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Cannabis sativa L.: An integrative review of its botanical diversity, phytochemistry, and therapeutic promise

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ABSTRACT

Cannabis sativa L. is a multifunctional plant of growing global importance for industrial, nutritional, and medicinal uses. Despite numerous publications, existing reviews often treat its botanical, chemical, and therapeutic aspects separately. The present work aims to provide an integrative synthesis of the species botanical diversity, phytochemical composition, and therapeutic promise, while highlighting the current gaps and future research needs. Accordingly, This review compiles and critically analyzes over 200 recent peer-reviewed studies (2016–2025) covering the taxonomy, morphology, secondary metabolite biosynthesis, and pharmacological applications of *C. sativa*. Data were compared across different plant varieties, geographical origins, and extraction techniques to reveal patterns and inconsistencies in chemical composition and biological activity. The analysis revealed more than 550 identified compounds, including over 120 cannabinoids and 150 terpenoids. The relative abundance of principal cannabinoids (CBD, CBN, CBG, Δ^9-THC, CBC) depends strongly on genotype, climatic conditions, and processing methods. Phytochemicals from *C. sativa* exhibit potent neuroprotective, anti-inflammatory, antioxidant and anticancer activities. However, the lack of standardized extraction, quantification, and clinical evaluation protocols limits reproducibility and pharmacological validation. Most available data derive from preclinical models or chemically undefined extracts, complicating translation to therapeutic use. Future work should integrate genomic, metabolomic, and clinical approaches to clarify structure-activity relationships and ensure product safety and efficacy. This synthesis provides a consolidated scientific framework useful for researchers, clinicians, and industry stakeholders seeking to optimize *Cannabis sativa* utilization for pharmaceutical, nutraceutical, and biotechnological development. Unlike previous reviews, this article offers a cross-disciplinary perspective linking the plant's botanical morphology, chemical diversity, and therapeutic mechanisms. It identifies critical research gaps that must be addressed to transform *C. sativa* from a controversial crop into a standardized bioresource.

Keywords: *Cannabis sativa,* cannabinoids, flavonoids, biosynthesis, therapeutics, secondary metabolites.

INTRODUCTION

Cannabis sativa L., widely referred to as hemp, is an annual species classified within the Cannabaceae family. It is among the earliest plant species domesticated by humans and has been appreciated for millennia for its industrial, nutritional, therapeutic, and psychoactive applications (Chandra et al., 2017; Andre et al., 2016). The earliest documented use of *Cannabis* traces back to ancient China, where it was employed in the manufacture of textiles, oils, and traditional remedies. Over time, its cultivation and utilization spread across various civilizations, notably in India and around the Mediterranean basin, reflecting the versatility and chemical richness of this remarkable plant (Zuardi, 2006).

From a botanical perspective, *Cannabis sativa* L. is primarily a dioecious species, although monoecious varieties also exist, presenting distinct female and male individuals. The species is characterized by an erect stem, palmate leaves

with serrated lobes, and dense inflorescences that serve as the main sites of secondary metabolite production (Small, 2015). These metabolites are predominantly synthesized in specialized structures known as glandular trichomes, located on the epidermis of female floral structures. These trichomes function as the plant's resin-producing structures and house a diverse spectrum of bioactive molecules including cannabinoids, flavonoids, and terpenes, that collectively contribute to its pharmacological effects, aroma, and organoleptic properties of the *Cannabis* plant (Chandra et al., 2017 ; Livingston et al., 2021).

On a chemical level, *Cannabis sativa* L. exhibits remarkable complexity. More than five hundred constituents have been identified, including over one hundred and twenty cannabinoids a distinct group of terpenophenolic molecules that occurs almost exclusively in this species (ElSohly and Slade, 2005 ; Brenneisen, 2007). The main cannabinoids include cannabidiol (CBD), cannabichromene (CBC), Δ^9-tetrahydrocannabinol (THC), cannabinol (CBN), and cannabigerol (CBG). All of them originate from a single biosynthetic precursor, cannabigerolic acid (CBGA), synthesized within trichomes in its acidic form before being converted into pharmacologically active neutral compounds through decarboxylation (Gagne et al., 2012 ; Fellermeier and Zenk, 1998). THC is widely recognized for its psychoactive properties, whereas CBD, which lacks such effects, has gained increasing scientific interest because of its wide range of therapeutic activities (Mechoulam et al., 2002; Pisanti et al., 2017).

In addition to cannabinoids, *Cannabis sativa* L. produces a diverse assortment of terpenes, flavonoids, and other phenolic metabolites. Although present in smaller quantities, these molecules play an essential role in the overall pharmacological synergy of the plant. Terpenes including limonene, myrcene, β-caryophyllene, pinene, and linalool, contribute not only to the characteristic aroma of *Cannabis* but also to the so-called "entourage effect", modulating the biological activity of cannabinoids (Booth and Bohlmann, 2019; Nuutinen, 2018). Flavonoids, including cannflavins A, B, and C, exhibit significant anti-inflammatory and antioxidant properties (Flores-Sanchez and Verpoorte, 2008; Barrett et al., 1985). This vast chemical diversity provides *Cannabis sativa* L. with a unique metabolic profile among higher plants.

From a morphological and physiological standpoint, glandular trichomes constitute the principal structures responsible for producing and accumulating secondary metabolites. These multicellular structures, composed of a secretory head and a stalk, are predominantly located on the female inflorescences and to a lesser extent, on leaves located adjacent to the flowers. Their density, morphology, and metabolic activity vary according to the developmental stage, environmental conditions, and genetic background of *Cannabis*, directly influencing the chemical composition of the secreted resin (Livingston et al., 2021; Happyana et al., 2013).

From a therapeutic perspective, *Cannabis sativa* L. has gained recognition as a valuable source of bioactive molecules. Numerous both preclinical and clinical investigations have shown that cannabinoids possess a wide range of pharmacological activities, including analgesic, anti-inflammatory, neuroprotective, anticonvulsant, anxiolytic, and antiemetic effects. These effects are mainly mediated through the activation of the CB_1 and CB_2 cannabinoid receptors within the endocannabinoid system, which regulate several physiological and pathological processes (Pertwee, 2008; Iversen, 2003). THC is primarily used in the management of chemotherapy-induced nausea and chronic pain, while CBD has exhibited clinical efficacy in specific forms of pharmacoresistant epilepsy (Devinsky et al., 2017). Moreover, recent studies highlight potential therapeutic applications in neurodegenerative, inflammatory, and metabolic diseases (Fernández-Ruiz et al., 2020 ; Pisanti et al., 2017).

However, despite the increasing number of scientific studies, existing reviews remain fragmented – most focus exclusively on either the botanical classification, chemical diversity, or pharmacological aspects of the plant. Few studies attempt to integrate these dimensions to elucidate the correlations between chemical variability, plant morphology, and therapeutic potential. Furthermore, many previous reviews overlook regional and environmental influences that shape the phytochemical profile and biological activities of *C. sativa,* particularly in underexplored areas such as North Africa.

Accordingly, the present review seeks to bridge these gaps by providing an integrative and updated synthesis that combines botanical, phytochemical, and therapeutic perspectives on *Cannabis sativa* L. It aims to identify patterns

and inconsistencies within current data, highlight methodological limitations, and outline future research priorities to better standardize and harness the plant's bioactive compounds for both industrial and pharmacological applications.

HISTORY OF *CANNABIS*

In the year 1753, Carl von Linné, a Swedish botanist reinstated hemp's classical Latin designation, *cannabis* derived from *canna* (meaning "reed") and *bis* (meaning "twice"), referring to a reed possessing two sexes.

Cannabis ranks among the earliest plant species domesticated and used by humans across the world. The first documented traces of its use dates back to approximately 4000 BCE in China, where fibers extracted from the plant's stems were employed in the production of textiles, paper and even ropes. The historical use of *Cannabis* as medicine in ancient Chinese culture is also well documented, appearing in one of the world's oldest medical compendiums, the *Shennong Bencao Jing*, which originates from the first century CE (Hui-Lin, 1974).

Even today, *Cannabis* seeds rich in fatty acids and proteins yet devoid of psychoactive compounds continue to be used in China for their laxative properties. The earliest references to the psychoactive effects of this plant also originate from ancient Chinese texts, which state: "Excessive use will produce visions of demons, and with prolonged consumption, one may communicate with spirits and lighten the body" (Touw, 1981).

In the Indian subcontinent, *Cannabis* was widespread as early as 1000 BCE, both for medicinal and recreational purposes. It was employed as an sedative, anticonvulsant, anti-inflammatory, analgesic, hypnotic, and even as a topical antimicrobial agent (Touw, 1981; Mikuriya, 1969).

In Tibet, *Cannabis* was traditionally regarded as a sacred plant and was notably used to facilitate meditation and spiritual practices (Touw, 1981). Additional evidence indicates that the Assyrians of the Middle East were also familiar with the psychoactive properties of *Cannabis*. They employed it both as incense in religious rituals and for medicinal purposes topically to reduce swelling, and systemically to treat conditions such as impotence, kidney stones, arthritis, and depression (Zuardi, 2006).

Since the 15th century, *Cannabis* has been known in Africa, where it was traditionally employed to treat snake bites, ease childbirth, and alleviate ailments such as malaria, fever, and dysentery (Du Toit, 1980).

On the American continent, *Cannabis* has been used since the 16th century in religious ceremonies and for the management of various ailments such as stomach pains and toothaches (De Pinho, 1975).

In Europe, *Cannabis* use dates back to the Christian era, particularly during funeral ceremonies in which the fumes from burning *Cannabis* seeds were inhaled for ritual and euphoric purposes. Later, *Cannabis* was grown exclusively for its plant fibers, which were used to make paper. Unlike in Asian countries, there is little evidence regarding the medicinal use of *Cannabis* in Europe before the 16th century.

Cannabis became part of modern medical practice in the mid-19th century, largely due to the the work of the Irish physician William B. O'Shaughnessy and the publications of the French psychiatrist Jacques-Joseph Moreau (Zuardi, 2006). O'Shaughnessy documented in detail the use of *Cannabis* in different parts of the world and described numerous successful clinical applications of *Cannabis*-based preparations for conditions such as convulsions, rheumatism, and, most notably, the severe muscle spasms associated with tetanus and rabies. Meanwhile, Jacques-Joseph Moreau conducted experiments with various *Cannabis* preparations starting by testing the preparations on himself and later applying them to his students. The findings from these investigations were compiled in his 1845 publication, which offered in-depth descriptions of the acute psychological effects of *Cannabis* in humans (Moreau de Tours, 1895). From the mid-20th century onward, the recognized therapeutic applications of the *Cannabis* plant were summarized as follows (M.L.M.R.N, 1997):

- analgesic action: relief from migraines, neuralgia, etc.;
- sedative and hypnotic action: treatment of melancholy, insomnia, etc.;
- other actions: anti-diarrheal, relief from male impotence, appetite stimulant, etc.

In the second half of the 20th century, *Cannabis* assumed significant social relevance due to a marked rise in its recreational consumption. Beginning in the 1960s, the consumption

of *Cannabis* for leisure purposes spread swiftly among younger generations throughout the Western world. In 1964, Professor Raphael Mechoulam identified the molecular structure of tetrahydrocannabinol (THC), the major psychoactive component responsible for *Cannabis* psychotropic effects, thereby laying the foundation for an extensive wave of research on the plant's active constituents (Mechoulam and Gaoni, 1964; Mechoulam, 1973).

BOTANICAL AND PHYSIOLOGICAL CHARACTERISTICS OF *CANNABIS*

Position in the taxonomy

Cannabis sativa is a dicotyledonous herbaceous plant assigned to the Cannabaceae family. In Cronquist's 1981 classification system, this family is placed within the order *Urticales*, whereas the Angiosperm Phylogeny Group II (APG II) phylogenetic system assigns it to a different evolutionary grouping based on molecular data (Bremer et al., 2003) classifies it in the order *Rosales.* The taxonomic classification of *Cannabis sativa* is presented in Table 1. Within both classification systems, within the Cannabaceae family, the genus *Cannabis* is represented by the species *Cannabis sativa* L., which is further divided into three subspecies (Figure 1):

- *C. sativa* ssp *ruderalis* or *spontanea* – the so-called wild form.
- *C. sativa* ssp *indica* (Indian hemp) – the psychotropic form.
- *C. sativa* ssp *sativa* – industrial variety, a source of both fibers and seeds.

According to Bouloc (2006), *Cannabis sativa* is classified into two subspecies: the wild form *C. sativa* ssp. *spontanea*, and the cultivated form *C. sativa* ssp. *culta*, which includes all domesticated varieties. The morphological and physiological traits of industrial hemp varieties depend heavily on the soil conditions under which they are grown. This relationship also extends to the quality of the plant's fibers, seeds, and the quantities of CBD and tetrahydrocannabinol (THC).

Industrial hemp (*Cannabis sativa* ssp. *sativa*) exists in two main forms**:** monoecious, which has been developed through genetic improvement, and dioecious, the naturally occurring type composed of separate male and female plants.

Table 1. Botanical classification of *Cannabis sativa L.*

Taxonomic rank	Scientific name / classification
Kingdom	*Plantae*
Subkingdom	*Tracheobionta* (Vascular plants)
Division	*Magnoliophyta* (Flowering plants)
Class	*Magnoliopsida* (Dicotyledons)
Order	*Rosales*
Family	*Cannabaceae*
Genus	*Cannabis L.*
Species	*Cannabis sativa*

Note: Prepared by the authors based on data from Bouloc (2006) and Bremer et al. (2003).

Botanical characteristics

Vegetative apparatus

Morphologically, *Cannabis sativa* is characterized by a grooved stem that can exceed 2 meters in height. In the lower part of the plant, the leaves are opposite, stipulate, and palmately lobed, typically composed of up to seven uneven, elongated, and serrated leaflets. Toward the upper

Figure 1. Sous espèces de *Cannabis sativa, C. sativa sativa, C. sativa indica et C. sativa ruderalis*

portion of the stem, the leaves become alternate and are either simple or divided into only three segments (Botineau, 2010).

The plant is distinguished by its long, slender flowers and the presence of glandular hairs, which secrete aromatic and resinous substances, giving it a characteristic fragrance and sticky texture (Anwar et al., 2006; Bouloc, 2006). It has different types of trichomes (or hairs):

- Cystolithic hairs – these are specialized structures containing *cystoliths*, which are masses of inorganic crystals, typically composed of calcium carbonate, formed within specific cells of the leaves in certain angiosperms. Their primary function is believed to be the regulation of cytoplasmic pH by neutralizing excess hydroxyl ions produced during nitrate reduction in the leaf.
- Resin-secreting hairs **(**trichomes) – these structures are involved in the biosynthesis and secretion of cannabinoids, the active chemical compounds characteristic of *Cannabis* species.

Sex differentiation in *Cannabis sativa* becomes evident only during the final growth stage, when flowering begins. At this stage, female flowers can be clearly distinguished from male flowers.

As illustrated in Figure 2, Female flowers lack petals and are composed of two elongated stigmas, which may be white, yellow, or pink. Their calyx, measuring approximately 3–6 mm in length, encloses the ovary that contains a single ovule and is entirely surrounded by a carpel. Female flowers are typically arranged in pairs and arise from the axillary positions of small bract leaves. These bracts are densely covered with glandular trichomes, which serve as the primary sites of cannabinoid accumulation in THC-rich varieties. Male floral structures consist of five sepals, roughly 5 mm in length, and are generally-white, yellow or green color. These flowers hang downward when in bloom and contain five stamens of similar length, which release pollen during maturation (Bouloc, 2006; Botineau, 2010). Figure 2(e), presents *Cannabis* seeds which are ovoid to spherical, generally measuring between 3 and 5 mm in length. Each seed contains two cotyledons that serve as storage organs rich in proteins and oils, while the endosperm is notably reduced in size compared to that of most other plant species (Bouloc, 2006).

The stem is structured as a hollow cylinder composed of several distinct layers: the xylem, measuring 1–5 mm in thickness; a cambium layer approximately 10–50 µm thick; a cortex ranging from 100–300 µm in thickness; an epidermis about

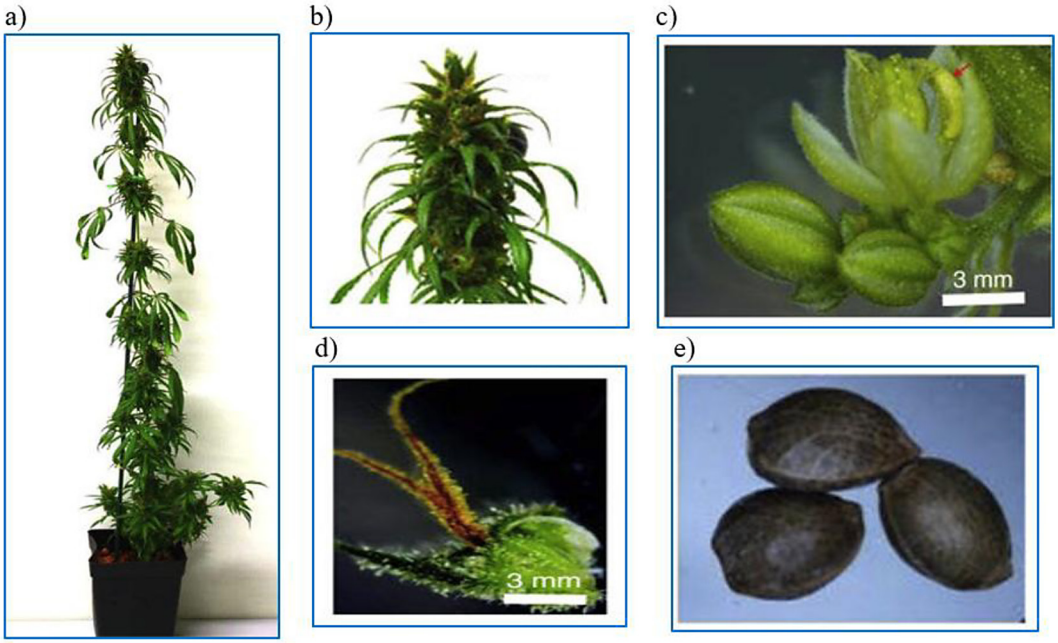

Figure 2. (a) female *Cannabis sativa;* (b) portion of the female flowers, (c) pistillate female flower, (d) portion of the female flowers show anther; (e) mature seed adapted from Farag and Kayser (2017). Source: https://doi.org/10.1016/B978-0-12-800756-3.00001-6

20–100 µm thick; and an outer cuticle measuring 2–5 µm in thickness (Dupeyre and Vignon, 1998).

The *Cannabis* stalk can be distinguished into two principal morphological regions:

- Primary fibers, situated along the outer periphery of the stalk, are held together by the middle lamella and arranged into bundles. These fibers are notable for their considerable length, thick cell walls, and distinctive chemical composition. They are separated by parenchyma cells that are abundant in hemicellulose and pectin. Structurally, these fibers contain a high proportion of cellulose and relatively low amounts of non-cellulosic polysaccharides, proteins, and lignin. Their thick secondary walls are particularly distinguished by the abundance of cellulose with a high degree of crystallinity (Crônier et al., 2005). The central portion of the stem, known as the xylem, also referred to as *chènevotte* or hemp wood, is composed of lignified cells, woody fibers, vessels, and medullary rays. This inner structure provides the plant with its mechanical strength, exhibiting properties comparable to those of hardwood (Crônier et al., 2005; Vignon et al., 1995).
- Secondary fibers, also known as extraxylem fibers, originate from the cambium layer. During the defibration process, these fibers typically remain attached to the woody core (shives) and are thus designated as technical fibers. The fibers are relatively short and loosely arranged. Although their diameter is comparable to that of hardwood fibers, they are generally shorter and possess thinner cell walls (Vignon et al., 1995).

The molecular composition characteristic of hemp fibers reveals a significantly higher content of holocellulose over two-thirds of which is alpha-cellulose compared to both hardwoods and softwoods. Additionally, hemp fibers contain substantially less lignin (approximately 10%) than hardwoods (20–22%) and softwoods (27–28%) (Correia et al., 2001).

At the stage of grain maturation, the bark of the stem consists of approximately 4% pectins, 4% hemicellulose, 2% lignin, and 75% cellulose. Evidence indicates that cellulose levels progressively increase throughout plant development. In contrast, at the onset of flowering, hemicellulose content declines, while lignin follows an opposite trajectory, showing a gradual rise (Toonen et al., 2004; Crônier et al., 2005).

Reproductive system

Cannabis is largely dioecious, with male and female floral structures arising on different individuals when propagated from seed. However, Monoecious variants, characterized by the presence of both male and female flowers on a single plant, also occur. Varieties selectively bred for fiber production are generally monoecious, as this trait contributes to the development of a more uniform and consistent raw material.

Sex determination in Cannabis is governed by heteromorphic chromosomes, where female plants are homogametic (XX) and male plants are heterogametic (XY). From a morphological standpoint, distinguishing between female and male individuals is challenging throughout the vegetative growth phase, that is throughout the plant's active growth phase.

Sexual dimorphism in *Cannabis* becomes evident only at a later stage of development, as female plants can be distinguished from male plants only after flowering begins. However, with current advances in molecular biology, several techniques are now available that allow to identify plant sex at an early stage, before flowering occurs (Mandolino et al., 1999; Flachowsky et al., 2008; Torjek et al., 2002).

Male inflorescences form panicles and include five separate green-tinted sepals and five episepalous stamens whose filaments stand erect within the floral bud.

Female inflorescences are grouped into dense cymes and accompanied by bracts. The calyx, which is urceolate in form, encloses a bicarpellate ovary ; however, one carpel usually degenerates, leaving only one ovule. The fruit that develops, often referred to as a hemp seed, is an ovoid, grayish achene with a smooth surface, approximately 3 mm in both length and diameter (Botineau, 2010).

Biotope and geographical distribution of *Cannabis* in the Rif Mountains

In the Rif region, the rapid shift toward modern *Cannabis* cultivation methods, along with the intensification of export-focused monoculture, has gradually established itself as the leading production approach. onoculture describes a farming or

forestry practice where one species is continuously cultivated across extensive land, typically without crop rotation and with heavy reliance on chemical inputs. In the Rif region, characterized by extremely rugged terrain, this practice typically occurs on small, fragmented plots devoted exclusively to a single, standardized, and uniformly aligned *Cannabis* crop. Over time, this shift toward monoculture has profoundly reshaped the Rif landscape, replacing the region's traditional polycultural farming systems (Afsahi, 2017; Afsahi, 2020).

Throughout the 1980s and 1990s, agricultural pressure increased, and *Cannabis* cultivation expanded into additional regions as growers replicated existing practices. This spread was facilitated by the exchange of agricultural knowledge, both among local laborers and between farmers from the traditional cultivation zones and those in newly converted areas.

Starting in the 1990s, faced with land scarcity and stricter forestry regulations, some farmers began seeking new areas suitable for *Cannabis* cultivation, especially in the Taounate province. By collaborating in collaboration with local producers, they rented agricultural land and introduced modern agricultural techniques including the use of fertilizers, pesticides, tractors, and advanced irrigation systems that were impractical in traditional growing regions due to their rugged topography. In these new cultivation zones, notably in the province of Chefchaouen, monoculture became predominant, particularly across the large irrigated valleys. As a result, the area devoted to *Cannabis* cultivation increased sharply, rising from a few dozen hectares in the 1950s to over 100,000 hectares by the early 2000s, and extending across the provinces of Taounate, Larache, Tetouan, Al Hoceima, and Chefchaouen. (Afsahi, 2017).

Analytical remarks and comparative discussion

The botanical and physiological characteristics of *Cannabis sativa* show remarkable diversity depending on variety, geographical origin, and environmental conditions. Comparative analyses of morphological and anatomical features among the three main subspecies *C. sativa* ssp. *Ruderalis, C. sativa* ssp. *indica* and *C. sativa* ssp. *sativa* reveal that *indica* types generally exhibit shorter and more compact morphologies, higher trichome densities, and increased resin production, while *sativa* varieties are taller and more fibrous, with lower cannabinoid concentrations (Bouloc, 2006; Small, 2015). These morphological differences correlate strongly with the chemical phenotype (chemotype) of each variety, suggesting a direct link between botanical form and metabolite biosynthesis capacity.

Geographical and ecological conditions also contribute significantly to determining the plant's phytochemical variability. Studies have shown that *C. sativa* cultivated in colder or high-altitude regions tends to accumulate higher proportions of CBD and CBDA, whereas plants grown in warmer, drier climates favor the biosynthesis of Δ^9-THC (Richard and Senon, 2010). Similarly, the Rif region of northern Morocco, characterized by semi-arid Mediterranean conditions, is known to produce chemotypes with distinct cannabinoid ratios compared to European or Asian cultivars, likely due to combined effects of temperature, soil type, and light exposure (Afsahi, 2017; Afsahi, 2020). Environmental stress factors such as drought, UV radiation, and nutrient limitation further modulate the density and metabolic activity of glandular trichomes, enhancing secondary metabolite production. This adaptive response reflects the plant's metabolic plasticity, an essential feature explaining its ecological success and chemical diversity (Happyana et al., 2013; Livingston et al., 2021).

From a physiological perspective, the correlation between environmental conditions and biosynthetic pathways suggests that secondary metabolism in *C. sativa* is not fixed genetically but dynamically regulated. This has important implications for both pharmacological research and industrial production. Understanding these regulatory mechanisms could help standardize cultivation parameters to optimize specific chemotypes for medical, nutritional, or fiber-oriented purposes.

Synthesis and implications

The data demonstrate that the diversity of cannabinoid and secondary metabolite biosynthesis in *Cannabis sativa* reflects the combined effects of genetic makeup, morphological traits, and environmental conditions. This variability poses challenges for standardization in pharmacological studies, as the same species may yield different chemical profiles under distinct ecological contexts. Future research integrating genetic characterization, controlled cultivation experiments, and advanced metabolomic analysis will

be essential to clarify these relationships and enable reproducible, chemotype-specific applications of *C. sativa* in biotechnology and medicine.

CHEMICAL COMPOSITION OF *CANNABIS*

As a polymorphic plant, *Cannabis* produces a variety of chemical constituents distributed across multiple plant parts, including sedes, leaves, stalks and flowers. In addition to alkaloids, terpenoids, carbohydrates, stilbenoids, flavonoids, fatty acids, steroids, polysaccharides, and their amin-acids, amides, esters, oils, phytosterols, sterols, proteins and waxes polyphenols, The most extensive group is represented by the cannabinoids, a remarkable category of terpenophenolic active molecules largely confined to *Cannabis.* (Mahlberg and Kim, 2004; Ashton, 2001; Liu et al., 2022, Mastellone et al., 2022; Pattnaik et al., 2022; Radwan et al., 2021; Bautista et al., 2021; Deidda et al., 2019; Hanuš et al., 2016). This chemical composition is primarily influenced by geographical factors, the plant variety, its developmental stage, as well as growth conditions for example humidity, nutrient availability and light exposure. Additionally, harvest timing and storage conditions serve a crucial function in in determining the final chemical profile (Monton et al., 2019; Mastellone et al., 2022; Christodoulou et al., 2023; Berman et al., 2018)

Cannabinoids

Variability of cannabinoids in Cannabis

The cannabinoid content of *Cannabis* is shaped by genetic determinants as well as environmental conditions, humidity, including light, temperature, oxygen levels, and the specific circumstances under which samples are stored. They are concentrated in the flowering tops (average THC content of 10–12%), leaves (1–2%), and stems and branches, which contain less (0.1–0.3%). With regard to THC, analyses of the whole dried plant reveal average concentrations usually ranging between 1 and 13%, with an average close to 8% in France, but sometimes exceeding 20%. This concentration was estimated at an average of 1% in samples grown in the United States and 3 to 5% for Mexican marijuana in 1960, compared to 10 to over 30% for varieties selected for their high THC content and grown in greenhouses in California and the Netherlands: the increasing trend in THC content is a real public health concern (Richard and Senon, 2010).

By gender

Female plants of resinous varieties are considered to be more active: they produce more resin but with the same THC concentration. Male plants flower earlier than female plants and reach peak THC synthesis earlier (Richard and Senon, 2010).

Depending on age and growing conditions

Young hemp or hemp grown in cool areas is particularly rich in cannabidiolic acid and cannabidiol (around 80% of total cannabinoids) but low in THC (less than 0.2%). When it is hot, the plant prolongs the biochemical reactions of biosynthesis involving the cannabinoid series: the proportion of cannabidiolic acid and cannabidiol is lower, while that of THC rises. Short-cycle varieties are therefore preferred by producers (Richard and Senon, 2010).

Depending on the type of Cannabis

There is a classification based on a distinction between two groups of *Cannabis*, depending on the quantitative composition of the resin. Fiber varieties contain no more than 0.2% THC. However, considering only the THC content of the plant does not facilitate analytical testing, and some specialists propose, in order to simplify legal testing, determining the cannabidiol content to calculate the THC/CBD ratio, which is virtually constant regardless of the part of the plant analyzed and the time of sampling. The concentration of resin varies for cannabinoids depending on the geographical origin of the plant. Careful chemical analysis can provide information on the origin of the drug (Richard and Senon, 2010).

Main cannabinoids and their biosynthesis

Most of the bioactive substances in *Cannabis sativa* plant are cannabinoids. Endocannabinoids, phytocannabinoids, and synthetic cannabinoids constitute the three major groups into which cannabinoids are divided. The type of cannabinoid found in C. sativa is called phytocannabinoids, and are produced spontaneously in the female C. sativa inflorescences (Baldino et al., 2020).

The skeleton of cannabinoids in their neutral state is made up of 21 carbon atoms. They

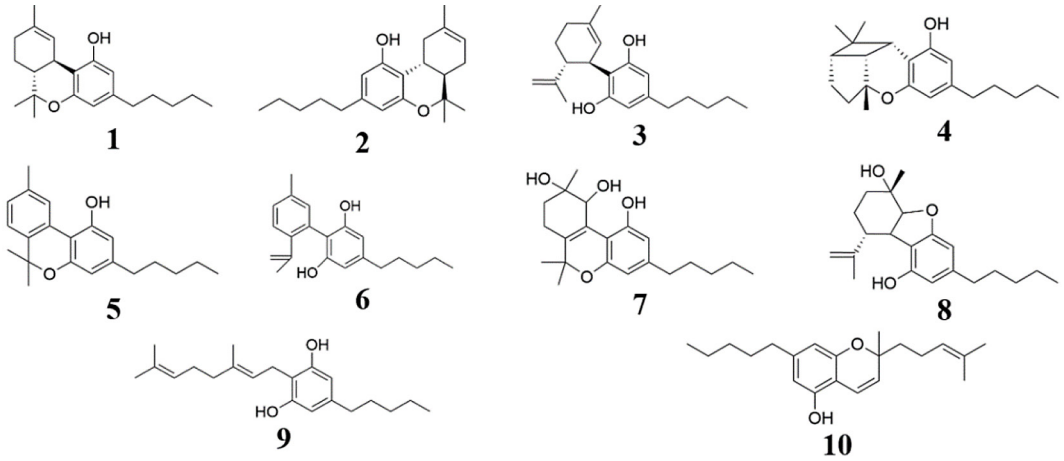

Figure 3. Structural representations of the key cannabinoids occurring in *Cannabis sativa: (1)* Δ9-tetrahydrocannabinol (Δ^9-THC), (2) Δ^8-tetrahydrocannabinol (Δ^8-THC), (3) Cannabidiol (CBD), (4) Cannabicyclol (CBL), (5) Cannabinol (CBN), (6) Cannabinodiol (CBND), (7) Cannabitriol (CBT), (8) Cannabielsoin (CBE), (9) Cannabigerol (CBG), (10) Cannabichromene (CBC)

have been divided into ten distinct subcategories, which include : Δ^9-tetrahydrocannabinol (Δ^9-THC), cannabidiol (CBD), Δ^8-tetrahydrocannabinol (Δ^8-THC), cannabinodiol (CBND), cannabigerol (CBG), cannabinol (CBN), cannabitriol (CBT), cannabicyclol (CBL), cannabielsoin (CBE), cannabichromene (CBC), and miscellaneous (Brenneisen, 2007). Figure 3 illustrates the core chemical structures of the major cannabinoids occurring in *Cannabis sativa L.*

Cannabinoids are biosynthesized and stored within the plant primarily as their carboxylic acid derivatives, mainly within the resin secreted by the glandular trichomes of the female (pistillate) flowers (Sirangelo et al., 2022; Nahar et al., 2021). Because they are chemically unstable, the acidic cannabinoids readily undergo non-enzymatic decarboxylation to form neutral analogues with enhanced pharmacological efficacy. This process is promoted by heating (e.g., smoking),

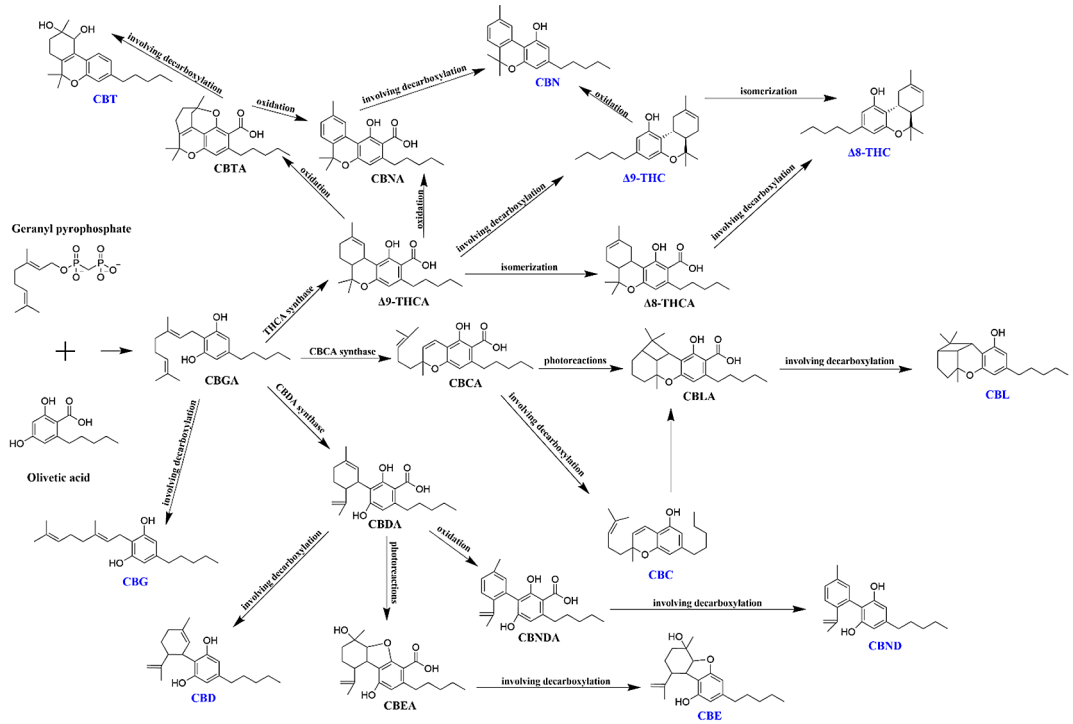

Figure 4. Biosynthetic Pathway of the primary phytocannabinoids found in *Cannabis sativa*: Δ9-THC, CBD, CBT, CBE, CBN, CBC, CBND, Δ8-THC, CBL, and CBG

drying, light exposure, or storage conditions after harvest (Deidda et al., 2019; Protti et al., 2019; Sainz Martinez et al., 2023, Odieka et al., 2022; Dos Santos and Romão, 2023; Fernandez et al., 2022). All cannabinoids originate from the precursor cannabigerolic acid (CBGA), albeit they vary in the way this precursor is cyclized (Johnson et al., 2020; ElSohly et al., 2017;).

Figure 4 illustrates the biosynthetic pathways of the predominant cannabinoids identified in *Cannabis sativa*, showing the conversion of CBGA into the acidic forms CBDA, CBCA, and THCA, followed by decarboxylation and oxidation reactions leading to the formation of neutral cannabinoids like CBG, CBD, CBC, Δ^9-THC, Δ^8-THC, CBN, CBL, CBT, CBE, and CBND:

- CBGA, or cannabigerolic acid, constitutes the major cannabinoid acid in fresh *Cannabis* material. Its formation involves the enzymatic condensation of olivetolic acid (OLA) and geranyl diphosphate (GPP) (Berman et al., 2018; Luca et al., 2021; Mariotti et al., 2016). CBGA serves as the biochemical precursor for several major cannabinoids, including CBCA, CBDA and tetrahydrocannabinolic acid (THCA). The acidic form of cannabigerol is CBGA, which, like other cannabinoids, is produced and accumulated in the glandular trichomes of *Cannabis*. Its concentration varies according to how quickly it is converted into downstream cannabinoids. CBGA biosynthesis proceeds through an enzyme-mediated pathway. In the initial step, hexanoyl-CoA and malonyl-CoA undergo condensation catalyzed by tetraketide synthase (TKS) and olivetolic acid cyclase (OAC), resulting in the formation of olivetolic acid (Gagne et al., 2012). When aromatic prenyltransferase and geranyl pyrophosphate (GPP) are present, olivetolic acid is recognized to be the main precursor in the prenylation reaction that forms CBGA (Fellermeier and Zenk, 1998). Under the catalytic action of tetrahydrocannabinolic acid synthase, cannabidiolic acid synthase, and cannabichromenic acid synthase, CBGA is converted into THCA, CBDA, and CBCA, respectively (Taura et al., 1996; Morimoto et al., 1998; Sirikantaramas et al., 2005).
- CBD, or cannabidiol, recognized as the second most prevalent cannabinoid after THC exhibits no psychotropic properties. It is structurally distinct from CBDA because the latter contains a carboxyl group (-COOH). Therefore, CBD corresponds to the decarboxylated derivative of CBDA, formed primarily through heat exposure. CBD is part of the alkylresorcinol family, which also includes CBDA. Notably, CBD can attenuate or balance the psychoactive response produced by THC by reducing its euphoric effects (Morgan et al., 2010).
- CBG, or cannabigerol, is a non-psychotropic cannabinoid derived from CBGA via decarboxylation. (Aizpurua-Olaizola et al., 2016). Because CBG lacks the carboxyl group (-COOH), it cannot be catalytically converted into other cannabinoids like CBGA can (Taura et al., 2007).
- CBC, or cannabichromene, it's present in trace amounts in *Cannabis* plants. Under the catalytic activity of CBCA synthase, cannabichromenic acid (CBCA) is converted into CBC, its decarboxylated form. (Thomas and ElSohly, 2016). In *Cannabis* plants, the decarboxylation reaction of CBCA is aided by warm weather and solar UV radiation, which eliminates CO2 and produces CBC (Havelka, 2017). CBCA, or cannabichromenic acid, is a cannabinoid produced from CBGA. When CBCA synthase is active, CBGA is transformed into CBCA, as well as other acidic cannabinoids, including THCA and CBDA (Morimoto et al., 1997).
- CBDA, or cannabidiolic acid, is structurally related to cannabidiol, distinguished by a carboxyl group (–COOH) located at the second position of the alkylresorcinol ring. CBDA is non-psychoactive, much as CBD itself. A decarboxylation reaction is used to heat CBDA into CBD. Higher percentages of CBDA may be made up of *Cannabis* plants located in colder climates and higher elevations. One could think of CBGA as the cannabinoid that precedes CBDA. Through the cyclization of the aliphatic chain and the catalytic action of CBDA synthase, CBGA is transformed into CBDA (Taura et al., 1996).
- Δ^9-THC, or Δ^9-tetrahydrocannabinol is one of the important and strong cannabinoids with psychotropic properties. THC content is typically higher in hashish (resin), marijuana, and drug-type in *Cannabis*, although it appears in lower amounts in hemp (fiber-type). (Protti et al., 2019). THCA and CBGA are intermediates used in the synthesis of THC in the *Cannabis* plant. When a particular enzyme is present, geranyl pyrophosphate and olivetolic acid react

to form CBGA. Following ring cyclization, CBGA is changed into THCA, which is then further decarboxylated to produce THC.

- Δ^8-THC, or Δ^8-Tetrahydrocannabinol, is a naturally occurring minor psychoactive cannabinoid that is chemically stable and structurally similar to Δ^9-THC, differing only by the location of a double bond within the cyclohexene ring. In *Cannabis sativa* L., Δ^8-THC is not biosynthesized de novo, but rather forms through the isomerization or oxidation of Δ^9-THC during storage, exposure to heat, or acidic conditions. This double-bond migration from the 9th to the 8th carbon atom of the terpenoid moiety produces a more thermodynamically stable compound. As a result, Δ^8-THC is commonly detected in aged *Cannabis* samples or during laboratory conversions of CBD or Δ^9-THC under controlled conditions. Pharmacologically, Δ^8-THC exhibits psychoactive properties similar to Δ^9-THC but with reduced potency, and has demonstrated antiemetic, anxiolytic, appetite-stimulating, and neuroprotective activities in preliminary studies. Due to its chemical stability and mild psychoactivity, Δ^8-THC has gained growing interest in both analytical and therapeutic research (Mechoulam and Gaoni, 1967; Hollister and Gillespie, 1973; ElSohly and Slade, 2005). THCA, or tetrahydrocannabinolic acid is the carboxylic acid precursor of THC. THCA, can be produced biosynthetically from CBGA when THCA synthase is present (Sirikantaramas et al., 2004). THC is found in living *Cannabis* plants as THCA, which is decarboxylated to produce THC when dried or kept for an extended period of time.
- CBN, or cannabinol is a cannabinoid has a slight psychoactive effect, its sedative properties make it more appealing. The process of oxidative conversion of a certain portion of THC in the Cannabis plant produces CBN. When Δ^9-THC is exposed to air and light, it breaks down into CBN through an oxidation reaction.
- CBNA, or cannabinolic acid is a naturally occurring oxidative degradation product of THCA, which itself is the acidic precursor of Δ^9-THC. During aging, air exposure, or heat treatment, THCA undergoes dehydrogenation and oxidation of its terpenoid moiety, resulting in the formation of CBNA. Subsequent decarboxylation of CBNA under thermal or light exposure leads to cannabinol (CBN), one of the most stable and well-known oxidation products of THC.
- CBL, or cannabicyclol is a non-psychoactive cannabinoid that is not biosynthesized directly by *Cannabis sativa L.*, but rather originates as a secondary degradation product of cannabichromene (CBC). Under UV irradiation or heat exposure, CBC undergoes a photo-induced intramolecular rearrangement that generates CBL, a compound with greater thermodynamic stability. This photochemical conversion involves the closure of an additional ring structure within the CBC skeleton, resulting in a bicyclic configuration that characterizes CBL. Consequently, CBL is typically found in aged or light-exposed *Cannabis* samples where CBC has undergone gradual photodegradation. Unlike the psychoactive cannabinoids such as THC, CBL exhibits no psychotropic activity and remains chemically stable against further oxidation or thermal transformation (Gaoni and Mechoulam, 1966; Hanuš et al., 2016; ElSohly and Gul, 2014).
- CBT, or cannabitriol is an uncommon phytocannabinoid that naturally occurs in *Cannabis* sativa L. at only trace levels. In contrast to the primary cannabinoids, such as Δ^9-THC and CBD. CBT is considered a secondary oxidative metabolite of Δ^9-THC or related THCA. Its formation is thought to occur through auto-oxidation and hydroxylation processes during plant aging, exposure to air, or prolonged storage. Structurally, CBT contains two hydroxyl groups on the aromatic ring of the THC skeleton, which explains its higher polarity and chemical instability under standard conditions. Several isomers of CBT have been reported (such as CBT-a and CBT-b), resulting from different positions of hydroxyl substitution. Although pharmacological data are still limited, preliminary studies suggest that CBT exhibits non-psychoactive properties and may possess mild anti-inflammatory and antioxidant effects. Overall, the presence of CBT in aged or oxidized *Cannabis* samples reflects the natural degradation and oxidation pathways of THC-like cannabinoids (Yoshimura et al., 1969; ElSohly and Slade, 2005; Hanuš et al., 2016).
- CBE, or cannabielsoin is a non-psychoactive cannabinoid that originates from the oxidative metabolism and degradation of CBD. It is generally formed through air oxidation, exposure

to light, or prolonged storage of *Cannabis* or purified CBD. During this process, the resorcinol ring of CBD undergoes oxidative rearrangement and hydroxylation, leading to the formation of a more polar bicyclic structure characteristic of CBE. Two main isomers, CBE and CBEA (its acidic precursor), have been characterized in aged *Cannabis* sativa samples and in in vitro oxidation experiments. CBE is chemically stable compared to its precursor but occurs only in trace amounts in fresh plant material, suggesting that its presence is mainly the result of post-harvest transformation of CBD. Pharmacological investigations remain limited, but early findings indicate that CBE lacks psychoactivity and may display mild antibacterial and metabolic modulation properties (Hively et al., 1966; Hanuš et al., 2016; ElSohly and Slade, 2005).

- CBND, or cannabinodiol is a neutral, non-psychoactive cannabinoid that results from the oxidative degradation of Δ^9-THC or its acidic precursor (THCA). It is considered a secondary oxidation product, formed during the aging or prolonged storage of *Cannabis*, particularly when exposed to air, light, or elevated temperatures. Structurally, CBND shares a close similarity with CBD but lacks its typical open-ring configuration, as oxidation of the THC molecule induces a conversion of the dihydropyran ring into a more stable dihydroxy aromatic system. This transformation reduces the psychoactivity of the parent compound and leads to the accumulation of CBND in old or degraded *Cannabis* samples. Due to its oxidative origin, CBND is often detected alongside other degradation products such as CBN. Although pharmacological data are scarce, preliminary research suggests that CBND is biologically inactive and serves mainly as a marker of oxidative aging in *Cannabis* material (Obata et al., 1967; Hanuš et al., 2016; ElSohly and Slade, 2005).

Terpenes

Terpenoids, which are abundant in C. sativa, are the main component that gives many plants their distinct scent (Booth and Bohlmann, 2019). Flowers, leaves, trichomes, roots, and essential oils are the main sources of them (Liu et al., 2022). Several well-known terpenes, such as linalool, caryophyllene, humulene, terpinolene, myrcene, limonene, ocimene and pinene as shown in Figure 5, are present in certain *Cannabis* plant varieties (Nuutinen, 2018; Casano et al., 2010; Stone, 2021). The synergistic effects of these substances with cannabinoids have been proven, (Pegoraro et al., 2021). *Cannabis* contains terpenes and terpenoids that fall into several categories:

- Monoterpenes – including two isoprene units and containing 61 different chemicals (Radwan et al., 2021; Zheljazkov and Maggi, 2021; Krill et al., 2020). Linalool, α-terpinolene, β-myrcene, α-pinene, limonene, and trans-ocimene are the principal constituents. Late harvest is when their content in the plant rises (Isidore et al., 2021).
- Sesquiterpenes – including three isoprenes and 51 compounds total (Radwan et al., 2021). These semi-volatile molecules further enhance the distinctive fragrance of the plant. (Krill et al., 2020; Zheljazkov and Maggi, 2021). Caryophyllene oxide, E-caryophyllene, E-β-farnesene, and β-caryophyllene are the primary components, and their concentration

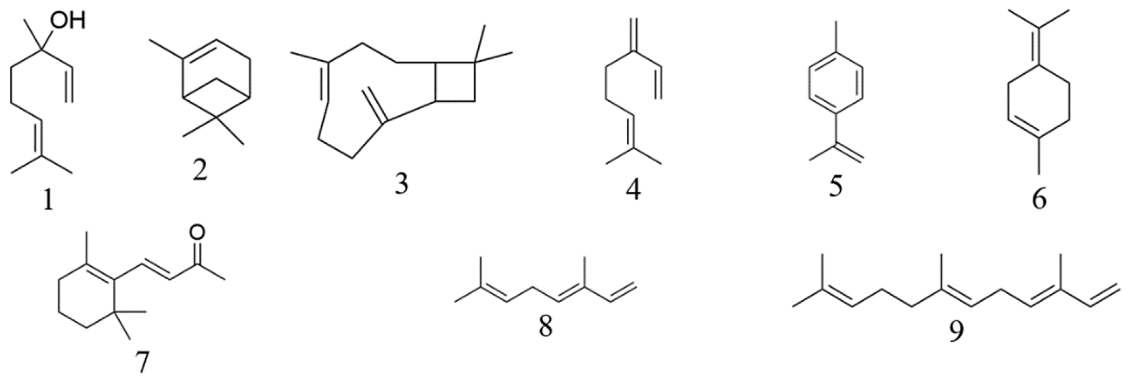

Figure 5. Principal terpenoids identified in *Cannabis sativa*: (1) Linalool, (2) α-pinene, (3) E-caryophyllene, (4) β-myrcene, (5) Limonene, (6) α-terpinolene, (7) β-ionone, (8) Trans-ocimene and (9) E-β-farnesene

is maximum during the earlier harvest period (Isidore et al., 2021).

- Diterpenes – steroids, waxes, and resins are examples of diterpenes of four isoprenes. There are now just two substances in *Cannabis sativa* – neophytadiene and phytol (Radwan et al., 2021).
- Triterpenes – comprising six isoprenes can be found in the roots, stem or leaves of plants (where the highest quantity has been found) as steroids, waxes, and resins. Friedelin, the main chemical, was found in 1971 together with epifriedelin, which has also been found in trace levels associated with β-amyrin (Isidore et al., 2021).
- Miscellaneous terpenes – four terpenes fall under this group; two, vomifoliol and dihydrovomifoliol, were extracted from the plant's stems and leaves, while the oil of the plant included β-ionone and dihydroactinidiolide (Radwan et al., 2021).

Because of the oxidative changes that occur during the decarboxylation and drying processes, terpenes and terpenoids may be lost (Fallahi et al., 2022; Isidore et al., 2021).

Flavonoids

Flavonoids are the most abundant class of phenolic chemicals found in natural plants and possess numerous significant bioactivities (Shang et al., 2020; Gandhi et al., 2020). Flavonoids make up around 10% of the known chemicals in *C. sativa*. This plant yielded over 34 flavonoids, including, quercetin, orientin, isovitexin, luteolin, vitexin, apigenin, kaempferol and three flavones called cannflavin A, B, and C presented in Figure 6, which contain prenyl or geranyl groups (Sainz Martinez et al., Liu et al., 2022; 2023; ElSohly, 2007; Bautista et al., 2021;) have been detected within multiple plant components, including pollen, flowers and leaves (Isidore et al., 2021; Tomko et al., 2020). Significant differences exist in their quantities within *Cannabis* between species and between different plant components. Environmental factors, particularly sun irradiance, temperature, moisture, and precipitation, also affect their production (Calzolari et al., 2017; Bautista et al., 2021; Dos Santos and Romão, 2023). Furthermore, some of these substances require the creation of unique conditions, such as abiotic and biotic stressors (Addo et al., 2021). According to one of the earliest investigations into *Cannabis*-specific flavonoids, these substances were approximately 30-fold more effective than aspirin at preventing human rheumatoid cells in culture from releasing prostaglandin E2 (PGE2) (Barrett et al. 1985).

Stilbenes

Another class of phenolic chemicals found in *C. sativa* are stilbenoids. They are mostly found in *C. sativa's* leaves, stems, resins, and flower heads. They are classified into three primary categories : spiroindans, dihydrostilbenes, and phenanthrenes (Isidore et al., 2021). The leaves of *Cannabis sativa* contain a special dihydrostilbene

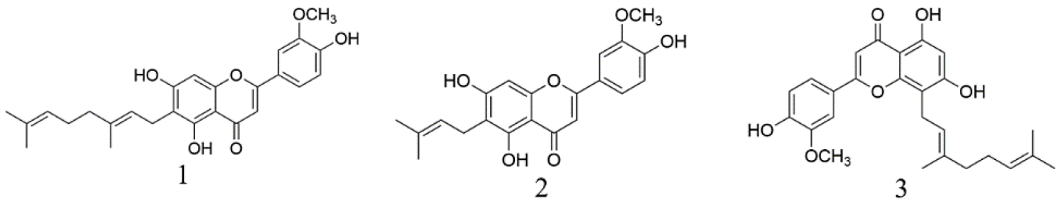

Figure 6. Chemical structures of major *Cannabis* flavonoids: (1) Cannflavin A, (2) Cannflavin B and (3) Cannflavin C

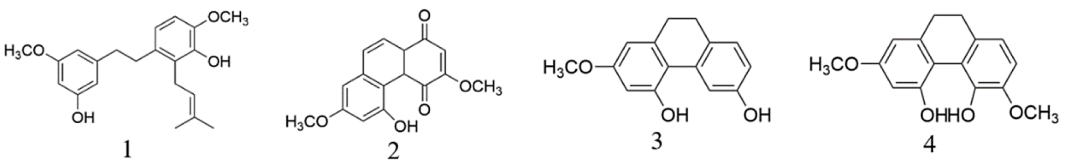

Figure 7. Most important stilbenes identified in *Cannabis sativa:* (1) Canniprene, (2) Denbinobin, (3) Cannithrene 1 and (4) Cannithrene 2

called canniprene, which may have therapeutic uses (Russo, 2017). The most common spiroindans, *Cannabis*-pirone and *Cannabis*-pirenone A, have also been shown to have anti-cancer and anti-inflammatory properties (Isidore et al., 2021). Moreover, the leaves and branches of a novel *C. sativa* variety included cannithrene 1 and cannithrene 2 (Cheng et al., 2010). Another study identified denbinobin as a distinct stilbenoid in *C. sativa* leaves and flowers, and because of its biological roles, it has garnered more attention (Sánchez-Duffhue et al., 2008). From *Cannabis* leaves, 19 stilbenoids were separated and identified (Guo et al., 2018). Figure 7 summarizes the most important stilbenes identified in *Cannabis sativa.*

Lignans

Phenolic amides and lignanamides are the two main types of lignans that are obtained from *C. sativa* (Isidore et al., 2021). Regarding the initial group, five compounds : N-trans-feruloyltyramine, N-trans-coumaroyloctopamine, N-trans-coumaroyltyramine, N-trans-caffeoyloctopamine and N-trans-caffeoyltyramine, were found in trace amounts in *Cannabis* (Isidore et al., 2021). Regarding lignanamides, over 14 compounds were identified in *Cannabis*, including 3,3′-dimethyl-heliotropamide, grossamide, and *Cannabis* in molecules A, B, C, D, E, F, G, M, N, and O (Isidore et al., 2021) (Figure 8). Strong antioxidant properties have been observed for *Cannabis* in A and N-trans-caffeoyltyramine while the capacity to control inflammation has been described for grossamide and *Cannabis* in F. Additionally, some lignanamides are thought to be intriguing potential medicines for multimodal therapy against Alzheimer's disease since they have antioxidant qualities in addition to acting as acetylcholinesterase inhibitors (Isidore et al., 2021; Montero et al., 2023).

Alkaloids

Alkaloids represent another important group of secondary metabolites present in *C. sativa*. Of the approximately 70 alkaloids found

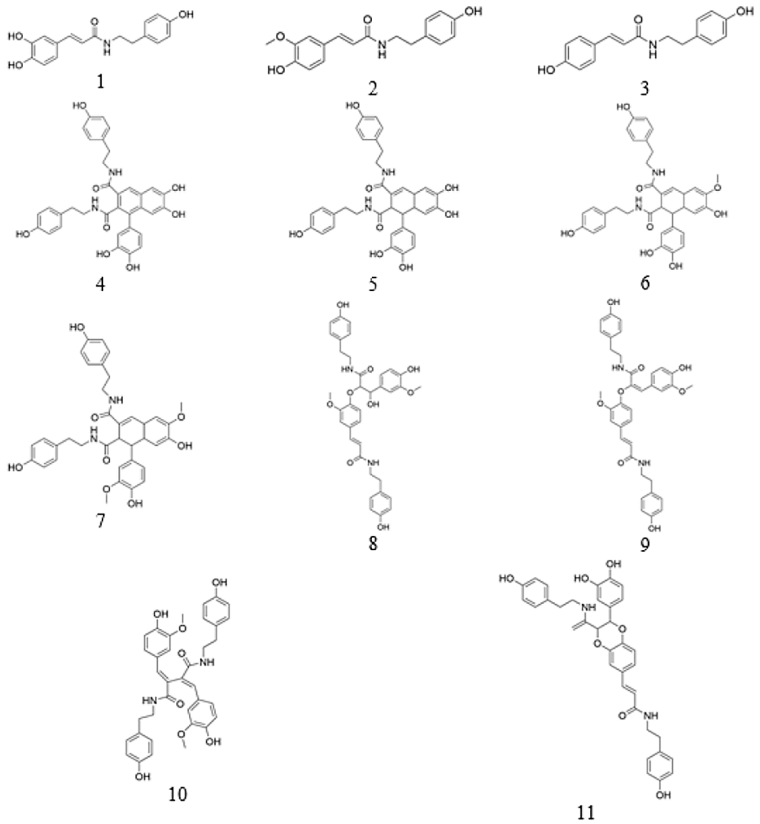

Figure 8. Structural representations of the key lignans identified in Cannabis: (1) N-trans-caffeoyltyramine, (2) N-trans-feruloyltramine, (3) N-trans-coumaroyltyramine, (4) Cannabisin A, (5) Cannabisin B (6) Cannabisin C, (7) Cannabisin D, (8) Cannabisin E, (9) Cannabisin F, (10) Cannabisin G and (11) Cannabisin M

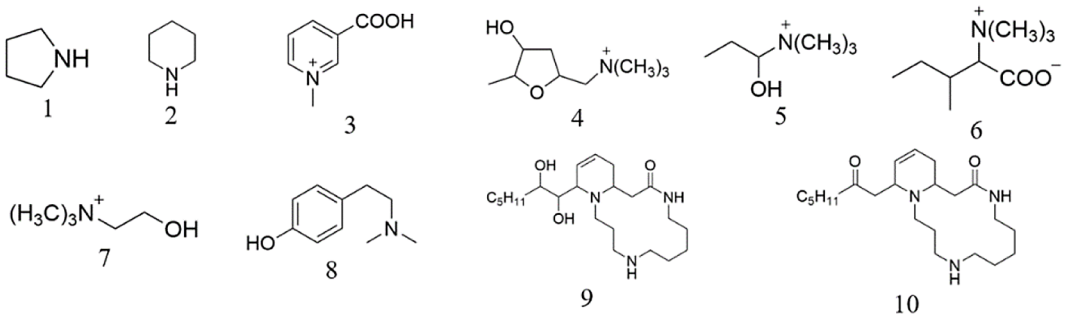

Figure 9. The structure of most important alkaloids identified in *Cannabis sativa:* (1) Pyrrolidine, (2), (3) Trigonelline, (4) Muscarine, (5) Neurine, (6) L-(+)-isoleucine-betaine, (7) Choline, (8) Hordenine, (9) ($_{+}$) Cannabisativine, and (10) Anhydrocannabisativine

in Indian *Cannabis*, D9-THC is the most psychotropic (Janeczek et al., 2018). The leaves, stems, pollen, roots, and seeds of *C. sativa* have yielded about ten common alkaloids, including anhydro-*Cannabis*-ativine, ($_{+}$)-*Cannabis*-ativine, piperidine, trigonelline, pyrrolidine, L-(+)-isoleucine-betaine, hordenine, muscarine, choline, and neurine (Figure 9).

Analytical discussion and comparative insights

The phytochemical composition of *Cannabis sativa* is characterized by exceptional complexity and variability, reflecting both genetic and environmental influences. Comparative phytochemical analyses across different cultivars and cultivation regions reveal that the relative abundance of cannabinoids, terpenes, flavonoids, and other secondary metabolites varies significantly depending on genotype, growth conditions, and post-harvest treatment (Radwan et al., 2021; ElSohly and Slade, 2005; Liu et al., 2022). From a genetic perspective, three major chemotypes have been identified according to the THC-to-CBD proportion, each corresponding to distinct cannabinoid biosynthetic pathways. Type I (drug-type) plants are rich in Δ^9-THC, Type II (intermediate) plants produce both CBD and THC, and Type III (fiber-type or hemp) plants accumulate mainly CBD and low THC levels (Small, 2015; Brenneisen, 2007). This classification highlights the genotype-dependent regulation of key synthase enzymes (THCAS, CBDAS, CBCAS), which determine the biochemical destiny of CBGA, the universal biochemical precursor feeding the biosynthesis of major cannabinoids (Gagne et al., 2012).

Environmental and agronomic factors, including light intensity, temperature, soil nutrients, and water availability, further modulate the biosynthesis and proportion of cannabinoids and terpenes. For instance, plants exposed to higher UV-B radiation or mild drought stress often exhibit increased cannabinoid accumulation, possibly as a protective biochemical response against oxidative or photic stress (Happyana et al., 2013). In contrast, excessive fertilization or low light intensity tends to reduce secondary metabolite content while promoting vegetative biomass, underlining the trade-off between growth and metabolite production (Mahlberg and Kim, 2004). Post-harvest processing including drying, storage, and extraction method also contributes to compositional variability. Thermal and oxidative degradation can convert acidic cannabinoids into their neutral or oxidized forms, for example, the conversion of THCA to THC or to CBN (Protti et al., 2019). Extraction techniques like Soxhlet, ultrasound, or supercritical CO_2 extraction yield different quantitative profiles of cannabinoids and terpenes due to variations in polarity and temperature conditions (Deidda et al., 2019; Monton et al., 2019). This underlines the need for standardized extraction protocols to ensure reproducibility in pharmacological testing and quality control.

Moreover, comparative studies suggest that the chemical diversity of *C. sativa* is strongly region-dependent. Samples from the Rif Mountains (northern Morocco) display distinct THC/CBD ratios compared to European hemp varieties, possibly due to selective breeding and adaptation to Mediterranean conditions (Afsahi, 2017; Afsahi, 2020). Such regional chemotypic differentiation demonstrates how traditional cultivation practices and ecological adaptation shape the phytochemical identity of *Cannabis* sativa populations worldwide.

From an applied perspective, examining the interconnections between genotype, environment, and extraction method is crucial for optimizing the plant's therapeutic potential. Pharmacologically relevant metabolites such as THC, CBD, and CBG exhibit synergistic interactions with terpenes and flavonoids the so-called entourage effect which enhances or modulates their biological activity (Russo, 2011; Booth and Bohlmann, 2019). This multidimensional interaction between metabolites calls for an integrated "chemotype-activity" approach combining analytical chemistry, plant physiology, and pharmacodynamics. Overall, the chemical diversity of *Cannabis sativa* is not a random feature but a dynamic reflection of its genetic background, environmental adaptation, and technological processing. This complexity represents both a challenge and an opportunity: while it complicates standardization in medical applications, it also opens avenues for the targeted development of specific chemotypes for pharmaceuticals, nutraceuticals, and industrial products.

THERAPEUTIC POTENTIAL OF *CANNABIS* AND ITS BIOACTIVE COMPOUNDS

Cannabis has long been utilized across the world as a medicinal herb. Commercial goods have recently been created for practical applications (Abuhasira et al., 2018). Many disorders, syndromes, diseases and health conditions, including epilepsy, Parkinson's disease, Alzheimer's disease, cancer, and their after effects, notably post-traumatic stress disorder (PTSD), chronic pain, appetite loss, and nausea, can be treated with *Cannabis* or cannabinoids. Also, according to a survey conducted with 953 participants in 31 countries, this plant is applied for addressing various clinical symptoms and health conditions, most notably pain, anxiety, sadness, and sleeplessness (Monton et al., 2019).

Alzheimer's disease

Alzheimer's disease (AD) is the leading type of dementia, characterized as a major neurological disorder that impairs daily activities due to deteriorating memory and cognitive functions (Keyvan et al., 2007; Katzman, 1976; Hardy and Selkoe, 2002; Lahiri et al., 2002; Malabadi et al., 2021). The hallmark of Alzheimer's disease is severe memory loss that interferes with day-to-day functioning (Katzman, 1976; Hardy and Selkoe, 2002; Keyvan et al., 2007; Lahiri et al., 2002; Malabadi et al., 2021).

Cannabis-derived compounds, particularly CBD, have exhibited neuroprotective properties in both in vivo and in vitro models of Alzheimer's disease, including reductions in β-amyloid aggregation, inhibition of tau hyperphosphorylation, and attenuation of oxidative stress (Xiong and Lim, 2021). The anti-inflammatory and immunomodulatory properties of CBD may further alleviate chronic neuroinflammation, a key driver of neuronal damage and cognitive decline in AD (Hickey et al., 2024). Clinical observations and small randomized trials have suggested that cannabinoid-based formulations such as dronabinol or CBD-rich extracts can improve behavioral and psychological symptoms including agitation and aggression in patients with dementia, although these studies remain limited in scale and duration (Hermush et al., 2022). Preclinical evidence strongly supports a multi-target neuroprotective mechanism of CBD and THC through anti-amyloid, anti-tau, antioxidant, and anti-inflammatory pathways, but further large-scale, well-controlled clinical investigations are essential to confirm any cognitive advantages and to establish standardized dosing and safety guidelines (Outen et al., 2021).

Parkinson's disease

Parkinson's disease (PD) is a serious neurological condition impacting millions of individuals worldwide (Goldberg et al., 2023; Aladeen et al., 2023; Gonzalez-Cuevas et al., 2023; Thanabalasingam et al., 2021; Varshney et al., 2023). A brain condition called Parkinson's disease results in unintentional or involuntary movements, including stiffness, shaking, and problems with balance and coordination (Varshney et al., 2023; Aladeen et al., 2023; Gonzalez-Cuevas et al., 2023; Thanabalasingam et al., 2021; Goldberg et al., 2023).

Cannabinoids including THC and CBD have shown potential to alleviate non-motor symptoms of PD, including pain, sleep disturbances, anxiety and mood disorders, primarily through their anxiolytic and analgesic properties (Urbi et al., 2022). Regarding motor symptoms, findings are mixed: some open-label studies and patient surveys report subjective improvements in tremor and dyskinesia, while randomized controlled trials have not consistently confirmed these effects (Bougea, 2020). Systematic reviews emphasize

that current clinical evidence remains weak and inconsistent, and that medical *Cannabis* use in PD should be restricted to experimental or highly individualized contexts given potential psychiatric and cognitive side effects (de Freitas et al., 2024). Nonetheless, cannabinoids appear promising for improving quality of life and non-motor symptom control, warranting further standardized, long-term trials to determine their efficacy, safety, and optimal formulations in PD (Urbi et al., 2022).

Asthma

Asthma is characterized as a persistent inflammatory condition affecting the respiratory airways (Kogan and Mechoulam, 2007; Quirt et al., 2018). The chronic respiratory condition known as asthma causes the airway to occasionally narrow, swell, and get coated with too much mucus (Quirt et al., 2018).

Studies conducted in animal models indicate that phytocannabinoids, including CBD and THC, are able to exert bronchodilatory effects and inhibit airway constriction, implicating the endocannabinoid system as a potential target in asthma therapy (Lewandowska et al., 2025). Additionally, minor cannabinoids and terpenes may add value: for example, some terpenes enhance cannabinoid receptor activity (entourage effect) and flavonoids in *Cannabis sativa* may reduce airway inflammation via their anti-inflammatory and antioxidant properties (Lewandowska et al., 2025). On the immunological side, activation of the cannabinoid receptor 2 (CB2) attenuates immune-cell infiltration and cytokine release in allergic airway models (Palomares, 2023). However, human epidemiological data caution against inhaled *Cannabis* for asthma: a systematic review and meta-analysis concluded that *Cannabis* use (especially vaping or smoking) was linked to a higher likelihood of asthma (Malvi et al., 2025), and a large U.S. cross-sectional study identified a dose-response association between daily inhaled *Cannabis* and asthma diagnosis (Rustagi et al., 2025).

Rheumatoid arthritis (RA)

Approximately 1% of the general population is affected by rheumatoid arthritis, a chronic inflammatory disorder (Lowin et al., 2023). Rheumatoid arthritis is a long-standing, systemic autoimmune and inflammatory condition, characterized primarily by persistent synovial membrane inflammation within affected joints. This ongoing inflammatory activity gradually erodes cartilage and bone, leading to symptoms including pain, stiffness, edema, and structural joint deformity. Additionally, RA can manifest beyond the joints, with potential involvement of the pulmonary, cardiovascular, ocular, and vascular systems (Smolen et al., 2016). Using preclinical models of rheumatoid arthritis, activation of CB2 receptors by cannabinoids (including minor cannabinoids like CBG and CBC has been shown to reduce synovial fibroblast activation, lower pro-inflammatory cytokines (e.g., IL-6, TNF-α) and limit joint destruction (Roseti et al., 2024). Flavonoids specific to *Cannabis sativa* such as cannflavins – exhibit COX-independent anti-inflammatory effects that might contribute additional benefit (Paland et al., 2023). Terpenes like β-caryophyllene (a CB2 agonist) may further support immune regulation and analgesia in arthritic joints. Notwithstanding the mechanistic promise, human data in RA remain scant: a scoping review found beneficial patient-reported outcomes (pain relief, functional improvement) but no firm clinical recommendations can yet be made (Paland et al., 2023). Moreover, a broader rheumatology review highlighted possible drug interactions and adverse events associated with cannabinoid use in these patients (Jain and Kras, 2022).

Wound healing (WH)

A wound is described as a break in the skin's continuity (Malabadi et al., 2022). An interruption in the continuity of the skin's or mucosa's epithelial lining brought on by heat or physical damage is another definition of a wound (Malabadi et al., 2022). Recent reviews indicate that topically applied cannabinoids (such as CBD) and full-spectrum *Cannabis sativ*a extracts which include flavonoids and terpenes can accelerate wound closure, reduce oxidative stress and inflammation in the wound microenvironment, promote fibroblast activation, and shift macrophages toward an M2 (healing) phenotype (Kolkar et al., 2025). For example, the antimicrobial and antioxidant properties of cannabinoid-rich seed oil in dressings may reduce microbial load and ROS damage in chronic wounds (Kolkar et al., 2025). Terpenes and flavonoids present in the plant enhance these effects by acting as free-radical scavengers and modulators of metalloproteinases. However, clinical human trials are extremely limited: most

evidence is preclinical or formulation-based, and the review emphasises the need for human studies to establish optimal dosing, delivery systems and safety profiles (Kolkar et al., 2025).

Covid-19 (SARS-CoV-2)

Coronavirus disease 2019 (COVID-19) results from infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an enveloped, positive-sense single-stranded RNA virus classified within the coronaviridae family. SARS-CoV-2 primarily targets the respiratory tract and can produce a wide range of clinical outcomes, from mild respiratory symptoms to severe pneumonia, acute respiratory distress syndrome (ARDS), and, in some cases, multi-organ failure. First detected in Wuhan, China, in December 2019, the virus spread rapidly across the globe, triggering a worldwide pandemic and creating major public health challenges (Hu et al., 2021).

Cell-based in vitro studies reveal that acidic precursors of cannabinoids such as CBDA and CBGA) can bind to the spike protein of SARS-CoV-2 and inhibit viral entry into human host cells (van Breemen et al., 2022). Concurrently, phytocannabinoids like CBD and minor cannabinoids (e.g., CBG) display anti-inflammatory and immunomodulatory effects that may mitigate the cytokine storm and lung-injury phase of COVID-19, with terpenes further enhancing CB2-mediated modulation of inflammation (Mahmud et al., 2021). According to a 2023 review evaluating *Cannabis*-based medicinal products (CBMPs) for Long COVID, notable improvements were observed in fatigue, sleep irregularities, and pain, all typical manifestations of post-COVID-19 syndrome (Thurgur et al., 2023).

Sleep disorders

Sleep disorders refer to a diverse group of conditions in which individuals experience chronic difficulties in falling asleep, maintaining sleep, or achieving restorative sleep, even when sufficient opportunity to sleep is available. These disturbances often lead to daytime impairments, affecting cognitive performance, emotional regulation, and physical health. Typical conditions within this category include insomnia, sleep apnea, narcolepsy, restless legs syndrome, and disturbances of the circadian sleep-wake cycle (Morin and Benca, 2012). *Cannabis sativa*-derived compounds influence multiple neurophysiological systems relevant to sleep: THC at lower doses may shorten sleep latency and increase slow-wave sleep, while CBD appears to modulate sleep in a dose-dependent manner and may improve sleep quality when comorbid with pain or anxiety (Lavender et al., 2024). Emerging minor cannabinoids such CBN demonstrate objective improvements in sleep architecture in early human trials (Bonn-Miller et al., 2024), and terpenes like myrcene and linalool may enhance sedative/anxiolytic effects by modulating GABA and TRP channels (Alfieri et al., 2025). The flavonoid and terpene components of *Cannabis sativa* also contribute to the "entourage effect" in sleep modulation (Alfieri et 2025). Nonetheless, systematic reviews highlight that while cannabinoid-based products can improve sleep in chronic pain populations, they show inconsistent outcomes in primary insomnia, and long-term safety data (especially for dependence, tolerance, and withdrawal) are lacking (Saleska et al., 2024).

Cancer

Several studies indicate that cannabinoids and more broadly, the endocannabinoid system may play a role in regulating cancer development and progression (Bifulco et al., 2007; Hall et al., 2005; Kogan, 2005; Woerdenbag et al., 2023; Häuser et al., 2023; Kogan and Mechoulam, 2007). Consequently, there is curiosity over how well *Cannabis* or cannabinoids work to cure cancer. In the 1970s, it was discovered that *Cannabis* inhibited the proliferation of cancer cells (Hall et al., 2005; Kogan, 2005; Bifulco et al., 2007; Häuser et al., 2023; Woerdenbag et al., 2023). Cannabinoids have since been discovered to affect different cancer cell lines via a variety of methods (Kogan and Mechoulam, 2007; Hall et al., 2005; Kogan, 2005; Bifulco et al., 2007; Häuser et al., 2023; Woerdenbag et al., 2023).

Cannabinoids, along with other phytochemicals derived from *Cannabis*, engage various molecular mechanisms with potential relevance to anticancer treatment, although current clinical evidence remains limited and should be interpreted with caution. Repeated findings from preclinical research indicate that THC and CBD are capable of diminishing tumor cell growth, promoting apoptosis and autophagy, impairing angiogenic processes, and restricting cellular invasion and metastasis in multiple experimental cancer systems (Hinz and Ramer, 2022). Non-psychoactive minor phytocannabinoids such as cannabigerol CBC, CBG and CBN

have demonstrated cytotoxic and anti-proliferative effects in vitro and in some in vivo models, suggesting these compounds may exert antitumour actions via distinct targets (Tomko et al., 2020; Kadriya et al., 2024). Terpenes (e.g., β-caryophyllene, limonene, myrcene) and flavonoids in *Cannabis* also present pro-apoptotic and anti-angiogenic activities and may modulate cannabinoid efficacy through synergistic "entourage" interactions (Tomko et al., 2020; Silva-Reis et al., 2023). Importantly, oncology guidelines emphasise that cannabinoids should not currently replace conventional cancer therapies and recommend use as symptom-directed treatments (e.g., refractory chemotherapy-induced nausea/vomiting, pain) or within clinical trials when considering anticancer intent (Braun et al., 2024). Overall, strong preclinical promise exists, but well-designed clinical trials are required to define safe, effective anticancer roles for THC, CBD, minor cannabinoids, terpenes and flavonoids (Hinz and Ramer, 2022; Braun et al., 2024).

Multiple sclerosis

Multiple sclerosis (MS) is a prolonged, immune-driven disorder of the central nervous system characterized by ongoing inflammation, myelin loss, and subsequent damage to nerve fibers. The disease produces a broad spectrum of neurological symptoms, such as visual problems, sensory déficits, muscle weakness, fatigue, and cognitive impairments. Its progression is variable, often following relapsing-remitting episodes or, in some cases, a gradual, progressive course (Compston and Coles, 2008).

Nabiximols (THC: CBD oromucosal spray) and other cannabinoid formulations provide the most consistent clinical evidence for symptomatic benefit in MS, particularly for patient-reported spasticity and related clinical manifestations including sleep disturbance and pain (Filippini et al., 2022; Novotná et al., 2011). Randomized enriched-design trials of nabiximols demonstrated small-to-moderate reductions in spasticity scores and improved global patient impression in subsets of responders (Novotná et al., 2011; Patti et al., 2016). Systematic reviews and meta-analyses conclude that THC: CBD sprays probably reduce MS spasticity versus placebo but warn that trial quality, heterogeneity and adverse effects (dizziness, somnolence) limit certainty and long-term conclusions (Martinez-Paz et al., 2023; Filippini et al., 2022). Oral synthetic cannabinoids (dronabinol, nabilone) and *Cannabis* extracts show mixed results for pain and spasticity but may help selected patients when used as add-on therapy (Haddad et al., 2022). Emerging preclinical and early clinical work suggests that minor phytocannabinoids (e.g., CBG, CBC), terpenes and flavonoids may have complementary anti-inflammatory, neuroprotective or muscle-tone-modulating properties (Nouh et al., 2024), but robust clinical data for these constituents remain limited and require further randomized trials (Martinez-Paz et al., 2023).

CONSTIPATION

Constipation is a digestive disorder marked by infrequent, difficult, or incomplete evacuation of the bowels, often associated with hard or lumpy stools and a feeling of straining or blockage. It can arise from dietary or lifestyle factors, certain medications, or underlying health conditions, and if persistent, may cause discomfort and additional complications (Lacy and Patel, 2017). The endocannabinoid system (ECS) plays a key role in controlling gastrointestinal motility, while cannabinoids modulate intestinal activity by acting on CB_1 and CB_2 receptors located in the enteric nervous system (Massa et al., 2020). Stimulation of CB_1 receptors normally reduces acetylcholine secretion and thereby slows intestinal motility, while activation of CB_2 receptors is associated with anti-inflammatory actions that help maintain gut homeostasis (Izzo and Sharkey, 2010). Although THC is generally associated with decreased gut motility, balanced formulations containing CBD, CBG, or CBC may normalize bowel movements through differential receptor targeting and 5-HT modulation (Brierley et al., 2023; De Filippis et al., 2019). Preclinical studies suggest that CBD can counteract hypermotility and visceral hypersensitivity in models of irritable bowel syndrome (IBS), potentially easing alternating diarrhea and constipation patterns (Brierley et al., 2023). Furthermore, *Cannabis*-derived flavonoids and terpenes such as β-caryophyllene and linalool exhibit enteroprotective and smooth muscle–modulating effects, enhancing intestinal relaxation and secretion balance (Russo, 2011; Di Giacomo et al., 2023). Clinical data remain limited, but cannabinoid therapies may hold promise for patients with functional constipation secondary to inflammation or dysmotility disorders, pending further controlled trials (Massa et al., 2020).

Traumatic brain injury

Traumatic brain injury (TBI) refers to an acquired injury to the brain caused by external mechanical forces, including impacts, blows, or rapid acceleration–deceleration of the head, which may lead to transient or long-lasting neurological deficits. The clinical presentation spans from mild concussive events to severe cerebral injury and is often associated with diverse cognitive, somatic, and emotional disturbances (Maas et al., 2008).

Cannabinoids display neuroprotective, anti-inflammatory, and antioxidant effects that could attenuate secondary injury processes associated with TBI or intracranial hemorrhage (ICH) (Schurman and Lichtman, 2023). Activation of CB_1 and CB_2 receptors reduces excitotoxic glutamate release, microglial activation, and oxidative stress, limiting neuronal apoptosis and blood-brain barrier disruption (Mechoulam et al., 2014; Greuter et al., 2023). Preclinical models show that CBD enhances post-injury recovery through modulation of 5-HT_1A and PPARγ pathways, improving neurogenesis and cognitive function (Jalloh et al., 2024; Mishima et al., 2005). Minor cannabinoids like CBG and tetrahydrocannabivarin (THCV) also demonstrate neuroprotective actions by attenuating neuroinflammation and excitotoxicity, while terpenes such as β-caryophyllene act as selective CB_2 agonists with cerebroprotective benefits (Galdino et al., 2020; Giacoppo and Mazzon, 2016). Moreover, *Cannabis* flavonoids particularly cannflavin A and orientin exhibit potent antioxidant and anti-apoptotic effects, offering adjunct potential in TBI/ICH management (Barth et al., 2023). Although promising, translation to clinical practice remains preliminary; human data are still limited to observational reports suggesting lower mortality rates among *Cannabis*-positive trauma patients (Nguyen et al., 2014; Schurman and Lichtman, 2023).

Posttraumatic stress disorder (PTSD)

Posttraumatic stress disorder (PTSD) is a mental health disorder that may emerge following traumatic exposure and is defined by recurrent intrusive memories, avoidance behaviors, persistent negative cognitive and emotional shifts, and heightened arousal. These symptoms must last longer than one month and result in clinically significant distress or impairment (Lancaster et al., 2016).

Cannabis and its bioactive compounds modulate key neurobiological pathways implicated in PTSD, including the endocannabinoid system (ECS), hypothalamic pituitary adrenal axis, and fear extinction circuits (Russo et al., 2023). THC and CBD exert complementary actions THC through partial CB_1 receptor agonism enhancing extinction learning and reducing hyperarousal, and CBD via indirect FAAH inhibition and 5-HT_1A activation that attenuate anxiety and intrusive memories (de Bitencourt et al., 2013; Blessing et al., 2015). Clinical and observational studies have reported that cannabinoid-based treatments can reduce nightmares, sleep disturbances, and hyperarousal symptoms in PTSD patients, though benefits vary depending on cannabinoid ratios and dosing (Shishko et al., 2018; Roitman et al., 2014). Lesser-studied cannabinoids – including CBC, CBG, and tetrahydrocannabivarin (THCV) – may provide anxiolytic or antipsychotic-like benefits via modulation of CB_2 and TRPV1 pathways, underscoring the importance of additional investigation (Stith et al., 2020; Murillo-Rodríguez et al., 2023). Additionally, terpenes such as linalool and limonene and flavonoids like apigenin show synergistic GABAergic and serotonergic modulation, which could support mood regulation in PTSD (Russo, 2011). Although early findings are promising, large-scale randomized trials are still needed to establish standardized cannabinoid profiles and optimal dosing regimens for PTSD treatment (Russo et al., 2023; Murillo-Rodríguez et al., 2023).

AIDS wasting syndrome

AIDS wasting syndrome is a clinical condition occurring in the later stages of HIV infection, characterized by unintentional weight loss greater than 10% of total body weight, along with symptoms such as chronic diarrhea, fatigue, and fever, ultimately causing severe physical debilitation (Bedimo et al., 2024). *Cannabis* and its bioactive compounds have shown therapeutic potential in managing AIDS wasting syndrome by improving appetite, caloric intake, and body weight while alleviating associated symptoms such as pain, nausea, and depression (Abrams et al., 2020). Δ^9-THC, via CB_1 receptor activation, stimulates appetite and enhances food palatability through hypothalamic pathways (Haney et al., 2007). Controlled clinical trials have demonstrated that smoked or oral THC (dronabinol) significantly increases appetite and weight gain in HIV/

AIDS patients with cachexia compared to placebo (Beal et al., 1995; Abrams et al., 2020). CBD, along with lesser-studied cannabinoids including CBG and THCV, may exert additional anti-inflammatory and metabolic-modulating actions that enhance energy homeostasis and promote gastrointestinal well-being (Whiting et al., 2015; Namdar et al., 2023). *Cannabis* terpenes, including β-caryophyllene and limonene, enhance appetite stimulation and mood regulation through dopaminergic and endocannabinoid interactions (Russo, 2011). Moreover, preclinical data indicate that flavonoids like cannflavin A possess antioxidant and anti-inflammatory properties that could mitigate systemic inflammation and muscle wasting (Dresen et al., 2022). Collectively, cannabinoids, terpenes, and flavonoids may offer multimodal benefits in AIDS Wasting Syndrome management, though individualized dosing and careful monitoring remain essential (Namdar et al., 2023; Abrams et al., 2020).

Depression and anxiety

Depression and anxiety are prevalent psychiatric disorders often occurring together, characterized by persistent feelings of loss of interest, sadness, excessive worry and physical symptoms including sleep disturbances and fatigue significantly affecting daily functioning (Kalin, 2020).

Cannabis-derived compounds modulate several neurobiological pathways involved in depression and anxiety, notably through the endocannabinoid system (ECS), serotonergic transmission, and neuroinflammatory regulation (Turna et al., 2020). CBD has shown the strongest preclinical and clinical evidence, exerting antidepressant- and anxiolytic-like effects via 5-HT_1A receptor activation, hippocampal neurogenesis, and modulation of anandamide levels (Linge et al., 2016; Blessing et al., 2015). THC displays a biphasic response low doses can reduce anxiety and depressive behaviors, whereas higher doses may exacerbate them through CB_1-mediated dysregulation of amygdalar circuits (Crippa et al., 2009; Hindocha et al., 2020). CBG, CBC, and THCV, although classified as minor cannabinoids, demonstrate antidepressant and anxiolytic activities through interactions with 5-HT and TRPV1 receptor systems, thereby expanding their pharmacological relevance (Brierley et al., 2023; Laprairie et al., 2021). Additionally, terpenes like linalool and limonene and flavonoids such as apigenin and quercetin enhance mood regulation and stress resilience via synergistic GABAergic and dopaminergic modulation (Russo, 2011; Fogaça et al., 2023). Clinical trials confirm that CBD significantly reduces anxiety in public-speaking tests and may improve sleep and mood in patients with generalized anxiety or depression (Skelley et al., 2020). Together, these findings highlight *Cannabis*' polypharmacological potential for mood disorders, though dose-dependent risks and long-term safety require careful evaluation (Turna et al., 2020; Fogaça et al., 2023).

Diabetes mellitus

Diabetes mellitus comprises a spectrum of metabolic diseases characterized by chronic elevation of blood glucose levels due to abnormalities in insulin production, insulin responsiveness, or both, resulting in widespread disturbances in carbohydrate, lipid, and protein metabolism (Harreiter et al., 2023).

Cannabinoids and other bioactive compounds from *Cannabis sativa* have been investigated for their potential to modulate glucose metabolism, insulin sensitivity, and diabetic inflammation. Activation of the ECS influences energy balance, lipid metabolism, and pancreatic β-cell function through CB_1 and CB_2 receptors (Pacher and Mechoulam, 2011). Chronic CB_1 receptor overstimulation contributes to obesity and insulin resistance, whereas selective CB_1 antagonism or modulation by non-psychoactive cannabinoids like CBD and THCV improves glycemic control and lipid profiles (Jadoon et al., 2016; Silvestri et al., 2015). THCV and CBG enhance glucose tolerance and insulin sensitivity in type 2 diabetes models by activating AMPK and PPARγ pathways (Booz et al., 2023; McKillop et al., 2018). CBD exhibits antioxidant and anti-inflammatory actions that attenuate pancreatic β-cell oxidative stress and protect against diabetic neuropathy (Rajesh et al., 2010; Bouabid et al., 2024). Additionally, *Cannabis*-derived terpenes (e.g., β-caryophyllene, limonene) and flavonoids (e.g., quercetin, cannflavin A) demonstrate synergistic effects through NF-κB inhibition and improved endothelial function (Russo, 2011; Gabbia et al., 2022). Collectively, emerging evidence suggests that phytocannabinoids, terpenes, and flavonoids from *Cannabis* may help regulate metabolic homeostasis and inflammatory responses in

diabetes, warranting further clinical validation (Booz et al., 2023; Bouabid et al., 2024).

Chronic pain

Chronic pain refers to pain lasting or recurring for more than three months, commonly associated with conditions including fibromyalgia, neuropathic disorders, and osteoarthritis. This persistent pain often leads to significant functional impairment and diminished quality of life (Treede et al., 2019). *Cannabis* and its bioactive constituents have shown significant promise in managing chronic pain through modulation of the ECS, neuroinflammation, and nociceptive signaling. Δ^9-THC acts primarily via CB_1 receptor activation in the central nervous system, reducing pain perception and central sensitization (Ware et al., 2015). CBD exerts analgesic effects by antagonizing GPR55, desensitizing TRPV1 channels, and attenuating microglial activation, contributing to reduced neuropathic and inflammatory pain (Costa et al., 2007; Xu et al., 2019). Beyond CBD and THC, minor cannabinoids such as CBG and CBC display antinociceptive and anti-inflammatory effects through modulation of TRPA1, 5-HT_1A, and α_2-adrenergic receptors (Maione et al., 2023; De Petrocellis et al., 2011). Flavonoids like cannflavin A and terpenes including β-caryophyllene synergistically enhance analgesic outcomes via COX-2 inhibition and CB_2 receptor agonism (Appendino et al., 2011; Gertsch et al., 2008). Clinical studies have confirmed that whole-plant *Cannabis* extracts and oromucosal sprays significantly alleviate neuropathic, arthritic, and cancer-related pain with manageable tolerability (Häuser et al., 2022; Mücke et al., 2018). These multimodal effects suggest that phytocannabinoids, terpenes, and flavonoids collectively target peripheral and central pain pathways, positioning *Cannabis*-based therapeutics as a promising adjunct in chronic pain management (Maione et al., 2023; Häuser et al., 2022).

Muscle spasticity

Muscle spasticity (MS) refers to an abnormal increase in muscle tone or rigidity resulting from hyperexcitability of the stretch reflex, typically associated with central nervous system damage, including in disorders such as cerebral palsy and multiple sclerosis (Khan et al., 2019).

Cannabis and its phytochemicals have demonstrated therapeutic benefits in alleviating muscle spasticity associated with neurological disorders such as spinal cord injury, MS, and cerebral palsy. Δ^9-THC acts as a partial agonist at CB_1 receptors in motor neurons, inhibiting excessive excitatory neurotransmission that contributes to spasticity (Collin et al., 2007; Wade et al., 2010). CBD enhances these effects by modulating CB_2, GPR55, and TRPV1 receptors, producing anti-inflammatory and neuromodulatory outcomes without significant psychoactivity (Notcutt et al., 2012; Wade et al., 2016). CBG and THCV, classified as minor cannabinoids, may further alleviate spasticity through facilitation of GABAergic and glycinergic neurotransmission (Laprairie et al., 2021; Morales et al., 2017). The synergistic action of cannabinoids with terpenes (e.g., myrcene, linalool) and flavonoids (e.g., apigenin, cannflavin A) amplifies muscle relaxation via enhancement of inhibitory neurotransmission and COX-2 suppression (Russo, 2011; Appendino et al., 2011). Clinical evidence from randomized controlled trials demonstrates that *Cannabis*-based oromucosal sprays containing THC: CBD (e.g., Sativex) ead to a significant decrease in measured spasticity levels and improve mobility and quality of life in MS patients (Zajicek et al., 2012; Collin et al., 2010). Collectively, these findings indicate that a broad spectrum of *Cannabis* constituents contribute to muscle relaxation through complementary neurophysiological and anti-inflammatory mechanisms (Laprairie et al., 2021; Wade et al., 2016).

Epilepsy

Epilepsy refers to a chronic neurological disorder involving a susceptibility to recurrent epileptic seizures, which manifest as short-lived symptoms or signs arising from abnormal, hypersynchronous neuronal activity in the cerebral cortex (Fisher et al., 2014).

Cannabis and its phytocannabinoids have attracted considerable attention for their anticonvulsant and neuroprotective properties in epilepsy management. CBD has demonstrated substantial clinical efficacy in reducing seizure rates in refractory epileptic conditions such as Dravet syndrome and Lennox-Gastaut syndrome (Thiele et al., 2018; Devinsky et al., 2017). Mechanistically, CBD modulates neuronal excitability by inhibiting GPR55 and voltage-gated sodium channels,

desensitizing TRPV1 receptors, and enhancing adenosine signaling (Iannotti et al., 2014; Silvestro et al., 2020). THC, though psychoactive, can exhibit anticonvulsant effects at low doses via partial CB_1 receptor agonism, though higher doses may induce proconvulsant responses (Rosenberg et al., 2017). Minor cannabinoids such as CBDV, CBGA, and THCV also display potent anticonvulsant actions by modulating T-type calcium channels and reducing neuronal hyperexcitability (Anderson et al., 2021; Hill et al., 2013). Moreover, terpenes such as linalool and β-caryophyllene contribute to seizure suppression through GABAergic enhancement and CB_2 activation, while flavonoids like apigenin and cannflavin A provide neuroprotective effects (Russo, 2011; Baron, 2018). Clinical trials and meta-analyses confirm that purified CBD formulations (e.g., Epidiolex) lead to marked improvements in seizure management and overall quality of life in refractory epilepsy, with favorable tolerability and little to no cognitive impairment (Thiele et al., 2018; Szaflarski et al., 2022).

Analytical remarks and critical discussion

Although the pharmacological benefits of *Cannabis sativa* and its active compounds are widely recognized, the translation of this evidence into clinical application is still restricted and lacks coherence. While THC and CBD are the most extensively studied cannabinoids, emerging evidence highlights the importance of other minor compounds such as CBG, and CBC, CBN, which may possess complementary or synergistic biological effects (Russo, 2011; Pisanti et al., 2017).

Comparative pharmacological studies demonstrate that THC-dominant extracts exhibit higher efficacy in pain relief and appetite stimulation, whereas CBD-rich formulations are more effective for anxiolytic, anti-inflammatory, and anticonvulsant applications (Pamplona et al., 2018; Devinsky et al., 2017). However, such differential responses depend strongly on the THC/CBD ratio, patient physiology, and route of administration, which complicates the establishment of standardized therapeutic protocols.

The "entourage effect" a synergistic interaction between cannabinoids, terpenes, and flavonoids has gained increasing recognition as a potential explanation for the superior efficacy of full-spectrum extracts compared to isolated compounds (Russo, 2019). For instance, β-caryophyllene and linalool have been demonstrated to potentiate the anxiolytic and anti-inflammatory properties of CBD, suggesting that *Cannabis*-derived therapeutics should be evaluated as polypharmacological systems rather than single-molecule drugs.

Nevertheless, several scientific and clinical limitations persist. Most reported activities are based on in vitro or in vivo preclinical models, often using poorly characterized or non-standardized extracts. The variability in extraction methods, plant chemotypes, and administration routes leads to inconsistent pharmacological outcomes (Atakan, 2012). Moreover, while cannabinoids interact with the endocannabinoid system through CB_1 and CB_2 receptors, recent evidence suggests the involvement of additional molecular targets such as TRPV1, PPARγ, and serotonin receptors, adding further complexity to the mechanistic interpretation (Iversen, 2003; Fernández-Ruiz et al., 2020).

From a comparative therapeutic standpoint, *Cannabis sativa* exhibits promising effects in neurodegenerative diseases (e.g., multiple sclerosis, Parkinson's, Alzheimer's,), chronic pain, epilepsy, and metabolic disorders. However, long-term clinical data remain scarce, and well-powered randomized controlled trials are necessary to confirm efficacy and safety profiles (Grotenhermen and Müller-Vahl, 2012). Regulatory constraints, ethical concerns, and differences in national legislation continue to impede robust clinical evaluation.

The therapeutic potential of *Cannabis sativa* lies in its extraordinary chemical complexity and multi-target pharmacology. However, this same complexity poses challenges for standardization, dosage optimization, and clinical validation. To fully realize the medicinal promise of *Cannabis*, future work should focus on:

- establishing standardized extraction and formulation protocols,
- elucidating dose–response relationships for major and minor cannabinoids,
- and conducting comparative clinical trials on full-spectrum versus purified extracts.

These steps are essential to transform Cannabis sativa from an empirically used plant into a scientifically validated therapeutic resource, capable of contributing to modern pharmacotherapy and personalized medicine.

CONCLUSIONS

This integrative review highlights the botanical diversity, chemical complexity, and therapeutic potential of *Cannabis sativa* L., demonstrating that the plant's biological and pharmacological characteristics result from a dynamic interplay between genotype, morphology, environmental conditions, and post-harvest processing. By synthesizing findings from more than two hundred recent studies, this work successfully fulfilled its objective of providing a cross-disciplinary and updated overview that connects botanical structure, metabolite biosynthesis, and bioactivity – dimensions that are often treated separately in previous reviews.

The present synthesis offers several contributions. First, it clarifies how morphological traits, especially trichome density and distribution, correlate with chemical variability and cannabinoid biosynthesis. Second, it consolidates dispersed phytochemical data by identifying more than 550 compounds across different plant parts and cultivation contexts. Third, it highlights the mechanistic basis underlying the therapeutic effects of cannabinoids, terpenes, and flavonoids in major pathological conditions, while emphasizing the importance of chemotype-specific activity.

Through this comparative analysis, important knowledge gaps were identified. These include the limited number of studies linking genotype to cultivation conditions, the scarcity of standardized extraction and quantification protocols, and the insufficient clinical evidence for many promising bioactivities. Such gaps reflect structural limitations in current research rather than methodological shortcomings of the present review.

Overall, this work provides a consolidated scientific framework for understanding *Cannabis sativa L.* as a botanical, chemical, and therapeutic entity. By identifying patterns, inconsistencies, and information gaps within the existing literature, this review opens pathways for future research aimed at improving chemotype standardization, enhancing reproducibility, and supporting the safe and effective development of *Cannabis*-based products for pharmaceutical and biotechnological applications.

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