

Research Article

MEDICAL CANNABIS SATIVA (MARIJUANA OR DRUG TYPE): THE STORY OF DISCOVERY OF Δ^9 -TETRAHYDROCANNABINOL (THC)

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ABSTRACT

This review paper highlights about the story of the discovery of Psychoactive constituent, Δ^9 -Tetrahydrocannabinol (THC) isolated, purified and identified from the Cannabis sativa (Marijuana or Drug type). Medical Cannabis sativa is also commonly known as marijuana, Bhang, Ganja, and Charas, which are still banned in India as An illicit drug. Sales and cultivation of Medical Cannabis (marijuana type) are still illegal in India. According to Ayurveda in India, the medicinal properties of Cannabis was well documented more than 3,000 years ago. This was the first Indian evidence to support the medicinal value of Cannabis plants. Cannabis sativa and Cannabis indica are widely found in the Himalayan mountain regions and other parts of India, China, Bhutan, Pakistan, Afghanistan and Nepal. However, the chemistry of biomolecules responsible for narcotic activity of Cannabis was unknown till 19th century.. This has created a wide interest of many scientists to study Cannabis and its compounds. The official discovery of Cannabidiol (CBD) in 1963 and Δ^9 -tetrahydrocannabinol (THC) in 1964 isolated from Cannabis sativa at Israel's Weizmann Institute of Science is commonly attributed to Dr. Raphael Mechoulam, known as the Godfather of Cannabis Science. Professor Raphael Mechoulam was active in Cannabinoids research work at the Hebrew University of Jerusalem in Israel. He died at the age of 92 on 9th March 2023, and his outstanding contribution in the field of Cannabis research work is very much appreciated. Finally, the contribution of Dr. Roger Adams and the Nobel laureate Dr. Alexander Robertus Todd, Robert Sidney Cahn and Frantisek Santavy and Roger G. Pertwee towards the Cannabinoids research work were also deserved mentioning. Finally, the Cannabis medicines, Sativex (Nabiximols), Epidiolex and Dronabinol are available in the market and used by Doctors prescriptions. This review paper is written in the Memory of Professor Raphael Mechoulam and Dedicated as a token of respect for his outstanding contribution in the field of Cannabis Science Research.

Keywords: Bhang, Cannabidiol (CBD), Charas, Cannabis sativa, Ganja, Illicit drug, Psychoactive compound, hemp, marijuana, Δ^9 -Tetrahydrocannabinol-THC.

INTRODUCTION: CANNABIS HISTORY

In 19th century, the use of Cannabis resin (Charas, Ganja) in India and hashish in Parisian literary has created a wide interest of many scientists to study Cannabis and its compounds (1-27; 89-117). The identification of Cannabis as a narcotic plant is associated to the British and French colonial expansion of the nineteenth century, whose penetration in India and North Africa led to the discovery of intoxicating strains of a plant (10-27; 89-117). Otherwise known in Europe essentially as a source of cordage and fiber material for cloth. In those times, the distinction between curative and recreational use was blurred (1-36). For this reason, interest for Cannabis was, at the outset of the studies, genuinely medicinal, and not forensic, since the therapeutic uses of the Cannabis plants were also well documented, especially in India (O'Shaughnessy 1843) (23; 1-27; 89-113). Cannabis sativa (Figure-1) as a medicine was used before the Christian era in Asia, mainly in India and China (1-20, 89-117). Cannabis has a long history in India, recorded in legends and religion (1-24; 25-36; 89-113). The earliest mention of cannabis has been found in The Vedas, or sacred Indian Hindu texts (1-27; 89-117). O'Shaughnessy served in India with the British Empire for several years and made his first contact with Cannabis sativa use in India (23). He studied the literature on the plant by referring to Ayurveda, described many popular preparations, evaluated its toxicity in animals, and, later, he tested its effect on patients with different pathologies (1-36; 89-113). In 1839, O'Shaughnessy published the work: 'On the preparations of the Indian hemp, or Gunjah', which, in

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the first paragraph, establishes a panorama of plant use (89-114). Cannabis or Industrial hemp has been employed medicinally in Ireland since at least the Anglo-Saxon era, more than 1000 years ago (1-36; 89-114).

According to Ayurveda in India, the medicinal value of the Cannabis plants was well documented more than 3,000 years ago (89-108). This was the first Indian evidence to support the medicinal value of Cannabis plants which was well documented in Ayurveda in India (1-24; 89-108). This was the first hand information about the medicinal value of Cannabis (1-25; 89-108). The earliest written reference to Cannabis in India may occur in the Atharvaveda, dating to about 2500 BCE (1-24;89-108). Cannabis also finds mentions in Ayurveda text as 'Vijaya' and has been recommended for its medicinal properties (1-27;89-114). Ayurveda literature like Charaka Samhita mentions properties of Vijaya as digestive and intoxicating which makes the cultivation and usage of the plant a religious and cultural phenomenon (1-25;89-114). In the Sushruta Samhita (meaning the verses of Sushruta), perhaps dating from the third to the eighth centuries BCE, Cannabis was recommended for phlegm, catarrh and diarrhea (89-108). As noted, an anti-phlegmatic would be interpreted in Ayurvedic medicine as possessing a wide variety of effects (1-24;89-114). Similarly, Dwarakanath has reported that cannabis was employed in Indian folk medicine in aphrodisiacs and treatments for pain in the same era (89-114). Aldrich documented the development of Tantric Cannabis usage around the seventh century as a mingling of Shaivite

Hinduism and **Tibetan Buddhism** (89-108). Apparently, the 11th century text, **Mahanirvana Tantra**, is currently still consulted with regard to sexual practices, withholding of **male ejaculation** and promotion of **sexual pleasure** in both genders (1-24; 89-114).

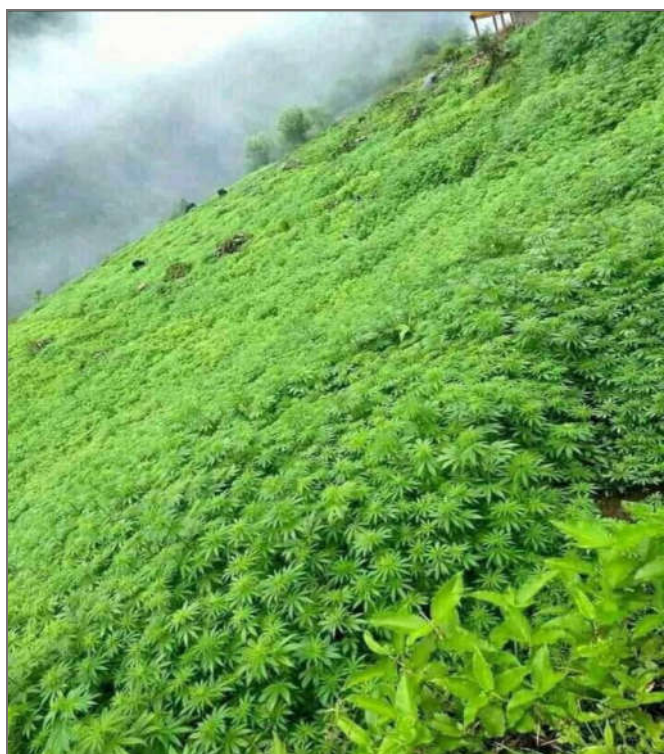


Figure 1: The wild growth of Cannabis sativa in the Himalayan region

Asia was the epicentre of the Cannabis sativa particularly **India** and China (1-36). The history of **Ayurveda** goes deep in the Indian roots (1-25; 89-108). **Ayurveda** was developed more than 5,000 years ago in India (89-117). In India, medical Cannabis sativa (marijuana or drug type) is also commonly known as marijuana, Bhang, Ganja, and Charas, which are still banned in India as **an illicit drug** (1-36). Majority of historians believed that the Cannabis sativa, Cannabis indica and Industrial Hemp (fiber type) plant is indigenous to both Central Asia and the **Indian subcontinent** and is widely found in the **Himalayan mountain regions** (Figure-1) extending to other parts of India, Pakistan, China, Afghanistan, Nepal and even Bhutan and Myanmar (3-29; 89-108). Scriptures like Vedas have estimated the plant to be at least 3500 years old and is even considered a sacred plant (1-27; 89-108).

India is a land steeped in faith and mysticism. **Ayurveda**, combining the Sanskrit words for life and knowledge, is a system of medicine intertwined inextricably with these traits (1-24; 89-108). That a core of belief combined with empirical experimentation could produce a viable medical regimen still widely practiced after well over 3000 years is astounding to Western physicians (89-108). **Cannabis was similarly bound to faith and mysticism in India** in the past, in the Hindu and Islamic traditions, as well as in numerous other minority religions (89-113). According to the **Materia medica** of India comprises in excess of 3000 drugs, mostly of vegetal origin, with 900 medicinal plants known even during Buddhist times, and Cannabis remains important among them (89-117).

According to The **Vedas**, Cannabis was one of five sacred plants and a guardian angel lived in its leaves (1-27; 89-113). The Vedas called Cannabis **as a source of happiness, joy-giver, liberator that was compassionately given to humans to help us attain delight and lose fear** (1-25). It releases from anxiety, and tension (1-27). During the Middle Ages, soldiers often took a drink of bhang before entering battle, just as Westerners took a swig of

whiskey (1-24; 89-113). Bhang is also rolled and eaten in small balls. Bhang is about the strength of Western marijuana. Because **milk contains fat, mixing Cannabis with milk is an effective means of extracting Δ^9 -tetrahydrocannabinol (THC)** but ingesting marijuana takes longer to feel the effects and is less consistent (1-27).

In India, the medical and religious use of Cannabis probably began together around **3000 years BC**. The plant was used for innumerable functions, such as: analgesic (neuralgia, headache, toothache), anticonvulsant (epilepsy, tetanus, rabies), hypnotic, tranquilizer (anxiety, mania, hysteria), anesthetic, anti-inflammatory (rheumatism and other inflammatory diseases), antibiotic (topical use on skin infections, erysipelas, tuberculosis), antiparasite (internal and external worms), antispasmodic (colic, diarrhea), digestive, appetite stimulant, diuretic, aphrodisiac or anaphrodisiac, antitussive and expectorant (bronchitis, asthma) (1-35; 89-117).

The British found the use of Cannabis so extensive in colonial India that they commissioned a large scale study in the late 1890s (1-27; 89-114). They were concerned that the abuse of Cannabis was endangering the health of the native Indian people and driving them insane (1-27; 89-114). Cannabis in its various forms remained the focus of intense scrutiny, and continued to harbor critics (1-24; 89-117). Because of concerns of its moral dangers, the **British Colonial authorities** in India **organized a commission** to examine all aspects of the issue (89-113). **Under British Colonial rule**, where other substances like opium were illegal, Cannabis derivatives were not banned outrightly (1-27; 89-113). The British government deliberated that a ban was likely to cause social unrest, and **decided to tax it** instead (1-27; 89-114).

At the dawn of the 20th century, Cannabis suffered further downturns. In 1914 it was dropped from the **British pharmacopoeia** and Sri Lanka (1-24; 89-113). The status of Cannabis was compounded by increasingly severe quality-control problems with **material exported from India to the UK** (98-113). These two factors, political and pharmacological, were paramount in the decline of Cannabis medicines in the West (89-113). Cannabis use remained common in 20th-century in India (89-113).

Cannabis continues to be available in India of the 20th and 21st centuries (1-24; 89-113). In their review in the mid-fifties, Chopra and Chopra (1957) found little changed since the **Indian Hemp Drugs Commission Report of 1894** (1-20; 89-113). Construction workers use bhang to feel refreshed at the end of the day and to fight fatigue (1-25). Hindus use bhang for religious ceremonies like Holi and ascetics use it to seek divinity (1-25; 89-113). **Sadhus are Indian ascetics who have shunned material life and use Cannabis to seek spiritual freedom** (1-20; 89-113). The herbal plant, Cannabis, has a long and continuous history in India. It has lived for thousands of years in stories of gods and warriors and it continues to live today in religious ceremonies and street stands (1-25; 89-117).

The second evidence was that Archaeologists have found evidence of cannabis with high levels of THC in Western **China** dating back 2,500 years (1-27). These artifacts suggested that humans may have been intentionally cultivating and selecting **Δ^9 -tetrahydrocannabinol (THC)** rich Cannabis specimens for a very long time (91-27). Furthermore, Cannabis was traditionally considered as sacred in **Tibet**, although little has been written about its religious or medicinal use. (1-27). In **Tantric Buddhism**, which was developed in the Himalayas, Cannabis was used to facilitate meditation (1-27; 89-113). Though seldom reported, it is believed that the medical use of **Cannabis in Tibet** was intense due to the following reasons: the concepts of Tibetan medicine stem from **Indian Hindu medicine**; botany was of great importance in its pharmacopoeia; and, finally, Cannabis was abundant in that region (1-27).

Before the **Christian Era**, **Assyrians** used the plant externally for swellings and bruises, and internally for depression,

impotence, arthritis, kidney stones, 'female ailment', and for the 'annulment of witchcraft' (1-27; 89-113). **In Persia**, Cannabis was also known before the Christian Era. The **Persians** knew about the plants biphasic effect, and made a clear distinction between its initial euphoric and its late dysphoric effects (1-27; 89-113). During the beginning of the Christian Era to the 18th century, the medical use of Cannabis remained **very intense in India** and was then spread to the Middle East and Africa (1-27; 89-113). In Arabia, well-known physicians mentioned Cannabis in their medical compendiums, as **Avicena**, in the year 1000 A.D (1-27). **Muslim texts** mention the use of Cannabis as a diuretic, digestive, anti-flatulent, 'to clean the brain', and to soothe pain of the ears (1-27). In 1464, Ibnal-Badri reported that the epileptic son of the caliph's chamberlain was treated with the plant's resin, and stated: it (Cannabis) cured him completely, but he became an addict who could not for a moment be without the drug (1-27).

Cannabis was known in **Africa** at least since the **15th century**, and its use was, possibly, introduced by **Arab traders**, somehow connected to **India** (1-27). This is evidenced by the similarity of the terms used for preparing the plant in **Africa and India** (1-27;89-113). In Africa, the plant was used for **snake bite, to facilitate childbirth, malaria, fever, blood poisoning, anthrax, asthma, and dysentery** (1-27;89-117).

The narcotic effects of Cannabis were popularly known in the India, China, Nepal, Bhutan, Tibet, Pakistan, Afghanistan, Iran, South Africa, Sri Lanka, South America, Turkey, Egypt, Middle East Asia, and the adjacent territories of the Malaysia, and Burma (Mynamar) (1-27; 89-113). In all these countries, Hemp was used in various forms, as the ready agent of a pleasing intoxication (1-27; 89-114). However, in **Western Europe**, its use either as a stimulant or as a remedy is equally **Unknown**. **O'Shaughnessy** in his book described various successful human experiments using cannabis preparations for rheumatism, convulsions, and mainly for muscular spasms of tetanus and rabies (1-27;89-114).

In America, the use of Cannabis probably began in **South America**. In the 16th century, the plant seeds reached **Brazil, brought by African slaves**, especially those from Angola, and its use was considerably common among Blacks in the Northeastern rural area (20-27;89-114). Most synonyms for cannabis in **Brazil (Maconha, Diamba, liamba, and others)** have their origin in the **Angolan language** (20-27;89-113). There are reports of the use of Cannabis in that region's popular religious rituals, especially the '**Catimbó**', which includes cult to African deities and presumes the value of the plant for magical practice and treatment of diseases (27; 89-114). In the rural environment, there are reports of the use of Cannabis for toothache and menstrual cramps (1-27;89-117).

The introduction of Cannabis in the Western medicine occurred in the midst of the **19th century**, reaching the climax in the last decade of that century, with the availability and usage of Cannabis extracts or tinctures (1-27;89-114). In the first decades of the 20th century, the Western medical use of Cannabis significantly decreased largely due to difficulties to obtain consistent results from batches of plant material of different potencies (1-27). The identification of the chemical structure of Cannabis components and the possibility of obtaining its pure constituents were related to a significant increase in scientific interest in such plant, since 1965 (1-27; 89-114). This interest was renewed in the 1990's with the description of Cannabinoid receptors and the identification of an **Endogenous cannabinoid (EC)** system in the brain (25-88). A new and more consistent cycle of the use of Cannabis derivatives as medication begins, since treatment effectiveness and safety started to be scientifically proven (1-27; 1-114).

In Europe, during this period, Cannabis was cultivated exclusively for fibers. Muslims introduced the manufacture of paper from Cannabis in 1150 first in Spain then in Italy (1-114). Cannabis

descriptions are found in many books about plants written in this period, which clearly state, since the mid 18th century, the distinction between male and female plants (previously described in a India in the beginning of the Christian Era) (89-113). References to the medical use of Cannabis are well written and documented in Indian **Ayurveda** (89-114). Europeans may have known about the plant's medical use in the Middle East and Africa, **but they confused it with opium** (1-35; 89-114). Thus, a new cycle begins for the use of Cannabis derivatives as medication, this time more consistently than in the past (1-117). The structures of chemical compounds derived from Cannabis are now known, the mechanisms of their action in the nervous system are being elucidated with the discovery of an endogenous Cannabinoid system, and treatment effectiveness and safety are being scientifically proven (1-35; 89-117).

In **1996, California** became the first state to permit legal access to and use of botanical Cannabis for medicinal purposes under physician supervision with the enactment of the Compassionate Use Act (116). As of January 1, 2017, 28 states as well as Washington, D.C., Guam, and Puerto Rico will have enacted legislation governing medicinal Cannabis sale and distribution (116). 21 US states and the District of Columbia will have decriminalized marijuana and eliminated prohibition for possession of small amounts, while eight states, including Alaska, California, Colorado, Maine, Massachusetts, Nevada, Oregon, and Washington, as well as the District of Columbia, will have legalized the use of marijuana for adult recreation (116).

The story of discovery of **Δ9-tetrahydrocannabinol (THC)**

During the period between 18th to 19th Century, there was a slow progress in Science particularly Organic Chemistry and distillation was used as a shortcut for the isolation of bioactive plant products, with menthol having been purified as early as 1771 (Drobnik and Drobnik 2016) (25-28). However, Cannabinoids are poorly volatile compounds with similar boiling point, and the distillation required high vacuum (25-28). It is therefore, unsurprising that the many nineteenth century investigations on Cannabis substantially missed the identification of its intoxicating principles (24-28; 70-88). The other problem is the lack of a **suitable animal model** for the sedative and narcotic activity of Cannabis (20-35). Therefore, in those days, the early **Investigators Self-administered** the products obtained from the plant, and demonstrated medicinal value of Cannabis and confirmed as a very safe medicine (23-28; 50-114). This was challenging and life risk for Scientists and compounds known at those times were all alkaloids (**Morphine, Nicotine, Scopolamine, Cocaine**) (1-114). The active principles of Cannabis were also the nitrogen-containing compounds (23-28; 40-117). However, the only Cannabis of interest in those times was the narcotic/medicinal material that was produced overseas and arrived in Europe variously named (hashish, bhang, charas, ganja) depending on the country of origin and the mode of preparation, and essentially already **decarboxylated** (23-28; 60-117). The isolation of the native Cannabinoids had therefore, to wait investigations based on a locally produced biomass (Krejčí and Šantavý 1955) (23-34; 40-114). The non-basic nature of the narcotic principle of Cannabis was suggested as early as in **1847 by the work of the Smith brothers**, a couple of Scottish pharmacists (Smith and Smith 1847) (23-35; 38-114). Although **Dr. Raphael Mechoulam was the first** to officially isolate **Δ9-tetrahydrocannabinol (THC)**, the problem is that humans have been aware of Cannabis' effects for millennia but the puzzle is what was causing them (20-35; 38-114).

The "**Red oil**" was found by a **Cambridge group (Wood, Spivey and Easterfield)** to consistently summarize the intoxicating properties of cannabis (Wood et al. 1896) (36-37; 38-114). **The red oil**, basically a **distilled Cannabis resin**, was the starting material for

all early studies on Cannabis, despite the difficulty of its preparation (24-37). The **ruby red color** developed already during the first distillation step and intensified with light (24-114). It could have been related to the formation of quinoid forms of the native Cannabinoids during heating (Caprioglio *et al.*, 2020) (38, 39; 50-114). After acetylation of the red oil, the **Cambridge group**, led by **Thomas Hill Easterfield** (1866–1949), obtained an optically inactive crystalline compound, whose native phenol was named **Cannabinol (CBN)** (Wood *et al.*, 1899) (25-39; 88-113) recycling the name previously given to the **narcotic red oil** (Wood *et al.*, 1896) (36-39). Cannabinol (CBN) high contents in the red oil was investigated by the **Cambridge group** (Wood, Spivey and Easterfield) and have been related to either the use of an old sample of hashish or, alternatively, to a harsh treatment of the resin (25-39; 88-113).

The death of **Spivey** abruptly ended research on **Cannabinoids in Cambridge**, and there was no follow-up to the article reporting the isolation of "Cannabinol" as red oil and "Cannabinol" as a pure compound (25-39). In 1899, **Easterfield moved to New Zealand**, where he established a natural product school (25-39). Clarity was finally done only 3 decades after the original isolation of Cannabinol, when **Robert Sidney Cahn** (1899–1981) of nomenclature and stereochemistry fame, investigated the structure and bioactivity of **Cannabinol** (Cahn, 1933) (25-39, 40; 88-113).

Cannabinol structure was elucidated in the early 1930s by **R.S. Cahn**, and its chemical synthesis was first achieved in 1940 in the laboratories of **Dr. Roger Adams** in the USA and Dr. Lord Todd in the UK (25-41; 88-113). A second phytocannabinoid, **Cannabidiol (CBD)**, was first obtained from Cannabis in the same year by Adams and colleagues, probably in combination with Cannabidiolic acid, while **Δ^9 tetrahydrocannabinol (THCs)** were first extracted from Cannabis in 1942 by Wollner, Matchett, Levine and Loewe, most likely as a mixture of **Δ^8 -tetrahydrocannabinol-type (-) and (-)- Δ^9 tetrahydrocannabinol (THC)** (25-113). Both **Δ^9 tetrahydrocannabinol (THC)** and **Cannabidiol (CBD)** were present in Cannabis mainly as acids that are **decarboxylated** when Cannabis is heated (25-41; 88-113).



Figure-2: Dr. Roger Adams was an American organic chemist at the **University of Illinois at Urbana-Campaign, Illinois, USA** (January 2, 1889 – July 6, 1971). He was the first to identify **Δ^9 -tetrahydrocannabinol (THC)** and explore its relationship to **Cannabidiol (CBD)**.

Dr. Roger Adams (Figure-2) was the most important **American organic chemist** of the first half of the past century, and had developed strong ties with Government agencies as well as with private companies, making it possible to assemble a large group of researchers at the **University of Illinois at Urbana-Campaign, USA**, where he tutored **184 Ph.D. students**, countless master's and bachelor's candidates and hired at least **50 post-docs** (Tarbell and Tarbell 1981) (25-41, 42; 88-113). As head of the Chemistry

department at the University of Illinois, USA from 1926 to 1954, **Dr. Roger Adams** has helped and guided many students and established Chemistry department and served in military science during World War I and World War II (48-59; 88-113). **Dr. Roger Adams** had significant difficulties in the isolation of Cannabinol (CBN) (48-59). Unable to obtain a direct crystallization of CBN from the red oil by acetylation (48-59). The note by **Dr. Roger Adams** on the isolation of CBD was submitted to the *Journal of America Chemical Society (JACS)* on December 4, 1939, (Adams *et al.* 1940a, b, c, d, e, f, g) (48-59) and the first one by Todd on this compound was published in *Nature* on March 2, 1940 (Jacob and Todd, 1940ab) (43, 44) without any detail apart from the positive Beam test of the compound (25-39; 43, 44-46; 48-59). **Dr. Roger Adams** (January 2, 1889 – July 6, 1971) died at the age of 82 was an American organic chemist who developed the eponymous Adams' catalyst, and helped to determine the composition of natural substances such as complex vegetable oils and plant alkaloids. He isolated and identified **Cannabidiol (CBD)** in 1940 (48-59).

Although **Dr. Raphael Mechoulam** and his team were responsible for isolating and describing **Δ^9 -tetrahydrocannabinol (THC)** structure, Harvard-trained chemist **Dr. Roger Adams** was also played a key role in the discovery of the compound (25-81; 88-113). **Adams was the first to identify Δ^9 -tetrahydrocannabinol (THC)** and explore its relationship to **Cannabidiol (CBD)**, but never isolated **Δ^9 -tetrahydrocannabinol (THC)** directly from the plant (25-81; 88-113). Rather, **Dr. Roger Adams** synthesized it in the laboratory. It was not until the 1960s that the technology became available, enabling **Dr. Raphael Mechoulam** and his team to isolate **Δ^9 -tetrahydrocannabinol (THC)** directly from the plant Cannabis sativa itself (25-38; 88-113).

It is in any case, unclear how strategic research on Cannabis actually was for Dr. **Alexander Robertus Todd** who had already started the studies on nucleosides and nucleotides that eventually led him to the **Nobel Prize in chemistry** (25-47). The British biochemist Dr. **Alexander Robertus Todd** was awarded the **1957 Nobel Prize in chemistry** for his work on the synthesis of nucleotides (the small units that make up the larger molecule of nucleic acids), the hereditary material of cells (47). This work led to many important advances in chemistry and biochemistry and made it possible to study the application of the Watson-Crick model of DNA and other nucleic acids more effectively (25-41, 47). Sir Dr. Alexander Robertus Todd died in Cambridge on January 10, 1997, at the age of 89 years (47). Besides receiving the Nobel Prize, he was awarded many honors and honorary doctorates (47).

By the **1930s and 1940s**, the chemical structure of the Cannabis plant and its pharmacological effects still evaded experts. As historical records indicated that, **Δ^9 -tetrahydrocannabinol (THC)** was used among ancient peoples, including the Indians, Chinese and Persians (1-24; 88-114). In the modern era, **research into Δ^9 -tetrahydrocannabinol (THC)** ramped up in the mid-1960s and early 1970s (88-113). This rise occurred in response to the widespread use of Cannabis as a recreational drug in the US and other Western nations (1-114). At the time, Scientists focused their research on testing whether the psychotropic properties of Cannabis could be attributed to **Δ^9 -tetrahydrocannabinol (THC)** (1-114). Any interest in **Δ^9 -tetrahydrocannabinol (THC)**'s therapeutic potential was **sidelined by an overwhelming preoccupation with the psychoactive effects** of the Cannabinoid and its influence on the human body and wider society (1-47; 88-114).

In 1964, when **Dr. Raphael Mechoulam** in Jerusalem isolated and characterized the native intoxicating principle of hashish (Gaoni and Mechoulam, 1964) (63) identifying it as the "low-rotation" semi-synthetic THC described by **Dr. Roger Adams** 2 decades earlier (25-63; 88-114). It was also in Dr. Raphael Mechoulam laboratory in 1965, that (\pm) **Δ^9 -tetrahydrocannabinol (THC)** and (\pm)

Cannabidiol (CBD) were first synthesized, developments that were soon followed by the synthesis of the (+)- and (-)-enantiomers, both of these two Cannabinoids and of **Δ^8 -tetrahydrocannabinol (THC)** (24-81; 88-114). These important advances and the identification of many of the other Cannabinoids present in Cannabis are described in greater detail elsewhere (Mechoulam, 1973; Mechoulam & Hanus, 2000) (25-81; 83-114). **The work by Dr. Raphael Mechoulam ended a century-long period of uncertainties**, and by the identification of additional Cannabinoids and their first synthesis, which has led the foundation of what in the following decades became a vibrant area of biomedical research (20-63). On the other hand, other researcher should not be neglected for their contributions to the era, **Dr. Roger Adams** and **Dr. Alexander Robertus Todd** (25-81;88-117).

Eager to unpack the mysteries of Cannabis, **Dr. Raphael Mechoulam** undertook research in Israel, where the government's stance on Cannabis was more permissive than in the US (24-81; 88-113). The 1960s saw technological advances that enabled Dr. Raphael Mechoulam and his team to embark on a chemical evaluation of Cannabis (25-81; 88-113). They hoped to uncover its active constituent, the substance that was largely responsible for producing the psychoactive, intoxicating effects seen in users (25-81; 83-113). Their research led to them discovering **Δ^9 -tetrahydrocannabinol (THC)** in hashish extract (1-113). When their team first isolated **Δ^9 -tetrahydrocannabinol (THC)**, the National Institutes of Health came knocking and launched US research into **Δ^9 -tetrahydrocannabinol (THC)**'s pharmacological effects (25-113). Much of the early research on **Δ^9 -tetrahydrocannabinol (THC)** was carried out using the **Δ^9 -tetrahydrocannabinol (THC)** isolated by Mechoulam and his team (20-81; 88-113).

Dr. Alexander Robertus Todd were among the finest organic chemists of their generation, and Cahn and Šantavý left remarkable contributions to organic chemistry and natural products chemistry, with Easterfield almost single-handedly established the chemical research in New Zealand (25-63; 80-113). **The tragic death in a laboratory accident of Spivey**, one of the discoverers of Cannabinol, should not be forgotten (25-63). The Guineapig experiences with cannabinoids of Marshal, wondering smiling in the lab surrounded by the flames of his diethyl zinc distillation (25-63). **Leonard**, unable to answer the question of his wife because it could not remember the word of her questions, vividly testifies the potent bioactivity of Cannabinoids (25-63; 70-113).

Finally, the significant contributions to the elucidation of the signature molecular scaffold of Cannabinoids were provided by some of the finest organic chemists of their generation, like **Dr. Roger Adams** and the Nobel laureate **Dr. Alexander Robertus Todd** (25-81; 88-113). The important studies of preeminent scientists like **Robert Sidney Cahn** and **František Šantavý** also deserved mentioning (25-81). The results of these studies include the structure elucidation of Cannabinol, and the preliminary structure elucidation of Cannabidiol, and various semi-synthetic **Δ^9 -tetrahydrocannabinol (THC)** (25-8188-113).

Dr. Raphael Mechoulam: The Godfather of Cannabis Science

The official discovery of **Δ^9 -tetrahydrocannabinol (THC)** is commonly attributed to **Dr. Raphael Mechoulam** (Figure-3) affectionately referred to as the **Godfather of cannabis science** (29-88; 88-117). **Δ^9 -tetrahydrocannabinol (THC)** was discovered in 1964 by **Dr. Raphael Mechoulam** and his colleagues at **Israel's Weizmann Institute of Science (Figure-3)** (1-117). Dr. Raphael Mechoulam's major scientific interest is the chemistry and pharmacology of **Cannabinoids** (25-82; 88-113). He and his research

group succeeded in the total synthesis of the major plant cannabinoids, **Δ^9 -tetrahydrocannabinol**, **Cannabidiol**, **Cannabigerol** and various others (25-82; 88-114). **Dr. Raphael Mechoulam** and his team were responsible for isolating and describing THC's structure, chemist **Dr. Roger Adams (Figure-2)** was the first to identify **Δ^9 -tetrahydrocannabinol (THC)** and explored its relationship to **Cannabidiol (CBD)** (25-81; 88-113).



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 **Δ^9 -tetrahydrocannabinol (THC)** in 1964 isolated from Cannabis sativa attributed to Dr. Raphael Mechoulam and his team.

The history of Israel marks it as a place of intense spirituality for many religions, most notably in **Jewish, Christian and Islamic cultures**. Ironically, a much more recent counter-culture can also point to the Holy Land as a major component of its heritage, not to mention the ground zero, of sorts, of the modern medical-marijuana movement. The **Eureka moments** of inspiration by a single talented scientist, **Dr. Raphael Mechoulam** is considered as the **Father of modern studies on Cannabis**, his "Eureka moments" being the identification of **Δ^9 -tetrahydrocannabinol (Δ^9 -THC)** as the intoxicating agent of the plant, and the discovery of Endocannabinoids, their endogenous analogues (25-81).

Dr. Raphael Mechoulam (Bulgarian: born on 5 November 1930-9th March 2023) is an **Israeli organic chemist** and professor of Medicinal Chemistry at the **Hebrew University of Jerusalem in Israel** (88-113). **Dr. Raphael Mechoulam** was born in Sofia, Bulgaria in 1930, to a Sephardic **Jewish family** but together with his Jewish parents, immigrated to Israel in 1949 (82). **Dr. Raphael Mechoulam** is best known for his work (together with Y. Gaoni) in the isolation, structure elucidation and total synthesis of **Δ^9 -tetrahydrocannabinol (THC)** the main active principle of Cannabis (1-113). **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 students, postdocs and collaborators (25-82). The structures and stereochemistry of **Cannabidiol (CBD)** and **Δ^9 -tetrahydrocannabinol (THC)**, each of which occurs naturally as its (\pm)-enantiomer, were elucidated in Dr. Raphael Mechoulam's laboratory in 1963 for **Cannabidiol (CBD)** and in 1964 for **Δ^9 -tetrahydrocannabinol (THC)**, when it was first isolated and purified from Cannabis sativa (25-113).

Dr. Raphael Mechoulam received his M.Sc. in biochemistry from the Hebrew University of Jerusalem, Israel (1952), and his Ph.D. at the Weizmann Institute, Rehovot Israel (1958), with

a thesis on the chemistry of steroids (82). After postdoctoral studies at the Rockefeller Institute, New York, USA (1959–60), he was on the Scientific staff of the Weizmann Institute, Israel (1960–65), before moving to the **Hebrew University of Jerusalem, Israel** where he became professor (1972) and Lionel Jacobson Professor of Medicinal Chemistry from 1975 (25-81). He was rector (1979–82) and pro-rector (1983–85). In 1994 he was elected a member of the Israel Academy of Sciences. **Dr. Raphael Mechoulam** is one of the founding members of the International Association for Cannabinoid Medicines (25-81;88-117).

On the **5th November 2022**, Professor Raphael Mechoulam, celebrated his 90th Birthday who is widely recognized as one of the greatest scientists in the field of Cannabinoid research, **died at age of 92 on 9th of March 2023** (25-82;88-113). It is at **The Hebrew University** where he began his prestigious Cannabinoid research career, and where he guided many students and discovered ECS (25-82; 88-113). For nearly two decades after the identification of **Δ9-tetrahydrocannabinol (THC)**, its mechanisms of action were believed to be entirely “non-specific” (82-113). These included findings obtained by **Dr. Raphael Mechoulam** and his collaborators showing that certain Cannabinoids display stereoselectivity (82-113). Such findings encouraged a search for a Cannabinoid receptor in mammalian tissues, and this research led to the discovery of two **G protein-coupled Cannabinoid receptors**; the **first (CB1)** was discovered between 1988 and 1990, and the second **(CB2)** was discovered in 1993 (25-82; 88-113). The race to discover such an “endocannabinoid” was won by **Dr. Raphael Mechoulam** (1-113). He led research that provided convincing evidence that (i) **N-Arachidonoyl ethanolamine**, which he and his collaborators named **Anandamide**, is an endogenously produced compound that can activate the **CB1 receptor**, and (ii) that **2-Arachidonoylglycerol** is also a Cannabinoid receptor-activating Endocannabinoid (82). He published more than 450 scientific articles (25-113).

THE ENDOCANNABINOID SYSTEM

The **Endocannabinoid system (ECS)** represented a critical part of understanding **Δ9-tetrahydrocannabinol (THC)** and its potent **effects** on the human body (25-88; 89-113). 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 (25-113). This unique **Endocannabinoid system (ECS)** also influences **regulatory processes** as diverse as appetite, sleep, mood, stress, energy levels, and reproduction (30-88; 89-113). The **Endocannabinoid system (ECS)** produces endogenous Cannabinoids (produced internally) and responds to exogenous Cannabinoids (produced externally), like the ones found in Cannabis, which are called Phytocannabinoids (25-88). **Endogenous Cannabinoids** are now generally referred to as ‘endocannabinoids’ and, together with cannabinoid receptors, constitute the **‘Endocannabinoid system’** (25-88, 118).

Evidence has also emerged that tissue concentrations of endocannabinoids, cannabinoid receptor density and/or cannabinoid receptor coupling efficiency increased in a range of disorders (25-88;89-113). In some of these disorders, for example, multiple sclerosis, certain types of pain, cancer, **schizophrenia**, post-traumatic stress disorders, some intestinal and cardiovascular diseases, excitotoxicity and traumatic head injury, this upregulation of the **Endocannabinoid system** may cause a **reduction in the severity of symptoms** or a **slowing of disease progression** (25-88). However, there are other disorders, for example, impaired fertility in women, obesity, cerebral injury in stroke, endotoxaemic shock, cystitis, ileitis and paralytic illness in which the unwanted effects appear to result from an upregulation of the endocannabinoid system, suggesting that this system has its own pathology and

possibly also that it sometimes mediates unwanted effects because it is being influenced by **pathological events** taking place in some other system from which it receives input (25-88; 89 113).

There was also an interest in the appetite-stimulating and antiemetic properties of **Δ9-tetrahydrocannabinol (THC)** and these effects did come to be exploited in the clinic by the 1980s when **Δ9-tetrahydrocannabinol (THC)** (**Dronabinol**, **Marinol**) and its synthetic analogue, **nabilone (Cesamet)**, both became licensed as medicines for suppressing **nausea and vomiting produced by chemotherapy** (both drugs) or for **stimulating appetite in AIDS patients** (dronabinol) (reviewed in Robson, 2005) (25-88;89-113).

More recently, attention has been focused on the possibility of using Cannabinoids as analgesics (88-113). Indeed, **Sativex**, a Cannabis-based medicine that contains both **Δ9-tetrahydrocannabinol (THC)** and **Cannabidiol (CBD)** (reviewed in Robson, 2005), was recently **licensed in Canada as adjunctive treatment** for the symptomatic relief of **neuropathic pain in adults with multiple sclerosis** (88-113). Finally, some pharmacologically active Cannabinoids that do not activate or block CB1 or CB2 receptors also have therapeutic potential (88-113). Among these are the phytocannabinoid, **Cannabidiol (CBD)**, which, for example, possesses **anti-inflammatory, antioxidant and neuroprotective properties** (reviewed in Pertwee, 2005b; Robson, 2005) (25-88; 89-113).

There are two main types of Cannabinoid receptors in the body: **CB1 and CB2** (25-113). CB1 and CB2 receptors are distributed throughout the central and peripheral nervous systems (35-113). “**In the brain, these receptors** are located in the brain stem, cerebral cortex, hippocampus, cerebellum, basal ganglia, hypothalamus, and amygdala (27-88-113). They are also found in the liver, kidneys, spleen, gonads, and heart (25-88-113). **Δ9-tetrahydrocannabinol (THC)** is what's known as a **partial agonist at both CB1 and CB2 receptors**, meaning that it **can partially bind to both receptor sites** (26-88). The psychoactive effects for which **Δ9-tetrahydrocannabinol (THC)** is famed arise **from its affinity for the CB1 receptor** (25-88). However, “After the discovery of the **CB2 receptor**, two graduate students of Raphael Mechoulam, Dr. Lumir Hanus and Dr. William Devane, and their team at The Hebrew University in Jerusalem discovered **Anandamide (AEA)**, an endogenous Cannabinoid that is produced by the body (25-88-113).

Ananda is the Sanskrit word for “**bliss**,” and is used to describe yogic ecstasy. It is a perfect name for the compound, as **Anandamide** is equal to **Δ9-tetrahydrocannabinol (THC)** in **psychoactivity** (26-88). In other words, make a compound in our own bodies that by its very nature, and by our basic biology, promotes mind expansion. The discovery led to **Anandamide** being dubbed as the **Bliss molecule** (25-88;89-118).

MEDICAL CANNABIS SATIVA: CONSUMER MARKETING

The global Cannabis pharmaceuticals market size was valued at USD 943.5 million in 2021 and is expected to expand at a compound annual growth rate (CAGR) of 104.2% from 2022 to 2028 (115). The global Cannabis pharmaceuticals market is expected to grow at a compound annual growth rate of 76.8% from 2020 to 2027 to reach USD 5.8 billion by 2027 (115). **Sativex** dominated the Cannabis pharmaceuticals market with a share of 83.0% in 2019. This is attributable to the growing approval of the drug for the treatment of spasticity caused due to multiple sclerosis in various countries (115).

Some key players operating in the Cannabis pharmaceuticals market include GW Pharmaceuticals; AbbVie Inc.; Valeant Pharmaceuticals; and Insys Therapeutics, Inc (115). Wide-scale applications of Cannabis in various medical applications are

driving the market (115). For instance, Cannabis is widely used for treating patients suffering from **chronic conditions, such as Parkinson's disease, cancer, arthritis, and Alzheimer's disease, as well as neurologic problems such as depression, anxiety, and epilepsy** (25-115). Moreover, there is a growing disease burden of chronic pain and pain management therapies. This, in turn, is increasing Cannabis product consumption as it is **effective in pain management** (25-118).

There is increasing **legalization and decriminalization of Cannabis** in various countries owing to its therapeutic effects (115-118). For instance, Medical Cannabis is legal in countries such as the USA, Canada, the UK, Croatia, Czech Republic, Cyprus, Columbia, Chile, Australia, Barbados, Denmark, Finland, Poland, and Portugal among others (115-118). The presence of major manufacturers and various initiatives by key Cannabis players in the region are supporting market growth (115-118). For instance, in August 2020, **INFARMED I.P.**, A regulatory authority in **Portugal**, granted a license to **Clever Leaves**, a provider of legal Cannabis, for the cultivation, import, and export of Medical Cannabis (115). In January 2017, **Germany** legalized Medical marijuana (115). Thus, increasing the legalization of Cannabis and its products for medical use is estimated to drive market growth potential (115). Additionally, cannabis cultivation in the African region is rapidly growing. Several countries such as **Lesotho, South Africa, Malawi, Zambia, Rwanda, and Ghana** among others have legalized Medical Cannabis cultivation. This in turn is estimated to drive the market in the region (115).

Moreover, a continuous political movement supporting Cannabis legalization is driving the market for Cannabis pharmaceuticals (115). For instance, in May 2021, the U.S. representative reintroduced the **MORE** (Marijuana Opportunity, Reinvestment, and Expungement) Act in the U.S. House of Representatives (115). Furthermore, in December 2020, the **MORE Act** was previously passed in the House of Representatives, but it did not advance in the Senate (115). **The MORE Act**, if passed, would drive the demand for Cannabis products in the U.S (115). This in turn is estimated to positively impact the growth of the pharmaceutical Cannabis market (115). **An increasing number of Cannabis physicians prescribing Cannabis products owing to increasing consumer acceptance is estimated to drive market potential** (115). For instance, the number of health care practitioners registered with federally licensed sellers in **Canada** in September 2019 was 6,700 which increased to 7,781 in March 2021 (115). Moreover, increasing consumer acceptance is supporting the growth of the market for Cannabis pharmaceuticals. According to the Centers for Disease Control and Prevention, 48.2 million people in the U.S., or 18% of the **American population** have consumed marijuana at least once in 2019 (115).

The major Cannabis pharmaceutical brand - **Epidiolex**, witnessed positive growth in sales (115). **Epidiolex** is used in the treatment of **seizures** associated with **Dravet syndrome** and **Lennox-Gastaut syndrome** (115). **EPIDIOLEX** is a prescription medicine that is used to treat seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients 1 year of age or older (EPIDIOLEX® (cannabidiol) Official Site | Home). **Epidiolex** is the brand name for the pharmaceutical-grade **Cannabidiol oil product produced by Greenwich**, whereas other CBD, "hemp," and Medical marijuana products available may contain small amounts of THC (115). The rising number of approvals of **Epidiolex** is driving the segment growth. **Sativex** is used to treat **muscle spasticity** due to **Multiple sclerosis** (115).

Increasing demand for **Sativex** for use in **muscle spasticity in Canada**, and European countries is driving the segment growth (115). **Sativex** is in the form of **spray** is a cannabis-based medicine. It is used to **treat the common MS symptom of muscle stiffness and spasms (known as 'spasticity')**. **Sativex is a spray**

used in mouth. **Sativex** each spray (100 µL) contains 2.7 mg delta-9-tetrahydrocannabinol (THC) and 2.5 mg Cannabidiol (CBD). **Nonmedicinal ingredients:** ethanol, propylene glycol, and peppermint oil (115). **Sativex** is **sprayed under the tongue or on the inside of the cheeks**. The usual starting adult dose of tetrahydrocannabinol - cannabidiol is one spray 2 times a day on the first day.

Nabiximols (USAN, trade name **Sativex**) is a specific **Cannabis** extract that was approved in 2010 as a botanical drug in the United Kingdom. **Nabiximols** is sold as a **mouth spray** intended to alleviate neuropathic pain, **spasticity**, overactive bladder, and other symptoms of multiple sclerosis. It was developed by the **UK company GW Pharmaceuticals**. It contains two chemicals from the Cannabis plant called Cannabinoids. **UK drugmaker GW Pharmaceuticals' Sativex**, is an adjunctive treatment for symptomatic relief of neuropathic pain in adults with Multiple sclerosis, **is now available by prescription in Canada, the first country to approve the Cannabis-derived therapy** (115). **Sativex** medication contains two ingredients: **Δ9-tetrahydrocannabinol (THC)** and **Cannabidiol (CBD)**. These ingredients belong to the family of medications known as **Cannabinoids** and are extracted from the **Cannabis sativa** (hemp) plant. This medication is used to treat **pain**. **Sativex** is thought to work by mimicking natural pain relievers called **Cannabinoids** that are released in the body (115). **Multiple sclerosis (MS)** is a chronic disease that affects the brain. It is caused by the destruction of myelin, a fatty tissue that allows the nerves to conduct signals to and from the brain (115).

Stakeholders in the Cannabis industry and research institutes are undertaking various research studies to prove various claims made on CBD products which in turn is driving the market for cannabis pharmaceuticals (115). Moreover, innovative products are introduced to cater to growing consumer demand. For instance, in November 2021, **Colorado State University, USA** opened a new research center for CBD (115). In November 2021, AMP Alternative Medical Products GmbH-a fully owned subsidiary of Greenrise Global Brands, Inc.-introduced **Dronabinol** products into the **German market** (115). Europe dominated the market for Cannabis pharmaceuticals and accounted for the highest revenue share of 43.8% in 2021. This is attributed to increasing Cannabis consumption, as well as raising awareness and positive attitude towards cannabis and its products (115).

Dronabinol is used to treat **nausea and vomiting caused by cancer chemotherapy**. It is used when other drugs usually used to control nausea and vomiting have not worked well. Dronabinol is also used to treat loss of appetite and weight loss in people with HIV infection. Dronabinol (also called THC) is a man-made form of a natural substance in marijuana (**cannabis**). This medicine is also used to increase appetite in patients with acquired immunodeficiency syndrome (AIDS). **Dronabinol** is the principal psychoactive constituent enantiomer form, (-)-trans-Δ⁹-tetrahydrocannabinol, found in Cannabis.

CONCLUSION

Finally, **Δ9-tetrahydrocannabinol (THC)** is valued both for its mind-altering **psychoactive properties** and its array of potential therapeutic benefits. Current research into **Δ9-tetrahydrocannabinol (THC)** is mostly focused on uncovering its effects on various illnesses and conditions. This research is helping to shift the stigmatization associated with the Cannabinoid and Cannabis itself while promoting an understanding of Cannabis as a medicinal compound. There is no doubt that ongoing research into **Δ9-tetrahydrocannabinol (THC)**, and its effects on the ECS, will continue to inform our understanding of this remarkable Cannabinoid.

In 1964, at the Weizmann Institute of Science in Rehovot, Israel, Dr. Raphael Mechoulam along with his colleagues, Dr. Yehiel Gaoni and Dr. Haviv Edery succeeded in the very first isolation and elucidation of the active constituent of cannabis, **Δ9-tetrahydrocannabinol (THC)**. The discovery of the **Δ9-tetrahydrocannabinol (THC)**, compound now almost 50 years ago – started a revolution in thinking about Cannabis that carries on to this day.

Dr. Mechoulam was a professor of medicinal chemistry and natural products at the Hebrew University of Jerusalem. His total synthesis of **Δ9-tetrahydrocannabinol (THC)**, as well as other Cannabinoids such as **Cannabidiol (CBD)**, is the cornerstone of the burgeoning Medical-cannabis industry. Furthermore, his major contributions in the field of organic chemistry and the interaction of human and plant biology have led to the discovery of Cannabinoid receptors in the human brain and the endocannabinoid system in the human body.

Professor Raphael Mechoulam, is also known as the **“Father of Cannabis Research,”** revealed his latest discovery, Cannabidiolic acid methyl ester (EPM301), only a few months ago. The introduction of this new, patented compound (synthetic, fully stable acid-based Cannabinoid molecules) caused a wave of excitement around the future of medicinal cannabis.

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