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Overview of cannabinoids with particular attention on the legal concerns, pharmacology, phytochemistry and its medicinal potential

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ABSTRACT

Due to the fast growing interest in marijuana (cannabis) research and its medicinal potential, the cannabidiol business is expected to reach $20 billion in sales by 2024. Marijuana has been used therapeutically for thousands of years. Additionally, with the discovery of the human endocannabinoid system and the identification of the molecular structures of tetrahydrocannabinol (THC) and cannabidiol (CBD), the medicinal potential of cannabinoids has been examined more thoroughly. The purpose of this paper is to address many aspects of cannabis, including its botanical characteristics, mechanism of action, pharmacokinetic parameters, and legal status. Articles were reviewed that were published in English literature reporting on cannabis and cannabinoid pharmacology, legal aspects, current scenario, and the articles reported activity of cannabidiol on different biological targets. The human data presented herein regarding the possible medicinal benefits and hazards of cannabis is limited to unprocessed, botanical cannabis, not isolated cannabinoids, some of which are medically recognised. Numerous research are currently underway to determine the function of cannabis in the treatment of a variety of ailments. The availability of various cannabis-based products may result in exposure to a variety of adverse consequences. Over the previous half-century, much information has been learned and the effects of marijuana and its cannabinoid components have been extensively researched in both non-medical and medicinal contexts. In 1964, delta-9-tetrahydrocannabinol (THC) was isolated from the cannabis plant as the primary psychoactive cannabinoid. Marijuana and synthetic cannabinoids have grown to be the most extensively used illegal narcotics in the world, and they are classified as drugs of abuse in the majority of nations. Chronic back pain, epilepsy, anxiety, depression, and post-traumatic stress disorder are all treated with marijuana. By considering the legal implications, medicinal potential, and probability of abuse, we find that it is difficult to sustain marijuana's legitimacy.

Keywords: Marijuana, Cannabis, delta-9-tetrahydrocannabinol, Cannabidiol, Pharmacokinetics, relief of muscle spasticity, analgesia, glaucoma**.**

1. INTRODUCTION

Cannabis Sativa (cannabis) is one of the first plants that humans cultivated [1]. As the legalisation of marijuana grows, one should equalise access to treatment rather than discriminate based on the therapeutic alternatives accessible to health care practitioners [2,3]. Marijuana is immediately seen as an unsuitable therapy choice by health care practitioners, despite the fact that it is useful in the treatment of chronic back pain, post-traumatic stress disorder, anxiety, epilepsy, and depression [4–6]. By researching the legal environment of medicinal marijuana for safety-sensitive professions, an action plan may be built to bridge the gap between federal and state restrictions. The global expansion of cannabis

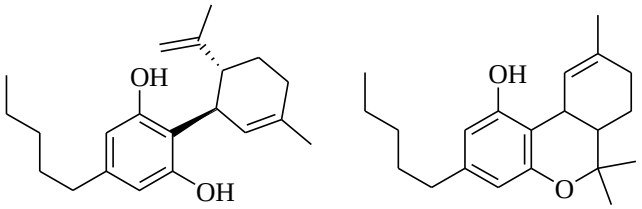
and cannabis-related goods has had a significant influence on the medical sector, in addition to the legal, sociological, and economic implications of these legislative developments [7]. Cannabis usage has risen in recent years, and it is now seen to be safer. In the United States, around 10% of cannabis users use the medication to treat a medical ailment [8–12]. Cannabis has a unique position as both a substance with a variety of purported health benefits (such as anti-depressant, hypnotic, and analgesic effects) and a schedule I narcotic (indicating that the drug has no recognised medical uses) that clinicians can directly offer to patients through certification [13–15].

A profusion of new marijuana goods, such as vaginal lubricants and skin care items, have been developed exclusively for women by a quickly increasing cannabis sector. Simultaneously, for teens, social media posts and pro-marijuana websites have become ubiquitous and virtually inescapable, making it difficult to objectively analyse the facts about marijuana's health impacts [10,16–23]. The purpose of this study is to identify the many medical disorders in which cannabis may be employed, such as analgesia, muscular spasticity alleviation, Alzheimer's disease, anticonvulsant, and glaucoma.

2. BOTANICAL AND PHYTOCHEMICAL FEATURES

Cannabis, the genus from which marijuana is derived, is a subset of the *Cannabaceae* plant family, which belongs to the angiosperm or seed-bearing vascular plant classification [24]. The three sprimary species of interest within this genus are *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*. The *C sativa* and *C indica* are most commonly harvested because *C ruderalis* is sparse and grown in more harsh environments like the Himalayas [25,26]. Cannabis is a broad phrase that refers to these three hemp plant types. There are as many as 565 phytochemical compounds found in these plants, but only around 120 of them (roughly) are unique to the cannabis plant and are referred to as cannabinoids internationally. The effects of not all of them are psychotropic. Delta-9-tetrahydrocannabinol (THC) and cannabidiol are two of the most well-studied phytoconstituents (CBD). THC is primarily responsible for the psychotropic effects of hemp, but CBD is often found in hemp-based commercial products including paper, building materials, and textiles [27–33]. Marijuana refers to the dried leaves, flowers, and seeds of these plants that are utilised for recreational and medicinal purposes. Variable strains of cannabis have different amounts of THC and CBD, which affects its medicinal effects.

Although the quantity of THC discovered in any particular batch of marijuana may vary significantly, the proportion of THC in recent years has grown due to cross-cultivation and the selection procedures involved in cultivating healthy harvests [34–36]. The chemical name of CBD is 2-[(1R,6R)-3-methyl-6-prop-1-en-2-ylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol and THC is 6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydrobenzo[c]chromen-1-ol. The structures of CBD and THC are represented in fig. 1.



Cannabidiol (CBD) delta-9-tetrahydrocannabinol (THC)

Fig. 1. The structures of Cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC)

3. THE MOLECULAR MECHANISM INVOLVED IN ENDOCANNABINOID SYSTEM

Cannabinoid receptors, ligands, and signalling molecules present throughout the human body are hypothesised to be linked to a range of homeostatic functions, such as mood, tiredness, appetite, memory, and pain. Cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2) are the major receptors in this system (CB2). The endocannabinoid system includes G protein-coupled receptors

like those in the endocannabinoid system. CB1 is present throughout the central nervous system, while CB2 is located in immune cells and is assumed to have an immunomodulatory role in the immune system [37].

N-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol, often known as endocannabinoids, are the two most well-studied endogenous ligands for these receptors [36,38,47,39–46]. Migraines, fibromyalgia, irritable bowel syndrome, depression, schizophrenia, multiple sclerosis, Parkinson disease, anorexia, and failure to thrive have all been linked to deficiencies or dysregulation of this system. Exogenous cannabinoids, particularly THC, are known to act primarily on the CB1 receptor, which is thought to contribute to their psychoactive effects [48,49,58,50–57].

4. MEDICAL CANNABIS AND CONCENTRATES

Whether or not it includes THC, the phrases "medical marijuana" and "medical cannabis" are interchangeable and may be used to describe any legal cannabis composition intended for therapeutic reasons. The legal definition of "medical cannabis" differs per state in terms of formulations, authorised ingredients, and qualifying health conditions. Several jurisdictions allow THC to be used medically, although the medicinal usage of chemicals like CBD, which have no psychoactive characteristics, is limited [59–64].

Another significant category of marijuana goods is "concentrates," which refers to items with high THC concentrations (potentially >80%-90%). These, as their name indicates, need fewer dosages to create more long-lasting and stronger effects, and may be taken recreationally or therapeutically. Concentrations come in a variety of compositions and formulations, and are variously classified as "hash," concentrates derived from "solvent and CO_2-based procedures," and dry or water-based extractions [65–70].

5. PHARMACOKINETICS PROFILE OF CANNABINOIDS

Cannabinoids may be ingested in a number of ways. Because of their high lipid solubility in places like the eye and nasal mucosa, topical administration is conceivable [71,72]. However, this has only had a limited use since previous THC formulations were known to irritate the eyes [73]. In aqueous solution, however, emerging vehicles that allow lipid-soluble compounds to be delivered to the eye may rekindle interest in this method [74–76]. Oral administration causes sluggish and variable absorption, with bioavailability ranging from 10% to 20%, and often less than 15%. Hepatic absorption from portal venous blood is likewise high, with active first-pass metabolism in the liver. However, there is no loss of pharmacological action as a consequence of this [77,78].

Intravenous injection or infusion is feasible due to cannabinoids' poor water solubility, but it requires a particular formulation, such as a solution in a water-miscible organic solvent or a combination of the cannabinoid with plasma protein [79]. Without such formulations, almost little active material may be delivered, and intravenous toxicity is mostly caused by the injection of insoluble particle material.

Smoking is perhaps the most well-known form of administration, and it is the most common way of utilising crude marijuana rather than purified cannabinoids [80,81]. THC in the plasma, like other highly lipid-soluble medicines, is mostly delivered as a loosely bound compound with plasma protein. As this complex dissociates quickly, free THC penetrates cell membranes quickly and reaches the tissues in accordance to their individual blood flow rates [73,80–83].

6. CANNABIS LEGALITY

The narcotic drugs and psychotropic substances act of 1985 is a fundamental legislation that controls the usage of cannabis. Cannabis is prohibited in India under this law. With the exception of bhang, the legislation has kept the same definition of cannabis. However, various states in India have varying rules regarding the usage of this plant. Uttarakhand, for example, was the first state to authorise cannabis usage for commercial growth. In Odisha, however, the usage of this plant is permitted. Section 66(1)(b) of the

Bombay Prohibition (B.P.) Act, 1949 prohibits the manufacturing, possession, and use of non-licensed bhang and bhang-containing drugs in Maharashtra. On February 21, 2017, Gujarat legalised bhang by removing it from the list of "intoxicating substances" covered by Section 23 of the Gujarat prohibition statute. As a result, cannabis is a useful plant, and India is progressively coming to terms with the idea that it may be used for both medicinal and commercial purposes [84,85,94–103,86–93].

For medicinal use several different products exist and these differ in THC/CBD profile, licensed indications, formulation, and quality for standards are given in Table 1.

Table 1.

An overview of cannabis-based products and cannabinoids

Cannabis based products for medicinal use					**Synthetic cannabinoids for medicinal use**	
Example	Bedrocan	Tilray	Sativex	Epidiolex	Dronabinol	Nabilone
Cannabinoid Profile	THC +/−CBD	THC +/−CBD	THC:CBD ratio 1:1	CBD	THC	THC
Formulation	Herbal cannabis	Oil	Oromucosal spray	Oral solution	Capsule or liquid	Capsule
Licensed indication (UK)	None	None	Multiple sclerosis	None	None	Chemotherapy induced nausea and vomiting
Quality standards	Good manufacturing practice	Good manufacturing practice	Good manufacturing practice	Good manufacturing practice	Good manufacturing practice	Good manufacturing practice

Table 2 summarises the evidence from systematic evaluations of cannabis-based products and cannabinoids for the treatment of treatment-resistant epilepsy, multiple sclerosis, chronic pain, nausea, and vomiting associated with chemotherapy. Looking at cannabis-based products for therapeutic purposes and their legality in India, it is garnering greater attention for medicinal purposes; some of the medicinal benefits of marijuana are detailed in the section below.

7. THE MEDICINAL USES OF CANNABIS AND CANNABINOIDS

7.1 As anti-emetics

In patients with nausea and vomiting associated to cancer treatment, controlled clinical studies compared the anti-emetic effects of THC (given orally) to those of a placebo or another anti-emetic medicine [104–107]. THC and other cannabinoids that produce similar effects (known as cannabinoid agonists) were found to be more effective than placebo and often had levels of effectiveness similar to the anti-emetic drugs with which they were compared in systematic reviews. Oral cannabis were shown to be beneficial in treating chemotherapy-induced nausea and vomiting, according to the US National Academies of Sciences, Engineering, and Medicine (NASEM) [104–113].

7.2 Analgesia

Although previous trials failed to establish, there is a constant useful degree of analgesia with intravenous THC, oral cannabinoids, or smoked cannabis. In humans, oral or parenteral THC, levonantrodol, and cannabis extract have been shown to reduce dental, surgical, visceral, and cancer pain in short-term studies. In open-label, uncontrolled research, both oral cannabinoids and smoked cannabis have been shown to be effective analgesics. Although the beginning of effect is faster with smoking, there are few cases when this is a significant factor. For example, in chronic pain, the treatment goal is to maintain

continuous and consistent analgesia, therefore the consecutive doses are scheduled, and only the difference in speed of action would be pertinent to the initial dosage. Indeed, the longer-lasting and less strong impact of oral THC seems to be preferable to the more intense but shorter-lasting effect of smoked cannabis. Furthermore, smoking's pulmonary consequences would be a significant disadvantage for long-term usage in chronic painful conditions like musculoskeletal issues [114–123].

7.3 Relief of muscle spasticity

Many claims have been made about cannabis' capacity to treat muscular spasms, particularly in multiple sclerosis, although most of these claims are based on unconfirmed subjective experiences rather than controlled trials [124–126]. In a case report of one patient, the suppression of pendular nystagmus was reported by smoking cannabis. Nonetheless, multiple controlled trials using objective measures of spasticity as well as subjective self-reports have indicated improvement following oral and rectal administration of THC or nabilone. There have been no controlled trials comparing the antispasticity effects of smoked marijuana and oral THC in the same individuals, and no controlled comparisons with other medicines presently used for spasm alleviation [127–131].

7.4 Glaucoma

In a case report of one patient, the suppression of pendular nystagmus was reported by smoking cannabis. Nonetheless, multiple controlled trials using objective measures of spasticity as well as subjective self-reports have indicated improvement following oral and rectal administration of THC or nabilone. There have been no controlled trials comparing the antispasticity effects of smoked marijuana and oral THC in the same individuals, and no controlled comparisons with other medicines presently used for spasm alleviation [132–135].

To have such a long-lasting impact from marijuana, you'd have to smoke it eight to ten times a day. Oral THC has a longer effect and requires fewer doses per day, but it is still impossible to prevent euphoric effects at THC dosages that would offer a meaningful decrease in intraocular pressure [136–139].

7.5 Anticonvulsant

THC and cannabidiol both show phenytoin-like effects in models of grand mal seizures, according to several animal studies, although tolerance to THC's activity develops quickly. One well-designed, but regrettably small-scale, double-blind controlled research was conducted in epileptics who did not have significant therapeutic benefit with conventional medicines, despite seemingly excellent compliance [140–143]. When cannabidiol oral capsules were administered as a complement to their normal therapies, their seizure frequency was much lower than when they got placebo capsules. Two further double-blind, placebo-controlled clinical studies of cannabidiol in epileptics have been conducted, but regrettably they have not been published in full, and are claimed to have showed no therapeutic efficacy since then [144–148].

Reduced Obesity Rates- According to a 2011 study published in the American Journal of Epidemiology, obesity is lower in those who use cannabis than in nonusers. In animal tests, the level of fat in the body as well as its response to insulin had an impact from the drug [149]. In rats, cannabis compounds were shown to raise metabolism leading to lower cholesterol and lower levels of fat in the liver. To find a drug targeting obesity-related diseases human trials are being conducted [150–154].

7.6 Alzheimer’s disease

Alzheimer's disease (AD) is the most prevalent form of dementia, and it is marked by a variety of severe symptoms such as cognitive loss, sleep disturbances, and behavioural abnormalities. Cannabinoids are being studied for their medicinal potential in Alzheimer's disease, particularly for calming effects and sleep disturbances [155–157]. Long-term use of cannabis affects memory, cognitive functioning, and balance in

frail older adults, therefore assessing memory and cognitive function as outcome measures is crucial. There are no RCTs using whole plant cannabis to treat Alzheimer's disease symptoms or progression [155,158–161]. Cellular or flawed animal models provide some fascinating beneficial advantages related to the ageing process. Four RCTs with isolated cannabinoids have been published, but little is known regarding their safety in this group, particularly because long-term cannabis exposure raises the risk of mental disorders and dysfunction (e.g., cognitive abnormalities, psychotic, mood disorders) [160].

7.7 Other medicinal uses of cannabinoids

Patient groups and some doctors have advocated using cannabis and cannabinoids to treat a variety of conditions in addition to those described so far. These conditions include anxiety disorders [162], such as post-traumatic stress disorder [163], depressive disorders [164], sleep disorders [165,166], types of chronic pain not included in the clinical trials to date; degenerative neurological conditions [167,168], and inflammatory bowel diseases [169,170] such as Crohn's disease. Some patients with these conditions have reported clinical benefits from using cannabis or cannabinoids. Medicinal use of cannabis based products and cannabinoids are mentioned in Table 2. Fig. 2 represents the medical uses of marijuana and cannabinoids.

Table 2. Summary of evidence for medicinal use of cannabis based products and cannabinoids.

Indication	Number of studies (participants)	Primary products tested	Comparator	Outcome	Summary estimate (95% confidence interval)
Chronic pain	9 (1734)	Sativex (THC+CBD)	Placebo	30% reduction in pain	Odds ratio: 1.46 (1.16 to 1.84). More effective than placebo
Treatment resistant epilepsy	2 (291)	Epidiolex (CBD)	Placebo	50% reduction in seizure frequency	Relative risk: 1.74 (1.24 to 2.43). More effective than placebo
Nausea and vomiting due to chemotherapy	3 (102)	Dronabinol (THC)	Placebo	Complete response in nausea and vomiting	Odds ratio: 3.82 (1.55 to 9.42). More effective than placebo

Fig. 2. The medical uses of marijuana and cannabinoids

8. OVERVIEW OF SAFETY AND EFFICACY STANDARDS

A solid scientific and evidence-based procedure has greatly improved the effectiveness, safety, and quality of medical items on the market in nations throughout the world. This should remain the overarching organisational concept for reviewing and approving drugs for medical use. The scientific, medical, and public communities may be confidence that judgments are made based on scientific facts and judgement by following a thorough procedure. This is the indication of a well-functioning public-safety system. If cannabis is subjected to the same standards as other pharmaceuticals, clinical trials must be developed and executed in a manner that gives regulatory authorities with the scientific facts they need to make approval decisions [171–173]. There would be no obligations for post-marketing monitoring or reporting of adverse occurrences without official authorisation. As a result, the negative effects of cannabis are mostly related to its usage for recreational reasons, even if worries about its negative effects when taken for medicinal purposes are growing. In addition, unlike contemporary pharmaceuticals, cannabis is a complex cocktail of hundreds of compounds with unknown quantities, pharmacological effects, and adverse effects, supplied primarily via a new and controversial means of administration for medicines: smoking or vaporisation [174–177].

9. ADVERSE EFFECTS

Regular marijuana usage is linked to a variety of behavioural problems. Adolescents who start smoking cannabis later in life smoke less and become less hooked than those who start earlier. Cannabis usage is linked to a reduction in short-term memory, poor academic or occupational performance, mood problems, psychosis, and cognitive function. Marijuana seems to have dose-dependent impacts on the functioning of motorbikes, vehicles, aircraft, and trains. For example, car accidents are 2-7 times more likely when marijuana is used. Perceptual alterations, including time distortion and "mild euphoria, relaxation" experienced by marijuana users. Intensification of ordinary experiences such as listening to music, hunger, eating, and perceptual alterations, including time distortion and "mild euphoria, relaxation" experienced by marijuana users. Paranoia, dysphoria, and anxiety are other common symptoms. Marijuana's pulmonary, cardiovascular, and carcinogenic effects are still debated [178–183].

CONCLUSION

Although cannabis has a long history of medicinal usage in both traditional and Western medicine, it went out of favour about a century ago when it was replaced by more dependable, stable, and effective new synthetic drugs. The extraction and synthesis of pure cannabinoids, including more powerful synthetic variants, as well as the identification of cannabinoid receptors and their endogenous ligands have reignited interest in possible medicinal applications. Many marijuana users say that they take the drug for medicinal rather than hedonistic reasons. Pure THC has previously been authorised for the stimulation of hunger as well as the alleviation of nausea and vomiting. Glaucoma, muscular spasms, pain relief, and epilepsy are among the prominent claims for additional applications. Animal trials and clinical observation have produced varying degrees of evidence for these claims, although the majority of the controlled clinical observations have been with pure cannabinoids given by mouth rather than smoked cannabis. The bulk of "proof" or claims about medical marijuana's usefulness are anecdotal, and the few studies that do exist are considered "poor quality." Many contend that legalising marijuana in the absence of substantial clinical evidence does not justify the drug's medical use. While numerous trials have been conducted over the last decade, the implications for medicinal and recreational marijuana users in the perioperative setting offer exciting new research opportunities. Maintaining patient safety as a priority, continued study into the provision of high-quality treatment to patients who use marijuana medicinally or recreationally is required. Additional investigations on dose and drug interactions, as well as studies with longer-term participant follow-up, research and clinical trials, especially bigger and better-designed trials, are needed. We conclude that maintaining the legitimacy of marijuana usage is challenging when considering the legal elements, medicinal potential, and probability of abuse.

LIST OF ABBREVIATIONS

CBD = Cannabidiol
THC = tetrahydrocannabinol
CB1 = Cannabinoid Receptor Type 1
CB2 = Cannabinoid Receptor Type 2
IOP = Intraocular Pressure
AD = Alzheimer’s Disease

CONSENT FOR PUBLICATION

Not applicable

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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