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Cannabis: Curse or cure?

Purvaj Barote[1], Shivani Desai[2*]
[1] M Pharm Research Scholar, Department of Pharmacology, Dr. D. Y. Patil Institute of Pharmaceutical Sciences and Research, Maharashtra, India
[2] Assistant Professor, Department of Pharm D, Dr. D. Y. Patil Institute of Pharmaceutical Sciences and Research, Maharashtra, India

Abstract
It appears an inexpensive hypothesis that the negative effects these long significant cannabis users rumored are because of being acutely intoxicated each day. Cannabis users who answer a billboard for a study might not be representative of the supply population from that they're drawn. Although CB1 receptors are present in extremely high concentrations throughout the brain, they're most dense within the hippocampus, basal ganglia and cerebellum. If this hypothesis were true, one would expect the long-term cannabis users to deny the adverse effects of cannabis use. The potential of glia and cannabinoid receptors in glia merits special attention in PD but also in AD (see below). Cannabis users may suspect that they might be rejected from the study, and not get the associated compensation if they rumored vital use of alternative medicine or psychiatric disorders. A splice variant of the CB1 receptor, CB1A, has also been described. Maybe regulated by ligands acting at the cannabinoid receptors have been detected in the vessels from a transgenic AD model. Additionally, mRNA coding for the CB2 receptor has been detected in cerebellar granule cells. However, the amount of faculty graduation among themselves was dramatically different, with fewer than half the heavy cannabis users having obtained a school degree as hostile almost 80% of the control subjects. The parental education in each team was virtually the same, with 58% of the significant cannabis users and 51% of the managements having a minimum of one parent who graduated from college. Apart from the difficulty in assessing neuroprotection in humans, it turns out that transgenic Alzheimer's disease models do not display neuronal death. CB1 Receptor a. CB2 Receptor a. The presence of undiscovered cannabinoid receptors isn't only limited to the CNS.

Keywords: cannabinoid, cannabis sativa, neuroprotection, neurodegeneration

Introduction

Cannabis (marijuana) has long been used for medical and recreational purposes. The C.sativa and C.indica are two common species used for consumption. Between the 2 species, C.sativa has a comparatively higher delta-9-tetrahydrocannabinol (THC) concentration while C.indica has a comparatively higher cannabidiol concentration. Cannabinoids are often classified into three subtypes, endocannabinoids (naturally present in the human body), phytocannabinoids (present in the cannabis plant) and artificial cannabinoids (produced chemically). Presently, over 60 differing types of pharmacologically active cannabinoids are identified and isolated from the cannabis plant. These include the exogenous cannabinoids like the psychoactive THC and non-psychoactive cannabidiol, also because the endogenous cannabinoids like anandamide, which affects most systems within the physical body, especially the central nervous system. The cannabinoid binds to 2 sorts of G protein-coupled receptors: CB1, which are most abundant in the brain, and CB2, which are expressed on cells within the system where inflammation is modulated. Hence, cannabinoids are involved in psychomotor coordination, memory, mood, and pain [1].

Marijuana or indica (cannabis) is one of the oldest plants known to men. The first evidence of its cultivation was found in China in 4000 years BC, which indicated that cannabis was employed by Chinese manufacturers to form ropes, textiles and paper. In one among the world's oldest pharmacopoeia compiled within the first century AD, records were found of cannabis getting used for medicinal purposes, like to treat malaria, rheumatic pain, and intestinal constipation, menstrual and surgical pain. Since 1000 BC, cannabis was used as a sacred plant in religious rituals in South Asia and it had been mentioned as a source of happiness and joy. The medicinal and recreational use of this plant has spread from India to the centre of East and Africa. Initially, in Arabic medical books it is mentioned as curative properties for digestive, urinary and respiratory ailments. [2] Cannabis was first delivered to America to Brazil by African slaves, who used it in their popular religious rituals. To Western medicine, cannabis was first introduced within the 19th century by Dr William O'Shaughnessy, who travelled to India with the British. Dr O'Shaughnessy was the primary scientist to check the toxicological and therapeutic properties of cannabis in animals and human studies [3]. Today, neurobiological research on C. sativa is complex and difficult, and its development and use are prohibited in a large portion of the nations. Recently, preclinical and clinical preliminaries on cannabidiol (CBD), a Phytocannabinoid without psychoactive impacts, have featured empowering results. Surely, CBD is the second most bountiful Phytocannabinoid after D9-THC and it speaks to a potential pharmacotherapy for rewarding side effects of different neuropsychiatric issues, for example, fixation, tension and psychosis, issues of motility, and epilepsy.

In any case, despite the helpful utility of CBD, its particular pharmacological component remains not so much clear. Indeed, CBD notwithstanding collaborating with the endocannabinoid framework (ECS), can likewise follow up on serotonin, adenosine, dopamine and narcotic receptors carrying on as a multitarget drug. Here, the amalgamation and digestion of CBD in C.sativa will be at first assessed. Besides, the most recent proof on the collaboration between CBD and the ECS will be investigated. At long last, a basic and extensive assessment of the CBD pharmacological system in a few issues will be introduced [4].

Methodology

Searches were conducted in the online database such as PubMed, search were performed using following keywords-

1. Role of CBD in neurodegenerative disorders.
2. Alzheimer's and cannabinoids
3. Parkinson's and cannabinoids

A filter to select the papers from the last 5 years, further sources were identified by following up internal citations and references within the papers collected in the initial search.

Endocannabinoid System

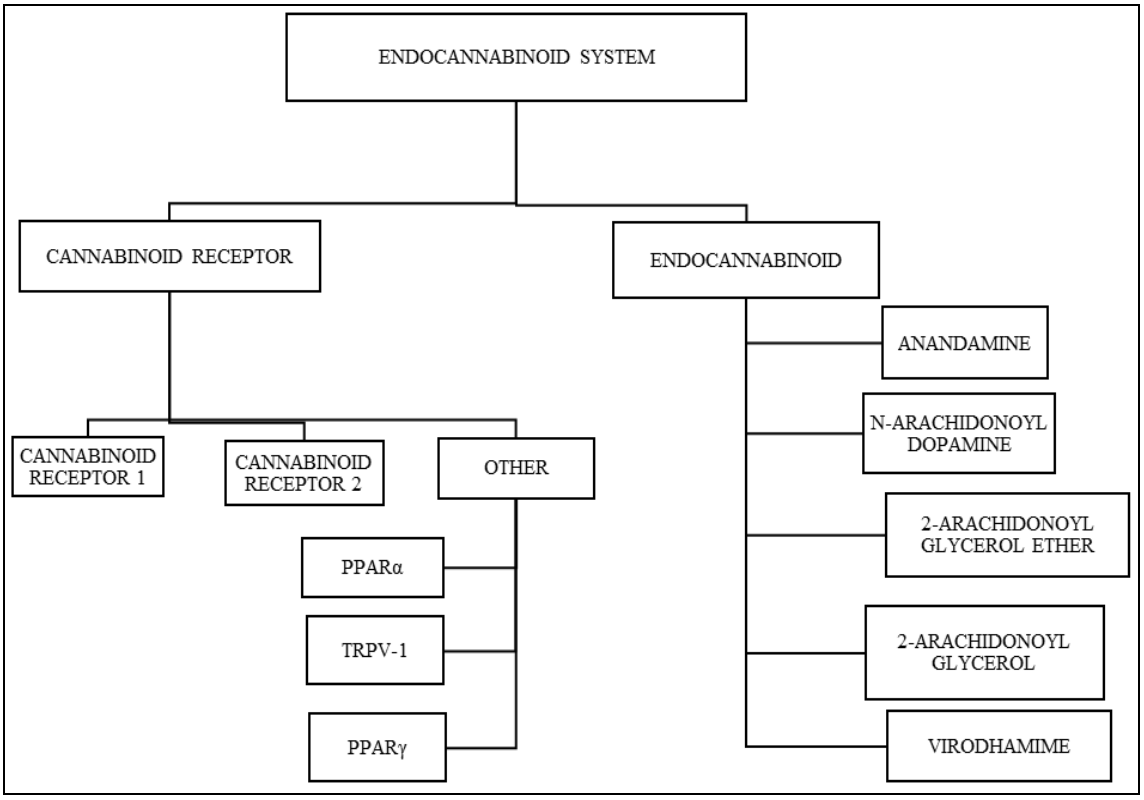


Fig 1: Endocannabinoid System.

Currently, two subtypes of cannabinoid receptors are isolated and cloned: CB1 and CB2 [5]. The inhibitory effects of CB1 receptor signalling cyclic AMP (cAMP) accumulation and its blockade by pertussis toxin [6, 7] are according to the CB1 receptor belonging to the reported loss of STM in users of the family of G-protein–coupled receptors. The human CB1 receptor exhibits 68% homology with the human CB2 receptor at the transmembrane level and 44% overall [8]. Interestingly, cannabinoid receptors, especially CB1 receptors, are shown to be present and comparatively conserved in many species including fish, hydra, mollusc, leech and echinoderm, suggesting the evolutionary conservation of the endocannabinoid system [9, 10] However, it's not thought to be present in insects [11]. A splice variant of the CB1 receptor, CB1A, has also been described.

The discovery of endogenous cannabinoid compounds, like anandamide, that acts as an agonist at these receptors has revealed the presence of an endocannabinoid system.

This has subsequently intensified research into the assembly of synthetic agonists and antagonists, which has been the cornerstone from which the fashionable study of the neuropharmacology of cannabinoids has been derived.

Cannabinoid CB1 Receptor Expression

CB1 receptors are predominately found pre-synoptically on neurons within the CNS, although they're expressed to a lesser degree within the periphery, on cells of the system, testis, vascular endothelium, intestine and peripheral nerve pre-synapses [12]. CB1 receptors are most abundant within the regions and structures of the brain liable for the behavioural and pharmacological effects seen following cannabinoid administration additionally anecdotal evidence associated with the adverse effects of cannabis usage supports the presence of cannabinoid receptors in these areas.

Although CB1 receptors are present in extremely high concentrations throughout the brain, they're most dense within the hippocampus, basal ganglia and cerebellum [5], The hippocampus is involved within the storage and processing of newly acquired information, and therefore the CB1 receptor is very expressed on cells of the molecular layer of Ammon's Horn [13]. The presence of CB1 receptors during this region may correlate with the reported loss of STM in users of the family of cannabis [14]. an artificial CB1 receptor antagonist, rimonabant (SR-141716A), has been shown to antagonise a variety of effects

mediated by cannabinoid ligand binding and signalling through the CB1 receptor [15]. However, when used alone, this drug has been reported to act as an 'inverse agonist': that's, it elicits the other effect thereto of the agonist, as it has been shown to enhance memory during a rodent model [16]. Another common adverse effect associated with cannabis use is decreased locomotor activity, which may correlate with the presence of CB1 receptors in regions that mediate coordination of motor function and motor learning like the basal ganglia, sustantia nigra and cerebellum. within the cerebellum, CB1 receptors are highly expressed within the molecular layer, which is vital for the relay of distal limb coordination and balance information between thalamus and medulla spinal [13]. The presence of cannabinoid receptors in these important brain structures and therefore the inhibitory effects of cannabinoids on neuropeptide secretion [17] suggest that cannabinoids may have potential as therapeutic agents during a big variety of CNS disorders.

CB2 Receptor Localisation

The CB2 receptor is usually described because of the 'peripheral' cannabinoid receptor, as many studies have shown high levels of CB2 receptor expression in some peripheral tissues, including cells of the system within the spleen [5]. The high level of expression of CB2 receptors on cells of the system has led investigators to review the potential role of cannabinoids in modulating the system during a sort of clinical applications. additionally, CB2 receptors are expressed within the tonsils, bone marrow, thymus and pancreas [18], adult rat retina [19], peripheral nerve terminals within the mouse vas deferens [5]. Although the CB2 receptor is not thought to be expressed within the CNS [8], it's not clear at the present whether CB2 receptor expression is often induced within the CNS in some circumstances. additionally, mRNA coding for the CB2 receptor has been detected in cerebellar granule cells [5].

Cannabinoid Receptor Signaling

CB1 and CB2 receptors are Gi/o protein-coupled receptors that, following cannabinoid agonist binding and signalling, exert an inhibitory effect on adenylate cyclase (AC) activity. This inhibits the catalytic reaction converting cyclic ATP to cAMP, a crucial cellular secondary messenger involved in cellular regulation [5]. additionally to the consequences on cAMP, cannabinoid signalling through CB1, but not CB2, receptors also can interact with ion channels [5]. it's been well established that CB1 receptor signalling negatively regulates calcium currents through both N- and P/Q-type voltage-sensitive Ca2+ channels [5] but activates G-protein–coupled inwardly rectifying K+ channels [20]. CB1 receptor signalling also results in the downstream activation of mitogen-activated protein kinase [21], p38 and c-Jun amino-terminal kinase [5], which are involved in cellular regulation of proliferation and differentiation. CB1 receptor signalling also results in the downstream activation of mitogen-activated protein kinase [21], p38 and c-Jun amino-terminal kinase [5], which are involved in cellular regulation of proliferation and differentiation. One outcome of presynaptic CB1 receptor stimulation on neurons is to reduce neuronal cell activity and attenuate, via retrograde signalling, the discharge of neurotransmitters such as dopamine, noradrenaline (norepinephrine), serotonin, GABA and glutamate [5] This property of cannabinoid agonist signalling is a beautiful characteristic for the utilisation of cannabinoids within the treatment of numerous medical disorders. There is also evidence that other undiscovered G-protein–coupled receptors may exist within the cannabinoid system. The binding of the cannabinoid receptor agonist [3H]R(+)WIN55,212-2 to CNS structures, including the hippocampus, cortex and brain stem, in CB1 receptor knockout (CB1 -/-) mice show the presence of other cannabinoid-identical receptors [5]. Interestingly, R(+)WIN55,212-2 and anandamide, but not Δ9-THC or CP-55940 (another cannabinoid agonist), stimulated guanosine 5′-O(γ[35S]-thio)triphosphate ([35S]GTPγS) binding in CB1 -/- mice, indicating that they're signalling through a G-protein–coupled receptor [22]. The stimulation of both basal and anandamide-induced [35S]GTPγS binding might be inhibited by the addition of the CB1 receptor antagonist rimonabant [22]. Apart from cannabinoid agonist binding and G-protein involvement, these unknown receptors appear to mediate a number of the consequences related to cannabinoid signalling through the known cannabinoid receptors.

Several behavioural effects induced by anandamide were still present in CB1 -/mice [23].The addition of anandamide, but not Δ9-THC, to CB1 -/- mice was shown to decrease their spontaneous activity, induce antinociception and increase immobility [23]. The presence of undiscovered cannabinoid receptors isn't only limited to the CNS. Mesenteric arteries isolated from either CB1 -/- or CB1 and CB2 -/- mice were aware of both 'abnormal CBD'[(2)-4-(3-3,4-trans-p-menthadien-1,8)-yl-olivetol, a cannabidiol derivative produced by transposition of the phenolic hydroxyl and therefore the pentyl side chain of CBD] and anandamide-induced vasodilation through a mechanism independent of both CB1 and CB2 receptors [5]. These responses were sensitive to the antagonist effect of rimonabant [5], and suggest the presence of undefined receptors for which anandamide is an agonist and rimonabant is an antagonist.

Table 1: Location of cannabinoid receptors

Location	Structure	Function	References
1. CB_1 Receptor a. CNS	Basal Ganglia	*Movement Control*	(15) (22)
	Cerebral Cortex	*Emesis*	
	Hippocampus	*Memory Storage*	
	Spinal Cord	*Nociception*	
	Hypothalamus	*Thermal regulation, Neuroendocrine release, appetite*	
	Cerebellum	*Coordination of motor function, posture, balance*	
b. Periphery	Eye ciliary body	*Intraocular pressure*	(23)
	Lymphoid Organs	*Cell-mediated and Innate immunity*	
	Vascular smooth muscle cells Duodenum, ileum, myenteric plexus	*Control of blood pressure Control of emesis*	
2. CB_2	Peripheral nerve terminals Retina	*Peripheral nervous system*	

Receptor a. Periphery	Lymphoid tissue	*Cell-mediated and innate immunity*	
b. CNS	Cerebellar granule cells mRNA	*Intraocular pressure Coordination of motor function*	

Product of Cannabis

The sticky organic compound made by the flowers and high leaves contains a variety of psychotropic substances, together called cannabinoids, these collectively structure the drug referred to as cannabis. The efficiency of the cannabis obtained from a plant relies on the content of delta-9-tetrahydrocannabinol (THC), the foremost vital of the cannabinoids [29].

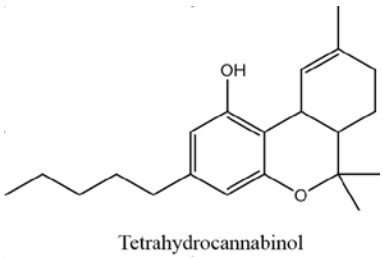
- Bhang obtained from the cut crack of uncultivated plants with low resin content is that the least potent.
- Ganja or marijuana from flowering tops and leaves from specially cultivated plants has higher resin content and is a lot of potent. Each of those flavouring preparations (also called 'grass' or 'weed') are typically preserved in hand-rolled cigarettes ('joints' or 'reefers'). Efficiency is variable, with a mind-altering drug content of 1-10 per cent. *f*
- Natural resin (hashish) is the resin itself, within the type of a sticky brown cake, which might be smoked or eaten.
- Liquid cannabis or soft drug oil is extracted from cannabis resin and is a lot potent. Tobacco is swayback during this before smoking

Cannabis contains over three hundred compounds. a minimum of sixty-six of those are cannabinoids, 5 vital cannabinoids found within the cannabis plant are

1. Tetrahydrocannabinol (THC)
2. Cannabidiol (CBD)
3. Cannabinol(CBN)
4. β-caryophyllene
5. Cannabigerol.

Tetrahydrocannabinol (THC)

It is the primary compound to blame for the psychotropic effects of cannabis. The compound may be a delicate analgesic, and cellular analysis has shown the compound has inhibitor activity.THC is believed to act with components of the brain commonly controlled by the endogenous cannabinoid neurotransmitter, anandamide. Anandamide is believed to play a job in pain sensation, memory, and sleep [29].

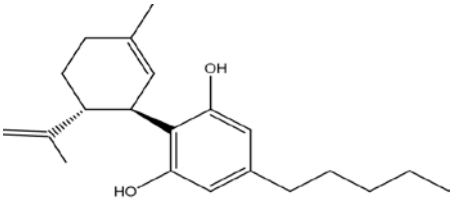


Tetrahydrocannabinol

Fig 2

Cannabidiol (CBD)

CBD could be a major constituent of medical cannabis. Cannabidiol has been shown to alleviate convulsion, inflammation, anxiety, cough and congestion, nausea, and inhibits neoplastic cell growth. Latest studies have shown cannabidiol to be as effective as atypical antipsychotics in treating schizophrenia. as a result of cannabidiol relieves the aforesaid symptoms, cannabis strains with a high quantity of CBD could profit folks with multiple sclerosis, frequent anxiety attacks and brain doctor syndromes [29].

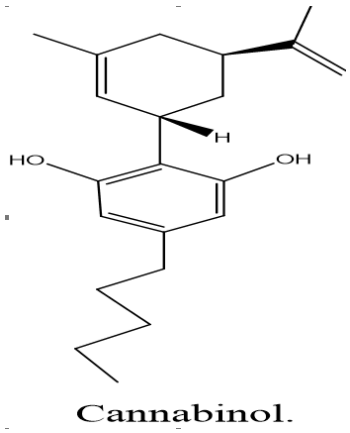


Cannabidiol.

Fig 3

Cannabinol (CBN)

CBN may be a therapeutic cannabinoid found in marijuana and Cannabis indica. it's conjointly created as a metabolite, or a breakdown product, of a consciousness-altering drug (THC).CBN acts as a weak agonist of the CB1 and CB2 receptors, with lower affinity as compared to THC [29]

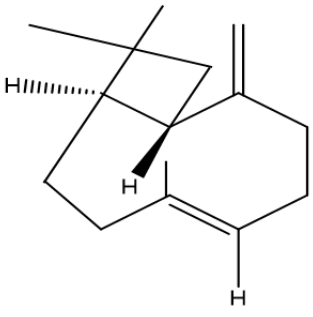


Cannabinol.

Fig 4

β-caryophyllene

Part of the mechanism by that medical cannabis has been shown to cut back tissue inflammation is via the compound β-caryophyllene. A cannabinoid receptor known as CB2 plays an important half in reducing inflammation in humans and different animals. β-Caryophyllene is a selective matter of the CB2 receptor. β-Caryophyllene is very focused on cannabis essential oil, which contains concerning 12-35% β-caryophyllene. (29)

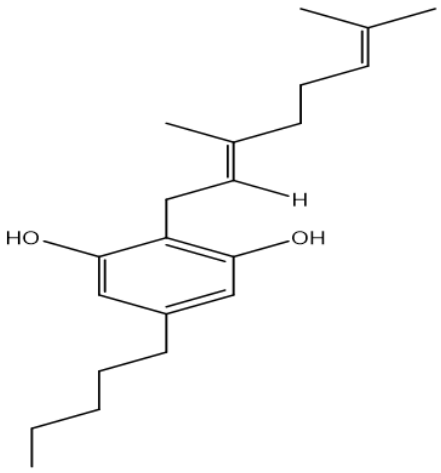


beta-caryophyllene.

Fig 5

Cannabigerol

cannabidiol, cannabigerol isn't psychoactive. Cannabigerol has been shown to alleviate intraocular pressure, which can be of profit to the treatment of eye disease. (29)



Cannabigerol.

Fig: 6

Addressing neuroprotection in Humans

Addressing neuroprotection is not easy, even in the case of laboratory animal models of neurodegenerative diseases, the demonstration that a certain drug is neuroprotective poses difficulties; furthermore, improvements in symptoms (in animal models) are quite often considered neuroprotective and this interpretation is incorrect. However, preclinical research has resulted in candidates that seem truly neuroprotective, i.e. they prevent neuronal death, and cannabinoids are among them. Demonstrating neuroprotection in humans is a serious concern as there is no "technique" that can demonstrate it. The administration does not have special rules that can serve to address this issue, in addition, clinical trials, by the concept and also by pressure from pharmaceutical companies, are limited in time, showing that neuroprotection requires time and safe drugs in administration patients urgently need protocols to address neuroprotection. To our knowledge, this requires new protocols and the use of drugs that are already considered safe in chronic use or of supplements that are considered "generally recognized as safe" and are commercially these specific topics applies to another promising class of drugs, the A2A receptor antagonists, it has been widely discussed elsewhere(30).

Longitudinal studies are seemingly needed in either **i)** healthy people taking memory enhancers (nootropics) for years and looking out for the age of look of neurodegenerative signs or **ii)**patients taking extra medication with a “safe” drug (already approved or provisionally approved on the idea of compassionate drug use) and menstruation illness progression exploitation accidental scores [31]. In either case, cannabinoids are candidates that need to be tested. Another advantage of cannabinoids is expounded to the comparatively recent development of PET tracers. Especially, relevant are people who are ready to find CB2R within the brain of living humans (healthy people or patients); the recent papers on tracer development prove the interest of *in vivo* picturing this receptor [47]. On the one hand, it's thought-about that PET for CB2R provides relevant hints for the neuroinflammation extent [34] for background. On the opposite hand, it is considered that reducing neuroinflammation in patients reflects less neurodegeneration and hence, reduced the progression of the illness [35]. Such a tracer can be a biomarker for neuroinflammation and/or for assessing neuroprotection in humans. Taking an easy example, CBD at high concentrations activates cannabinoid receptors, whereas CBD at lower doses behaves as a negative allosteric modulator [36] (See below section on AD) for an additional example involving psychoactive drug.

Potentials of cannabinoid In Parkinson’s Disease

Parkinsonian patients need drugs that delay the progression of the disease, i.e. preventing the death of dopaminergic neurons in the substantia nigra. Although there are efficacious interventions to address symptoms, they are not exempt from undesirable effects, mainly dyskinesias, i.e. involuntary movements arising after long periods of chronic pharmacological treatment. There is evidence that cannabinoids may be useful for neuroprotection but also for addressing symptoms and for reducing the chances to suffer from dyskinesias. There are other aspects of the disease, particularly those are known as non-motor symptoms. A recent protocol has been disclosed to address the safety and efficacy of nabilone in a cohort of approximately 38 patients entering into a randomized, placebo-controlled, double-blind clinical study. The primary outcome will be the MDS-UPDRS score and the results are expected by the end of 2019. Confirming data in animal and cell models analysis of post-mortem samples and positron emission tomography (PET) in living patients shows that cannabinoid signalling is altered in Parkinson’s disease and that cannabinoid receptors exist in the brain regions susceptible of targeting by therapeutic drugs. The expression of CB1R and endocannabinoid synthesizing/degrading enzymes is also altered in the basal ganglia as a consequence of side effects of levodopa treatment, more precisely during the active phase of dyskinesia [37]. Accordingly, the CB1 and CB2 receptors (individually or forming heteromers with other GPCRs) are potential targets of drugs aimed at affording neuroprotection. At present, the evidence for efficacy in humans is scarce. The authors for a systematic review on Medical Cannabis and Neurodegenerative and Psychiatric indicated that: “Evaluation of these low-quality trials, as rated on the Cochrane risk of bias tools, was challenged by methodological issues such as inadequate description of allocation concealment, blinding and underpowered sample size. More adequately powered controlled trials that examine the long and short term efficacy, safety and tolerability of cannabis for medical use and the mechanisms underpinning the therapeutic potential are warranted”[1]. In what concerns PD-related pain, prospects are already good; a meta-analysis considering >25 clinical trials (randomized) with idiopathic parkinsonian patients showed that greater pain reductions were achieved with safinamide but followed by cannabinoids and opioids [37], in the cannabinoid field, Israelian laboratories and hospitals have significantly contributed to finding evidence for cannabinoid clinical potential. A human-based report by laboratories in this country indicates that cannabinoids are efficacious in “reducing tremor, dyskinesia, rigidity and pain, and improving sleep” [37]**.** The authors add that 84 C. Pérez-

Olives *et al*. medical cannabis may be useful in dementia "although clinical data are still inadequate". As they are often altered in neurodegenerative models, research on mitochondrial metabolism and mitochondrial biogenesis is gaining momentum in the field. For instance, THC up-regulates proteins involved in biogenesis to MPP+ toxicity in a dopamine transporter-positive cell line (SH-SY5Y) [37]. The mechanisms are dependent on up-regulating a PPARγ co-activator 1α, PGC-1α, and a mitochondrial transcription factor, TFAM. The potential of glia and cannabinoid receptors in glia merits special attention in PD but also in AD (see below). In the rotenone model of PD, a phytocannabinoid, β-caryophyllene reduces, among other, glial activation and this leads to the protection of dopaminergic neurons [37]. While these results indicate that glial activation may be detrimental, as it was currently thought, they contrast with those reporting that targeting the CB2R reduces the progression of motor symptoms in the LRRK2-transgenic mice [37]. Interestingly, the authors want to correlate without taking glia into account. Indeed, CB2R expression in CNS neurons (mainly restricted to the globus pallidus and cerebellum) could not explain the results in the LRRK2 mice; therefore, the effects are likely due to CB2R expressed in the activated microglia (see the section on AD, below). In any case, it would be good to know the status of the glia in the LRRK2 mice and the expression of activation markers and cannabinoid receptors. As of today, there are no hits in Pubmed for "LRRK2-transgenic mice" and "microglia". The authors were even able to find the upregulation of the receptors in the glial cells of patients using post-mortem samples. It should be noted that VCE-003.2, which is a synthetic quinone derivative of cannabigerol, provided (in a PPARγ receptor-dependent way) benefits against inflammation-driven neuronal deterioration in a PD model in (37). As also commented below, it is needed to establish not only the target but the pharmacological properties of the "therapeutic" cannabinoid, i.e. whether a more efficacious one will be an agonist, an inverse agonist, or an allosteric modulator. In this sense, it is informative the case of the patient displaying mild cognitive impairments and living independent but who became seriously affected when nabilone was administered. To know the reasons for such psychosis, exacerbation would help in designing the most appropriate type of cannabinoid to address PD (37). Familial early-onset PD may be caused by mutations in the (PINK1) gene, which codes for PTEN-induced putative kinase 1 Reported in PINK1 knockout mice a CB1 receptor dysfunction that was dependent on dopaminergic transmission. The usefulness of such a finding in terms of PD therapy will require further experimental effort (37).

Potential of Cannabinoids in Alzheimer's Disease

Cannabinoids are among the myriad of drugs that transgenic models are efficacious in reducing the pathological hallmarks of Alzheimer's disease (AD) but that, unfortunately, have failed to reach the patient (37). The handicap is double, i.e. apart from the difficulty in assessing neuroprotection in humans, it turns out that transgenic Alzheimer's disease models do not display neuronal death. Accordingly, these models serve more for hereditary cases (around 10% of total cases) and less for sporadic non-hereditary cases (around 90% of total cases). Can cannabinoids on delaying disease progression? Part of the answer came from analogies, i.e. if cannabinoids are seemingly neuroprotective in other neurodegenerative diseases they may be also efficacious in Alzheimer's patients. The conclusion of synergism upon coadministration is notable (Sativex™/nabiximols is, in fact, a mixture of compounds), but the conclusion that the agonists of the CB1 receptors are affording neuroprotection, must be taken with caution as i) previous data do not support this view and ii) phenotypic platforms may not be suitable to measure neuroprotection in this disease. In fact, in one of the newest transgenic models with quicker cognitive impairment onset, the triple 3xTg-AD mice, desensitization of the CB1 receptor may be a "plausible strategy to improve behaviour alterations associated with genetic risk factors for developing Alzheimer's disease"(37). Other recent results on cannabinoid action on animal models of Alzheimer's disease are provided below. In what symptoms are concerned, the use of cannabinoids has been suggested to reduce agitation and/or the aggressive behaviour found in some patients (38). A clinical trial to know the efficacy of a synthetic cannabinoid, nabilone, on agitation in moderate-to-severe Alzheimer's disease (39) has seemingly been completed in March 2019 (https://clinicaltrials.gov/ct2/show/NCT02351882) though no results have been posted. A recent meta-analysis based on double-blind, placebo-controlled trials have retrieved six studies with a total of 251 cases; the conclusion is that the results are inconclusive in what concerns aggression or agitation [39]. Cannabidiol, which has recently reported as an allosteric modulator of the CB1 and CB2 receptors [37], may activate peroxisome proliferator-activated receptor γ (PPARγ) and via the Wnt/β-catenin pathway, may reduce the oxidative stress and neuroinflammation associated with the disease. The modulation of genes in the mesenchymal stem cells suggests that cannabidiol leads to an expression pattern that could be more beneficial with any efficacious anti-Alzheimer's disease therapy [37]. Rats with intracerebroventricularly administered okadaic acid appear as a model of Alzheimer's disease as they present, in some brain regions, pathological hallmarks (phosphorylated tau and ß-amyloid) and display cognition deficits. Consistent with the potentially relevant role of activated microglia in what concerns neuroprotection, a selective CB2 receptor agonist was effective in reducing cognitive impairment, neurodegeneration and neuroinflammation [37]. The potential of the receptor as a target for neuroprotection is reinforced by the detection of memory impairment and Tau pathology in the CB2 receptor knockout mice. Animals presented Tau hyperphosphorylation, on a decrease of AMPK activity and mitochondrial dysfunction [37]. Classical activation of microglia has been considered detrimental but this view has changed. Two different phenotypes arise from the activation of resting M0 microglia such as M1 of proinflammatory and M2 of neuroprotective [37]. A recent discovery has linked the activated microglia to neuroprotection in Alzheimer's disease. We found that the primary cultures of microglia from a transgenic AD mouse model present the activated phenotype with an important regulatory role of cannabinoids via cannabinoid receptors and receptor heteromers [37]. These results in animals that, unlike human patients, do not present any neuronal death lead to the suggestive hypothesis that microglia may be neuroprotective and prevent neuronal death and consequently, the progression of the disease. Results from the effects of ß-amyloid in a novel

immortalized microglial cell line [37], may help in designing drugs leading to microglial M2 phenotype skewing. In addition, it should be noted that blood flow is important for any neurodegenerative condition. In this sense, both functional impairments that 86 C. Pérez-Olives *et al*. may be regulated by ligands acting at the cannabinoid receptors have been detected in the vessels from a transgenic AD model [37]. The negative regulation of ß-amyloidactivated astroglial hemichannels is seen as a neuroprotective mechanism exerted by cannabinoids [37]. Synthetic cannabinoids constituted by indazolylketones are postulated to be potential to combat Alzheimer's disease as some of the generated compounds can target the CB2 receptor to inhibit ß-secretase 1 (the enzyme that participates in the production of the ß-amyloid toxic peptide) and to inhibit butyrylcholinesterase (one of the enzymes that degrade a neurotransmitter reduced in the disease: acetylcholine) [37]. Finally, an interesting hypothesis has been emitted to explain the biphasic effects of THC that can alter short-term memory, while it improves neurological function in old animals and in animal models of Alzheimer's disease in which the compound prevents neurodegenerative processes. This paradox may be reconciled by one of the properties of hormetic mechanisms, namely different effects depending on the dose [37]. Interestingly, the benefits of THC on cognitive deficits in transgenic Alzheimer's disease mice models do not happen in the healthy ageing of wild-type animals [37]. In addition, it should be noted that the metabolism of an endocannabinoid, 2-arachidonoylglycerol, is altered by different aggregates of ß-amyloid [37], thus suggesting that endocannabinoid metabolism is altered in patients.

Cognitive Effect of Cannabis

Evaluating the psychological feature results of long cannabis use is troublesome thanks to several contradictory variables. The judgment on whether or not a given effect may be a result of cannabis use is difficult by numerous sources of bias that will occur in representational studies. Experimental knowledge is lacking as a result of one cannot ethically recruit a bunch of people to consume giant amounts of cannabis for twenty years, whereas having a comparison group abstain. The solely obtainable data return from naturalistic studies of individuals victimization cannabis in uncontrolled settings, that is beset by all the standard method issues that afflict naturalistic and retrospective studies. First is that the issue of choice bias. Cannabis users who answer a billboard for a study might not be representative of the supply population from that they're drawn. For example, cannabis users who get a study could also be notably distressed regarding their psychological feature functioning and need to be evaluated, or might have psychiatric symptoms and want to be evaluated by a mental state professional, or maybe self-selected in another way. thus for a variety of reasons, one might predict that selection factors might bias the ends up in favour of finding a deficit in cannabis users and rejecting the null hypothesis (type I error). The second is that the issue of knowledge or recall bias. Cannabis users may suspect that they might be rejected from the study, and not get the associated compensation if they rumoured vital use of alternative medicine or psychiatric disorders. this could end in denial or minimizing of their use of other doubtless toxic drugs or the presence of psychiatric disorders, that, in turn, would result in a bias removed from the null hypothesis (type I error). Third, and most serious, is the issue of unmeasured contradictory variables, which impacts all representational studies. Even if we tend to may do an ideal study within which we utterly eliminated choice bias and eliminated info bias, if we found that cannabis users exhibited psychological feature deficits, however, would we all know that these deficits were owing to cannabis use and to not another contradictory issue equivalent to impaired cognitive functioning before cannabis use? There are several studies measurement the cognitive effects of long cannabis use. This literature lacks consensus, and a 2003 metaanalysis of existing studies that met acceptable method criteria did not realize vital cognitive deficits in long-term users [40], support these findings. They administered psychology tests to sixty-three current significant cannabis users who had preserved cannabis a minimum of 5,000 times in their lives and to seventy two management subjects who had smoked no quite fifty times in their lives. though variations between the teams when seven days of supervised abstinence were reported, no deficits were found after twenty-eight days of abstinence, after adjusting for numerous doubtless contradictory variables. These findings counsel that psychological feature deficits related to long cannabis use are reversible and involving recent cannabis exposure. If any analysis finds that there are, indeed, irreversible psychological feature effects related to long cannabis use, the consequences may be delicate and not robust. despite whether or not cannabis causes permanent or irreversible effects, the study of chronic long-term users. Created some distressing findings. They asked long-term significant users regarding numerous demographic attributes and conjointly about their experiences with cannabis itself. Some placing results appeared once they compared ten8 heavy cannabis users to seventy two management subjects who had preserved cannabis fewer than fifty times, and a median of solely 10 times, in their entire lives. The parental education in each team was virtually the same, with 58% of the significant cannabis users and 51% of the managements having a minimum of one parent who graduated from college. However, the amount of faculty graduation among themselves was dramatically different, with fewer than half the heavy cannabis users having obtained a school degree as hostile almost 80% of the control subjects. Similarly, the family financial gain in both groups was roughly the same, with regarding 20–25% of the families news an income of under $30,000 greenbacks a year. However, the income of the subjects themselves was dramatically different, with quite 50% of the significant user's news incomes of under $30,000 each year virtually double as often because of the controls. One may hypothecate that the consequences of cannabis use had nothing to try to do with these variations in instructional attainment and income that instead, the differences arose from a choice by the long cannabis users to not pursue cultural norms like attending to faculty or functioning at a high-level job. If this hypothesis were true, one would expect the long-term cannabis users to deny the adverse effects of cannabis use. However, once cannabis users were asked to rate the effects of their cannabis use as positive, neutral, or negative, they gave overpoweringly negative ratings of the consequences that cannabis had had on their social life (70%), their physical health (81%), their mental state (60%), their knowledge (91%), their memory (91%), and their career (79%). It appears an inexpensive

hypothesis that the negative effects these long significant cannabis users rumoured are because of being acutely intoxicated each day. folks intoxicated with cannabis demonstrate impairments in an exceeding style of cognitive, perceptual, and cognitive content tasks. Tasks showing the foremost impairment involve short memory, sustained or divided attention, complicated decision-making, and reaction time. 97 % of the significant users within the Gruber study rumored driving on an everyday basis whereas intoxicated. Studies victimization driving simulators show marked impairment throughout acute cannabis intoxication, and accident statistics show that a disproportionate range of accidents occurs in people intoxicated with cannabis and alcohol. Forty-five per cent of the heavy users have children. It's cheap to presume that chronic psychological feature impairment can adversely affect one's ability to boost children. Moreover, 44% of the heavy users control jobs that doubtless may endanger themselves or others, jobs equivalent to electricians, nurses and pharmacists, chefs, nannies and childcare employees, and truck drivers. alternative significant users control jobs that, poorly performed, may greatly inconvenience others, jobs like communicating workers and directors of varied sorts [40]

Conclusion

The studies reviewed here indicate that cannabinoids might influence the event of AD & PD among the cannabinoids investigated up to now, CBD seems one in every of the foremost promising drug in preclinical trials, Clinical evidences reviewed here related to already report safety profile of CBD in human clearly indicates that CBD represent new chance for treatment of neurodegenerative and neuropsychiatric disorders wherever neural loss or harm plays a big role.

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