Review Article **Phytopharmacology Research Journal (PRJ) Open Access**

Received: 12 Dec, 2025 Revised: 15 January, 2026 Accepted:18 January 2026 Published online: 21 January 2026 ISSN : 2959-9687

Medically Approved Cannabinoids of Medicinal Cannabis for Neurological disorders and its legalization in Pakistan

Kishwar Sultana[1*], Sohail Ameer Marwat[2], Uzma Ameer Marwat[3], Mehnaz Liaquat[4], Waheed Alam[5], Durdana Ghaffar[6], Aftab Hussain[7], Mushahid Hussain[8]

[1]*National Industrial Hemp and Medicinal Cannabis Analytical Laboratory, Pakistan Council of Scientific and Industrial Research (PCSIR) Laboratories Complex, H-9 Islamabad, Pakistan*

[2]*Pakistan Council of Scientific and Industrial Research (PCSIR), Head Office, 1 Constitution Avenue, G-5/2 Islamabad 44000, Pakistan*

[3]*Medical Equipment & Devices Innovation Center (MEDICen), Pakistan Council of Scientific and Industrial Research (PCSIR) Laboratories Complex, Jamrud Road Peshawar, Pakistan.*

[4]*Center of Biotechnology & Microbiology, University of Peshawar, KP, Pakistan*

[5]*Department of Neurosurgery, Frontier Corps (FC) Teaching Hospital,Hayatabad Peshawar, KP, Pakistan*

[6]*Department of General Surgery, Hayatabad Medical Complex, KP, Pakistan*

[7]*Department of Finance, University of Agriculture, Peshawar, KP, Pakistan*

[8]*Department of Material Management, Peshawar Institute of Cardiology (PIC) Hospital, Hayatabad Peshawar, KP, Pakistan*

Correspondence
Kishwar Sultana

Funding information
This research was supported and financed by the PCSIR Laboratories Complex, Peshawar.

Abstract

Despite being used as a cured for a number of medical issues, Medical Cannabis (Marijuana) has long been listed as an unlawful medication. However, there is no firm scientific backing for its use; it has only been based on personal experiences. Its widespread recreational use has largely eclipsed its beneficial aspects. Due to numerous studies demonstrating its function in numerous medical conditions, particularly neurological illnesses, it has recently become a contentious topic of discussion. An electronic database search was catalogued using PubMed, Science Direct, Scopus and Google Scholar were done to find articles on Neurological disorders of medicinal Cannabis published between 1995 to 2023. The globe is still split over the legalization of these new results for therapeutic use. It has lately been legalized in a number of nations and jurisdictions, several scholars have voiced care about its potential misuse and the long-term effects on the law, ethics, finances, and health that have not yet been addressed. Pakistan is regarded as the major Cannabis producing country. We need to reach an agreement on this issue, considering legal, health and ethical viewpoints related to its medical usage in our society, given the growing body of data suggesting possible medicinal advantages.

KEYWORDS

Cannabis, Marijuana, Hemp, Cannabinoids, Epilepsy, Legalization

1.0 INTRODUCTION

The Cannabis is a sort of significant herbal plant that is grown all over the world and a member of Cannabaceae family. It has been utilized for therapeutic purposes in various parts of the world. According to UNODC (2016), there are expected to be 182.5 million users of cannabis worldwide. In Pakistan, cannabis was the most commonly used drug, with almost four million users, or 3.6 percent of the population, according to a 2013 UN poll. All illicit drug use was 10.9% and cannabis use was 4.7% according to United Nations Office on Drugs and Crime (UNODC) (2012) as shown in Figure 1 and 2. Cannabis use between the ages 15 and 64, or approximately four million people, according to a 2013 UNODC report in Pakistan illustrated in Figure 2. Cannabis is widely grown, sold, and used as a drug. Cannabis-related compounds were the most widely used medicines in the world in 2011, accounted for 65% of all global cases of seizure (1.65 million instances). In 2006, authorities seized 1000 tonnes of resin and 5200 tonnes of herbs. Cannabis trafficking affects almost every country on the planet. Likewise, cannabis remains the most commonly used drug globally, with 166 million users estimated in 2006, or 4% of the world's population between the ages of 15 and 64.Upto now, about 86 different cannabinoid compounds have been recognized in nature, and more can be produced chemically. Delta-9-tetrahydrocannabinol (THC) is the primary psychoactive ingredient in these substances, and some of them, including nabilone, dronabinol, and cannabidiol, have been prescribed drugs [1]. Due to the availability of numerous hemp products on the illicit market with widely varying concentrations of delta-9-tetrahydrocannabinol (THC), the primary psychoactive component of cannabis as shown in Figure 3, the production process for the drug has gotten increasingly sophisticated since the turn of the 20th century.

Since ancient times, cannabis has been utilized for a variety of therapeutic uses and neurological disorders. Hemp was first planted as a crop in China and then spread throughout Asia, Africa and the Middle East. There, in addition to its recreational applications, it was long used for treating pain and a variety of other ailments, including malaria, gout, poor memory, rheumatism, in addition to its recreational uses [2]. It was classified as a Schedule 1 medication in 1970 and classed as having no recognized medical value; subsequent study was prohibited until it was recently discovered to have multiple uses and fewer negative effects than earlier reported as shown in Figure 3 [2]. Due to these discoveries, it was approved as medical use in April 2015 in roughly 23 US states. Numerous nations, such as Spain, Germany, Holland, Canada, the Czech Republic, Colombia, and France have all approved its medical use. According to a survey, 17% of Americans who had used marijuana in the previous year said they had done so for medical purposes [3].

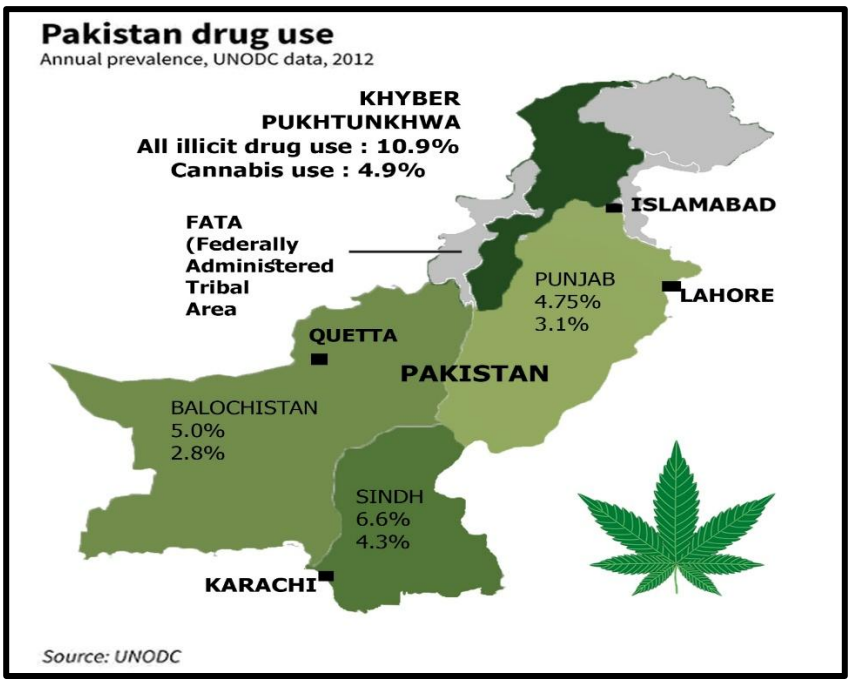

Figure 1. Annual Prevalence of Pakistan drug use, UNODC data (2012) [1].

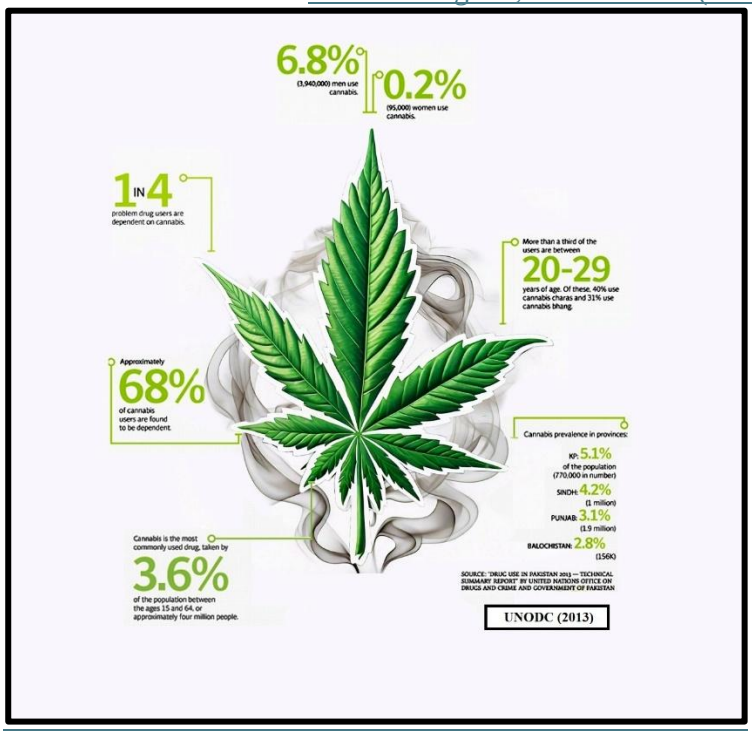

Figure 2. Drug use in Pakistan (2013)-Technical summary report by UNODC, Government of Pakistan [1].

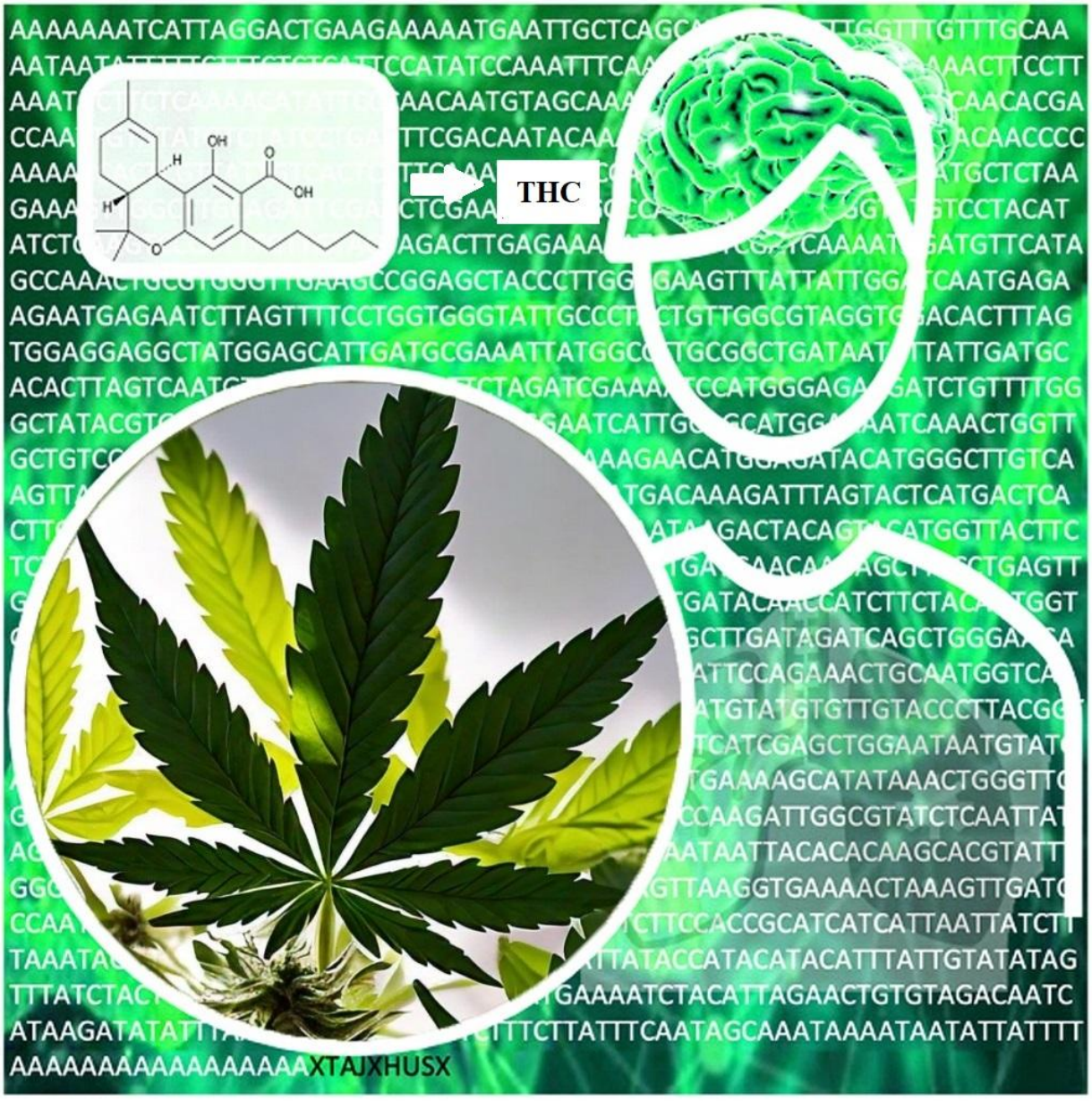

Figure 3. Chemical structure of tetrahydrocannabinol (THC) of Medical Cannabis [2].

2. Cannabinoid receptors

Two cannabinoid-specific receptors, the seven transmembrane G protein-coupled cannabinoid receptors type 1 (CB1 receptor) [4] and type 2 (CB2 receptor) [4], have so far been cloned and characterized from mammalian tissues. The central nervous system exhibits high levels of CB1 receptor expression, whereas the immune system is the only organ where CB2 receptor expression is found. Peripheral nerve terminals and a number of extra neuronal locations, including the uterus, uterus, vascular endothelial cells, eye, adipocytes, and spleen, express the CB1 receptor [5–8]. There is confirmation for the presence of additional cannabinoid receptors [9], but they are not yet cloned.

Just 44% of the overall identity and 68% of the

transmembrane domains of CB1 and CB2 receptors are shared. The G proteins, primarily of the Gi/o type, are linked to both cannabinoid receptors. It is through the α subunit of these proteins that they block adenylate cyclases and activate mitogen-activated protein kinases. Nevertheless, further research revealed that receptors cannabinoid connected to ion channels, which led to the blocking of Ca2+ influx via N type calcium channels [10]. Additionally, receptors o CB1 are linked to the activation of PI-3-kinase and phospholipase C (via the G protein's βγ subunits). Conversely, ceramide production is persistently activated by CB2 receptors [11].

2.1. The endocannabinoid system

It has been determined that a number of endogenous fatty-acid ligands, or endocannabinoids, exhibit activity at the cannabinoid receptor. Arachidonoylethanolamide (anandamide, AEA) earliest identified in 1992, and 2-arachidonoylglycerol (2-AG) came next. These two substances are derived from arachidonic acid and bind to CB1 and CB2 receptors, however their activation efficacies and affinities vary [8]. They are conjugated with either ethanolamine or glycerol. A number of other bioactive lipid mediators have been reported in recent years; these seem to function by binding to CB1 and/or CB2 receptors and eliciting particular in vivo pharmacological effects. The chemicals in question are N-arachidonoyl-dopamine, o-arachidonoyl-ethanolamine (virodhamine), 2-arachidonoyl-glyceryl-ether (noladin ether), and maybe oleamide [12–14, 8].

The endocannabinoid system, linked to an excess of physiological processes, are cannabinoid receptors, endocannabinoids, and entire machinery designated for their production and degradation [15, 16]. In past few years, significant amount of data has been presented to gain a deeper understanding of this system.

Endocannabinoid system fulfills numerous tasks under physiological situations. Endocannabinoids affect the mesolimbic system's reinforcement of drug misuse substances as well as the neural circuits of the cortex, hippocampus, and amygdale that regulate emotions and cognitive processes in central nervous system [17].

Additionally, endocannabinoids affect how movement and posture are controlled [18], how pain is perceived [19], how the cardiovascular system [20], the gastrointestinal system [21, 22], the respiratory system, and the reproductive system. On the other hand, CB2 receptors are linked to humoral immune response and cellular processes, which may have consequences for chronic pain and (neuro)inflammation [23].

In addition to the previously mentioned of the endocannabinoid system physiological roles, pathological situations cause significant alterations in tissue and blood endocannabinoid signaling. In animal models Parkinson's, Alzheimer's, and amyotropic lateral sclerosis, higher levels of endocannabinoids are observed [24].

3. USES OF CANNABINOIDS IN VARIOUS NEUROLOGICAL DISORDERS:

The brain regions for memory, attention, learning, decision-making, coordination, reaction time and emotions are specifically affected by using marijuana as shown in Figure 4a & b [25]. To date, the regulatory agencies, Federal Drug Administration and the European Medicines Agency have not yet authorized a cannabis marketing application for the purpose of treating any illness or ailment. Nevertheless, only a small number of cannabis medications have undergone extensive testing for safety and been granted national licenses for use by regulatory bodies such as the FDA and the EMA. Nonetheless, the agency has authorized a single medication made from cannabis: Cannabidiol, or Epidiolex [25] and three drug products related to synthetic cannabis have been validated by the agency: Cesamet (nabilone), Marinol (dronabinol), and Syndros (dronabinol). [25, 26].

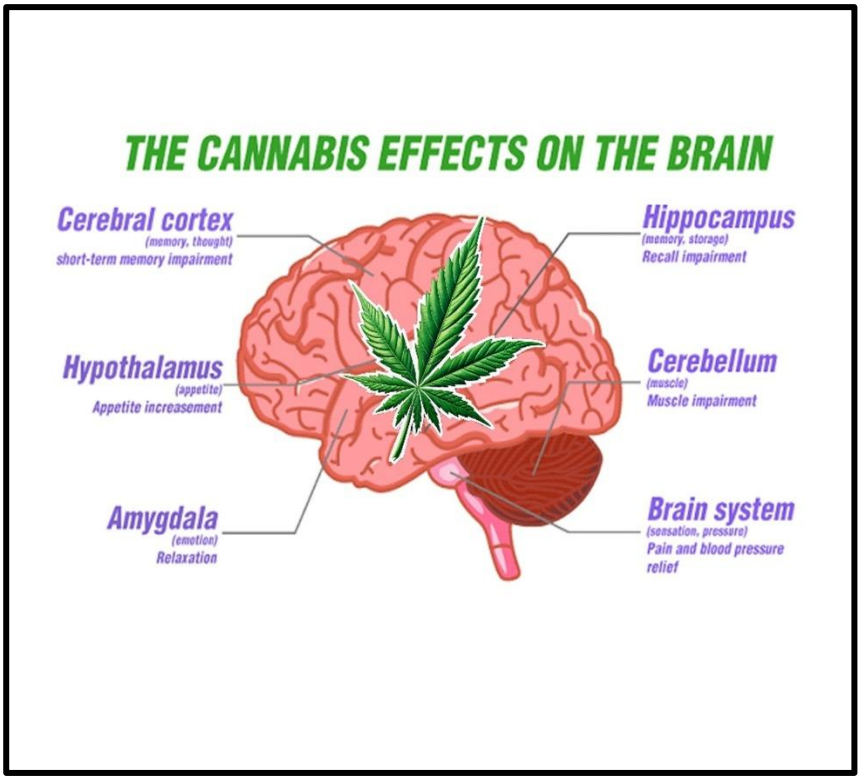

Figure 4a. Effects of Cannabis on central Nervous System [25].

Figure 4b. Effects of Cannabis on Brain [25].

3.1. Medically Approved Plant Derived Cannabinoid Drugs

3.1.1. Cannabidiol (Epidiolex®)

Cannabidiol (Epidiolex®) made from cannabis plants, is a 98% pure oral CBD solution [25] as shown in Figure 5. After completing extensive toxicological testing, it is validated for the cure of seizures related to Lennox-Gastaut or Dravet syndrome in pediatric patients [26]. In 2018, Epidiolex receive EMA approval as well as FDA clearance [27]. When examining the possible safety and therapeutic efficacy of the latter substance, CBD oil, this medication may be the closest analogue because it is a highly pure version of CBD. Hepatocellular toxicity, decreased appetite, diarrhea, sleepiness, and fatigue are a few of the side symptoms [28].

3.1.2. Dronabinol (Marinol®)

Δ^9-tetrahy-drocannabinol (also known as Δ^9-THC) is a synthetic compound that is synthesized and supplied orally under the trade name Dronabinol (Marinol®) [29] as shown in Figure 5. The FDA and EMA both gave their approval to it in 1985 [30] for AIDS patient's weight loss, anorexia, and chemotherapy-induced nausea and vomiting. Heart palpitations, asthenia, stomach pain, and amnesia are among the most often reported side effects of this schedule III medicine. Depersonalization is a rare yet severe adverse effect [30].

3.1.3. Nabilone (Cesamet™)

Nabilone (trade name Cesamet™) is an oral synthetic cannabinoid that shares structural similarities with Δ^9-THC and shares Δ^9-THC's CB1 receptor characteristics [30] as shown in Figure 5. The FDA and EMA have both approved this substance for the treatment of CINV (first in 1985 and again in 2016). Nabilone is a schedule II substance because of its psychoactivity. The most often reported complications include headache, dry mouth, drowsiness/vertigo, euphoria, dyspnea, and orthostatic hypotension, all of which are mild. Psychosis is a rare yet severe adverse effect [30].

3.1.4. Rimonabant (Acomplia®)

From 2006 to 2009, the synthetic CB1 receptor antagonist rimonabant (trade name Acomplia®) was marketed in Europe for the healing of type II diabetes, dyslipidaemia, and obesity [31] as shown in Figure 5. The European Medicines Agency removed this medication from the market in 2009 due to substantial adverse effects include major depression, suicidal ideation, nausea, and upper respiratory infections [32].

3.1.5. Nabiximols (Sativex®)

Sativex is a *C. sativa* plant extract oromucosal spray that primarily comprises Δ^9-THC and CBD in about equal proportions [33] as shown in Figure 5. Sativex has been licensed in Europe (as of 2010) for the healing of spasticity, and the most often revealed adverse effects are lethargy, dizziness, depression, blurred vision, and vertigo [33]. Palpitations, variations in blood pressure, and hallucinations are uncommon but dangerous adverse effects [33]. Each spray has a roughly equal amount of CBD and Δ^9-THC (for a total of 5 milligrams).

Only a prescription from a qualified healthcare professional is required to purchase these approved medication products [34].

Recent studies have demonstrated its positive effects in treating a number of neurological illnesses. When standard therapies were proven to be ineffective, significant data was found to support its use. However, for many other illnesses, its use is still experimental, and there is not yet enough data to support its use.

BIOLOGICAL EFFECT	APPROVED THERAPEUTIC PRESCRIPTION
Inhibition of nausea and vomiting	Co-adjuvant in antitumoral therapy in cancer patients
Stimulation of Appetite	Co-adjuvant in anorexia-cachexia syndrome in AIDS patients
Analgesic action	Treatment of chronic pain in multiple schlerosis patients (also oncologic and neuropathic pain)
Reduction of spasticity	Treatment of spasticity multiple schlerosis patients (also tremor)
Anticonvulsant action	Reduction of seizures in pediatric refractory epileptic syndromes (Dravet, Lennox-Gastaut)

Figure 5. Medically approved Cannabinoid drugs from Cannabis [33]

4. Indications with good evidence, Cannabinoids and Neurodegenerative Diseases of the Central Nervous System (mental and motor dysfunctions)

4.1. Alzheimer disease

The most prevalent neurodegenerative disease in Western Europe is Alzheimer's disease, which is posing a threat to public health due to its rising incidence as the population ages. It shows up as a progressive loss of memory and cognitive function, poor language proficiency, confusion, and behavioral issues. Amyloid angiopathy, neurofibrillary tangles (NFT), and senile plaques (SP) are the three main neuropathological features of AD. Brain lesions like NFT and SP, which are linked to AD, are typified production of a wide range of inflammatory mediators by brain cells, including neurons. There is convincing evidence that inflammation aggravates the loss of neuronal cells, even if it is of secondary relevance in relation to the underlying cause that defines the development of tangles and plaques. As a result, a number of polymorphisms in the promoter region of genes and other non-coding areas for inflammatory mediators have a significant impact on AD risk. Compared to controls, patients with AD are more likely to have genotypes that favor either the reduced expression of anti-inflammatory mediators or the increased expression of inflammatory mediators. Everyone has a high chance of inheriting one or more high risk alleles because the polymorphisms are fairly widespread in the general population [35, 36].

Enhanced beta-amyloid peptide deposition, selective neuronal death, glial activation in senile plaques, and cognitive impairments are further characteristics of AD.

Ramirez et al.'s research [37] examined the function of cannabinoid receptors in AD and their potential preventive effects following betaA therapy. This study demonstrated the expression of CB1 and CB2 cannabinoid receptors along with indicators of microglial activation in senile plaques in AD patients. In addition, although control cases have a large concentration of CB1-positive neurons, these neurons are significantly less in regions where microglial

activation is occurring [37]. Additionally, protein nitration is elevated in AD brains, G-protein coupling and CB1 receptor protein expression are significantly reduced [37]. Cannabinoids (HU-210, WIN55,212-2, and JWH-133) inhibit both betaA-induced microglial activation, cognitive impairment, and loss of neuronal markers and abrogate microglia-mediated neurotoxicity after betaA addition to rat cortical cocultures [37]. Data indicate that cannabinoid receptors are implicated in pathogenesis of AD and they may govern the neurodegenerative process occurring in illness.

Iuvone et al. [38] also examined the neuroprotective effects of CBD in AD by assessing how cannabidiol, a significant non-psychoactive ingredient of marijuana plant, affected the toxicity of β-amyloid peptide in cultured rat pheocromocytoma PC12 cells. The administration of β-amyloid peptide resulted in significant decrease in cell survival, along with heightened formation of reactive oxygen species (ROS), lipid peroxidation, the appearance of caspase 3 (a crucial enzyme in death cell-signaling cascade), DNA fragmentation, and intracellular calcium. Prior to cells being exposed to β-amyloid peptide, cannabidiol treatment greatly increased cell survival while lowering intracellular calcium, lipid peroxidation, ROS generation, caspase 3 levels, and DNA fragmentation. Findings show that cannabidiol protects neurons from the harmful effects of β-amyloid peptides, which may indicate that cannabidiol involved in signaling system that causes this neuroprotection. A second study that found that CBD prevented the generation of nitrite and the expression of the nitric oxide synthase (iNOS) protein when beta-A was present [39] confirmed this theory. A mouse model of AD-related neuroinflammation was used to validate the in vivo findings of these in vitro investigations. Human beta-A was injected into the right dorsal hippocampus of the mice, and for seven days, the mice were given either vehicle or CBD (2.5 or 10 mg kg, i.p.). Compared to the vehicle, glial fibrillary acidic protein (GFAP) mRNA and protein expression in beta-injected rats were dramatically reduced by CBD in a dose-dependent manner. Furthermore, CBD decreased expression of iNOS and IL-1beta proteins as well as the corresponding release of NO and IL-1beta under the same experimental settings [40]. The potential for CBD to impede beta-A-induced neurodegeneration is highly encouraging for the prevention of AD.

4.2. Epilepsy:

When treating childhood epilepsies Dravet and Lennox-Gastaut syndromes, which are resistant to conventional treatments, dronabinol and nabilone have been proven to be effective. They could cut the median monthly frequency of seizures by roughly 36.5% [41]. In the treatment of super refractory status epilepticus, they were also found to be helpful [41]. However, we still need proof before we can suggest it as a first-line treatment for drug-resistant epilepsies and as an alternative to conventional antiepileptics in more widespread epilepsies.

4.3. Cannabinoids for Multiple Sclerosis*:*

Nabilone and nabiximols, two cannabinoids, have been reported to be effective for treating multiple sclerosis symptoms like pain, stiffness, and urine dysfunction as shown in Figure 6 [42]. Although the FDA has not approved these indications, health organizations like the American Academy of Neurology (AAN) advise considering them in patients who qualify as an alternative to standard treatments [43].

Axonal myelin sheaths are attacked by the immune system in multiple sclerosis (MS), a chronic illness. The Latin word sclerosis, which means "scar," is the source of the disease's name because the site of inflammatory injury is scarred [44, 45]. Since these lesion sites can occur in the brain or spinal cord, patients typically experience a range of symptoms from the disease. These consist of exhaustion, numbness, altered vision, weakness in the muscles, incontinence, and paralysis.

Myelin sheath loss and oligodendrocyte impairment resulted from chronic inflammatory foci in multiple sclerosis (MS), an autoimmune disease. Axonal injury and the ensuing neuronal degeneration occur next. Axonal damage and brain shrinkage can happen months after an acute innate immune response, indicating that neurodegeneration and inflammation do not always happen at the same time [44, 45]. Many medications currently available target immune system in an attempt to slow the course of multiple sclerosis (MS), but their efficacy is only moderate, and MS is still mostly treated with symptoms that are not very

satisfying [46].

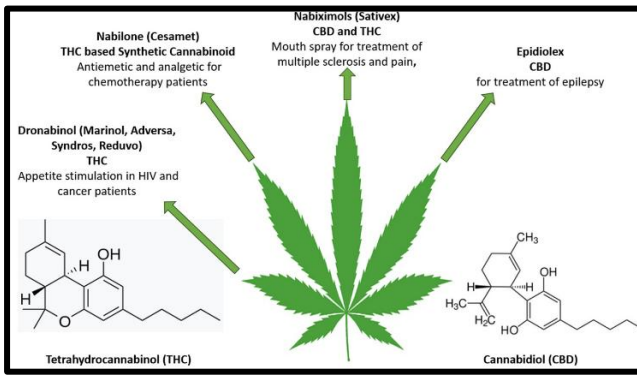

Figure 6. Approved cannabis-related drugs [42].

Cannabis was used to treat pain, spasms, and cramps in muscles in ancient Greece, Rome, China, and India [47–49]. Its potential efficacy in treating multiple sclerosis has recently been the subject of intense discussion [50–59]. Rats with an experimental form of autoimmune encephalomyelitis (EAE) were used to examine the effects of THC on MS [60]. When compared to a placebo, THC treatment in this MS experimental model was to decrease neuroinflammation, improve neurological prognosis, and increase survival. Additionally, the nonpsychotropic drug dexanabinol and the less psychoactive analogue of THC, Δ8-THC, were able to lessen incidence and severity of neurological impairments in rats with EAE [61–63]. The endocannabinoid system in EAE is responsible for the tonic regulation of muscle tone, as demonstrated by the effectiveness of THC in a mouse model of chronic relapsing EAE [64, 65]. The aforementioned observations were further corroborated by the use of CB1-deficient mice, who showed poor tolerance to inflammatory and excitotoxic stimuli and acquired significant neurodegeneration upon induction of EAE [66-70].

Another mouse model of multiple sclerosis is Theiler's murine encephalomyelitis virus-induced demyelinating illness. In this MS model, cannabis administration prevented the expression of proinflammatory cytokines in central nervous system, decreased development of symptoms, and down-regulated the production of interferon-γ and delayed-type hypersensitivity reactions [71–74].

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In light of the results from animals mentioned above, cannabis treatment for MS in humans appears promising. During CNS inflammation in MS patients, the endocannabinoid system was highly activated, and it was found to protect neurons from inflammatory damage by activating a negative feedback loop in microglial cells via CB1/2-mediated epigenetic regulation of mitogen-activated protein kinase. This finding raises the possibility of an underlying mechanism.

Early open or single-blind observations with oral THC or smoked marijuana, involving limited numbers of patients, provided evidence to substantiate anecdotal claims demonstrating the effectiveness of marijuana smoking in treating MS symptoms [75, 76]. The study's findings demonstrated a statistically significant improvement in bladder control, mood, tremor, mobility, spasticity, and nystagmus. The use of nabilone reduced nocturia, muscle spasms, and overall well-being in a double-blind crossover trial involving a single MS patient [77]. While several bigger, population-based clinical trials of cannabis-based medications for MS patients have been sparked by these optimistic stories, the outcomes have been conflicting [78–81].

The UK Medical Council funded a large multicenter study called "Cannabinoids in Multiple Sclerosis (CAMS) study" that involved 33 clinical centers, 660 MS patients, and the United Kingdom and the United States. The study's goal was to compare the effects of synthetic THC (Marinol) or cannabis extract (Cannador) on bladder function, pain, tremor, spasticity, and cognitive function to a placebo [82,83]. Following a 15-week course treatment with Marinol or Cannador, patients' reported levels of pain, spasticity, and sleep quality significantly improved, and hospital admissions for relapse decreased in the two active treatment groups [84,85]. Nevertheless, there were no improvements in the Ashworth score, and the negative

side effects—which were mostly mild and comparable to those of a placebo—included tremor, irritability, sadness, and fatigue [86–88]. In other studies, with a similar design, the benefits of THC with CBD on spasm frequency and mobility in MS patients were validated [89-95].

In summary, controlled clinical trials including cannabis have shown that they are effective in causing symptomatic improvements in patients with multiple sclerosis. These findings imply that cannabis treatment for multiple sclerosis has a place, and this should be verified by larger-scale clinical trials in the future.

4.4. Neuropathic and other type of pain:

In diseases resistant to treatments, such as refractory neuropathic pain brought on by diabetes mellitus, central neuropathic pain, pain in cancer patients, and pain in HIV-positive individuals, use of cannabis may offer effective analgesia. A study found that after using cannabis, 90% of patients experienced lessening of their nerve pain [96]. When conventional therapy is ineffective, using it is advised by a number of guidelines.

4.5. Depression and anxiety:

Data on anxiety indicated that cannabinoids (dronabinol, nabilone, and nabiximols) were more beneficial than placebo and should considered for individuals who qualify [97]. However, there was no distinction between cannabis and a placebo in terms of the results of depression, and some people claimed that excessive doses had an adverse effect.

4.6. Tics and Tourette syndrome:

To support or disprove the clinical usage of cannabis for tics, there is not enough evidence. The beneficial effects of THC were only sometimes observed in studies, although they might be an option in cases of resistance [98].

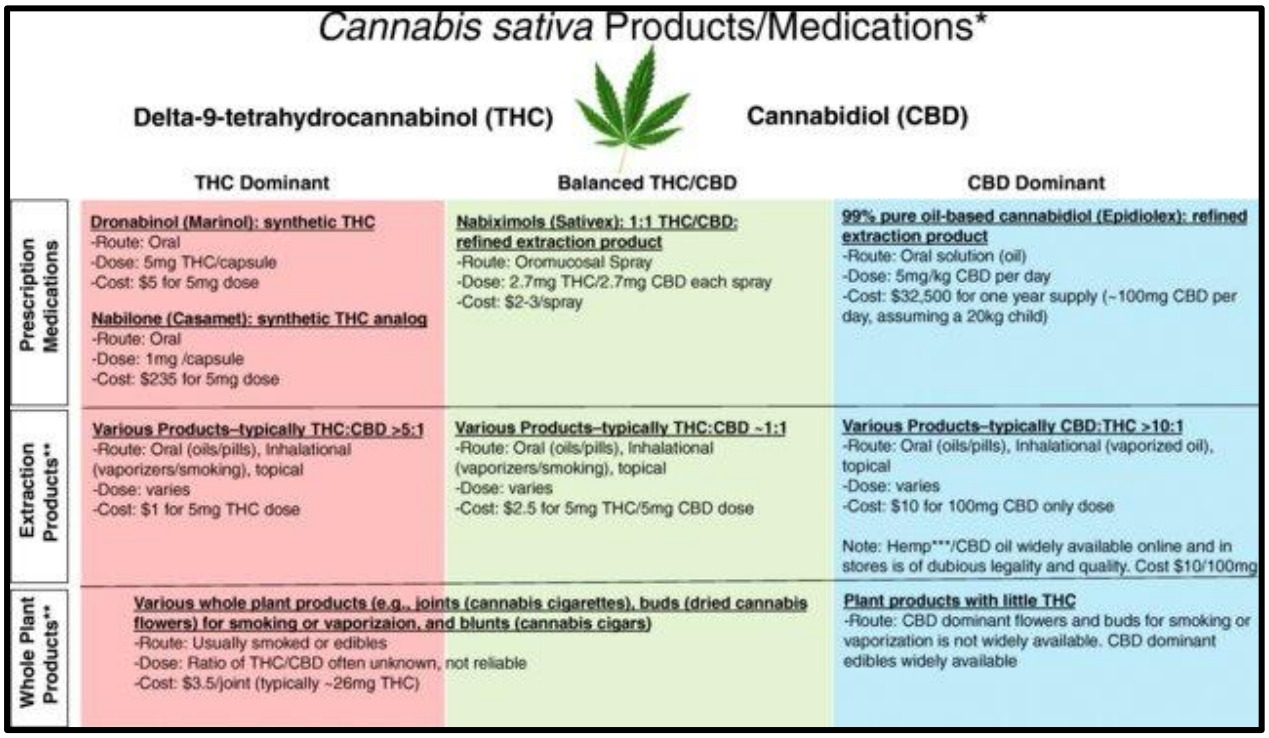

Figure 7. Types of Cannabis sativa products/medications available [98].

5. Diseases of the Central Nervous System (Indications with benefits but insufficient evidence)

5.1. Dementia:

Tetrahydrocannabinol and other substances may lessen B-Amyloid in brain, according to a few recent studies [99]. A recent study indicated that cannabis extracts containing THC are a safe and effective therapy option for Alzheimer's disease and can alleviate a variety of cognitive and mental symptoms [100]. However, more information is needed before it may be used clinically in dementia.

5.2. Cannabinoids for Parkinson's disease:

With varying degrees of success on cannabis research, it has been researched in relation to enhancing motor characteristics, functional outcomes, and dopa-related dyskinesias [101]. Its advice for these and other targeted Parkinson's disease symptoms (such as dystonia, psychosis, and sleep) needs more support.

(Parkinson disease) is second most frequent neurodegenerative illness, while AD (Alzheimer's disease) is the most common neurological disorder in the elderly population. Numerous investigations reveal existence of inflammatory mediators in the cerebrospinal fluid (CSF) and post-mortem substantia nigra pars compacta of PD patients' brains, such as TNF-a, IL-1β, IL-6, and interferon-g (IFNγ) [102, 103]. Proinflammatory cytokine levels in the CSF and nigrostriatal areas of Parkinson's disease (PD) brains are elevated. Furthermore, the substantia nigra of PD patients contains a high concentration of activated microglia. These might continuously generate ROS, which would deplete antioxidant reserves and endanger mitochondrial function. Since the majority of ROS produced by cells originate from aerobic respiration in the mitochondria, anomalies in these organelles may make oxidative stress worse [102, 103].

According to a recent study [104], CBD may promote neuroprotection in Parkinson's disease (PD) animal models. When CBD was administered on a daily basis for two weeks, the toxicity caused by injecting 6-hydroxydopamine into the medial forebrain bundle was dramatically reduced [104]. Cu/Zn-superoxide dismutase is an essential enzyme in the body's defense against oxidative stress, and CBD increased mRNA levels in this Parkinson's disease model. According to the findings, CBD can offer neuroprotection against the PD-related progressive degradation of nigrostriatal dopaminergic neurons [105]. An further study supported this one by demonstrating that CBD inhibited the in vivo striatal atrophy brought on by 3-nitropropionic acid via mechanisms unrelated to the activation of cannabinoid, vanilloid TRPV1, and adenosine A2A receptors [106]. Additionally, the robust correlation observed between the N-acetylaspartate/total creatine ratio and CBD in the putamen/globus pallidum of recreational cannabis users provided additional evidence for the neuroprotective effect of CBD in human basal ganglia. This may indicate that CBD has improved the neuronal and axonal integrity in these areas [107].

In light of the aforementioned preclinical data, a clinical trial assessed safety, tolerability, and efficacy of CBD in patients with Parkinson's disease (PD) for the first time [108]. Six consecutive outpatients with PD were included in an open-label pilot research and administered a flexible-dose regimen of CBD for four weeks, commencing with an oral dose of 150 mg/day, in addition to their regular medication. Along with the CBD treatment, there was a considerable reduction in the psychotic symptoms associated with PD, and the overall score on the scale used to monitor the course of PD also showed a significant decline. These early findings point to a potential benefit of CBD for Parkinson's disease [109].

5.3. Phytocannabinoids Huntington's disease:

Although there is no proof to support cannabis usage in Huntington's disease, several case studies and small trials found that it significantly reduced chorea and other neuropsychiatric symptoms in patients with the condition. To determine its usefulness for these indications, additional extensive research may be required [110].

Although many neurodegenerative disorders, including PD, ALS, and AD, have targeted neuroinflammation, the HD community has not given it much consideration. Though they may not have specifically addressed neuroinflammation, a number of published trials may have focused on this process [111].

According to a number of studies, inflammation develops in the central nervous system as HD and HD-like diseases advance. Increased gliosis and the expression of genes linked to inflammation, such as

complement proteins and glial fibrillary acidic protein, were seen in a number of brain areas from HD patients compared to controls. The caudate putamen, where brain disease is most severe in HD patients, showed the greatest increases [111]. Additionally, HD patients had altered immune profiles prior to the onset of clinical HD symptoms and increased levels of pro-inflammatory cytokines involved in the innate immune response, such as IL-6, which suggests that inflammation may worsen striatal and cortical neurodegeneration [111]. Therefore, it is evident that neuroinflammation processes such as disturbance of normal microglial functions and neuronal distress are also associated with HD. Once the nature of this neuroinflammation is better known, targeted interference with reactive or active neuroinflammatory processes may prove useful in the development of novel therapeutic strategies. This neuroinflammation may also contribute to the death of additional neurons [111].

The endocannabinoid system may have a role in pathogenesis of HD and other neurological illnesses, according to research that has shown alterations in CB1 receptor activation and levels [112–114].

According to post-mortem research on HD patients and animal models, the expression of the mutant Huntingtin protein causes the CB1 receptors in basal ganglia to be downregulated and/or desensitized. This process appears to happen early in the disease's progression, before overt clinical symptoms manifest [113–124]. These results are corroborated by a recent in vivo PET investigation of HD patients, which shows significant decrease in CB1 receptor availability even in the early stages of the disease across the gray matter of the brainstem, cerebellum, and cerebrum of HD patients [125]. Moreover, pre-clinical and post-mortem investigations on HD patients show an inverse correlation between the rise in CB2 receptor levels in reactive microglial cells, astrocytes, and glial components and the fall in CB1 receptor levels [126]. Changes in endocannabinoid system are closely linked to pathogenesis of HD, according to additional clinical and pre-clinical findings [127–131].

A study employing an animal model of HD further validated the substantial correlation between cannabis and HD [132]. The study's findings supported the idea that a decrease in CB1 receptors in the basal ganglia causes an increase in symptoms similar to Huntington's disease. Additionally, the development of HD may be further aided by the decreased levels of BDNF in mice lacking CB1 receptors. In fact, BDNF supplementation has been demonstrated in animal models of HD to reduce excitotoxicity, attenuate motor impairment, and slow cell death, suggesting that it may be a potential treatment for HD.

5.4. Dystonia:

Only a few modest randomized placebo-controlled clinical trials with inconsistent findings provide data on cannabis usage in dystonia. To clarify its involvement, more extensive research is required [110].

5.5. Cannabinoids for Amyotrophic Lateral Sclerosis (ALS):

According to certain studies, cannabis may aid ALS sufferers in some ways, such as delaying the disease's beginning and reducing its course. These may also aid in treating pain, lack of appetite, depression, difficulty sleeping, spasticity, and drooling [133]. However, additional research is required before it can be advised for usage in ALS.

A progressive neurodegenerative illness called ALS causes the selective destruction of motor neurons in brain and spinal cord. Although there are a few uncommon occurrences of early-onset ALS, the disease often first appears in people in their mid-50s. Muscle atrophy and wasting are the disease's signs, which eventually result in paralysis and death [134, 135]. Because of a progressive, broad paralysis that eventually affects breathing muscles and results in respiratory failure, ALS is usually fatal within five years of diagnosis [134, 135]. T cells, activated microglia, astrocytes, and other cytokines and immune cells are indicative of areas where degenerating motor neurons found in both ALS patients and mice models [134, 135].

Not all inflammatory mediators have been significantly linked to ALS, despite the possibility that a widespread neuroinflammatory response is causing the increasing loss of motor neurons. For example, the genetic deletion of IL-1β does not alter the lifespan or rate of motor neurodegeneration in mutant SOD-1

mice, suggesting that IL-1β may not be essential to the pathophysiology of ALS [134, 136]. There are currently no effective pharmaceutical treatments for this debilitating illness, and neuroinflammation may hasten the disease's course. On the other hand, it has been shown that cannabis, via both CB1 and CB2 receptors, can slow the progression of neuroinflammatory illnesses like ALS [137]. Using G93A-SOD1 mutant mice as an ALS animal model, the role of CB receptors in the development of ALS neuroinflammation was established [137]. Treatment with non-selective cannabinoid partial agonists before or upon symptom presentation modestly slows illness onset and prolongs survival through unclear mechanisms [137]. The symptomatic mice revealed higher endogenous cannabinoids. Moreover, CB2 receptors, which are typically found mostly in the peripheral, are markedly up-regulated in inflammatory brain regions linked to ALS problems in this animal model of the disease [137]. The selective CB2 agonist AM-1241 has been shown to be effective in increasing life intervals by 56% [137]. This suggests that CB2 agonists may decrease motor neuron degradation and retain motor function, making them a promising new therapeutic option as the treatment of ALS.

5.6. Migraine:

Clinical trials are necessary before recommending cannabis use for migraine indication, but have been reported to suppress the pain response in migraine sufferers [138].

5.7. Prion disease:

Cannabis have been demonstrated to protect against prion toxicity and lower the risk of prion illness in laboratory settings, although clinical trials are still pending [139].

5.8. Stroke:

Cannabis appears to promote neurobehavioral recovery, decrease infarct size, increase functional, histological, and functional recovery, although there are no large-scale data to support their prescription [140].

5.9. Sleep disorders:

There is evidence to suggest that cannabinoids may help certain patients sleep better. Compared to the placebo, cannabinoids were linked to a larger average improvement in sleep quality and sleep disturbance [141]. To determine its value for this purpose, additional extensive research is required.

5.10. Other uses:

Studies demonstrated its anti-tumor effect since it stopped the proliferation of cancer cells. Additionally, its advantages have been noted in fibromyalgia and spinal cord injury [142]. Despite a lot of encouraging data, there are a few things that make its application as medication difficult. These include ethical, legal, and medical aspects as well as economic ones. Cannabis has been discovered to have a significantly lower risk for addiction than conventional pharmaceutical drugs, making it far safer for medical use. Long-term cannabis users are said to be at 9% risk of developing dependent, much lower than the rates of addiction to heroin, cocaine, alcohol, and prescribed anxiolytics [143]. Euphoria, disorientation, tiredness, dizziness, motor incoordination, and poor focus are its adverse effects.

Tachycardia, hypotension, conjunctival injection, bronchodilation, muscular relaxation, and impaired gastrointestinal motility are some of the side effects in the periphery. The chance of developing psychiatric problems, apathy, cognitive decline, and pregnancy-related risks is just a few of the long-term impacts [144]. Therefore, it should only be used if the benefits outweigh the risks, as determined by a professional. Its usage and possession are associated ethically in many cultures with negative connotations. A successful awareness campaign may enable patients, families, and society to make informed decisions. In the end, the controversy around medicinal marijuana is not about making it widely accessible for a variety of health issues, but rather about giving a select group of patients a choice where they may otherwise have none. Cannabis is still the most often used drug in Pakistan, where it is legal to possess it under The Anti-Narcotic Policy 2010 [145], even though the prevalence of recreational use is 3.6% in our population. Law modifications will be required in Pakistan to loosen restrictions on its usage for therapeutic purposes due to growing support for its use as medicine, as in many other wealthy nations. For its controlled use, certain necessary steps should be performed, such as: (1) Only

be prescribed by professionals. (2) Particularly designated places that have monitoring devices to continuously check the dose or quantity. (3) Ongoing expert monitoring of adverse effects and examination of potential abuse. (4) When to cease using it or cut back if there are any bad effects. Law changes will be necessary because there is a chance that patients would start obtaining it illegally if its prudent use is not legalized, which could result in subpar quality and unregulated use, opening up more dangers than benefits [146].

CONCLUSION

Numerous neurological and medical conditions have been reported to benefit from cannabinoids of Medical Cannabis. The health authorities should cooperate with law enforcement to create a framework to ensure that its use is justified and strictly regulated in order to keep it in check. This will allow it to be available when all other options have failed. To reach an agreement regarding medicinal usage of Medical Cannabis, three forces of scientific understanding, social and political acceptance, and legislation may be helpful.

REFERENCES

1. Atakan, Z. (2012). Cannabis, a complex plant: different compounds and different effects on individuals. *Therapeutic advances in psychopharmacology*, *2*(6), 241-254.
2. Kalant, H. (2001). Medicinal use of cannabis: history and current status. *Pain Research and Management*, *6*, 80-91.
3. Morris, R. G., TenEyck, M., Barnes, J. C., & Kovandzic, T. V. (2014). The effect of medical marijuana laws on crime: evidence from state panel data, 1990-2006. *PloS one*, *9*(3), e92816.
4. Munro, S., Thomas, K. L., & Abu-Shaar, M. (1993). Molecular characterization of a peripheral receptor for cannabinoids. *Nature*, *365*(6441), 61-65.
5. Eldeeb, K., Leone-Kabler, S., & Howlett, A. C. (2016). CB1 cannabinoid receptor-mediated increases in cyclic AMP accumulation are correlated with reduced Gi/o function. *Journal of basic and clinical physiology and pharmacology*, *27*(3), 311-322.
6. Howlett, A. C., Breivogel, C. S., Childers, S. R., Deadwyler, S. A., Hampson, R. E., & Porrino, L. J. (2004). Cannabinoid physiology and pharmacology: 30 years of progress. *Neuropharmacology*, *47*, 345-358.
7. Herkenham, M., Lynn, A. B., Johnson, M. R., Melvin, L. S., de Costa, B. R., & Rice, K. C. (1991). Characterization and localization of cannabinoid receptors in rat brain: a quantitative in vitro autoradiographic study. *Journal of Neuroscience*, *11*(2), 563-583.
8. Porter, A. C., & Felder, C. C. (2001). The endocannabinoid nervous system: unique opportunities for therapeutic intervention. *Pharmacology & therapeutics*, *90*(1), 45-60.
9. Begg, M., Pacher, P., Bátkai, S., Osei-Hyiaman, D., Offertáler, L., Mo, F. M., ... & Kunos, G. (2005). Evidence for novel cannabinoid receptors. *Pharmacology & therapeutics*, *106*(2), 133-145.
10. Rodríguez de Fonseca, F., Del Arco, I., Bermudez-Silva, F. J., Bilbao, A., Cippitelli, A., & Navarro, M. (2005). The endocannabinoid system: physiology and pharmacology. *Alcohol and Alcoholism*, *40*(1), 2-14.
11. Rodríguez de Fonseca, F., Del Arco, I., Bermudez-Silva, F. J., Bilbao, A., Cippitelli, A., & Navarro, M. (2005). The endocannabinoid system: physiology and pharmacology. *Alcohol and Alcoholism*, *40*(1), 2-14.
12. Hanuš, L., Abu-Lafi, S., Fride, E., Breuer, A., Vogel, Z., Shalev, D. E., ... & Mechoulam, R. (2001). 2-arachidonyl glyceryl ether, an endogenous agonist of the cannabinoid CB1 receptor. *Proceedings of the National Academy of Sciences*, *98*(7), 3662-3665.
13. Huang, S. M., Bisogno, T., Trevisani, M., Al-Hayani, A., De Petrocellis, L., Fezza, F., ... & Di Marzo, V. (2002). An endogenous capsaicin-like substance with high potency at recombinant and native vanilloid VR1 receptors. *Proceedings of the National Academy of Sciences*, *99*(12), 8400-8405.
14. Leggett, J. D., Aspley, S., Beckett, S. R. G., D'antona, A. M., Kendall, D. A., & Kendall, D. A. (2004). Oleamide is a selective endogenous agonist of rat and human CB1 cannabinoid receptors. *British journal of pharmacology*, *141*(2), 253-262.
15. Piomelli, D. (2003). The molecular logic of endocannabinoid signalling. *Nature Reviews*

Neuroscience, *4*(11), 873-884.
16. Petrocellis, L. D., Cascio, M. G., & Marzo, V. D. (2004). The endocannabinoid system: a general view and latest additions. *British journal of pharmacology*, *141*(5), 765-774.
17. Gerdeman, G. L., Partridge, J. G., Lupica, C. R., & Lovinger, D. M. (2003). It could be habit forming: drugs of abuse and striatal synaptic plasticity. *Trends in neurosciences*, *26*(4), 184-192.
18. Van Der Stelt, M., & Di Marzo, V. (2003). The endocannabinoid system in the basal ganglia and in the mesolimbic reward system: implications for neurological and psychiatric disorders. *European journal of pharmacology*, *480*(1-3), 133-150.
19. Iversen, L., & Chapman, V. (2002). Cannabinoids: a real prospect for pain relief. *Current opinion in pharmacology*, *2*(1), 50-55.
20. Randall, M. D., Harris, D., Kendall, D. A., & Ralevic, V. (2002). Cardiovascular effects of cannabinoids. *Pharmacology & therapeutics*, *95*(2), 191-202.
21. Carlo, G. D., & Izzo, A. A. (2003). Cannabinoids for gastrointestinal diseases: potential therapeutic applications. *Expert opinion on investigational drugs*, *12*(1), 39-49.
22. Maccarrone, M., & Wenger, T. (2005). Effects of cannabinoids on hypothalamic and reproductive function. *Cannabinoids*, 555-571.
23. Klein, T. W. (2005). Cannabinoid-based drugs as anti-inflammatory therapeutics. *Nature Reviews Immunology*, *5*(5), 400-411.
24. Di Marzo, V., & Petrosino, S. (2007). Endocannabinoids and the regulation of their levels in health and disease. *Current opinion in lipidology*, *18*(2), 129-140.
25. Raup-Konsavage, W. M., Carkaci-Salli, N., Greenland, K., Gearhart, R., & Vrana, K. E. (2020). Cannabidiol (CBD) oil does not display an entourage effect in reducing cancer cell viability in vitro. *Medical Cannabis and Cannabinoids*, *3*(2), 95-102.
26. Legare, C. A., Raup-Konsavage, W. M., & Vrana, K. E. (2022). Therapeutic potential of cannabis, cannabidiol, and cannabinoid-based pharmaceuticals. *Pharmacology*, *107*(3-4), 131-149.
27. Hasan, N., Imran, M., Sheikh, A., Saad, S., Chaudhary, G., Jain, G. K., ... & Ahmad, F. J. (2022). Cannabis as a potential compound against various malignancies, legal aspects, advancement by exploiting nanotechnology and clinical trials. *Journal of Drug Targeting*, *30*(7), 709-725.
28. Corroon, J., & Kight, R. (2018). Regulatory status of cannabidiol in the United States: a perspective. *Cannabis and cannabinoid research*, *3*(1), 190-194.
29. Kocis, P. T., Wadrose, S., Wakefield, R. L., Ahmed, A., Calle, R., Gajjar, R., & Vrana, K. E. (2023). CANNabinoid drug interaction review (CANN-DIR™). *Medical cannabis and cannabinoids*, *6*(1), 1-7.
30. Feliciani, G. (2022). Cannabis Drug Development and the Controlled Substances Act. *Duke J. Const. L. & Pub. Pol'y Sidebar*, *18*, 153.
31. Gøtzsche, P. C., & Jørgensen, A. W. (2011). Opening up data at the European Medicines Agency. *Bmj*, *342*.
32. Hampton, T. (2011). European drug agency under fire. *JAMA*, *306*(6), 593-595.
33. Braillon, A. (2011). EMA urgently needs a cure. *BMJ*, *342*.
34. Fallon, M. T., Albert Lux, E., McQuade, R., Rossetti, S., Sanchez, R., Sun, W., ... & Kornyeyeva, E. (2017). Sativex oromucosal spray as adjunctive therapy in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy: two double-blind, randomized, placebo-controlled phase 3 studies. *British journal of pain*, *11*(3), 119-133.
35. Licastro, F., & Chiappelli, M. (2003). Brain immune responses cognitive decline and dementia: relationship with phenotype expression and genetic background. *Mechanisms of ageing and development*, *124*(4), 539-548.
36. Pizza, V., Agresta, A., W D'Acunto, C., Festa, M., & Capasso, A. (2011). Neuroinflamm-aging and neurodegenerative diseases: an overview. *CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders)*, *10*(5), 621-634.
37. Ramírez, B. G., Blázquez, C., Del Pulgar, T. G., Guzmán, M., & de Ceballos, M. L. (2005). Prevention of Alzheimer's disease pathology by cannabinoids: neuroprotection mediated by blockade of microglial activation. *Journal of Neuroscience*, *25*(8), 1904-1913.
38. Esposito, G., De Filippis, D., Carnuccio, R., Izzo, A. A., & Iuvone, T. (2006). The marijuana component cannabidiol inhibits β-amyloid-

induced tau protein hyperphosphorylation through Wnt/β-catenin pathway rescue in PC12 cells. *Journal of molecular medicine*, *84*, 253-258.

39. Esposito, G., De Filippis, D., Maiuri, M. C., De Stefano, D., Carnuccio, R., & Iuvone, T. (2006). Cannabidiol inhibits inducible nitric oxide synthase protein expression and nitric oxide production in β-amyloid stimulated PC12 neurons through p38 MAP kinase and NF-κB involvement. *Neuroscience letters*, *399*(1-2), 91-95.
40. Esposito, G., Scuderi, C., Savani, C., Steardo Jr, L., De Filippis, D., Cottone, P., ... & Steardo, L. (2007). Cannabidiol in vivo blunts β-amyloid induced neuroinflammation by suppressing IL-1β and iNOS expression. *British journal of pharmacology*, *151*(8), 1272-1279.
41. American Academy of Neurology. (2019). Summary of Systematic Review for Patients and Their Families: Medical Marijuana in Certain Neurological Disorders.; 2014.
42. Rosenberg, E. C., Tsien, R. W., Whalley, B. J., & Devinsky, O. (2015). Cannabinoids and epilepsy. *Neurotherapeutics*, *12*(4), 747-768.
43. Zajicek, J. P., & Apostu, V. I. (2011). Role of cannabinoids in multiple sclerosis. *CNS drugs*, *25*, 187-201.
44. Pizza, V., Agresta, A., W D'Acunto, C., Festa, M., & Capasso, A. (2011). Neuroinflamm-aging and neurodegenerative diseases: an overview. *CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders)*, *10*(5), 621-634.
45. Nguyen, M. D., Julien, J. P., & Rivest, S. (2001). Induction of proinflammatory molecules in mice with amyotrophic lateral sclerosis: No requirement for proapoptotic interleukin-1β in neurodegeneration. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society*, *50*(5), 630-639.
46. Killestein, J., Uitdehaag, B. M., & Polman, C. H. (2004). Cannabinoids in multiple sclerosis: do they have a therapeutic role?. *Drugs*, *64*, 1-11.
43. Mechoulam R (1986) The pharmacohistory of cannabis sativa, in Cannabis as Therapeutic Agent (Mechoulam R ed) pp 1-19, CRC Press, Boca Raton, FL.
44. Mechoulam, R., Fride, E., & Di Marzo, V. (1998). Endocannabinoids. *European journal of pharmacology*, *359*(1), 1-18.
45. Mechoulam, R., & Hanuš, L. (2000). A historical overview of chemical research on cannabinoids. *Chemistry and physics of lipids*, *108*(1-2), 1-13.
46. Grundy, R. I. (2002). The therapeutic potential of the cannabinoids in neuroprotection. *Expert opinion on investigational drugs*, *11*(10), 1365-1374.
47. Pertwee, R. G. (2007). Cannabinoids and multiple sclerosis. *Molecular neurobiology*, *36*, 45-59.
48. Baker, D., & Pryce, G. (2003). The therapeutic potential of cannabis in multiple sclerosis. *Expert Opinion on Investigational Drugs*, *12*(4), 561-567.
49. Croxford, J. L. (2003). Therapeutic potential of cannabinoids in CNS disease. *CNS drugs*, *17*, 179-202.
50. Killestein, J., Uitdehaag, B. M., & Polman, C. H. (2004). Cannabinoids in multiple sclerosis: do they have a therapeutic role?. *Drugs*, *64*, 1-11.
51. Sirven, J. I., & Berg, A. T. (2004). Marijuana as a treatment for epilepsy and multiple sclerosis? A "grass roots" movement. *Neurology*, *62*(11), 1924-1925.
52. Jackson, S. J., Diemel, L. T., Pryce, G., & Baker, D. (2005). Cannabinoids and neuroprotection in CNS inflammatory disease. *Journal of the neurological sciences*, *233*(1-2), 21-25.
53. Pryce, G., & Baker, D. (2005). Emerging properties of cannabinoid medicines in management of multiple sclerosis. *TRENDS in Neurosciences*, *28*(5), 272-276.
54. Robson, P. (2005). Human studies of cannabinoids and medicinal cannabis. *Cannabinoids*, 719-756.
55. Smith, P. F. (2005). The safety of cannabinoids for the treatment of multiple sclerosis. *Expert Opinion on Drug Safety*, *4*(3), 443-456.
56. Lyman, W. D., Sonett, J. R., Brosnan, C. F., Elkin, R., & Bornstein, M. B. (1989). Δ9-Tetrahydrocannabinol: a novel treatment for experimental autoimmune encephalomyelitis. *Journal of neuroimmunology*, *23*(1), 73-81.
57. Wirguin, I., Mechoulam, R., Breuer, A., Schezen, E., Weidenfeld, J., & Brenner, T. (1994). Suppression of experimetal autoimmune encephalomyelitis by cannabinoids. *Immunopharmacology*, *28*(3), 209-214.
58. Achiron, A., Miron, S., Lavie, V., Margalit, R., &

Biegon, A. (2000). Dexanabinol (HU-211) effect on experimental autoimmune encephalomyelitis: implications for the treatment of acute relapses of multiple sclerosis. *Journal of neuroimmunology*, *102*(1), 26-31.

59. Berrendero, F., Sánchez, A., Cabranes, A., Puerta, C., Ramos, J. A., García-Merino, A., & Fernández-Ruiz, J. (2001). Changes in cannabinoid CB1 receptors in striatal and cortical regions of rats with experimental allergic encephalomyelitis, an animal model of multiple sclerosis. *Synapse*, *41*(3), 195-202.
60. Baker, D., Pryce, G., Croxford, J. L., Brown, P., Pertwee, R. G., Huffman, J. W., & Layward, L. (2000). Cannabinoids control spasticity and tremor in a multiple sclerosis model. *Nature*, *404*(6773), 84-87.
61. Ligresti, A., Cascio, M. G., Pryce, G., Kulasegram, S., Beletskaya, I., De Petrocellis, L., ... & Di Marzo, V. (2006). New potent and selective inhibitors of anandamide reuptake with antispastic activity in a mouse model of multiple sclerosis. *British journal of pharmacology*, *147*(1), 83-91.
62. Pryce, G., Ahmed, Z., Hankey, D. J., Jackson, S. J., Croxford, J. L., Pocock, J. M., ... & Baker, D. (2003). Cannabinoids inhibit neurodegeneration in models of multiple sclerosis. *Brain*, *126*(10), 2191-2202.
63. Jackson, S. J., Diemel, L. T., Pryce, G., & Baker, D. (2005). Cannabinoids and neuroprotection in CNS inflammatory disease. *Journal of the neurological sciences*, *233*(1-2), 21-25.
64. Jackson, S. J., Pryce, G., Diemel, L. T., Cuzner, M. L., & Baker, D. (2005). Cannabinoid-receptor 1 null mice are susceptible to neurofilament damage and caspase 3 activation. *Neuroscience*, *134*(1), 261-268.
65. Ni, X., Geller, E. B., Eppihimer, M. J., Eisenstein, T. K., Adler, M. W., & Tuma, R. F. (2004). Win 55212-2, a cannabinoid receptor agonist, attenuates leukocyte/endothelial interactions in an experimental autoimmune encephalomyelitis model. *Multiple Sclerosis Journal*, *10*(2), 158-164.
66. Witting, A., Chen, L., Cudaback, E., Straiker, A., Walter, L., Rickman, B., ... & Stella, N. (2006). Experimental autoimmune encephalomyelitis disrupts endocannabinoid-mediated neuroprotection. *Proceedings of the National Academy of Sciences*, *103*(16), 6362-6367.
67. Croxford, J. L., & Miller, S. D. (2003). Immunoregulation of a viral model of multiple sclerosis using the synthetic cannabinoid R (+) WIN55, 212. *The Journal of clinical investigation*, *111*(8), 1231-1240.
68. Arévalo-Martín, Á., Vela, J. M., Molina-Holgado, E., Borrell, J., & Guaza, C. (2003). Therapeutic action of cannabinoids in a murine model of multiple sclerosis. *Journal of Neuroscience*, *23*(7), 2511-2516.
69. Mestre, L., Correa, F., Arévalo-Martín, A., Molina-Holgado, E., Valenti, M., Ortar, G., ... & Guaza, C. (2005). Pharmacological modulation of the endocannabinoid system in a viral model of multiple sclerosis. *Journal of neurochemistry*, *92*(6), 1327-1339.
70. Ortega-Gutiérrez, S., Molina-Holgado, E., Arévalo-Martín, Á., Correa, F., Viso, A., López-Rodríguez, M. L., ... & Guaza, C. (2005). Activation of the endocannabinoid system as a therapeutic approach in a murine model of multiple sclerosis. *The FASEB journal*, *19*(10), 1338-1340.
71. Eljaschewitsch, E., Witting, A., Mawrin, C., Lee, T., Schmidt, P. M., Wolf, S., ... & Ullrich, O. (2006). The endocannabinoid anandamide protects neurons during CNS inflammation by induction of MKP-1 in microglial cells. *Neuron*, *49*(1), 67-79.
72. Grinspoon, L. G., Grinspoon, L., & Bakalar, J. B. (1997). *Marihuana, the forbidden medicine*. Yale University Press.
73. Grinspoon, L., & Bakalar, J. B. (1998). The use of cannabis as a mood stabilizer in bipolar disorder: anecdotal evidence and the need for clinical research. *Journal of psychoactive drugs*, *30*(2), 171-177.
74. Grinspoon, L., & Bakalar, J. B. (1998). The use of cannabis as a mood stabilizer in bipolar disorder: anecdotal evidence and the need for clinical research. *Journal of psychoactive drugs*, *30*(2), 171-177.
75. Petro, D. J. (1980). Marihuana as a therapeutic agent for muscle spasm or spasticity. *Psychosomatics*, *21*(1), 81-85.
76. PETRO, D. J., & ELLENBERGER Jr, C. A. R. L. (1981). Treatment of Human Spasticity with Δ9-Tetrahydrocannabinol. *The Journal of Clinical Pharmacology*, *21*(S1), 413S-416S.
77. Clifford, D. B. (1983). Tetrahydrocannabinol for tremor in multiple sclerosis. *Annals of Neurology:*

Official Journal of the American Neurological Association and the Child Neurology Society, *13*(6), 669-671.

78. Meinck, H. M., Schönle, P. W., & Conrad, B. (1989). Effect of cannabinoids on spasticity and ataxia in multiple sclerosis. *Journal of neurology*, *236*, 120-122.
79. Brenneisen, R., Egli, A., Elsohly, M. A., Henn, V., & Spiess, Y. (1996). The effect of orally and rectally administered delta 9-tetrahydrocannabinol on spasticity: a pilot study with 2 patients. *International journal of clinical pharmacology and therapeutics*, *34*(10), 446-452.
80. Schon, F., Hart, P. E., Hodgson, T. L., Pambakian, A. L. M., Ruprah, M., Williamson, E. M., & Kennard, C. (1999). Suppression of pendular nystagmus by smoking cannabis in a patient with multiple sclerosis. *Neurology*, *53*(9), 2209-2209.
81. Martyn, C. N., Illis, L. S., & Thom, J. (1995). Nabilone in the treatment of multiple sclerosis. *Lancet*, *345*(8949), 579-579.
82. Greenberg, H. S., Werness, S. A., Pugh, J. E., Andrus, R. O., Anderson, D. J., & Domino, E. F. (1994). Short-term effects of smoking marijuana on balance in patients with multiple sclerosis and normal volunteers. *Clinical Pharmacology & Therapeutics*, *55*(3), 324-328.
83. Consroe, P., Musty, R., Rein, J., Tillery, W., & Pertwee, R. (1997). The perceived effects of smoked cannabis on patients with multiple sclerosis. *European neurology*, *38*(1), 44-48.
84. Killestein, J., Hoogervorst, E. L. J., Reif, M., Kalkers, N. F., Van Loenen, A. C., Staats, P. G. M., ... & Polman, C. H. (2002). Safety, tolerability, and efficacy of orally administered cannabinoids in MS. *Neurology*, *58*(9), 1404-1407.
85. Thompson, A. J., & Baker, D. (2002). Cannabinoids in MS: potentially useful but not just yet!. *Neurology*, *58*(9), 1323-1324.
86. Zajicek, J., Fox, R., Sanders, H., Wright, D., Vickery, J., Nunn, A., & Thompson, A. (2004, September). The cannabinoids in MS study-final results form 12 months follow-up. In *Multiple Sclerosis* (Vol. 10, No. 7032, pp. S115-S115). 338 EUSTON ROAD, LONDON NW1 3BH, ENGLAND: ARNOLD, HODDER HEADLINE PLC.
87. Zajicek, J., Fox, P., Sanders, H., Wright, D., Vickery, J., Nunn, A., & Thompson, A. (2003). Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *The lancet*, *362*(9395), 1517-1526.
88. Fox, P., Bain, P. G., Glickman, S., Carroll, C., & Zajicek, J. (2004). The effect of cannabis on tremor in patients with multiple sclerosis. *Neurology*, *62*(7), 1105-1109.
89. Vaney, C., Heinzel-Gutenbrunner, M., Jobin, P., Tschopp, F., Gattlen, B., Hagen, U., ... & Reif, M. (2004). Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled, crossover study. *Multiple Sclerosis Journal*, *10*(4), 417-424.
90. Vaney, C., Heinzel-Gutenbrunner, M., Jobin, P., Tschopp, F., Gattlen, B., Hagen, U., ... & Reif, M. (2004). Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled, crossover study. *Multiple Sclerosis Journal*, *10*(4), 417-424.
91. Wade, D. T., Robson, P., House, H., Makela, P., & Aram, J. (2003). A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. *Clinical rehabilitation*, *17*(1), 21-29.
92. Smith, P. F. (2004). GW-1000. GW Pharmaceuticals. *Current opinion in investigational drugs (London, England: 2000)*, *5*(7), 748-754.
93. Wade, D. T., Makela, P., Robson, P., House, H., & Bateman, C. (2004). Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. *Multiple Sclerosis Journal*, *10*(4), 434-441.
94. Russo, E., & Guy, G. W. (2006). A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Medical hypotheses*, *66*(2), 234-246.
95. Russo, E. B. (2008). Clinical endocannabinoid deficiency (CECD). *Neuroendocrinology Letters*, *29*(2).
96. Noel, C. (2017). Evidence for the use of "medical marijuana" in psychiatric and neurologic

disorders. *Mental Health Clinician*, *7*(1), 29-38.
97. Boychuk, D. G., Goddard, G., Mauro, G., & Orellana, M. F. (2015). The effectiveness of cannabinoids in the management of chronic nonmalignant neuropathic pain: a systematic review. *J oral facial pain headache*, *29*(1), 7-14.
98. Patel, S., & Hillard, C. J. (2009). Role of endocannabinoid signaling in anxiety and depression. *Behavioral neurobiology of the endocannabinoid system*, 347-371.
99. Kluger, B., Triolo, P., Jones, W., & Jankovic, J. (2015). The therapeutic potential of cannabinoids for movement disorders. *Movement disorders*, *30*(3), 313-327.
100. Currais, A., Quehenberger, O., M Armando, A., Daugherty, D., Maher, P., & Schubert, D. (2016). Amyloid proteotoxicity initiates an inflammatory response blocked by cannabinoids. *NPJ aging and mechanisms of disease*, *2*(1), 1-8.
101. Ferrer, I. (2014). Cannabinoids for treatment of Alzheimer's disease: moving toward the clinic. *Frontiers in pharmacology*, *5*, 81375.
102. Pizza, V., Agresta, A., W D'Acunto, C., Festa, M., & Capasso, A. (2011). Neuroinflamm-aging and neurodegenerative diseases: an overview. *CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders)*, *10*(5), 621-634.
103. Banati, R. B., Daniel, S. E., & Blunt, S. B. (1998). Glial pathology but absence of apoptotic nigral neurons in long-standing Parkinson's disease. *Movement disorders: official journal of the Movement Disorder Society*, *13*(2), 221-227.
104. Möller, T. (2010). Neuroinflammation in Huntington's disease. *Journal of neural transmission*, *117*, 1001-1008.
105. García-Arencibia, M., González, S., de Lago, E., Ramos, J. A., Mechoulam, R., & Fernández-Ruiz, J. (2007). Evaluation of the neuroprotective effect of cannabinoids in a rat model of Parkinson's disease: importance of antioxidant and cannabinoid receptor-independent properties. *Brain research*, *1134*, 162-170.
106. Sagredo, O., Ramos, J. A., Decio, A., Mechoulam, R., & Fernández-Ruiz, J. (2007). Cannabidiol reduced the striatal atrophy caused 3-nitropropionic acid in vivo by mechanisms independent of the activation of cannabinoid, vanilloid TRPV1 and adenosine A2A receptors. *European Journal of Neuroscience*, *26*(4), 843-851.
107. Hermann, D., Sartorius, A., Welzel, H., Walter, S., Skopp, G., Ende, G., & Mann, K. (2007). Dorsolateral prefrontal cortex N-acetylaspartate/total creatine (NAA/tCr) loss in male recreational cannabis users. *Biological psychiatry*, *61*(11), 1281-1289.
108. Frank-Cannon, T. C., Alto, L. T., McAlpine, F. E., & Tansey, M. G. (2009). Does neuroinflammation fan the flame in neurodegenerative diseases?. *Molecular neurodegeneration*, *4*, 1-13.
109. Iuvone, T., Esposito, G., Esposito, R., Santamaria, R., Di Rosa, M., & Izzo, A. A. (2004). Neuroprotective effect of cannabidiol, a non-psychoactive component from Cannabis sativa, on β-amyloid-induced toxicity in PC12 cells. *Journal of neurochemistry*, *89*(1), 134-141.
110. Giacoppo, S., & Mazzon, E. (2016). Can cannabinoids be a potential therapeutic tool in amyotrophic lateral sclerosis?. *Neural regeneration research*, *11*(12), 1896-1899.
111. Milano, W., & Capasso, A. (2018). Neuroprotection by cannabinoids in neurodegenerative diseases. *Alzheimers Dement. Cogn. Neurol*, *2*(1), 1-7.
112. Fernández-Ruiz, J. (2009). The endocannabinoid system as a target for the treatment of motor dysfunction. *British journal of pharmacology*, *156*(7), 1029-1040.
113. Glass, M., Dragunow, M., & Faull, R. L. M. (2000). The pattern of neurodegeneration in Huntington's disease: a comparative study of cannabinoid, dopamine, adenosine and GABAA receptor alterations in the human basal ganglia in Huntington's disease. *Neuroscience*, *97*(3), 505-519.
114. Lastres-Becker, I., Fezza, F., Cebeira, M., Bisogno, T., Ramos, J. A., Milone, A., ... & Di Marzo, V. (2001). Changes in endocannabinoid transmission in the basal ganglia in a rat model of Huntington's disease. *Neuroreport*, *12*(10), 2125-2129.
115. Denovan-Wright, E. M., & Robertson, H. A. (2000). Cannabinoid receptor messenger RNA levels decrease in a subset of neurons of the lateral striatum, cortex and hippocampus of transgenic Huntington's disease mice. *Neuroscience*, *98*(4), 705-713.

116. Lastres-Becker, I., Gómez, M., De Miguel, R., Ramos, J. A., & Fernández-Ruiz, J. (2002). Loss of cannabinoid CB 1 receptors in the basal ganglia in the late akinetic phase of rats with experimental Huntington's disease. *Neurotoxicity research*, *4*(7-8), 601-608.
117. Naver, B., Stub, C., Møller, M., Fenger, K., Hansen, A. K., Hasholt, L., & Sørensen, S. A. (2003). Molecular and behavioral analysis of the r6/1 huntington′ s disease transgenic mouse. *Neuroscience*, *122*(4), 1049-1057.
118. McCaw, E. A., Hu, H., Gomez, G. T., Hebb, A. L., Kelly, M. E., & Denovan-Wright, E. M. (2004). Structure, expression and regulation of the cannabinoid receptor gene (CB1) in Huntington's disease transgenic mice. *European journal of biochemistry*, *271*(23-24), 4909-4920.
119. Centonze, D., Rossi, S., Prosperetti, C., Tscherter, A., Bernardi, G., Maccarrone, M., & Calabresi, P. (2005). Abnormal sensitivity to cannabinoid receptor stimulation might contribute to altered gamma-aminobutyric acid transmission in the striatum of R6/2 Huntington's disease mice. *Biological psychiatry*, *57*(12), 1583-1589.
120. Pazos, M. R., Sagredo, O., & Fernandez-Ruiz, J. (2008). The endocannabinoid system in Huntington's disease. *Current pharmaceutical design*, *14*(23), 2317-2325.
121. Dowie, M. J., Bradshaw, H. B., Howard, M. L., Nicholson, L. F. B., Faull, R. L. M., Hannan, A. J., & Glass, M. (2009). Altered CB1 receptor and endocannabinoid levels precede motor symptom onset in a transgenic mouse model of Huntington's disease. *Neuroscience*, *163*(1), 456-465.
122. Blazquez, C., Chiarlone, A., Sagredo, O., Aguado, T., Pazos, M. R., Resel, E., ... & Guzman, M. (2011). Loss of striatal type 1 cannabinoid receptors is a key pathogenic factor in Huntington's disease. *Brain*, *134*(1), 119-136.
123. Casteels, C., Vandeputte, C., Rangarajan, J. R., Dresselaers, T., Riess, O., Bormans, G., ... & Van Laere, K. (2011). Metabolic and type 1 cannabinoid receptor imaging of a transgenic rat model in the early phase of Huntington disease. *Experimental neurology*, *229*(2), 440-449.
124. Mievis, S., Blum, D., & Ledent, C. (2011). Worsening of Huntington disease phenotype in CB1 receptor knockout mice. *Neurobiology of disease*, *42*(3), 524-529.
125. Van Laere, K., Casteels, C., Dhollander, I., Goffin, K., Grachev, I., Bormans, G., & Vandenberghe, W. (2010). Widespread decrease of type 1 cannabinoid receptor availability in Huntington disease in vivo. *Journal of Nuclear Medicine*, *51*(9), 1413-1417.
126. Palazuelos, J., Aguado, T., Pazos, M. R., Julien, B., Carrasco, C., Resel, E., ... & Galve-Roperh, I. (2009). Microglial CB2 cannabinoid receptors are neuroprotective in Huntington's disease excitotoxicity. *Brain*, *132*(11), 3152-3164.
127. Dowie, M. J., Howard, M. L., Nicholson, L. F. B., Faull, R. L. M., Hannan, A. J., & Glass, M. (2010). Behavioural and molecular consequences of chronic cannabinoid treatment in Huntington's disease transgenic mice. *Neuroscience*, *170*(1), 324-336.
128. Consroe, P., Laguna, J., Allender, J., Snider, S., Stern, L., Sandyk, R., ... & Schram, K. (1991). Controlled clinical trial of cannabidiol in Huntington's disease. *Pharmacology Biochemistry and Behavior*, *40*(3), 701-708.
129. Curtis, A., Mitchell, I., Patel, S., Ives, N., & Rickards, H. (2009). A pilot study using nabilone for symptomatic treatment in Huntington's disease. *Movement disorders: official journal of the Movement Disorder Society*, *24*(15), 2254-2259.
130. Müller-Vahl, K. R., Schneider, U., & Emrich, H. M. (1999). Nabilone increases choreatic movements in Huntington's disease. *Movement disorders: official journal of the Movement Disorder Society*, *14*(6), 1038-1040.
131. Curtis, A., & Rickards, H. (2006). Nabilone could treat chorea and irritability in Huntington's disease. *The Journal of neuropsychiatry and clinical neurosciences*, *18*(4), 553-554.
132. Blazquez, C., Chiarlone, A., Sagredo, O., Aguado, T., Pazos, M. R., Resel, E., ... & Guzman, M. (2011). Loss of striatal type 1 cannabinoid receptors is a key pathogenic factor in Huntington's disease. *Brain*, *134*(1), 119-136.
133. Baron, E. P. (2015). Comprehensive review of medicinal marijuana, cannabinoids, and therapeutic implications in medicine and headache: what a long strange trip it's

been…. *Headache: The Journal of Head and Face Pain*, *55*(6), 885-916.

134. Pizza, V., Agresta, A., W D'Acunto, C., Festa, M., & Capasso, A. (2011). Neuroinflamm-aging and neurodegenerative diseases: an overview. *CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders)*, *10*(5), 621-634.
135. Nguyen, M. D., Julien, J. P., & Rivest, S. (2001). Induction of proinflammatory molecules in mice with amyotrophic lateral sclerosis: No requirement for proapoptotic interleukin-1β in neurodegeneration. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society*, *50*(5), 630-639.
136. Hampson, A. J., Grimaldi, M., Axelrod, J., & Wink, D. (1998). Cannabidiol and (−) Δ9-tetrahydrocannabinol are neuroprotective antioxidants. *Proceedings of the National Academy of Sciences*, *95*(14), 8268-8273.
137. Shoemaker, J. L., Seely, K. A., Reed, R. L., Crow, J. P., & Prather, P. L. (2007). The CB2 cannabinoid agonist AM-1241 prolongs survival in a transgenic mouse model of amyotrophic lateral sclerosis when initiated at symptom onset. *Journal of neurochemistry*, *101*(1), 87-98.
138. Dirikoc, S., Priola, S. A., Marella, M., Zsürger, N., & Chabry, J. (2007). Nonpsychoactive cannabidiol prevents prion accumulation and protects neurons against prion toxicity. *Journal of Neuroscience*, *27*(36), 9537-9544.
139. Fernández-Ruiz, J., Moro, M. A., & Martínez-Orgado, J. (2015). Cannabinoids in neurodegenerative disorders and stroke/brain trauma: from preclinical models to clinical applications. *Neurotherapeutics*, *12*(4), 793-806.
140. Babson, K. A., Sottile, J., & Morabito, D. (2017). Cannabis, cannabinoids, and sleep: a review of the literature. *Current psychiatry reports*, *19*(4), 1-12.
141. Grotenhermen, F., & Müller-Vahl, K. (2012). The therapeutic potential of cannabis and cannabinoids. *Deutsches Ärzteblatt International*, *109*(29-30), 495.
142. Russo, E. B. (2013). *Cannabis and cannabinoids: pharmacology, toxicology, and therapeutic potential*. Routledge.
143. Volkow, N. D., Baler, R. D., Compton, W. M., & Weiss, S. R. (2014). Adverse health effects of marijuana use. *New England Journal of Medicine*, *370*(23), 2219-2227.
144. Rubin, R. (2017). Medical marijuana is legal in most states, but physicians have little evidence to guide them. *Jama*, *317*(16), 1611-1613.
145. ur Rahman, K. (2021). Use of Narcotics in Pakistan: Situation Analysis and Way Forward. *FWU Journal of Social Sciences*, *15*(4), 163-174.
146. Rafiq, M., & Ghayur, S. (1995). An Analysis of Drug Abuse Networking in Pakistan [with Comments]. *The Pakistan Development Review*, *34*(4), 971-984.