



## Medicinal Cannabis in the Argentine Republic. A Historical- Pharmaceutical Perspective for a Natural Health Product and its Insertion on Local Treatments

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### Abstract

Cannabis is used around the world for various purposes (medicinal, religious and recreational). It's utility varies depending on the point of view and approach that is presented. The Argentine Republic approved a new legislation, in line with the provisions of the World Health Organization. The Law No 27.350 regulates medical and scientific research on the medicinal, therapeutic and / or palliative use of the Cannabis plant and its derivatives. This review aims to find adequate terms to classify, without pigeonholing, an ancient medicinal plant, which "is also" a psychoactive drug and "is also" a mystical religious portal. Paraphrasing Paracelsus, the poison is in the dose, but "is also" in the misinformation and prejudices. Palliative treatments in degenerative diseases, cancer, epilepsy and some diseases classified as mental, such as depression are just some of the options that this medicinal plant has to offer us. So, in this framework, let's go through a little beat of history, myths and science, to bring down hypotheses and re-start new ones.

**Keywords:** Cannabis, Medicinal use, Pharmaceutical challenges, Historical application

### INTRODUCTION

*Cannabis indica*, *Cannabis sativa*, *Cannabis americanus*, *Cannabis ruderalis*, Indian hemp and marijuana (or marihuana) all refer to the same plant. Cannabis is used around the world for various purposes (medicinal, religious and recreational) and has a long history characterized by therapeutic, magic, euphoric, malignant and intoxicated plant [1]. Cannabis utility varies depending on the point of view and approach that is presented [2]. This review aims to find adequate terms to classify, without pigeonholing, an ancient medicinal plant, which "is also" a psychoactive drug and "is also" a mystical religious portal. Paraphrasing Paracelsus, the poison is in the dose, but "is also" in the misinformation and prejudices.

According to literature, 108 phytocannabinoids have been classified so far in various chemovars of the cannabis plant [3]. The phytocannabinoids of greatest clinical interest are Cannabidiol (CBD) and  $\Delta^9$ -tetrahydrocannabivarin (THCV). The compound best known for its affinity to endocannabinoid receptors is  $\Delta^9$ -tetrahydrocannabinol (THC). THC and CBD are biosynthesized by almost identical enzymes in cannabis [4]. Chemically, THC and CBD are C21 terpenophenols with pentyl alkyl tails, while the analog THCV is a C19 propyl tailed structural analog [4].

In 2018, experts from the World Health Organization (WHO) recommended "eliminating cannabis and cannabis oil from Schedule IV of narcotic drugs", it is the strictest category in terms of controls typified in "the single convention of 1961

about narcotics". Schedule IV is made up particularly of "harmful substances with limited medical benefits". Typifying Cannabis "at that level of control" would severely restrict access and research on potential plant-derived therapies. In December of 2020, the Argentine Republic approved a new legislation, in line with the provisions of the WHO. The Law No 27.350 regulates medical and scientific research on the medicinal, therapeutic and / or palliative use of the Cannabis plant and its derivatives. In the 2nd and 3rd article of the regulation, the "National Program for the Study and Research of the Medicinal Use of the Cannabis Plant, Its Derivatives and Non-Conventional Treatments" was created, in the orbit of the Ministry of Health and the limits and objectives were defined [5]. In recent years, 30 countries have created specific laws and programs to decriminalize the use of medicinal preparations that contain cannabis as an active pharmaceutical ingredient [6]. In alphabetical order, the countries that legislate the use of medical cannabis are: Argentina, Australia, Canada, Chile, Colombia, Croatia,

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Cyprus, Czech Republic, Denmark, Finland, Germany, Greece, Israel, Italy, Jamaica, Lesotho, Luxembourg, Macedonia, Malta, Mexico, Netherlands, Norway, Peru, Poland, Romania, San Marino, Switzerland, Turkey, Uruguay, Zimbabwe [7].

The growing interest of the world population in a natural gaze at the resolution of their illness, the holistic approach to health, the search for general well-being its evident. The conscious movement towards a new or should we say, old therapy that aligns body, mind and spirit, demand a paradigm shift in regard these therapeutic options. The notorious appearance of patients who choose the alternative of cannabis treatment as a solution to their ailments is an indicator of acceptance. Special attention should be paid in treatment to obstetrics and gynecology. Palliative treatments in degenerative diseases, cancer, epilepsy and some diseases classified as mental, such as depression are just some of the options that this medicinal plant has to offer us [8].

So, in this framework, let's go through a little beat of history, myths and science, to bring down hypotheses and re-start new ones.

#### A LITTLE BIT OF STORY

Although its use in medicine dates back to 2700 BC, it continues to be an area barely explored by scientists and therapists in the 21<sup>st</sup> century AC. Oriental medicine used marijuana for pain treatments in topical pharmaceutical forms such as plasters and ointments. Leaves and flowers were mixed with kaolin for this purpose. On 200-year AC, the cannabis use as an analgesic was described by the physician Hoa-tho [9]. The oldest texts found on the use of cannabis in the treatment of diseases belong to the Chinese Pharmacopoeia of the second century BC, and also mention the Emperor Shen Nung, as Chinese medicine father. Shen Nung lived around 2700 BC, and he supported the systematic exploration of herbal remedies, greatly expanding the empire's herbal catalog [10]. Albert Hoffman refers information in this regard about medicinal preparations such as tinctures from seeds, also reports its use mixed white wine for pain treatment and as an analgesic for surgeries [11].

Records of the use of cannabis in the treatment of nocturnal seizures and other diseases were found on Akkadian and Sumerian tablets dating back to 1800 BC [12].

Its use as an anti-infective agent and as a relaxant for vaginal muscles is reported in Egyptian papyri from the same period [12] for the treatment of inflammation of the vaginal mucosa, cannabinoids are ground and mixed with honey. The sensation of increased temperature could be due to an inflammatory process due to microbial imbalance in the mucosa. The mixture of honey and cannabis is a medicinal preparation with synergistic antibacterial and anti-inflammatory activity, technically it would take on the appearance of an ointment [13,14]. Medicinal cannabis was also prepared in the form of plasters and formulas for its

preparation were found on papyri. For the treatment of infected ulcers, with bacterial colonization and worms, Egyptian doctors applied the plaster of the ground cannabis plant and honey. A formula for toenail mycosis treatment (Formula 618 from the Ebers Papyrus) is described below: honey: 1/4; ocher 1/64; cannabis: 1/32; hedjou resin: 1/32, ibou plant: 1/32, prepare as above, in the form of an ointment and apply and sell the affected area. The oldest example of cannabis is found in Papyrus Ramesseum III, A 26, in 1700 BC [15]: An eye treatment: cannabis; it is ground up and dropped into the dew overnight. Both eyes of the patient should be flushed with it early in the morning. This could be to treat a similar glaucoma condition, but also as an anti-infective and anti-inflammatory product [16,17]. The therapeutic action of cannabis in the treatment of glaucoma is due to the presence of CB1 receptors located in the vascular system of the retina [18]. These trigger a cascade of reactions that increase the excretion of aqueous humor through the uvero-scleral pathway. THC interacts with the CB1 receptors of the cannabinoid system. In studies carried out in patients, the routes of administration of cannabis were intravenous, oral and inhaled, with a decrease in intraocular pressure between 5% and 45%, present in the stroma and unpigmented epithelium of the blood vessels of the ciliary system of the retina, triggering an intracellular signaling cascade [19]. The moderate efficacy could be due to the routes of administration, with the intravenous route being the most effective to date. However, as we will develop later, solving the problem of insolubility in water could open up endless possibilities, such as the direct instillation of eye drops at the site of action, thus increasing the percentage of decrease in intraocular pressure [20,21]. As we can see that the Egyptians prepared a compound aqueous solution for cannabis and a dewy night, these data could indicate that some active pharmaceutical ingredients useful for these eye treatments could be soluble in water. The same procedure was used in cosmetic dermatology for Egyptian physicians, where the maceration of cannabis leaves was applied to the scalp to remove dandruff and promote healthy growth [22].

In India, 300 years later, the anxiolytic effects of cannabis were recorded in Vedic texts [23]. The anxiolytic therapeutic action of CBD could replace traditional anxiolytics, in the treatment of a disease that by 2021, and in the global post-pandemic era, is increasing alarmingly worldwide. Currently, the form of administration of CBD for this type of treatment is cannabis oil, which contains a complex mixture of substances and their derivatives produced by heating during the extraction process. An optimal anxiolytic relieves or suppresses anxiety symptoms, calming nervous hyperexcitability and decreasing activity without producing sedation or sleep, as in the case of low-dose hypnotics, which can act as sedatives. However, physical dependence and the development of tolerance on the part of the patient lead to the abuse of these substances, whose small therapeutic window makes them highly regulated and dangerous substances [24].

In texts found in Asia and North Africa dating back to the 1st and 2nd centuries BC, references to the medicinal use of cannabis were also found. In North and Central Africa, the entire plant was used to treat malaria, dysentery, anthrax and fever [11].

The Islamic medicine treatises that came with the Moorish conquests in Spain and North Africa, incorporated cannabis into their already extensive herbal therapeutic arsenal. Specific mentions of the treatment of epilepsy are found in 11 writings by the Arab physician al-Mayusi, who defended the use of nosed or inhaled cannabis extracts [25]. The medical, pharmacological and botanical literature of the Greeks on herbalism in general and cannabis in particular dominated medical circles in Asia Minor, Syria, Egypt, and their neighboring regions until the 7th century with the advent of Islamic medicine. *Materia Medica* from Dioscorides (1<sup>st</sup> century), translated into Arabic in 861 AD, and Galen from *Simplicium medicamentorum temperamentis ac facultatibus liber VII* (199 AD) translated into Arabic in 873 AD, represented the most important sources for physicians, chemists, ethnobotanists and apothecaries and was a decisive stimulus in the development of their knowledge of the plant [26,27]. The part of the marijuana plant most used in therapeutic treatments were the seeds and to a lesser extent the leaves. Preparation methods differ according to the ailment to be treated, using the oil obtained from the seeds and the juice from the green leaves and sedes [28]. For topical administration, ointments were used that were applied to the nasal mucosa, for oral and optic administration, vegetable oils were used that contained the product of the extraction of the compounds present in dried cannabis seeds. In optic preparations, it was prepared to unclog the ears, eliminate worms and release gases. Its use to eliminate worms, extends to other parts of the body, demonstrating its vermifugal activity in topical application on skin and mucous membranes. The juice of the leaves (product of the maceration of the leaves in water), was used as a lotion for topical application in the treatment of vitiligo, leprosy, pityriasis (ibriya) and lichen (hazaz). The same lotion was used in dermatological cosmetic treatments. Other interesting applications of the aqueous macerate were related to its carminative and antiepileptic properties [25]. Islamic medicine, lived its golden age during medieval times, Arab doctors record the properties of diuretics, emetics, anticonvulsants, anti-inflammatories, analgesics (analgesics) and antipyretics of medical cannabis, including cannabis sativa, widely used as a medicine among the 8th century and the 18th century [29].

Numerous authors also refer to its recreational uses in ancient times, in peoples as diverse as Sumeria, ancient Greece and the Arab countries of the fourteenth and fourteenth centuries. In all these cases, its use is described only as social [29,30]. Although today cannabis is fundamentally known as a psychoactive agent, in ancient medicine and herbalism, it was used mainly for its curative and nutritional properties off the

seeds, especially in the case of mentions of its narcotic effects were more related to the treatment of pain and religious rituals as we will see.

### A MYSTIC APPROACH TO CANNABIS CONSUME [11,31,32]

History tends to become legend and legend tends to become myths, let's go through a small review of the mysticism associated with the use of cannabis. And we will comment on the most beautiful and ancient stories about the religious rituals that use this plant as a common thread to the afterlife. Ancient Indian traditions relate how the gods gave the cannabis plant to man so that he could obtain pleasure, courage and sexual potency from it. Gods and demons united, they gave birth to the divine nectar, cannabis and this was consecrated as Shiva's drink and as Indra's favorite. Legend has it that after its creation, gods and demons fought a war over cannabis. When the gods triumphed, they gave him the name Vijaya, which means victory, which is why it is believed to grant supernatural powers. Bhang is such a sacred drink that it separates man from sin and confers on him eternal good fortune. The sacred oaths are made on a hemp plant. During planting, after removing weeds, it is important to plant a cannabis specimen for a good harvest. Both the planting and the harvesting of cannabis are carried out to the sound of a melody where the word Bhangi is repeated insistently.

Tibetans also take the cannabis plant as sacred. In the hayana buddhist tradition, Buddha consumed a cannabis seed daily, during the six steps of the ascetic life.

The Kasai tribes of the Congo in Africa, revived the ancient cult of Rivalba personified in the cannabis plant elevating it to the category of god.

But let's go back to this story and how a conventional treatment in eastern medicine comes to the shores of western medicine. In the 19<sup>th</sup> century, recreational use ceased to be reported, to give rise to a series of investigations that focused attention on its medicinal properties. It is the first time that western medicine takes this medicinal plant into account as a potential therapeutic agent.

The use of cannabis derivatives for medicinal purposes spread rapidly throughout western physician, as is evidenced in the report of the Committee on Cannabis Indica of the Ohio State Medical Society, published in 1860. In that report medical doctors exposed the success in treating stomach pain, childbirth psychosis, chronic cough, and gonorrhoea with cannabis derivatives products [33]. In 1839 the physician WB O'Shaughnessy tested the analgesic and sedative activities in the first western clinical study on animals with cannabis. This work resulted in the absence of an observable deleterious and adverse effect, before the administration of cannabis extracts in animals and began its clinical study in humans. Using the aforementioned effects, he treated patients with seizures, chronic pain, rheumatism with encouraging results [2]. This American physician brings together popular knowledge and

scientific method for studying the therapeutic properties of cannabis. Quickly, it incorporates the use of extracts and cannabis tinctures in North America. He introduced herbal material from Calcutta and also introduced the cannabis tinctures to the English Medical Society. In 1984, stored samples of the tinctures were analyzed by mass spectrometry and the main active compounds were known [34].

In the 1930's in the United States, many pharmaceutical formulations containing marijuana among their active principles, were sold under the legend of free sale to public. In 1931 the Chairman of the Research Committee of the American Medical Association mentioned that the drugs "Piso's Cure", "One Day Cure" and "Neurosin" contained cannabis [35]. In 1937, twenty-eight pharmaceuticals contained cannabis as an active pharmaceutical ingredient [36]. At the same year, the American Medical Association's Legislative Activities Committee concluded that: "There is no evidence to positively indicate the abuse of cannabis as a medicinal agent or to show that its medicinal use is leading to the development of cannabis addiction. At present, cannabis is used lightly for medicinal purposes, but it seems desirable to maintain its status as a medicinal agent for its current purposes. There is the possibility that a new study of the drug by modern means could show other advantages derived from its medicinal use" [37].

#### PHARMACO-TECHNOLOGICAL CHALLENGES

Medicinal cannabis preparations are based on three main forms of raw material and are known by the Indian names: Bhang, Ganja and Charas. The Bhang is understood as the whole plant except the root, using a mixture of seeds, flowers, leaves and stems of cannabis, Ganja, is understood as the female flower cups without unfertilized seeds and Charas also known in Arabic language as hashish that it consists of a cannabis resin product of the collection by manual rubbing of the trichomes of unfertilized female cannabis flowers, obtained by the sieving operation [38,39].

In their study of the medical applications of cannabis, physicians of the nineteenth century repeatedly encountered a number of difficulties. Recognizing the therapeutic potential of the drug, many experimenters sought ways of overcoming these drawbacks to its use in medicine, in particular the following:

Cannabis products are insoluble in water [40]. As the historical data mentioned so far refers, there is a great variety of compounds that can be extracted in water and polar solvents such as alcohol. This option removes the focus from the traditional cannabis oil in all its presentations containing mostly CBD, and leads to research on the role of these other compounds such as flavonoids, terpenes and phytosterols in dermatological and cosmetic therapeutics.

Long time to therapeutic effect appearance. Although it is reported that the appearance of the therapeutic effects of

cannabis oil preparations takes about an hour, their metabolism and excision are also slower, so the effect is prolonged over time. This is beneficial in the case of patients who consume cannabis treatments for the control of chronic pain [41].

Different batches of cannabis derivatives vary greatly in potency. Moreover, there genetic plasticity has made it difficult to catalog, and there is still an ongoing discussion about its proper classification. But the availability of synthetic  $\Delta^9$ -tetrahydrocannabinol (THC), the major component of cannabis, and the chemical techniques for quantifying its content in cannabis preparations and in blood have made possible for the first-time pharmacological studies which provide some precision in dose [42].

Variable individual responses to cannabis as well as the intensity of the effects would be due to the dose and the environment. However, one study indicated that, with pharmacologically active doses of the drug, extreme variations in the environment produced little alteration in the effects of the drug, which were clearly different from those produced by placebo. Regarding the dose, a personalized follow-up is necessary by the therapists who implement this type of phytomedicines [43].

Although the potency and dosage as well as the mode of administration are still unclear. The appearance of legislation that authorizes the study and tests with the complete plant, it is possible that in the coming years, we will have a new and greater form of administration, ease of dosage. Even with these technological disadvantages, cannabis has a potential replacement over other substances used as analgesics, sedatives and hypnotics:

The prolonged use of cannabis does not lead to the development of physical dependence, but there are studies that reflect a psychological dependence [44-46]. It is documented that other anxiolytic drugs such as benzodiazepines also produce psychological dependence and this is related to the feeling of general well-being that the patient assumes that he obtains with the consumption of the drug, although the dose is often minimal [47].

Cannabis products have exceedingly low toxicity [48]. A very wide therapeutic window is one of the most technologically interesting features. It is reported that the dose required to kill a mouse in laboratory experiments was 40.000 times higher than the dose necessary to obtain a therapeutic effect [12]. This provides safety at the time of manipulation by drug-technologists and wide safety for the patient.

It is also reported that the molecule  $\Delta^9$ -tetrahydrocannabinol (THC) has physiological action through the endocannabinoid system and its receptors. The prominent homeostatic roles of endocannabinoid system were described as "Relax, eat, sleep, forget and protect" [49]. The pathological states related to the endocannabinoid system are related to its malfunction [50,51]. Studies carried out in vivo, by the administration of

THC, show that adverse psychological effects are more frequent when the pure compound is consumed than by the consumption of the synergistic mixture present in the oils produced by the extraction of the unfertilized female flower [52]. In 1970 Gill et al, verified the synergistic action of THC [53] with other components present in the cannabis plant that act as modulators, reducing the side effects of THC, but improving the therapeutic activity of THC [54].

Cannabis produces no disturbance of vegetative functioning, whereas the opiates inhibit the gastrointestinal tract, the flow of bile and the cough reflex [55].

## CONCLUSION

Besides investigating the physical effects of medicinal preparations of cannabis, nineteenth-century physicians observed the psychic effects of the drug in its therapeutic applications [12]. They found that cannabis first mildly stimulates, and then sedates the higher centers of the brain. Hare suggested in 1887 a possible mechanism of cannabis' analgesic properties:

“During the time that this remarkable drug is relieving pain a very curious psychical condition manifests itself; namely, that the diminution of the pain seems to be due to its fading away in the distance, so that the pain becomes less and less, just as the pain in a delicate ear would grow less and less as a beaten drum was carried farther and farther out of the range of hearing. This condition is probably associated with the other well-known symptom produced by the drug; namely, the prolongation of time” [12].

Adequate regulations allow access to the controlled cultivation of the cannabis plant, and derivatives, for medicinal treatment, both therapeutic and palliative of pain. There are international experiences indicate that within a framework of safety and quality, along with medical support, reducing potential damage that the use of cannabis uncontrolled market can produce. To advance in production projects, it is essential to encourage research on the subject, promote the training of health professionals, weigh the role of pharmacists, chemists and physicians in accompanying users of Cannabis and its derivatives with the objective to achieve their informed and safe use. This review only intends to surf on a sea of unanswered questions and others that, although answered, need more evidence to support them. More investigations are requested on the medicinal cannabis acute care setting and the relative implications. Metabolic pathways of action and detoxification need to be explored by pharmacists. Chronic toxicity studies to know the long-term effect consumption are also a pending debt that can be resolved with the application of the new law in our country. However, the cost benefit ratio heralds a promising future for this traditional medicine, that is therapeutic and “also” a recreational drug and “also” a sacred plant.

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## CONFLICT OF INTEREST

Authors declare there is no conflict of interest.

## REFERENCES

1. Vedelago L, Metrik J, Amlung M (2020) Differentiating medicinal and recreational cannabis users via cannabis use motives. *Cannabis* 3(1): 52-63.
2. Mikuriya TH (1969) Marijuana in medicine: past, present and future. *California medicine*, 110(1): 34.
3. Hanuš L (2008) Pharmacological and therapeutic secrets of plant and brain (endo) cannabinoids. *Med Res Rev* 29: 213-271.
4. de Meijer EPM, Bagatta M, Carboni A, Crucitti P, Cristiana Moliterni VM, et al. (2003) The inheritance of chemical phenotype in *Cannabis sativa* L. *Genetics* 163: 335-346.
5. Legislation and Official Notices. Medical and Scientific Research of the Medicinal Use of the Cannabis Plant and its Derivatives. Available online at: [https://www.boletinoficial.gob.ar/detalleAviso/primer\\_a/237208/20201112](https://www.boletinoficial.gob.ar/detalleAviso/primer_a/237208/20201112)
6. Bifulco M, Pisanti S (2015) Medicinal use of cannabis in Europe: the fact that more countries legalize the medicinal use of cannabis should not become an argument for unfettered and uncontrolled use. *EMBO Rep* 16(2): 130-132.
7. Bewley-Taylor D, Jelsma M, Rolles S, Walshe J (2016) Cannabis regulation and the UN drug treaties: Strategies for reform. Accessed on: August 25, 2016. Available online at: [https://www.tni.org/files/publication-downloads/cannabis\\_regulation\\_and\\_the\\_un\\_drug\\_treaties\\_june\\_2016\\_web\\_0.pdf](https://www.tni.org/files/publication-downloads/cannabis_regulation_and_the_un_drug_treaties_june_2016_web_0.pdf)
8. National Academies of Sciences, Engineering, and Medicine (2017) The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research. National Academies Press.
9. Walton, Robert P (1938) *Marihuana: America's New Drug Problem*, JB Lippincott, Philadelphia pp: 1-18, 86-157.
10. Friedman D, Sirven JI (2017) Historical perspective on the medical use of cannabis for epilepsy: Ancient times to the 1980s. *Epilepsy & Behavior* 70: 298-301.

11. Hofmann A, Schultes RE (1982) Plants of the gods. Culture background. Mexico, Mexico.
12. Russo EB (2007) History of cannabis and its preparations in saga, science, and sobriquet. *Chem Biodivers* 4(8): 1614-1648.
13. Rodríguez MIR, Aguilar DD, León JAM (2020) Anti-inflammatory activity of medicinal plants (REVIEW). *Redel. Granmense Magazine of Local Development* 4: 320-332.
14. López A, Brindis GE, Cristians Niizawa FS, Ventura Martínez R (2014) Cannabis sativa L., a unique plant. *Mexican J Pharm Sci* 45 (4): 1-6.
15. Manniche L (1989) An ancient Egyptian herbal A, University of Texas, Austin pp: 176.
16. Jarvinen T, Pate D, Laine K (2002) Cannabinoids in the treatment of glaucoma. *Pharmacol Ther* 95(2): 203-220.
17. Tomida I, Azuara-Blanco A, House H, Flint M, Pertwee RG, et al. (2006) *Glaucoma* 15: 349.
18. Cairns EA, Baldrige WH, Kelly ME (2016) The endocannabinoid system as a therapeutic target in glaucoma. *Neural Plasticity* 2016: 1-10.
19. Pertwee RG (1997) Pharmacology of CB1 and CB2 receptors, *Pharmacol Ther* 74: 129-141.
20. Aljerf L, Al Masri N (2018) In Modern Ocular Pharmacology-Dexamethasone the Top Active Corticosteroid. *EC Pharmacol Toxicol* 6(6): 463-468.
21. Aljerf L, Al Masri N (2018) Syrian Case Study: Behçet's Disease Clinical Symptomatology, Ocular Manifestations, and Treatment. *Chron Pharm Sci* 2: 502-509.
22. Gras A, Parada M, Rigat M, Valles J, Garnatje T (2018) Folk medicinal plant mixtures: Establishing a protocol for further studies. *J Ethnopharmacol* 214: 244-273.
23. Russo EB (2014) The pharmacologic history of cannabis. In: Pertwee RG, editor. *Handbook of cannabis*. Oxford, UK: Oxford University Press pp: 23-43.
24. Pérez Rocha J (2013) Experimental biobehavioral evaluation, in rats, of the analgesic and anxiolytic effect of a cannabis plant extract cultivated in Costa Rica.
25. Lozano I (2001) The therapeutic use of *Cannabis sativa* L. in Arabic medicine. *J Cannabis Ther* 1(1): 63-70.
26. Alqethami A, Aldhebani AY, Teixidor-Toneu I (2020) Medicinal plants used in Jeddah, Saudi Arabia: A gender perspective. *J Ethnopharmacol* 257: 112899.
27. Bremón MR, Pedraz MPSN (2010) Sick in ancient times. Editorial UNED.
28. Lozano IC (1996) Arabic scientific terminology of hemp. In: C. Álvarez de Morales (Ed.). *Natural Sciences in al-Andalus (Texts and studies IV)*. Granada: C.S.I.C.
29. Dioscorides, Pedanius: The Greek Herbal of Dioscorides, edited by Robert T. Gunther, Hafner Publishing Co., New York 1959 pp: 390-91.
30. Walton, Robert P (1938) Marihuana: America's New Drug Problem, J. B. Lippincott, Philadelphia pp: 1-18, 86-157.
31. Wagner CG (1984) Psychoactive, mysticism and religion in the ancient world. *Geryon. Journal of Ancient History* 2: 31.
32. Glockner J (2016) The Inner Look: Sacred Plants of the Amerindian World. Debate.
33. McMeens RR (1860) Report of the committee on cannabis indica; Prom Transactions of the Fifteenth Annual Meeting of the Ohio State Medical Society, Follett, Foster and Co., Columbus, Ohio. pp: 75-100. Available online at: <https://www.cannabiscure.info/wp-content/uploads/2016/07/Report-of-the-Ohio-State-Medical-Committee-on-Cannabis-Indica-1860.pdf>
34. Harvey DJ (1985) Examination of a 140-year-old ethanolic extract of Cannabis: identification of new cannabitril homologues and the ethyl homologue of cannabinol A, eds. D. J. Harvey, W. Paton and G. G. Nahas, IRL Press, Oxford, UK. pp: 23-30.
35. Barrett ML, Gordon D, Evans FJ (1985) Isolation from *Cannabis sativa* L. of cannflavin: A novel inhibitor of prostaglandin production. *Biochem Pharmacol* 34(11): 2019-2024.
36. de Bunge MA (1860) Letter TOM. *Decaisne. Bulletin of the Botanical Society of France* 7(1): 29-31.
37. Schultes RE, Klein WM, Plowman T, Lockwood TE (1974) Cannabis: An example of taxonomic neglect. *Botanical Museum Leaflets, Harvard University* 23(9): 337-367.
38. Russo EB (2006) The role of cannabis and cannabinoids in pain management A, eds. B. E. Cole and M. Boswell, CRC Press, Boca Raton, FL. pp: 823-844.

39. Russo EB, in @Cannabis in India: Ancient lore and modern medicine A, Ed. R. Mechoulam, Birkhäuser Verlag, Basel (2005) pp: 1-22.
40. Méndez Pérez FA (2018) Optimización de la obtención del extracto hidroalcohólico de las inflorescencias de *Cannabis sativa* L "marihuana". Ayacucho 2018.
41. Rodríguez Venegas EDLC, Zamora Fung R (2019) Cannabis, a therapeutic option? April 16th 58(272): 29-30.
42. Rodrigues MA (2019) Cannabis sativa, a plant with a future. Magazine of the Portuguese Horticulture Association 135: 24-28.
43. Hollister LE, Overall JE, Gerber ML (1975) Marihuana and setting. Arch Gen Psychiatry 32: 798-801.
44. Compton DR, Dewey WL, Martin BR (1990) Cannabis dependence and tolerance production. Advances in alcohol & substance abuse 9(1-2): 129-147.
45. Dennis M, Babor TF, Roebuck MC, Donaldson J (2002) Changing the focus: The case for recognizing and treating cannabis use disorders. Addiction 97: 4-15.
46. Kouri EM, Pope Jr HG (2000) Abstinence symptoms during withdrawal from chronic marijuana use. Exp Clin Psychopharmacol 8(4): 483-492.
47. de las Cuevas C, Sanz E, de la Fuente J (2003) Benzodiazepines: More "behavioural" addiction than dependence. Psychopharmacology (Berl) 167(3): 297-303.
48. Zuardi AW, Crippa JADS, Hallak JEC, Moreira FA, Guimarães FS (2006) Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug. Braz J Med Biol Res 39(4): 421-429.
49. Di Marzo V, Melck D, Bisogno T, De Petrocellis L (1998) Endocannabinoids: Endogenous cannabinoid receptor ligands with neuromodulatory action. Trends Neurosci 21: 521-528.
50. Russo EB (2004) Clinical endocannabinoid deficiency (CECD): Can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions? Neuro Endocrinol Lett 25: 31-39.
51. Di Marzo V (2008) Targeting the endocannabinoid system: To enhance or reduce? Nat Rev Drug Discov 7: 438-455.
52. Grinspoon L, Bakalar JB (1997) Marihuana, the Forbidden Medicine. Yale University Press: New Haven, CT.
53. Gill EW, Paton WDM, Pertwee RG (1970) Preliminary experiments on the chemistry and pharmacology of Cannabis. Nature 228: 134-136.
54. McPartland JM, Duncan M, Di Marzo V, Pertwee RG (2015) Are cannabidiol and  $\Delta^9$ -tetrahydrocannabinol negative modulators of the endocannabinoid system? A systematic review. Br J Pharmacol 172(3): 737-753.
55. Baron EP (2015) Comprehensive review of medicinal marijuana, cannabinoids, and therapeutic implications in medicine and headache: What a long strange trip it's been. Headache 55(6): 885-916.