Review Article

The Endocannabioids System and their Implications in Various Disorders

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ABSTRACT

With the increased use of cannabis, research on cannabis has become extremely important. Approximately 500 compounds have been isolated from Cannabis sativa with around 105 being cannabinoids. Of those 105 compounds, Δ9-tetrahydrocannabinol has been determined as the primary constituent, which is also responsible for the psychoactivity associated with Cannabis in the human. The endogenous cannabinoid system (ECS) has been described as "an ancient lipid signaling network, which in the mammals modulates neuronal functions, inflammatory processes, neurodegeneration, post traumic stress disorder, rheumatoid arthritis, AIDS and cancer. Cannabinoid receptors belong to the superfamily of G protein-coupled receptors. Receptors for cannabinoids are highly expressed in the hippocampus, which plays a key role in certain forms of memory and substance dependence. Improvements in the current therapy of cannabis can make it a safe and effective medicine. On the contrary to uses, the plant has some serious risks associated with it if consumed on a chronic basis like psychosis, schizophrenia, respiratory disorders, loss of libido, dependence etc. Therefore, the aim of this review is to study the role of cannabis in various disorders and the risks associated with it.

Keywords: Cannabis, role of cannabis, cannabinoid signaling, neurodegeneration ,substance dependence, inflammation

INTRODUCTION

Cannabis is obtained from *Cannabis sativa, Cannabis indica, Cannabis ruderalis* belonging to the family Cannabaceae. Cannabinoids are mainly collected from the appendages of sepal and specialized leaves of a female plant. There are 483 different chemical components out of which 66 are known. It comprises of nitrogenous compounds, amino acids, proteins, glycoproteins, amino acids, enzymes, aldehydes, alcohols, amino acids, hydrocarbons, ketones, flavonoids, cannabinoid phenolic steroids, vitamins[1]. There are a total of 13 phytocannabinoids discovered till date, namely tetrahydrocannabinol, cannabidiol (CBD), cannabigerol, cannabichromene, tetrahydrocannaivarin, cannabigervarin, cannabigerol, virodhamine, 2–arachidonylglycerol, 2-arachidonyl glyceryl ether, Dronabinol, nabilone, delta-9-THC and out of these main components aretetrahydrocannabinol (THC), delta-9-THC. All the constituents contribute to its medicinal value. *Cannabichromene* affects memory, increases neuronal growth and is used in Alzheimer's disease, autoimmune diseases, pruritus, schizophrenia, depression, inflammation, fungal infections, viral diseases. It improves positive and negative symptoms of psychiatric illness. *Cannabidiol* is used in seizures, convulsions, anxiety. Cannabidiol is the major compound that is used in epilepsy in convulsion. *CBG* is an alpha-2 adregeneric agonist, serotonin antagonist (5HT1A). Cannabigerol have neuroprotective properties and isused for the treatment of neurodegenerative diseases such as Huntington's disease and multiple sclerosis. CBG has potential for alleviating pain especially neuropathic pain. *THCV* improves the psychoactive properties of tetrahydrocannabinol. Tetrahydrocannabivarin has therapeutic potential both as an anti-inflammatory agent and for the relief of inflammatory, or indeed, neuropathic pain. *2–arachidonyl glycerol* is an agonist of CB1 and CB2 receptors. It plays important role in the regulation of the circulatory system via direct and/or indirect, through their metabolites, effects on blood vessels and/or heart. *2-arachidonyl glyceryl* ether decreases intestinal mobility, used in pain, hypothermia and causes sedation. *Virodhamine* is a CB2 agonist, a partial agonist of CB1 receptors. Virodhamine lowers body temperature in mice, demonstrating cannabinoid activity in vivo. *Dronabinol* is used in the loss of appetite in HIV patients, nausea vomiting in cancer patients. *Nabilone* is an antiemetic[2]. Delta-9-THC and THC nearly possess the same effects. Medical marijuana named dronabinol and Nabilone has been approved by FDA to be used as antiemetic in cancer therapy. Hashish oil, hashish, weed are the methods to consume marijuana. On the contrary to uses, the plant has some serious risks associated with it if consumed on a chronic basis like psychosis, schizophrenia, respiratory disorders, loss of libido, dependence etc[3].

THC –(tetrahydrocannabinol)

THCis a mind-altering ingredient which is found in the Cannabis plant. The main psychoactive component, which is responsible for the psychotogenic effect of cannabis, is Δ9-tetrahydrocannabinol (Δ9-THC). It is an analgesic which is used in psychiatric illness, delta-9 THC mimics the action of endocannabinoids like anandamide. It exerts its psychotogenic role by modulating the dopamine neurotransmission, which is directly involved in the development of psychotic symptoms[4]. THC's chemical structure is same as brain chemical anandamide.

Similarity in its structure allows the body to recognize THC and alter the normal brain communication[5]. THC is one of the most important compounds found in the resin secreted by the glands of the marijuana plant. According to Wu *et al in 2011* the brain releases dopamine when THC stimulates the astrocytes in the brain, creating euphoria. It also interferes with how information is processed in the hippocampus, which is part of the brain responsible for forming new memories. Information process also gets interrupted in the hippocampus, which is part of the brain responsible for forming new memories. Various NIDA reports showed that THC exposure before birth, after birth and during adolescence shown to have problems in rats with specific learning and memory tasks later in life[6].

Cannabidiol

Till now CBD is the only non–Δ9-THC phytocannabinoid to have been assessed in preclinical and clinical studies for anticonvulsant effects. In mice, CBD blocked MES-induced seizures in one study but had no effect on pentylenetetrazol (PTZ)–induced or MES-induced seizures in another[7]. More recently, CBD has been shown to have antiepileptiform and anticonvulsant effects in invitro and invivo models. In two different models of spontaneous epileptiform local field potentials (LFPs), CBD decreased epileptiform LFP burst amplitude and duration. CBD also exerted anticonvulsant effects against PTZ-induced acute generalized seizures, pilocarpine-induced temporal lobe convulsions, and penicillin-induced partial seizures in Wistar-Kyoto rats[8]. The mechanisms by which CBD and CBDV exert their antiseizure effects are not fully known, although several of the potential targets of cannabidiols described earlier may be involved Via modulation of intracellular calcium through interactions with targets such as TRP channels, G-coupled protein receptor protein 55 (GPR55), or voltage-dependent anion-selective channel protein 1 (VDAC1), CBD and related compounds may reduce neuronal excitability and neuronal transmission[9]. Unlike Δ9-THC, CBD does not activate CB1 and CB2 receptors, which likely accounts for its lack of psychotropic activity. However, CBD interacts with many other, non-endocannabinoid signaling systems. CBD is also highly protein bound, and ~10% is bound to circulating red blood cells. Preferential distribution to fat raises the possibility of accumulation of depot in chronic administration, especially in patients with high adiposity. It is active in both dopamine-based and glutamate-based laboratory models of schizophrenia symptoms. In healthy humans, CBD reverses Δ9-THC–induced psychotic symptoms and binocular depth inversion (an endophenotype of schizophrenia) and ketamine-induced depersonalization (a human glutamate model of psychosis[10].

Effects Of Cannabis on Various Signalling Pathways

Presences of any receptors determine the cellular responses that specifically bind the signaling molecules. This binding of signal molecules causes a conformational change within the receptor, which triggers the subsequent signaling cascade[11]. The effects of cannabis mainly depend on cannabis receptors (CB1 and CB2) which are the endocannabinoid system located in the brain and the periphery, regulate neuromodulation through neuromodulatory lipids[12]. CB1 and CB2 receptors get bound with two endocannabinoids that act as ligands namely arachidonylethanolamide and 2-arachidonylglycerol and out of the two receptors; ligands have a greater expression towards CB1 receptors. The CB1 receptors are present in the synaptic bouton(end foot),when endoligands bind to it , release of classical neurotransmitters is inhibited. Amide hydrolase inactivates the endocannabinoids and this enzyme is targeted towards the cell body and dendritic sites excluding axon. Arachidonylethanolamide is synthesized by postsynaptic neuron cells and messages in an inferior direction to attune the release of neurotransmitters from presynaptic terminals. This endocannabinoid signaling control memory pain and smooth muscle contractility[13].

The retrograde signaling of synaptic transmission is modulated by the calcium release or calcium signaling. The endocannabinoids like arachidonylethanolamide are released by the increased levels of calcium at the postsynaptic compartment or by the activation of G-protein coupled receptors that causes the retrograde signaling from postsynaptic to presynaptic transmission and causes the Modulation of neurotransmitters. The GPCR pathway requires phospholipase Cβ and the calcium pathway is independent of phospholipase Cβ[14]. As we know cannabis is involved in retrograde signaling from postsynaptic to presynaptic terminals thus affecting the release of neurotransmitters. Parira et al. in 2017 shows that chronic exposure to ethanol decreases the expression of CB1 receptors by an increase in activity caused by endocannabinoids like arachidonoyl ethanolamide and arachidonylglycerol and this stimulation was linked to chronic alcohol intake. Due to this activity the levels of peroxisome proliferator-activated receptor alpha-α (PPAR-α) was decreased. On the other hand, the activity of CB2 receptors was increased[15]. Haspula and clark studied the role of Cannabinoid type1 receptor CB1R.activation in hypertensive rats via MAPK activation and concluded that CB1R functionality reduction through MAPK activation lead to development of hypertensive states[16]. Tetrahydrocannabinol or cannabis treats psychosis by depressing glutamate synaptic compartments or glutamate transmission that improves the dopaminergic transduction pathways in the mesocortical and mesolimbic area. The outcomes were lowered by the activation of CB1 receptors and distorting glutamate synaptic activity[17]. Another receptor in the body that is GPR55 found in the liver and immune cells and also in the periphery.GPR55 is a seven transmembrane G protein-coupled receptor and was originally identified as a putative third cannabinoid receptor. Recently, lysophosphatidylinositol (LPI) was reported to be a GPR55

ligand. GPR55 is associated with G alpha13 on activation.GPR55 increases calcium levels; activate Rho GTPases pathways and factors like nuclear factor kappa-beta and cellular transcription factor. The changes in the body by gene expression studies by cannabis were studied[18].

Mechanism of Cb1 & Cb2 Receptors and Cannabinoid Signalling

There are basically two cannabinoid receptors: CB1 and CB2. CB1 and CB2 are present in high densities at neuronal terminals of the neocortex, basal ganglia, hypothalamus, and limbic cortex, cerebellum and hippocampus. The CB1 receptors are expressed mainly at presynaptic sites in GABAergic neurons they are located in periaqueductal gray, dorsal horns, and immune cells to a lesser extent. The CB2 receptor is essentially focused towards the human immune system; they can affect inflammation and immunosuppression when activated.CB1 receptors are coupled to Gi alpha subunit (heterotrimeric G protein subunit), on activation by endocannabinoids there is activation of CB1 receptors and Gi subunit[19]. Demuth and Molleman in 2006 showed that upon activation of CB1 receptors by coupling with Gs protein caused stimulation of adenylate cyclase that inhibits cAMP from ATP that increases potassium channel activity in the cells and decreases calcium channel activity and as a result there is no neurotransmitter release[20].

CB2 receptors are coupled to Gi heterotrimeric subunit and also with Ras-RAF-MEK-ERK pathway upon activation affects central developmental processes in organisms like immune responses and also affects the activity of EGR-1 thus affecting neuronal plasticity, long-term memory, mitogenesis[21]. Cannabinoid receptors play an important role in learning, working, short-term memory. The Endocannabinoids modulates neurotransmission by inhibitory and excitatory neurotransmitters and THC plays an important role in memory due to its action on N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxyzolepropionic acid (AMPA) type glutamate receptor[22]. Cannabis can also prevent adipose degeneration which is alcohol induced that caused autophagy by knocking out ATG5 gene. Cannabis treats hepatic inflammation by an increase in the expression of CB2 receptors by blocking liver macrophages action. While acute consumption of alcohol increased the activity of CB1 receptors that are used in treating negative states like euphoria and cravings in alcohol dependence. Increased consumption of marijuana decreased the inflammatory process as it has reduced the release of cytokines from dendritic cells in the periphery. Consumption of alcohol after the period of childbirth caused neurodegeneration of newly born by an increase in the expression of CB1 receptors by an increase in histone acetylation of H4K8 and decreased methylation of H3Ka that caused neuronal abnormalities[23].

Role of cannabis in various diseases

Epilepsy

Epilepsy is a chronic disorder that causes unprovoked, recurrent seizures. A seizure is a sudden rush of electrical activity in the brain. The triggers for seizure may include high fever, head trauma, very low blood sugar, alcohol withdrawal. Interest incannabis revived in the 1990s with the discovery of an ECS (endogenous cannabinoid system) in the brain named 2- (2-AG) & anandamide. Cannabidiol (CBD), a compound which is derived from cannabis contains no amount of psychoactive tetrahydrocannabinol (THC), is effective in reducing the frequency and severity of seizures for other forms of epilepsy, such as Lennox-Gastaut syndrome. CBD may be a promising new treatment for children having a Dravet syndrome, which is also known as severe myoclonic epilepsy of infancy (SMEI), a type of epilepsy with seizures that are mostly triggered by hot temp. or fever, but only after its benefit has been confirmed in long-term trials[24].

Clinical seizures are affected by decrease in cAMP via binding of agonist to CB1 receptor as a result of adenyl cyclase inhibition, potassium influx through A type and G protein coupled receptors and also reduction of calcium influx. These changes attenuate hyperexcitability of neuron and seizure frequency is decreased. Endocannabinoid system (ECS) and the expression of the CB1 protein is highly affected by seizures in the animal hippocampus. This can increase the level of CB1 receptors in the CA1 through CA3 regions of the hippocampus and hence it is postulated to be the mechanism of action (MOA) for epilepsy control. Basically, marijuana has two main Neuro-active components which influence the ECS: the psychoactive delta-9- tetrahydrocannabinol (THC) and the non-psychoactive CBD[25]. Medical marijuana has been approved for clinical studies of subjects with the type of epilepsy with more CBD and a low THC content. Both CBD and THC reportedto have anticonvulsant properties as per in the animal models of epilepsy. In general THC acts via CB1 receptors, i.e. CBD acts synergistically with THC[26].

Post Traumatic Stress Disorder (PTSD)

PTSD is a disorder that develops in some people who have experienced a shocking, scary, or dangerous event. When a patient is introduced to one or more traumatic events it may give the result of PTSD leading to the growth of typical characteristic symptoms following exposure. Patients may exhibit fear-based behavioral and emotional symptoms. Others may have dysphoric or anhedonic states and negative cognition. PTSD is related to amygdala dysfunction, hippocampi, Structural impairments, the anterior cingulate cortex (ACC), the medial prefrontal cortex (mPFC), include decreased hippocampal volume and decreased ACC volume[27]. Dysregulation in process related to threat in response to trauma exposure leads to a cascade of neural changes, causing amygdala hyperresponsivity, which triggers hyperarousal and vigilance. Inadequate top-down control

by the mPFC and ACC perpetuates the amygdala hyperresponsivity state, increasing attention to stimuli related to trauma[28]. Neuroimaging recently helped to elucidate the underlined neurological processes which are to be involved in the symptomatology of PTSD as well as in the role of the endocannabinoid system which manages these neurological pathways. CB1 receptor availability is enhanced in an amygdala-hippocampal-cortico-striatal neural circuit implicated in PTSD .This may be a result of the combination of both receptor up-regulation and low receptor tendency by an endogenous cannabinoid i.e. anandamide (also known as N-arachidonoylethanolamine or AEA, is a fatty acid). This suggests the fact that abnormal CB1 receptor-mediated anandamide signaling is involved in the PTSD etiology[29]. Nabilone, a synthetic cannabinoid, showed its potential benefits in patients having PTSD experiences poor control of nightmares with STD pharmacotherapy by increasing the levels of endocannabinoids and improving the binding capacity of endocannabinoids with CB1 and CB2 receptors. Improvement in the quality of sleep, sleep time, the reduction of daytime flashbacks and night sweats were also noticed by some patients[30].

Migraine

Migraine begins with a headache. Headache is a pervasive, debilitating and often invisible disease without a cure. The pathophysiology of a headache is still under investigation. However, it is believed that cluster headaches and migraine are initiated in the brain areas such as the brainstem, hypothalamus or possibly cortex. Tension-type headaches cannot only begin in the CNS, but may also be triggered by the myofascial tissue, which often develops in response to stress. Headaches usually involve over activation of the trigeminovascular pathway, which results in the release of vasoactive peptides, such as, calcitonin gene-related peptide (CGRP), substance P, vasoactive mediators such as NO, which may lead to sensitization of nociceptive receptors in the head and neck. Parasympathetic efferents, inflammation, Serotoninergic signaling and increased intracranial pressure (IP) also play key roles in headache disorders[31]. Case report by Lochte in 2017showed that smoking cannabis has been reported to relieve pain associated with pseudotumor cerebri, a condition characterized by an increase in the intracranial pressure of an uncertain etiology. This suggests another therapeutic effect of cannabis in some headache conditions could be a result of reducing intracranial pressure dexanabinol, a synthetic cannabinoid, has been found to relieve intracranial pressure and improve outcomes after traumatic brain injury. Nabilone, a synthetic cannabinoid mimicking tetrahydrocannabinol (THC), has been shown to decrease analgesic intake while reducing medication overuse headache (MOH) pain in a double-blind, placebo-controlled trial[32]. A study has shown that a decrease in the expression of the cnr1 gene, which encodes the cannabinoid receptor type 1 (CB1) receptor, is related to a migraine and trigeminovascular activation. Women's experiencing migraine has increased activities of fatty acid amide hydrolase (FAAH), an enzyme used to degrade the endocannabinoid anandamide (AEA), and the endocannabinoid membrane transporter (EMT), a membrane transporter for AEA, leading to an overall decrease in levels of endocannabinoids. This revealation partially explains the increased incidence of migraines in women. An examination of cerebro-spinal fluid shows that individuals who experience migraines have decreased levels of AEA and increased levels of CGRP(Calcitonin gene-related peptide) and NO (normally inhibited by AEA)[33].

Rheumatoid Arthritis

Rheumatoid Arthritis (RA), which is an autoimmune disorder, that causes inflammation in multiple joints can be treated by cannabis, which is an herb full of inflammation-fighting compounds. Breakdown of the soft tissues in the joints and surrounding of your bones by an overactive immune system. This action of immune response causes excess inflammation, which then leads to scarring, tissue deterioration and notable pain with time. Patients with rheumatoid arthritis are deluged with inflammation. Researchers from the South Carolina University (2014) found that psychoactive THC dampens the immune system and deactivates inflammatory proteins. This makes THC a suitable option for the treatment of different varieties of autoimmune disorders, including arthritis, multiple sclerosis, colitis, and lupus. In 2003 non-psychoactive CBD was tested on rats induced with an arthritis-mimicking condition and after injecting the rats with specific pro-inflammatory compounds, they treated them with an oral dose of CBD[34]. CBD continued to reduce the inflammatory markers by reducing lymphocyte proliferation, TNF levels, INF and reactive species from granulocytes after continuous three consecutive days of treatment. The scientists noticed the fact that when they treated the rats with a compound that activated the CB1 receptor, results showed up to be like such as bone loss slowed down in older, aging mice. As CB1 receptor is the foremost primary binding site for psychoactive THC. The compound has prevented the excess fat accumulation in the bone, which proves to happen during osteoporosis. This averted bone material from wasting off[35.] In 2016, researchers monitored the dentistry of the bone of genetically engineered mice missing the CB1 or CB2 receptors and from the experiment, they found the fact that mice without these receptors were more likely to have a bone weakness, a precursor to both osteoporosis and osteoarthritis. Further, mice without the CB2 receptors resulted in accelerated age-related bone and cartilage deterioration in comparison to their equal CB1 deficiency. The CB2 receptor is the one which was targeted by the cannabinoid, the same receptor which helped the inflammation to be controlled in the patients with rheumatoid arthritis. The CB2 receptor also helped to manage the sensation of body pain. Researchers in their studies showed activation the CB2 receptor is leading to

decreased pain signals. After success with rats, they then moved on to humans. They noticed that CB2 receptors are present in the spinal cord tissue. This is important to note because the spinal cord is considered to be one of the primary pain messengers within the body. Nerves in the spinal cord send pain messages to the brain[36]. Blake *et al.2005,* studied that 25 mg of 9.4% herbaltetrahydrocannabinolcannabis, when inhaled alone three times daily for five days reduced the intensity of pain, improvement in sleep and was well tolerated. As in inflammation finally β-sitosterol, a phytosterol which is found in cannabis, reduced the following with the mentioned percentage -Topical inflammation 65%, Chronic edema 41% in the skinny models[37].

AIDS/HIV

AIDS refers to a set of symptoms and illnesses that occur at the very final stage of HIV infection. HIV is a virus that attacks the immune system, which is our body's natural defence against illness. In the progression of HIV-1 infection in the CNS, Monocytesand Macrophages play a crucial role. Medicinal cannabis shown to reduce the neurologic complications (neuropathic pain) in the HIV-infected patients and it is proposed that the effects of medicinal cannabis may be related to the activation of the nonpsychoactiveCB2 receptor[38]. Previously, a study by Rock in 2007 suggested that CB2 signaling may affect the expression of HIV-1 coreceptors, CXCR4 & CCR5[39]. Observations in macrophages support results by other groups showing no effect of CB2 on CXCR4 expression in CD4+ T cells[40]. Evidence shows that Surface protein expression of CXCR4 or say its gene regulation is not altered by the CB2 agonist in Monocyte-Derived Macrophages. Similar results on CCR5 in MDMs. In contrast to the inhibitory effect, results showed that WIN55, 212-2 inhibits the CCR5 expression in microglia and reported for GP1a in CD4+ T cells (human PBLs). However, CCR5 expression in CD8+ cells was unchanged with GP1a in the same study. Perhaps, CCR5 could be a regulatory target of CB2 receptor signaling. Results suggest that in MDMs, there is not any interference in the HIV-1 viral entry, at least not at the level of coreceptor expression, which is a result of CB2 activation. In light of the inhibitory effect by CB2 receptor agonists, possibly the expression of HIV-1 coreceptors is altered by the CB2 signaling, thereby preventing the re-entry of HIV-1 virions inside the cells. To test this expression profiles for CXCR4 and CCR5 were evaluated by FACS (fluorescence-activated cell sorting) and gene expression[41]. Interestingly, 7 days of HIV-1 infection did not change the gene expression of CXCR4 or CCR5 in MDMs (monocyte-derived macrophages). Therefore, Down-regulation of CXCR4 or CCR5 is not involved in the CB2- mediated inhibition of HIV-1 in the primary human macrophages. The decrease in HIV-1 replication is noticed by the synthetic CB2 receptor agonists. CB2 activation does not appear to interfere with the viral entry, as lack of regulation was seen by CB2 receptor agonists on gene protein expression of CXCR4 or CCR5[42]. Another studied data showed that the inhibition of gp120-mediated suppression of DA uptake and apoptosis by WIN55, 212-2 involved CB2 receptors more than CB1 receptors. The inhibition of gp120-induced apoptosis confirmed the involvement of CB2 receptors by the CB2 agonist synthetic cannabinoid WIN55,212-2 ((R) -(+) -[2,3-dihydro-5-methyl-3-[(4-morpholinyl)-methyl] pyrrolo-[1,2,3-de]-1,4benzoxazinyl] -(1-naphthalenyl) methanone mesylate) which is able to protect against gp120-induced structural, functional, apoptotic, and oxidative damage to dopaminergic neurons, as well as it examines the role of microglia that it plays in this process[43].

Parkinson's disease

It is a disease in which there is degeneration of dopaminergic neurons in the substantia nigra pars compacta.One possible mechanism for the disease is the accumulation of alpha synuclein in the astrocytes that bind to ubiquitin and damage senses by affecting pathways like motor areas and limbic areas[44]. CB1 agonists inhibit dopamine release from basal nuclei in the substantia nigra pars compacta while some showed improvement by G9 (alphas) coupled A2A receptor. CB1 antagonist showed improvement in motor symptoms[45]. Blockade of the CB1 receptor with rimonabant reduced loss of voluntary motor abilities at lower doses by acting on glutamate release from neostriatum in subcortical basal ganglia[46]. Endocannabinoids used with levodopa-induced dyskinesia improving cAMP pathway and cAMP is released from the ATP and increased phosphorylation of neuronal phosphoprotein DARPP-32 (Dopamine and cyclic AMP-regulated phosphoprotein) and which further inhibits protein phosphatase[47]. Cannabinoids reduced levodopa-induced dyskinesia activating glitazone receptor PPAR-ϒ (Peroxisome proliferator activated receptor-gamma)[48]. Clinical studies showed Smoking marijuana improved voluntary motor movements in a 30 minute motor exam.46% of patients improved symptoms like rigidity, tremors, bradykinesia, sleep[49]. The dose selected was 1.25 mg cannabinoid and 2.5 mg tetrahydrocannabinol[50].

Alzheimer's disease

Alzheimer's disease is an irreversible, progressive brain disorder that slowly destroys memory and thinking skills, and eventually the ability to carry out the simplest tasks. Alzheimer's is the most common cause of dementia among older adults. Dementia is the loss of cognitive functioning. Alzheimer's disease is named after Dr. Alois Alzheimer. In 1906, Dr. Alzheimer noticed changes in the brain tissue of a woman who had died of an unusual mental illness. Her symptoms included memory loss, language problems, and unpredictable behavior. After she died, he examined her brain and found many abnormal clumps (now called amyloid plaques) and tangled bundles of fibers (now called neurofibrillary, or tau, tangles).These plaques and tangles in the brain are still considered some of the main features of Alzheimer's disease. Another feature is the loss of connections between nerve cells

(neurons) in the brain[51]. Cannabidiol regulates central processes of development of organisms and prevents the loss of structure and function of neurons by decreasing tau hyperphosphorylation of tau protein[52]. Cannabidiol protects the synaptic dysfunction and immune defense in central nervous system caused by Aβ neurotoxicity and microglial cell toxicity. Also, cannabidiol decreases protein degradation via proteasome and improve cell migration processes, prevents lipid peroxidation[53].CP55940 is a cannabinoid that mimics the actions of tetrahydrocannabinol and is an agonist of CB1 and CB2receptors that acts as an inverse agonist of CB2 receptors and inhibits abnormalities caused by cell developmental processes[54]. Esposito in 2007 showed that Cannabidiol (2.5mg or 10mg/kg) for a period of 7 days inhibits the actions of glial fibrillary acidic protein and inhibits cascaded activation of deformation mechanisms and in the CNS it treats hypertrophy of glial cells. Cannabidiol tends to decrease the inducible nitric oxide release from the wnt/β catenin pathway and regulates gene transcription properly[55].Cannabidiol prevents the cleavage of Aβ42 by APP by inhibiting S100 Calcium-binding protein B and treats hypertrophy of glial cells and in the CNS[56].

Cancer

Cancer is a group of diseases in which the abnormal cells divide rapidly and disfunction the organs due to altered cell differentiation and proliferation. The common factors responsible for the disease are oncogenes, tumour suppressor genes, mutations, changes in the nucleotide sequencing of DNA. Cannabinoids improve the weakness and wasting of the body in cachexia patients by acting on the MAPK / ERK pathway and P13K/AKT/mTOR pathway. Cannabinoids treat adenoma liver tumors, benign tumors and also tumors in the uterus, pituitary, testis. Delta 9 THC and Delta 8THC inhibit carcinoma cell growth in Lewis lung cancer cell lines by inhibiting DNA synthesis, cell growth, inhibits signals from tumor cells to form new blood vessels. Cannabinoids do not harm other cells as CB1 receptor-induced apoptosis only affect the astrocytes and prevents other glial cells. Cannabinoids treat an estrogen-stimulated growth in cancer lines and nonestrogen stimulated cancer lines and have also a role in treating hepatic carcinoma by causing apoptosis through activation of autophagy[57].

CVS

Atherogenesis

Endothelial injury caused by mechanical and chemical stress, toxins, immunological changes, abnormal lipid levels is an underlying factor for the pathophysiology of atherogenesis. The endothelial injury caused the adherence of platelets that results in the activation of tumour necrosis factor (TNF-α),nitric oxide, fibroblast growth factor and these mitogens further cause smooth cell proliferation. Another cause of the disease is high levels of LDL that gets oxidized in the cytoplasm in normal cells thus making it foam cells. After this there is activation of inflammatory mediators like cytokines, monocytes and this oxidized LDL is bad for the normal endothelial cells and leads to endothelial injury[58]. Endocannabinoids found in heart reduces chances of having diabetes, heart disease or stroke, cardiometabolic disorders.It also treats adhesion of monocytes and lymphocytes on the endothelial cell surface in atherogenesis[59]. Cannabis plays a protective role in cardiac remodelingin preventing cardiac damage and thus providing a vasorelaxing effect. Tetrahydrocannabinol treats chemical and mechanical stress by activating *ankyrin type 1 channel (TRPA-1 Channel).* Anandamide activates capsaicin receptors that cause the release of calcitonin related gene peptide that further cause peptide vasodilation and regulates the transmission of pain[60].

Myocardial infarction

Myocardial infarction is caused by obstruction of blood flow which might be due toany reason like atherosclerosis, thrombosis, and embolism. This leads to diminished coronary perfusion pressure, which creates an imbalance in the pressure gradient between diastolic and aortic pressure. Due to this there is an ischaemic cell injury and release of inflammatory mediators and inflammation of granulating tissue .Then there is healing by fibrous scarring and there is development of infarct caused by necrosis[61]. Cannabinoids play a vital role in treating MI through lipid signalling. Cannabinoids like anandamide acts on receptors like calcitonin like receptor (CALCRL) and receptor activity modifying protein(RAMP1) that activatesTrpv1(transient receptor potential cation channel subfamily V MEMBER 1) receptors and calcitonin gene related peptide ,this leads to vasodilating effect that treats shock and myocardial infarction[62].

Hypertension

Hypertension is a chronic medical condition in which systolic blood pressure is greater than 139mmHg and diastolic is greater than 89mmHg.It is caused due to sodium and water retention due to overactive renin angiotensin system, oxidative stress, inflammation, endothelial dysfunction, Vascular remodeling[63.] Cannabinoids have an antihypertensive effect by the activation of CB1 receptors in the periphery, with the activation of CB1 receptors there is inhibition of norepinephrine in the nerve terminals of periphery mediated by presynaptic Cb1 receptors and there is vasodilation[64]. (Bátkai *et al.*, 2004) Anandamide is an agonist of CB1 receptor that mediates cardiac centres, vascular functions, and cardiovascular centres and also an agonist of TRPV1 receptors, on activation of these channels, there is decrease in blood pressure. The mechanism responsible were vagal stimulation, FAAH inhibition, inhibition of sympathetic transmission[65].

Multiple Sclerosis

Multiple sclerosis is a disease in which there is destruction of myelin sheath and inflammation. The main

factor responsible for the disease is dysfunctioning of axonal conduction and ion channels (sodium channels), inflammatory mediators causing damages like optic neuritis[66]. Cannabinoids like tetrahydrocannabinol and cannabidiol act against inflammatory mediators like cytokines and results in reduction of pain.Medium to high level of smoking marijuana reduced pain in patients as it slowed down the release of neurotransmitters from pre to postsynaptic terminals controlled by 2 receptors named CB1&CB2 receptors. It aids in digestion by increasing the flow of digestive juices and reducing the inflammation caused by immune cells in the gut. Cannabis reduced involuntary contractions, rigidity, tremors. Tetrahydrocannabinol (5mg) and codeine (50mg) together reduced pain and spasticity. Cannabis improved neurological signs of abnormalities in muscle movements(gait abnormality)and also improved vision in Nystagmus. Tetrahydrocannabinol at a dose of 7.5 mg improved reflexes, limb movement and coordination[67]. In preclinical evidence, delta-8-THC, delta-9THC at a dose of 5mg/kg treated the swelling of brain and spinal cord in encephalomyelitis. These two cannabinoids reduced the partial loss of movement in paraplegia, ataxia, and atonia. Another cannabinoid named Dexanibinol reduced symptoms of encephalomyelitis by blockade of N-methyl-D –Aspartate. Possible lead compounds used in Multiple sclerosis are 6 azidohex-2-yne-deltas 8 THC and 6 azidohex-cis-2-ene-delta8 THC. Cannabinoids improved hindlimb spasticity by treating the damage caused to myelin sheath by myelin antigens in demyelinating disease[68].

Diabetes Mellitus

Diabetes mellitus is a condition in which there is an elevation in blood sugar levels when the metabolism of fats, carbohydrates and protein is impaired. Beta cell destruction, insulin resistance, insulin deficiency are the main reasons for the progression of the disease[69]. Cannabis extract showed antioxidant activity and reduced pain in diabetic neuropathy by increasing the pain perception, relieved central pain sensitization in neurons. The mechanism responsible was decreased glutathione content in liver, decreased oxidative stress by decrease in lipid peroxidation[70]. Cannabis treats type 2 diabetes mellitus by acting as anti autoimmune agent and reduced beta cell destruction. The drug reduced glucose intolerance, improved glucose metabolism, increased glucose sensitivity and glucose tolerance. The drug reduced inflammation by reducing the levels of cytokines, reduced fibrosis and oxidative stress[71].

Liver Disease

Hepatic encephalopathy is a disease in which there is dysfunction in brain due to non removal of toxins from the liver, symptoms are change in personality, mood, consciousness. The disease is caused when the hepatocytes are not able to metabolise the waste products from nitrogen containing foods after urea cycle through portal vein. These waste products gets accumulated in the portal circulation and generate toxins and then cross blood brain barrier and are absorbed in the brain by astrocytes[72]. Cannabidiol treated hepatic encephalopathy by decreasing the levels of ammonia, TNF-αmonocytes, adhesion molecules and also possess anti-inflammatory action. The anti-inflammatory property of cannabidiol was found to be the result of activation of 5HT1a in brain and liver[73].

Acute hepatic toxicity

Hepatotoxicity is a drug induced liver injury caused by factors like enzyme induction, drug overdose, drug interaction. This leads to increase in the levels of oxidants that damage the mitochondria and damage to the endoplasmic reticulum in the liver thus disturbing the normal liver metabolism process[74]. Findings suggest that activation of cannabinoid system may have protective actions on liver induced by cocaine, minimizing inflammatory injury enhanced by cocaine. Thus, CBD is currently attracting considerable interest as a potential medicine due to its anti-inflammatory, neuroprotective, antipsychotic, anxiolytic, antiepileptic, and anticancer effects[75].

Risks Associated with Cannabis Use

The use of cannabinoids for long-term use causes dependency, respiratory disorders, cancer, and psychosis.

Psychosis

Long-term use of cannabis increases the positive and negative symptoms of psychosis and on discontinuation makes the symptoms even worse. Cannabis-related CB1 receptor dysfunction is the mechanism responsible for psychosis. Tetrahydrocannabinol binds to CB1 receptors and affects other receptors like spare receptors and affects the cortex of the brain during neurodevelopment that further causes increase in anxiety, damage to myelin sheath by myelin antigens, impaired dopaminergic transduction pathways. In neurobiology, the mechanism by which THC causes psychosis is an increase in the dopamine levels in the striatal area, dorsolateral and prefrontal cortex[76]. Positron emission tomography (PET) showed the neuroimagesin which there were changes in the impulses in amygdala due to changes in GABAergic and glutamate transmission[77].

CVS

Cannabis may decrease the duration of the action potential as a result of which there is altering of myocardium properties, stimulation of adrenergic activation that causes tachycardia, postural hypotension, atrial fibrillation, and ischemia. Decreased duration of the action potentialand hyper stimulation of vagal tone causes sudden cardiac death. Cannabis reduces the oxygen-carrying capacity of blood due to decreased carboxyhemoglobin levels and that causes myocardial infarction. Cannabinoids cause the formation of prothrombins to thrombins by increasing the levels of Glycoproteins-1-b-11a and P-selectin[78].

Schizophrenia

Long-term use of cannabis increases the levels of anandamide in the hippocampus, substantia nigra, prefrontal cortex that affects the state of patient due to impairment in glutamate, dopaminergic and GABAergic pathways. All these changes lead to the development of psychotic symptoms in schizophrenic patients[79].

Dependance

Cannabis causes a withdrawal syndrome due to addiction, dependence towards THC and dysfunction of CB1 receptors functioning[80].

Respiratory disorders

Long-term use of cannabis causes obstruction and inflammation of the airway that causes COPD, respiratory cancer, lung cancer.Other issues include impaired thinking, memory loss, problem while concentrating, and bronchitis [81].

CONCLUSION

The review discussed all the merits and demerits associated with marijuana. Only a few phytocannabinoids are explored for medicinal purposes and many more are left due to the fact that the plant is illegal in many countries. Based on current evidence, the plant is used as in diabetic neuropathy, HIV, Cancer, Alzheimer's disease, Parkinson's disease, liver damage, anxiety, neurogenesis, multiple sclerosis etc. The neurobiological and neurochemical mechanisms are under research to explain its role in various diseases and. The plant should be legalized to evaluate its clinical and preclinical safety and efficacy studies.

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