Exploring the Legitimisation of Cannabis: A Narrative Review of Historical uses, Legislative changes and Medical Implication

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ABSTRACT

The exploration of cannabis, particularly its legitimisation and multifaceted uses, is pivotal in understanding its historical significance, chemical composition, therapeutic potential, and societal implications. This narrative review traverses millennia of cannabis usage for medicinal, recreational, and spiritual purposes, juxtaposed with contemporary legislative shifts, notably in the United States. As perceptions evolve, especially with state-level legalisation contrasting federal prohibition, the review scrutinises the burgeoning use of cannabis products, particularly among youth, and the evolving regulatory frameworks. Neurological effects of cannabis use, including impacts on brain structure and function, are examined alongside potential benefits and risks in various medical contexts. Challenges in conducting rigorous clinical research, primarily due to legal and pharmaceutical constraints, are outlined. The review delves into the complexities of cannabis usage during pregnancy and the conflicting scientific data, presenting challenges in advising expectant mothers. Cannabis' diverse applications in treating various disorders, ranging from chronic pain to neurological conditions, are explored, shedding light on the potential benefits and limitations. The review highlights the pharmacological dynamics and clinical implications of cannabis-based therapies, emphasising the need for further research to elucidate their efficacy and long-term safety comprehensively. Moreover, the review discusses the pros and cons of CB therapy with high-Cannabidiol (CBD) medicinal cannabis, addressing challenges such as product quality, safety concerns, potential psychoactive effects, drug interactions, and limited research. It underscores the importance of informed decision-making and personalised guidance in navigating the complexities of CB therapy. In conclusion, while cannabis exhibits a wide range of potential medical applications, further research is essential to fully comprehend its therapeutic potential and weigh the associated risks. The review contributes to informed discourse and evidence-based policymaking, emphasising the need for continued research to unlock the full potential of cannabis in healthcare.

INTRODUCTION

Marijuana, or cannabis, contains several chemicals, especially Delta-9-Tetrahydrocannabinol (Δ9-THC) and CBD, that may have therapeutic and medical uses. Cannabis sativa has been used for medicinal, recreational, and spiritual purposes for thousands of years. The class of chemicals known as phytocannabinoids is present in the cannabis plant, which is well known for its euphoric and psychoactive properties. The Δ9-THC is the primary psychoactive component of cannabis [1]. With the legalisation of cannabis for medical and recreational purposes at the state level in the United States and the nationwide legalisation of the drug for recreational purposes in Canada and Uruguay throughout the past 25 years, perceptions toward the drug have drastically changed [2].

Consequently, there has been a significant rise in the use of cannabis products, especially among young people. Over the past fifty years, states have experimented with marijuana legalisation policies, even though federal law has outlawed the use and distribution of marijuana in the United States since 1937 [3]. The 1970s saw the enactment of state decriminalisation measures, the 1990s saw the adoption of patient medical access laws, and more recently, several jurisdictions have started experimenting with legalising recreational markets. As a result, there is a range of marijuana liberalisation laws in the US that are frequently overlooked or underappreciated when assessing more recent legislative initiatives. Research on structural neuroimaging has consistently demonstrated that individuals who use cannabis display irregularities in the volume and density of their hippocampus [2]. Since white matter contains a high concentration

of Cannabinoid-1 (CB1) receptors, there is also compelling evidence in the literature that cannabis usage damages this area of the brain [4]. One way to interpret the term "medical marijuana" is as a marketing ploy meant to lower the perceived danger associated with drug use [5].

From this angle, the misconception that marijuana is safe for medical usage has led to the perception in the general unconscious that it is beneficial to health. The female marijuana plant has the most significant levels of over 100 cannabinoids, whereas both the male and female varieties of the plant have over 400 chemical substances in total [6]. The primary component in cannabis that has psychoactive properties is Δ9-THC, and this compound's effects are linked to problems with memory, learning, attention, and motor coordination [7]. Although there are pharmacological grounds for the possibility that cannabinoids have positive benefits, there is insufficient data from clinical trials to make certain judgments. Studies have shown that pure Δ9-THC is beneficial in increasing appetite, managing nausea and vomiting, and reducing spasticity in those with Multiple Sclerosis (MS) [1,5,6,8].

Additionally, CBD is beneficial in treating paediatric epilepsy disorders. The federal laws governing high-THC cannabis in the USA and the reluctance of big pharmaceutical companies to fund clinical trials that won't result in a prescription medicine with patent protection are the main obstacles to research on cannabis, cannabis extracts, and CBD oil [9]. Cannabis exposes foetuses and neonates since it crosses the placenta and enters breast milk [10]. Many pregnant women provide medical justifications for using marijuana, including

chronic pain, anxiety, and pregnancy-related nausea and vomiting [6]. Due to conflicting scientific data on marijuana use during pregnancy, professionals are unsure how to advise expectant mothers about the hazards associated with marijuana usage.

In this review, the authors aim to explore the multi-faceted landscape surrounding marijuana, or cannabis, shedding light on its historical significance, chemical composition, therapeutic potential, and societal implications. By delving into the rich history of cannabis usage spanning thousands of years for medicinal, recreational, and spiritual purposes, the authors set the stage for a comprehensive examination of its modern-day complexities. With the shifting legal landscape, particularly in the United States, where state-level legalisation contrasts with federal prohibition, understanding the implications of these policies becomes paramount. This present review also scrutinises the burgeoning use of cannabis products, especially among youth, and the evolving regulatory frameworks that attempt to navigate this cultural and medical phenomenon. Furthermore, the authors here delve into the scientific literature to explore the neurological effects of cannabis use, including its impact on brain structure and function, as well as its potential benefits and risks in various medical contexts. By addressing the challenges in conducting rigorous clinical research due to legal and pharmaceutical constraints, as the aim of this review was to provide a nuanced understanding of the complexities surrounding cannabis use and its potential therapeutic applications. This review helps to contribute to informed discourse and evidence-based policymaking in this rapidly evolving field.

LITERATURE SEARCH

A comprehensive review of scholarly databases, medical literature, and reliable sources was conducted to learn about the legal developments, historical uses, and potential medical benefits of cannabis. A few of the most crucial search terms, including "cannabis," "medical marijuana," "CB," "THC," "CBD," and "neurological disorders," An extensive evaluation of research papers, reviews, and clinical trials was done to summarise the topic comprehensively. The exclusion criterion ensured that redundant or non-peer-reviewed materials were excluded, while the inclusion criteria concentrated on relevance to the research topic. By integrating varied viewpoints, endeavoured to offer an all-encompassing and empirically grounded investigation of the diverse facets of cannabis consumption.

Cannabis: Origins, Components, and Therapeutic Applications

Often known as marijuana or weed, cannabis is a psychoactive drug extracted from the cannabis plant. Cannabis naturally comes from the same class of drugs that people use regularly, including tobacco, alcohol, and coffee [11]. The cannabis plant, native to Central or South Asia, has long been used in traditional remedies and as a recreational and entheogenic narcotic [3]. THC, one of the plant's 483 identified compounds, is the main psychoactive component of cannabis. Atleast 65 other cannabinoids, such as CBD, are also present [12]. Overuse of marijuana has been linked to several adverse health impacts as well as socio-economic consequences [13]. Preventing kids from experimenting with and routinely consuming marijuana has emerged as a significant public health problem.

Cannabis can be consumed as an extract, smoked, vaped, or added to food. In addition to treating chronic pain, headaches, migraines, anxiety, and post-traumatic stress disorder, medicinal cannabis is recommended for the treatment of numerous other illnesses' symptoms [14]. The active components of cannabis, THC and CBD, influence the symptoms of the patient. The endo-cannabinoid system represents these substances that reduce nociception and the frequency of symptoms [5]. Rimonabant, an inverse agonist of the CB1 receptor, substantially decreased body weight, enhanced tolerance to glucose, and reduced other cardiovascular risk factors [15].

Rimonabant and its Adverse Effects: Unveiling Pharmacological Dynamics and Clinical Implications

Although rimonabant was approved in Europe, it was later taken off the market due to reports of depression and suicide. It is significant to remember that a drug that lowers a receptor's activity below the baseline level is referred to in pharmacology as an inverse agonist. In contrast, a neutral antagonist raises the receptor's activity to the baseline level [3]. Given that euphoria and increased appetite are recognised effects of marijuana, it is not surprising that an inverse agonist causes anorexia, depression, and weight loss [9]. Current recommended medications, such as pregabalin, gabapentin, duloxetine, and other tricyclic anti-depressants, provide meaningful pain relief for over fifty percent of patients; this suggests that there is a clinical need that is not being satisfied for the treatment of neuropathic pain [7]. Medical Cannabis (MC) and Cannabis-based Medicines (CbMs) have been proposed as potential treatments for people who experience chronic neuropathic pain [16]. The CbMs/MC come in a variety of forms: legal pharmaceuticals or medical goods (plant-derived and synthetic products like THC or CBD); medicinal applications of cannabis plant derivatives with defined molecular content, like dronabinol (THC); and natural cannabis with defined levels of THC and CBD along with additional active ingredients (phytocannabinoids in addition to CBD/THC, aromatic compounds, and flavonoids) [6,11,13]. CB1 in medical treatment is represented in [Table/Fig-1].

Drug	Type	Effect
Rimonabant	Inverse agonist	Anorexia, depression, and loss of weight
Pregabalin, gabapentin, duloxetine, and other tricyclic antidepressants	Neutral antagonist	Meaningful pain relief
Medical Cannabis (MC) and Cannabis-based Medicines (CbMs)	CbMs/MC	Potential treatments for neuropathic pain
CbMs/MC	Legal pharmaceuticals or medical goods	THC and CBD are examples of synthetic and plant-based compounds
CbMs/MC	Applications for medicinal cannabis plant derivatives with specific molecular composition	Dronabinol (THC)
CbMs/MC	Natural cannabis with extra active components and specified concentrations of CBD and THC	Together with flavonoids, aromatic chemicals, and THC, phyto-cannabinoids

[Table/Fig-1]: Cannabinoids (CB) in medical treatment [6,10,11,13].

Recreational Cannabis Legalisation: Unveiling Health Concerns and Historical Perspectives

Cannabis usage for recreational purposes is now legal in Colourado and Washington, thanks to recent laws reflecting shifts in public opinion. Unfortunately, the discussion surrounding the legalisation of marijuana for recreational purposes has not focused much on the drug's detrimental health effects [17]. These detrimental effects are frequently more noticeable in teenagers. Based on the detrimental consequences on the health of adults and adolescents, a strong case can be made to veer away from the path that society is taking in favour of legalising marijuana for recreational use [8,14]. However, given that cannabis exposure may have long-term effects on this population, children and adolescents may be more susceptible to cannabis infection than adults [18]. In the US, marijuana usage was mainly restricted to specific demographics until it was legalised. The 1960s counter-culture saw a sharp rise in marijuana use before the Controlled Substances Act of 1970 [19]. These included anti-war demonstrators, college staff and students, and "hippies" in the mid-1960s [3]. Medical marijuana patients use the drug for things like pain, epileptic fits, vomiting, desire to eat, and psychological problems have become more and more apparent [20].

Medical Marijuana: Diverse Applications and Complex Considerations in Treatment

The use of medical marijuana is limited to treating a variety of disorders, such as extreme pain, muscular spasms, and terminal illnesses. Still, it can also be used to treat cancer, HIV/AIDS, epilepsy, glaucoma, and other conditions [21]. It includes everything from mental health diseases like post-traumatic stress disorder to neurological conditions like Alzheimer's and MS [2]. Medical marijuana and its related substances may help treat a variety of ailments, such as behaviour and development problems in kids and teenagers [22]. Marijuana's potential applications in treating behavioural and developmental disorders, including Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD) [8]. Natural CBD is effective for a limited range of children's seizures in rigorous scientific testing [23]. Known adverse effects of that medicine include drowsiness, liver impairment, and suicidal thoughts and actions [23].

It is challenging to treat Cystic Fibrosis (CF) with marijuana because the drug is frequently smoked or vaporised, and it is not advised for those with chronic lung diseases to breathe in marijuana smoke or vapour [24]. There is no proof that using vaporisation or other alternate delivery methods is safer than smoking. The complexity of ASD makes it extremely difficult to identify a suitable treatment, necessitating numerous drug adjustments or trials of treatment throughout a patient's lifetime [23]. Medical cannabis in diverse health conditions is represented in [Table/Fig-2].

Condition	Potential benefits	Limitations
Extreme pain, muscular spasms, and terminal illnesses	Pain relief, symptom management	Limited research, potential addiction
Cancer, HIV/AIDS, epilepsy, glaucoma	Symptom management, treatment support	Limited research, potential side-effects
Mental health conditions (PTSD)	Anxiety and depression reduction	Limited research, potential dependence
Neurological conditions (Alzheimer's, MS)	Symptom management, improved quality of life	Limited research, potential side-effects
Behavioural and developmental problems in children and teenagers	Potential for ADHD and Autism Spectrum Disorder (ASD) treatment	Limited research, lack of long-term studies
Cystic Fibrosis (CF)	Possible symptom relief	Concerns about inhalation method, lack of research
Autism Spectrum Disorder (ASD)	Treatment complexity, lack of universal benefit	Limited research, need for individualisation

[Table/Fig-2]: Medical Cannabis (MC) in diverse health conditions [8,21,23,24].

Medical Cannabis (MC): Addressing Varied Symptoms and Conditions through Cannabinoid (CB) Therapy

Patients and symptoms seek different degrees of safety, tolerability, and efficacy with commonly prescribed drugs. Some of the most often reported adverse effects are aggression, anxiety, irritability, and a detrimental impact on cognition, which are also thought to be the most concerning symptoms associated with ASD [2]. As a result, many patients stop using the medication because the side effects exceed the benefits. The potential efficacy, safety, and tolerance of using medicinal cannabis high in CBD for treating ASD symptoms, including irritability and sleep disturbances, have been demonstrated by recent case reports and retrospective investigations [25].

The quality of life of patients is significantly impacted by inadequate management of neuropathic and chronic pain related to cancer. Alternative therapeutic options are necessary for patients who do not respond well to opioid analgesics or who experience severe adverse effects from using standard analgesics [4]. Medical cannabis may be able to help this patient population manage cancer pain [26]. Marijuana use can help control sickle cell disease, although more research is required for the same [27]. THC and its derivatives are psychotropic. Δ9-THC is used to treat Chemotherapy-Induced Nausea and Vomiting (CINV) [28]. Marijuana laws have been extended to cover the following common medical conditions: illnesses such as

MS and muscle spasms, immunodeficiency syndrome, carcinoma, Crohn's disorder, Amyotrophic Lateral Sclerosis (ALS), cachexia, glaucoma, epileptic seizures, hepatitis C virus, and MS [29]. Following therapy with medical marijuana, a notable improvement can be shown in the neurologic symptoms of spasms, tremors, spasticity, chorea, and sleep quality [30]. The interactions between cannabinoids and the CB1 and CB2 receptors, found in many locations throughout the human body, produce the pharmacological effects of cannabinoids [1]. Cannabis is a medicinal substance used to alleviate emesis and discomfort [30].

Pros of Cannabinoid (CB) Therapy with High-CBD Medicinal Cannabis

Cannabinoid (CB) therapy, mainly using high-CBD medicinal cannabis, has emerged as a promising avenue for addressing diverse health concerns. CBD, the non-psychoactive compound found in cannabis, offers a range of potential benefits. Firstly, its analgesic properties provide hope for individuals coping with chronic pain conditions, potentially offering relief where other treatments have fallen short [2]. Additionally, CBD's anti-inflammatory effects hold the potential for managing conditions characterised by inflammation, such as arthritis and inflammatory bowel diseases, offering a natural alternative to traditional anti inflammatory medications [25,31].

Moreover, research suggests that CBD may play a role in anxiety and depression management, acting as an anxiolytic and anti-depressant, thereby enhancing mental well-being [27]. Furthermore, the neuroprotective properties of CBD present opportunities for combating neurodegenerative diseases like Alzheimer's and Parkinson's by reducing inflammation and oxidative stress in the brain, potentially slowing disease progression [25]. Lastly, the FDA approval of CBD for certain types of epilepsy underscores its anti-seizure effects, providing hope for individuals with treatment-resistant forms of epilepsy to achieve better seizure control [29-31].

Cons of Cannabinoid (CB) Therapy with High-CBD Medicinal Cannabis

However, despite the potential benefits, Cannabinoid (CB) therapy, especially with high-CBD medicinal cannabis, presents notable challenges. The lack of regulation in the cannabis industry raises concerns regarding product quality, potency, and safety, leaving consumers vulnerable to exposure to contaminants or mislabeled products [2,3,31]. Additionally, while CBD itself is non-psychoactive, high-CBD cannabis products may contain trace amounts of THC, potentially leading to unwanted psychoactive effects, particularly in individuals sensitive to THC or when consumed at higher doses [25,31]. Furthermore, CBD can interact with certain medications, altering their metabolism and efficacy, necessitating caution and close monitoring, especially for individuals on multiple medications [27].

Although generally well-tolerated, CBD may induce side effects such as fatigue, diarrhoea, and changes in appetite or weight, affecting the overall tolerability of CB therapy [3,5,30,31]. Lastly, despite growing interest, research on CB like CBD is still in its early stages, with limited conclusive evidence regarding their efficacy and long-term safety for various conditions, highlighting the need for further research and clinical trials to elucidate their therapeutic potential and risks comprehensively [28,30]. Thus, while CB therapy offers promise for addressing various health issues, it's essential for individuals to carefully weigh the potential benefits against the risks and consult with healthcare professionals for personalised guidance and monitoring [31].

CONCLUSION(S)

In summary, the extensive historical usage of cannabis for medicinal, recreational, and spiritual purposes has led to recent changes in legislation, most notably the legalisation of marijuana in several

states for both medical and recreational purposes. The two main psychotropic ingredients, CBD and Δ9-THC, have received the most attention from scientists. The review underscores the historical and recent shifts in cannabis legislation, noting its multi-faceted usage and the attention CBD and THC receive from researchers. Concerns about cognitive effects in cannabis users are raised, alongside critiques of the term "medical marijuana" for potentially downplaying risks. While acknowledging its medical potential, caution is urged due to known adverse effects, particularly in conditions like MS and cancer symptoms. Challenges in cannabis research and complexities in US legalisation are highlighted, emphasising the need for further research to fully grasp its medical applications.

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