

Review

Medical Cannabis - A Historical Perspective

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ABSTRACT: The cannabis plant has been known for millennia for its properties such as textile fiber, food, recreational and medicinal use. Since the origin of its domestication in Asia, cannabis has been transported to the rest of the continents by merchants, nomads, settlers, and slaves, who have also carried with them valuable knowledge about its uses. Its medical use was one of the major contributions of this plant in the various civilizations through which it passed. This article aims to understand its origins, dissemination, and medical use over the years to the present day.

Keywords: Medical Cannabis; history of cannabis; medicine; cannabinoids

1. Introduction

Cannabis is a globally known plant whose origin is thought to have been in Asia and has accompanied the unfolding and advancements of civilization until the present moment. Its use as a domesticated plant comes from the years 10,000 BC and has been cultivated and used for millennia in the manufacture of textiles for clothing, ropes, and fishing nets, as fiber for paper, as food, especially its seeds, for recreational use due to its psychoactive properties, and as a medicinal product in the treatment of various pathologies or symptoms (Crocq, 2020; Li, 1974).

Its fascinating journey to the present day has spanned many different societies such as the Greek, Roman, Indian, Arabic, African, and the Chinese empire and all the civilizations it has passed through have left its mark for its immense capacities and uses (Grosso, 2020).

This article aims to understand the history of this plant, going through what is believed to be the origin of its domestication and the path it has taken to be present throughout the world. It also intends to look back over its medicinal use over time, passing through its illegalization in the 20th century and ending in the current days.

2. Methodology

To conduct this literature review on the history of Cannabis uses, the keywords "cannabis/hemp history", "history of medical cannabis" and "origins of cannabis/hemp" were searched in Pubmed, Google Scholar, and Web of Science databases. The search was carried out without filtering dates to be able to cover older articles but filtering the language, in Portuguese and English. The articles were chosen considering the adequacy of the title and abstracts to the theme. No filters were applied regarding the type of study, so research articles, as well as literature reviews, were used.

To reach more articles, bibliographical references of articles extracted from the databases were also consulted. This strategy allowed us to reach more articles and books, especially original research articles, although many of them used the same citations.

Books, in particular pharmacopeias and national forms, have also been consulted.

Finally, grey literature sources were also searched, such as institutional websites, legislation, and reports available on the subject so that the legal and historical context could be analyzed.

3. Cannabis – Origins, and Domestication

According to the Russian botanist Nikolai Vavilov (1926), it is very likely that the cultivation of cannabis has arisen in different parts of the world simultaneously, being impossible to prove its true origin (McPartland et al., 2019).

However, some studies indicate the possible origins of this plant and the beginning of its domestication.

Paleobotanical studies report the presence of cannabis probably domesticated in Central Asia, in the Altai Mountains, today Mongolia, about 11,700 years ago, leading to believe that this may be its origin. Studies on the cultivation of this plant refer to the possibility that humans have moved from harvesting wild plants to their selection and cultivation due to the quality of the fiber it originated and psychoactive capacity, with cannabis having been taken by nomadic populations throughout Asia and Europe (Crocq, 2020). In the processes of colonization and globalization, the plant was taken to other continents and ended up being disseminated throughout the globe.

Another study published in 2019 gathered available data on fossilized cannabis pollen and analyzed the geolocation of evidence of seeds, phytoliths, and stem fragments to identify the geographical areas where the plant thrived, concluding that its probable origin would be the Tibetan plateau (near Lake Qinghai). They also assume that from there the plant migrated first to the west (Europe) and then to the east (China) (McPartland et al., 2019).

The truth is that although there is no certainty of its origin, it is consensual that the plant was first discovered in Asia and that ancient peoples not only knew it but cultivated it for different purposes and to obtain the desired results.

The discovery of a grave of a man of about 45 years of clearly a high social class (probably a Shaman), buried in Xinjiang-Uighur, an autonomous region of China, caught the attention of scientists. This man was buried with a set of 800g of plants and scientists later identified it as cannabis with a high content of tetrahydrocannabinol (THC), the compound with the greater psychoactive capacity of the plant. The grave was dated to 750 years BC and associated with the Tocharian culture, a nomadic population. The botanical and phytochemical analysis carried out on the plants showed that the plant was of human and not wild cultivation and that the plants would have been selected for their high THC content and the male parts of the plants having been removed, which are the parts of the plant with lower THC content. This discovery revealed that as early as 750 BC, cannabis was already being cultivated for its psychoactive effects and not just to produce textile fibers and food (Crocq, 2020; Jiang et al., 2006). It is thought that the psychoactive uses of the plant in the Chinese empire were only allowed to shamans, who, because of restrictions imposed by the empire, left China heading for other locations like Siberia and India taking with them the knowledge about cannabis (Li, 1974; Touw, 1981).

In Japan, there was also found evidence of human cultivation of the plant with the discovery of macrofossils of seeds and fruits in ruins at the archaeological site in Okinoshima, which date back 10,000 years, during the Jomon culture (Okazaki et al., 2011). Other evidence has also been found at the archaeological sites of Matsugasaki and Torihama, in Japan, dated between 4050 BC and 3270 BC (Matsui & Kanehara, 2006; Okazaki et al., 2011).

The dissemination of cannabis in Europe and the Mediterranean basin is said to have been carried out through its transport by the Scythian people, a nomadic Indo-European group, who moved from Central Asia through Russia around 3500 years ago. Cannabis remains, dating back to 450 BC, have been found in Scythian tombs in Germany, Siberia, and Ukraine. However, some findings point to the presence of pollen from wild cannabis species dating from 8250 to 6550 BC in Romania, Bulgaria, and Hungary and dating from 11000 BC near Lake Albano in Italy (McPartland & Hegman, 2018; Mercuri et al., 2002).

The arrival of cannabis in Egypt is unknown and may have also been transported by the Scythians, but there is a possibility that the plant already existed in the area before their arrival. Traces of hemp were found in the tomb of Akhenaten dating back to 1335 BC and pollen in the tomb of Ramses II (1303-1212 BC) (Pisanti & Bifulco, 2019). Its appearance in the Arab countries is also unknown, being possible that it arrived by sea through travelers or merchants who transported it from India and then disseminated to other countries of the African continent (Pisanti & Bifulco, 2019). It is thought that cannabis was diffused to Eastern Africa through Egypt and Ethiopia, most likely brought by these travelers (Warf, 2014).

The spread of cannabis across the American continent was accomplished through the slave trade coming from the African continent at different moments in time during the 16th century (Pisanti & Bifulco, 2019; Warf, 2014). Spain introduced the planting of this species in Chile (Valparaíso) in the first decade after its conquest (Crocq, 2020), and also in Colombia and Portugal took this species

from Angola to Brazil in the 16th century (Warf, 2014). Louis Herbert was the first apothecary (from Paris) to grow hemp in 1606 in Acadia (now Nova Scotia in Canada) (Crocq, 2020).

By the end of the 17th century, cannabis was already a known species in almost the entire globe, whether it was for the use of its fibers, for its psychoactive properties, or its therapeutic properties.

4. Cannabis as A Medicine

According to legend, Emperor Shen Nung (2700 BC) instructed the Chinese people in the practice of agriculture, cultivating not only cereals but also hemp as one of the main crops. Hemp was registered in the ancient agricultural treaty over 3000 years old, called "Xia Xiao Zeng" or the small calendar of the Xia dynasty. Emperor Shen Nung was considered the patron of herbalists and pharmacists and the father of Chinese herbal medicine, as he instructed people on the medicinal powers of plants. It is mentioned that he tried several plants on himself to find out their medicinal properties and made a compilation of the first "Pen-ts'ao" or "Chinese materia medica" (Hou, 1977; Jiang et al., 2006; Pisanti & Bifulco, 2019). The first historical evidence of the use of cannabis in traditional medicine was documented in the oldest Chinese pharmacopeia, the "Sen Nung Pen-ts'ao Ching" written in the first century BC and where we can find all products used and administered orally in Chinese medicine during the previous 2,000 years (Pisanti & Bifulco, 2019).

At that time, cannabis was considered a superior plant, meaning without danger to human health. According to the "Pen-ts'ao Ching", the preparation based on cannabis flowers was associated with the treatment of rheumatic pain, constipation, malaria, beriberi and gynecological problems, diseases caused by the loss of yin, based on the yin/yang principle of Chinese philosophy. However, it also mentioned that excessive use would cause visions of demons (hallucinations) or even the ability to speak with spirits (Li, 1974).

Also, the herbarium wrote in 1108 AD, the "Cheng Lei Pen-ts'ao", described the properties of the same cannabis preparation as being useful in blood purification and fever control. "Ho Han Su", the story of the Han dynasty from 25 to 221 AD, describes for the first time the analgesic properties of cannabis, citing surgeon Hua Tuo (117-207 AD), who in his work mentioned performing surgeries without pain in his patients, using a mixture of cannabis resin oil, a poisonous plant, Datura, and wine (Li, 1974). Other indications have also been reported in traditional Chinese medicine, such as laxative effects, body tonic for the treatment of asthma and other pathologies associated with the skin (Li, 1974; Pisanti & Bifulco, 2019).

In India, the spread of cannabis was made quickly as it was considered a plant that brought happiness and could produce feelings of joy and freedom. Its medical use was also widespread in India around 1000 BC, and its application in medicine also intersects with religious and ritual activities. One of the main texts of Ayurvedic medicine dating from about 800 BC (Susrita Samhita) describes the plant as having analgesic, anesthetic, antiparasitic, antispastic and diuretic capacity, being also used in medical practice as an expectorant, aphrodisiac, anticonvulsant, appetite stimulator, nausea, induce sleep, muscles relaxation, to produce a euphoric effect and reduce anxiety, and as relief from tiredness (Crocq, 2020; Jiang et al., 2006; Pisanti & Bifulco, 2019; Touw, 1981). Even in Tibet, cannabis was considered a sacred plant, playing a significant role in traditional Tibetan medicine and also as an aid to meditation (Touw, 1981).

The Scythians used cannabis as a fiber, but also for fumigation at funeral events, banquets and relaxation saunas. Knowledge of this plant is thought to have been learned from the Assyrian and Thracian peoples in the region of the eastern Balkan peninsula and Dacia around 650 BC. The Assyrians had a great knowledge of this plant and its uses in swelling, bruises, depression, sexual impotence, arthritis, kidney stones and gynecological disorders (Pisanti & Bifulco, 2019; Warf, 2014).

Present in the Egyptian pharmacopeia since Pharaonic times, cannabis was used in Egypt under various forms of administration (oral, rectal, vaginal and fumigation). As stated in the "Papyrus of Ramesseum III" (1700BC) cannabis was used in the treatment of eye diseases and in the "Papyrus of Ebers" (1550AD) it was used to induce contractions during childbirth and to treat infections in the toenails (Russo, 2007).

During the Greek and Roman empires, cannabis was used in the production of fiber for ropes and tarpaulins, and seeds and flowers as food, and it was probably introduced either from the Middle East or Eastern Europe (Warf, 2014). In the 1st century AD, medical

writings by Pliny, Galen, and Dioscorides reported for the first time the medicinal capabilities of the plant in relieving pain, when consumed in the form of an infusion or juice made from seeds and flowers. The work "Naturalis Historia", written by Pliny the Elder (23 to 79 AD), also describes the positive properties, such as muscle relaxation, treatment of gout and burns, and the negative properties of the medicinal use of the plant, such as impotence and headaches (Brunner, 1977). The famous work "De materia medica" written by the Greek physician Dioscorides (40-90dc), Nero's physician, is an account of several plants used in medicine where cannabis can be found, highlighting its properties in reducing inflammation and swelling and also ear pain. (Brunner, 1977). In the "Cannone of Medicine", the physician Avicenna (980-1037 AD) suggests the use of cannabis for the treatment of headache, bone and joint degenerative diseases, eye inflammation, edema associated with gout, treatment of wounds and uterine pain. In Arabic medicine it was common to use hemp oil for ear application for the treatment of ear infections and local application in skin diseases, but also flatulence, intestinal parasites, neuropathic pain, fever and vomiting. During medieval times it was also common to use it to increase urinary flow, increase blood flow in the pelvic area, anticonvulsant, analgesic and anti-inflammatory and was also used for its psychoactive abilities (Lozano, 2001).

In the 11th century AD, the "Anglo Saxon Herbarium" described cannabis as an anesthetic and its roots and seeds were used to relieve pain caused by gout, urinary problems and birth pains and indicated for weight loss (Pisanti & Bifulco, 2019).

Evidence of the presence of cannabis within monasteries has also been found, one example being works written by St. Hildegard (1098-1179dc), a German Benedictine abbess, and one of the first women in history to write scientific medical treatises. In her works "Physica" and "Book of medicinal simples", she describes the pharmacological properties of cannabis following the prevailing theory of humors (Mechoulam, 1986).

Unlike the Arab countries, where cannabis continued to be used even for its psychoactive effects, in Europe, during the Middle Ages, the use of this plant declined, with the fact that it was often confused with opium. In 1484, the papal bull issued by Pope Innocent VIII condemned the use of cannabis and the practices of healers who used plants, calling them "the profane sacrament of the satanic mass". However, and as required by the four Italian maritime republics, its production was maintained, essentially to cover the needs of fiber for ropes, moorings and sails for the boat fleet (Pisanti & Bifulco, 2019; Warf, 2014; Zuardi, 2006).

Several English scholars throughout the 16th and 17th centuries also described various uses for the plant, such as the botanical John Parkinson (1567-1650) for gastrointestinal problems, pain, tumors and burns, Oxford Robert Burton (1577-1640) for depression and the herbalist Nicholas Culpeper (1616-1654) as an antiseptic, anticonvulsant among other uses (Pisanti & Bifulco, 2019). The Polish botanist Symon Sirenius (1540-1611) also described cannabis as a useful drug to treat skin burns, joint pain and toothache (Pisanti & Bifulco, 2019).

It is thought that Arab travelers have transported cannabis to other places in Africa where evidence of its presence dates to the 15th century, having been used in these places to fight fever, malaria, asthma, dysentery, facilitate childbirth and bites. snake and contact with anthrax (Pisanti & Bifulco, 2019).

However, during its presence on the American continent, more specifically, in South America, cannabis was used for other applications. Its roots were used with purgatives, the stems and seeds as sleep inducers, the juice for seizures, rheumatism and urinary problems and the dyes for neuralgias and headaches (Pisanti & Bifulco, 2019).

Cannabis was introduced into Western medicine in the late 19th, early 20th century. The medical use of cannabis in the modern era began in the 19th century with the investigation of the Irish doctor William Brooke O'Shaughnessy, regarding the plant's properties in various diseases such as rheumatisms, cholera or tetanus and even to an infant suffering from convulsions. During the years O'Shaughnessy stayed in India, he described details contained in Sanskrit, Persian and Arabic historical texts, and carried out preclinical studies of safety and efficacy and, finally, clinical trials. He concluded that the plant species used in India (*Cannabis indica*) was different from the species cultivated in Europe (*Cannabis sativa*), not only in its appearance but also in its pharmacological properties. His pre-clinical studies were conducted in animals with plant extracts, followed by the administration of alcoholic tinctures to their patients who suffered from rheumatism, cholera, tetanus and even a child who suffered from

convulsions, all of which reacted well to the therapy used (Crocq, 2020; Pisanu et al., 2019; Warf, 2014). Thus, he deduced the analgesic and muscle relaxant properties, useful as anticonvulsants and also in the palliative treatment of tetanus. O'Shaughnessy returned to England in 1841 with cannabis Indica seeds, sharing his knowledge with the European medical community, which, however, were unable to isolate the active principles of the plant (Pisanti & Bifulco, 2019).

Queen Victoria's physician, J. Russell Reynolds, 1890, summarized more than 30 years of medical experience using cannabis in The Lancet. He highlighted the biggest obstacle of this plant as the fact that the active substance has not yet been discovered and isolated, a fact that only happened in 1964. Thus, the extracts of the plant were not uniform, depending on the time of year and the places where it was planted. This author also considered that the use of this plant was extremely beneficial for several painful conditions, including toothaches in children (Crocq, 2020; Reynolds, 1890).

Also in France, interest in cannabis increased again when Baron Sylvestre de Sacy (1758-1838) translated Arabic manuscripts describing the medicinal properties of the plant and its constituents, namely its resin, the "Hashish" (Pisanti & Bifulco, 2019).

During the 19th century, numerous attempts have been made to isolate the compounds from cannabis but without success. In 1849, Carlo Erba, the Italian pharmacist, opened a laboratory to create and sell cannabis in several galenic formulations, but since the compounds were not known, all formulations were tested for safety and efficacy in various health problems, such as migraine, nausea and arthritis. The preparations were a commercial success, however, the preparation costs were high due to the need to import the plant from Egypt and the ability to import enough stock for the preparations was sometimes not supplied by the producers, generating stock shortages and consequently, failure to supply market demands (Pisanti & Bifulco, 2019). Another Italian pharmacist, Pietro Burgo, tried to solve the problem by using oil from cannabis sativa grown in Italy. Likewise, the physician Raffaele Valieri, head of the former "Hospital for the Incurables" in Naples, in 1887, found that cannabis sativa that grew in Italy could be used instead of cannabis indica from abroad, but it should be used by duplicating the dose. In this way, production would be less costly and equally efficient. In his essay called "About local hemp and its preparations in place of *C. indica*", Valieri also stated that Cannabis sativa produced in Campania was effective in other pathologies, through inhalation, such as neuralgia, insomnia, hysteria, asthma, pulmonary emphysema and exophthalmic goiter (Pisanti & Bifulco, 2017).

The end of the 19th century was considered the golden age for cannabis, as its medicinal use grew significantly, several scientific studies and publications on the plant were conducted, mainly in Europe and the USA. At the same time, several laboratories have launched different cannabis formulations to the market with analgesic, anti-inflammatory and anti-spastic properties. Examples of this were the Bristol-Meyers and Squibb laboratories in the USA and Merck in Germany (Pisanti & Bifulco, 2017).

5.The Fall of Cannabis

The spread of cannabis for medical use in Europe and the United States started to decline in the 20th century as a result of two main events. First, the introduction of other non-psychoactive substances for the same purposes such as aspirin, and secondly, the extended consumption showed great therapeutic variability between patients (Crocq, 2020; Zuardi, 2006)

In 1925, at the 2nd International Opium Convention, a revision of the agreement was signed between the participating countries, which included preparations based on cannabis in the group of controlled substances. They stated that cannabis preparations or derivatives should only be authorized for medicinal and scientific purposes, except for resin (hashish) for which no pharmacological or medicinal benefit was known, so it would be forbidden. Even though India held out against this position, due to the importance of cannabis as a cultural element in the country, its position was not considered (Pisanti & Bifulco, 2019).

The definite fall of Cannabis in the USA in 1937, started when a prohibitionist policy was put into practice, the "Marijuana Tax Act" (Public law n° 238 of August 2, 1937), that not only affected the recreational production, but also the industrial and medical production (Brunner, 1977). Its application did not forbid the use of medical cannabis but increased production costs to such an

extent that even medical research in the field of cannabis was also stopped and physicians were persuaded not to prescribe it (Musto & New Haven, 1972; Pisanti & Bifulco, 2019).

Even with the opposition of the Medical American Association, through Dr. William Woodward, who maintained his position on the benefits of cannabis as a medicine, the fee application continued, contributing to the reduction of the use for medical purposes and, eventually, its total removal from the medical practice (Musto & New Haven, 1972).

The enforcement of the "Marijuana Tax Act" was the result of an aggressive campaign by Harry Anslinger, the first commissioner of the Federal Bureau of Narcotics in the Treasury Department, who associated cannabis with the promotion of violence, crime, sexual depravity and insanity, particularly in communities of ethnic minorities (Grossman, 2019). Some studies admit that the enforcement of this law was not related to its medicinal power, but rather to issues of moral order and minority discrimination. They also admit that it was not the result of an imposition created by society, but by the Bureau itself, leading cannabis to be removed from the American Pharmacopeia and the US National Form, thus ending its application for medical uses in the country in 1941 (Bender, 2016; Dickson, 2018; Grossman, 2019).

In 1961, during the United Nations Single Convention on Narcotic Drugs, the use of cannabis, except for fiber production, was expressly prohibited in several countries, placing it in the same group of substances as heroin (Crocq, 2020; United Nations, 1962). The debate over the legalization of cannabis use emerged in the 1960s by a fringe of society that experienced post-World War II deprivations, culminating in opposition to the Vietnam War and the growth of the hippie philosophy (Crocq, 2020).

6. Discovery of The Endocannabinoid System and Legalization of Medical Cannabis

More than one hundred cannabinoids have been identified and isolated from cannabis, but the two most significant are Cannabidiol (CBD) and THC. CBD was the first compound to be isolated, in 1940, however, its structure was only known in 1963. The structure of THC (the psychoactive compound) was determined by Mechoulam and Gaoni in 1964. The studies carried out by these scientists launched the impetus for the discovery of the endocannabinoid system at the beginning of the 90's, which means, its receptors in the human body, the endogenous cannabinoids and mainly its mechanism of action (Grosso, 2020). Devan et al. (1992) characterized the first cannabinoid receptor (CB1R) in rat and human brains and four years later, the same scientist discovered the first endocannabinoid, arachidonoyethanolamide (AEA) or anandamide (Devane et al., 1992). The endocannabinoid system is understood today as having endocannabinoids (AEA and 2-arachidonoylglycerol or 2-AG) and two main cannabinoid receptors: CB1R, present in the central nervous system and organs of the digestive system, and CB2R, involved in immune and inflammatory regulation (Crocq, 2020; Pisanti & Bifulco, 2019).

The discovery of the endocannabinoid system launched a new era for cannabis use. The increasing scientific interest in the pharmacological properties of the plant has led to a new increase in publications of scientific articles with important medical contributions for different pathologies. The discoveries resulting from greater knowledge of the plant and, also, on new scientific technologies, and the pressure from society have led several countries to introduce more permissive laws regarding the medical use of cannabis, and also decriminalize or even legalize its recreational use (Pisanti & Bifulco, 2019).

Despite decades of demonization of the use of cannabis, whether for recreational or medical use, society's interest in the medical potential of this plant has grown, spreading to the scientific community. The discovery of the endocannabinoid system and, later, its action on biological functions, such as cognition, memory, pain, sleep and the immune system, led to the approval of cannabis for medicinal purposes in some countries around the world, such as Canada (1999), Israel (2001), Netherlands (2003), Switzerland (2011), Czech Republic (2013), Australia (2016), Germany (2016) and finally Portugal (2018). Even the United States of America, the leader in the political prosecution of cannabis, applied the use of these drugs in many of its states (European Monitoring Centre for Drugs and Drug Addiction, 2018).

7. Conclusions

Cannabis is an ancient plant that has crossed the history of humanity, having served as an unparalleled material for textiles, used for its psychoactive abilities and as medicine. It is thought that its domestication predated 10,000 BC and that by that time many of its features and many of its uses were already known to the people. It crossed continents in the hands of merchants, nomadic peoples, colonizers and slaves until it became a crop present in almost the whole globe.

This review wanted to know and make known the history of this plant, from its origins in Asia to the present day. This article also aimed to present the path from the first references to its medicinal use, to its presence in pharmacopeias in some countries of the world, then through its illegalization, to reach the current moment, with a timid reintroduction into the pharmaceutical market that is spreading.

Medical cannabis is an example of how scientific progress has brought to light ancient knowledge, overcoming barriers of prejudice. As Ethan Russo wrote in 2007 in one of his articles, regarding the knowledge of our ancestors, "their discoveries and experiments demonstrate important insights that may well retain valid lessons that modern science should utilize as starting points of departure for further research"(Russo, 2007).

The way forward will be more research in the area of medical cannabis to better understand its potential and risks to health, deepening the scientific knowledge about this plant.

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