History of Cannabis

The relationship between humans and cannabis reaches back into ancient times, with its centuries-long history having been well-documented by physicians, scholars, and explorers from all over the world. <u>Cultivated since ancient times</u> in both Asian and Europe, scientists believe that cannabis originated in Western and Central Asia¹.

Ancient Origins of Cannabis

Paleobotanical studies have indicated that cannabis was likely present as a wild plant approximately 11,700 years ago in Central Asia near the Altai Mountains². The discovery of a large cache of THC-dominant cannabis in a 2,700-year-old grave of a shaman in northwest China suggests that cannabis was likely cultivated for more than its utility as a fiber material by human civilization as early as 900 B.C. The tomb itself, combined with dry climate conditions and alkaline soil, kept the cannabis remarkably well-preserved. Close examination showed the shaman had been buried with two pounds of cannabis, and phytochemical analyses indicated that only female cannabis plants were included—more evidence that the ancient world had a longstanding link with cannabis as a psychoactive substance³.

¹ Kuddus, M., Ginawi, I.A.M., Al-Hazimi, A. *Cannabis sativa*: An ancient wild edible plant of India. Emir J Food Agric. 2013;25:736-745. https://doi.org/10.9755/ejfa.v25i10.16400

² Pisanti, S., & Bifulco, M. (2019). Medical Cannabis: A plurimillennial history of an evergreen. *Journal of cellular physiology*, 234(6), 8342–8351. https://doi.org/10.1002/jcp.27725

³ Russo, E. B., Jiang, H. E., Li, X., Sutton, A., Carboni, A., del Bianco, F., Mandolino, G., Potter, D. J., Zhao, Y. X., Bera, S., Zhang, Y. B., Lü, E. G., Ferguson, D. K., Hueber, F., Zhao, L. C., Liu, C. J., Wang, Y. F., & Li, C. S. (2008). Phytochemical and genetic analyses of ancient cannabis from Central Asia. *Journal of experimental botany*, *59*(15), 4171–4182. https://doi.org/10.1093/jxb/ern260

Ancient Cannabis as a Source of Fiber

The fast-growing cannabis plant has long been important as a source of <u>fiber material</u>; carbon dating has confirmed that cannabis was used as a textile material as far back as 4000 B.C. The ancient Greeks and Romans, as well as the ancient Chinese, used cannabis fibers for boat sails, rope, wickerwork, clothes, and paper. Cannabis seeds were also used for oil. It's generally accepted by scholars that cannabis was an everyday item in the ancient world⁴. Since then, the industrial uses of cannabis have expanded to include building materials (such as "hempcrete"), manufacturing, oil paints, solvents, fuel, soaps, shampoos, and cosmetics^{5,6}.

Ancient Cannabis as Medicine

Cannabis had a significant role as a pharmacological compound in the ancient world, specifically on the Eurasian landmass. Early historical records indicate that cannabis was used and grown in vastly distant parts of Eurasia from, with explorers and travelers carrying cannabis seeds with them as they traveled across the continent. In the various cultures that cannabis was brought to, it was commonly used to make materials such as rope and cloth, and also played a major role in ancient medicine. This dissemination of cannabis across the continent is further evidenced by the fact that the different words for cannabis in several languages are closely related: English *hemp* and German *hanf* are etymological relatives of the Latin *cannabis*, Italian *canapa*, Russian *konoplja*, and Turkish *kendir*⁷.

⁴ Sumler, A. (2021). Cannabis in the ancient greek and roman world. Lexington Books.

⁵ Li, H. (2008). An archaeological and historical account of cannabis in China. *Economic Botany*, 28, 437-448.

⁶ Russo E. (1998). Cannabis for migraine treatment: the once and future prescription? An historical and scientific review. *Pain*, 76(1-2), 3–8. https://doi.org/10.1016/s0304-3959(98)00033-5

⁷ Crocq M. A. (2020). History of cannabis and the endocannabinoid system *Dialogues in clinical neuroscience*, 22(3), 223–228. https://doi.org/10.31887/DCNS.2020.22.3/mcrocq

Cannabis in Ancient Asia

Some of the oldest records of cannabis use come from Asia. In India, it's likely that cannabis was used for medical and religious purposes sometime around 1000 B.C. The plant was used as an analgesic, anticonvulsant, hypnotic, tranquilizer, anesthetic, anti-inflammatory, antibiotic, antiparasitic, appetite stimulant, and more⁸.

Records of cannabis in China are found in the world's oldest pharmacopeia, a compendium of medical herbs. Known as the Pen-ts'ao Ching, it was compiled in the1st century A.D., based on oral information that had been passed down for centuries. Its contents are attributed to Shen Non (also referred to as Sheng-nung and meaning "Divine Farmer"), an ancient emperor who lived in 2700 B.C. The Pen-ts'ao Ching detailed the uses of cannabis to alleviate rheumatic pain, intestinal constipation, disorders of the female reproductive system, and others⁹.

Other extremely early mentions of cannabis in the historical record include in the Ebers Papyrus, a description of medical knowledge that was written in Egypt around 1500 B.C. and described the topical application of cannabis for inflammation. There are also mentions of cannabis seeds and cannabis-like plants used for depression and "delight" in Scythian and Assyrian culture^{10,11}.

⁸ Mikuriya T. H. (1969). Marijuana in medicine: past, present and future. *California medicine*, 110(1), 34–40.

⁹ Touw M. (1981). The religious and medicinal uses of Cannabis in China, India and Tibet. *Journal of psychoactive drugs*, *13*(1), 23–34. https://doi.org/10.1080/02791072.1981.10471447

¹⁰ Grotenhermen, F., Russo, E., & Fankhauser, M. (2002). History of cannabis in Western Medicine. In *Cannabis and cannabinoids: Pharmacology, toxicology, and therapeutic potential* (pp. 37–51). essay, Haworth Integrative Healing Press.

¹¹ Nahas, G. G., Nahas, G. G., & Brill, H. (1984). Cannabis intoxication and mental illness. In *Marihuana in science and medicine* (pp. 263–306). essay, Raven Press.

Cannabis in the Bible

Given that cannabis was such a widely known and used plant in ancient times, many scholars—including Dr. Raphael Mechoulam of the Hebrew University of Jerusalem, one of the foremost cannabis scholars in the world—are surprised there is no explicit mention of cannabis in the Old Testament. There are theories that some references to "anointing oil" and "plants of renown" could be a cloaked reference for cannabis. Another potential mention comes in the form of "pannag," an unidentified product mentioned by the prophet Ezekiel, which could be the original Hebrew etymology for the Sanskrit and Persian words for cannabis, "bhanga" and "bang," respectively¹².

Cannabis in Ancient Rome

Further west in the Roman Empire, the Greek physicians Pliny the Elder (23-79 A.D.), Pedanius Dioscorides (40-90 A.D.), and Claudius Galen (131-216 A.D.) described medical indications for cannabis. Pliny the Elder's *Naturalis Historia* is the oldest living encyclopedia from the Greco-Roman world and in it he described all the knowledge known at that time of the natural world in comprehensive detail. He detailed not only the cultivation of cannabis as a material for making ropes and nets but also discusses its medicinal uses. He indicated pain-relieving and anti-inflammatory properties that helped symptoms of gout, for example. Another Greek physician, Pedanius Dioscorides, wrote a five-volume textbook on pharmacology, *De Materia Medica*, that described cannabis's utility as a medicinal resource. In Volume III, Dioscorides made clear references to the cannabis plant and its uses in medicine:

¹² Mechoulam, R., Devane, W. A., Breuer, A., & Zahalka, J. (1991). A random walk through a cannabis field. *Pharmacology, biochemistry, and behavior*, 40(3), 461–464. https://doi.org/10.1016/0091-3057(91)90347-5

Kannabis; is a plant of much use in this life for the twisting of very strong ropes, it has leaves like to the Ash, of a bad scent, long stalks, empty, a round seed, which being eaten of reduces sexual activity, but being juiced when it is green is good for the pains of the ears¹³.

Less medically focused, though still a remarkable picture of cannabis's well-accepted role in ancient civilization, Galen wrote how it was customary to serve desserts made using cannabis in Italy^{7,14}.

The Rise and Fall of Cannabis in the United States and Europe

Cannabis eventually spread westward in the 16th century during the age of global exploration, migration, and trade, its uses in medicine, textiles, cosmetics, <u>cuisine</u>, and other industries rapidly expanding as more cultures and civilizations than ever before came into contact with each other and with the plant.

The Rise of Cannabis in Europe during the 19th and 20th Centuries

Standard pharmacological use of cannabis in the United States and Europe in the 1800s was largely catalyzed by the work of Dr. William Brooke O'Shaughnessy, a physician at the University of Edinburgh who moved to Calcutta, India, where he spent many years studying cannabis and its uses. He published his findings on cannabis safety and effects in 1839,

¹³ Freund, T. F., Katona, I., & Piomelli, D. (2003). Role of endogenous cannabinoids in synaptic signaling. *Physiological reviews*, 83(3), 1017–1066. https://doi.org/10.1152/physrev.00004.2003

¹⁴ Grinspoon, L. (1999). *Marihuana reconsidered*. Quick american archives.

describing the successes he encountered using cannabis preparations for rheumatism, convulsions, and muscular spasms resulting from tetanus and rabies⁶.

There were several notable advocates of cannabis use for medical ailments in the late 19th century, including Dr. Jacques-Joseph Moreau, a French psychiatrist who is credited with the first systematic study on drugs' effects on the central nervous system. In 1845, he wrote one of the most comprehensive descriptions of the acute effects of cannabis on the mind. Sir John Russell Reynolds was president of the British Medical Association and in 1878 was appointed the physician to the royal family¹⁵. It has been documented that, under the care of Dr. Reynolds, Queen Victoria took cannabis for painful menses¹⁶. But even with such influential support at the end of the 19th century, momentum for widespread acceptance and use of cannabis into the 20th century was eventually derailed by political factors in the United States and racial prejudices that associated cannabis use with low-income and minority populations.

Anti-Cannabis Sentiment in the United States during the 20th Century

In the 1930s, the Federal Bureau of Narcotics, led in large part by Harry J. Anslinger, attempted to associate cannabis use with psychosis, mental deterioration, addiction, and violent crimes based on misrepresentation and sensationalization of a handful of newspaper articles (that later proved to be false). In a radio address, Anslinger warned that young people "are slaves to this narcotic, continuing addiction until they deteriorate mentally, become insane, turn to violent crime and murder.¹⁷"

¹⁵ McGeeney B. E. (2013). Cannabinoids and hallucinogens for headache. *Headache*, *53*(3), 447–458. https://doi.org/10.1111/head.12025

¹⁶ Mechoulam, R. (1973). Marihuana: Chemistry, pharmacology, metabolism and clinical effects. Academic Press.

¹⁷ Hari, J. (2019). Chasing the scream: The search for the truth about addiction. Bloomsbury.

Historians have contended that this agenda was influenced by business leaders who held investments in industries that were threatened by hemp as a natural resource. Some have gone so far as to say that Anslinger and the Federal Bureau of Narcotics colluded with these private business owners to minimize competition from the hemp fiber industry against resources such as nylon and timber. In either case, this propaganda led to a significant shift in the political and social climate around cannabis, with far-reaching implications including the misclassification of cannabis as a narcotic and Congress's eventual passage of the Marihuana Tax Act of 1937, which was the first national regulation measure to tax and restrict the sale of marijuana¹⁸.

The American War on Cannabis

A few years later, cannabis was removed from the U.S. Pharmacopeia and the 1961 United Nations Single Convention on Narcotic Drugs placed cannabis in the same strict control category as heroin. Though much of this legislation was met by opposition from strong coalitions such as the American Medical Association, these determinations had a significant impact on the medical community's and public's perception of cannabis 19,20.

For the first half of the 20th century in the United States, cannabis was banned by the political powers and came to be associated with drugs of abuse. There was a resurgence in cannabis use during the anti-establishment countercultural phenomenon that characterized the 1960s and 1970s, although this increase was more related to the psychedelic counterculture movement than it was about the history of medicinal use that had existed for centuries. In 1970,

¹⁸ Peet, P. (2004). *Under the influence: The disinformation guide to drugs*. Disinformation Co.

¹⁹ Papaseit, E., Pérez-Mañá, C., Pérez-Acevedo, A. P., Hladun, O., Torres-Moreno, M. C., Muga, R., Torrens, M., & Farré, M. (2018). Cannabinoids: from pot to lab. *International journal of medical sciences*, 15(12), 1286–1295. https://doi.org/10.7150/ijms.27087

²⁰ Bonnie, R. J., & Whitebread, C. H. (1975). *The marihuana Conviction: A history of marihuana prohibition in the United States*. University of Virginia Press.

it was recommended that cannabis be classified as a Schedule I substance because of what the Assistant Secretary of Health at the time deemed "a considerable void in our knowledge of the plant and effects of the active drug contained in it²¹." Cannabis was officially classified as a Schedule I drug by President Richard Nixon in 1971 when he declared a "war on drugs"—and the restriction has remained since.

Ironically, this classification has made research on cannabis extremely difficult, leaving exploration of the potential therapeutic applications of cannabis at a standstill for decades despite the myriad benefits described throughout history, international research findings, and extensive anecdotal accounts. The Schedule I classifications blocks any federal funding for research, going so far as to make it illegal to proceed with any research in the United States, the necessary research that the initial classification said was missing.

The Discovery of the Endocannabinoid System

The chemical structure of THC was discovered and synthesized for the first time several decades later by Mechoulam²². In collaboration with his research partner of the time, Dr. Yehiel Gaoni, the two scientists were the first to identify and isolate the compound from the plant, suggesting THC as the primary psychoactive agent in cannabis. Mechoulam and his research group went on to synthesize not only THC but also several other cannabinoids, including cannabidiol (CBD) and cannabigerol (CBG).

²¹ Gupta, S. (2013, August 8). Why I changed my mind on weed. *CNN Health*. CNN. https://www.cnn.com/2013/08/08/health/gupta-changed-mind-marijuana/index.html.

²² Gaoni, Y., & Mechoulam, R. (1964). Isolation, structure, and PARTIAL synthesis of an active constituent of hashish. *Journal of the American Chemical Society*, 86(8), 1646–1647. https://doi.org/10.1021/ja01062a046

In 1985, the FDA approved the first cannabinoid drugs, dronabinol and nabilone, which were synthetic THC formulations that had been shown to be effective in treating the nausea and vomiting experienced by chemotherapy patients. A few years later in 1992, dronabinol was approved for use in patients suffering from HIV-associated anorexia.

The Discovery of Anandamide and Endogenous Cannabinoids

The next breakthrough in the biochemical understanding of cannabis came when, in 1992, Mechoulam, Dr. William Devane, and Dr. Lumír Ondřej Hanuš discovered the existence of a cannabinoid produced by the human brain that was analogous to cannabis-extracted cannabinoids, demonstrating another remarkable relationship between a cannabis compound and the mammalian brain. The research team named this endogenous cannabinoid anandamide (AEA), derived from the Sanskrit word, "ananda," meaning "eternal bliss" or "supreme joy."

Anandamide was the first endocannabinoid receptor ligand to be identified as an essential component of the mammalian endocannabinoid system (ECS). Its discovery, along with the identification of its derivatives, 2-arachidonoylglycerol (2-AG, the second endocannabinoid receptor ligand to be identified), and arachidonic acid furthered our understanding of this innate regulatory system of ligands, receptors, and non-cannabinoid players that are involved in a breadth of bodily functions including emotional regulation, homeostasis, pain, and sleep. The ECS's involvement in analgesia, cognition, memory, locomotion, appetite, emesis, and immune function have given rise to a significant increase in biomedical research (mostly in other countries than the United States) on the therapeutic potential of cannabis.

The Future of Cannabis

The legal status of cannabis (including so-called hemp, the nondrug fiber-type of cannabis plant that is <u>low in THC</u> and consequently high in other less psychoactive or nonpsychoactive cannabinoids) is still controversial. The United Nations still classifies cannabis, its resins, extracts, and tinctures as Schedule I and Schedule IV drugs; THC and its natural and synthetic variants are classified as psychotropic substances²³.

Medical Cannabis Around the World

Different countries treat the possession, consumption, manufacture, and sale of cannabis with varying severity. In the United States, states decide whether cannabis use is legal: medical cannabis use is widely accepted and legal in most states, and recreational use is legal in 19 states plus Washington, DC, and Guam²⁴. Each year, more states legalize recreational use. Medical and recreational use is becoming legal in countries including the Netherlands, Germany and Italy, although there are initiatives for approval in other countries. Currently, commercial availability of different cannabinoid drugs varies depending on the country^{25,26}.

On November 5, 1996, voters in California passed the Proposition 215, the Compassionate Use Act of 1996, the first law of its kind that allowed patients with a valid doctor's recommendation to possess and cultivate cannabis for personal medical use. After this law was passed in California, more states were emboldened to reconsider their own state laws

²³ Office of the Secretary-General, Commentary on the Single Convention on Narcotic Drugs (1961). United Nations Office on Drugs and Crime (UNDOC).

²⁴ Hansen, C., & Alas, H. (2021, June 30). Where is marijuana legal? A guide to marijuana legalization. *US News & World Report*.

²⁵ Center for Drug Evaluation and Research. (n.d.). *Drugs*. U.S. Food and Drug Administration. https://www.fda.gov/Drugs/.

²⁶ Dimitrova, EK. (2021, July 21). Epidyolex. European Medicines Agency. https://www.ema.europa.eu/en/medicines/human/EPAR/epidyolex.

and ask for input from residents and community leaders as to whether to stay aligned with federal laws, which many feel are outdated and discriminatory. Other states such as Alaska, Washington, and Oregon passed similar legislation in 1998, with Colorado, Hawaii, and Nevada passing their own laws that legalized medical use of cannabis in 2000. Montana, Vermont, New Mexico, and even our nation's capital enacted similar legislation for medicinal access to cannabis. As of July 2021, 36 of the country's states allow medicinal use of cannabis, with a clear trend of more states planning to place measures on the ballots in the coming year.

Several different cannabinoids have been investigated in preclinical studies over the past decade, with a number progressing to the advanced stages of clinical study. Companies engaged in active pharmaceutical research on cannabinoids include Echo Pharmaceuticals and GW Pharmaceuticals, the latter of which already has Epidiolex, a 98% CBD formulation that is approved by the FDA for treatment of seizure disorders included Lennox-Gastaut and Dravet syndromes and tuberous sclerosis²⁷.

The Liberation of Cannabis: Where Things Stand

The United States's history with cannabis is a narrative fraught with ups and downs. While many states have legalized recreational cannabis use (and the majority have legalized medical cannabis use), cannabis still faces obstacles to <u>rigorous scientific research</u>. In a scientific review of THC's effects on the human body, psychopharmacologist Dr. Elisaldo A Carlini put it succinctly:

²⁷ Perucca E. (2017). Cannabinoids in the Treatment of Epilepsy: Hard Evidence at Last? *Journal of epilepsy research*, 7(2), 61–76. https://doi.org/10.14581/jer.17012

Very few drugs, if any, have such a tangled history as [cannabis as] a medicine. In fact, prejudice, superstition, emotionalism, and even ideology have managed to lead cannabis to ups and downs concerning both its therapeutic properties and its toxicological and dependence-inducing effects²⁸.

Scientists Against Cannabis Prohibition

Perhaps the biggest obstacle to robust scientific research on cannabis has been its classification as a Schedule I drug (defined as "a drug with no medical use"), putting it in the same group as street drugs with high abuse potential such as heroin, quaaludes, lysergic acid diethylamide (LSD), and ecstasy. The U.S. Congress's decision from 50 years ago has engendered a federal climate that blocks access to cannabis.

One cannabis researcher, the physician Dr. Mark A. Ware, laments that cannabis research in the country occurs "under a paradigm of prohibition and the study of risk is not yet balanced by much-needed research on benefits.²⁹" The only federally authorized source of cannabis since 1968 has been a cultivar grown at the University of Mississippi expressly for research. Scientists can gain access to the federally approved cannabis oly by applying to the National Institute on Drug Abuse, which is reluctant to support medical research and has historically focused nearly all its efforts on demonstrating the drug's harmful effects. Many scientists say the federally

²⁸ Carlini E. A. (2004). The good and the bad effects of (-) trans-delta-9-tetrahydrocannabinol (Delta 9-THC) on humans. *Toxicon: official journal of the International Society on Toxinology*, *44*(4), 461–467. https://doi.org/10.1016/j.toxicon.2004.05.009

²⁹ Ware M. A. (2007). Is there a role for marijuana in medical practice? Yes. *Canadian family physician Medecin de famille canadien*, *53*(1), 22–25.

approved cannabis is out of date (low in THC content) and in poor condition (moldy on arrival, or with sticks and stones in it), unlike what is commercially available now³⁰.

But cannabis's categorization by the FDA seems out of place, considering the types of drugs that are found in Schedule II, the category that includes drugs with high potentials for abuse but which are currently accepted for medical use. Schedule II drugs include medically relevant drugs such as morphine, so it's clear that there is a precedent for potential drugs of abuse with Schedule II status that also possess medical benefits. These substances are made readily available for laboratory scrutiny, and the medically active molecules from Schedule II substances are isolated and purified for even further medical benefit and research. Schedule II drugs benefit from a huge body of past and ongoing research that sets the stage for better understanding as well as better applications for patients, oftentimes while reducing the potential for misuse by patients.

The public's <u>wide support</u> and use of botanical cannabis should align with a research-driven body of scientific knowledge. But that patient-centered approach to science and medicine can't become a reality until federal prohibitions on research are lifted.

Professional groups urging the federal government to reconsider its stance include the American Medical Association, the country's largest association of physicians. Such statements help immensely as a boon to the cultural, political, scientific, and social confidence in cannabis's potential for benefit in medicine.

³⁰ Hellerman, C. (2017, March 8). *Scientists say the government's only pot farm has moldy samples - and no federal testing standards*. Public Broadcasting Service (PBS). https://www.pbs.org/newshour/nation/scientists-say-governments-pot-farm-moldy-samples-no-guidelines.