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## THE ULTIMATE HERB CANNABIS FOR AFFECTING DISEASES

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### ABSTRACT

Based on continuing and validated clinical trials, this review focuses on the medicinal benefits and effectiveness of cannabis. Indian medical professionals have been using cannabis plant parts for the treatment of numerous illnesses, syndromes, and disorders since 5,000 years ago. The synthetic cannabinoid nabilone is authorized for the treatment of severe Vomiting and nausea brought on by chemotherapy for cancer. In lung epithelial cells, cannabidiol (CBD) and its metabolite 7-OH-CBD potently inhibit SARS-cov-2 replication, but neither THC nor any other tested generic cannabinoid did. Cannabis may have an anti-inflammatory and bronchodilator effect on the airways, but it also has many detrimental effects on asthmatic patients' lungs. The active components of this plant are cannabidiol (CBD), which is thought to be less harmful to the nervous system and more effective in treating seizures than delta-9-tetrahydrocannabinol (THC). New receptors, ligands, and mediators associated with the endocannabinoid system have been discovered by science, and these findings have made it possible to develop novel therapeutic targets for the treatment of various pathological disorders while reducing the unwanted Certain components of this plant have the potential to be psychoactive. FDA-approved medications, such as cannabiximols, which are a combination of THC and non-psychoactive cannabidiol (CBD), are now used to treat multiple sclerosis pain and spasticity. Cancer patients who experience nausea and vomiting as a result of chemotherapy can be treated with dronabinol and nabilone. Dronabinol has been authorized for the management of anorexia in individuals suffering from acquired immune deficiency syndrome (AIDS).

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### I. INTRODUCTION

Cannabis is an annual herbaceous flowering plant called *Cannabis sativa*. Carl Linnaeus classified the species for the first time in 1753.[1] *sativa* is the specific epithet, meaning "cultivated." Originally from Eastern Asia, the plant is now widely cultivated and has a global distribution.[2] It has been grown for food, medicinal purposes, industrial fibre, and seed oil throughout recorded history. In addition, it is used for religious and spiritual purposes as well as recreational drug use.[3] One of the five sacred plants mentioned in the Atharva Veda, a collection of sacred writings attributed to an unidentified author, is cannabis, which is described as a source of happiness, a giver of joy, and a bringer of freedom. Therefore, the use of cannabis was incorporated into many religious rites in that area. [4]

The two species that make up the genus *Cannabis* (hemp), also known as marijuana, were initially recognized in 1753. *Cannabis sativa* is one of these species, and the subspecies *Cannabis ruderalis*, as well as *Cannabis indica*. Subvarieties of the species are referred to as strains. One variety of *C sativa* is hemp.[5] In India, the plant was widely recognized for its intoxicating properties, possibly as a result of the three different ways it was prepared for consumption. Bhang, the weakest variety, is made up of dry leaves that have had the flowers carefully removed. The flowers of the female plant are used to prepare the stronger variety, Ganja. The Charas, which is composed only of the resin that covers female flowers, is the strongest of all of them. These forms of preparation guarantee the presence of active cannabinoids. [4]

The presence of active cannabinoids is ensured by these preparation methods. As of right now, we know that the plant has secreting hairs, which are primarily found on the flowers of the female plant and, to a lesser extent, on the leaves of its superior third. Most frequently, solitary resin glands develop at the ends of the trichome stalks. There are a lot of active cannabinoids in these glands. The active cannabinoids are released when the glands break. [6] Cannabis was likely first used for both medicinal and religious purposes in India approximately a millennium B.C. . Numerous uses for the plant have been documented, including: analgesic (for headaches, migraines, and toothaches); anticonvulsant (for epilepsy, tetanus, and rabies); hypnotic; tranquilizer

(for anxiety, mania, and hysteria); aesthetic; anti-inflammatory (for rheumatism and other inflammatory diseases); antibiotic (for topical use on skin infections, erysipelas, and tuberculosis); antiparasite (for internal and external worms); antispasmodic (for diarrhea, colon); digestive; appetite stimulant; diuretic; aphrodisiac or anaphrodisiac; antitussive and expectorant (for bronchitis, asthma).[4, 7,8] With the support of a Canadian company, the Cannabis Research Project at CSIR-IIIM Jammu is the first of its kind in India and was started under Prime Minister Narendra Modi's direction. It has enormous potential to use drugs of abuse for the benefit of all people, particularly those with neuropathies, cancer, and epilepsy. Dr. Jitendra Singh commended the CSIR-IIIM for their innovative research into the medicinal uses of cannabis, a plant that is usually illegal and associated with abuse. The Minister acknowledged the great potential of cannabis-based treatments in treating a range of health conditions and expressed his satisfaction with the research work done on the Cannabis Project by CSIR-IIIM.

Cannabis sativa is commonly known as hemp, Indian hemp, marihuana, and marijuana Footnote [9]



**Figure 1.1** Cannabis plant

Synonyms for Cannabis. Sativa include:

Cannabis sativa subsp. sativa

Cannabis indica Lam.

Cannabis sativa subsp. indica (Lam.) E. Small & Cronquist

Cannabis ruderalis Janisch.[9]

**Chemical constituents:-**

1. Cannabidiol  $C_{21}H_{30}O_2$
2. Tetrahydrocannabinol  $C_{21}H_{30}O_2$
3. Cannabichromene  $C_{21}H_{30}O_2$
4. Cannabigerol  $C_{21}H_{32}O_2$
5. Cannabielsoin  $C_{21}H_{30}O_3$
6. Tetrahydrocannabivarin  $C_{19}H_{26}O_2$
7. Kaempferol  $C_{15}H_{10}O_6$

Tetrahydrocannabinol shows narcotic effect, Cannabidiol and other chemical constituents shows medical effect

**Table 1.1** Taxonomic classification of cannabis sativa Linn:-[10-13]

Sr. No	Taxon	Scientific name and common name
1.	Kingdom	Plantae (plants)
2.	Subkingdom	Tracheobionta (vascular plants)
3.	Super division	Spermatophyta (seed plants)
4.	Division	Magnoliophyta (flowering plants)
5.	Class	Equisetopsida
6.	Subclass	Magnoliidae
7.	Order	Rosales

8.	Family	<b>Cannabaceae</b>
9.	Genus	Cannabis
10.	Species	Cannabis sativa L.

## II. PHARMACOLOGY THE ENDOCANNABINOID SYSTEM

Early in the 1990s, researchers identified a novel signalling system within the body, which led to the discovery of an entirely new field of inquiry. This system, also referred to as the endocannabinoid system (ECS) or endogenous cannabinoid signalling system, is involved in maintaining the body's homeostasis and has an impact on several physiological processes. It is a neuro-modulatory system, which means that a particular neuron regulates different populations of neurons by using one or more chemicals. In contrast, only one partner neuron is targeted during synaptic transmission. Enzymes that create, transport, and/or degrade endogenous ligands—molecules that bind to receptors and can either induce or block actions—and cannabinoid receptors make up the ECS. With the identification of the endogenous cannabinoid anandamide (AEA) and the subsequent cloning of the cannabinoid receptor types 1 and 2 in 1990 and 1993, the ECS was identified in the early 1990s.[14,15]

As a complex molecular/biological system dispersed throughout the body, the endocannabinoid system regulates brain development, neurotransmitters, and cytokine release from microglia, and it directly affects emotional behaviour, cognition, fertility, and pregnancy. These functions are essential to many physiological processes for maintaining an internal balance in the brain, skin, digestive tract, and liver, as well as the respiratory, cardiovascular, and reproductive systems. The pharmacological modulation of the system has piqued the interest of medical research because it has been found that changes in the components of the endocannabinoid system (ECS) are linked to a number of pathological diseases, including cancer, neurodegenerative, and cardiovascular diseases. This is because drug discovery and development can be influenced by the changes in the signalling pathways that are downstream of the DAG system[16] Certain effects of cannabis cannot be fully explained by the binding of cannabinoid receptors alone; binding to other receptors such as the serotonin,  $\beta$ -opioid, and  $\beta$ -adrenergic receptors can also cause certain effects. [17, 18]

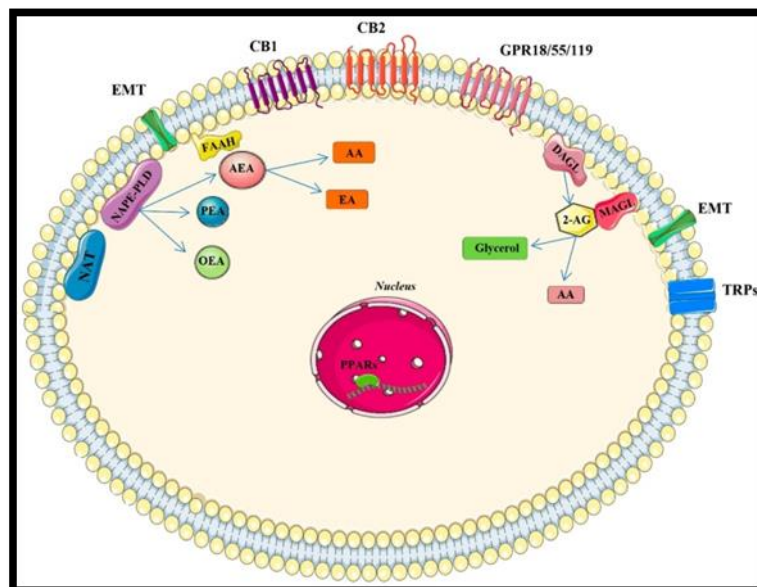


Figure 2.1 Endocannabinoid system

Endogenous substances known as endocannabinoids attach to cannabinoid receptors. In contrast to exogenous compounds, which come from outside the body, these compounds are fatty substances that are made by the body. Over time, numerous substances possessing endocannabinoid properties have been identified or created. The two most researched endocannabinoids are 2-arachidonylglycerol and AEA (Ananda means “bliss” in Sanskrit).[19, 20]

The ongoing and completed clinical trials of THC, CBD, and other Cannabinoids used as medicines and their side effects have been updated and highlighted in the section that follows.

**Cancer :-**

The term “cancer” refers to a broad category of related diseases that are all marked by aberrant, uncontrollably dividing cells. A biological condition called cancer frequently leads to the growth of tumours. Cancer cells are offspring of a single cell that has undergone genetic mutations or errors. When cells divide, these mistakes can happen naturally or at random, or they can show up as a result of exposure to toxins in the environment, or carcinogens. When these aberrant cells keep growing unchecked, cancer develops. These aberrant cells have the potential to divide and eventually form a solid mass known as a tumour.[21-25]It has been discovered that cannabis and Its components have enormous therapeutic potential for the treatment of cancer. [26]Beyond its proven efficacy as a symptomatic medication to relieve nausea and vomiting associated with cancer chemotherapy, CBD is a potent natural drug candidate for further testing its direct anticancer effects. An increasing body of published evidence points to CBD's ability to modulate various signal transduction pathways that regulate cell proliferation, differentiation, senescence, and cell death.[27]Particularly, it has been demonstrated that CBD causes cell cycle arrest from the G0 to G1 phase, which immediately lowers the levels of CDK2/cyclin E protein. [27]

This probably represents a few different ways that cannabis can alter the cell cycle. By modifying p38 mitogen-activated protein kinase, cannabinoids use ceramide to cause apoptosis in leukemic cells. Cannabis causes glioma cells to up regulate genes linked to endoplasmic reticulum stress, which triggers apoptosis. CBD induces lung cancer cells to undergo apoptosis by upregulating the expression of prostaglandin E2 and cyclooxygenase-2.[28]Each of these instances highlights a key mechanism by which CBD causes cancer cells to die, as well as the possible medical application of CBD as an anticancer agent. In order to reduce proliferation, cannabinoid also down regulate vascular endothelial growth factors. Similarly, by altering matrix metalloproteinase 2 (MMP2), MMP9, tissue inhibitor of metalloproteinase 1 (TIMP1), and causing endoplasmic reticulum stress, cannabinoids can prevent metastasis. [27]Smooth muscle layers, submucosalmyenteric plexus, and colonic epithelium all have high expression levels of CB1 and CB2 receptors. By activating CB1, TRPV1, and PPAR $\gamma$  receptors, CBD inhibited the growth of colorectal cancer. Remarkably, antagonists of these receptors significantly diminished the anti-proliferative effects of CBD. Similarly, by activating the CB1 receptor and blocking the P13K-AKT, RAS-MAPK cascade, which includes the activation of BAD, THC caused cancer cells to undergo apoptosis. [29]

THC exposure was shown to cause a dose-dependent decrease in colorectal cancer cells' ability to survive. However, the survival of cancer cells in vitro was little to unaffected by low doses. The authors reported very encouraging results from a 6-month clinical trial involving 2970 prier patients, more than half of whom were in stage 4 disease and receiving medical cannabis for a range of cancers, including breast (20.7%), lung (13.6%), pancreatic (8.1%), and colorectal (7.9%). The study found that 1211 (60.6%) of the 2970 patients responded, 682 (18.8%) stopped their treatment, and 902 (24.9%) of the patients died. Remarkably, 0.3% of respondents reported a decline in their condition, 3.7% reported no change, and 95.9% of respondents reported improved health. [30]A CB1 antagonist called rimonabant caused a G2-M cell cycle arrest in a human colorectal cancer cell line, DLD-1, in an in vitro experiment without causing apoptosis. [31]In cell lines of human colorectal cancer. CBD inhibited cell proliferation and shielded DNA from oxidative damage in Caco-2 and HCT116. While THC and CBD have garnered the most research attention among phytocannabinoids, other minor cannabinoid found in the Cannabis sativa plant have also demonstrated potential in the treatment of colorectal cancer. Tetrahydrocannabinolic acid (THCA) and cannabigerolic acid (CBGA), for instance, have been shown to have minimally harmful effects on normal cell lines but to have cytotoxic effects on colorectal cancer cell lines (HCT116, CCD-1800). [27]

**HIV- AIDS:-**

Worldwide, more than 40 million people are afflicted with HIV/AIDS.[32]Despite the fact that there is currently no treatment for this illness, there have been notable advancements in the survival rate of those living with HIV.[33]Due to their increased survival, the number of people living with HIV is rising, and many of them are receiving combination antiretroviral therapy for an extended period of time. As a result, managing chronic

symptoms linked to HIV and antiretroviral medication side effects has gained more clinical attention. Cannabis has been used medicinally to treat a variety of symptoms in small sample studies of HIV patients in recent times.[34-38]Cannabinoids have been shown to enhance appetite and reduce nausea and vomiting. One such cannabinoid is delta-9-tetrahydrocannabinol (THC), which is currently offered as a licensed pharmaceutical preparation.[39]In addition to THC, cannabis plant material also contains other cannabinoid like cannabidiol (CBD), which may lessen the effects of THC on psychotic mood.[40]Wasting syndrome is defined as unintended weight loss of more than 10% of body weight accompanied by fever, weakness, and/or diarrhea that lasts for at least 30 days . This translates to a weight loss of at least 15 pounds for a 150-pound man. Losing weight can lead to the loss of muscle and fat. It is hard to gain back weight once it has been lost The Condition can arise in individuals with advanced HIV disease and be brought on by a variety of factors, including opportunistic infections, inflammation, or HIV .The individual may not be hungry at all or become full quickly Effective HIV treatment with antiretroviral drugs is the most crucial treatment for wasting syndrome. [41-43] A common side effect of HIV infection is wasting syndrome, which is characterized by progressive weakness and weight loss and is frequently accompanied by fever and diarrhea. A poor diet, malabsorptive phenomena, metabolic disturbances, and cytokine activity are among the factors to be taken into account. There is currently no effective treatment for AIDS patients, but potential cytokines that may encourage weight loss include tumour necrosis factor, interleukin-1, interleukin-6, and alpha-interferon. [41-43]

A study came to the conclusion that there was evidence to support the effectiveness of cannabinoids in helping HIV patients gain weight.The studies contrasted inhaled cannabis or dronabinol with a placebo or with one another. In one study, the subjects who received higher doses of dronabinol (10 mg) and cannabis (3.9 percent THC) saw a significantly greater increase in weight ( $p < 0.01$ ) than those who received lower doses. In a follow-up study, the median weight increased by 3.0 kg ( $p = 0.021$ ) with inhaled cannabis (3.5 percent) and 3.2 kg ( $p = 0.004$ ) with dronabinol (2.5 mg) when compared to a placebo (a 1.1-kg increase over a 21-day exposure). In an investigation with eighty-evaluable patients, the placebo group lost an average of 0.4 kg ( $p = 0.14$ ), while the dronabinol group gained an average of 0.1 kg. These researchers came to the conclusion that there was insufficient data to support the use of cannabis and cannabinoids as a treatment for AIDS-related anorexia. [41-43]

#### **Rheumatoid arthritis:-**

A chronic autoimmune disease, rheumatoid arthritis (RA) affects approximately 1% of the general population. It is typified by the production of pro-inflammatory cytokines and autoantibodies, which ultimately cause the local synovial fibroblasts (SF) to become activated. [44]Patients with rheumatoid arthritis who use cannabis nearly tripled in number between 2014 and 2019, from 6.3% to 18.4%. States with legal cannabis use have the highest prevalence of use. The majority of users (74% in 2014; 62% in 2019) claimed that cannabis helped them with the symptoms of their arthritis. The survey also revealed that many rheumatoid arthritis patients who experiment with cannabis are those whose pain needs are not sufficiently met by conventional treatments. In comparison to users of strong opioids like morphine, fentanyl, or oxycodone, cannabis users were more likely to be taking weak opioids like codeine, tramadol, or hydrocodone, have a history of tobacco use, and perform worse on all patient-reported outcomes that were measured.[45]A non-intoxicating phytocannabinoids derived from Cannabis sativa, cannabidiol (CBD) has shown anti-inflammatory properties in a number of inflammatory conditions, including arthritis. But because cannabidiol (CBD) binds to a variety of receptors and enzymes, its exact mechanism of action is still unknown. According to a study published in 2020 by Lowen et al., CBD activates transient receptor potential ankyrin (TRPA1) and

Mitochondrial targets, which raise intracellular calcium levels, decrease cell viability, and increase the production of IL-6, IL-8, and MMP-3 by rheumatoid arthritis synovial fibroblasts (RASf). [46]10 Antigen-activated CD4+ T cells stimulate proinflammatory cytokines like IL-1 $\beta$ , IL-6, and tumour necrosis factor alpha (TNF- $\alpha$ ) in monocytes, macrophages, and synovial fibroblasts—also known as RA synovial fibroblasts, or rasfs. These have been referred to as the master regulators of chronic inflammation and tissue destruction and have been extensively linked to the inflammatory responses observed in inflammatory and autoimmune diseases.[47]The synthetic non-psychoactive cannabinoidhu-320 has strong anti-inflammatory and immunosuppressive properties. These anti-arthritic effects were observed in a mouse model of collagen-

induced arthritis. In addition, daily peritoneal administration of HU-320 significantly improved CIA by protecting foot joints from pathological damage and inhibiting tnf $\alpha$  secretion by macrophages in serum [48]

**Covid19:-**

The SARS-cov-2 pandemic has gripped the globe and poses a significant global threat to human lives and livelihoods [49-67]. Severe acute respiratory syndrome coronavirus-2 (SARS-cov-2) is a novel coronavirus that causes a human pandemic. (Covid-19). The coronaviruses are a large family of enveloped single-stranded positive RNA viruses. Coronavirus disease-19, caused by the novel RNA betacoronavirus SARS-cov2, first appeared in Wuhan, China in December 2019, then it developed into a global pandemic, infecting more than 99 million people and causing more than 2.1 million deaths. 24. January 2021. SARS-cov-2 targets the lower respiratory tract, causing pneumonia with fever, cough and shortness of breath.. [49-67] Cannabis is a plant known for its psychoactive effects, but when used correctly, it offers many medical benefits. Cannabis has more than 400 active compounds with therapeutic properties and is widely accepted for medicinal and recreational purposes in several countries. The compounds have various clinical benefits, including, but not limited to, anticancer, antimicrobial, and antioxidant properties. Among the many compounds, several studies have shown that cannabinoid such as cannabidiol and delta-9-tetrahydrocannabinol have antiviral effects [49-55]

The hyper inflammatory patterns of COVID-19 are like cytokine release syndrome (CRS). The background of COVID-19 is excessive inflammatory events that cause an increase in the number of white blood cells, but a decrease in the number of CD4+ and CD8+ lymphocytes. This leads to an imbalance between neutrophils and lymphocytes [35]. Once an infection is detected, inflammatory cells enter the local site of infection, releasing pro-inflammatory cytokines, causing CRS at a very early stage of the disease. The anti-inflammatory properties of hemp phytoconstituents can be used to prevent CRS. The endocannabinoid system regulates the immune system by regulating immune cell trafficking through cannabinoid receptors [35]. Therefore, the use of phytocannabinoids such as THC and CBD can inhibit the proliferation of lymphocytes and pro inflammatory cytokines [68]. In vitro studies, CBGA and CBDA were excellent allosteric and orthosteric ligands for the spike protein with affinity at micro molar levels. More importantly, both CBGA and CBDA successfully prevented the entry of SARS-cov-2 alpha variants B.1.1.7 and B.1.351 into cells in vitro [69]. Using a combination of in vitro and in vivo approaches, Nguyen et al. [70] showed CBD and not THC to successfully inhibit SARS-cov-2 infection of lung epithelial cells and mice. In addition to blocking viral entry, CBD also inhibited the expression of virally encoded genes and reversed the effects of SARS-cov-2 on host gene transcription in infected cells. Follow-up studies showed that CBD exerted its anti-SARS-cov-2 effects partly by up-regulating the IRE1 $\alpha$  RNase endoplasmic reticulum stress response and interferon-stimulated signalling pathways in host cells.

**Alzheimer's disease:-**

The most prevalent type of dementia, Alzheimer's disease (AD), is a dangerous brain ailment that affects daily functioning by causing memory loss and cognitive abnormalities. The hallmark of Alzheimer's disease is severe memory loss that interferes with day-to-day functioning. The primary symptom of Alzheimer's disease is memory impairment, also known as short memory loss. The brain ailment known as Alzheimer's disease is named for the German physician Aloes Alzheimer, who initially reported it in 1906. Alzheimer's disease is one of the age-related neurodegenerative diseases that results in the progressive loss of neuronal cell death due to a loss of neuronal structure or function. Patients with Alzheimer's disease are acetylcholine deficient. Stressful environments, oxidation, and free radical scavenging are frequently linked to memory loss and cognitive decline, which raises the risk of schizophrenia and Alzheimer's disease. [71-75] Alzheimer's disease (AD) is typified by the pathological accumulation of abnormal amyloid-peptide peptides into extracellular plaques, neuroinflammation, and hyperphosphorylation of the microtubule-associated protein Tau, which leads to the formation of neurofibrillary tangles (nfts) [76]. Certain cannabinoids, such as THC and CBD, may have pharmacological effects on the cholinergic system and amyloid-beta aggregation, according to preclinical study. All of these things combine to promote brain atrophy, which is characterized by gradual, irreversible neuronal malfunction and cell death [77]. Moreover, scientists have been searching for novel anti-AD medications derived from inhibitors of secretase enzymes that target certain secretases including  $\gamma$ -secretase and BACE-1. These are the main enzymes that convert the neurotoxic A $\beta$  fragments (A $\beta$ 42) from the amyloid precursor protein (APP). [78-81]

Lastly, no studies have demonstrated that cannabis or products like cannabis oil (CBD oil) can halt, slow down, reverse, or avoid the dementia-causing Alzheimer's disease (AD) [71-75,82-86] According to some research, cannabis may be able to help control some behavioural signs of dementia, like agitation and hostility. However, additional study is required to determine the long-term effects of cannabis use and whether or not it is a safe and effective strategy to treat dementia symptoms [71-75, 82-86].As a result, it serves as a warning to medical professionals, dementia patients, and their families that further research is necessary before recommending cannabis as a sedative. More research is required to confirm findings and explore potential negative effects of cannabinoids, such as drowsiness and memory impairment. Further studies will help to dispel any confusion regarding the possible advantages and disadvantages of medical marijuana and promote well-informed standards, recommendations, and regulations [71-75, 82-86]

**Diabetes mellitus:-**

463 million adults worldwide suffer from diabetes, a metabolic disease that is predicted to afflict 592 million by 2035 and 700 million by 2045.[87] Diabetes can harm numerous body organs, resulting in symptoms such as improper kidney function, neuropathy, loss of vision, cardiovascular and cerebrovascular illnesses, among other conditions.[88]Hyperglycaemia, a condition induced by either insufficient insulin or insulin resistance as a result of the autoimmune death of pancreatic islet cells, is the hallmark of diabetes. It is currently clinically classified as type one diabetes (T1D) and type 2 diabetes (T2D) based on its pathophysiology.Insulin secretion is impaired in T1D (insulin-dependent diabetes) patients, and their blood typically contains a range of autoimmune antibodies. Through immune-mediated harm, these aberrant autoantibodies can destroy pancreatic  $\beta$ -cells and impair their ability to secrete insulin as needed.[89, 90] Non-insulin-dependent diabetes (T2D) affects 2%–4% of the population and is more common in men. It is primarily characterized by a gradual lack of insulin secretion from pancreatic cells and resistance to insulin action by surrounding target tissues [89, 91].Research has demonstrated that in a T1D animal model, CBD can reduce the incidence of diabetes, pancreatic inflammation, and  $\beta$ -cell loss.[92, 93] In T1D-associated immunological responses, CBD can change the preponderance of type 1 to type 2 lymphocytes, which lowers the amounts of pro-inflammatory cytokines such TNF- $\alpha$  and interferon  $\gamma$  (IFN- $\gamma$ ).[93] In a T1D mouse model, CBD improves early diabetic symptoms as well.[94]There aren't many clinical studies on cannabis use for diabetes treatment at the moment, but a few preclinical studies that suggest Cannabinoids may be able to slow down the disease's progression and alleviate some symptoms have been published [95.96]. Injections of the nonpsychoactive cannabinoid CBD (5 mg/day) considerably decreased the mice's diabetes maidens, according to a 2006 study. 86% of the study's control mice, who were not given any medication, developed diabetes, according to the researchers. Conversely, the disease only affected 30% of the mice given CBD treatment [97].The majority (60%) of mice treated with CBD remained free of diabetes at 26 weeks, according to a different study carried out by the same researchers. All control mice developed diabetes in a mean of 17 weeks (range 15 to 20 weeks) [97,98].It has been demonstrated that hyperplasia and food cravings are also enhanced in humans when CBI receptors are activated [99]. Endocannabinoid receptor antagonists were subsequently developed as a treatment for DM2 and obesity as a result [100]. However, because of serious adverse psychological effects, these medications were taken off the market early.[ 101-103].

Through up regulating the expression of protein kinase B, mitochondrial uncoupling protein 2, and glucose transporter protein 2 in pancreatic  $\beta$ -cells in a rat model of diet-induced obesity, it has been discovered that CBD could decrease weight gain and boost energy expenditure.[104] Adiposities and preadipocytes treated with CBD exhibit increased glucose absorption, decreased fat formation, and improved insulin resistance reversal.[105] Consequently, CBD may be used therapeutically to treat diabetes and its side effects. We go into great detail in this review of the pharmacological activities of CBD in diabetes and how it affects different problems such nephropathy, retinopathy, neuropathy, and diabetic cardiovascular failure. Additionally, the identification of the molecular target(s) of CBD in the management of diabetes and associated complications, along with additional modifications to CBD, will be emphasized.[106].

**Chronic pain:-**

Treatment for chronic pain can be costly, time-consuming, and difficult. Many people who suffer from chronic pain have resorted to using cannabis as an alternate method of pain relief.[107]. Furthermore, because cannabis

and cannabinoids may reduce the need for high doses of opioid medications, interest in using them to treat chronic non-cancer pain is growing [108]. Some people are more curious about them since they are safer than opioids and because using them may reduce the need for opioid doses by having an opioid-sparing effect.[108]. It has been suggested that both of these factors lower the number of deaths linked to opioid [108].The safety and effectiveness of using cannabis for medical purposes are still hotly debated, but it is believed to be helpful for treating a number of illnesses and symptoms.[109]According to the findings of a recent study, over 62% of people who use medical cannabis do so to manage chronic pain.[110]Cannabis is the most commonly used drug worldwide, with an estimated 2.5% of the world's population using it annually, according to the World Health Organization.[111] Both patients and prescribers are still having discussions over medical cannabis, and it is obvious that further research is needed

Researchers are weighing the advantages and disadvantages of using cannabis-based medications, which is gaining popularity among prescribers and patients alike.[112] Cannabinoids from the cannabis plant, such as delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), or a mix of THC and CBD, are used in cannabis-based medications.[113] Regarding the use of cannabis-based medications for the treatment of chronic pain, there remains, still, controversy and misunderstanding.[113]Increased concerns about managing the current opioid-abuse pandemic are thought to be connected to the increased interest in medicinal cannabis.10 Patients who consume cannabis may take fewer opioid, according to some preliminary findings, but further research is required.[114, 115]Cannabis acts on both CB1 and CB2 receptors, which is why it has been used to relieve pain.[116] It has been discovered that CB receptor agonists control neuronal and non-nervous system inflammatory activity to provide antinociceptive and anti hyperalgesic effects.[116] According to one idea, mast cell activation of CB1 receptors increases cyclic adenosine monophosphate and inhibits degranulation.[116]Moreover, CB1 receptor activation that results in negative regulation of the P2X3 receptor in primary afferent neurons can also cause analgesia.28 When CB2 receptors are activated, proinflammatory factors are inhibited, which suppresses mast-cell degranulation and neutrophil build up brought on by nerve growth factor.[116, 117]Cannabis has been shown in an increasing number of clinical studies to be beneficial for the treatment of neuropathic pain, which is one form of chronic pain, and spasms related to multiple sclerosis.[118, 119]The National Academies of Sciences recently conducted a thorough analysis of the available research on the health benefits of cannabis and cannabinoids and found that adult patients with chronic pain who received treatment with cannabis and cannabinoids had a higher likelihood of experiencing a clinically significant improvement in pain symptoms.[119]These effects were given a “modest” rating.[118, 119]Research suggests that there may be some benefit for migraines, fibromyalgia, cancer-related pain, and other pain disorders.[118, 120]These substances have been proposed as potential treatments for rheumatoid arthritis, osteoarthritis, and other acute and chronic musculoskeletal pain disorders.[121, 122]But it's unclear how various cannabis species, dosages, and administration methods affect things differently, necessitating more study.[118]

### III. CONCLUSION

To ascertain the dangers connected to the medical use of cannabis, more investigation is required. Research on long-term cannabis use, however, has connected the drug to hazards and negative effects like lowered cognitive function and unpleasant respiratory symptoms. The consistent, standardized, and repeatable dosage that patients ingesting cannabis for medical purposes would have otherwise obtained from using products containing Cannabinoids administered in controlled doses (e.g., capsules, oral sprays) is not guaranteed. the medical use of cannabis to treat chronic pain, nausea, vomiting, and appetite stimulation; however, research on the drug's potential uses for treating other medical conditions is still in its early stages. The main goals of future research will probably be to increase the specificity of synthetic Cannabinoids and their delivery through less hazardous means than smoking, as well as to take advantage of CBD and perhaps other non-psychoactive Cannabinoids. Cannabis doesn't seem to have the full therapeutic potential that has been noted in research on the Endocannabinoid system's effects. Products that contain THC or other medications that target the two recognized cannabinoid receptors will still experience side effects due to their extremely broad mechanism of action. There is hope for more clinical trials of CBD and in creating customized drugs derived from Cannabinoids for particular ailments or symptoms that have better risk-benefit ratios. A new generation of safe



and efficient CBD drugs that do not have the side effects of smoking or consuming whole cannabis plants are presently being researched.

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