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Original Article

Comprehensive Pharmacological Study of Cannabis Sativa Plant

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ABSTRACT

Cannabis, also known as marijuana, contains several chemicals, especially Δ-9 tetrahydrocannabinol and cannabidiol, that may have therapeutic and medical benefits. Though few of them are cardiovascular in nature, cannabis may have medicinal advantages. On the other hand, cardiovascular disorders are among the many alarming health effects of cannabis, however delivery systems may play a role. This statement assesses the safety and efficacy profile of cannabis, especially in regard to cardiovascular health, and critically examines its usage for medical and recreational purposes from a clinical, policy, and public health standpoint. Although the identification of its botanical basis, cannabis, as a substance of abuse has hindered the development and clinical application of cannabinoids, they exhibit promise as therapeutic agents, especially as analgesics. More cannabis study is required to better understand the pharmacological potential of cannabinoids as medicines and to ascertain the impact of growing herbal cannabis use on both individual and public health. In order to help doctors provide patients who use cannabis with informed advice and care, this article discusses clinical, research, and regulatory problems linked to herbal cannabis. It also looks at potential and challenges to further study on the health consequences of cannabinoids and herbal cannabis. It used to have a significant place in medical history and was advised by various distinguished doctors for a variety of illnesses, most notably headache and migraine.This plant has had an interesting transformation over the years, going from being legal and often recommended to being outlawed due to social and political considerations rather than scientific ones. But as evidence of its many therapeutic benefits grows, the false stigma associated with cannabis is eroding, and there has been a significant drive to legalize medical marijuana and research. Since patients may unavoidably ask about cannabis for a variety of conditions, including chronic pain and headache disorders for which there is some intriguing supporting evidence, doctors must be knowledgeable about the drug's history, pharmacology, therapeutic indications, and appropriate clinical use.

Keywords: Cannabis Sativa, cardiovascular disorders

INTRODUCTION

The existence of several chemicals that cause psychoactive effects in those who consume it defines the complexity of the Cannabis sativa plant. Through a sequence of pyrolysis events, more than 500 chemical compounds have been found in marijuana to date, including over 60 cannabinoids, which produce more than 2000 chemicals in marijuana smoke [1],[2] When tetrahydrocannabinol (THC) is introduced into the body, it causes a variety of effects, including changes in mood, perception, memory, movement, and cognition. In certain situations, it also causes an increase in dopamine release, which ultimately results in euphoric feelings and anxiolytic effects [3] As a result, this study has also studied the usage of marijuana as a pharmaceutical medicine, particularly its application in the treatment of severe acute respiratory syndrome coronavirus-2 (SARs-Cov-2). [4] [5] Notwithstanding the fact that efforts to curb its use have been met with a push to legalize it primarily for medical purposes, marijuana's increased illegal trading in black markets and consumption patterns raise concerns about its potentially harmful effects on human health, particularly its role as a precursor to the development of cancer. This is true even though there are few documented mortality cases linked to marijuana use among consumers. However, some systematic and epidemiological investigations have identified marijuana use as a risk factor for respiratory problems and pulmonary function. [6]

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From sea level to the mountain slopes of the Himalayas, where it may have originated, Cannabis sativa L. (Cannabaceae) can be found in a range of environments and elevations [7]. Since ancient times, cannabis sativa has been used for therapeutic purposes. Its medicinal usage was first documented in the sixth century B.C. in the Middle East and Asia. It wasn't until the early nineteenth century that it was first used in western medicine. [8, 9] By evaluating a few published studies from various journals and databases, this study aims to investigate the apparent harm and psychotic effects that result from recurrent use of this psychoactive chemical substance as well as the scientific attempts made to stop it. The main goal of this effort is to evaluate the known emerging compounds from cannabis cigarette smoke and their potential for cancer. Additionally, this survey has assessed scientific initiatives aimed at lowering marijuana toxicity. Furthermore, the legalization of marijuana for medical use due to its anti-inflammatory, antioxidant, neuroprotective, and anticonvulsant properties has expanded in several states and countries worldwide on the grounds that it contains chemical compounds that are effective in treating a variety of illnesses and symptoms, regardless of the risks involved [10]. The system of endocannabinoids (ECS) It was discovered in 1964 that delta-9-tetrahydrocannabinol (THC), commonly referred to as dronabinol, is the main psychoactive component of cannabis. Early research into its mode of action mostly focused on electrophysiological evidence, which revealed that euphoria could result from a decrease in inhibitory activity in the thalamus, cerebellum, and septum. [11] There is mounting evidence that the ECS is disrupted in a variety of physical and mental health disorders, either as a component of the underlying disease or as a physiological reaction. [Therefore, the ECS is a likely target for a novel pharmacological approach to many illnesses that are currently untreatable, either by boosting the endocannabinoids themselves or by directly targeting the receptors with agonists or antagonists. [12,13]

Fig no.1 Cannabis sativa

HISTORY:

For thousands of years, people have utilized the herb cannabis, commonly known as marijuana, for medical purposes. [14] [15] In 1850, it was formally included to the U.S. Pharmacopeia, and during the early 1900s, a variety of cannabis products and extracts were sold. Cannabis prescriptions became less common in medical practice as highly regulated pharmaceuticals with identified active constituents at known doses gradually replaced whole plant medicines and herbs in western allopathic medicine. This was also the case as public concern over cannabis use on the streets grew. It maintained its important position until 1937, when the American Medical Association rejected the Cannabis Tax Act, which led to cannabis' exclusion from the National Formulary and the 1941 U.S. Pharmacopeia. [16] Cannabis is one of the oldest plant sources of food and textile fibre, and its use and cultivation date back between 5000 and 6000 years, making its origin difficult to determine. [17,18] Following his stay in Calcutta, India, Dr. William

Brooke O'Shaughnessy brought the medical applications of C. indica, also known as "Indian hemp," to the Western world in 1839. He recommended using it as a muscle relaxant and for analgesia. [19,20]. He was a physician and scientist who graduated from the University of Edinburgh, and a professor of chemistry at the Medical College of Calcutta. [21,22] In the 1840s, Dr. Clendenning of London was among the first Western doctors to use cannabis to treat migraines. [23,24]

Pharmacology and pharmacokinetics:

Two naturally occurring, on-demand cannabinoids (anandamide and 2-arachidonoylglycerol) and two CBD receptors (CB1) make up the vast and intricate endogenous endocannabinoid system and CB2. [25,26,27] Cannabis, like any other drug substance, follows a systematic pathway from the moment it enters the body system until it is eliminated through a number of biological processes that include absorption, distribution, metabolism, and excretion. These processes are all reliant on the drug's bioavailability, which establishes the beginning, length, and severity of the effects the drug produces. [28] Many times, cannabidiol has been used in unregulated settings to provide therapeutic results, which raises questions about its therapeutic drug monitoring. Although CBD has been used for many therapeutic purposes, there is still a dearth of information regarding its pharmacokinetics, according to Millar et al. (2018).[29] Because of changes in drug concentration throughout ingestion, the method of administering cannabis to the human body system affects how quickly it is absorbed and how it is metabolized.[30] When THC is taken orally, the psychotropic effects take between 30 and 90 minutes to manifest, peaking after 2 hours and remaining active in the smoker for 4 to 12 hours, depending on the dosage smoked. In contrast, when THC is inhaled and absorbed through the pulmonary system, the associated psychotropic effects appear within 1 minute but peak after 20 to 30 minutes. [31,32,33] The bioavailability of cannabis is significantly influenced by the puff counts, residence and interval times, inhalation volume, and hold durations. [34] Particularly in the liver, where microsomal hydroxylation and oxidation processes take place, metabolic activities on THC occur. [35] The hydroxylation stage entails the cytochrome P-450 (CYP2C19) complex enzyme catalysing the conversion of THC to 11-hydroxy-THC, which is then oxidized to 11-nor-9-carboxy-THC, which glucuronates to THC-COOH beta glucuronide, which is not psychotropic. [36,37] As a result of slower rates of redistribution from deeper fatty acid compartment tissues, heavy cannabis users have a somewhat prolonged THC elimination half-life of roughly 22 hours. [38,39]

Therapeutic Effects:

There is growing evidence that both neuropathic and non-neuropathic pain can be relieved by herbal cannabis. [40,41] There is the strongest evidence for neuropathic pain, and at least five excellent randomized controlled clinical trials have demonstrated the analgesic effectiveness of smoked cannabis. [42,43,44,45,46,47] The relative analgesic effects of the various herbal cannabis components are not entirely clear. THC and CBD are the two cannabinoids that are usually found in the highest concentrations in herbal cannabis, and there is evidence that both of them may have analgesic properties. Given that THC produces rewarding (euphoric) effects but CBD does not, this is clinically significant. Dronabinol, an FDA-approved THC-based drug sold in the US, and smoked cannabis did not differ in their analgesic effects, according to one well-conducted study. [48] In addition to pain, there is some evidence and ongoing research supporting the potential therapeutic effectiveness of cannabis for common pain-related symptoms and conditions, such as migraine, sleep disturbance, anxiety and post-traumatic stress disorder, nausea and vomiting, cachexia, inflammatory bowel diseases, and spasticity linked to multiple sclerosis or stroke. Patients who experience pain may also choose to use cannabis to treat these symptoms. [49,50,51,52,53,54,55,56,57]

Side Effects and Risks:

It is crucial to remember that the majority of the known dangers associated with cannabis use have been found through research on recreational use; caution should be used when presuming that medical users have the same risk profile. Different patterns and purposes of use may result in reduced risk rates, whereas possible drug interactions or co-occurring conditions may result in greater risk rates. A review

has been conducted on the negative effects of prescription cannabis in clinical studies. [58] They are often mild to moderate in severity, with the most common symptoms being dry mouth, sleepiness, and dizziness. According to a recent study, individuals who used 2.5 g of herbal cannabis with 12.5% THC on average for one year as a pain reliever experienced more adverse events than control subjects, although not more significant ones. [59] As a result of decreased availability of the cannabinoid receptors, primarily the CB1 receptor, tolerance will develop with prolonged use. [60] When the dosage is lowered, the formulation is altered, or cannabis is abruptly withdrawn, long-term users may suffer from withdrawal symptoms. Anger, anxiety, restlessness, irritability, depression, insomnia, odd nightmares, appetite loss, headaches, and night sweats are some of the warning signs and symptoms. These effects usually start a few days after stopping cannabis use or reducing dosage, peak after about 10 days, and subside around 30 days. [61,62]

FORMULATIONS:

Pure THC, CBD, or both may be present in cannabis products. The formulation and administration of products can differ. [63] A dispensary sells goods for both medical and recreational purposes, depending on state legislation. Since the Farm Bill was passed, pharmaceutical companies are now able to market and sell topically pure CBD products over-the-counter. 16 Unlike other over-the-counter products, these topical medications are exempt from the US Food and Drug Administration's drug approval procedure since they do not make any claims to prevent, diagnose, treat, or cure illnesses. Some of these topical items have had their CBD content tested by the US Food and Drug Administration, and many of them were found to lack the CBD concentrations stated on the label. [64]

Dosing:

The potency of the substance, how it is processed, and the various smoking and vaporizing methods all affect the dosage needed for smoked or vaped cannabis in order to produce therapeutic results and prevent side effects. [65] Although the effects of oral cannabis administration are less well defined, a dose of 0.15 to 0.30 mg/kg THC (i.e., 10–20 mg THC taken orally) seems to be adequate to produce psychotropic effects, and a dose of 0.45 to 0.6 mg/kg THC (i.e., 30–40 mg THC taken orally) should result in noticeable intoxication. [66] 5. Patients should be advised that they should be especially cautious when stacking oral doses because the effects start to manifest 30 minutes to ≥1 hour after ingestion and peak in 3 to 4 hours. Edibles should be consumed gradually, in small amounts at a time, and with enough intervals between doses. Administration with a high-fat meal significantly increases the absorption of oral cannabinoid and may exacerbate these effects. [67], [68], [69]

Considerations in Special Populations:

Young Adult's

Cannabis is the most often used narcotic that teenagers abuse globally, aside from nicotine. There have been reports of lower sustained attention, a lower verbal or overall IQ, and inferior executive functioning linked to early-onset use, which is generally characterized as usage beginning before the ages of 16 to 18. [70] [71] [72] Regular cannabis use during adolescence may cause structural alterations such altered cortical gray matter development and decreased white matter myelination, according to several neuroimaging studies. [73,74,75] The effects of cannabis usage on adolescents and young adults are less obvious, despite the fact that a few observational studies in older individuals have shown improvements in affective symptoms including anxiety and depression. A recent meta-analysis of 11 studies with 23,317 participants evaluated depression and cannabis usage at various intervals from youth to early adulthood. [76] Lastly, Parekh et al. conducted an analysis using the Behavioral Risk Factor Surveillance System. [77]

Pregnant women

Tetrahydrocannabinol can affect the endogenous endocannabinoid system in both the mother and the fetus by entering the fetal brain through the mother's blood flow. [78] In a state where medical and recreational cannabis use are legal, a study analysing state-level prevalence estimates of prenatal and early postnatal cannabis use found that the self-reported prevalence of cannabis use at any point during pregnancy was 5.7±0.5%, and the prevalence of early

postnatal cannabis use among breastfeeding women was 5.0% (95% CI, 4.1–6.2). Regardless of maternal age, race/ethnicity, educational attainment, or tobacco use during pregnancy, prenatal cannabis use was linked to a 50% higher risk of low birth weight (OR, 1.5 [95% CI, 1.1–2.1]; P=0.02). [79] Compared to women who did not use cannabis during pregnancy, those who did had a higher chance of anaemia (OR, 1.36 [95% CI, 1.10–1.69), according to a systematic review and meta-analysis of prenatal exposure to cannabis and maternal and child health outcomes. The risk of low birth weight was also higher for infants exposed to cannabis in utero than for those whose mothers did not use it throughout pregnancy (OR, 1.77 [95% CI, 1.04–3.01]; pooled mean difference for birth weight, 109.42 g [95% CI, 38.72–180.12, respectively]). [80] Additionally, tetrahydrocannabinol has been detected in breast milk for as long as six days following the last documented use, which may have an impact on the developing newborn's brain and cause hyperactivity, impaired cognitive function, and other long-term effects. [81]

Patient Education and Considerations:

When deciding whether to use cannabis for medical or recreational purposes, the patient and provider should jointly consider state and federal regulations, potential risks and advantages for different administration methods, and side effects. [82] All cannabis products sold on the black or gray market should be avoided due to the possibility of contamination and adulteration, particularly synthetic illegal cannabinoids. Similar to tobacco and nicotine products, it is generally not advised to smoke or vape cannabis, particularly in patients who have respiratory conditions like asthma or chronic obstructive pulmonary disease. Patients with severe liver disease should also refrain from using cannabis due to the possibility of fibrosis or steatorrhea. [83] Blood THC concentrations of 2 to 5 ng/mL are linked to significant driving impairment; thus, it is best to avoid operating heavy machinery or driving a car. [84] To reduce any potential negative effects, it is important to explain why edible cannabis takes longer to start working. Due to the possibility of cannabis withdrawal syndrome, patients who have been heavy users of cannabis for a long time should not abruptly stop using it. In the event that symptoms of hyperemesis syndrome or cannabis withdrawal appear, patients should get in touch with their doctor right away. Furthermore, due to the risk of exacerbation, patients with a personal history of psychiatric disorders (such as psychosis, schizophrenia, anxiety, and mood disorders), a history of substance abuse, including alcohol or concurrent psychoactive drugs, or a family history of schizophrenia should not use cannabis that contains primarily THC (with little to no CBD), especially higher levels of THC. Patients who use cannabis should be aware that, despite the fact that more than 30 states have authorized the drug for medical use, less than half of them offer protection against being fired or turned down for a job due to a positive cannabis test. This is because state laws vary. Lastly, even in cases when a patient has a verified medicinal justification, it is illegal to transfer cannabis across state lines. [85]

CONCLUSION:

Cannabis has been used historically for a variety of medical conditions. Its numerous pharmaceutical applications and possible advantages in treating some types of headache disorders, including as cluster and migraine, are extensively supported. Patients will become more aware of cannabis as a potential treatment for chronic pain and headache disorders as more states legalize it for medical purposes and/or restrict its use to CBD alone. As a result, it is critical that doctors are educated on the history and appropriate medicinal use of cannabis. There are many pharmacological and biochemical components in cannabis, but only a small portion of them are known to have therapeutic use. Triptan modes of action and other migraine-related pathways seem to be modulated and interacted with by cannabinoids. and opiate pathways, indicating a possible complementary or associated advantage, many new classes of medications may be based on altering the endocannabinoid system by agonizing or antagonizing its receptors, focusing on its metabolic pathways, such as inhibiting endocannabinoid-degrading enzymes, or combining cannabinoids with other atialgesics for synergistic effects. Randomized clinical trials are required for confirmation and additional assessment, even if there is little data and research indicating a therapeutic potential for cannabis and cannabinoids in some headache diseases

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