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Positive Results Using Cannabinoids in Respiratory, Metabolic, Immunological, and Neurodegenerative Disorders, A Narrative Review

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Abstract

Cannabinoids' therapeutic potential has garnered significant attention worldwide, with studies displaying their remarkable effectiveness in treating a variety of ailments. These compounds are known for their anti-inflammatory and neuroprotective properties, leading to investigations into their antipsychotic, anxiolytic, and anticonvulsant properties. This narrative review aims to provide an up-to-date overview of the primary therapeutic applications of cannabinoids and their outcomes. We conducted an extensive search across three databases: PubMed, Google Scholar, and Scopus, selecting relevant materials following the PRISMA 2020 guidelines for systematic reviews, while recognizing that this review adopts a narrative approach. *Cannabis*, a plant with psychotropic attributes, has been subject to strict legal restrictions since the early 20th century, rooted in religious, socio-cultural, and political principles. Nevertheless, cannabinoids derived from the plant offer substantial therapeutic potential, particularly as adjuncts in pain management. Moreover, their efficacy has been demonstrated in various conditions, including respiratory, metabolic, immunological, and neurodegenerative disorders like Parkinson's and Alzheimer's. Recognizing the significance of the *Cannabis* plant in scientific research is crucial, as it paves the way for safer therapeutic alternatives with minimal side effects. Therefore, facilitating and prioritizing its study across various medical disciplines is essential.

Keywords: Positive cannabinoids effects, Positive *Cannabis* medical properties, Medical *Cannabis*, Medical hemp, Medical marijuana, Medical uses of marijuana

Background

Recent trends indicate a global rise in the recreational use of addictive substances among individuals aged 15 to 64, with an estimated 269 million people, or 5.3% of the global population, consuming illicit substances in 2018.[1]

The World Drug Report highlights a significant variance in substance use trends between 2000 and 2018, showing a 16% increase in developing countries and a 10% decrease in developed nations. Notably, the use of *Cannabis* for recreational purposes surpasses that of other widely used addictive substances, including heroin, cocaine, nicotine, barbiturates, amphetamines, and ecstasy.

This trend is significantly pronounced when contrasted with the rising consumption of morphine derivatives and synthetic drugs (Figure 1).[1]

Psychoactive Substance	Millions of consumers
Cannabis	192
Opioids	58
Opiates	30
Amphetamines and other prescription psychostimulants	27
Ecstasy	21
Cocaine	19

Figure 1: Psychoactive substances for recreational purposes users in the world, according to the World Drug Report,[1] expressed in millions of users.

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Despite legislative efforts in various countries to regulate the use of such substances to diminish drug trafficking and protect vulnerable populations, particularly children and adolescents,[2-4] the availability and consumption of illegal drugs continue to escalate.This increase is attributed to the sophisticated distribution channels of drug traffickers, including the black market and online platforms.[5]

Conversely, the therapeutic potential of Cannabis's active components has garnered attention for their efficacy in treating certain medical conditions. In Mexico, for instance, the legislation supports the medical use of cannabinoids as an alternative to traditional pharmacological treatments across various medical disciplines, promoting an environment conducive to diverse medical research tailored to societal needs.[6]

However, fostering public respect for the pharmacological advantages of cannabinoids remains a crucial challenge. Addressing this implies sustained educational and informational efforts by health authorities. This narrative review aims to synthesize and present the latest developments in the therapeutic applications of the *Cannabis* plant and evaluate their impact.

Method

This study utilized the PRISMA 2020 guidelines for systematic reviews, as outlined by Campo[7] to conduct a narrative review. Although the review protocol was not formally registered, a comprehensive literature search was undertaken using PubMed, Google Scholar, and Scopus databases. The search strategy involved the following keywords, Booleans, and queries: 'medicinal *Cannabis* uses,' 'illegal *Cannabis* uses,' '*Cannabis* in pregnancy and lactation,' 'industrial use of *Cannabis*,' '*Cannabis* AND mental disorders',and 'medical *Cannabis* AND cancer'.

The inclusion criteria for this review encompassed studies on the use of medicinal *Cannabis*, its recreational and illegal use, the adverse effects of *Cannabis* on cognitive functions, the role of cannabinoids in pain management, cancer, Alzheimer's, Parkinson's, schizophrenia, and other mental disorders. The focus was also on *Cannabis* consumption among young adults, the elderly, and mothers during pregnancy and breastfeeding, as well as populations consuming *Cannabis* in conjunction with alcohol and tobacco. Only articlespublished in English and Spanish were considered.

Exclusion criteria were set to omit articles in languages other than English and Spanish. The elimination criteria targeted studies not explicitly focusing on *Cannabis*, those considering other addictive substances or drugs, research focusing solely on national or regional legislation related to *Cannabis*, and articles where full access was not available.

The selected studies were categorized based on their relevant topics for subsequent analysis. Using the Rayyan website[8] (unregistered protocol) duplicates across databases and articles in non-English or non-Spanish languages were first filtered out. The remaining articles underwent manual and independent screening by two researchers, adhering to the defined inclusion, exclusion, and elimination criteria. To minimize information bias, especially given the narrative nature of this review, any incomplete articles were excluded, and no other bias assessment methods were employed.

Results and Discussion

Cannabis, a genus within the Cannabaceae family, is classified into three primary species: *Cannabis sativa, Cannabis indica, and Cannabis ruderalis*.[9,10] *Cannabis sativa* is predominantly cultivated due to its high delta-9-tetrahydrocannabinol (THC) content, the principal psychoactive compound in *Cannabis*. In contrast, *Cannabis indica* is known for its higher cannabidiol (CBD) content, a compound with notable pharmacological effects, and lower THC levels Figure 2. *Cannabis ruderalis* is distinguished by its lower cannabinoid production. The variance in cannabinoid concentrations, especially THC and CBD, across these species is believed to be a result of evolutionary adaptation to diverse geographical environments, enabling the *Cannabis* plant to modulate these molecules' production.[11-13]

The cannabinoid receptor (6KPG) is a G protein-coupled transmembrane protein that selectively binds the endocannabinoids 4AZP (AEA) and 4AZQ (2AG). Organic syntheses have been carried out to generate synthetic cannabinoid compounds that also bind to the receptor such as Nabilone and Dronabiol. Other synthetic compounds used as antiemetics are also specific for this receptor and bind specifically to it, such as Chloroperazine, Domperidone and Aliprazide, among others. On the other hand, other organic compounds produced by the hemp plant may have action on the cannabionoid receptor such as CBD and THC, which are currently being the subject of more in-depth studies to evaluate their activity in therapies against pain and anxiety. All images were made with the Pymol program (The PyMOL Molecular Graphics System, Version 2.0 Schrödinger, LLC.). The atomic coordinates of the antiemetic and synthetic drugs were taken from the ZINC15 database. The coordinates of the endocannabinoids and cannabinoids were taken from the crystallographic structures of the PDB under the codes 4AZP (AEA) and 4AZQ (2AG), 3LS4 (THC) (79) and 7TE8 (CBD) (Cao et al., 2022). The coordinates of the human Cannabinoid receptor-1 complex and the α, β and γ subunits of the G proteins were taken from the PDB under the code 6KPG.

Cannabis sativa, originally native to Central Asia, particularly Mongolia and southern Siberia, has been distributed worldwide. Adaptability to diverse climatic conditions its remarkable, ranging from semi-arid to tropical, subtropical, and cold climates, has facilitated its proliferation across various ecosystems.[14,15] Hemp and *Cannabis sativa* L.refer to the same organism, with the plant

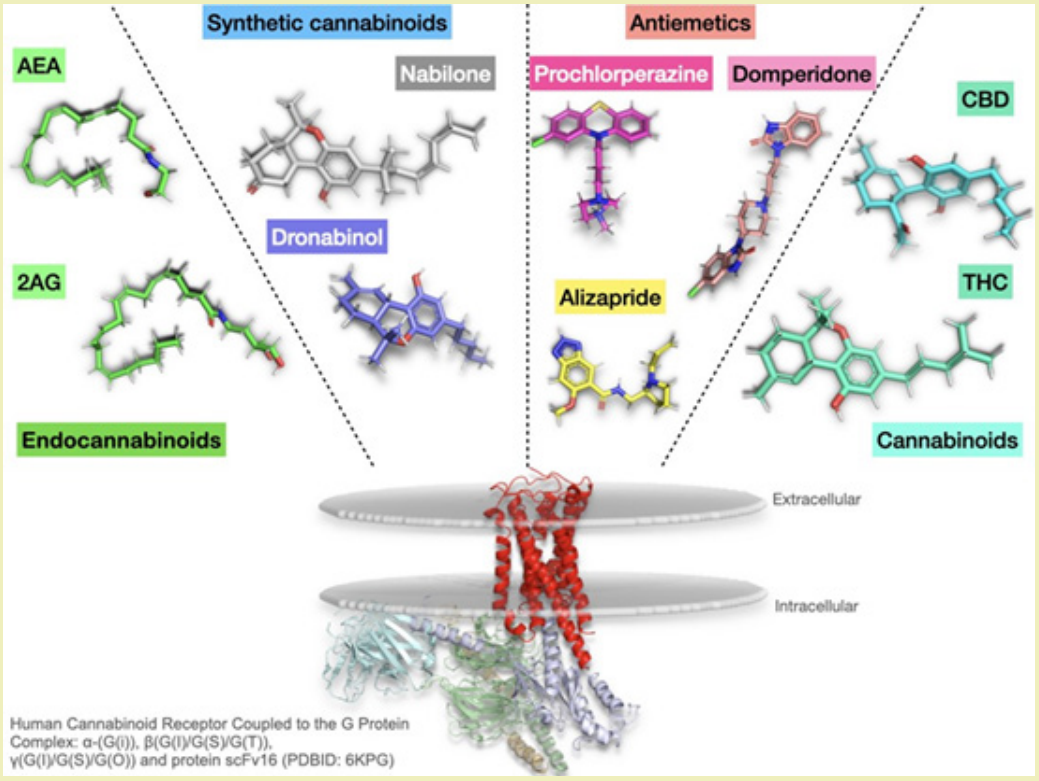

Figure 2: Cannabinoids and their receptors.

playing a significant role in human history, fulfilling needs such as fiber for clothing, naval sails, paper, ropes, and cords.[16,17]

Historically, *Cannabis sativa* was cultivated in ancient China for multiple purposes, including the extraction of fibers for rope, food, and medicinal applications. The Chinese recognized the plant's medicinal properties for treating conditions like rheumatism, gout, and malaria, and acknowledged its psychoactive properties.[18,19]

Following the Spanish conquest of the Mesoamerican region, the Spanish crown introduced hemp to New Spain (modern-day Mexico) to stimulate the local economy, leading to the adoption of hemp cultivation and textile production methods.[20]

By the 18th century, *Cannabis sativa* had integrated into the medicinal and magical- religious practices of healers and herbalists in New Spain. The cultural amalgamation of native New Spain inhabitants and enslaved Africans fostered a unique syncretism in mystical-religious practices, incorporating *Cannabis* into their religious and healing rituals.[17,21]

The biological and pharmacological study of *Cannabis* gained formal recognition in 1964, with the identification of its active components.[22]

Cannabinoids

Cannabis sativa, commonly known as herb or marijuana, is a complex plant containing over 460 identified compounds, with 60 of these classified as cannabinoids. Apart from delta-9-tetrahydrocannabinol (Δ^9THC), various cannabinoids such as delta-8-tetrahydrocannabinol (Δ^8THC), cannabinol (CBN), cannabidiol (CBD), cannabicyclol (CBL), cannabichromene (CBC), and cannabigerol (CBG) have been identified. These cannabinoids are typically present in minor quantities and do not produce the psychotropic effects characteristic of THC.[23,24]

Cannabinoids exert their influence in biological systems by binding to specific receptors, namely cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2).[25-27] The discovery of endogenous cannabinoids or endocannabinoids, such as anandamide or arachidonoylethanolamide (AEA) and 2-arachidonylglycerol (2-AG) in the 1990s (Figure2).[28,29] has shed light on how cannabinoids like THC and CBD interact with cannabinoid receptors and influence biological processes in individuals consuming marijuana.[30-32]

The non-spiritual and non-medicinal use of these substances, such as hemp or marijuana, has led to their widespread and indiscriminate consumption, similar to tobacco and alcohol. Notably, *C. indica* tends to produce a relaxing or sedative effect, attributed to its interaction with CB2 receptors predominantly found in the immune system. In contrast, *C. sativa* is associated with an invigorating sensation, owing to the interaction of its bio-cannabinoid THC with CB1 receptors, which are abundant in the brain and nervous system.[29]

Cannabinoids are characterized by a hydrocarbon structure and limited chemical functionalities that enhance their hydrophilicity. Generally, they are highly hydrophobic, enabling them to cross

the blood-brain barrier through simple diffusion. Upon reaching the CB1 receptors, they stimulate dopamine secretion in the ventral tegmental area, leading to the nucleus accumbens, the dopaminergic pathway. This results in feelings of gratification, motivation, pleasure, and euphoria while simultaneously causing lethargy, reduced reflexes, and slower response times.[33]

Overall, THC in Cannabis tends to amplify the consumer's mood state. In situations of distress and anxiety, THC often exerts a calming effect. However, the relaxing properties of Cannabis can lead to addiction in some individuals.[34,35]

Illegal use of marijuana or *Cannabis*

Global restrictions on Cannabis consumption, dating back to the early 20th century,[36] have been influenced by various governments' religious, socio-cultural,[37] and political principles.[38,39] Despite these restrictions, the use of Cannabis via illicit channels has been on the rise.[38] The legal status of Cannabis varies signoificantly across regions, with some countries decriminalizing its possession while others impose strict penalties, including fines or imprisonment.[40] In certain Asian countries, marijuana trafficking is punishable by death, whereas a few nations have legalized its recreational use, allowing it to be sold in food and beverages.[41]

The illegal marketplace for marijuana has broadened its accessibility, attracting first-time users, occasional social users, habitual consumers, and those who feel compelled to use it.[1] Many users are unaware of the long-term health implications, including deteriorating physical and neurological health, resulting from regular Cannabis use. This clandestine nature of marijuana has also led to its integration into social circles where tobacco, alcohol, and certain inhalants are consumed, offering an affordable alternative that provides shortterm pleasure.[4]

A significant lack of awareness about the medium and long-term effects of THC, the psychoactive component in marijuana, contributes to addiction. THC can exacerbate existing psychological disorders like anxiety, depression, and schizophrenia, potentially leading to more severe psychotic episodes.[42]

Tobacco smokers who also consume Cannabis face an increased risk of lung diseases, including lung cancer and chronic obstructive pulmonary disease. The current medical prohibition on Cannabis hinders the accurate assessment of its risk potential in diseases caused by tobacco use.[43]

The impact of *Cannabis* consumption during pregnancy and lactation is a growing concern. Studies have observed psychiatric symptoms like depression and anxiety in pregnant women and potential vision and visual-motor coordination issues in newborns due to THC'sability to cross the placental barrier.[43]

The focus of recent studies has been on the effects of THC through marijuana smoking on the consumer's mood, with different impacts observed in naive, occasional, or habitual smokers. Symptoms can range from euphoria-dysphoria, anxiolytic and sedative effects, to impaired motor function, perception, memory, and cognition.[44,45]

Cannabis overconsumption, mainly through smoking, can lead to cognitive impairments and mental disorders such as anxiety, depression, and schizophrenia, along with mood fluctuations. There are also increased risks of fatal traffic accidents when driving under the influence of *Cannabis*.[46]

THC consumption, akin to other psychoactive substances like morphine, heroin, and cocaine, tends to be addictive depending on the frequency and amount consumed.[47]

In regions where medicinal and recreational *Cannabis* use is decriminalized, there is an alarming risk of infant exposure to high concentrations of *Cannabis* smoke, with reportedpediatric toxicities including encephalopathy, coma, and respiratory depression in emergency centers.[48,49]

Not all *cannabis* is harmful

Cannabis sativa has been a versatile companion to humanity throughout various stages of development, proving useful in textile and craft industries and occasionally in treating specific human ailments.[50,51] The responsibility for the correct or abusive use of *Cannabis* falls on the individual user. Numerous chemical components in *C. sativa*, which have been of interest to humans in understanding its psychotropic and medicinal properties, are present in the plant kingdom. These bioactive components in *Cannabis*, known as cannabinoids, have been the subject of ongoing research.[52]

One of the challenges for governments and society is to move beyond the stigma surrounding *Cannabis*. This plant presents potential for economic development across various sectors, including the burgeoning interest in its medicinal applications, the development of new drugs (CBD and derivatives), and its use in the beauty, food, and beverage industries.[53]

To fully appreciate the utility of *Cannabis* and mitigate its health risks, particularly from the abuse of its psychotropic component THC, collaborative efforts between governments and public health institutions are essential. This involves promoting long-term educational campaigns to foster responsible and rational use among the population, thereby diminishingthe indiscriminate and uninformed recreational use of THC-rich *C. sativa*, which can lead to serious mental health disorders.

In the textile industry, the antioxidant properties of hemp fibers and their interaction with skin have been studied.[54,55] Hemp's low THC and high CBD content make it beneficialin the food industry, with its seeds being a rich source of essential amino acids, minerals, vitamins, and other nutrients. Hemp seed oil is high in polyunsaturated acids, and its sprouts contain antioxidants.[53]

In medical contexts, ancient Chinese texts described the therapeutic properties of *Cannabis*.[43] The mid-20th century saw the

isolation and stereochemical definition of THC, *Cannabis*'s primary psychoactive component, later its stereochemistry was defined. CBD, present in lower concentrations than THC, is known for its neuroprotective and anti-inflammatory effects.[56]

Medically, THC has applications in managing chronic pain, controlling nausea and vomiting, and reducing spasms in multiple sclerosis. Conversely, CBD possesses antipsychotic, anxiolytic, and anticonvulsant properties and may alleviate symptoms of Parkinson's disease.[56,57]

Cannabis and medical sciences

The therapeutic potential of cannabinoids, contrasting with the detrimental effects of *Cannabis* abuse, has garnered significant interest in the medical and scientific communities .[58] There is growing recognition of the opportunities for developing treatments for chronic conditions, potentially augmenting or replacing existing pharmacological interventions for diseases such as cancer,[56] respiratory ailments, chronic pain, metabolic and immunological disorders, and mental health issues.[58]

Cannabinoids exert their medicinal effects primarily through the cannabinoid receptor types 1 and 2 (CB1, CB2), widespread throughout human tissues, facilitating their interaction with gastrointestinal, nervous, and immune systems.[59,60]

Initial studies in the 21st century on inflammatory bowel diseases (IBD) have shown promising anti-inflammatory and anti-motility effects in animal models. However, clinical trials in this area are limited, underscoring the need for more research to validate *Cannabis* as a safe and effective treatment option for IBD.[40] In chemotherapy patients, traditional antiemetics such as prochlorperazine, domperidone, or alizapride sometimes yield suboptimal results. In contrast, early cannabinoid synthetics such as nabilone and dronabinol demonstrated greater efficacy in clinical studies, although their psychotropiceffects have led to their replacement by 5-HT_3 receptor antagonists.[39,61]

In South American countries, *Cannabis* is used, in several formulations, for pain management, exploiting its nerve impulse transmission inhibition properties. This quality has linked *Cannabis* derivatives to controlling chronic pain from various cancers and neuropathic pain, either alone or in conjunction with conventional therapies.[62]

Neurodegenerative diseases like Parkinson's and Alzheimer's are major public health challenges. Current clinical research has not established definitive therapies for preventing neuro degeneration or promoting neuronal repair. Consequently, the endocannabinoid system is explored as a potential pharmacological target in neurodegenerative processes.[56] Studies involving THC in Alzheimer's have shown it may inhibit acetylcholinesterase and prevent beta-amyloid protein aggregation, reducing symptoms like delusions and agitation/aggression.[57] In Parkinson's disease, a disease characterized by the loss of dopaminergic neurons has caused widespread concern among mental health specialists, cannabinoid agonist derivatives have shown neuroprotective properties in experimental stages, suggesting potential for future clinical applications.[62,63]

Researchers emphasize the critical role of the endocannabinoid system in modulating physiological systems associated with it via CB1 and CB2 receptors. *C. sativa*, particularly through THC and CBD, influences a range of conditions. Preclinical and clinical studies have explored the use of CBD and its derivatives, alone or combined with THC, for treating brain tumors, Parkinson's and Alzheimer's diseases, seizure disorders, and psychiatric conditions like schizophrenia, anxiety, and depression.[64-66] The antitumor properties ofcannabinoids like CBD have been observed in animal model studies, showing potential in slowing cancer progression in various types. Studies in animal models showed that CBD and other cannabinoids inhibit the progression of some types of cancer: breast, lung, prostate, and colon, reducing invasion and metastasis. It mentions the activity of non- psychoactive cannabinoids to promote autophagy and death of cancer cells by apoptosis.[67-69]

CBD, the second-most prevalent component in *C. sativa*, has garnered attention for its broad pharmacological potential. It demonstrates antiproliferative, cytotoxic, antiangiogenic, anti-inflammatory, and immunomodulatory properties *in vitro* and *in vivo* studies.[70,71] The use of medicinal *Cannabis* was approved in Minnesota in 2014 for pediatric and young adult oncology patients, providing an alternative to traditional pharmacological therapies.[70]

Notably, many studies have used synthetic cannabinoid derivatives or isolated CBD from *C. sativa*. It's important to acknowledge that plants produce primary metabolites essential for their biological processes, and secondary metabolites in phytochemistry are known as alkaloids and terpenoids. These can have biological effects when consumed by humans. The pharmacological effect of a plant like *C. sativa* is determined by the combined action of these bio-compounds.[72,73] The synergy between cannabinoids and terpenoids in *C. sativa*, known as the "entourage effect," is a topic of current research interest, although some groups remain skeptical about its significance.[74]

The potential of *Cannabis* in scientific research is substantial, yet legal barriers in many countries restrict its cultivation and use, limiting studies on various pathologies. Despite promising preclinical and clinical results, there's a fear that legalizing marijuana could increase public health costs due to inappropriate use.[56] The role of *Cannabis* in certain psychiatric conditions remains a contentious topic, with literature presenting divided opinions among scientists.[75]

Evidence suggests that early and prolonged marijuana smoking can lead to severe cognitive issues during the developmental stage of mental health in compulsive smokers.

Recreational users may gradually increase their *Cannabis* consumption, leading to dependency and potentially experiencing mystical sensations and hallucinations. [76-80]

Conclusion

Globally, there has been a progressive shift in legal frameworks regarding the use of cannabinoids for medical and experimental purposes. This change has garnered positive responses from authorities, facilitating access for patients in need of these treatments and researchers exploring this field.

This review underscores the significant potential of cannabinoids in pharmaceutical development. It highlights their role in potentially improving health outcomes for patients with a variety of conditions. The evidence presented here supports the notion that cannabinoids could be a crucial component in the next generation of therapeutic agents, addressing a range of diseases that currently challenge the medical community.

However, this emerging field requires continued research and development. We advocate for further studies to deepen our understanding of the pharmacological properties of cannabinoids and their long-term effects. Additionally, there is a need for ongoing adjustments in policies and regulations to ensure the safe, controlled, and effective use of these compounds in clinical settings. Such efforts are essential to fully realize the therapeutic potential of cannabinoids and integrate them effectively into modern medicine.

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Data Availability

No underlying data was collected or produced in this narrative review.

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Conflicts of Interest

Regarding the publication of this article, the authors declare that they have no conflicts of interest.

References

1. Nations U. World Drug Report 2020.
2. Perales JC, Maldonado A, López Quirantes EM, et al. Association patterns of cannabis abuse and dependence with risk of problematic non-substance-related dysregulated and addictive behaviors. *PLoS One.* 2021;16(8):e0255872.
3. Csete J, Kamarulzaman A, Kazatchkine M, et al. Public health and international drug policy. *Lancet.* 2016;387(10026):1427-1480.
4. Uchtenhagen A. Which policy for new psychoactive drugs? *Addiction.* 2017;112(1):32-33.
5. Tuv SS, Krabseth HM, Strand MC, et al. New designer drugs from the web. Tidsskr Nor Laegeforen. 2016;136(8):721-723.
6. Oficial D. Secretaria de salud. Diario Oficial de la Federación 2021;Enero(12):328-345.
7. Page MJ, McKenzie JE, Bossuyt PM, et al. Declaración PRISMA 2020: una guía actualizada para la publicación de revisiones sistemáticas. *Revista española de cardiología (English ed.*). 2021;74(9):790-799.
8. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan-a web and mobile app for systematic reviews. *Systematic reviews.* 2016;5(1):210.
9. Barbosa ALA, Vermeulen SHHM, Aben KK, et al. Smoking intensity and bladder cancer aggressiveness at diagnosis. *PLoS One.* 2018;13(3):e0194039.
10. Lapierre É, Monthony AS, Torkamaneh D. Genomics-based taxonomy to clarify cannabis classification. *Genome.* 2023;66(8):202-211.
11. Malabadi RB, Kolkar KP, Chalannavar RK. Medical Cannabis Sativa (Marijuana Or Drug Type): The Story Of Discovery Of Δ9-Tetrahydrocannabinol (THC). 2023;5(3):4134-4143.
12. Kopustinskiene DM, Masteikova R, Lazauskas R, et al. Cannabis sativa L. Bioactive Compounds and Their Protective Role in Oxidative Stress and Inflammation. *Antioxidants (Basel*). 2022;11(4):660.
13. Klumpers LE, Thacker DL. A Brief Background on Cannabis: From Plant to Medical Indications. *J AOAC Int.* 2019;102(2):412-420.
14. ElSohly MA, Radwan MM, Gul W, et al. Phytochemistry of Cannabis sativa L. *Prog Chem Org Nat Prod.* 2017;103:1-36.
15. Jehangir S, Khan SM, Ahmad Z, et al. Distribution of the Cannabis sativa L. in the Western Himalayas: A tale of the ecological factors behind its continuous invasiveness. *Global Ecology and Conservation.* 2023;49:12-20.
16. Crini G, Lichtfouse E, Chanet G, et al. Applications of hemp in textiles, paper industry, insulation and building materials, horticulture, animal nutrition, food and beverages, nutraceuticals, cosmetics and hygiene, medicine, agrochemistry, energy production and environment: a review. *Environ Chem Lett.* 2020;18(5):1451-1476.
17. Leal galicia P, Betancourt D, González gonzález A, et al. Breve historia sobre la marihuana en Occidente. *Rev Neurol.* 2018;67:133-140.
18. Olvera Hernández N, Schievenini Stefanoni J. Denominaciones indígenas de la marihuana en México. Investigación documental de la relación entre el pipiltzintzintli y la planta de cannabis (siglos XVI-XIX). *Cultura y Droga.* 2017;22(24):59-77.
19. Crocq M. History of cannabis and the endocannabinoid system. *Dialogues in Clinical Neuroscience*. 2020;22(3):223-228.
20. Mechoulam R. Marihuana Chemistry. *Science.* 1970;168(3936):1159-1166.
21. Díaz Ordóñez M, Rodríguez Hernández AJ. Cannabis Yarn in the Spanish and English Empires. Different Policies, but the Same Results? *War & Society.* 2021;40(1):25-42.
22. Appendino G. The early history of cannabinoid research. *Rend Fis Acc Lincei.* 2020;31(4):919-929.
23. Pieracci Y, Ascrizzi R, Terreni V, et al. Essential Oil of *Cannabis sativa* L: Comparison of Yield and Chemical Composition of 11 Hemp Genotypes. *Molecules.* 2021;26(13):4080.
24. Mazzara E, Carletti R, Petrelli R, et al. Green extraction of hemp (Cannabis sativa L.) using microwave method for recovery of three valuable fractions (essential oil, phenolic compounds and cannabinoids): a central composite design optimization study. *J Sci Food Agric.* 2022;102(14):6220-6235.
25. Devane WA, Hanus L, Breuer A, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science.* 1992;258(5090):1946-1949.

26. Capozzi A, Caissutti D, Mattei V, et al. Anti-Inflammatory Activity of a CB2 Selective Cannabinoid Receptor Agonist: Signaling and Cytokines Release in Blood Mononuclear Cells. *Molecules.* 2021;27(1):64.
27. Pertwee RG, Howlett AC, Abood ME, et al. International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB_1 and CB_2. *Pharmacol Rev.* 2010;62(4):588-631.
28. Solinas M, Yasar S, Goldberg SR. Endocannabinoid system involvement in brain reward processes related to drug abuse. *Pharmacol Res.* 2007;56(5):393-405.
29. Howlett AC, Barth F, Bonner TI, et al. International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. *Pharmacol Rev*. 2002;54(2):161-202.
30. Pagano C, Navarra G, Coppola L, et al. Cannabinoids: Therapeutic Use in Clinical Practice. *IJMS.* 2022;23(6).
31. Sholler DJ, Huestis MA, Amendolara B, et al. Therapeutic potential and safety considerations for the clinical use of synthetic cannabinoids. *Pharmacol Biochem Behav.* 2020;199:173059.
32. Pagano C, Navarra G, Coppola L, et al. Molecular Mechanism of Cannabinoids in Cancer Progression. *Int J Mol Sci.* 2021;22(7):3680.
33. Paz Ballesteros WC, Zavala Arciniega L, Gutiérrez Torres DS, et al. Evaluación de la dependencia física y psicológica al tabaco en fumadores mexicanos adultos, Encodat 2016. *Salud Publica Mex.* 2019;61(2).
34. Moltke J, Hindocha C. Reasons for cannabidiol use: a cross-sectional study of CBD users, focusing on self-perceived stress, anxiety, and sleep problems. *J Cannabis Res.* 2021;3(1):5.
35. Crocq M. History of cannabis and the endocannabinoid system. *Dialogues Clin Neurosci.* 2020;20(3):223-228.
36. Seddon T, Floodgate W. Regulating Cannabis: A Global Review and Future Directions, Palgrave Macmillan. 2020.
37. Schlimme J, Rada US. Cannabis consumption and its psychosocial effects in a comparison of different cultures. *Fortschr Neurol Psychiatry.* 2001;69(8):367-373.
38. Moscati A, Mezuk B. Losing faith and finding religion: religiosity over the life course and substance use and abuse. *Drug Alcohol Depend.* 2014;136:127-134.
39. Perisetti A, Rimu AH, Khan SA, et al. Role of cannabis in inflammatory bowel diseases. *Ann Gastroenterol.* 2020;33(2):134-144.
40. Ghiabi M, Maarefvand M, Bahari H, et al. Islam and cannabis: Legalisation and religious debate in Iran. *Int J Drug Policy.* 2018;56:121-127.
41. Tremlová B, Mikulášková HK, Hajduchová K, et al. Influence of Technological Maturity on the Secondary Metabolites of Hemp Concentrate (*Cannabis sativa* L.). *Foods.* 2021;10(6):1418.
42. Gracie K, Hancox RJ. Cannabis use disorder and the lungs. *Addiction*. 2021;116(1):182-190.
43. Joseph P, Vettraino IM. Cannabis in Pregnancy and Lactation - A Review. *Mo Med.* 2020;117(5):400-405.
44. Matheson J, Mann RE, Sproule B, et al. Acute and residual mood and cognitive performance of young adults following smoked cannabis. *Pharmacology Biochemistry and Behavior.* 2020;172937.
45. Sorkhou M, Bedder RH, George TP. The Behavioral Sequelae of Cannabis Use in Healthy People: A Systematic Review. *Front Psychiatry*. 2021;12:630247.
46. Agarwal K, Manza P, Chapman M, et al. Inflammatory Markers in Substance Use and Mood Disorders: A Neuroimaging Perspective. *Front Psychiatry.* 2022;13:863734.
47. Atumeyi AU, Ligom TT, Tivkaa JT. Intake and abuse of psychoactive substances and its relative consequences: a review. *Sci J Anal Chem.* 2021;9(2):39–49.
48. Zimniewska M, Pawlaczyk M, Romanowska B, et al. Bioactive Hemp Clothing Modified with Cannabidiol (CBD) *Cannabis sativa* L. *Extract. Materials (Basel).* 2021;14(20):6031.
49. Mcfadden BR, Malone T. Homegrown perceptions about the medical use and potential abuse of CBD and THC. *Addictive Behaviors.* 2020;115.
50. H MMM, Lewin L. Cannabis Throughout History: Past and Present. *Cult.drog*. 2008;13(15):95-110.
51. Klumpers LE, Thacker DL. A Brief Background on Cannabis: From Plant to Medical Indications. *J AOAC Int.* 2019;102(2):412-420.
52. Uchtenhagen A. Which policy for new psychoactive drugs*? Addiction.* 2017;112(1):32-33.
53. Rupasinghe HPV, Davis A, Kumar SK, et al. Industrial Hemp (Cannabis sativa subsp. sativa) as an Emerging Source for Value-Added Functional Food Ingredients and Nutraceuticals. *Molecules*. 2020;25(18):4078.
54. Id MZ, Roza W. Antioxidant Potential of Hemp and Flax Fibers. 2018.
55. Cerino P, Buonerba C, Cannazza G, et al. A Review of Hemp as Food and Nutritional Supplement. *Cannabis Cannabinoid Res.* 2021;6(1):19-27.
56. Verma R, Hoda F, Arshad M, et al. Cannabis, a Miracle Drug with Polyvalent Therapeutic Utility: Preclinical and Clinical-Based Evidence. *Med Cannabis Cannabinoids*. 2021;4(1):43-60.
57. More SV, Choi DK. Promising cannabinoid-based therapies for Parkinson's disease: motor symptoms to neuroprotection. *Mol Neurodegener.* 2015;10:17.
58. Cherkasova V, Wang B, Gerasymchuk M, et al. Use of Cannabis and Cannabinoids for Treatment of Cancer. *Cancers (Basel).* 2022;14(20):5142.
59. LaVigne JE, Hecksel R, Keresztes A, et al. Cannabis sativa terpenes are cannabimimetic and selectively enhance cannabinoid activity. *Sci Rep.* 2021;11(1):8232.
60. Pertwee RG, Howlett AC, Abood ME, et al. International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB_1 and CB_2. *Pharmacol Rev.* 2010;62(4):588-631.
61. Nso N, Nyabera A, Nassar M, et al. Cannabis and Its Potential Protective Role Against Inflammatory Bowel Disease: A Scoping Review. *Cureus.* 2021;13(10):e18841.
62. Cooray R, Gupta V, Suphioglu C. Current Aspects of the Endocannabinoid System and Targeted THC and CBD Phytocannabinoids as Potential Therapeutics for Parkinson's and Alzheimer's Diseases: a Review. *Mol Neurobiol.* 2020;57(11):4878-4890.
63. Cassano T, Villani R, Pace L, et al. From Cannabis sativa to Cannabidiol: Promising Therapeutic Candidate for the Treatment of Neurodegenerative Diseases. *Front Pharmacol.* 2020;11:124.
64. Spinella TC, Stewart SH, Naugler J, et al. Evaluating cannabidiol (CBD) expectancy effects on acute stress and anxiety in healthy adults: a randomized crossover study. *Psychopharmacology (Berl).* 2021;238(7):1965-1977.
65. de Faria SM, de Morais Fabrício D, Tumas V, et al. Effects of acute cannabidiol administration on anxiety and tremors induced by a Simulated Public Speaking Test in patients with Parkinson's disease. *J Psychopharmacol.* 2020;34(2):189-196.
66. Van den Elsen GA, Tobben L, Ahmed AI, et al. Effects of tetrahydrocannabinol on balance and gait in patients with dementia: A randomised controlled crossover trial. *J Psychopharmacol.* 2017;31(2):184-191.
67. Kis B, Ifrim FC, Buda V, et al. Cannabidiol-from Plant to Human Body: A Promising Bioactive Molecule with Multi-Target Effects in Cancer. *Int J Mol Sci.* 2019;20(23):5905.
68. Pugazhendhi A, Suganthy N, Chau TP, et al. Cannabinoids as anticancer and neuroprotective drugs: Structural insights and pharmacological interactions-A review. *Process Biochemistry.* 2021;111:9.

69. Zimniewska M, Rozańska W, Gryszczynska A, et al. Antioxidant Potential of Hemp and Flax Fibers Depending on Their Chemical Composition. *Molecules.* 2018;23(8):1993.

70. Skrypek MM, Bostrom BC, et al. Medical Cannabis Certification in a Large Pediatric Oncology Center. *Children (Basel).* 2019;6(6):79.

71. Lyu X, Illamola SM, Marino SE, et al. Medical Cannabis Received by Patients According to Qualifying Condition in a US State Cannabis Program: Product Choice, Dosing, and Age-Related Trends. *Curr Ther Res Clin Exp.* 2023;99:100709.

72. Yang L, Wen KS, Ruan X, et al. Response of Plant Secondary Metabolites to Environmental Factors. *Molecules*. 2018;23(4):762.

73. Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Br J Pharmacol*. 2011;163(7):1344-1364.

74. Oh H, DeVylder J. Cannabis and psychotic experiences. *Addiction*. 2017;112(9):1688-1689.

75. Shover CL, Humphreys K. Six policy lessons relevant to cannabis legalization. *Am J Drug Alcohol Abuse.* 2019;45(6):698-706.

76. Sterling T, Irwin JJ. ZINC 15--Ligand Discovery for Everyone. *J Chem Inf Model.* 2015;55(11):2324-2337.

77. Sanson B, Wang T, Sun J, et al. Crystallographic study of FABP5 as an intracellular endocannabinoid transporter. *Acta Crystallogr D Biol Crystallogr.* 2014;70(Pt 2):290-298.

78. Niemi MH, Turunen L, Pulli T, et al. A structural insight into the molecular recognition of a (-)-Delta9-tetrahydrocannabinol and the development of a sensitive, one-step, homogeneous immunocomplex-based assay for its detection. *J Mol Biol.* 2010;400(4):803-814.

79. Cao S, Kang S, Mao H, et al. Defining molecular glues with a dual-nanobody cannabidiol sensor. *Nat Commun.* 2022;13(1):815.

80. Hua T, Li X, Wu L, Iliopoulos Tsoutsouvas C, et al. Activation and Signaling Mechanism Revealed by Cannabinoid Receptor-Gi Complex Structures. *Cell*. 2020;180(4):655-665.e18.