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Research Article

Δ9-TETRAHYDROCANNABINOL (THC): THE MAJOR PSYCHOACTIVE COMPONENT IS OF BOTANICAL ORIGIN

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ABSTRACT

This review paper highlights the medicinal value of Cannabis sativa belongs to Cannabaceae family. The use of the female inflorescence of Medical Cannabis sativa (marijuana or drug type) for medical purposes has increased greatly in the past decade. The constituents of Cannabis sativa responsible for its pharmacological effects are known as Cannabinoids. Cannabinoids are terpenophenolic compounds, and the most abundant and well-known phytocannabinoids are **Δ9-tetrahydrocannabinol (THC)** and **Cannabidiol (CBD).** According to ***Ayuverda*** in India, the medicinal value of the Cannabis sativa was well documented more than 3,000 years ago. However, chemistry of biomolecules responsible for narcotic principle of Cannabis sativa was unknown. The Botanical originated Δ9-tetrahydrocannabinol (THC) is known for the psychoactive activity accumulated in the trichomes of female inflorescences of Cannabis sativa. The official discovery of **Cannabidiol** (CBD) in 1963 and **Δ9-tetrahydrocannabinol (THC)** in 1964 isolated and identified from Cannabis sativa at **Israel's Weizmann Institute of Science** is commonly attributed to **Dr. Raphael Mechoulam**, known as the **Godfather of Cannabis science** died at the age of **92 on 9th March 2023.** The discovery of **Δ9-tetrahydrocannabinol (THC)** has led to the Endocannabinoid system (ECS) which is a major breakthrough in medical science. The lower concentrations (0.2 to 0.3%) of **Δ9-tetrahydrocannabinol (THC)** is used as medicine for pain management, cancer, for controlling nausea and omitting in AIDS patients and etc. However, the consumption of very high concentration (20-30%) of **Δ9-tetrahydrocannabinol (THC)** for a long period led **to psychoactive activity** and other adverse side effects in terms of emotional instability, body movement disorder, cognitive functioning, mental health effects such as a dependence syndrome and schizophrenia.

Keywords: Bhang, Cannabidiol (CBD), Charas, Cannabis sativa, Ganja, Illicit drug, Psychoactive compound, hemp, marijuana, Δ9-Tetrahydrocannabinol-THC, India.

INTRODUCTION

Cannabis sativa (Figure-1) belongs to **Cannabaceae** family is one of the well known medicinal plant of oldest civilization found as a wild weed in the Himalayan region particularly **India** and China **(**1-25). Cannabis was originated in the **Indian Himalaya Mountains** and is endemic to **the Indian landmass** and Asia (China, Nepal, Bhutan, Pakistan, Afghanistan) (1-25). Cannabis sativa L. (hemp, or marijuana) produces male and female inflorescences on different plants (dioecious). Therefore, the plants are obligatory out-crossers. In commercial production, medical Cannabis (marijuana type) plants are all genetically female; **male plants are destroyed** as seed formation reduces flower quality (1-20). Cannabis sativa is a **dioecious cross pollinated** plant with compound racemose type of **inflorescences** (**Figure-2**) producing separate male and female plants (15, 16-25).

Cannabis sativa contains hundreds of secondary metabolites such as, cannabinoids, terpenes, and flavonoids, which are produced and accumulated in the glandular trichomes that are highly abundant mainly on female inflorescences (1-35). The earliest written reference to Cannabis sativa in India may occur in the ***Atharvaveda***, dating to about 2500 BCE (1-25; 49-52). **India** is the land of **botanical pharmacy** and world leader **in the production of herbal drugs.** According to ***Ayuverda*** in India, the medicinal value of the Cannabis sativa was well documented more than 3,000 years ago (1-25). This was the first Indian evidence to support the medicinal value of Cannabis sativa which was well documented in ***Ayuverda*** in India (1-25; 35-52). ***Ayurveda*** literature like **Charaka Samhita** mentions properties of **Vijaya** as digestive and intoxicating which makes the cultivation and usage of the Cannabis sativa at a religious and cultural phenomenon (1-25). Medical Cannabis sativa is also commonly known as marijuana, **Bhang, Ganja,** and **Charas**, which are banned in **India** as **an illicit drug**. Sales and cultivation of **Medical Cannabis sativa (marijuana type)** are still **illegal in India** (1-25). As a plant, it is valued for its hallucinogenic and medicinal properties, more recently being used for pain, glaucoma, nausea, asthma, depression, insomnia, and neuralgia (1-25). Derivatives are used in HIV/AIDS and multiple sclerosis (1-40). The pharmacology and therapeutic efficacy of cannabis preparations and its main active constituent Δ9-tetrahydrocannabinol (Δ9-THC) have been extensively reviewed (1-40). C(marijuana or drug typeannabis legalization fueled the scientific research in Cannabinoid compounds for potential in medicinal, pharmaceutical, and neurological applications.

Industrial Cannabis sativa (**hemp** or fiber type) refers to non-intoxicating, low (0.2 to 0.3%) Δ9-tetrahydrocannabinol (Δ9-THC) cultivars of Cannabis sativa (1-30; 53). On other hand **Medical Cannabis sativa (Marijuana type)** refers to cultivars with high levels (20-35%) of **Δ9-THC**, the primary narcotic psychoactive Cannabinoid found in the plant and a federally controlled substance used for both recreational and therapeutic purposes (1-25; 53). Although marijuana and hemp belong to the same genus and species, they differ in terms of chemical and genetic composition, production practices, product uses, and regulatory status (1-30; 53).

CANNABIS HYBRID STRAINS

Cannabis is a genus of annual flowering plant. Cannabis is often divided into 3 species—**Cannabis sativa, Cannabis indica**, and **Cannabis ruderalis**—but there is significant disagreement about

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this, and some consider them subspecies of the same parent species (53-59). Each species can interbreed with the other species, leading to hybridization (53-59). Cannabis sativa can grow to 5–18 feet or more, and often has a few branches (50-59). Cannabis indica typically grows 2–4 feet tall and is compactly branched (53-59). Cannabis ruderalis contains very low levels of Δ-9-tetrahyocannabinol so is rarely grown by itself (53-59). **Cannabis ruderalis** flowers matures as a result of age, not light conditions, which is called **Autoflowering** (59). It is principally used in hybrids, to enable the hybrid to have the **Autoflowering** property (50-59). There **are >700 recreational hybrid Cannabis**, often with colourful names (45-59). Some are strains of Cannabis sativa and Cannabis indica subspecies and the most are crossbred hybrids (45-59). The hybrid strains can be named in a variety of ways: **smell or lineage** are common ways of naming (50-59). There are only a few rules about how the hybrid strains are named, and most hybrid strains' names do not follow the rules (50-59). There are a couple of examples where there does seem to be some sort of naming convention (50-59). **Kush** typically indicates either pure Cannabis indica or a Cannabis indica hybrid (55-59). **Afghan Kush, Hindu Kush, Green Kush,** and **Purple Kush** are all pure **Cannabis indica** strains (55-59). **Blueberry Kush** and **Golden Jamaican Kush** are hybrids based on Cannabis indica (50-59). For Cannabiss sativa, there are similar examples using the words Diesel and Haze, with some hybrid strains being pure Cannabis sativa, and some strains being hybrids of Cannabis sativa (55-59). Diesel strain is named for its smell (59).

The **hybrid** strains have a special place in the heart of many customers because there is something for everyone with this type of varieties. There are balanced hybrids but there are also those with a predominance towards Cannabis indica or Cannabis sativa, which is a whole range of options and effects to choose from (60). Most of the **Cannabis strains** are **hybrids**, as there are very few Cannabis sativa or Cannabis indica strains completely pure (60). Cannabis sativa hybrid strains are known for their energetic effects, while Cannabis indicas are known to be calming (50-60). Hybrid strains of Cannabis run the spectrum of possibilities, which makes them so special (50-60). These **hybrid Cannabis** strains produce several potential holistic properties that promise pain relief, mental stimulation, and feelings of intense euphoria (60).

Most of the Cannabis varieties on the market today are hybrids with both Cannabis sativa and Cannabis indica genetics. Hybrid refers to a strain created by combining both Cannabis indica and Cannabis sativa strains (30-60). Many producers crossbreed Cannabis plants to develop new strains with specific characteristics. Experts suggest that there are over 700 hybrid strains of cannabis. Some of the strains are 1) **Kush**-Pure *Cannabis indica* or *Cannabis indica* hybrid. 2) **Afghan Kush**, **Hindu Kush**, Green Kush, Purple Kush-Pure *Cannabis indica* **3)** Blueberry Kush, Golden Jamaican Kush- *Cannabis indica* hybrid 4) Diesel Haze-Pure *Cannabis sativa* or *Cannabis sativa* hybrid. The breeders at **Royal Queen Seeds**, for example, use specialized breeding techniques to produce strains with unique traits such as shorter flowering times, specific flavours, and more (**Royalqueenseeds.com).**

Following are some of the most potent **Cannabis hybrids** with high THC levels and mind-blowing effects (60).

1) Chiquita Banana: Chiquita Banana has earned the title of one of the **strongest strains in the world** (60). In some tests, **Chiquita Banana** has reached over 33% THC (60). Further, on average this hybrid strain has a percentage of 26-30% THC making it one of the strongest strains in the world (60). **Chiquita Banana** is a cross between the famous OG Kush and Banana (60). The sweet flavours of these potent buds offer happy, giggly, and relaxed sensations (60).

2) Cherry Pie: The parental origins of this delicious hybrid are Granddaddy Purple and F1 Durban (60). Its taste resembles sweet and sour cherries, with a perfect balance between sweet and sour (60). **Cherry Pie** is credited with its giggly effects, overall mood enhancement, and a balance of energetic and calming effects (59-60). Cherry Pie is known for its flavourful buds that contain between 20-26% THC levels (60).

3) Strawberry Banana: Also known as **Strawnana,** is an uplifting hybrid strain (60). This Cannabis indica-dominant crop produces a THC level ranging from 22-26% and is the perfect bud with large yields, great terpene production (60). It combines the taste of tropical fruit with the aroma of fresh strawberries for a potent and sweet flavour (60).

4) White Widow: This hybrid is a classic in its category (60). It is the embodiment of the word hybrid by having a percentage of THC and CBD in equal parts with a ratio of 1:1 (60). This makes both Cannabinoids boost and work synergistically creating a potent strain with euphoric effects (60). This exotic strain is a cross between a Brazilian Cannabis sativa and a **South Indian Cannabis indica** (60). Its effects are balanced but powerful and the THC level can be up to 22% (59-60).

5) Sour Space Candy: One of the strongest CBD-dominant hybrids and is the direct descendant of the classic strains Sour Tsunami and Early Resin Berry (60). With 16.7% CBD, 1% THC, and a very attractive terpene profile (60). Sour Space Candy has some of the strongest effects among hybrid strains (60). The smell of this flower is fruity and grows strong and has a flavour profile similar to Gorilla Glue #4 and Sour Diesel (60). The dense buds are multicoloured, showing purple, orange, and green hues (60).

6) Gorilla Glue #4: Gorilla Glue #4 rocked the Cannabis world with test results reaching up to **33% THC** (60). There are several Gorilla Glue phenotypes available, although #4 is the most popular, followed by #1 (60). Gorilla Glue produces a very strong hybrid (60). However, this hybrid strain also provides some intensely euphoric effects. This complex strain is packed with flavours, making it a popular ingredient for edibles. With a high THC content and low CBD content, this strain is famous for its intense high (60).

7) Bruce Banner #3: Bruce Banner #3 is hard to find, and the demand for this bud is increasing (60). Bruce Banner #3 is a very potent hybrid that has up to 25% THC (60). One of the strongest strains in the world, **Bruce Banner** is a great medical hybrid cannabis bud and can be extremely helpful for those with chronic pain, including neuropathic pain and pain after an injury (60 Created from OG Kush and Strawberry Diesel, Bruce Banner #3 is known for its fast-acting effects that lean toward invigoration (60).

8) Girl Scout Cookies: Girl Scout Cookies have become one of the most popular hybrid strains on the West Coast (60). This potent weed has up to **28% THC** (60). As a hybrid, Girl Scout Cookies provides a strong high with a significant amount of body relaxation and mood elevation (60). This strain is known to inspire some giggles and a hazy, euphoric feeling (60). However, in large doses, this strain can cause sedation, which could make it difficult to get off the couch (60).

9) OG #18: Released by DNA Genetics under the Reserva Privada label, OG #18 is a phenotype of the OG Kush (60). OG #18 has been tested with up to 27% THC (60). OG #18 hybrid strain has won several awards, including Best Hydro at Spannabis 2011 (60). This strain is certainly potent, and OG Kush is a potent strain suitable for THC lovers, without CBD content (60).

10) King Tut: King Tut, also known as **Tutankhamon**, is a sativa-dominant hybrid with THC levels that can reach 30% (60). This strain is believed to be an offspring of the legendary AK-47, a potent sativa that produces a fast-acting, clear-headed cerebral high (60).

11) Kynn Labs Delta 8 Disposable – Gelato: This hybrid strains is the sweet combination of euphoria and relaxation (60). Besides, it's sweet flavour reminds of vanilla with a minty touch (60).

CANNABIS SATIVA: BOTANY

Figure-1: What are the difference between Cannabis Indica and Cannabis sativa ? - RQS Blog (royalqueenseeds.com).

Based on morphological, anatomical, phytochemical, and genetic studies, Cannabis sativa is generally considered as a single highly polymorphic species (1-25). **Cannabis sativa** and **Cannabis indica (Figure-1)** are widely distributed as a weed in **Indian Himalayan** region and other parts of **India, China, Bhutan, Pakistan,** and **Nepal** (1-25). The stunted growth of Cannabis sativa and Cannabis indica is very common in the Himalayan region. Further, Cannabis ruderalis is hardier and grows in the northern Himalayas and the southern states of the former Soviet Union but is rarely cultivated for drug content (1-40; 49-52). Both Cannabis indica and Cannabis ruderalis are now recognized as varieties of Cannabis sativa L. (var. indica and var. ruderalis, respectively) (1-28). *Cannabis sativa* is native to warmer, tropical climates and can be found growing naturally in India, China Bhutan, Pakistan, Afghanistan, Thailand, Vietnam, Colombia, Mexico, and even other parts of Africa (1-30). In order to deal with the long, hot, and humid summers, Cannabis sativa plants adapted by growing tall, with larger internodal spacing, wispy buds, and narrower leaves (1-40). This naturally helps the plants to stay protected against the high humidity in these areas and threats like mould or pests (1-25). Because Cannabis sativa plants tend to be taller, they are typically better suited for outdoor growing. They do particularly well in warm, tropical climates with long summers (1-45).

Cannabis indica plants typically contain higher amounts of **Cannabidiol** (CBD) than Δ9-tetrahydrocannabinol (Δ9-THC) (1-59). On the other hand Cannabis sativa plants typically have higher amounts of Δ9-tetrahydrocannabinol (Δ9-THC) than **Cannabidiol** (CBD). **Cannabis indica (Figure-1)** is more broad-leaved than Cannabis sativa (1-60). It is most commonly shorter and has more leaves and buds, giving it a more bushy appearance. The buds tend to be wider. It typically grows 2–4 feet tall, and is compactly branched (1-59).

Cannabis indica is believed to cause more of a **calming or relaxing effect.** Cannabis indica tend to decrease energy and are better for consumption in the evening or at night, after the conclusion of the day's work and activities (**Indica vs Sativa - Cresco Labs).** Potent Cannabis indica strains may give some patients what is called "Couchlock," a condition in which they become so relaxed that they care barely get up from the sofa (Indica vs Sativa - Cresco Labs). Cannabis sativa is known to cause an uplifting feeling. Cannabis sativa, on the other hand, are uplifting and cerebral, enhancing creativity and productivity (25-59). **Cannabis indica** provide what has been called a "body high," while **Cannabis sativa** deliver more of a "mind high." Unfortunately, Cannabis sativa plants required longer to grow and yield less medicine (flowers) than Cannabis indica varieties (Indica vs Sativa - Cresco Labs).

Cannabis is a species of flowering herb that is split into three subspecies: indica, sativa, and ruderalis. Cannabis ruderalis plants are small and yield relatively little medicine. Because of this, Cannabis ruderalis strains are typically avoided by breeders and cultivators. Cannabis ruderalis may have originated from southern Russia (25-60). It contains very low THC, so is rarely grown by itself (25-60). It has the property of **Autoflowering**: flowers appear as a result of plant age rather than light conditions (25-60). It is principally used in hybrids, to enable the hybrid to have the Autoflowering property (25-60). The plants are smaller than Cannabis sativa and have adapted to colder temperatures than Cannabis sativa (25-60). It does not typically grow to be more than 2 feet tall and is unbranched (25-60).

Therefore, focus of the medical Cannabis community is on Cannabis indica and Cannabis sativa strains (25-60). Cannabis indica and Cannabis sativa plants differ not only in their physiological effects, but also in their appearance (Figure-1). Cannabis indica plants are short and stocky, featuring leaves that are broad and "chunky. (1-60). Cannabis sativa plants tend to be taller and skinnier and may even be lanky in appearance, with leaves that are thin and pointed (Indica vs Sativa - Cresco Labs).

The main morphological difference between Cannabis indica and Cannabis sativa is in their **leaves** (**Figure-1**) (Royalqueenseeds.com). Both Cannabis indica and Cannabis sativa are found abundant and grown as common weed plant in the Indian Himalayan region and other parts of India, Bhutan, Nepal, Pakistan, Afghanistan and China (1-30, 49-52). **Cannabis sativa** as a medicine was used before the **Christian era** in Asia**,** mainly **in India,** China, Bhutan, Nepal, Pakistan and Afghanistan (1-52). However, the chemistry of biomolecules responsible for the narcotic activity was unknown. The leaves of Cannabis sativa are much smaller and thinner, whereas those of Cannabis indica have wide fingers and are deep green, often tinged with **purple (Figure-1)** (1-40). At maturity, **Cannabis indica** turn **dark purple** (1-40). Cannabis indica plants are shorter and bushier, usually under 6 ft tall and rarely over 8 ft (1-25,49-52). Cannabis indica has short branches laden with thick, dense buds, which mature early, usually at the beginning of September in the Northern Hemisphere (1-30). Cannabis indica buds also vary in color from dark green to purple, with cooler conditions inducing more intense coloration (1-52). Cannabis indica flowers earlier. The natural distribution of Cannabis indica in Himalayan region of India, Afghanistan, Pakistan, Nepal, Bhutan, China and surrounding areas (1-30). The plants of Cannabis sativa have long branches, with the lower ones spreading 4 ft or more from the central stalk, as on a conical Christmas tree (1-40, 49-52). Height varies from 6 ft to more than 20 ft, with 8-12 ft being the most common (1-40). Buds are long and thin and far less densely populated than in Cannabis indica, but longer, sometimes 3 ft or more (1-52). Maturation time varies considerably depending on the variety and environmental conditions. **Buds of Cannabis sativa required intense light to thicken and swell and Cannabis indica does not** (1-30). Cannabis sativa tends to be higher in Δ9-tetrahydrocannabinol (Δ9-THC) and lower in **Cannabidiol** (CBD) than Cannabis indica (1-40). Cannabis sativa is found all over the world particularly in **Indian Himalayan region** and other parts of India, Bhutan, Pakistan, Nepal, China, Afghanistan and comprises the most of the drug type equatorial varieties such as Colombian, Mexican, Nigerian, and South African, where marijuana plants can be very potent (1-52).

The most obvious differences between Cannabis indica and Cannabis sativa are in their **physical traits** (25-60). American botanist Richard E. Schultes and a team of researchers described Cannabis sativa and Cannabis indica as Cannabis **sativa**: Tall and laxly branched with narrow leaves. Cannabis **indica**: Shorter with a conical shape and wider leaves **(Figure-1).** Cannabis indica and Cannabis sativa plants tend to display drastically different growth rates and patterns depending upon the geographical locations (25-60). However, these distinctions does not become very apparent until the beginning of the flowering stage. Whereas Cannabis indica plants

shift their growth rate up a gear, gaining some height and forming a dense, bushy canopy (25-60).

On the other hand Cannabis sativa plants undergo some serious stretching (30-60). The change in light cycle triggers a hormonal cascade that causes them to shoot upwards towards the light. In some cases, this phenomenon (called "The Flowering Stretch") can cause plants to double in size (30-60). When planted deep in the ground or in large containers, Cannabis sativas can grow to 3m and beyond. Cannabis indica developed shorter flowering times and denser foliage and buds (30-60). Due to their smaller stature and shorter flowering phase, **Cannabis indica** plants are perfectly suited for **indoor cultivation** (30-60). Cannabis indica can easily be manipulated using training techniques and tend to produce nice, thick buds with a lot of "bag appeal" (30-60). Further due their flowering speed, **Cannabis indica** plants also allowed some growers to produce multiple harvests over a shorter amount of time (25-60).

Cannabis sativa L. is a widespread species in nature. It is found in various habitats ranging from sea level to the temperate and alpine foothills of the Himalayas particularly in India, Bhutan, Nepal, Pakistan, Afghanistan, and China from where it was probably spread over the last 10,000 years (1-52). Cannabis has a long history of medicinal use in the India, Middle East and Asia, with references as far back as the 6th century BCE, and it was introduced in Western Europe as a medicine in the early 19th century to treat epilepsy, tetanus, rheumatism, migraine, asthma, trigeminal neuralgia, fatigue, and insomnia (1-40).

Industrial Hemp (fiber type) grown for fiber in India, Bhutan, China, Pakistan, Afghanistan, and Nepal was introduced in Western Asia and Egypt and subsequently in Europe between 1000 and 2000 BCE (1-52). Cultivation of hemp in Europe became widespread after 500 CE. The crop was first brought to South America (Chile) in 1545, and to North America (Port Royal, Acadia) in 1606 (30-60). Normally, Cannabis exhibits a dioecious (male and female flowers develop on separate plants) and occasionally a monoecious (hermaphrodite) phenotype (1-60). Industrial Hemp (fiber type) flowers in the shorter days (below 12-h photoperiod) and continues growing vegetatively in the longer photoperiod (1-52). Sex is determined by heteromorphic chromosomes (males being heterogametic XY, females homogametic XX) (1-30; 49-52). Male flowers can be differentiated from female by their different morphological appearance (1-60). At the vegetative stage, differentiation is difficult because of morphological similarities. Molecular techniques, however, can differentiate at an early stage (1-52) (**Royalqueenseeds.com).**

Besides the physical differences between Cannabis indica and Cannabis sativa, some research also suggests that the two varieties may contain different concentrations of **terpenes**, which could be another factor that plants produce different effects (**Royalqueenseeds.com) (50-60).** For example, some sources pin the characteristic sedative quality of "heavy indica" cannabis strains on a high concentration of **myrcene (50-60).** **Myrcene** is a **terpene** found in many plants, including hops, thyme, lemongrass, mango, cardamom, and, of course, cannabis. It is said to give off an earthy, slightly peppery smell, and, in high concentrations, is thought to give some Cannabis strains that uniquely sleepy effect (**Royalqueenseeds.com)** (50-60).

In one of the recent study (61) the analysis of over 100 *Cannabis* samples quantified for terpene and cannabinoid content and genotyped for over 100,000 single nucleotide polymorphisms indicated that Cannabis sativa- and Cannabis indica-labelled samples were **genetically indistinct** on a genome-wide scale (61). Instead, this study reported that *Cannabis* labelling was associated with variation in a small number of **terpenes** whose concentrations are controlled by genetic variation at tandem arrays of terpene synthase genes (61).

Cannabis sativa is wind pollinated. For the production of Vannabinoids (or phytocannabinoids), female plants are preferred for several reasons (1-40). First, they produce higher amounts of Cannabinoids (1-25). Second, once pollinated, female plants produce seeds at maturity, whereas seed-free plants are preferred for their higher yield of secondary metabolites (1-40; 49-52). Third, if several cannabis varieties are being grown together, cross-pollination would affect the quality (chemical profile) of the final product (1- 52). To avoid this, removing male plants as they appear, screening female clones for higher metabolite content, and conservation and multiplication using biotechnological tools ensures the consistency in chemical profile that is desirable for pharmaceuticals (1-52) (**Royalqueenseeds.com).**

CANNABIS SATIVA: TWO TYPES BASED ON THC CONTENT

There are two main Cannabis sativa phenotypes according to **Δ9-tetrahydrocannabinol** (THC) content frequently taken into consideration (1-25). The **first one** is Medical Cannabis sativa (marijuana or drug type) with high **Δ9-tetrahydrocannabinol** (THC) content (**30-35%)** issued for medical and recreational purposes (1-25). The **second one** is Industrial Cannabis sativa (fiber-type) with **Δ9-tetrahydrocannabinol** (THC) less than **0.2%** (1-30). The main Cannabinoids in Cannabis sativa are Cannabidiol (CBD), Cannabinol (CBN), and Δ9-tetrahydrocannabinol (Δ9-THC) (25-45). Only THC is a psychoactive compound (25-48).

Cannabis sativa: Female inflorescence and Δ9-tetrahydrocannabinol (THC)

Figure-2: The female inflorescence is the main product of Medical Cannabis sativa (Marijuana or drug type)

The **female inflorescence (Figure-2)** is the main product of Medical Cannabis sativa (marijuana or drug type) (1-40). Cannabis sativa produces a unique class of terpenophenolic compounds, called **Cannabinoids**, as well as non-Cannabinoid compounds (15-40). **Δ9-tetrahydrocannabinol** (THC) is the major **psychoactive component** and the toxicity of this metabolite of Cannabis sativa is the most studied (20-40). The utilization of this multipurpose Medical Cannabis sativa (marijuana or drug type) has been restrained for a long time because of the **psychoactive effects** of a specific Cannabinoid, **Δ9-tetrahydrocannabinol** (THC) **($C_{12}H_{30}O_2$)** (20-48). These are produced by Cannabis sativa in their carboxylic acid forms, Δ9-tetrahydrocannabinolic acid (THCA) and Cannabidiolic acid (CBDA) respectively, which are decarboxylated by heating (e.g., smoking or baking), by light, or by natural degradation (47). Further, Δ9-THC, the decarboxylated form of THCA, is the Cannabinoid predominantly

responsible for the psychoactive properties of Cannabis sativa. Both THCA and CBDA share the precursor molecule Cannabigerolic acid (CBGA) (47). This precursor is formed by condensation of olivetolic acid, originating from the **Polyketide biosynthetic pathway**, and geranyl pyrophosphate, originating from the Deoxyxylulose phosphate pathway, also known as the Methylerythritol phosphate pathway (47).

Interestingly, the Cannabis sativa plant also uses **Δ9-tetrahydrocannabinol** (THC) and other Cannabinoids to promote its own health and prevent disease. Therefore, the synthesis of **Δ9-tetrahydrocannabinol** (THC) by Cannabis sativa helps in the defensive mechanism of plant (1-42). Cannabinoids have **antioxidant properties** that protect the leaves and flowering structures from ultraviolet radiation (1-41). These are also known as **Phytocannabinoids** since are produced and accumulated by Cannabis sativa plant (20-41). **Cannabinoids neutralize** the harmful **free radicals** generated by UV rays, protecting the cells (40-48). In humans, free radicals cause aging, cancer, and impaired healing. Antioxidants found in plants have long been promoted as natural supplements to prevent free radical harm (1-48).

Synthetic **Δ9-tetrahydrocannabinol** (THC) marketed as **Dronabinol** (Marinol), and Nabilone (Cesamet), a **Δ9-tetrahydrocannabinol** (THC) analog, are both FDA approved drugs for the treatment of **severe nausea** and **wasting syndrome** (30-48). Some clinicians have found them helpful in the off-label treatment of **chronic pain, migraine**, and other serious conditions. Many other synthetic Cannabinoids are also used in animal research, and some have the potency up to 600 times that of **Δ9-tetrahydrocannabinol** (THC).

Discovery of Δ9-tetrahydrocannabinol (THC)

Figure-3: Professor **Raphael Mechoulam**, the Godfather of Cannabis Science was active in Cannabinoids Research work at the Hebrew University of Jerusalem, Israel died at the age of 92 **on 9th March 2023.** The credit of the discovery of Cannabidiol (CBD) in **1963** and Δ9-tetrahydrocannabinol (THC) in **1964** isolated and identified from plant Cannabis sativa attributed to Dr. Raphael Mechoulam and his team**.**

However, the chemistry of biomolecules responsible for narcotic activity of Cannabis sativa was unknown in 19th Century (1-25). This has created a wide interest of many scientists to study cannabis and its compounds. The official discovery of **Cannabidiol** (CBD) in 1963 and **Δ9-tetrahydrocannabinol (THC)** in 1964 isolated and identified from Cannabis sativa at **Israel's Weizmann Institute of Science** is commonly attributed to **Dr. Raphael Mechoulam**, known as the **Godfather of Cannabis science** **(Figure-3)** (25-45). **Dr. Raphael Mechoulam** is best known for his work (together with **Y. Gaoni**) in the isolation, structure elucidation and total synthesis of **Δ9-tetrahydrocannabinol** (THC) the main narcotic active principle of Cannabis (1-48). **Professor Raphael Mechoulam (Figure-3)** was active in Cannabinoids research work at the **Hebrew University of Jerusalem in Israel** and died at the age of 92 on **9th of March 2023** (25-45).

The official discovery of **Cannabidiol** (CBD) in 1963 and **Δ9-tetrahydrocannabinol (THC)** in 1964 isolated and identified from Cannabis sativa has also further led to the discovery of **Endocannabinoid system (Figure-4) (ECS)** (20-45). Humans and other mammals contain an **Endocannabinoid system (ECS)** within their bodies, which plays a significant role in maintaining homeostasis, or balance, in the body (25-48). This unique **Endocannabinoid system (Figure-4) (ECS)** also **influences regulatory processes** diverse as appetite, sleep, mood, stress, energy levels, and reproduction (20-48). The **endocannabinoid system (ECS)** represented a critical part of understanding **Δ9-tetrahydrocannabinol (THC)** and its potent **effects** on the human body (25-48). The Endocannabinoid system (ECS) is a complex cell-signaling system identified in the early 1990s by researchers exploring **Δ9-tetrahydrocannabinol (THC)** a well-known Cannabinoid (20-48).

Discovery of Endocannabinoid system (ECS)

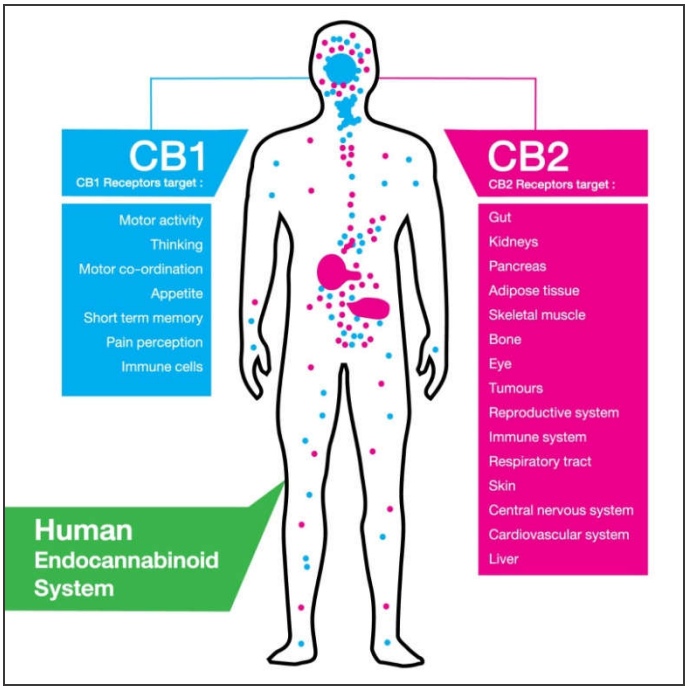

Figure-4: Human Endocannabinoid system (ECS) with CB-1 and CB-2 receptors

The **Endocannabinoid system (ECS)** (Figure-4) is a naturally occurring **Neuroendocrine** network that is present throughout the body, including the brain, nervous system, heart and organs (25-48). The ECS regulates many physiologic functions including pain, inflammation, immunity, appetite and metabolism, gastrointestinal (GI) function, memory and movement (30-48). THC, CBD and other Cannabinoids found in marijuana interact with the ECS to provide their therapeutic benefits (25-45).

The human body naturally produces **endocannabinoids** (25-48). They are present in various organs and tissues, such as the muscle, brain, and circulating cells (**Figure-4)** (30-45). Endocannabinoids become active when they bind with a Cannabinoid

receptor (25-45). The receptors are also located throughout the body (Figure-4) (28-48). The Endocannabinoid system (ECS) has been recently recognized as **an important modulatory system in the function of brain, endocrine, and immune tissues** (25-45). ECS appears to play a very important regulatory role in the secretion of hormones related to reproductive functions and response to stress (20-48). **Some of the healthy and natural ways to boost endocannabinoid system: Increase the intake of Omega-3 Fatty Acids, Exercise regularly, Manage stress better, Lower alcohol consumption and increase the consumption of Phytocannabinoids** (20-45). **Medium and high-intensity exercise** has been shown to activate the endocannabinoid system (30-48). Research also showed that exercise significantly up-regulates **CB1 receptors** and enhances CB1 receptor sensitivity, which is why exercise can protect against the consequences of stress (40-48). CB1 receptors are mostly found in the brain and impact a number of **neurotransmitters**, including **GABA**, glutamate, **dopamine** and serotonin (25-48). **CB2** receptors, on the other hand, are mostly found within the immune system and blood cells (Figure-4) (25-48). However, it is important to note that some CB1 receptors are still located outside the brain, and some CB2 receptors can be found within the brain. So, there is some overlap (Figure-4) (30-48). Endocannabinoids as mentioned before, these Cannabinoids are produced naturally within the body. **Anandamide** is the main endocannabinoid in human body (25-48). It can be found in humans, but also found in many other animals and plants. It binds to both CB1 and CB2 receptors and has similar effects as **Δ9-tetrahydrocannabinol (THC)** (25-48). Further, **2-Arachidonoylglycerol** (2-AG) is another critical endocannabinoid in human body that also binds to the CB1 and CB2 receptors (25-48). Its effects are similar to Cannabidiol (CBD) (28-48). **Low endocannabinoids levels, are mainly due to illness followed by** major depression**,** generalized anxiety disorder**,** post-traumatic stress disorder (PTSD)**,** multiple sclerosis**, attention, Sleep disorders, fibromyalgia, and Parkinson's disease** (25-48).

Phytocannabinoids are the plant-derived Cannabinoids, such as **Δ9-tetrahydrocannabinol (THC)** and **Cannabidiol (CBD)** found in Cannabis sativa and Cannabis indica (1-48). Phytocannabinoids are synthesised in, secreted by and stored in trichomes, hair like epidermal structures that can be found across most aerial parts of the Cannabis sativa plant (1-25; 26-48). Phytocannabinoids appear in the highest abundancy over pistillate inflorescences are the key elements in the plants defence mechanism against biotic (e.g., insect predation) and abiotic (e.g., ultraviolet radiation and nutrient deficiency) stresses under which cannabis plants have evolved (46).

In addition to regulating human body internal and cellular homeostasis, Cannabinoids influence a person's relationship with the external environment. Socially, the administration of Cannabinoids clearly alters human behavior, often promoting sharing, humour, and creativity (25-48). Sea squirts, tiny nematodes, and all vertebrate species share the endocannabinoid system as an essential part of life and adaptation to environmental changes (25-48). Endocannabinoids are the substances in human bodies naturally make to stimulate these receptors (25-45). The two most well understood of these molecules are called **Anandamide and 2-arachidonoylglycerol (2-AG).** They are synthesized on-demand from cell membrane arachidonic acid derivatives, have a local effect and short half-life before being degraded by the enzymes Fatty acid amide hydrolase (FAAH) and Monoacylglycerol lipase (MAGL) (25-48).

The endogenous Cannabinoid system (ECS), named for the Cannabis sativa that led to its discovery is one of the most important physiologic systems involved in establishing and maintaining human health (20-48). Endocannabinoids and their receptors CB1 and CB2 are found throughout the body: in the brain, organs, connective tissues, glands, and immune cells (20-48). With its complex actions in human immune system, nervous system, and virtually all of the body's organs, the endocannabinoids are literally a **bridge between body and mind** (25-48). By understanding this system, a mechanism that could connect brain activity and states of physical health and diseases (20-48).

Δ^9-tetrahydrocannabinol (THC) is referred to as a "Cannabinoid" (like the dozens of other unique constituents of cannabis), acts on the brain by muscling in on the intrinsic neuronal signaling system, mimicking a key natural player, and basically hijacking it for reasons best known to the plants (20-48). Since the time when exogenous Cannabinoids revealed their existence, the entire natural complex came to be called the "**Endogenous Cannabinoid system**," or "**Endocannabinoid system**" (ECS) (25-48).

The **Endocannabinoid system (ECS**) produces endogenous Cannabinoids (produced internally) and responds to exogenous Cannabinoids (produced externally), like the ones found in Cannabis sativa which are called as phytocannabinoids (20-45). Cannabinoids are compounds found in Cannabis sativa (20-45). **Δ9-tetrahydrocannabinol (THC)** is one of the main Cannabinoids found in Cannabis sativa. It is the compound that gets "high." Once in human body, **Δ9-tetrahydrocannabinol (THC)** interacts with **Endocannabinoid system (ECS)** by binding to receptors, CB1 and CB2 just like endocannabinoids (25-48). It is powerful partly because it can bind to both CB1 and CB2 receptors (20-48).

Endocannabinoid system (ECS) : How It Works

The **Endocannabinoid system** (ECS) is a biological network distributed throughout the entire body (25-48). It is composed of Endocannabinoids, which are endogenous lipid-based retrograde neurotransmitters that bind to Cannabinoid receptors and proteins that are expressed throughout the central nervous system, including the brain and peripheral nervous system (25-48). The ECS is comprised of two important receptors; Cannabinoid receptor type 1 (CB_1) and Cannabinoid receptor type 2 (CB_2). CB_1 and CB_2 are **transmembrane G-protein** coupled receptors (GPCRs) located throughout the central and peripheral nervous system (25-48).

The **Endocannabinoid system (ECS)** involves three core components: Endocannabinoids, Receptors, and enzymes (20-45). Endocannabinoids are also called as endogenous cannabinoids, since molecules produced in human body (25-45). They are similar to Cannabinoids, but they are produced by human body (20-45). The 2 key endocannabinoids are **Anandamide** and **2-Arachidonoyl glycerol (2-AG)** (20-45). **Dr. Raphael Mechoulam** is also known for the isolation and the identification of the endogenous Cannabinoids **Anandamide** from the brain and **2-Arachidonoyl glycerol (2-AG)** from peripheral organs together with his collaborators (25-48).

The receptors CB1 and CB2 are found throughout human body. Endocannabinoids bind to them in order to signal that the **Endocannabinoid system (ECS) (Figure-4)** needs to take action (20-45). There are two main two **G protein**-coupled endocannabinoid receptors: CB1 receptors, which are mostly found in the central nervous system (25-48). CB2 receptors, which are the mostly found in peripheral nervous system, especially immune cells (25-48). Endocannabinoids can bind to either receptor (25-48). CB1 and CB2 receptors are distributed throughout the central and peripheral nervous systems (25-45). "**In the brain, these receptors** are located in the brain stem, cerebral cortex, hippocampus, cerebellum, basal ganglia, hypothalamus, and amygdala (25-48). They are also found in the liver, kidneys, spleen, gonads, and heart (20-48).

Δ9-tetrahydrocannabinol (THC) is what is known as a **partial agonist at both CB1 and CB2 receptors**, meaning that it

can partially bind to both receptor sites (26-48). The psychoactive effects for which **Δ9-tetrahydrocannabinol (THC)** is famed arise **from its affinity for the CB1 receptor** (25-41). The effects that result depend on where the receptor is located and which endocannabinoid it binds to (25-48). For example, endocannabinoids might target CB1 receptors in a spinal nerve to relieve pain (30-48). Others might bind to a CB2 receptor in immune cells to signal that body is experiencing inflammation, a common sign of autoimmune disorders (14-48).

Enzymes are responsible for breaking down endocannabinoids once they have carried out their function (30-48). There are two main enzymes responsible for this: Fatty acid amide hydrolase, which breaks down AEA (20-48). Further Monoacylglycerol acid lipase, which typically breaks down 2-AG (25-48). Further **Endocannabinoid system (ECS)** is linked to the processes: appetite and digestion metabolism, chronic pain, inflammation, and other immune system responses mood learning and memory motor, control sleep, cardiovascular system function, muscle formation, bone remodeling, growth, liver function, reproductive system function, stress, skin and nerve function (20-48). These functions are all contributed to homeostasis, which refers to stability of internal environment (41-48). For example, if an outside force, such as pain from an injury or a fever, throws off human body's homeostasis, then **Endocannabinoid system (ECS)** kicks into help the body return to its ideal operation (15-48).

Cannabidiol (CBD): Medicinal Importance

Cannabidiol (CBD) is one of many Cannabinoids extracted from the industrial hemp plant, *Cannabis sativa*. Another famous Cannabinoid is **Δ9-**tetrahydrocannabinol (THC). However, **Cannabidiol** (CBD) has unique properties that make it attractive for therapeutic purposes over **Δ9-tetrahydrocannabinol** (THC) (25-48). **Cannabidiol** (CBD) is a non-toxic, non-psychotropic, powerful dietary supplement that can help to maintain **Endocannabinoid system (ECS)** and **Hypothalamic-Pituitary-Adrenal Axis** (HPA) axis homeostasis (28-48). It supports lower levels of stress, anxiety and inflammation, along with antioxidant and neuroprotective properties (25-48). Therefore, **Cannabidiol** (CBD) is a great natural dietary supplement, and when used right, can be an excellent therapy for a wide variety of acute and chronic health and wellness issues (25-48).

Cannabidiol (CBD) also has anti-inflammatory and neuroprotective effects (25-48). A major component of inflammation is the response to **Reactive Oxygen Species** (ROS), which can accumulate and cause DNA damage and cytotoxicity (25-48). Antioxidants are molecules that have the ability to detoxify ROS (48). **Cannabidiol** (CBD) has been shown in various studies to have a much higher antioxidant ability than vitamin C and E, and comparable to that of **Butylated hydroxytoluene** (BHT) – A synthetic antioxidant used as a food and drug preservative (25-48). In addition to acting as an antioxidant itself, **Cannabidiol** (CBD) causes a noted increase in the presence of other antioxidants as well (40-48). **Cannabidiol** (CBD) upregulates an important antioxidant, glutathione, as well as the enzyme superoxide dismutase (SoD), which is the body's strongest antioxidant and responsible for around a third of the total antioxidation in human bodies (25-48).

Further, glutamate, which is the brain's primary excitatory neurotransmitter. When **glutamate levels** are too high, excitotoxicity and oxidative stress both occur (25-48). **Cannabidiol** (CBD) is shown to prevent this by agonizing serotonin 5-HT1a receptors, which have the opposite effect of glutamate receptors, thereby reducing **excitotoxicity and oxidative stress** (38-48). Many neurodegenerative diseases are characteristic of **excitotoxicity**, including **Alzheimer's Disease and Parkinson's** disease, anxiety, schizophrenia, and even autism (25-48). Finally, **Cannabidiol** (CBD) is fast becoming a treatment of choice for effective pain relief, spasticity and seizures, with plenty of high-quality evidence supporting ECS (25-48). **Cannabidiol** (CBD) action as a protectant against inflammation and oxidative stress could explain the success that many have found using **Cannabidiol** (CBD) to add to their therapeutic strategy for these conditions and others (25-48).

REFERENCES

1. Eckler CR. Deterioration of Crude Indian Cannabis, Jour. Am. Pharm. Assoc. 1917: vol. 6.
2. Chopra RN. The Present position of the Opium habit in India, Ind. Jour. Med. Res . 1928: 16(2):389.
3. Chopra RN, Chopra GS. 1931 Cocaine Habit in India, Ind. Jour. Med. Res . 1031: 18, No. 3, Jan.
4. Chopra RN, Chopra GS. Med. Res ., 23.2.Oct., 359. 1965.
5. Chopra RN 1935, Drug Addiction in India and its treatment, Ind. Med. Gaz ., 70, No. 3, March 121.
6. Chopra RN, Chopra GS 1938, The Opium Smoking habit in India and present position of the Opium smoking habit in India, Parts I, II, III, Ind. Med. Gaz . 73, Nos. 2, 3, 4 (Feb. Mar. Ap.)
7. Walton, RP. Marihuana, J. B. Lippincott Co., New York. 1938.
8. Chopra RN, Chopra GS 1939, The present position of Hemp Drugs. Addiction in India, Ind. Jour. Med. Res . 1939. Memoir, No. 31.
9. Chopra RN. Use of Hemp Drugs in India, Ind. Med. Gaz. 1940. 75, No. 6, June.
10. Chopra RN, Chopra GS, Chopra IC. 1942, Cannabis sativa in relation to Mental diseases and Crime in India, Ind. Jour. Med. Res . 1942: 30.1. Jan.
11. Chopra RN, Chopra IC. Bulletin on Narcotics (United Nations), vol. 7, No. 3-4. United Nations Economic and Social Council, 1956, Commission on Narcotic Drugs, 11th session, doc.: E/CN/7/286/Add.12. 1955.
12. Chopra RN, Chopra IC. The Use of the Cannabis Drugs in India. Sir R. N. Chopra Director, Drug Research Laboratory, Jammu and Kashmir (India), Member of thc Expert Advisory Panel on Addiction-producing Drugs of the World Health Organization. 1957/01/01.
13. Andre CM, Hausman JF, Guerriero, G. Cannabis sativa: The plant of the thousand and one molecules. Frontiers in plant science. 2016; 7: 19.
14. **O'Shaugnessy** WB. On the preparations of the Indian hemp, or gunjah (Cannabis indica). Prov. Med. J. 1843; 123:363–369.
15. **Malabadi RB**, Kolkar KP, Chalannavar RK. **Cannabis sativa**: Ethnobotany and Phytochemistry. International Journal of Innovation Scientific Research and Review. 2023; 5(2): 3990-3998.
16. **Malabadi RB**, Kolkar KP, Acharya M, Chalannavar RK. Cannabis sativa: CANNABIS SATIVA: MEDICINAL PLANT WITH 1000 MOLECULES of Pharmaceutical Interest. International Journal of Innovation Scientific Research and Review. 2023; 5 (2):3999-4005.
17. Clendinning J. Observation on the medicinal properties of Cannabis sativa of India. Medico-Chirurgical Transactions. 1843; 26: 188–210.
18, Dwarakanath C. Use of opium and cannabis in the traditional systems of medicine in India. Bull Narc. 1965; 17: 15–19.
19. Sanyal PK. A story of medicine and pharmacy in India: Pharmacy 2000 years ago and after. Shri Amitava Sanyal, Calcutta. 1964.
20. Aldrich MR. Tantric cannabis use in India. J. Psychedelic Drugs. 1977; 9: 227–233.

21. Wujastyk D. Cannabis in traditionnal Indian herbal medicine. In: A Salema (ed.): Ayudveda at the crossroad of care and cure. Universidade Nova, Lisbon. 2002; 45–73.
22. O'Shaughnessy WB. On the preparations of the Indian hemp, or gunjah (Cannabis indica). Their effects on the animal system in health, and their utility in the treatment of tetanus and other convulsive diseases. Provincial Medical Journal and Retrospect of the Medical Sciences. 1843 5: 343–347, 363–369: 397–398.
23. O'Shaughnessy WB (1838–1840) On the preparations of the Indian hemp, or gunjah (Cannabis 18 E. Russo indica); Their effects on the animal system in health, and their utility in the treatment of tetanus and other convulsive diseases. Transactions of the Medical and Physical Society of Bengal. 71–102, 421–461.
24. Ley W. Observations on the Cannabis indica, or Indian hemp. Provincial Medical Journal and Retrospect of the Medical Sciences. **1843;** 5: 487–489.
25. **Malabadi RB**, Kolkar KP, Chalannavar RK. CANNABIS SATIVA: Industrial hemp (fiber type) - An Ayurvedic Traditional Herbal Medicine. International Journal of Innovation Scientific Research and Review. 2023; 5 (2): 4040-4046.
26. **Pertwee RG.** The 90th birthday of Professor Raphael Mechoulam, A Top Cannaboid Scientist and Pioneer. Int. J. Mol. Sci. **2020**; 21: 7653.
27. Mechoulam R, Hanus LO, Pertwee R, Howlett AC, Early phytocannabinoid chemistry to endocannabinoids and beyond. Nat. Rev. Neurosci. **2014**; 15: 757–764.
28. Mechoulam R, Gaoni Y. The absolute configuration of D1-tetrahydrocannabinol, the major active constituent of hashish. Tetrahedron Lett. **1967**; 8: 1109–1111.
29. Mechoulam R, Shani A, Edery H, Grunfeld Y. Chemical basis of hashish activity. Science. **1970**; 169: 611–612.
30. Mechoulam R. Marijuana: Chemistry, Pharmacology, Metabolism, and Clinical E_ects; Academic Press: New York, NY, USA, 1973.
31. **Pertwee** RG. Endocannabinoids and their pharmacological actions. In Endocannabinoids; Pertwee, R.G., Ed.; Springer: Berlin, Germany, 2015; Volume 231, pp. 1–37. 2015.
32. **Devane WA**, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Grin G, Gibson D, Mandelbaum A, Etinger A, Mechoulam R. Isolation and structure of a brain constituent that binds to the Cannabinoid receptor. **Science**. **1992**; 258: 1946–1949.
33. **Gaoni Y, Mechoulam** RJ. Isolation structure and partial synthesis of an active constituent of hashish. J. Am Chem Soc. 1964;86:1646-7.
34. Gaoni Y, Mechoulam R. Isolation, structure and partial synthesis of an active constituent of hashish. J. Am. Chem. Soc. 1964; 86:1646–1647.
35. **MECHOULAM** R. Cannabinoid chemistry. In: Marijuana, ed. Mechoulam, R. pp. 1–99. New York: Academic Press. 1973.
36. Mechoulam R, Hanuš L. A historical overview of chemical research on cannabinoids. Chem Phys Lip. 2000; 109:1–13.
37. Mechoulam R, Shvo Y. Hashish—I: The structure of Cannabidiol. Tetrahedron. 1963; 19:2073–2078
38. **MECHOULAM** R. The pharmacohistory of Cannabis sativa. In: Cannabinoids as Therapeutic Agents, ed. Mechoulam, R. pp. 1–19. Boca Raton, FL: CRC Press. 1986.
39. MECHOULAM R, HANUS L. A historical overview of chemical research on Cannabinoids. Chem. Phys. Lipids. 2000; 108: 113.
40. Andre CM, Hausman JF, Guerriero, G. *Cannabis sativa*: The plant of the thousand and one molecules. Frontiers in plant science. 2016; 7: 19.
41. Alger BE. Getting High on the Endocannabinoid System. Cerebrum. November 2013.
42. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature. 1993; 365: 61–65.
43. Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature. 1990; 346: 561–564.
44. Sugiura T, Kondo S, Sukagawa A, Nakane S, Shinoda A, Itoh K, Yamashita A, Waku K. 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. Biochemical and Biophysical Research Communications. 1995; 215: 89–97.
45. Wilson RI, Nicoll RA. Endogenous cannabinoids mediate retrograde signalling at hippocampal synapses. Nature. 2001; 410: 588–592.
46. Naim-Feil E, Elkins AC, Malmberg MM, Ram D, Tran J, Spangenberg GC, Rochfort SJ, Cogan NOI. The Cannabis Plant as a Complex System: Interrelationships between Cannabinoid Compositions, Morphological, Physiological and Phenological Traits. Plants. 2023; 12: 493. https://doi.org/10.3390/ plants12030493.
47. Sarma BD, Waye A, ElSohly MA et al. Cannabis Inflorescence for Medical Purposes: USP Considerations for Quality Attributes. J. Nat. Prod. 2020; 83: 1334−1351.
48. Hampson AJ, Grimaldi M, Axelrod J, Wink D. Cannabidiol and () 9-Tetrahydrocannabinol Are Neuroprotective Antioxidants. Proc. Natl. Acad. Sci. **1998**.
49. Razdan RK. Structure-activity relationships in cannabinoids. Pharmacol Rev. 1986;38 (2):75-149.
50. Ahmed SA, Ross SA, Slade D, et al. Cannabinoid ester constituents from high-potency Cannabis sativa. J Nat Prod. 2008;71(4):536-542.
51. Gill EW, Paton WD, Pertwee RG. Preliminary experiments on the chemistry and pharmacology of cannabis. Nature. 1970;228(5267):134-136.
52. Thomas BF, ElSohly MA. The Botany of Cannabis sativa L. The Analytical Chemistry of Cannabis. Quality Assessment, Assurance, and Regulation of Medicinal Marijuana and Cannabinoid Preparations 2016; 1-28; DOI: http://dx.doi.org/10.1016/B978-0-12-804646-3.00001-1.
53. Salehi A, Puchalski K, Shokoohinia Y, Zolfaghari B, Asgary S. Differentiating Cannabis Products: Drugs, Food, and Supplements. Front. Pharmacol. 2022;13:906038.
54. Anderson LC. Leaf variation among cannabis species from a controlled garden. Botanical Museum Leaflets Harvard Univ 1980;28;61–69.
55. Potter DJ. The propagation, characterisation and optimisation of Cannabis sativa L. as a phytopharmaceutical. PhD thesis, King's College, London, 2009.
56. Hillig KWand Mahlberg PG. A chemotaxonomic analysis of cannabinoid variation in Cannabis (Cannabaceae). Am J Botany 2004;91:966–975.
57. Russo EB. History of cannabis and its preparations in saga, science, and sobriquet. Chem Biodivers. 2007;4:1614–1648.
58. Erkelens JL, Hazenkamp. That which we call indica, by any other name would smell as sweet. Cannabinoids. 2014;9:9–15.
59. Gloss D. An Overview of Products and Bias in Research. Neurotherapeutics (2015) 12:731–734 DOI 10.1007/s13311-015-0370-x.
60. Melissa Jaramillo. Strains Sense | 01.23.2023 Strains Sense: The Strongest Hybrid Strains On Earth Right Now. Strains Sense: The Strongest Hybrid Strains On Earth Right Now | Herb.
61. Watts S, McElroy M, Migicovsky Z, Maassen H, van Velzen R, Myles S. *Cannabis* labelling is associated with genetic variation in terpene synthase genes. **Nature Plants** | VOL **1330** 7 | October 2021 | 1330–1334.

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