

Cannabis: from plant condemned by prejudice to one of the greatest therapeutic options of the century

Adriana F. Grosso¹



¹Especialista em Pesquisa Clínica e Medical Affairs pela Santa Casa de SP
Doutora em Cardiologia pelo Incor FMUSP

Corresponding author

adriana.grosso@hempmedsbr.com

Manuscript received: September 2019

Manuscript accepted: February 2020

Version of record online: March 2020

Abstract

Background: Cannabis sativa has a fascinating history and has been used by mankind for millennia. Many societies such as Greek, Roman, Chinese, African, Indian and Arabic take advantage of the plant's qualities, which are consumed as food, medicine, fuel, fibers or tobacco. The first reference found related to the therapeutic use of the plant data from 2700 B.C. and is present in the pharmacopoeia of the Chinese Emperor Shen-Nung, where this plant was recommended in the treatment of malaria, rheumatic pain, in irregular and painful menstrual cycles. The book "De Matéria Médica", written by the doctor Pedânio Dioscórides considered the founder of pharmacology, exposes Cannabis as one of the natural substances that can relieve inflammatory pain. In Brazil, African slaves brought a cannabis during the colonial period, around 1549. Then, its use spread quickly among black slaves and Indians, who started to cultivate it. Once the plant was popularized among French intellectuals and English doctors in the Indian imperial army, it started to be considered in our country as an excellent medicine for men, until it was suppressed by the police authorities in the 1930s. Only 60 years later important findings were highlighted around Cannabis with the System Endocannabinoid and its receptors, neurotransmitters such as anandamide and 2-AG, revolutionizing the understanding of molecular signaling that modulates pain and analgesia, inflammation, appetite, gastrointestinal motility and sleep cycles, immune cell activity and hormones among others. We are in front of a huge revolution in the therapeutic area, in which phytocannabinoids represent one of the great therapeutic options of the century. We need a widespread disclosure that CBD is not marijuana and that its use for recreational purpose has nothing to do with the use of medical cannabis. Scientific research is seriously committed to the use of the substance in various pathologies. The role of information is absolute, being the main tool to clarify a society.

Keywords: Cannabis sativa, cannabinoids, Endocannabinoid System, CBD, therapeutic option.

Suggested citation: Grosso AF. Cannabis: from plant condemned by prejudice to one of the greatest therapeutic options of the century. *J Hum Growth Dev.* 2020; 30(1):94-97. DOI: <http://doi.org/10.7322/jhgd.v30.9977>

Authors summary

Why was this study done?

To report a c

What did the researchers do and find?

T

What do these findings mean?

Th

INTRODUCTION

Cannabis sativa, the scientific name of the most discussed herbaceous plant in the media today has a fascinating history and has been used by humanity for millennia. The plant is present in the evolution of human civilization being used by men as a source of fibers for garments by the Chinese and Greeks and in cordage by the Romans. Other societies such as Africans, Indians and Arabs also took advantage of the plant's qualities, whether it was consumed as food, medicine, fuel, fibers or tobacco. Between 1000 BC and the mid-19th century, marijuana and hemp produced most paper, fuel and textile articles. Its great historical importance is due to the fact that hemp has a more resistant and stronger natural fiber than all the others, and can be grown in almost any type of soil^{1,2}.

The first reference found regarding the therapeutic use of the plant dates back to 2700 BC and is present in the pharmacopoeia of the Chinese Emperor Shen-Nung, where this plant was recommended in the treatment of malaria, rheumatic pain, irregular and painful menstrual cycles. The book "De Matéria Médica", written by the doctor Pedânio Dioscórides³ - considered the founder of pharmacology, brings *Cannabis* as one of the natural substances that can relieve pain. In the work, the plant is attributed to the improvement of joint pain and inflammation. From the 1st century to the 18th century, the book became a reference on the theme.

In Brazil, it is estimated that *Cannabis* was brought by African slaves in the colonial period, around 1549. Then, its use spread rapidly among black slaves and Indians, who started to cultivate it. Due to the popularization of the plant among French intellectuals and English doctors of the imperial army of India, it started to be considered in our country as an excellent medicine for many ills⁴. It was in the 1930s that the repression of marijuana use gained strength in Brazil, although it remained cited in medical textbooks and its recognized therapeutic properties⁴.

Until the late 1980s, quotes about *Cannabis* remained in the most esoteric field involving a small number of scientists in the United States and other countries. A few surveys were subsidized by the American National Institute on Drug Abuse (NIDA), which intended to prove the deleterious effects of *Cannabis* while blocking investigations into its potential benefits. It was then that a series of discoveries about the functioning of the human brain occurred. In the two decades following the identification and synthesis of Tetrahydrocannabinol (THC) by Mechoulam and his colleague Y. Gaoni in Israel in 1964⁵, scientists learned a lot about the pharmacology, biochemistry and clinical effects of *Cannabis*. This was

followed by discoveries of receptors in the central nervous system (CNS) where opioid substances (such as morphine and heroin) bound, the abundant cannabinoid receptors (CB1 and CB2) were found throughout the body and their locations were mapped in brain tissue until its genetic cloning, facilitating the discovery of agonist and antagonist substances that could "turn on" and "turn off" activities in certain brain regions⁶⁻¹⁰.

In the 1990s, Mechoulam and his collaborators¹¹ described the first neurotransmitter whose The molecule was very similar to THC and was associated with receptors where THC itself bound. This molecule was called anandamide (a word that, in Sanskrit, means "happiness"). Years later, the discovery of the second molecule, 2-arachidonoylglycerol, or "2-AG", whose interaction occurs between the cannabinoid receptors CB1 and CB2¹¹.

In tracing the metabolic pathways of THC, the scientists identified a molecular signaling scheme involved in the regulation of a wide range of biological functions, which was called the Endocannabinoid System, in reference to the plant that led to its discovery. This system with specific receptors and neurotransmitters has been identified in countless species of earthworms, leeches, fish, reptiles, amphibians, mammals, including man, supposedly a signal system so old in evolutionary history that it should serve important and basic functions in physiology. Today it is known that the signaling generated by the association between a receptor and a cannabinoid substance is capable of modulating pain and analgesia, inflammation, appetite, gastrointestinal motility and sleep cycles, together with the activity of immune cells, hormones and other neurotransmitters that alter mood, such as serotonin, dopamine and glutamate. CB1 and CB2 receptors are able to recognize and respond to three types of cannabinoid agonists: endogenous fatty acid cannabinoids; phytocannabinoids concentrated in the oily resin of the buds and leaves of the marijuana plant and synthetic cannabinoids marketed as medicines^{10,11}.

Failure in the Endocannabinoid System activity leads to major diseases, so current attention is focused on *Cannabis* products rich in Cannabidiol (CBD) with or without THC^{12,13}.

CBD is the main non-psychoactive component of *Cannabis sativa* and has attracted interest for its therapeutic potential in several disease states investigated in animal and human models¹⁴⁻¹⁶. It has anxiolytic, antidepressant, antipsychotic, anticonvulsant, anti-nausea, antioxidant, anti-inflammatory, antiarthritic and antineoplastic properties. Within the CNS, CBD is protective in animal

models of epilepsy, anxiety, psychosis and diseases of the basal ganglia, such as Parkinson's and Huntington's diseases¹⁷⁻²². CBD does not cause the classic CB1 mediated "tetrad" of hypolocomotion, analgesia, catalepsy and hypothermia, according to its low affinity for CB1 receptors.

The release of cannabis-based products for medicinal purposes in Brazil and in other countries occurs at a time of accentuation of conservatism in the country. Even so, this can be considered the first step towards expanding the uses of Cannabis. We need widespread disclosure that CBD is not marijuana and that recreational use of marijuana has nothing to do with the use of medical cannabis, that scientific research is seriously committed

to establishing the substance's effectiveness in various pathologies, including tumors. Medical cannabis can be used in several neuropsychiatric disorders such as anxiety and depression, as it works by increasing the production of neurotransmitters. This is the main focus of current studies.

The role of information is absolute and constitutes the main tool for clarifying society. Knowing the products derived from cannabis, differentiating CBD, which is not psychoactive from THC, which, as we have seen, also has therapeutic effects and high concentration in marijuana, unlike other varieties of the plant such as hemp. Only with the dissemination of the press, scientists and doctors, this information can reach the population as a whole.

■ REFERENCES

1. Ren M, Tang Z, Wu X, Spengler R, Jiang H, Yang Y, et al. The origins of cannabis smoking: Chemical residue evidence from the first millennium BCE in the Pamirs. *Sci Adv.* 2019;5(6):1391. DOI: <http://doi.org/10.1126/sciadv.aaw1391>
2. Serviço de Intervenção nos Comportamentos Aditivos e nas Dependências (SICAD). Serviços de Monitorização e Informação. Relatório Anual 2016: a situação do país em matéria de drogas e toxicodependências. Divisão de Estatística e Investigação, 2017.
3. Riddle JM. Dioscorides on Pharmacy and Medicine. Austin: University of Texas Press, 1985.
4. Carlini EA. A história da maconha no Brasil. *J Bras Psiquiatr.* 2006;55(4): 314-17. DOI: <http://doi.org/10.1590/S0047-20852006000400008>
5. Gaoni Y, Mechoulam R. Isolation, Structure, and Partial Synthesis of an Active Constituent of Hashish. *J Am Chem Soc.* 1964;86(8):1646-7. DOI: <https://doi.org/10.1021/ja01062a046>
6. Hassanzadeh P. Discovery of the endocannabinoid system: a breakthrough in neuroscience. *Arch Neurosci.* 2014;1(3):e15030. DOI: <https://doi.org/10.5812/archneurosci.15030>
7. Fonseca FR, Del Arco I, Bermudez-Silva FJ, Bilbao A, Cippitelli A, Navarro M. The endocannabinoid system: physiology and pharmacology. *Alcohol Alcohol.* 2005;40(1):2-14. DOI: <https://doi.org/10.1093/alcalc/agh110>
8. Heifets BD, Castillo PE. Endocannabinoid Signaling and Long-Term Synaptic Plasticity. *Annu Rev Physiol.* 2009;71:283-306. DOI: <https://doi.org/10.1146/annurev.physiol.010908.163149>
9. Castillo PE, Younts TJ, Chávez AE, Hashimoto Y. Endocannabinoid signaling and synaptic function. *Neuron.* 2012;76(1):70-81. DOI: <https://doi.org/10.1016/j.neuron.2012.09.020>
10. Ligresti A, Petrocellis L, Di Marzo V. From Phytocannabinoids to Cannabinoid Receptors and Endocannabinoids: Pleiotropic Physiological and Pathological Roles Through Complex Pharmacology. *Physiol Rev.* 2016;96(4):1593-659. DOI: <https://doi.org/10.1152/physrev.00002.2016>
11. Lee MA. The Discovery of the Endocannabinoid System. [cited 2020 Feb 20] Available from: <https://www.beyondthc.com/wp-content/uploads/2012/07/eCB-SystemLee.pdf>
12. Russo EB. Clinical Endocannabinoid Deficiency Reconsidered: Current Research Supports the Theory in Migraine, Fibromyalgia, Irritable Bowel, and Other Treatment-Resistant Syndromes. *Cannabis Cannabinoid Res.* 2016;1(1):154-65. DOI: <https://doi.org/10.1089/can.2016.0009>
13. Smith SC, Wagner MS. Clinical endocannabinoid deficiency (CECD) revisited: can this concept explain the therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions? *Neuro Endocrinol Lett.* 2014;35(3):198-201.
14. Black N, Stockings E, Campbell G, Tran LT, Zagic D, Hall WD, et al. Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis. *Lancet Psychiatry.* 2019;6(12): 995-1010. DOI: [https://doi.org/10.1016/S2215-0366\(19\)30401-8](https://doi.org/10.1016/S2215-0366(19)30401-8)
15. Allan GM, Finley CR, Ton J, Perry D, Ramji J, Crawford K, et al. Systematic review of systematic reviews for medical cannabinoids: Pain, nausea and vomiting, spasticity, and harms. *Can Fam Physician.* 2018;64(2):e78-94.
16. Armour M, Sinclair J, Chalmers KJ, Smith CA. Self-management strategies amongst Australian women with endometriosis: a national online survey. *BMC Complement Altern Med.* 2019;19(1):17. DOI: <https://doi.org/10.1186/s12906-019-2431-x>

17. Agarwal R, Burke SL, Maddux M. Current state of evidence of cannabis utilization for treatment of autism spectrum disorders. *BMC Psychiatry*. 2019;19 (328). DOI: <https://doi.org/10.1186/s12888-019-2259-4>
18. Capasso R, Borrelli F, Aviello G, Romano B, Scalisi C, Capasso F, et al. Cannabidiol, extracted from *Cannabis sativa*, selectively inhibits inflammatory hypermotility in mice. *Br J Pharmacol*. 2008;154(5):1001-8. DOI: <https://doi.org/10.1038/bjp.2008.177>
19. Iuvone T, Esposito G, De Filippis D, Scuderi C, Steardo L. Cannabidiol: a promising drug for neurodegenerative disorders?. *CNS Neurosci Ther*. 2009;15(1):65-75. DOI: <https://doi.org/10.1111/j.1755-5949.2008.00065.x>
20. Fernández-Ruiz J, Sagredo O, Pazos MR, García C, Pertwee R, Mechoulam R, et al. Cannabidiol for neurodegenerative disorders: important new clinical applications for this phytocannabinoid?. *Br J Clin Pharmacol*. 2013;75(2):323-33. DOI: <https://doi.org/10.1111/j.1365-2125.2012.04341.x>
21. Valdeolivas S, Satta V, Pertwee RG, Fernández-Ruiz J, Sagredo O. Sativex-like combination of phytocannabinoids is neuroprotective in malonate-lesioned rats, an inflammatory model of Huntington's disease: role of CB1 and CB2 receptors. *ACS Chem Neurosci*. 2012;3(5):400-6. DOI: <https://doi.org/10.1021/cn200114w>
22. Shannon S, Lewis N, Lee H, Hughes S. Cannabidiol in Anxiety and Sleep: A Large Case Series. *Perm J*. 2019;23:18-041. DOI: <https://doi.org/10.7812/TPP/18-041>

Resumo

A *cannabis sativa* tem uma história fascinante e é utilizada pela humanidade há milênios. Muitas sociedades como a grega, a romana, a chinesa, a africana, indiana e árabe aproveitaram as qualidades da planta, fosse ela consumida como alimento, medicina, combustível, fibras ou fumo. A primeira referência encontrada relativa à utilização terapêutica da planta data de 2700 a.C. e está presente na farmacopeia do Imperador chinês Shen-Nung, onde esta planta era recomendada no tratamento da malária, de dores reumáticas, nos ciclos menstruais irregulares e dolorosos. O livro "De Matéria Médica", escrito pelo médico Pedânio Dioscórides considerado o fundador da farmacologia, traz a Cannabis como uma das substâncias naturais que podem aliviar dores de origem inflamatória. No Brasil, a Cannabis foi trazida por escravos africanos no período colonial, por volta de 1549. Em seguida, o seu uso disseminou-se rapidamente entre os negros escravos e índios, que passaram a cultivá-la. Devido à popularização da planta dentre intelectuais franceses e médicos ingleses do exército imperial da Índia, ela passou a ser considerada em nosso meio como excelente medicamento para muitos males, até ser reprimida pelas autoridades policiais na década de 1930. Descobertas importantes foram destaque no campo da Cannabis somente 60 anos depois com o Sistema Endocanabinoide e seus receptores, neurotransmissores como a anandamida e o 2-AG, revolucionando o entendimento da sinalização molecular que modula dor e analgesia, inflamação, apetite, motilidade gastrointestinal e ciclos de sono, atividade de células imunes, hormônios e muito mais. Estamos diante de uma enorme revolução na área terapêutica em que os fitocanabinoides representam uma das grandes opções terapêuticas do século. Precisamos de uma divulgação ampla de que o CBD não é maconha e que o uso recreativo da maconha nada tem a ver com o uso da Cannabis medicinal, que as pesquisas científicas estão seriamente empenhadas em estabelecer a eficácia da substância em várias patologias. O papel da informação é absoluto e se constitui na principal ferramenta para esclarecer a sociedade.

Palavras-chave: Cannabis sativa, canabinoides, Sistema Endocanabinoide, CBD, opção terapêutica.

©The authors (2020), this article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated.