Cannabis: 12,000 years of experiences and prejudices

Cannabis: 12.000 anos de experiências e preconceitos

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ABSTRACT

BACKGROUND AND OBJECTIVES: *Cannabis Sativa* has been part of human evolution and has been used by different populations for different purposes. By reviewing the history and main advances in cannabinoid medicine, the aim of this study was to identify the major discoveries in recent years, which have prompted the publication of articles.

CONTENTS: The following topics were searched: "history of cannabis", "history of hashish", "history of marijuana" and "main advances in endocannabinoid medicine"; in SCIELO, Pubmed, Google Scholar, Brazilian Digital Library of Theses and Dissertations (BDTD), Latin American and Caribbean Literature in Health Sciences (LILACS) and Medline (Capes platform) databases.

CONCLUSION: There has been an increase in the number of publications following major discoveries about the endocannabinoid system, including receptors and endocannabinoids, but prejudice and the difficulty of accessing this therapeutic tool prevent further development.

Keywords: Cannabis, Cannabinoids, History, Tetrahydrocannabinol, Therapeutic use.

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HIGHLIGHTS

• Cannabinoids have been described in medical literature for several years, showing the progressive evolution of published articles.

• New discoveries about the endocannabinoid system have changed knowledge about the treatment of diseases.

• The Cold War and the prohibition of cannabis associated the plant with other toxic substances. In Geneva, testimonies attributed to cannabis the same effects as heroin, and Brazil is one of the defenders of this prohibition.

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JUSTIFICATIVA E OBJETIVOS: A *Cannabis Sativa* acompanha a evolução humana e foi utilizada por diversas populações para diversos propósitos. Ao revisar a história e os principais avanços na medicina canabinoide, o objetivo deste estudo foi identificar as maiores descobertas nos últimos anos, que fomentaram a publicação de artigos.

CONTEÚDO: Os seguintes tópicos foram foram pesquisados: "história da cannabis", "história do haxixe", "história da maconha" e "principais avanços na medicina endocanabinoide"; nos bancos de dados SCIELO, Pubmed, Google Scholar, Biblioteca Digital Brasileira de teses e dissertações (BDTD), Literatura Latino-Americana e do Caribe em Ciências da saúde (LILACS) e Medline (plataforma Capes).

CONCLUSÃO: Foi demonstrado o aumento no número de publicações após as grandes descobertas a respeito do sistema endocanabinoide, incluindo os receptores e os endocanabinoides, porém o preconceito e a dificuldade de acesso a essa ferramenta terapêutica impede um maior desenvolvimento.

Descritores: Cannabis, Canabinoides, História, Tetraidrocanabinol, Usos terapêuticos.

INTRODUCTION

RESUMO

Cannabis sativa has been with the human species since the Neolithic period and has been used by various populations for a wide variety of purposes. New studies on the plant have shown its need over time, all the way to the regulatory medicinal use of the plant.

This study is a narrative review that sought to map and retrace historical facts related to the cultivation and use of *Cannabis sativa* and how prejudices about its use have arisen in different cultures and nations, which interfere with the difficulty of access.

CONTENTS

The scientific methodology consisted of integrative bibliographic research, through active searches in databases such as SCIELO, Pubmed, Google scholar, the Brazilian Digital Library of Theses and Dissertations (BDTD), Latin American and Caribbean Health Sciences Literature (LILACS) and MEDLINE (Capes platform). The search used keywords such as "cannabidiol", "cannabis", "legislation", "prescription" and "pharmacology". Scientific papers were searched for in Portuguese, English and Spanish, published between 1980 and 2023.

Cannabis sativa has been around since the Neolithic period. Fossils prove that it was one of the first plants to be domesticated by mankind¹, and in the first agricultural practices, around 12,000 years ago in central Asia, the plant was already consumed as food, as well as being used to make fabrics and administered as a drug².

With the development of writing, there are references to the use of cannabis in various cultures, such as in the Chinese book Pen Tsao³, written from 2700 BC, describing the use of the plant by the emperor Shen Neng, administered for the treatment of joint pain, menstrual cramps and intestinal alterations⁴.

Ancient Egypt has provided us with several references to the plant. One of them is the Ebers papyrus, dating back to 1550 BC, which records the use of more than 700 medical formulations, some of which contain cannabis for the treatment of pain, emotional disorders and even for "well-being"⁵. In addition to its medicinal use, the Egyptians used cannabis for various other purposes, including the production of papyrus⁶. These benefits elevated the plant to the level of sacredness, and it was represented by the goddess of wisdom, Sechat, with an adornment on her head (Figure 1).



Figure 1. Goddess Sechat

In India, the plant was used for two main purposes: religious use, as described in the book "Atharvaveda"⁷ (1200-800 BC), which placed cannabis as one of the five sacred plants, a gift from the god Shiva⁸, so that humanity could build a better world; the other use was for purely medicinal purposes, being indicated in the treatment of various diseases (pain, dentistry, anticonvulsant, anxiolytic, anesthetic, anti-inflammatory, antispasmodic, orexigenic, aphrodisiac and expectorant)². In Tibet area, in addition to the above-mentioned indications, the plant was used to facilitate the meditation of monks⁹.

A surprising find took place in 1993, when a mummy was found in Siberia. After intensive research on the corpse, the body was associated with an aristocrat from Ukok, who lived 2,500 years ago. Its good state of preservation made it possible to identify the cause of death, which was breast cancer. The "Princess of Ukok" was buried with various belongings, including three horses, a bag full of cosmetics, jewelry, a mirror with a Chinese frame and a box full of cannabis which seems to have been used to treat the symptoms of her cancer¹⁰.

In what is considered to be the first book on medical pharmacology, "*De Materia Medica*", by Pedanius Dioscorides⁶, written in 70 AD, cannabis features among more than 1000 plants, being effective for pain and inflammation¹¹ (figure 2: cover of the book "*De Materia Medica*", by Pedanius Dioscorides).



Figure 2. Cover of the book "*De Materia Medica*" - 1.554 AD https://pt.wikipedia.org/wiki/Sobre_Material_M%C3%A9dico

Furthermore, between 110 and 207 AD, the physician Hua Tuo, the founder of Chinese surgery, lived in China and described the use of a compound of wine and hemp as an anesthetic for the first abdominal surgeries¹². This description occurred 1600 years before the first anesthetics in Europe.

In the Middle East, Muslim medical texts described the use of cannabis as one of the main medicinal plants¹³. As described in the works of Avicenna, around 1,000 AD, cannabis was used as diuretic, antispasmodic, analgesic, anti-inflammatory and anxiolytic¹⁴.

During the Muslim invasion of Europe, the plant was used to make paper and fabrics. On the other hand, its medicinal use was not as widespread². In 1464, the physician Ibn al-Badri made the first description of cannabis use to treat the seizures suffered by the son of the Caliph's chamberlain¹⁵. The boy stopped having seizures, but began to abuse the drug.

On the African continent, cannabis was possibly spread by Arab traders who traveled the route between India and the countries of the continent². In Africa, cannabis was used to treat snake bites, analgesia in childbirth, symptoms related to malaria, respiratory and intestinal problems, as an analgesic and anxiolytic¹⁶.

It was through Africans, especially Angolans, that cannabis reached South and Central America, where its use was fundamental for treating the symptoms of physical and emotional aggression suffered during the period of slavery¹⁷. Cannabis was present in the formation of the first *quilombola* villages and was absorbed by their members during Brazil's colonial era.

The medical use of cannabis derivatives in Europe began in the early 19th century in two ways. In 1798, the French army, commanded by Napoleon Bonaparte, invaded Egypt with the aim of interrupting the British route to India. However, French interests were not only aimed at territorial conquest.

A contingent of 167 scientists from various fields was taken to explore the country in search of treasures and new knowledge. However, the discovery that attracted the most attention at the time did not come from this group of scientists, but from the soldiers. Hashish was discovered by the troops of the Napoleonic army and was soon consumed on a large scale.

The soldiers' commitment to fighting was no longer proving effective, leading the French army to significant defeats. Napoleon then banned the use of cannabis resin by his soldiers, claiming that the substance created savage attitudes. In practice, Napoleon's ban had no effect. After the expedition failed, the soldiers returned to France in 1801, taking hashish to Europe⁵.

Another route for cannabis derivatives to enter Europe took place in the same period, but through England, which dominated India. William O'Shaughnessy, a 24-year-old Irish doctor, accepted an offer to work in Calcutta as a surgical assistant for the then famous East India Company, a British company that controlled and governed a large part of India. During the eight years he worked in Calcutta, O'Shaughenessy learned about various plants, including cannabis. After carrying out various studies on animals, he began to use the plant in his patients with cholera, rheumatic diseases, rabies, tetanus and, above all, to control seizures.

The young doctor and researcher began to publicly defend the use of the plant in medical journals, through which he reported his experiences. One of the examples of this interest was recorded in 1839, in London's Provincial Medical Journal, which described the treatment carried out on a newborn child using a cannabis extract to combat refractory convulsions. Back in Europe in 1841, O'Shaughenessy took small quantities of cannabis and presented it to the Royal Pharmaceutical Society as an innovative drug. From then on, cannabis was used and studied in several countries in Europe and North America¹⁸.

During the second half of the 19th century, the use of cannabis became widespread, with one of the main indications being the treatment of addiction to opium and its derivatives. While the medical use of cannabinoids was growing in England, its social use was becoming popular in France. At this time, French doctor Jacques Joseph Moreau became interested in the properties of cannabis and set out to travel to various countries, such as Egypt and Syria, to understand its effects. In 1840, he decided to ingest some hashish with the intention of experiencing the sensations and reporting its effects, describing them as a mixture of euphoria, hallucination and incoherence; however, he found an extremely rapid flow of ideas¹⁹.

In 1844, Moreau met the French philosopher, writer and journalist Theophile Gautier, who was impressed by Moreau's description of the cannabis' effects. Gautier defined the effects of cannabis as "an intellectual intoxication preferable to the heavy and ignorant drunkenness of alcohol". Excited by these effects, both invited a group of intellectuals to share their experiences, forming the *Club des Hachichins* (Hashish Club). Among its participants were Alexandre Dumas, Victor Hugo, Gerard de Neval, Honoré de Balzac, Charles Baudelaire, Eugene Delacroix, among others*20*.

The members of the group met regularly between 1844 and 1849 at the Pimodan house, dressed in Arabic clothes, and drank strong coffee, richly mixed with hashish, nutmeg, cinnamon, pistachios, orange juice, sugar and butter, which they called "*dawameska*". Some of them recorded their experiences. In reality, all the participants in the meetings were lab rats for Dr. Moreau, who had a group of extremely articulate intellectuals in his hands and could observe their reactions to the use of hashish. In 1846, he described his observations in scientific terms in a 439-page book entitled "*Du Hachish et de l'Alienation Mentale - Études Psychologiques*" (Hashish and Mental Problems - Psychological Studies).

In 1860, the first clinical conference on cannabis was held in the United States, organized by the Ohio State Medical Society². At the beginning of the 20th century, cannabis-based products could be found in pharmacies in several countries, including Brazil, such as Índios cigarettes and Grimault cigarillos¹⁷. During this period, products enriched with cannabinoids were produced by important pharmaceutical laboratories such as Merck, Burroughs Wellcome, Bristol Meyers Squibb, Parke-Davis and Eli Lilly. However, the development of other medications and the lack of a standard meant that their medicinal use declined slowly and progressively.

In the 1920s, the USA began to receive many immigrants, mainly Latinos and Arabs who were already using cannabis. Soon its consumption became rampant in the country, especially in black areas of the South.

In 1925, at the Geneva Convention on illicit drugs, there was testimony from several countries, including Brazil, which, through the doctor Pernambuco Filho, compared cannabis to the effects of heroin. In addition, Brazil has one of the first bans on marijuana in the Americas (*Pito do Pango* law, RJ, 1830). The declaration mentioned above was decisive in alerting the world to the risks of using the plant²¹.

1933 saw the first of Roosevelt's four terms in office, which ended the prohibition, without, however, abolishing the federal treasury's narcotics department, headed by Harry Jacob Anslinger. Roosevelt strengthened the department, which now has the goal of stop the cannabis consumption, a drug that threatened white American youth who began to frequent black jazz bars²².

Cannabis was a natural competitor to the cultivation of cotton, which was important to the American South oligarchy²². It was also a competitor to the adult use of alcoholic beverages produced in the north of the US, consumed by poor immigrants, favoring interracial relations. For any or all of the reasons described above, cannabis became "the number one villain" and various actions were taken to put an end to its existence.

The strategy was to crack down on jazz venues in order to keep white audiences away from black artists like Louis Armstrong, Fats Waller, Duke Elligton and Billie Holiday. The latter, in turn, was handcuffed on her deathbed by Anslinger, proof of the black artists' persecution²⁴.

In 1936, the movie "Reefer Madness" was released, showing young white men becoming psychopaths, depraved or insane with just a few puffs of a cannabis cigarette¹¹. Thus, in 1937, the law known as the "Marijuana Tax Act" was passed in the US, with the aim of prohibiting adult or social use, while maintaining medicinal use. However, in practice, it became impossible to use it for any purpose²³.

In 1938, cannabis was banned from being planted, cultivated, harvested and sold on American soil. It seemed that Anslinger had convinced everyone of the dangers of the plant, but not everyone²⁵. In 1938, the mayor of New York, Fiorello La Guardia, appointed a commission of inquiry made up of doctors, professors and researchers to assess the risks of cannabis use. The report of this study, known as the La Guardia Committee Report, took five years to be published. In the meantime, many important events took place in the world, including the Second World War.

World War II began in September 1939, and the US remained aloof from the conflict until December 1941, when its Pearl Harbor base was bombed by the Japanese²⁶. The US armed forces, as well as those of several other countries, used hemp fiber (a species of cannabis with low psychoactivity) to produce uniforms, parachutes, sea ropes and tarpaulins for tents.

However, with planting banned on national territory, and the largest producer of this commodity, China, being under Japanese rule, the US government, through the Ministry of Agriculture, paused the law banning the cultivation of the plant, releasing the documentary "Hemp for Victory" in 1942, in order to encourage American farmers to produce as much hemp as possible²⁷.

In 1944, while the Second World War was still going on, the results of La Guardia Committee Report were delivered, supported by the scientific community of the time, contesting all the arguments used by Anslinger, which led to the prohibition of cannabis²⁸. The report was challenged by Anslinger, who classified it as unscientific, so hemp production was banned again as soon as the Second World War ended in 1945²⁹. After the end of the Second World War, the world was practically divided into two large blocs, one under the influence of the USA and the other of the then Soviet Union, thus beginning the so-called "cold war" in 1947. With the discourse of the communist threat in the West, strengthened by Soviet support for the Cuban revolution of 1959, USA and USSR became involved in various conflicts around the world, one of the best known being the Vietnam War³⁰.

In 1964, the US Congress authorized the country's entry into the war, which was immediately met with strong opposition from society. After five years of war, under Richard Milhous Nixon, a relentless fight against drugs was implemented. The then US president, faced with protests by hippie groups against the war, countered the opposition by persecuting them on the grounds that they were addicts³¹.

At the same time, a group of scientists from the chemistry department of the Hebrew University of Jerusalem, led by Professor Raphael Mechoulam, began to study the cannabis plant in an unpretentious way. In the first half of the 1960s, the group described the structure of the plant's chemical elements, which would be known as phytocannabinoids, including "delta9-tetrahydrocannabinol" (THC) and "cannabidiol" (CBD). Israel was in a dilemma, as it was embarking on research into a plant that was considered a public health risk by its main ally, the USA³².

In the West, actions against cannabis were still growing. In 1970, Nixon created the "National Commission on Marijuana and Drug Abuse", known as the "Shafer Commission". After conducting studies, the commission concluded that there was nothing to support the arguments for prohibition. Nixon ignored the report.

The following year, the United Nations (UN) classified cannabis as a non-therapeutic plant with a high power of abuse. At the same time, Robert Randall, an American with glaucoma, regained his sight after using cannabis, and years later he became the first patient to be authorized to use the plant medicinally in the USA³². With the end of the Nixon administration, Presidents Gerald Ford and Jimmy Carter were more lenient on cannabis.

Because of a legend that arose during Ronald Reagan's administration, cannabis has once again been fought against. The legend arose from a study carried out in California while Reagan was still governor of that state. The research carried out with Rhesus monkeys involved having them inhale the equivalent of 60 cannabis cigarettes for five minutes a day.

The experiment, which lasted 90 days, resulted in the deaths of the monkeys, whose necropsies showed areas of encephalomalacia theoretically caused by cannabis²³. Later, it was concluded that there had been negligence in the methodology used, and scientific evidence revealed that the cause of death was cerebral hypoxia, and not a direct effect of the use of the plant.

As the war against cannabis grew, Professor Raphael Mechoulam's group continued to inspire scientists in various parts of the world, including Brazil. In this country, the group of researchers led by Elisardo Luiz de Araujo Carlini, who in 1980 carried out, together with Professor Sanvito and Mechoulam himself, the first scientific study on the use of isolated cannabidiol to control seizures in refractory epileptic patients. The double-blind study involved 15 patients divided into two groups, one of which received a placebo. In just eight weeks of study, the researchers proved the effectiveness of cannabidiol in the control of epileptic seizures, prompting further research in various centers around the world³⁴.

There was a new discovery, in 1988, that changed the whole way of understanding the pharmacological mechanisms of cannabis: the group of researchers led by Professor Allyn Howlett, from the department of physiology and pharmacology at Wake Forest School of Medicine, in Winston-Salem, North Carolina, discovered, in rat brains, an exclusive receptor for THC, which wouldn't make sense unless the animals produced something similar intrinsically²³. A few years later, Professor Raphael Mechulam's group found this endogenous form of cannabinoid and named the molecule anandamide (*ananda* in Sanskrit means "full happiness") after three decades of studying phytocannabinoids. This discovery elucidated the functioning of the endocannabinoid system present in all vertebrates and fundamental to the homeostasis process in mammals².

Today, the medicinal use of cannabis is recognized in dozens of countries and new articles highlight the complexity of the endocannabinoid system, as well as its relevance to human health and well-being¹⁷. According to data from Google Scholar, in 2011 there were a total of 59 articles published with the title "medical cannabis"; in 2021, 379 articles were published, an increase of more than 320% in 10 years. However, much remains to be elucidated on this subject.

CONCLUSION

The medicinal use of cannabis has been described for almost 5,000 years, but scientific knowledge of the plant has not yet reached 80 years. The greatest advances were the elucidation of the endocannabinoid system with the discovery of CB receptors and endocannabinoids at the end of the last century. There is an undeniable need for more comprehensive and elaborate studies, but prejudice and the difficulty of accessing this therapeutic tool hinder this development.

AUTHORS' CONTRIBUTIONS

Pedro Antonio Pierro Neto

Data Collection, Project Management, Research, Writing - Preparation of the Original, Supervision

Luiz Marcelo Chiarotto Pierro

Conceptualization, Research, Writing - Review and Editing, Supervision

Sergio Tadeu Fernandes

Methodology, Writing - Review and Editing

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