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Review article

EXTRACTS FROM THE HISTORY OF CANNABIS

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Abstract

Cannabis (*Cannabis sativa* L. Fam. *Cannabaceae*) has been cultivated and used for millennia for industrial purposes, as food, for recreational and religious purposes, but also as a medicine in the treatment of various pathologies or symptoms. This paper traces the cultural and medicinal history of cannabis use, from the earliest human contact with the plant to its subsequent global expansion. The discovery of the endocannabinoid system in the 20th century started a new era of renewed scientific interest in the pharmacological properties of cannabis, which enabled the successful integration of cannabis into modern clinical practices. Due to the new evidence-based research of its potential therapeutic value, in the last few decades the support for its decriminalization and legalization for medicinal purposes has also been revived.

Keywords: cannabis; history of cannabis; therapeutic use; endocannabinoid system; decriminalization and legalization of medical cannabis

Introduction

The most commonly used scientific name for cannabis is *Cannabis sativa* L. The "L." refers to Carolus Linneaeus, the great Swedish naturalist and taxonomist who first gave this common herb its scientific classification in his published work "Species Plantarum" in 1753. In 1785, the famous French biologist Lamarck described a distinctive second species of cannabis, *Cannabis indica* as shorter, more psychoactive plant than *Cannabis sativa* L., which was a taller, more fibrous plant. After more than 1 century, in 1924 the Russian botanist D. E. Janishevsky described the third species of the genus cannabis - *Cannabis ruderalis*, which grows wild in the region of the Volga River, Western Siberia and Central Asia[1].

The cannabis plant is the source of both "hemp" and "marijuana". The term "hemp" is used for its industrial purposes. The long fibers have traditionally been used to make rope and cloth, and also the seeds and the seed oil have many commercial and industrial uses - paint, varnishes, fuel, and even as food.

In recent decades, the term "marijuana" has been used for the medicinal and the intoxicating properties of the plant. Over 100 different cannabinoids have been found in marijuana. However, the main psychoactive component has been identified as tetrahydrocannabinol (THC)[2].

Marijuana has a long history of medicinal use. Most of its therapeutic properties do not derive from modern discoveries. They rely on empirical observations due to its medical use in the ancient cultures over many centuries[3]. In the 20th century, the discovery of the endocannabinoid system launched a new era of cannabis use. Greater understanding of the plant, as well as societal pressure, have led some countries to introduce more lenient laws regarding the medical use of cannabis, as well as to decriminalize or even legalize its recreational use[4].

Origin of cannabis plant

According to some paleobotanical studies, cannabis was already present as early as 11,700 years ago, in the territories of Central Asia, near the Altai Mountains, which leads to the belief that this is where its origin may be. The Russian botanist Nikolai Vavilov (1926) on the other hand, assumes that the cultivation of Cannabis probably originated in different parts of the world at the same time[5,6].

Seeds macrofossils have been found attached to broken pieces of ceramic material at the Okinoshima archeological site of Mesolithic Age, dating back to the Jomon culture (12500-2300 BCE). Also, during the Jomon culture, other archaeobotanical evidence was found at the Matsugasaki and Torihama sites (6000–5220 BCE) as well as in a pot at the Shobuzaki Shell Midden site. Cannabis was also widely used in ancient China for its industrial use, but also as a psychoactive plant. Images of the plant have been found on pottery from the Yangshao era dating back to 6,200 BCE[4]. The discovery that also attracted the attention of the scientists was a grave found in Xinjiang Uygur, that dates back to 750 BCE associated with the Tocharian culture. The grave held the remains of a 45-year-old man, probably a shaman, in which scientists found cannabis with high THC content. The later botanical and phytochemical analysis showed that only the male parts of the plant were removed due to its lower THC content, which confirms that the plant back then was also cultivated for its psychoactive effects[7,8].

Other findings show that wild cannabis pollen was present in Europe, dating back to 10200-8500 BCE in Romania, Bulgaria and Hungary and from 11000 BCE near the Lake Albano in Italy[4].

Because of the constantly changing glacial-interglacial periods covering hundreds of thousands of years, the exact geographical origin of cannabis is still unclear today. However, the most plausible location for the primary origin and early evolution of cannabis is believed to be Central Asia[1].

The earliest use of cannabis for medicinal purposes

Ancient China

Cannabis was first used for its therapeutic benefits in ancient China, dating back to around 2900 BCE, when the Chinese emperor Fú Xī mentioned the term "Ma" (the term used for cannabis in Chinese). He emphasized its widespread use as a medicinal remedy that encompassed both yin and yang qualities. The character "Ma" was devised by mimicking the drying procedure of hanging cannabis stems[9,2]. It is believed that the Chinese emperor Shennong, approximately 2700 years BCE, reportedly conducted research on the healing properties of cannabis. According to the legend, Shennong possessed a transparent abdomen that allowed him to directly observe the effects of ingested plants, leading him to uncover their therapeutic qualities. He was revered as the pioneer of both Chinese medicine and agriculture[1]. Approximately two millennia following Emperor Shennong's rule, the earliest historical proof of cannabis being used in traditional medicine was found in the ancient Chinese pharmacopoeia known as the "Shénnóng Běncǎo Jīng," created during the first century BCE. This book incorporated an extensive range of traditional medicinal remedies that had been used and orally passed down[10].

The ancient Chinese pharmacopoeia "Shénnóng Běncǎo Jīng" mentions that a preparation called MáFěn, made from the female flowers of cannabis, was believed to be effective in conditions related to the depletion of yin, such as rheumatic pain, constipation, malaria, beriberi, and gynecological issues. Another text from 1108 CE, titled "Chêng Lei Pen Ts'ao", describes the properties of MáFěn, including its ability to purify the blood and lower body temperature. Another historical account "Hòu Hànshū" documents the analgesic properties of cannabis for the first time, referring to the practices of the renowned surgeon Hua

Tuo (110-207 CE), who successfully performed painless surgical procedures on his patients using máyóu, an oil derived from a combination of cannabis resin, datura, and wine[11,12].

Cannabis in India

The knowledge of cannabis traveled from China to the western regions, including India. Around 2000 BCE, nomadic tribes migrated from central Asia, and it was the Aryans who introduced the term "bhang" (meaning cannabis) in India.

Cannabis has a fascinating history in India, intertwined with legends and religious beliefs. The earliest mentions of cannabis can be found in the Vedas, the revered Hindu scriptures. In the Atharvaveda, cannabis preparation called "bhang" made from dried leaves, seeds, and stems is extensively celebrated as one of the "five sacred plants." The Bhagavad Gita, a significant text from the Mahabharata epic, refers to cannabis's ability to enhance memory and alleviate fatigue, maintaining its spiritual association with the goddess Ganga, from where the term "ganja" was born. It was consumed during weddings and festivals as an offering to Lord Shiva, known as the Lord of Bhang, who is believed to have discovered it in the Himalayas. Even today, cannabis is offered to Shiva in temples on the day of Shivaratri[12,13,9]. The religious use of cannabis in India led to the discovery of its medicinal benefits, resulting in its widespread application for various health conditions. As a result, the plant was used as an analgesic for neuralgia, headaches, and toothaches, as well as an anticonvulsant for epilepsy, tetanus, and rabies. It was also used as a hypnotic, sedative (for anxiety, mania, hysteria), anesthetic, and anti-inflammatory agent for ailments like rheumatism. Additionally, cannabis functioned as an antibiotic, antiparasitic and antispasmodic, while also offering diuretic, aphrodisiac, antitussive and expectorant effects[14].

Cannabis in Europe and the Mediterranean region

Evidence from Europe and the Mediterranean region indicates the use of cannabis prior to the Christian era. It is believed that the spread of cannabis was most likely started by the ancient Scythian civilization, which migrated from Central Asia through Russia about 3,500 years ago. On the other hand, paleobotanical findings suggest the presence of wild cannabis pollen in Romania, Bulgaria, and Hungary dating back as far as 10,200 to 8,500 BCE[14,4].

The renowned Greek historian Herodotus was the first to record accounts of the Scythians ritual and recreational use of cannabis. Herodotus's dedication to details provided scientists with insights into long-forgotten civilizations, particularly the Scythians. Without Herodotus's descriptions of Scythian burial customs, one of the most well-known uses of marijuana use in the ancient world would have remained unnoticed. Herodotus documented that the Scythians used the plant for purification rituals, where they would throw cannabis seeds onto hot stones, creating dense vapors that they inhaled and absorbed the fragrant smoke[15]. In 1937, Professor S.I. Rudenko, a Russian anthropologist, uncovered the remains of a Scythian burial site and made significant findings. These included a bronze cauldron filled with burnt cannabis seeds, shirts made from hemp fibers, and metal censers used for inhaling marijuana smoke. Rudenko concluded that the evidence suggested marijuana inhalation was not limited to religious contexts, but was a common daily activity in which both men and women participated[2].

Ancient Egypt

There is evidence suggesting that the hieroglyphic term “shemshemet” in ancient Egypt might have referred to cannabis. The medicinal plant “shemshemet” was believed to be associated with Ra, the God of the Sun. Archaeological discoveries have revealed fragments of ancient cannabis in the tomb of Akhenaten (Amenhotep IV) dating back to around 1350 BCE. Cannabis pollen has also been found in the tomb of Ramesses II, dating from 1224 BCE.

Ancient Egyptian medical texts contain multiple mentions of the therapeutic use of cannabis[1]. For instance, the Ebers Papyrus, the Papyrus of Ramesses III, the Berlin Papyrus, and the Papyrus Chester Beatty VI, mention the use of cannabis as a medicine. These texts are significant sources of knowledge about ancient Egyptian medicine and provide evidence of the historical application of cannabis for therapeutic purposes.

The Papyrus of Ramesses III (1700 BCE), preserved in the British Museum, plate A26, contains a recipe where cannabis is used in the treatment of glaucoma by grinding it with celery, allowing it to sit in dew overnight, and using the resulting mixture to rinse both eyes of the patient in the morning.

The Ebers Papyrus (1600-1550 BCE), found in the University of Leipzig, Plates XCVI, LXXVIII, includes a recipe that mentions ground cannabis with honey to be inserted in the vagina for cooling the uterus and reducing its inflammation.

The Berlin Papyrus, also known as the "Brugsch Papyrus" (1300 BCE), contains a recipe in line 8 of sheet 7, where cannabis is mentioned as an ointment for fever relief and as suppositories. It is currently preserved at the Ägyptisches Museum und Papyrussammlung[16].

Medical use of cannabis in the Roman Empire

During the Roman Empire, notable figures such as Pliny the Elder, Dioscorides, and Galen mentioned the medicinal use of cannabis. Pliny the Elder's "Naturalis Historia" described both the beneficial aspects of cannabis, such as muscle relaxation and treatment of gout and burns, as well as its negative effects like impotence and headaches. Dioscorides in his renowned work "De materia medica" documented various medicinal plants, including cannabis, emphasizing its anti-inflammatory and pain-relieving properties, particularly for ear pain[5,4]. Galen, the famous physician in the Roman Empire, who also served as the personal doctor to Emperor Marcus Aurelius, wrote around 160 CE that consuming cannabis cakes in moderation can induce feelings of euphoria, but excessive consumption can result in intoxication, dehydration, and impotence[12].

Cannabis use in the Arabic countries

It is believed that cannabis reached Arabic countries at an early stage, likely through Arab travelers and traders who procured it directly from India. This is recorded in the medical writings of Avicenna, a Persian physician from the Islamic Golden Age in the 10th century[4]. “The Canon of Medicine" by Avicenna is one of the most renowned books in the history of medicine. It provides a clear and organized summary of the entire medical knowledge of that time, including a long list of medicines. This book mentions hundreds of substances and recipes from various sources for the treatment of various diseases[17]. Within the pages of "The Canon of Medicine," Avicenna recommends the use of cannabis for treating headaches, degenerative bone and joint diseases, eye inflammation, edema linked to gout, wound care, and uterine pain. This medical masterpiece left a profound and enduring imprint on the Western medicine, shaping its development and practices for several centuries, from the 13th to the 19th century[18].

Medieval Arabic medical texts also contain some of the earliest documented descriptions of cannabis for the treatment of epilepsy. As far back as the 10th century, the Persian medical writer al-Majusi recommended a method where cannabis leaf juice is poured into the nostrils as a preventive measure against epileptic seizures[19]. Between the years 1000 and 1700 AD, a collection of Arabian stories known as "One Thousand and One Nights" introduced hashish to many Europeans for the first time[11]. These stories revealed the presence of resin, derived from glandular fibers predominantly found around the plant's flowers, as the primary component of hashish[13]. In ancient Arabic texts, "hashish" had a wider meaning, encompassing not only cannabis resin but also dried leaves, flower heads, and sweets made with them. Surprisingly, hashish was consumed orally rather than being smoked at that time[12].

Notably, the term "assassin" originates from Arabic and is believed to stem from "Hashishin" or "hashish eater." During his extensive travels from 1254 to 1324, the celebrated Venetian merchant, explorer, and author Marco Polo documented the use of hashish by the assassins in his well-known book "The Travels of Marco Polo"[13].

Cannabis use in the United States

The origin of cannabis in North America is subject to debate. It is speculated that Vikings may have introduced it long before Columbus discovered the continent, or it could have reached the western coast through Chinese explorers who navigated the northern Pacific. Additionally, there is speculation that cannabis could have been transmitted through the Bering Strait, either by birds or animals, during a time when Asia and America were connected by a land bridge[12].

Colonial Americans were aware of the medicinal properties of cannabis and used it as a remedy, much like aspirin is used today. They consumed cannabis by smoking, brewing it as tea, or ingesting it. Historical records show that George Washington cultivated cannabis with high levels of THC for medical purposes on Mount Vernon for about 30 years. He specifically tried to cultivate only the female plants which are known for their high THC content[2].

Modern history of medical cannabis

The use of cannabis in Western medicine was introduced towards the end of the 19th century and the beginning of the 20th century. Dr. William O'Shaughnessy, an Irish physician and army surgeon who served in India, played a significant role in introducing his Western colleagues to the medicinal properties of cannabis. After reaching India, he quickly developed a keen interest in exploring the medicinal potential of cannabis. He conducted thorough experiments, studied relevant literature, recorded popular usage methods, evaluated its toxicity in animals and finally tested its effects on patients with various health conditions. O'Shaughnessy's publication in 1843, titled "On the Preparations of the Indian Hemp, or Gunjah," provided detailed evidence of the effectiveness of cannabis extracts in treating a range of conditions, such as rheumatism, hydrophobia, cholera, tetanus, infantile convulsions, and delirium tremens[1,20]. This groundbreaking work piqued the curiosity of his medical colleagues in England, who soon sought his assistance in obtaining cannabis for their own medical practices[11]. O'Shaughnessy's research findings quickly resulted in the widespread adoption of medical cannabis. As time passed, scientific research in this area became more rigorous and met higher standards. In 1889, an article published in The Lancet by Dr. E. A. Birch highlighted the use of cannabis for managing withdrawal symptoms and reducing opium cravings. Dr. Reynolds, Queen Victoria's personal physician, wrote an article the following year in the same journal. He declared cannabis as a powerful remedy for treating conditions like uterine bleeding, migraines, neuralgia, and epileptic spasms. However, he expressed doubts about its effectiveness in cases of asthma, depression, and delirium tremens, and stated that it had no benefits for joint pain and epilepsy[12].

In 1851, cannabis was included for the first time in the United States Pharmacopeia (USP-3rd edition), about ten years after O'Shaughnessy's research in India. During that time, cannabis tincture became widely prescribed in America, likely ranking second only to aspirin[2]. Patented cannabis tinctures were commercially available as treatments for a wide range of conditions, including neuralgia, tetanus, typhus, cholera, rabies, dysentery, alcoholism, opioid addiction, anthrax, leprosy, incontinence, gout, convulsive disorders, tonsillitis, excessive menstrual bleeding and uterine bleeding[21]. Towards the end of the 19th century, the medical application of cannabis experienced a notable growth, supported by numerous scientific studies and publications worldwide, especially in Europe and the United States. At the same time, pharmaceutical laboratories like Bristol-Myers Squibb in the US, and Merck in Germany,

introduced diverse cannabis formulations with pain-relieving, anti-inflammatory, and muscle-relaxing properties to the market[4].

20th century - Decline and rediscovery

In the early 1900s, the medical use of cannabis decreased significantly. The active principle of cannabis had not been isolated yet and it was administered in tinctures or extracts with varying potency. Additionally, advancements in medicine, such as the development of vaccines for infectious diseases like tetanus, the introduction of effective analgesics like aspirin, and the availability of other sedatives like chloral hydrate and barbiturates, posed as competing alternatives to cannabis[14].

The medical use of cannabis in American medicine was significantly impacted by the increased use of opioids in the latter half of the 19th century. Meanwhile, in Mexico, marijuana was commonly smoked by impoverished individuals as a means of relaxation and coping with heat and fatigue[22]. Following the Mexican Revolution, Mexican immigrants brought recreational cannabis use to the United States. While cannabis has been intertwined with the history of the country since its early days, the notion of recreational marijuana smoking was not as prevalent as other forms of consumption. However, in the 1930s, recreational cannabis use gained popularity among all American citizens, prompting drug enforcement officials to advocate for restrictive legislation regarding both recreational and medical cannabis use[18].

Legal restrictions on the use of cannabis

At the beginning of the 20th century, legal restrictions emerged regarding the medical use and experimentation with cannabis. In 1906, President Roosevelt signed the Pure Food and Drugs Act, commonly referred to as the Wiley Act. This act mandated precise labeling of the content and dosage of substances such as alcohol, morphine, opium, cocaine, heroin, alpha or beta eucaine, chloroform, *Cannabis indica*, chloral hydrate, and acetanilide. After the adoption of the Harrison Narcotics Tax Act in 1914, which grouped cannabis with illicit drugs such as cocaine and heroin, the marketing and use of cannabis-derived preparations experienced a notable decline. Fears surrounding the widespread abuse of marijuana led to the enactment of the Marihuana Tax Act in 1937. According to this law, anyone using the plant had to register and pay a tax of one dollar per ounce (28.35 grams) for medical purposes and one hundred dollars per ounce for any other type of use. Failure to pay the tax led to severe consequences, including hefty fines of $2,000 and the possibility of imprisonment for up to five years, posing significant challenges and risks for its use[14]. The aggressive campaign led by Harry Anslinger, the first commissioner of the Federal Bureau of Narcotics, associating cannabis with promoting violence, crime, mental illnesses, particularly within minority communities, resulted in the enactment of the Marihuana Tax Act and the elimination of cannabis from the American pharmacopeia and the national formulary in 1941 [23]. Since the enactment of the Marihuana Tax Act in 1937, a series of federal laws, including the Boggs Act, Narcotics Control Act, Controlled Substances Act and Anti-Drug Abuse Act, were introduced to govern the sale, possession, use, and cultivation of marijuana[24].

With the 1961 United Nations Convention on Narcotic Drugs cannabis was banned in many countries, along with substances like heroin, but 59 years later in December 2020, the UN Commission on Narcotic Drugs made significant decisions to remove and reclassify cannabis, reducing barriers for research and development of medical cannabis products, and categorizing it similarly to opioids like morphine and oxycodone in terms of abuse potential [25,26].

Discovery of the endocannabinoid system, therapeutic potential and legalization of medical cannabis

Despite the challenges, scientific research on cannabis continued thanks to the discoveries of the scientists Yechiel Gaoni and Raphael Mechoulam in Israel. In 1964, they identified the chemical structure of the main psychoactive compound in cannabis-delta-9-tetrahydrocannabinol (THC). Mechoulam, who was a Holocaust survivor, obtained confiscated cannabis, isolated compounds and studied their effects on primates and human volunteers, noting various psychological reactions, including laughter, panic attacks, and enhanced receptiveness to discussion. In 1940, cannabidiol (CBD), an important non-psychoactive compound found in marijuana, was isolated and its chemical structure was later described in 1963[5].

Prior to the late 1980s, scientists held the belief that the effects of cannabis were not influenced by receptors, as cannabinoids were thought to easily diffuse through cell membranes due to their lipophilic nature. However, in 1988, the first cannabinoid receptor (now known as CB1) was isolated and cloned, leading to a renewed interest in cannabinoids as possible therapeutic agents[27]. Devane and his colleagues (Devane et al.,) were the first to study and describe the initial cannabinoid receptor (CB1R) in both rodents and human brains. Just four years later, they isolated the first endocannabinoid called anandamide (AEA), which derives its name from the Sanskrit word for bliss or happiness. This discovery aligns with the experiences of the Scythians, who reported similar sensations when inhaling cannabis fumes, as documented by Herodotus. Currently, the ECS is recognized to consist of several identified endocannabinoids, primarily AEA and 2-arachidonoylglycerol (2-AG), as well as the two main cannabinoid receptors (CB1R, primarily found in the central nervous system and digestive organs, and CB2R, involved in regulating immunity and inflammation)[5].

The discovery of the endocannabinoid system has ushered in a new era in the use of cannabis. With growing scientific interest, the therapeutic effects of cannabis are being reexamined using more precise research methods. Studies are underway to explore the potential benefits of Δ9-THC in conditions such as epilepsy, insomnia, nausea, pain, glaucoma, asthma, Tourette's syndrome and more. Various cannabinoids, including cannabidiol (CBD), are also being investigated for their therapeutic properties in epilepsy, insomnia, anxiety, inflammation, neuroprotection, psychosis, and other areas[14]. Cannabigerol (CBG) is shown to demonstrate a potential as an antibiotic and has been linked to antitumor, antidepressant, analgesic, and glaucoma-alleviating properties. Another cannabinoid, cannabichromene (CBC) has been found to demonstrate anti-inflammatory, antitumor, antidepressant and antifungal effects. Cannabinol (CBN) is reported to exert anti-asthma and tranquilizing properties. It has also been identified as a potential analgesic and appetite stimulant[28]. Beyond cannabinoids, cannabis also contains terpenes and phenolic compounds that synergistically enhance its pharmacological effects. Studies highlight terpenes' potential therapeutic benefits, including anti-inflammatory, analgesic, and anxiolytic properties, while the polyphenols in cannabis, such as flavonoids, phenolic acids, and lignans are known for their antioxidant, anti-inflammatory, and neuroprotective effects. Cannabis also contains unique compounds like cannflavins, including cannflavin A, B, and C, which have been researched for their diverse biological activities, notably their anti-inflammatory and anticancer effects[29]. The continuous scientific investigations are offering promising prospects for uncovering the therapeutic properties of cannabis and its potential medical uses[14].

Despite years of resistance and strict regulations surrounding cannabis usage both for recreational and medical purposes, there has been an increasing societal curiosity about the plant's medical benefits, which has extended to the scientific community. In 1996, California took a groundbreaking step in the United States, by legalizing medical cannabis through the

"Compassionate Use Act". Today, both medical and recreational use of cannabis is allowed in California.

Many other American states have embraced this progressive approach. Canada implemented a medical cannabis program in 1999. Other countries such as Israel (2001), the Netherlands (2003), Switzerland (2011), Czech Republic (2013), Australia (2016), and Germany (2017) have passed laws permitting medical cannabis use under certain circumstances[23,30]. Amendments were introduced to the Law on Control of Narcotic Drugs and Psychotropic Substances in the Republic of North Macedonia in 2016. These changes focused on the legalization of cannabis for medical and scientific purposes. They included provisions related to cultivating cannabis, producing medical cannabis products, and importing pharmaceutical and cosmetic goods that contain cannabis or cannabinoids[31].

Conclusion

Attitudes towards cannabis are changing worldwide in the 21st century, as its value and potential are increasingly recognized. Medical cannabis is an illustration of how scientific progress has brought ancient wisdom to the forefront, overcoming biases. The active compounds in cannabis inspire the development of helpful synthetic drugs and deepen our understanding of cannabinoids produced by the human body. Research has discovered that cannabinoids impact numerous physiological processes and biochemical pathways, each of which holds the potential for the development of new medications. The legislation governing the use of medical cannabis is continually advancing, requiring pharmacists and other healthcare providers to keep up with changing regulations and institutional implications. Understanding the lessons from the past is crucial for the proper use of the incredible therapeutic potentials of cannabis, emphasizing the health benefits for the patients.

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