Cannabis for pain management: Pariah or panacea?

Historical perspectives and pharmacological mechanisms

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ABSTRACT

Cannabis has been used in a medicinal context throughout recorded history and across diverse cultures to aid in the treatment of a wide array of ailments. Remarkably, clinical and preclinical investigations are only recently beginning to reveal the neurobiological mechanisms responsible for the clinically-relevant actions of cannabis that have been acknowledged by medical pharmacopeia for millennia. The therapeutic potential of cannabis-derived phytochemicals such as delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are currently being explored in several contexts. Experimental evidence suggests that modulation of signal transduction pathways underlying cellular excitability, as well as interactions with the endocannabinoid and serotonin systems, which modulate emotion and pain sensitivity under physiological conditions, are among the mechanisms responsible for its clinical efficacy. Interestingly, the diverse pharmacodynamic profile of CBD suggests a synergistic interaction with current first- and second-line medications used in the treatment of neuropathic pain to produce clinically meaningful therapeutic benefits. To advance understanding of the neurobiological mechanisms underlying therapeutic cannabis use in pain management and to integrate its use into modern clinical practices, it is important to understand medicinal cannabis use in historic and medical contexts. This review highlights the copious history of medical practices incorporating the use of cannabis, and discusses the potential pharmacological mechanisms responsible for its therapeutic efficacy in the management of neuropathic pain.

INTRODUCTION

For as long as humans have experienced pain, there have been efforts to identify its causes and to relieve suffering through the use of ritualistic or herbal remedies.¹ In early human history, available treatments for pain were trifling, and included trepanning and ritualistic healing ceremonies.¹ As collective understanding of pain progressed, the use of plant-derived extracts from the willow bark tree, opium poppy, and cannabis plant became common.²⁻⁴ In modern times, a comprehensive understanding of pain neurobiology and its various molecular and psychophysiological underpinnings are contributing to increasingly innovative and individualized therapies for those suffering from chronic pain and neuropathy.⁵ Advancements and discoveries within these areas have aided in the renaissance of cannabis as a pharmacotherapy for pain management, and stimulated research into the biological mechanisms underlying

the therapeutic qualities of specific compounds derived from cannabis, also known as phytocannabinoids.⁶⁻⁸

Although cannabis has been used in various forms for millennia to aid in the treatment of an abundance of ailments, it is only relatively recently that we have begun to understand the phytochemical complexities differentiating cannabis plant strains, and the pharmacological mechanisms responsible for their therapeutic effects.^{4,7-9} The primary non-intoxicating phytocannabinoid in cannabis, cannabidiol (CBD), was initially isolated in 1940, but its pharmacology and therapeutic benefits were unknown until decades later.¹⁰⁻¹¹ In contrast, the primary psychotropic compound in cannabis, delta-9-tetrahydrocannabinol (THC), was first isolated in 1964, and has remained the subject of the majority of cannabis-related scientific research.¹² Insight into these chief phytocannabinoids within cannabis prompted subsequent research into the pharmacological mechanisms through which THC and CBD act, and led to the more recent discovery of the body's own cannabis-like receptor system, the endocannabinoid system (ECS).¹³⁻¹⁶ Recent preclinical and clinical evidence suggests that the ECS plays an important role in modulating pain sensitivity under physiological conditions. This review highlights the copious history of medical practices incorporating the use of cannabis, and discusses the potential pharmacological mechanisms responsible for its therapeutic efficacy in the management of neuropathic pain.

BRIEF HISTORY OF CANNABIS USE IN PAIN MANAGEMENT

Extensive dialogue among physicians and researchers currently exists surrounding the recreational and medicinal use of cannabis and its various phytochemical derivatives. An often overlooked but critical source of information that may contribute to this exchange is the historical documentation from nearly 5000 years of human cannabis use in medicinal contexts.^{4,9} The utilization of cannabis seeds, leaves, tinctures and extracts have been identified across the globe, from ancient through to contemporary civilizations, and for numerous ailments that strikingly resemble the bases for its use in modern medicine.^{4,18}

The earliest recorded evidence of medicinal cannabis use is documented in the ancient Chinese pharmacopeia 'Shennong Bencaojing' (Figure 1).¹⁹ It depicts the use of all parts of the cannabis plant including the seeds, leaves, female flowering heads, and stalks for over 100 ailments, including chronic rheumatic and gastrointestinal pains, inflammation, epilepsy, and acceleration of wound healing.²⁰ The founder of Chinese surgery, Hua Tuo (140-208 AD) was renowned amongst generations of Chinese physicians who studied the Shennong Bencaojing, and championed cannabis as a potent analgesic.²¹ He was also the first to recognize its

anaesthetic qualities, and administered a boiled cannabis powder preparation laced with wine to patients prior to surgery.²² Notably, the prehistoric cultivation of cannabis, coupled with its extensive therapeutic applications and a large body of untranslated medical literature suggest the Chinese historical account to be a particularly rich source of practical information.²³

Cannabis use in ancient Egyptian medicine has been recorded in dynastic medical papyri since the Old Kingdom, and is among the earliest civilizations to utilize cannabis plant parts in medical treatments. Early indications that cannabis was prescribed medicinally in ancient Egypt are contained in the papyrus Ramesseum III, dated to 1700 BCE, and reference its application for the treatment of abscesses and inflammation of the eyes, a potential parallel to the modern equivalent of cannabis for the treatment of glaucoma.^{4,24} Physicians of the time showed meticulous understanding of the diverse pharmacological qualities of cannabis, as the anti-inflammatory, analgesic, antiemetic, and insecticidal properties of cannabis were illustrated in several ancient papyri dating back to 1550 BCE.^{25,26}

Cannabis is also well-documented throughout history as a critical component of ancient Indian, Greek and Arab medical practices dating back as early as 1000 BCE (Figure 1).⁹ Overwhelming evidence indicates that these groups were aware of its anti-inflammatory, analgesic, and sedative properties as it was often used for the relief of headaches, edema, fever, insomnia, dysentery and a variety of other gastrointestinal issues.^{27,28} Despite comparable exploitation of the anti-inflammatory and analgesic effects of cannabis throughout human history and across cultures, these and other medical applications were entirely unknown to Western medicine until the mid 1800s AD.

While employed as a member of the Medical and Physical Society of Calcutta in India in 1836 AD, the Irish physician Dr William O'Shaughnessy validated various folk claims and subjective reports on the therapeutic value of cannabis through experimentation.¹⁸ Dr O'Shaughnessy discovered multiple new applications for cannabis, and ultimately recommended its use for an array of therapeutic purposes.^{30,31} Through the administration of component extracts and tinctures, he effectively relieved tetanus-induced spasticity, reduced pain and suffering provoked by rheumatism, and calmed convulsions in children caused by epilepsy.³⁰⁻³¹ Following his seminal publication on the medical applications of cannabis in 1839 entitled 'On the preparations of Indian hemp, or gunjah', the availability of cannabis extracts in over-the-counter medications, as well as its use in Western medicine increased rapidly.³⁰ By 1850, cannabis extract had entered the United States Pharmacopeia and was listed as a treatment for nearly 100 afflictions, including acute or chronic pain, opiate addiction, and convulsive disorders, and was readily available in over-the-counter formulations.^{21,31-32} However, following the development of analgesics such as synthetic opiates in the mid 19th century, which were viewed as a substitute therapy to wean patients off of opium, as well as chloral hydrate and non-steroidal anti-inflammatory drugs (NSAIDS) in the early 20th century, the prevalence of cannabis as a medicine and its

necessity as an analgesic and adjunctive therapy in addiction began to decline.⁹ In recent years, experimental evidence has started to reveal the pharmacological mechanisms through which cannabis exerts its therapeutic effects. In fact, the precise mechanisms of action largely substantiate claims made to the therapeutic qualities of cannabis throughout recorded history.^{18,24}

Figure 1. Select chronological history of the use of medical cannabis in various cultures throughout human history

POTENTIAL PHARMACOLOGICAL MECHANISMS OF CANNABIS IN PAIN MANAGEMENT

Pain is an evolutionarily conserved and highly complex process regulated by diverse psychophysiological mechanisms in the nervous system at the molecular and cellular scales.³³ In particular, neuropathic pain is often treatment-resistant and idiopathic, thus presenting a major issue for physicians seeking to relieve patients' suffering.³⁴ Compounds that activate the ECS, including cannabis and specific phytocannabinoids, are currently being investigated as independent and adjunct pharmacotherapies to treat persistent neuropathic pain.³⁵ The ECS is centrally active in regions regulating pain including the periaqueductal gray (PAG) and rostral ventromedial medulla (RVM), and its activation inversely regulates cellular processes related to pain transmission, such as neuronal hyper-excitability.^{36,37}

Neuropathic pain is a chronic pain syndrome associated with drug-induced, traumatic, or disease-induced damage of nerve fibers involved in the transmission of pain.³⁴ It can originate from a large number of ailments, and affects nearly 3% of the population worldwide, including roughly 900,000 Canadians. Phytocannabinoids such as THC and CBD have received a large amount of attention in the context of pain management due to their interactions with nociceptive transmitters and numerous neurotransmitter systems, including the endocannabinoid and serotonin systems.³⁸

By activating ECS receptors, endogenous cannabinoids contribute to the body's natural ability to relieve pain and reduce inflammation.³⁹ Upon activation of ECS receptors, intracellular potassium efflux increases while calcium and sodium influx decrease, thus contributing to a reduction in neuronal hyper-excitability.³⁶ In terms of phytocannabinoids, THC is a potent partial agonist of the Cannabinoid type 1 Receptor (CB1R),³⁸ but its therapeutic range is restricted by its intoxicating qualities. In contrast, CBD does not directly interact with CB1Rs, and produces no intoxicating effects, but instead increases endogenous cannabinoid signaling, and up-regulates CB1Rs following chronic administration.^{11,40-41} Furthermore, the pharmacodynamic profile of CBD resembles those of many currently prescribed treatments for neuropathic pain. CBD is an agonist of the serotonin (5-HT) 1A receptor, a negative allosteric modulator of mu and delta opioid receptors, and a positive allosteric modulator of GABA-A receptors.⁴²⁻⁴⁴ Thus, the hypothesis that CBD may work in synergy with current first- and second-line medications including selective 5-HT reuptake inhibitors, synthetic opiates, or anti-epileptic medications is in line with theoretically predicted synergistic drug interactions.^{45,46}

CONCLUSIONS

Modern clinical and preclinical investigations are just recently beginning to reveal the neurobiological mechanisms responsible for the clinically-relevant actions of specific phytocannabinoids, many of which have been acknowledged by medical pharmacopeia for nearly 5000 years. Despite the medicinal use of cannabis since

antiquity, research revealing the clinical efficacy for medicinal cannabis in a variety of contexts is still in its infancy with much to be explored. Increasing understanding of the biological processes underlying pain, including neuronal hyperexcitability and the influence of innate inflammatory responses have shed light on how the endocannabinoid system and various phytocannabinoids interact with and modulate these organic systems. Further research is needed to clarify the distinct clinical voids that cannabis and its specific phytocannabinoids such as THC and CBD fill, either alone or in adjunct with other pharmacotherapies. Thus, for now, historical indices of medicinal cannabis use may be some of the richest sources of knowledge still yet to be fully explored.

REFERENCES

1. Chen J. History of pain theories. *Neuroscience bulletin*. 2011 Oct 1;27(5): 343-50.
2. Hedner T, Everts B. The early clinical history of salicylates in rheumatology and pain. *Clinical rheumatology*. 1998 Jan 31;17(1):17-25.
3. Brownstein MJ. A brief history of opiates, opioid peptides, and opioid receptors. *Proceedings of the National Academy of Sciences*. 1993 Jun 15;90(12):5391-3.
4. Russo EB. History of cannabis and its preparations in saga, science, and sobriquet. *Chemistry & biodiversity*. 2007 Aug 1;4(8):1614-48.
5. Gatchel RJ, Peng YB, Peters ML, *et al*. The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychological bulletin*. 2007 Jul;133(4):581.
6. Sessa B. The 21st century psychedelic renaissance: heroic steps forward on the back of an elephant. *Psychopharmacology*. 2017 Aug 23:1-0.
7. Hudson R, Rushlow W, Laviolette SR. Phytocannabinoids modulate emotional memory processing through interactions with the ventral hippocampus and mesolimbic dopamine system: implications for neuropsychiatric pathology. *Psychopharmacology*. 2017 Oct 24:1-10.
8. Renard J, Rosen LG, Loureiro M, *et al*. Adolescent cannabinoid exposure induces a persistent sub-cortical hyper-dopaminergic state and associated molecular adaptations in the prefrontal cortex. *Cerebral Cortex*. 2016 Jan 1:bhv335.
9. Hand A, Blake A, Kerrigan P, *et al*. *Pain Manage* 2016;9(4):387-394
10. Adams R, Pease DC, Clark JH. Isolation of cannabinol, cannabidiol and quebrachitol from red oil of Minnesota wild hemp. *Journal of the American Chemical Society*. 1940 Aug;62(8):2194-6.
11. Mechoulam R (1970) Marijuana chemistry. *Science* 168:1159-1163
12. Gaoni Y, Mechoulam R. Isolation, structure, and partial synthesis of an active constituent of hashish. *Journal of the American chemical society*. 1964 Apr;86(8):1646-7.
13. Devane WA, Dysarz F3, Johnson MR, Melvin LS, Howlett AC. Determination and characterization of a cannabinoid receptor in rat brain. *Molecular pharmacology*. 1988 Nov 1;34(5):605-13.
14. Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature*. 1990 Aug 9;346(6284):561-4.
15. Griffin G, Gibson D, Mandelbaum A, Etinger A, Mechoulam R. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science*. 1992 Dec;258:18.
16. Kaminski NE, Abood ME, Kessler FK, *et al*. Identification of a functionally relevant cannabinoid receptor on mouse spleen cells that is involved in cannabinoid-mediated immune modulation. *Molecular*

- Pharmacology. 1992 Nov 1;42(5):736-42.
17. Walker JM, Huang SM, Strangman NM, *et al.* Pain modulation by release of the endogenous cannabinoid anandamide. *Proceedings of the National Academy of Sciences.* 1999 Oct 12;96(21):12198-203.
 18. National Academies of Sciences, Engineering, and Medicine. The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research. National Academies Press; 2017 May 1.
 19. Zuardi AW. History of cannabis as a medicine: a review. *Revista Brasileira de Psiquiatria.* 2006 Jun;28(2):153-7.
 20. Joy J, Mack A. Marijuana as medicine?: the science beyond the controversy. National Academies Press; 2000 Dec 30.
 21. Mikuriya TH. Marijuana in medicine: past, present and future. *California medicine.* 1969 Jan;110(1):34.
 22. Li, H. L. 1974. An archaeological and historical account of Cannabis in China. *Econ. Bot.* 28(4): 437-448
 23. Brand EJ, Zhao Z. Cannabis in Chinese medicine: Are some traditional indications referenced in ancient literature related to cannabinoids?. *Frontiers in Pharmacology.* 2017;8.
 24. Fleming MP, Clarke RC. Physical evidence for the antiquity of Cannabis sativa L. *Journal of the International Hemp Association.* 1998;5(2):80-95.
 25. Balabanova S, Parsche S, Pirsig W. First identification of drugs in Egyptian mummies. *Naturwissenschaften.* 1992 Aug 1;79(8):358-.
 26. Manniche, L. (n.d.). *An Ancient Egyptian Herbal* (1989). First University of Texas Press Edition.
 27. Butrica JL. The medical use of cannabis among the Greeks and Romans. *Journal of Cannabis Therapeutics.* 2002 Jun 1;2(2):51-70.
 28. Lozano I. The therapeutic use of Cannabis sativa (L.) in Arabic medicine. *Journal of Cannabis Therapeutics.* 2001 Jan 1;1(1):63-70.
 29. Touw M. The religious and medicinal uses of Cannabis in China, India and Tibet. *Journal of psychoactive drugs.* 1981 Jan 1;13(1):23-34.
 30. O'Shaughnessy WB. On the preparations of the Indian Hemp, or Gunjah: Cannabis indica their effects on the animal system in health, and their utility in the treatment of tetanus and other convulsive diseases. *Provincial Medical Journal and Retrospect of the Medical Sciences.* 1843 Feb 4;5(123):363.
 31. Brecher EM. *Licit and illicit drugs.* Boston: Little, Brown; 1972.
 32. Reynolds JR. On the therapeutical uses and toxic effects of cannabis indica. *The Lancet.* 1890 Mar 22;135(3473):637-8.
 33. Pace MC, Mazzariello L, Passavanti MB, *et al.* Neurobiology of pain. *Journal of cellular physiology.* 2006 Oct 1;209(1):8-12.
 34. Dworkin RH, Backonja M, Rowbotham MC, *et al.* Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. *Archives of neurology.* 2003 Nov 1;60(11):1524-34.
 35. Herzberg U, Eliav E, Bennett GJ, *et al.* The analgesic effects of R (+)-WIN 55,212-2 mesylate, a high affinity cannabinoid agonist, in a rat model of neuropathic pain. *Neuroscience letters.* 1997 Jan 17;221(2):157-60.
 36. Lynch ME. Preclinical science regarding cannabinoids as analgesics: an overview. *Pain Research and Management.* 2005;10(Suppl A):7A-14A.
 37. Hains BC, Saab CY, Waxman SG. Changes in electrophysiological properties and sodium channel Nav1.3 expression in thalamic neurons after spinal cord injury. *Brain.* 2005 Aug 18;128(10):2359-71.
 38. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Δ^9 -tetrahydrocannabinol, cannabidiol and Δ^9 -tetrahydrocannabivarin. *British journal of pharmacology.* 2008 Jan 1;153(2):199-215.
 39. Walker JM, Huang SM, Strangman NM, *et al.* Pain modulation by release of the endogenous cannabinoid anandamide. *Proceedings of the National Academy of Sciences.* 1999 Oct 12;96(21):12198-203.
 40. Leweke FM, Piomelli D, Pahlisch F, *et al.* Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Translational psychiatry.* 2012 Mar 1;2(3):e94.
 41. Hayakawa K, Mishima K, Hazekawa M, *et al.* Cannabidiol potentiates pharmacological effects of Δ^9 -tetrahydrocannabinol via CB1 receptor-dependent mechanism. *Brain research.* 2008 Jan 10;1188:157-64.
 42. Russo EB, Burnett A, Hall B, *et al.* Agonistic properties of cannabidiol at 5-HT1a receptors. *Neurochemical research.* 2005 Aug 1;30(8):1037-43.
 43. Kathmann M, Flau K, Redmer A, *et al.* Cannabidiol is an allosteric modulator at mu- and delta-opioid receptors. *Naunyn-Schmiedeberg's archives of pharmacology.* 2006 Feb 1;372(5):354-61.
 44. Bakas T, van Nieuwenhuijzen PS, Devenish SO, *et al.* The direct actions of cannabidiol and 2-arachidonoyl glycerol at GABA A receptors. *Pharmacological research.* 2017 May 31;119:358-70.
 45. Moulin DE, Clark AJ, Gilron I, *et al.* Pharmacological management of chronic neuropathic pain—consensus statement and guidelines from the Canadian Pain Society. *Pain Research and Management.* 2007;12(1):13-21.
 46. Prud'homme M, Cata R, Jutras-Aswad D. Cannabidiol as an intervention for addictive behaviors: a systematic review of the evidence. *Substance abuse: research and treatment.* 2015;9:33.