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INVITED REVIEW

Legalisation and Liberalisation of Cannabis: The Benefits and Drawbacks of the Global Trend

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Summary

Cannabis sativa is a complex domesticated plant that has an unstable taxonomy. It is the most utilised illicit substance that has gained prominence in some parts of the world as it is used for therapeutic and recreational purposes. *C. sativa* has also been used to manage numerous medical conditions since antiquity. The pharmacological benefits of *C. sativa* are still subject to intense research due to inconsistent outcomes. *C. sativa*, like other psychoactive substances, has both medical and psychological side effects. Despite the lack of knowledge, medical practitioners continue to recommend this substance. This review aims to highlight the effects of legalisation and liberalisation on the global trend of cannabis use. A search was conducted on Google Scholar and Medline from 2012 to date. The results showed that cannabis was found to be effective in the management of some medical conditions, though more work is required. Recreational use is rising due to a reduced perception of harm and the availability of more potent species. Cannabis use persists despite the several medical and psychological side effects. It is concluded that there is a shortage of information on the safety and pharmacological properties of *C. sativa*, and more work is required.

Keywords: *Cannabis sativa*, *Cannabis-related Disorders*, *Dependence*, *Legalization*, *Medicinal plant*, *Pharmacology*.

Introduction

Cannabis is a public health concern.^[1] It is one of the most cultivated and widely used illicit substances globally, especially among the youth,^[2-4] with a total number of 188 million adult users ranging between 164-219 million (3.8% of the global adult population) users.^[3] Since the mid to late 2000s, the proportion of cannabis use and demand for treatment has increased worldwide with regional differences^[5], with the highest rates found in Oceania, the Americas, and Africa.^[6] For more than a decade, cannabis-related disorders

(CRD) have dominated drug treatment in Africa, with treatment rates consistently over 60%^[1] and approximately half of the global first-time treatment seekers being managed for cannabis use disorders (CUD).^[4] In Africa and Oceania, more than half of those in treatment for drug use are concerned about their cannabis use.^[4] Globally, the use of cannabis has increased significantly, with a doubled rate of users in Europe, South America, and Oceania, where the rate has tripled.^[4] Although in 2013, the prevalence of treatment demand dropped in North America,^[4] but was preceded by an increased cannabis admissions rate of 32%

between 1996-2006 [7] and 1980s-2012, due to THC content increase from 3% to 12%. [8] The current rise in cannabis preparation potency has exposed users to higher doses of THC. In contrast, treatment-seekers may have a long history of CUD and may have attempted to quit cannabis. [9]

The reformation of cannabis policy and regulation in western countries has been drastic and progressive. Cannabis sales for adult recreational use were legalised in nine US states in 2012, Uruguay in 2013, and Canada in 2018. [10] So far, 30 US states and Washington, DC have endorsed medicinal use, while nine states added non-medicinal use. [11] In the European Union and Australia, therapeutic cannabis use is permitted, while Uruguay and Canada include non-medicinal use, thereby increasing access to retail cannabis and novel cannabis product formulation. [11]

The adjusted legislation has encouraged users' innovation in the mode of administration for pleasurable effects. Cannabis users in laissez-faire states now use appealing devices like inhaling aerosol or vapour of desiccated cannabis or concentrated extracts and resins via sophisticated vaporisers. [12] These new techniques cause more impairments than those caused by using conventional implements. [11]

The US Comprehensive Drug Abuse Prevention and Control Act of 1970 listed cannabis in the Drug Enforcement Agency Schedule I, which forbade its use for any purpose. [13, 14] With time, the US government constituted a comprehensive program to authorise therapeutic cannabis use for specific medical conditions [15] following the masses' protest to identify those with qualifying ailments and ensure that certified healthcare practitioners are registered with the endorsing states. [13] Cannabis liberalisation has both beneficial and detrimental effects. This access has afforded researchers freedom and funding to study the plant, detect the chemical constituents, and certify it as suitable for human consumption. Cannabis liberalisation

has encouraged cultivation, unhindered access without fear of arrest, the availability of more potent cannabis, and increased user hospital bed occupancy for CRD. Therefore, healthcare workers should be well informed about the impacts of prevailing cannabis use in our modern society.

Biology of *Cannabis sativa*

Cannabis, a plant known for its complexities, has more than 600 commercial varieties [16] worldwide. [17, 18] Family Cannabaceae has unstable taxonomic foundations, and more than 60 variants are cannabinoid compounds, some of which oppose the effects of the others. [18, 19] Cannabis strength depends on the habitat's altitude, soil, climate conditions [18] and liberality of the country. In Colorado, cannabis products and potent preparations are allowed freely [20], while in Uruguay, there is an upper limit on potency and sales are regulated to five strains. [20] Cannabis domestication persisted till the wild species disappeared. With continuous escape during cultivation, more wild cannabis develops and more strains that have lost some peculiar features are produced. [18]

Cannabis plants contain a range of active metabolites, with the major chemical groups being cannabinoids and terpenoids. The cannabinoids are made up of two basic chemical components: delta-9-tetrahydrocannabinol (THC), the primary psychoactive constituent in cannabis [21], and cannabidiol (CBD), which is the non-psychoactive constituent and also has moderating effects on TCH potency. [22] Other cannabinoids identified are cannabidiolic acid (CBDA), cannabigerol (CBG), and cannabichromene (CBC). [23]

Hitherto, cannabis research and use have been hindered by legality disputes. [24] Cannabis globalisation and decriminalisation encourage researchers to work and solicit support from countries where commercial cultivation for psychoactive benefits, therapeutic, or industrial

products aside from consumption, such as clothing fibres or food [22] are allowed. Therefore, in the coming decades, global understanding of the benefits and safety of this controversial plant, which has gained the attention of global leaders, policymakers, and scientists, of cannabis sativa is expected to deepen. [25] Therefore, this review aims to gather information on the pros and cons of the legalisation and liberalisation of cannabis Sativa from published research and the way forward.

History of Cannabis

As established by the Paleobotanical studies, cannabis was confirmed authentic around 12 000 years ago near the Altai Mountains in Central Asia. [26] Progressively, the properties of Cannabis (fibres for ropes and nets, food, seeds for oil) were discovered, and the female Cannabis strain was found to produce euphoria when heated. [27] Sooner, the interest of humans changed from mere gathering to cultivating and separating the strains for fibres from those with THC. Cannabis seeds then became the nomads' companions for commercial exchanges, and gradually, powerfully inebriating hashish was sold in Al-Junayna (the small garden), formerly called Ṭabbāla, in Cairo. [27]

Medicinal cannabis use predated Common China, Egypt, and Greece (Herodotus) era but much after in the Roman Empire (Pliny the Elder, Dioscorides, and Galen). In the 19th century, orientalist (Silvestre de Sacy, and Western physicians) contact with Islam and Indian cultures, (O'Shaughnessy and Moreau de Tours) culminated in the medicinal use of cannabis in Europe. In 1964, Mechoulam and Gaoni determined the structure of the main psychoactive phytocannabinoid, tetrahydrocannabinol (THC), in Israel. This discovery opened the gate for several developments in the field of endocannabinoid system (ECS) research. [27]

The cannabis designation during the Eurasia

cannabis movement depended on the location and the native language. Some examples of the etymologically similar designations are English hemp, German Hanf, Greek κάνναβις and Latin *cannabis*, while pot, dope, grass, weed, Mary Jane, bud, hash, bhang, keif, ganja and more are the informal names. [27] In the early days of cosmogony, the Indians regarded cannabis as a divine ingredient of worship for mystic inspiration, favoured by the god Shiva. Vijaya, or cannabis, has been used for many years in Ayurvedic medicine for pain, nausea, anxiety, appetite and sleep improvement, muscle relaxation, and euphoria. [27]

Cannabis' global spread ended when it got to Africa and America, while cultivation started in central Chile and Spain within the first decade after the Conquista. [3] In Shennong Ben Cao Jing, dated 2900 BC, constipation, rheumatic pain, female reproductive tract disorders, and malaria [3] were the first groups of ailments managed with very low levels of THC seeds. [3] Cannabis was also mixed with wine to anaesthetise patients during surgical procedures. By 1000 BC, Indians started using female cannabis flowers and prepared different potencies. More potent cannabis was used as an analgesic, hypnotic, tranquiliser, antispasmodic, and topical anti-inflammatory agent. It was probably administered for depression by Helen, Zeus' daughter, to alleviate Greek veterans' pain and strife during the Trojan war and to help them forget war experiences on their return. With more discoveries, Claudius Galen (ad 129-199/217) reported that small cakes containing cannabis were routinely served as dessert in Italy in the early days, generating an encounter. Galen says, "the seeds create a feeling of warmth, and if consumed in large amounts, affect the head by emitting a warm and toxic vapour." [27]

With time, several publications on cannabis were released for public use and the knowledge was shared among different religious groups and leaders. [27] In 1964, THC was discovered, but somewhat later, it was observed that plant

extracts varied based on different seasons, weather, geographical location, and the concentration of the therapeutic agents. [27] By the 20th century, cannabis was confronted with a series of embargos, especially in the United States. A few years ago, cannabis was removed from the American pharmacopoeia as directed by the Marihuana Tax Act in 1937. In the 1961 United Nations Single Convention on Narcotic Drugs, cannabis was enlisted in Schedule IV, the most stringent control rule alongside heroin. In 1970, due to its detrimental effects, cannabis was declared a Schedule I drug in the USA because of its propensity for abuse and was no longer accepted for medical use. After that, research and legal cultivation of cannabis ended abruptly, but illicit use persisted. [27]

With time, cannabis restrictions were reduced due to legislative review in the USA and some other countries. The interest in the therapeutic effects of cannabis and cannabinoids waned until the upsurge in the 1960s during the anti-war and other social protest movements. [29] Before this, American youth had started experimenting with cannabis and other drugs and identified therapeutic cannabis properties. [30] By March 2017, about 28 states and the District of Columbia passed laws that permitted the medical use of cannabis, while 8 states, including the District of Columbia, legalised recreational cannabis use. [3]

Mechanism of action

Of the two significant phytocannabinoids, CBD was the first compound discovered from marijuana in 1940, and the structure was documented by 1963. [31] In 1941, the THC structure was identified by Mechoulam and Gaoni in Israel. [32, 33] Raphael Mechoulam would later discover that the cannabis-spiced cake he fed healthy volunteers in his experiment triggered psychological reactions depending on their personality. Mechoulam's work on the endocannabinoid system (ECS), the novel receptor system, was inspiring, but four years later, Devane et al., who categorised

the first cannabinoid receptor (CB1 R) in rat and human brains 30 discovered the first endocannabinoid, arachidonylethanolamide (AEA). [34] So far, the ECS has few endocannabinoids (AEA and 2-arachidonoylglycerol [2-AG]), and the two primary cannabinoid receptors (CB1 R, found in the central nervous system and digestive organs, and CB2 R, implicated in immunity and inflammation regulation). [35]

ECS triggers a retrograde signal when the excited postsynaptic neurons signal/act on the presynaptic terminals. The AEA and 2-AG produced in the postsynaptic neuron are released into the synaptic space and then, in a retrograde direction, journey to the presynaptic terminal to interact with CB1 receptors and prevent the neurotransmitter release by the presynaptic neuron. [36] The ECS is a widespread and complex brain signalling system vital in affective and cognitive functions and psychotic disorders. It may also be the target of various therapeutic compounds. The exposition of the ECS also explains the human attraction to cannabis, which seems to be the only plant that can produce potent phytocannabinoid stimulation on the CB1 receptors. [37]

The Benefits of Cannabis

Cannabis has been adopted for economic reasons, [18] medical illnesses (joint pain, muscle spasms, gout, dementia, multiple sclerosis, Parkinson's disease, social anxiety disorder, depression, tobacco use disorder, neuropathic pain, and malaria), [11, 38] source of textile fibres, edible plants, [5, 18] narcotic and psychoactive compounds [18], and hemp fibres for bioplastic and antibacterial agents, [18] In the early 19th century, over 100 publications on medicinal cannabis were published in Europe and the US. [3]

Genetics, growing environments (especially light), harvest time, part of the plant used, drying, storing, and processing may contribute to cannabis potency. [39] THC concentrations

positively correlate with cannabis effectiveness [21][40], while CBD moderates THC potency by hindering or dulling the domains of action. [21, 41] Unlike THC, CBD is neglected and obscured [27] but was found to reduce cannabis withdrawal symptoms in an open-label case study. [42] CBD effectively neutralises dose-dependent psychosis, [43] THC-induced paranoia, positive psychotic symptoms, [43, 44] lessens THC-induced anxiety, [45] and memory impairment. [43, 44] The THC: CBD concentration ratios contribute to the overall psychotropic and therapeutic effects [46] while CBD's protective effect on THC is not yet proven. [27]

Additionally, CBD has antioxidant, anti-inflammatory, and analgesic properties [23] and is highly effective as a sedative, anxiolytic, anticonvulsive, hypnotic, and anti-nausea compound. [23] A Phase III clinical trial on treatment-resistant epilepsies proved that CBD has well-documented anti-seizure and anti-epileptogenic properties against CB1/CB2R independent epilepsy. [23] On the other hand, CB1-selective antagonists reportedly prevent 19-THC or synthetic cannabinoid-induced seizures in mice when administered intraperitoneally. [23] Other cannabinoids, cannabidiol and cannabinoic acids (for example, 19-THC, CBD, CBC, CBG, CBN) have limited or no psychoactive benefits, pharmaceutical constituents, and bioactivities to manage pain, inflammation, depression, anxiety, epilepsy, cancer, fungal/bacterial infections [47] and as a safe substitute for other psychoactive substances in the case of addiction, hence, reducing the public health impacts of cannabis authorisation.

Depending on the ratio of THC to CBD content, cannabis products [21] can be classified into three categories: (1) high potency indoor-grown cannabis floral material of unfertilised/seedless plants (skunk), (2) low potency outdoor-grown imported floral material (herb/grass/weed) and (3) compressed blocks of plant matter (resin/hashish). [21] Skunk has the highest THC

content (15%), followed by imported herbs/grass (9%) that have no or low CBD, and lastly, resin/hashish (presumably landrace) that contain comparable quantities of THC (5%) and CBD. [39]

In 2017, the US National Academy of Medicine concluded that scientific knowledge of cannabis is limited in a document titled "The Health Effects of Cannabis and Cannabinoids – The Current State of Evidence and Recommendations for Research." [27] The document further revealed that there is "conclusive or substantial evidence" that cannabis or cannabinoids, effectiveness is only limited to relieving chronic pain in adults, as an anti-emetic to treat nausea and vomiting from chemotherapy, and improvement of spasticity in patients who have multiple sclerosis. [27]

With medical cannabis legalisation, patients now boldly barrage their healthcare providers with questions about cannabis's efficacy for pain and other ailments. Significantly, pain complaints have been responsible for more than half of all annual clinic visits in the US. Countless people have also been self-medicating on cannabis, while some have attested that cannabis relieved their pain significantly. In the early 19th century, cannabis was used mainly as a hypnotic and for analgesia. Recently, cannabis studies expanded exponentially, and the use of cannabis to manage pain has become one of the most widely researched subtopics. [3] There has been difficulty replicating cannabis-related analgesia between individuals because of the intricacies. Several studies, including multiple randomised, controlled clinical trials, proved cannabis effective pharmacotherapy for pain, but further pre-clinical studies of cannabis in pain models emphasised the distinction between cannabis analgesic effects. [3, 48] Wallace and his colleagues reported a likely therapeutic window of modest analgesia when cannabis is smoked, and in another experiment, it was proven that cannabis extract did not produce any analgesic or antihyperalgesic

effects. [49] These authors confirmed that cannabis could exert acute pain-inhibitory actions among those with chronic pain. Still, its efficacy for acute pain relief is limited by the poorly understood medical advantage and the dose-dependent incidence of antipsychotic side effects. The authors concluded that more research is needed due to the mixed results.

Significantly, cannabis use for pain management has reduced the need for opioid prescriptions. States with medical cannabis authorisation now have a lower rate of annual opioid overdose mortality compared to states that do not have authorisation. This reduction was also confirmed by the recent Medicare claims investigation in the US permissive states. In addition, the proportion of drivers that test positive for opioids after traffic fatalities have significantly decreased in states that allow cannabis use. Although some research proved that cannabis is potentially safer compared to opioids in pain management, it was also documented that more studies are still needed to confirm this claim. [3]

Effects of Cannabis Legalization

The liberalisation and legalisation of cannabis in certain countries, coupled with the reduced perception of harm, have significantly increased cannabis use and CUD rates. In the US, the citizens' struggle for medical and recreational cannabis legalisation led to the enactment of cannabis laws. The public opined that cannabis use was common among young adults despite the illegality and that cannabis causes less harm than alcohol, tobacco, and opioids. [10] They submitted that criminalising cannabis use, from users' arrests and criminal records, has caused more harm than cannabis use on its own. The masses also argued that these criminal laws disproportionately target minority populations, such as African Americans and Latinos. The legalisation of adult-use is a better social rule than criminalisation. Legalisation will eradicate the illicit market, enable cannabis use regulation, curtail adolescent access, monitor the THC

content of cannabis products, and reduce impurities like fungi, heavy metals, and pesticides found in illicit cannabis. As part of public opinion, legalisation is expected to minimise policing expenses and increase revenue from cannabis product sales. [10] Consequent to the legalisation of recreational cannabis use in the US, a substantial reduction in the cost of cannabis was recorded. There was a positive impact on revenue generation. Growers now produce on a large scale and no longer in secret to further reduce wholesale and retail prices. [10] Furthermore, legalisation has increased the potency by increasing THC content to 70% or more/gram in cannabis extracts, edible cannabis, and cannabis-infused beverages for maximum profits. [10] There is also increased availability and marketing of cannabis without criminal penalty, making cannabis use more socially acceptable and increasing the frequency and duration of use. Legalisation has also increased the frequency of emergency treatment seekers and hospitalisations and the wide distribution of cannabis to meet the needs of daily or near-daily cannabis users. [10]

Using the alcohol and tobacco regulations as a template, making more potent cannabis products accessible at a lower price will likely increase the rate of cannabis use among current users in the short term, while in the long run, activities to promote sales will be encouraged, hence, increasing the number of users while focusing on profit-making. Experience with alcohol shows that the larger the percentage of cannabis users and the frequency, the larger the adverse public health impacts of cannabis legalisation. [10]

Since the past decade, we have witnessed a colossal upsurge in the prevalence of the highly preferred high-potency cannabis globally [21, 40, 50] because of the availability, intense pleasure [21], low cost, and reduced perception of cannabis harm by users, [11] giving rise to high demand for cannabis treatment in addiction services. [51] Younger people, likely to be

chronic and heavy users, are especially vulnerable. Hence, more people under 18 years seek cannabis treatment compared to adults and other drugs.^[51]

The clinical and public health implication of preference and availability of high-potency cannabis is that more users are likely to consume high-potency cannabis, and those who prefer the low potency will have to settle for the readily available high-potent ones,^[21] oblivious of the harmful side effects.^[21, 40] The acute effects of short-term cannabis use include impaired memory, impaired motor coordination with an increased risk of motor vehicle accidents and emergency department visits, altered judgement, and, in high doses, paranoia and psychosis.^[1, 8] The long-term or heavy use of cannabis is linked with CUD, chronic bronchitis, and an increased risk of chronic psychotic disorders among the susceptible.^[1, 8, 21]

Early use in adolescence and long-term or heavy cannabis use is associated with altered brain development, poor educational outcomes, cognitive impairment, and diminished life satisfaction and achievement.^[1] Also, early-onset psychosis may develop from high-potent cannabis consumption, while resin/hashish does not produce a similar effect, even if used regularly.^[1] An extensive epidemiological survey in the USA estimated that 47.4% of males and 32.5% of females exposed to cannabis in their lifetime would develop a CUD, contrary to another study that stated that 7.0% of males and 5.3% of females who use cannabis at some point in their life might develop a CUD and more people would be diagnosed with cannabis abuse.^[3, 52]

A global estimate in 2017 indicated that more than 19 million people had CUD, and about 10% of cannabis users will develop at least an episode of CUD in their lifetime^[3]. The risk of developing dependency is multifactorial. However, intensive use of cannabis on a daily or almost daily basis may increase CUD risk^[53]

as well as early onset of cannabis use.^[9] Other factors include consuming more potent brands (particularly the flowering heads of the female specie) and using more water pipes may increase the quantity of THC consumed, hence, possibly increasing the rates of CUD.^[19] However, according to van der Pol *et al.*, there is no independent relationship between indices of cannabis use (including preferred type and THC concentrations) and the consequent incidence of dependence.^[54]

In addition, several cannabis users will experience withdrawal, but there is limited documented evidence on factors influencing the severity of cannabis withdrawal. Nonetheless, studies have shown that the quantity of cannabis use predicts the intensity of withdrawal when abstinent, while smoking behaviour may strongly predict cannabis dependence severity.^[5]

Regarding the aetiological factors of cannabis use disorders, about 50–70% of cases of CUD are due to genetic factors^[55] and developing CUD is linked to other comorbidities like a history of alcohol consumption, alcohol use disorders, and other psychiatric disorders and traits.^[55] CUD is vulnerable to an increased risk of infectious diseases and respiratory illnesses, male infertility (causing erectile dysfunction, testicular atrophy, and semen parameter issues), and mental health disorders. There is a substantial relationship between increased polygenic liability for cannabis use disorder and low white matter volume in cannabis-naive children born to mothers who use cannabis, signifying a potential role of cannabis-related genetic predisposition in early brain development.^[55]

Cannabis use has been linked with other mental health disorders, like anxiety and mood disorders,^[47, 52] particularly in the young.^[19] Cannabis is predominantly associated with bipolar disorder, substance use disorders, suicide, deliberate self-harm, and personality disorders (antisocial, dependent, and histrionic).^[52] According to a 15-year follow-up

study of a cohort of 45,570 Swedish participants, cannabis is an independent risk factor for schizophrenia. [27] There is a possibility that the pathology of the cannabinoid system in schizophrenia patients is associated with both increased rates of cannabis use and an increased risk for schizophrenia outside of the use of cannabis. [27]

Heavy cannabis use can also cause hyperemesis syndrome (HS), wherein the person visits the emergency room with severe abdominal pain, cyclical vomiting, and possibly mortality. HS is often reported by daily cannabis users in the absence of any other medical cause. [10] Heavy cannabis use may increase cardiovascular disease risk in young heavy cannabis smokers, and middle-aged men with myocardial infarction may experience angina if they smoke cannabis. [10] There is no established link between cannabis use and cancer of the head, neck, or lung, but a slight increase in the risk of testicular cancer has been reported among heavy cannabis users and those who have used cannabis for about ten years or more. [10] The fame of cannabis is increasingly a globalisation phenomenon, and the business continues to thrive. More consumers patronise cannabis daily without considering the effects and the shortage of information considering its efficacy. Like other substances, there are potential adverse effects of cannabis with acute and chronic use. [10]

Conclusion

Since antiquity, cannabis has been used to manage numerous neurological, psychiatric, and medical conditions with varying outcomes, even without prescription. The justification for the efficacy of cannabis for these conditions is not clear. Therefore, work is still ongoing to identify the medical conditions cannabis is effective in treating after years of its discovery. World leaders have opposed cannabis legality due to the many side effects encountered by users. These effects have not deterred the

increasing number of medicinal and recreational users who commonly patronise the high-potent brand, sometimes unintended, which is more in circulation. Given unresolved disputes about the advantages of medical and recreational cannabis policies, the strong movement toward correcting negative public attitudes and attempts to expunge cannabis from narcotics lists, more convincing evidence-based research is needed to guide policymakers, legislators, and medical practitioners on the safety of cannabis among the masses. This will also equip healthcare professionals to provide patients with quality care and information.

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