutic potential in preclinical models of diseases of the central nervous system, such as neurodegenerative diseases, affective disorders, schizophrenia, epilepsy, multiple sclerosis, and the central modulation of feeding behavior [65,98,99]. After THC and CBD, CBC is the third most common phytocannabinoid. CBC has notable anti-inflammatory, sedative, analgesic, antibacterial, and antimycotic effects. CBC is also a powerful inhibitor of the uptake of the endogenous ligand of CB receptors, anandamide [100]. CBN is a byproduct of THC decomposition and is most prevalent in *cannabis* that has aged. CBN's affinity for CB1 receptors is half that of THC; whereas its affinity to CB2 receptors is three times that of THC. Thus, immune system cells

are impacted more than central nervous system cells [12,90,101].

Terpenes are the biggest group of phytochemicals, with more than 100 compounds discovered in *Cannabis*. Terpenes are responsible for the aroma and taste of *Cannabis* spp. [103]. Therefore, they probably contributed to the selection of *Cannabis* narcotic species throughout domestication. Terpenes are lipophilic substances that readily traverse membranes and the blood-brain barrier. They exhibit a wide range of pharmacological properties, which have been documented in several reviews [104-106].

Phenolic chemicals, commonly known as phenylpropanoids, are among the most extensively distributed secondary plant metabolites. Under specific physiological settings, phenolic compounds in *C. sativa* may function as antioxidants and protect plants from oxidative damage [13]. A link between dietary phenolic compounds intake and a lower prevalence of chronic diseases such as malignancies, cardiovascular disor-

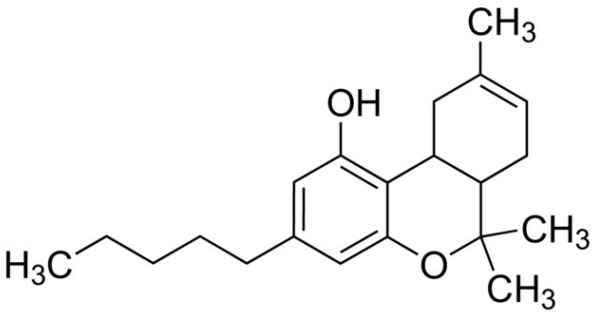

Figure 2. Molecular structure of Δ^8-THC.

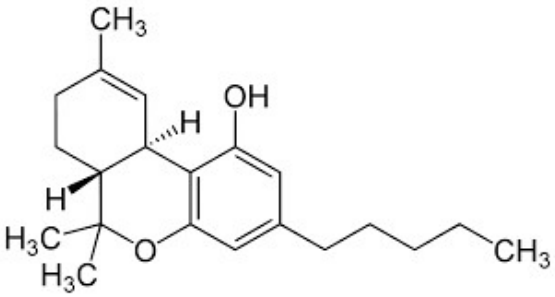

Figure 3. Molecular structure of Δ^9-THC

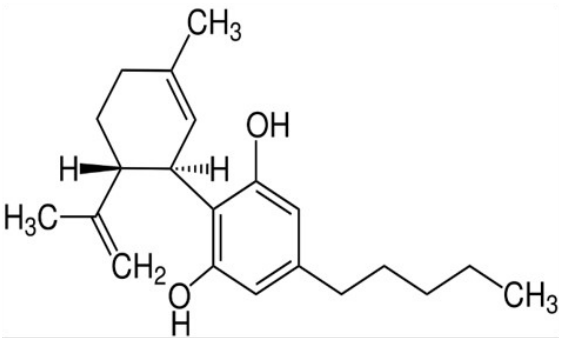

Figure 4. Molecular structure of Cannabidiol

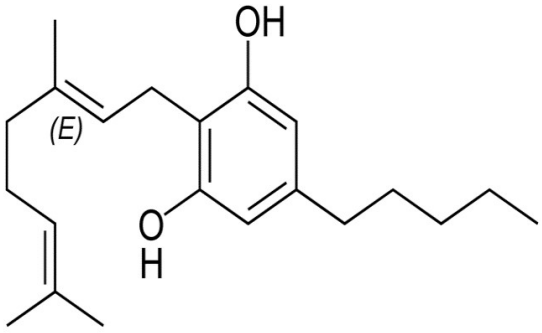

Figure 5. Molecular structure of Cannabigerol

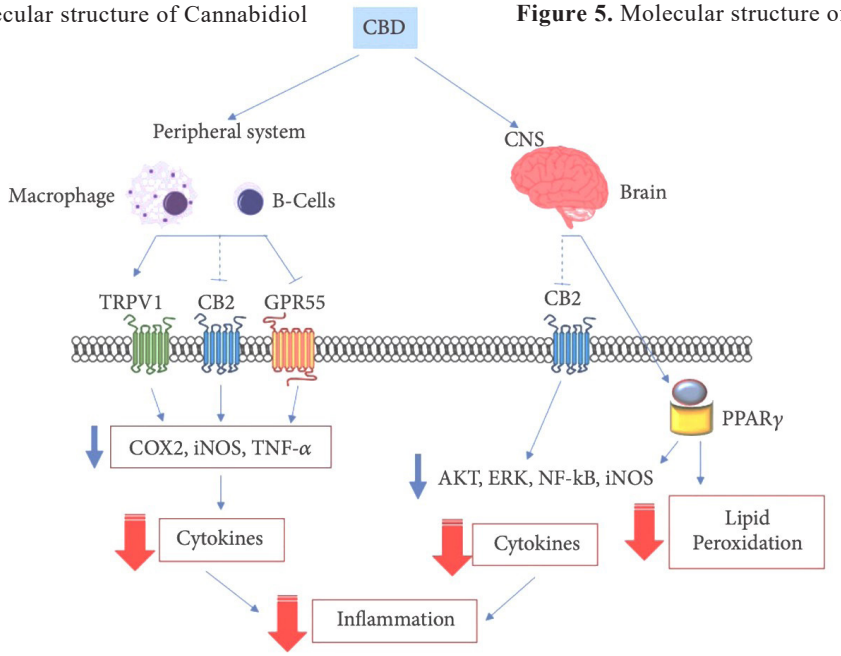

Figure 6. General representation of the signaling pathways involved in Cannabidiol anti-inflammatory effects [102].

ders, and neurological diseases has been demonstrated in humans. The flavones and flavonols present in *Cannabis* exert a vast array of biological effects, including features shared by terpenes and cannabinoids [107]. They are anti-inflammatory, anticancer, and neuroprotective [108].

Moreover, apigenin has been demonstrated to contain anxiolytic and estrogenic effects. By inhibiting prostaglandin, cannflavins A and B are strong anti-inflammatory chemicals. The enzymes E2 and 5-lipoxygenase. Few health-related investigations have been conducted on lignin amides, which have demonstrated In vitro anti-inflammatory and cytotoxic properties [109]. Lignans exhibit numerous health-promoting characteristics, including antioxidant, antiviral, antidiabetic, antitumorigenic, and anti-obesity properties [108,110] (Table 4).

Pharmacological activities of *C. sativa*

C. sativa, because of the number of secondary metabolites like cannabinoids, phenolic compounds, and terpenes, is one of the most researched plant species for phytochemistry. These phytochemical constituents have exhibited interesting pharmacological properties, including analgesic, anxiolytic, anticonvulsant, antidepressant, antiemetic, antifungal, antihypertensive, anti-inflammatory, antimelanogenesis, antimicrobial, antioxidant, antiproliferative, antipruritic, antispasmodic, antitumor, cytotoxic, expectorant, gastroprotective, and numerous other pharmacological effects. The details about the pharmacological activities are recapitulated in table 5.

The pharmacokinetic and pharmacodynamic aspects of *C. sativa*

The formulation and route of administration determine the pharmacokinetics and effects of *cannabis*-based medicines [16,176]. Cannabinoids delivered by inhalation have comparable pharmacokinetics to those supplied intravenously [177]. After inhalation, peak plasma concentrations of THC and CBD are achieved promptly (within 3-10 minutes) [178], and maximal concentrations are greater than oral administration. The most prevalent method of recreational *Cannabis* administration is smoking [179]. Maximum THC concentration and area under the curve were shown to be higher in frequent smokers than in occasional smokers, likely owing to more efficient smoking by regular smokers [180]. Using a vaporizer to distribute cannabinoid compounds eliminates the respiratory hazards of smoking *cannabis* and the exposure to hazardous pyrolytic chemicals created during combustion [97]. Both vaporized and smoked *Cannabis* exhibit comparable pharmacokinetics. The many cannabinoids found in *Cannabis* have distinct features that contribute to their pharmacokinetic profiles and eventually influence prenatal exposure [181]. Due to its lipophilic characteristics, THC, for example, quickly divides into fat tissue and crosses the placenta. Cannabinoids are rapidly distributed to well-vascularized organs (such as the lung, heart, brain, and liver) [182], with subsequent equilibration into less vascularized tissue [183]. Distribution may be influenced by body size and composition and illness conditions that alter the permeability of the blood–tissue barriers [184]. Cannabinoids may accumulate in adipose tissue with continuous use.

Subsequent release and redistribution may cause *Cannabis* activity to remain for several weeks after consumption. THC is primarily metabolized by the liver's cytochrome P450 (CYP 450) isozymes CYP2C9, CYP2C19, and CYP3A4. THC is predominantly converted to 11-hydroxy THC (11-OH-THC) and 11-carboxy-THC, which undergo glucuronidation and are then eliminated in feces and urine [185]. In addition to the liver, CYP450-expressing extrahepatic organs, such as the small intestine and brain, participate in metabolism [177]. 11-OHTHC has psychedelic properties, according to reports [177]. Lipophilic THC can pass the placenta and is secreted in human breast milk, raising concerns about brain development toxicity [186–188]. Due to the limited availability of relevant pharmacokinetic data, initiating the prescription of *Cannabis*-based medications with a "start low and go slow" strategy while closely monitoring the patient for desired and unwanted effects is necessary. Only via additional clinical trials involving the collection of pharmacokinetic data in the actual patient population for whom prescribing may be considered will a better knowledge of these medications, hence improving safe and optimal prescribing.

The safety and toxicity of *C. sativa*

Cannabis is a relatively safe drug and is not associated with fatal overdoses. The active ingredients of this plant are present in the brown resin released by the hairs on the female inflorescences. Although the active ingredients are found throughout the plant, they are most concentrated in the flower buds [189,190]. Despite variations in research methodology and quality, there are generalizable conclusions on the acute and long-term effects of exogenous . Exposure to high concentrations of THC may result in psychological and neurological effects, including ataxia, dizziness, drowsiness, hypotonia, coma, stupor, seizures, and ocular features such as mydriasis and conjunctival hyperemia, in addition to gastrointestinal disorders and cardiovascular effects such as tachycardia, arterial hypertension, and postural hypotension. Considerable toxicity from *Cannabis* and cannabinoid-containing substances is uncommon in adults, unlike youngsters

who may experience significant symptoms [191-193]. These poisoning effects are often short-lived, lasting only a few hours. Intoxication from *cannabis* is dose-dependent, and its absorption relies on the mode of administration and concentration employed. Inhaled doses of 2–3 mg and ingested doses of 5–20 mg of THC can affect memory and cause short-term memory impairment and loss of attention, whereas inhaled doses greater than 7.5 mg/m2 in adults and oral doses of 5–300 mg in pediatric subjects can cause more severe effects, including respiratory depression, panic, anxiety, hypotension, myoclonic jerking, and other symptoms [75,194]. Due to ethical considerations, the LD50 (the lethal dose at which 50 percent of the sample population dies) of THC has not been measured in humans; however, it ranges between 40 and 130 mg/kg intravenously in animals. The LD50 of THC inhaled from smoked *Cannabis* in Fisher rats is 42 mg/kg, comparable to the IV vascular access port value, indicating that THC is the psychoactive component

Table 4. Constituents of Cannabis sativa L. by chemical class

Cannabis constituents	Chemical class	References
Cannabinoid compounds (125 Compounds)	Δ^9-TH Type (25 Cannabinoids)	[35,87,88,90-96, 111-115]
	Δ^8-THC Type (5 Cannabinoids)	[35,87,88,90-96, 111-115]
	CBG Type (16 Cannabinoids)	[35,87,88,90-96, 111-115]
	CBC Type: (10 Cannabinoids)	[35,87,88,90-96, 111-115]
	CBD Type: (2 Cannabinoids)	[35,87,88,90-96, 111-115]
	CBND Type: (5 compounds)	[35,87,88,90-96, 111-115]
	CBE Type: (3 compounds)	[35,87,88,88,90-96, 111-115]
	CBL Type: (9 compounds)	[35,87,88,90-96, 111-115]
	CBN Type: (11 compounds)	[35,87,88,90-96, 111-115]
	Cannabitriol (CBT) Type: (9 compounds)	[90]
	Miscellaneous Types: (30 compounds)	[35,87,88,88,90-96, 111-115]
Non-cannabinoid compounds (125 Compounds)	Phenols (42 compounds): Spiro-indans (16 compounds), Dihydrostilbenes (12 compounds), Dihydrophenanthrenes (7 compounds), and simple Phenols (7 compounds).	[90]
	Flavonoids (34 compounds): Apigenin, Canniflavin, Chrisoeriol, Cytisoside, Cytisoside glucoside, Geranyl flavone, Glycosides Iso-prenoid flavones, Isovitexin, Kaempferol, Luteolin, Naringin, Orientin, Prenyl flavone, 6- Prenylapigenin, Rutin, Quercetin, Vitexin.	[35,87,88,88,90-96, 111-115]
	Terpenes (120 compounds): Monoterpenes (61 compounds), Sesquiterpenes (51 compounds), Diterpenes (2 compounds), Triterpenes (2 compounds), Miscellaneous Terpenes (4 compounds).	[35,87,88,88,90-96, 111-115]
	Alkaloids (2 compounds): Anhydrocannabisativine, Cannabisativine.	
	Lignans: (Phenolic amides and lignanamides)	[35,96,111,114,115]
	Steroids (11 compounds): Sitosterol, stigmasterol, β-sitosterol, campesterol, and ergosterol types	[35,96,111,114,115]

Δ^9-THC: (-)-Δ^9-trans-Tetrahydrocannabinol; Δ^8-THC: (-)-Δ8-trans-Tetrahydrocannabinol; CBG: Cannabigerol; CBC: Cannabichromene; CBD: Cannabidiol; CBND: Cannabinodiol; CBE: Cannabielsoin; CBE: Cannabielsoin; CBL: Cannabicyclol; CBN: Cannabinol; CBT: Cannabitriol

Table 5. Phytochemical constituents of *C. sativa* and its pharmacological activities.

Pharmacological activities	Groups/ Name of compounds	Type of study	Dosage	Characteristics of participants or animal	Duration of usage	References
Analgesic	Δ^9-THC, CBD	Experimental trial	Bedrocan (22.4-mg THC, <1-mg CBD; Bediol (13.4-mg THC, 17.8-mg CBD; Bedrolite (18.4-mg CBD, <1-mg THC	20 chronic pain patients with fibromyalgia	3 hours	[116]
	Δ^9-THC	Experimental trial	THC content of 20 mg in total	18 healthy female volunteers	1 Day	[117]
	Δ^9-THC	Animal study	Graded doses of Δ^9-THC and phenylbutazone	Pyretic rats	5 days	[118]
	Aspirin, Petroleum extract, Ethanolic extract, Δ^1-THC, CBN, CBD, CBG, Olivetol, Cannflavon	Animal study	100 mg/kg	Male CDI mice	20 min	[119]
	Δ^9-THC, Terpenes (α-pinene, β-pinene, β-caryophyllene, linalool, α-terpineol, β-myrcene, limonene, terpinolene, α-humulene, caryophyllene oxide).	Animal study	18 mg/kg	Animals received intraperitoneal administration of either vehicle or extract	30 min	[120]
	Aspirin, CBN, Δ^9-THC, morphine SO^4, CBD, CME	Animal study	Total cannabinoid content of CME was 21.1%	Non-fasted, Charles River male CD rats	2 hours	[121]
	Δ^9-THC	Animal study	2 ml/kg	Male Sprague-Dawley rats and male Dublin DBL/ICI mice	30 min	[122]
	Aspirin, Petroleum extract, Ethanolic extract, Δ^1-THC, CBN, CBD, CBG, Olivetol, Cannflavon.	Animal study	10 mg/kg	Male CDI mice	20 min	[119]
Antianxiety	CBD	Animal study	2.5, 5.0 and 10.0 mg/kg	Male Wistar rats	5 min	
Antibiofilm	*Cannabis sativa* L. seeds extract	*In vitro* study	0.5 mg/mL vs 1 mg/mL	*Staphylococcus aureus*	3 hours	[124]
Anticonvulsant	CBD	Animal study	1.2 µg/0.5 µL/minute (5 µM)	Immature male Sprague-Dawley P20 rats	30 min	[125]
	CBDV	Animal study	50, 100 or 200 $mg \cdot kg^{-1}$	Rat hippocampal brain slices by 4-aminopyridine	30 min	[126]
	Δ^9-THC	Animal study	1.2 ml/kg	Lower body temperature in mice at an ambient temperature of 22°C	30 min	[127]
	Δ^8-THC	Animal study	2 mg/kg	Rats	2 hours	[128]
	(–) and (+) Isomers of CBD	Clinical trial	114 to 181 ng/mL	Electroconvulsive shock model in mice	1.5 to 3 hours	[129]

Antidepressant	CBD	Animal study	30 mg·kg^{-1}	Male Swiss mice	30 min	[130]
	Ethanol extract	Animal study	Chlorpromazine (0.1% of medium)	Wild-type Drosophila (Canton-S strain)	7 days	[131]
	Δ^9-THC	Animal study	1.18, 1.0 mg/kg	Male Lister hooded rats	14 days	[132]
Antiemitic	Δ^9-THC	Clinical trial	7 mg/m^2	Females and males participants	4 hours	[133]
Antifungal	Leaf extract of *Cannabis*	*In vitro* study	1.562 to 200 mg mL^{-1}	*Aspergillus flavipes*	8 days	[134]
	The n-hexane extracted volatile component of high-power *Cannabis*	*In vitro* study	33.1 µg/mL	*Cryptococcus neoformans*	4 min	[135]
Antihypertensive	*Cannabis* seed meal protein hydrolysate	Animal study	0.5 mg/mL	Rats	2, 4, and 6 hours	[136]
	Δ^9-THC	Animal study	Δ^9-THC, 25 mg/kg	Hypertensive rats	8 days	[137]
Anti-inflammatory	Aspirin, Petroleum extract, Ethanolic extract, Δ^1-THC, CBN, CBD, CBG, Olivetol, Cannflavon	Animal study	100 mg/kg	Male CDI mice	20 min	[119]
	Terpenoids	Animal study	10, 25, or 50 mg/kg	Female Sabra mice	24 hours	[138]
	Δ^9-THC	Animal study	Graded doses of Δ^9-THC and phenylbutazone	Pyretic rats	5 days	[118]
	CBD	Animal study	5, 7.5, 10, 20, and 40 mg/kg; 0.5 ml/kg	Male Wistar rats	3 days	[139]
	Combination of CBD and moringin	*In vitro* study	0.64 U/mL	The murine macrophage cell line RAW 264.7	1 hour	[140]
Antimicrobial	Essential oils	*In vitro* study	5 µl	Bacterial cultures were grown overnight in Iso-Sensitest	5 min	[141,142]
	CBD	*In vitro* study	20 mg/mL	Methicillin-Resistant *S. aureus* (USA300)	24 hours	[143]
	Hydro-alcoholic extract of *Cannabis*	*In vitro* study	100 µg/mL	Standard strains of *S. aureus* 25923, *E. coli* ESBL+:, and *Klebsiella pneumoniae*	10-14 mm	[144]
	Δ^9-THC	*In vitro* study	MIC 39.06 and MBC 39.06–78.13 µg/ml	Methicillin-resistant clinical strains of *Staphylococcus aureus*	10 min	[145]
	Cannabidiolic acid and CBD	*In vitro* study	1 to 2 µg/mL	*S. aureus*, methicillin-resistant *S. aureus*, methicillin-resistant S. *epidermidis*, a clinical strain of S. *epidermidis*, E. *coli*, and *P. aeruginosa*	2 days	[146]
	Petroleum ether, methanol extracts of the whole plant, and Oil of the seeds	*In vitro* study	One ml of the standardized bacterial stock suspension (108 - 109) C.F.U/mL were thoroughly mixed with 100 mL of molten sterile nutrient agar	Two Gram-positive organisms, *Bacillus subtilis* and *Staphylococcus aureus*, two Gram negative bacteria, *Escherichia coli*, and *Pseudomonas aeruginosa* and two fungi *Aspergillus niger* and *Candida albicans*.	18 hours	[147]

	Δ^9-THC	*In vitro* study	MIC 39.06 and MBC 39.06–78.13 µg/mL	Methicillin-resistant clinical strains of *Staphylococcus aureus*	10 min	[145]
	Cannabis seed meal protein hydrolysate	Animal study	0.5 mg/mL	Rats	2, 4, and 6 hours	[136]
	Hemp protein isolates	*In vitro* study	0.1 mg/mL	Hydrolysis and SDS-PAGE profiles	2 hours	[148]
	CBD and CBG	*In vitro* study	1.04–1.88 mM	Rat astrocytes	24 hours	[149]
	CBD	*In vitro* study	500 ng of RNA per sample	Normal human epidermal keratinocytes and Keratinocyte growth medium	24–48 hours	[150]
	Combination of CBD and moringin	*In vitro* study	0.64 U/mL	The murine macrophage cell line RAW 264.7	1 hour	[140]
Antioxidant	Lignanamides: 3,3′-dimethyl-heliotropamide, cannabisin N, cannabisin O, and cannabisin M	*In vitro* study	1.72 mg	Optical rotations were measured on an MCP 200	9.5 min	[151]
	Cannabis root extracts: stigmasta-3,5-diene, stigmasta-3,5,22-triene, oleamide, fucosterol, Glutinol, β-amyrone, stigmastanol.	*In vitro* study	1-50 µg/mL	Reduction of Fe3+ to Fe2+ by the antioxidant compound, which forms a colored complex with an absorption maximum at 593 nm with 2,4,6 tripyridyl-s-triazine in acetate buffer at pH 3.6.	12–16 hours	[152]
	Polar hemp extracts	*In vitro* study	150 µg/mL	Caco-2 and HT-29 cell lines, both derived from human colorectal adenocarcinoma were employed	24 hours	[153]
	Protein-derived from hemp seed	*In vitro* study	0.5 mg/mL	*In vitro* inhibition of the activity of human recombinant renin assay	2-6 hours	[136]
Antiproliferative	Polar hemp extracts	*In vitro* study	150 µg/mL	Caco-2 and HT-29 cell lines, both derived from human colorectal adenocarcinoma were employed	24 hours	[153]
	CBD	*In vitro* study	0.5% serum, adding CBD at 10 µM	HT29 cells and SW480 cells	5 days	[154,155]
Antipruritic	Cannabinoids	Animal study	1, 3 and 10 mg/kg	Male Balb/c mice 8.	30 min	[156,157]
	CBD	*In vitro* study	0.5 mg/mouse	U87 and U373 human glioma cell lines	24 hours	[100,158, 159]
	Cannabis flowers extracted	*In vitro* study	1 mg/mL	Various human tumor cells and non-tumor cells	0.5 or 2.0 hours	[160]
Anxiolytic	CBD	Animal study	2.5, 5 or 10 mg/kg	Male Wistar rats	24 hours	[123,161–166]
Cytotoxic	Terpenoids, phytocannabinoids	*In vitro* study	20 µg/mL	Cell viability assay	35 days	[167]
	CBD	*In vitro* study	0.5% serum, adding CBD at 10 µM	HT29 cells and SW480 cells	5 days	[154,155]
Neuroprotective	CBD and CBG	*In vitro* study	2.5 and 5 µM	NSC-34 motor neurons cells line	30 min	[168]
	Δ^9-THC	Animal study	200 µl of 0.5 µg/µl or 2.5 µg/µl (0.4 or 2 mg/kg of body weight) of THC, 1 or 2 mg/kg of SR141716A, or 2 mg/kg of CBD	Adult male albino Sprague-Dawley rats from Harlan	7 days	[169-173]
	CBD	Animal study	10 mg/kg	Diabetic male Sprague-Dawley rats after	1, 2, or 4 weeks	[174]
	CBD and CBG	*In vitro* study	1.04–1.88 mM	Rat astrocytes	24 hours	[149]

Sedative	CBD	Animal study	(0.98 to 1.15) mg/kg for THC; 4.72 (4.22 to 5.27) mg/kg for cannabidiol and 1.26 (1.22 to 1.80) mg/kg for chlorpromazine.	LAC A Tuck No. 1 strain albino female mice	6 hours	[175]
	Δ^9-THC	Animal study	(0.98 to 1.15) mg/kg for THC; 4.72 (4.22 to 5.27) mg/kg for cannabidiol and 1.26 (1.22 to 1.80) mg/kg for chlorpromazine.	LAC A Tuck No. 1 strain albino female mice	6 hours	[175]

CBD: Cannabidiol; CBDV: Cannabidivarin; CBG: Cannabigerol; CBN: Cannabinol; Δ9-THC: (-)-Δ9-trans-Tetrahydrocannabinol; Δ8-THC: (-)-Δ8-trans-Tetrahydrocannabinol; CME: Crude marihuana extract; MIC: Minimum Inhibitory Concentration; MBC: Minimum Bactericidal Concentration.

of smoked *cannabis* [191,195]. Individual responses to *Cannabis* vary and are impacted by potency, mode of use, patient age and gender, the presence of other psychoactive substances, and *Cannabis* or different drug tolerance [196]. Combining *Cannabis* with other psychoactive chemicals, such as alcohol, can raise the risk of toxicity and lead to greater intoxication than using either substance alone. Other variables, such as genetic variation, age, gender, ethnicity, and the duration and frequency of *Cannabis* usage, may influence *Cannabis*-induced negative consequences [190]. Despite the wider debate around the safety and efficacy of medical and recreational *Cannabis* usage, several recurring themes exist. There are distinct acute cardiovascular, pulmonary, cognitive, psychological, and public health impacts associated with *Cannabis* usage. Moreover, enduring cardiovascular and respiratory effects are well known for chronic users.

Future directions and limitations

According to the literature, current national and state legislation, popular opinion, and scientific data are at odds with medical and recreational *Cannabis*. Besides, this discrepancy appears to impede the adoption of high-quality research and effective safeguards. Frequently, the scientific data is equivocal and plagued by methodological inconsistencies. The categorization of *Cannabis* as a Schedule I drug restricts the type and quality of research, forcing safeness and effectiveness evaluations to rely on observational investigations [196]. Despite methodological limitations, the studies to date demonstrate reasonably clear acute cardiovascular, psychosocial, cognitive, respiratory, and public health impacts of recreational and medical *Cannabis* use. The cardiovascular and pulmonary effects of *Cannabis* use over the long-term are substantiated to a reasonable degree. However, the long-term evidence of cognitive, psychological, and immunological consequences is less conclusive. Few studies have evaluated the long-term effects of *Cannabis* on the immune system, and uncertainties remain about the relative impacts of THC and CBD on the immune system [101,197]. However, the reported duration of these acute effects is significantly more variable. Given these results, one possibility for the future course of *Cannabis* research is to investigate it as a valid therapeutic agent [3]. This would include categorization and stricter and more consistent oversight of its use and distribution in a safe, ethical, and scientifically justifiable manner. In addition to reclassifying *Cannabis*, policy design may pay additional consideration. As state-based legalization becomes increasingly prevalent, authorities must evaluate the effects of their rules on production, price, and consumption.

Evidence shows that legalization reduces manufacturing costs [198,199], decreasing market price. Nonetheless, it has been proposed that a price decrease could contribute to increased usage, particularly among teens [198]. Therefore, policymakers should adopt cost-controlling methods. Taxes may be an effective measure for influencing pricing and then use [200]. Moreover, the cash generated by these levies might be used to fund preventative programs [198]. C. sativa has a variety of therapeutic and industrial applications, but it also has certain limits. The presence of cannabinoids in *C. sativa* causes psychological, neurological, and cardiovascular effects and gastrointestinal disorders. The most serious health problems can be avoided if all preventative steps are taken.

Conclusions and future perspectives

Cannabis has been grown throughout human civilization as a supply of textiles, fiber, oil, and food because of its health-promoting properties. Several parts of this plant have been used to cure and prevent various illnesses, including glaucoma, insomnia, epilepsy, Alzheimer's disease, cancer, and pain. Phytocannabinoids such as Δ^9-tetrahydrocannabinol, cannabidiol, cannabinol, cannabicyclol, cannabitriol, and cannabinodiol are the main bioactive ingredients of this

medicinal plant. This review has presented a comprehensive overview of the botany, phytochemistry, and pharmacological properties of *C. sativa* and its traditional uses. The phytochemicals of *Cannabis* show high potential for offering new compounds that could significantly benefit the drug discovery approach to developing new medications. However, more bioactive components in *Cannabis* oils and extracts should be found utilizing bio-guided extraction techniques. Furthermore, there are few published reports on the toxicological properties of *C. sativa*. Thus, the additional toxicological investigation is required to determine the safety of this plant. Lastly, there is a significant void in the pharmacokinetic research on *Cannabis*. Thus, further research on the crude extracts' absorption, distribution, metabolism, and excretion in vivo is required.

Conflict of Interests
None.

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