(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 5, Issue 2, Page No: 1201-1210
March-April 2022

IJMSCR

Effects and Approach Of Cannabidiol In Cannabis Associated In The Cure Of Parkinson's Disease

Pawat Katanyuwong
Triam Udom Suksa Pattanakarn school, Suanluang, Bangkok, Thailand 10250

***Corresponding Author:**
Pawat Katanyuwong
Triam Udom Suksa Pattanakarn school, Suanluang, Bangkok, Thailand 10250

Type of Publication: Original Research Paper
Conflicts of Interest: Nil

Abstract

Parkinson's disease (PD) is a degenerative disorder characterized by dopaminergic neuron loss. While dopaminergic medication has been shown to improve some non-motor symptoms of Parkinson's disease, many non-motor symptoms have not improved and, in some cases, have worsened, with significant consequences for patient quality of life. Although there are no neuroprotective therapies for PD, the endocannabinoid system has emerged as a prospective target. The endocannabinoid system regulates various physiological mechanisms and has been discovered to be dysfunctional in a variety of pathological illnesses, including movement disorders. They modulate other neurotransmitters (GABA, glutamate, opioids, peptides) and activate distinct receptor subtypes in the basal ganglia (cannabinoid receptor type 1 and 2). Cannabidiol (CBD) has generated interest as a possible therapeutic option for Parkinson's disease (PD) due to the identification of many putative sites of action in the central nervous system (CNS). Although new cannabinoid-based medications have been offered to treat motor and nonmotor symptoms of Parkinson's disease, clinical trial results have been inconsistent and inconclusive thus far. Additional clinical trials with larger patient samples, proper biological targets, and precise clinical outcome metrics are necessary to elucidate the efficacy of cannabinoid-based treatments.

Keywords: Cannabidiol, Cannabis sativa, endocannabinoid system, Parkinson's disease

Introduction

Parkinson's disease (PD) is a disorder that is found secondly abundant after Alzheimer's disease (1, 2). There exists some apparent symptoms such as rigidity, bradykinesia, resting tremor along with postural instability (3). Levodopa is considered as a dopamine precursor that is used as a primary treatment against PD (4). However, the continuous usage of this medicine can contribute to the deterioration of drug efficiency and could further cause motor complications (4, 5). With the interest of novel treatment aiming at the non-dopaminergic systems such as endocannabinoid system (ECS) (6, 7). Cannabinoids can be categorized into three main types: endogenous, plant-derived phytocannabinoids and synthetic types (8, 9). This review aims to explore the efficacy of cannabinoids for motor symptoms in PD as well as the safety of CBD.

Cannabidiol

Cannabis sativa belongs to the Cannabaceae family, taxonomically. There are three varieties of Cannabis Sativa consisting of *sativa, indica and ruderalis* (10, 11). The active agents which are found in *C. sativa* are phytocannabinoids (12). Phytocannabinoids mostly consist of Δ9-tetrahydrocannabinol or THC has psychoactive effects pharmacologically (13, 14). In addition, cannabidiol or CBD is the second abundantly found compound with the psychoactive or non-psychotropic pharmacological effects (8, 10). Both THC including CBD are exhibited in carboxylic acid structures that are decarboxylated into their original form (15, 16). Surprisingly, both of the

compounds have shown the effects of inflammation and anxiety (17, 18). Furthermore, both THC and CBD can act as both neuroprotective agents and antioxidants (19). The strategic usage has reported that both are involved in cancer pain and neuropathic pain in multiple sclerosis (MS) remedies (20-22). Further examinations on CBD have shown that there is an involvement to, the regulation of the endocannabinoid system or ECS, a complex lipid network consisting of cannabinoid receptors (CBRs), endogenous ligands, and the enzymes involved in endocannabinoid degradation and synthesis. Endocannabinoids are originated and produced in the body helping to regulate memory, pleasure, concentration which they acted on CB1 and CB2 receptors (17, 23).

Parkinson's disease

Parkinson's disease (PD) is attributable to the deterioration of dopaminergic neurons in the substantia nigra resulting in an uncontrolled over voluntary movements, the symptoms are rigidity, tremor and bradykinesia (24). The additional non-motor symptoms include psychosis, anxiety and depression (25). Although, while the etiology is unknown, both environmental and genetic factors are suspected contributions (26). A biosynthetic precursor to dopamine is Levodopa (27, 28). Levodopa is used in the patient's dopamine receptors, but the results have shown the effectiveness only in the early and intermediate stages (5, 29). Consequently, causing irreversibility in the following stages (30). Thus, Levodopa could mitigate the Parkinson's disease symptoms but does not prevent the progression (31). A neuromodulatory effect is enhanced by the activation of presynaptic CB1 receptors in the corticostriatal pathway both indirect and direct BG pathways through retrograde eCB signaling (28, 31, 32). This is valid in these motor-controlling brain structures (28). This particular action is crucial for the excitatory and glutamatergic neurons which have the role to transmit the information from the CPu to the output nuclei are inhibitory and GABAergic in nature (33). Dopamine is linked to cannabinoid action intimately (34). The CB1 receptor do not expressed in the dopaminergic neurons of the nigrostriatal pathway at the equal levels as the dopaminergic neurons of subpopulations of neurons (33, 34). For example, the mesostriatal pathway and the cortico-limbic system which has been hypothesized that the CB1 is the primary receptor which contributes to the synaptic activity of the neurons (6). On the contrary, the dopaminergic neurons of the ventral tegmental area had been detected with CB2 receptors (35). CB2 expressions in the nigrostriatal pathway have been illustrated in the human brains (36). Furthermore, CB2 is involved with pathological disorders. CB2 plays a significant role in modulating psychomotor behaviors, depression and anxiety as well as the rewarding effects of alcohol and cocaine which is shown by the explicit deletion of CB2 from the dopaminergic neurons in DAT-Cnr2 conditional knockout (cKO) mice (35-37). In addition, human genome-wide association studies have found the link between the Cnr2 gene and Parkinson's disease and substance abuse disorders. Therefore, the regulation of dopaminergic neurons by the CB2 receptor and the GABAergic neurons of the striatum, GPi and SNpr by the CB1 receptor may be important for the neuroprotective and neuromodulatory cannabinoid therapy with the CBD (38, 39).

Advantages of cannabis in PD

Marijuana usage in the medical field has illustrated that the marijuana can mitigate motor and non-motor symptoms such as bradykinesia, rigidity, tremor, sleep and pain (40, 41). The beneficial effects contributing to cannabis was shown in a study consisting of 85 individuals (41). The majority consumed a half-teaspoon of cannabis leaves additionally to their prescribed Parkinson's disease pharmacotherapy (41, 42). Relatively 46% of this particular group of individuals have reported a relief from PD symptoms, occurring on average 1.7 months after the first usage of cannabis (41). This implies that chronic cannabis use is important for improved symptoms (41). Bradykinesia is the most relieved symptom among cannabis users, followed by muscle rigidity and tremor. Fourteen per cent of the patients have reported that cannabis enhanced their levodopa-induced dyskinesia (41). In addition, the increased urine levels (greater than 50 ng/ml) of a THC metabolite in the individuals who have the relation cannabis usage over a period of time resulted in an apparent improvement in bradykinesia and rigidity (43).

THC has been demonstrated to enhance activities and hand-eye coordination in the animal of Parkinson's

Volume 5, Issue 2; March-April 2022; Page No 1201-1210

disease (41). In a clinical study consisting of 22 patients who suffered from Parkinson's disease with the cannabis smoking activity which has motor symptoms such as bradykinesia, resting tremor, rigidity (44). The results showed that the posture has improved in the motor symptoms as well as non-motor symptoms such as sleep and pain. Furthermore, the results have also shown improvement in the individuals with PD rapid eye movement (REM) sleep behavior disorder (45, 46). Nabilone can be defined as a synthetic cannabinoid receptor that reduces dyskinesia and aids the levodopa action by 76% (41, 47). Contrasting to the CB1 antagonist rimonabant, which shows no improvement on motor symptoms in patients who are affected with Parkinson's disease (48, 49). The "calming effect" has been reported in cannabis with an association to tremors and dyskinesia by individuals who are diagnosed with PD (41). Another study has shown that there is 30% improvement in dyskinesia without deteriorating the symptoms in the patients with PD. Furthermore, with the CBD, there is a removal causing dystonia (41). A study has performed cannabis use and compared with non-cannabis users in the individuals with PD and multiple sclerosis (50). The ones who use cannabis exhibit a substantially lower level of disability than non-users (32). Additionally, cannabis enhances memory, mood and fatigue (51). Relatively around 85% of patients have evaluated the high effectiveness (52).

Depression is a well-known symptom in PD with a popularity up to 50% when not diagnosed and treated (53). Endocannabinoids are considered to have an association in mood and behavior regulation which their deficiency has linked to depression (54). In epidemiological studies, it is illustrated that cannabis users who use cannabis as a daily or weekly basis will tend to exhibit a better mood when compared to the non-users (55). However, it is unclear whether the symptoms associated with depression arise from cannabis or other factors (20, 56). Consequently, cannabis usage is proven to be possible helping the treatment of depressive symptoms in PD patients (57). In addition, cannabis has demonstrated to improve sleep with a clinical trial which involves 2000 patients facing several pain disorders (36, 58). Research suggests that cannabis may alleviate spasticity and pain which is involved in Parkinson's disease and multiple sclerosis (MS) and may further have neuroprotective effects. PD patients survey, conducted in Colorado which showed the consistent results with previous reports of cannabis lessening the non-motor symptoms (40). Furthermore, cannabis improves the motor and non-motor functions which constitute the neuroprotective properties, helping in the treatment of PD and postpone its progression (4). Therefore, cannabis can be used as an alternative or adjunct therapy with PD adults so as to enhance patients' life quality (44, 57, 59).

Disadvantages of cannabis in PD

Cannabis can deteriorate cognitive abilities, however, temporarily and fade away when the drug is not given (50). Marijuana is known for the deterioration of memory for working and enhance depression effects (60). In contrast to a particular study in which individuals with Parkinson's disease who consumed marijuana have reported that there is an improvement in memory and mood (60). This is because the individuals with mood problems or memory are holding back from the drug with the worsening symptoms considered (20, 60). Weight gain is another possible effect, which is believed to be the increments of caloric intake (61, 62). Even though the usage of marijuana is contributed to obesity in adolescence which studies of adults have discovered that cannabis users exhibit a lower prevalence in obesity than others (41). A survey of adults associating with Parkinson's disease and multiple sclerosis has discovered that marijuana users is not associated with high risk of obesity (41). There is a suggestion that an acute usage of marijuana can convince a transient motivational state which is associated with non-users (41, 47). However, there is detection for those who has the regular usage of marijuana (41). Additionally, there is a detrimental effect on motor skills associated with marijuana (41). On the contrary, a recent investigation PD and multiple sclerosis patients has illustrate that the equivalent amount of time performing physical activity and sitting for both users and non-users (22, 46).

CBD as an adjuvant for PD

Several studies have shown that genetic and idiopathic factors might have an association to the neurodegeneration which is seen in PD (63). However, an etiology of this particular disease is still

Volume 5, Issue 2; March-April 2022; Page No 1201-1210

unknown. Multitude of studies have linked PD's idiopathic factors (such as ageing and environmental factors like heavy metals, pesticides, head trauma, and viral infections) to idiopathic factors (16, 63). Both oxidative and neuroinflammation are closely linked to both genetic factors and idiopathic factors that is in Parkinson's disease (64). SNpc's dopaminergic neurons are likely to have oxidative damage due to its low levels of antioxidant enzymes such as glutathione peroxidase and high levels of pro-oxidants, for instance, free iron and neuromelanin (16). The SNpc's oxidative properties encourages an increment in reactive oxygen species (ROS) (65, 66). This inhibits the mitochondrial electron transport chain, boost glutamate levels, stimulating NMDA receptors and induce excitotoxicity and neuronal death (67). Neuroprotective therapeutic strategies for PD is to alleviate the cytotoxic effects of oxidative stress, specifically lipid peroxidation, protein nitration and DNA oxidation is considered to be one of its aim (68). Regarding the neuronal population, glial cells (both astrocytes and microglia) can be viewed as a material to develop PD (69). Microglia and astrocytes guide neurons with dopaminergic injury in neuroinflammation which is characterized by the reactive microglia and the presence of astrocytes (70). Robust chemotaxis, phagocytosis and cytokine production and a release in the form of resident innate immune cells can be induced by the microglia . Recent research has classified microglia cells as M1(pro-inflammatory) or M2 (anti-inflammatory) phenotypically. Microglia encourages the survival of neurons via secreting glial cell line-derived neurotrophic factor (GDNF) (71, 72). Furthermore, they contribute to the tissue repair and degeneration of genes (1, 63). In contrast, microglia advanced the neurodegeneration of the nigrostriatal pathway in the M1 state (16, 73). The increased levels and production of ROS levels in a pro-inflammatory state constitute microglia (70). This results in IL-1, IL-6, TNF, chemokines, NO and O_2 (74, 75). The signaling pathways are activated via pro-inflammatory cytokines which leads to an increment in the engaging of microglia which in turn results in the death of dopaminergic cells (70).

Safety and adverse effects of CBD

One compelling consideration regarding the safety of CBD as a therapeutic strategy (65). In various preclinical and clinical studies, CBD has been demonstrated that there is no affect in metabolic and physiological parameters (40, 76). For instance, glycemia, prolactin levels, blood pressure, or heart rate (47). Moreover, CBD have no consequences in hematocrit, leukocyte, erythrocyte counts or bilirubin or creatine levels in normal human. Osmolarity, pH, albumin, leukocyte, or erythrocyte amount does not shown in urine with contribution of CBD (70, 77). Furthermore, in vitro research has shown that CBD has no affect embryonic development or the viability of non-tumour cell lines (78). The majority that reported the side effects of CBD are usually fatigue, diarrhea and appetite alteration. CBD is not analogous to toxin (79). CBD does not promote catalepsy which is exhibited in rodents. It is illustrated to alleviate some cataleptic agents, as discussed previously (80). On the contrary, CBD does not generate extrapyramidal effects in humans (80, 81). It is mandatory to assess the potential motor and cognitive side effects of CBD within the context of movement disorders with concurrent cognitive symptoms, for instance as those discussed here (49, 82).

Taking cognitive consequences into consideration, studies have indicated that CBD does not deteriorate and in certain cases, there is a potential for improvement. In various animal studies, including the mice that received MK-801 (a protocol used to excite schizophrenia) and rats that received iron overload in the neonatal period, transgenic mice with Alzheimer's disease and the mice that were given cerebral malaria (83). The study demonstrated that CBD can reverse the recognition of the loss of novel objects in preclinical animals (47, 82). Furthermore, CBD reconstructs the deficits in the Morris water maze, a particular task where spatial learning is assessed, in the rodent models of Alzheimer disease, brain ischemia and cerebral malaria (47). In addition, CBD does not impair cognitive performance in animals and does not promote withdrawal following prolonged treatment (47). Accordingly, in the latest clinical trial assessing CBD as adjunctive therapy for schizophrenia, the group with CBD involvement shows significant cognitive improvement (measured by Brief Assessment of cognition in Schizophrenia) for this group than the placebo group (47). In contrast, the difference was not statistically significant (47). Furthermore, CBD improves

Volume 5, Issue 2; March-April 2022; Page No 1201-1210

cannabis users' ability in facial emotion recognition (47, 82).

It is vital to know that CBD is not beneficial in some certain circumstances which is apparent seen in multiple sclerosis and HD clinical studies (76). In contrast, therapeutic effects are observed when there are combinations of Δ9-THC and CBD and assessing possible adverse effects of this combination (56). Several reports point out that Δ9-THC had negative effects on the cognition of human, mainly memory and emotional processing (76, 84). However, research indicates that CBD can alleviate the effects of Δ9-THC in rodents and monkeys in cognitivity (84). The clinical evidence point out that CBD does not provoke the effects related to cognitive of Δ9-THC and depends on the dose which defends against the cognitive effects (84). Nevertheless, this protective effect depends on the dose and depends on the interval between CBD and the consumption of Δ9-THC administration and is paradigm dependent (82). Some preclinical studies point out that CBD has no protective effect against the cognitive effect of Δ9-THC, sometimes improvement can be shown (74). Several clinical trial with Sativex have revealed that there are no adverse effects related to motor or cognitive function (85, 86). However, the latest open label study made a comparison to the multiple sclerosis patients who continues the treatment with Sativex to those who quits and found out that the ones who continues using had perform a poor balance and cognitive performance (87). To justify, an observational study to a large population of Italian patients whom affected by multiple sclerosis found out that 3.9% of the cases are discovered with cognitive/psychiatric performances (20, 88).

Conclusion

It is evident that PD is associated with disabling which consists of bradykinesia, resting tremor, rigidity and depression. The treatment diminished the motor symptoms effectively with a limited extent, only the initial phase and side effects. The medication that can be done by the individuals with the usage of cannabis has been demonstrated to reduce numerous symptoms which consist of bradykinesia, tremor, rigidity, depression, sleep and pain. Nonetheless, there are short and long term consequences with marijuana usage which includes cognitive problems. The long-term use of cannabis is obligatory for its effect to be shown. This poses an individual risk of developing an addiction to the illicit drug. More and thorough research is required in order to determine the effects of marijuana on PD patients where the options are limited.

References

1. Harris JP, Burrell JC, Struzyna LA, Chen HI, Serruya MD, Wolf JA, et al. Emerging regenerative medicine and tissue engineering strategies for Parkinson's disease. npj Parkinson's Disease. 2020;6(1):1-14.
2. Han Z, Tian R, Ren P, Zhou W, Wang P, Luo M, et al. Parkinson's disease and Alzheimer's disease: a Mendelian randomization study. BMC medical genetics. 2018;19(1):1-9.
3. Di Biase L, Summa S, Tosi J, Taffoni F, Marano M, Cascio Rizzo A, et al. Quantitative analysis of bradykinesia and rigidity in Parkinson's disease. Frontiers in neurology. 2018;9:121.
4. Müller T. Pharmacokinetics and pharmacodynamics of levodopa/carbidopa cotherapies for Parkinson's disease. Expert Opinion on Drug Metabolism & Toxicology. 2020;16(5):403-14.
5. Gonzalez-Latapi P, Bhowmick SS, Saranza G, Fox SH. Non-dopaminergic treatments for motor control in Parkinson's disease: An update. CNS drugs. 2020;34(10):1025-44.
6. Navarrete F, García-Gutiérrez MS, Jurado-Barba R, Rubio G, Gasparyan A, Austrich-Olivares A, et al. Endocannabinoid system components as potential biomarkers in psychiatry. Frontiers in psychiatry. 2020:315.
7. Lavanco G, Castelli V, Brancato A, Tringali G, Plescia F, Cannizzaro C. The endocannabinoid-alcohol crosstalk: Recent advances on a bi-faceted target. Clinical and Experimental Pharmacology and Physiology. 2018;45(9):889-96.
8. Martínez V, Iriondo De-Hond A, Borrelli F, Capasso R, Del Castillo MD, Abalo R. Cannabidiol and other non-psychoactive cannabinoids for prevention and treatment of gastrointestinal disorders: useful nutraceuticals? International Journal of Molecular Sciences. 2020;21(9):3067.
9. Thanabalasingam SJ, Ranjith B, Jackson R, Wijeratne DT. Cannabis and its derivatives for the use of motor symptoms in Parkinson's

Volume 5, Issue 2; March-April 2022; Page No 1201-1210

disease: a systematic review and meta-analysis. Therapeutic Advances in Neurological Disorders. 2021;14:17562864211018561.
10. Pellati F, Brighenti V, Sperlea J, Marchetti L, Bertelli D, Benvenuti S. New methods for the comprehensive analysis of bioactive compounds in Cannabis sativa L.(hemp). Molecules. 2018;23(10):2639.
11. Nuutinen T. Medicinal properties of terpenes found in Cannabis sativa and Humulus lupulus. European journal of medicinal chemistry. 2018;157:198-228.
12. Navarro G, Varani K, Lillo A, Vincenzi F, Rivas-Santisteban R, Raïch I, et al. Pharmacological data of cannabidiol-and cannabigerol-type phytocannabinoids acting on cannabinoid CB1, CB2 and CB1/CB2 heteromer receptors. Pharmacological research. 2020;159:104940.
13. Banister SD, Arnold JC, Connor M, Glass M, McGregor IS. Dark classics in chemical neuroscience: Δ9-tetrahydrocannabinol. ACS chemical neuroscience. 2019;10(5):2160-75.
14. Citti C, Linciano P, Russo F, Luongo L, Iannotta M, Maione S, et al. A novel phytocannabinoid isolated from Cannabis sativa L. with an in vivo cannabimimetic activity higher than Δ9-tetrahydrocannabinol: Δ9-Tetrahydrocannabiphorol. Scientific reports. 2019;9(1):1-13.
15. McPartland JM, Small E. A classification of endangered high-THC cannabis (Cannabis sativa subsp. indica) domesticates and their wild relatives. PhytoKeys. 2020;144:81.
16. Patricio F, Morales-Andrade AA, Patricio-Martínez A, Limón ID. Cannabidiol as a therapeutic target: Evidence of its neuroprotective and neuromodulatory function in parkinson's disease. Frontiers in Pharmacology. 2020:2092.
17. de Almeida DL, Devi LA. Diversity of molecular targets and signaling pathways for CBD. Pharmacology research & perspectives. 2020;8(6):e00682.
18. Shebaby W, Saliba J, Faour WH, Ismail J, El Hage M, Daher CF, et al. In vivo and in vitro anti-inflammatory activity evaluation of Lebanese Cannabis sativa L. ssp. indica (Lam.). Journal of Ethnopharmacology. 2021;270:113743.
19. di Giacomo V, Chiavaroli A, Recinella L, Orlando G, Cataldi A, Rapino M, et al. Antioxidant and neuroprotective effects induced by cannabidiol and cannabigerol in rat CTX-TNA2 astrocytes and isolated cortexes. International journal of molecular sciences. 2020;21(10):3575.
20. Jones É, Vlachou S. A critical review of the role of the cannabinoid compounds Δ9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD) and their combination in multiple sclerosis treatment. Molecules. 2020;25(21):4930.
21. Haleem R, Wright R. A scoping review on clinical trials of pain reduction with cannabis administration in adults. Journal of clinical medicine research. 2020;12(6):344.
22. Hansen JS, Hansen RM, Petersen T, Gustavsen S, Oturai AB, Sellebjerg F, et al. The Effect of Cannabis-Based Medicine on Neuropathic Pain and Spasticity in Patients with Multiple Sclerosis and Spinal Cord Injury: Study Protocol of a National Multicenter Double-Blinded, Placebo-Controlled Trial. Brain Sciences. 2021;11(9):1212.
23. Tham M, Yilmaz O, Alaverdashvili M, Kelly MEM, Denovan-Wright EM, Laprairie RB. Allosteric and orthosteric pharmacology of cannabidiol and cannabidiol-dimethylheptyl at the type 1 and type 2 cannabinoid receptors. British journal of pharmacology. 2019;176(10):1455-69.
24. Masato A, Plotegher N, Boassa D, Bubacco L. Impaired dopamine metabolism in Parkinson's disease pathogenesis. Molecular neurodegeneration. 2019;14(1):1-21.
25. Marinus J, Zhu K, Marras C, Aarsland D, van Hilten JJ. Risk factors for non-motor symptoms in Parkinson's disease. The Lancet Neurology. 2018;17(6):559-68.
26. Ferreira-Junior NC, Campos AC, Guimaraes FS, Del-Bel E, Zimmermann PMdR, Brum Junior L, et al. Biological bases for a possible effect of cannabidiol in Parkinson's disease. Brazilian Journal of Psychiatry. 2019;42:218-24.
27. Mendonça IP, Duarte-Silva E, Chaves-Filho AJM, Peixoto CA. Neurobiological findings

Volume 5, Issue 2; March-April 2022; Page No 1201-1210

underlying depressive behavior in Parkinson's disease: A review. International immunopharmacology. 2020;83:106434.
28. Cilia R. Molecular imaging of the cannabinoid system in idiopathic Parkinson's disease. International review of neurobiology. 2018;141:305-45.
29. Zhang X, Gao F, Wang D, Li C, Fu Y, He W, et al. Tau pathology in Parkinson's disease. Frontiers in neurology. 2018;9:809.
30. Balestrino R, Schapira AHV. Parkinson disease. European journal of neurology. 2020;27(1):27-42.
31. Sgroi S, Tonini R. Opioidergic modulation of striatal circuits, implications in Parkinson's disease and levodopa induced dyskinesia. Frontiers in Neurology. 2018;9:524.
32. Han Q-W, Yuan Y-H, Chen N-H. The therapeutic role of cannabinoid receptors and its agonists or antagonists in Parkinson's disease. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2020;96:109745.
33. Peters KZ, Cheer JF, Tonini R. Modulating the neuromodulators: dopamine, serotonin, and the endocannabinoid system. Trends in Neurosciences. 2021;44(6):464-77.
34. Di Bartolomeo M, Stark T, Maurel OM, Iannotti FA, Kuchar M, Ruda-Kucerova J, et al. Crosstalk between the transcriptional regulation of dopamine D2 and cannabinoid CB1 receptors in schizophrenia: Analyses in patients and in perinatal Δ9-tetrahydrocannabinol-exposed rats. Pharmacological research. 2021;164:105357.
35. Canseco-Alba A, Schanz N, Sanabria B, Zhao J, Lin Z, Liu Q-R, et al. Behavioral effects of psychostimulants in mutant mice with cell-type specific deletion of CB2 cannabinoid receptors in dopamine neurons. Behavioural brain research. 2019;360:286-97.
36. Yu H, Liu X, Chen B, Vickstrom CR, Friedman V, Kelly TJ, et al. The Neuroprotective Effects of the CB2 Agonist GW842166x in the 6-OHDA Mouse Model of Parkinson's Disease. Cells. 2021;10(12):3548.
37. Canseco-Alba A, Sanabria B, Hammouda M, Bernadin R, Mina M, Liu Q-R, et al. Cell-Type Specific Deletion of CB2 Cannabinoid Receptors in Dopamine Neurons Induced Hyperactivity Phenotype: Possible Relevance to Attention-Deficit Hyperactivity Disorder. Frontiers in psychiatry. 2021;12.
38. Cooray R, Gupta V, Suphioglu C. Current aspects of the endocannabinoid system and targeted THC and CBD phytocannabinoids as potential therapeutics for Parkinson's and Alzheimer's diseases: a review. Molecular neurobiology. 2020;57(11):4878-90.
39. Junior NCF, dos-Santos-Pereira M, Guimarães FS, Del Bel E. Cannabidiol and cannabinoid compounds as potential strategies for treating Parkinson's disease and L-DOPA-induced dyskinesia. Neurotoxicity Research. 2020;37(1):12-29.
40. Crippa JAS, Hallak JEC, Zuardi AW, Guimarães FS, Tumas V, Dos Santos RG. Is cannabidiol the ideal drug to treat non-motor Parkinson's disease symptoms? European archives of psychiatry and clinical neuroscience. 2019;269(1):121-33.
41. Patel RS, Kamil S, Shah MR, Bhimanadham NN, Imran S. Pros and Cons of Marijuana in Treatment of Parkinson's Disease. Cureus. 2019;11(6).
42. Zain-ul-Abidin S, Khan R, Ahmad M, Bhatti MZ, Zafar M, Saeed A, et al. Ethnobotanical survey of highly effective medicinal plants and phytotherapies to treat diabetes mellitus II in South-West Pakistan. 2018.
43. Bonomo Y, Norman A, Collins L, O'Neill H, Galettis P, Trinca J, et al. Pharmacokinetics, Safety, and Tolerability of a Medicinal Cannabis Formulation in Patients with Chronic Non-cancer Pain on Long-Term High Dose Opioid Analgesia: A Pilot Study. Pain and Therapy. 2022;11(1):171-89.
44. Yenilmez F, Fründt O, Hidding U, Buhmann C. Cannabis in Parkinson's disease: the patients' view. Journal of Parkinson's Disease. 2021;11(1):309-21.
45. Kuhlman GD, Flanigan JL, Sperling SA, Barrett MJ. Predictors of health-related quality of life in Parkinson's disease. Parkinsonism & related disorders. 2019;65:86-90.
46. Figura M, Koziorowski D, Sławek J. Cannabis in Parkinson's Disease—the patient's perspective versus clinical trials: a systematic literature review. Neurologia i Neurochirurgia Polska. 2022.

Volume 5, Issue 2; March-April 2022; Page No 1201-1210

47. Elsaid S, Kloiber S, Le Foll B. Effects of cannabidiol (CBD) in neuropsychiatric disorders: a review of pre-clinical and clinical findings. Progress in molecular biology and translational science. 2019;167:25-75.
48. Eckard ML, Trexler KR, Kotson BT, Anderson KG, Kinsey SG. Precipitated Δ9-THC withdrawal reduces motivation for sucrose reinforcement in mice. Pharmacology Biochemistry and Behavior. 2020;195:172966.
49. Hoffman KL. From the Clinic to the Laboratory, and Back Again: Investigations on Cannabinoids and Endocannabinoid System Modulators for Treating Schizophrenia. Frontiers in Psychiatry. 2021;12:1008.
50. Feinstein A, Meza C, Stefan C, Staines RW. Coming off cannabis: a cognitive and magnetic resonance imaging study in patients with multiple sclerosis. Brain. 2019;142(9):2800-12.
51. Deuel LM, Seeberger LC. Complementary therapies in Parkinson disease: a review of acupuncture, Tai Chi, Qi Gong, yoga, and cannabis. Neurotherapeutics. 2020;17(4):1434-55.
52. Furgiuele A, Cosentino M, Ferrari M, Marino F. Immunomodulatory potential of cannabidiol in multiple sclerosis: a systematic review. Journal of Neuroimmune Pharmacology. 2021;16(2):251-69.
53. Arjmand S, Behzadi M, Kohlmeier KA, Mazhari S, Sabahi A, Shabani M. Bipolar disorder and the endocannabinoid system. Acta Neuropsychiatrica. 2019;31(4):193-201.
54. Botsford SL, Yang S, George TP. Cannabis and cannabinoids in mood and anxiety disorders: impact on illness onset and course, and assessment of therapeutic potential. The American journal on addictions. 2020;29(1):9-26.
55. Onaemo VN, Fawehinmi TO, D'Arcy C. Comorbid cannabis use disorder with major depression and generalized anxiety disorder: A systematic review with meta-analysis of Nationally Representative Epidemiological Surveys. Journal of affective disorders. 2021;281:467-75.
56. Fiani B, Sarhadi KJ, Soula M, Zafar A, Quadri SA. Current application of cannabidiol (CBD) in the management and treatment of neurological disorders. Neurological Sciences. 2020;41(11):3085-98.
57. Urbi B, Corbett J, Hughes I, Owusu MA, Thorning S, Broadley S, et al. Effects of Cannabis in Parkinson's Disease: A Systematic Review and Meta-Analysis. Journal of Parkinson's Disease. 2021(Preprint):1-14.
58. Prakash S, Carter WG. The Neuroprotective Effects of Cannabis-Derived Phytocannabinoids and Resveratrol in Parkinson's Disease: A Systematic Literature Review of Pre-Clinical Studies. Brain Sci. 2021, 11, 1573. s Note: MDPI stays neutral with regard to jurisdictional claims in published …; 2021.
59. Bougea A, Koros C, Simitsi A-M, Chrysovitsanou C, Leonardos A, Stefanis L. Medical cannabis as an alternative therapeutics for Parkinsons' disease: Systematic review. Complementary therapies in clinical practice. 2020;39:101154.
60. Longoria V, Parcel H, Toma B, Minhas A, Zeine R. Neurological Benefits, Clinical Challenges, and Neuropathologic Promise of Medical Marijuana: A Systematic Review of Cannabinoid Effects in Multiple Sclerosis and Experimental Models of Demyelination. Biomedicines. 2022;10(3):539.
61. Černe K. Toxicological properties of Δ9-tetrahydrocannabinol and cannabidiol. Arhiv za higijenu rada i toksikologiju. 2020;71(1):1-11.
62. Boggs DL, Nguyen JD, Morgenson D, Taffe MA, Ranganathan M. Clinical and preclinical evidence for functional interactions of cannabidiol and Δ9-tetrahydrocannabinol. Neuropsychopharmacology. 2018;43(1):142-54.
63. Schneider SA, Tahirovic S, Hardy J, Strupp M, Bremova-Ertl T. Do heterozygous mutations of Niemann–Pick type C predispose to late-onset neurodegeneration: a review of the literature. Journal of neurology. 2021;268(6):2055-64.
64. De Ternay J, Naassila M, Nourredine M, Louvet A, Bailly F, Sescousse G, et al. Therapeutic prospects of cannabidiol for alcohol use disorder and alcohol-related damages on the liver and the brain. Frontiers in Pharmacology. 2019;10:627.
65. Vallée A, Vallée J-N, Lecarpentier Y. Potential role of cannabidiol in Parkinson's disease by targeting the WNT/β-catenin pathway, oxidative

Volume 5, Issue 2; March-April 2022; Page No 1201-1210

stress and inflammation. Aging (Albany NY). 2021;13(7):10796.
66. Kim J, Choi H, Kang EK, Ji GY, Kim Y, Choi IS. In Vitro Studies on Therapeutic Effects of Cannabidiol in Neural Cells: Neurons, Glia, and Neural Stem Cells. Molecules. 2021;26(19):6077.
67. Brakatselos C, Delis F, Asprogerakas M-Z, Lekkas P, Tseti I, Tzimas PS, et al. Cannabidiol modulates the motor profile and NMDA receptor-related alterations induced by ketamine. Neuroscience. 2021;454:105-15.
68. Atalay S, Jarocka-Karpowicz I, Skrzydlewska E. Antioxidative and anti-inflammatory properties of cannabidiol. Antioxidants. 2019;9(1):21.
69. Wu J, Chen N, Liu Y, Godlewski G, Kaplan HJ, Shrader SH, et al. Studies of involvement of G-protein coupled receptor-3 in cannabidiol effects on inflammatory responses of mouse primary astrocytes and microglia. Plos one. 2021;16(5):e0251677.
70. Cardinal von Widdern J, Hohmann T, Dehghani F. Abnormal cannabidiol affects production of pro-inflammatory mediators and astrocyte wound closure in primary astrocytic-microglial cocultures. Molecules. 2020;25(3):496.
71. Auzmendi J, Palestro P, Blachman A, Gavernet L, Merelli A, Talevi A, et al. Cannabidiol (CBD) inhibited rhodamine-123 efflux in cultured vascular endothelial cells and astrocytes under hypoxic conditions. Frontiers in Behavioral Neuroscience. 2020;14:32.
72. Zhang B, Gu X, Han X, Gao Q, Liu J, Guo T, et al. Crosstalk between DNA methylation and histone acetylation triggers GDNF high transcription in glioblastoma cells. Clinical epigenetics. 2020;12(1):1-16.
73. Cortez IL, Rodrigues da Silva N, Guimarães FS, Gomes FV. Are CB2 receptors a new target for schizophrenia treatment? Frontiers in Psychiatry. 2020:1137.
74. Jarrahi A, Braun M, Ahluwalia M, Gupta RV, Wilson M, Munie S, et al. Revisiting traumatic brain injury: from molecular mechanisms to therapeutic interventions. Biomedicines. 2020;8(10):389.
75. omid Sadatpoor S, Salehi Z, Rahban D, Salimi A. Manipulated mesenchymal stem cells applications in neurodegenerative diseases. International Journal of Stem Cells. 2020;13(1):24.
76. Chiurchiù V, van der Stelt M, Centonze D, Maccarrone M. The endocannabinoid system and its therapeutic exploitation in multiple sclerosis: Clues for other neuroinflammatory diseases. Progress in neurobiology. 2018;160:82-100.
77. Fitzpatrick J-M, Minogue E, Curham L, Tyrrell H, Gavigan P, Hind W, et al. MyD88-dependent and-independent signalling via TLR3 and TLR4 are differentially modulated by Δ9-tetrahydrocannabinol and cannabidiol in human macrophages. Journal of Neuroimmunology. 2020;343:577217.
78. Hohmann U, Walsleben C, Ghadban C, Kirchhoff F, Dehghani F, Hohmann T. Interaction of Glia Cells with Glioblastoma and Melanoma Cells under the Influence of Phytocannabinoids. Cells. 2022;11(1):147.
79. Stefani A, Cerroni R, Pierantozzi M, D'Angelo V, Grandi L, Spanetta M, et al. Deep brain stimulation in Parkinson's disease patients and routine 6-OHDA rodent models: Synergies and pitfalls. European Journal of Neuroscience. 2021;53(7):2322-43.
80. Crippa JA, Guimarães FS, Campos AC, Zuardi AW. Translational investigation of the therapeutic potential of cannabidiol (CBD): toward a new age. Frontiers in immunology. 2018;9:2009.
81. Boggs DL, Surti T, Gupta A, Gupta S, Niciu M, Pittman B, et al. The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia a randomized placebo controlled trial. Psychopharmacology. 2018;235(7):1923-32.
82. Kozela E, Krawczyk M, Kos T, Juknat A, Vogel Z, Popik P. Cannabidiol improves cognitive impairment and reverses cortical transcriptional changes induced by ketamine, in schizophrenia-like model in rats. Molecular neurobiology. 2020;57(3):1733-47.
83. Kruk-Slomka M, Biala G. Cannabidiol Attenuates MK-801-Induced Cognitive Symptoms of Schizophrenia in the Passive Avoidance Test in Mice. Molecules. 2021;26(19):5977.
84. Sanchez-Ramos J, Louis BW-S. Cannabinoid medications for treatment of neurological

Volume 5, Issue 2; March-April 2022; Page No 1201-1210

disorders. Cannabis: A Clinician's Guide. 2018:43-52.
85. Boivin M. Nabiximols (Sativex®). Cannabinoids and Pain. 2021:119-26.
86. Inglet S, Winter B, Yost SE, Entringer S, Lian A, Biksacky M, et al. Clinical Data for the Use of Cannabis-Based Treatments: A Comprehensive Review of the Literature. Ann Pharmacother. 2020;54(11):1109-43. Epub 20200602. doi: 10.1177/1060028020930189. PubMed PMID: 32483988.
87. Morris J, Bond J, Taylor C. Results of an audit of 'real-world'patient-reported outcomes following a therapeutic trial of Sativex® for persistent non-cancer pain within a Jersey pain centre, local guideline adherent, self-selecting patient cohort. Pain News. 2019;17(3):154-9.
88. Turri M, Teatini F, Donato F, Zanette G, Tugnoli V, Deotto L, et al. Pain modulation after oromucosal cannabinoid spray (SATIVEX®) in patients with Multiple Sclerosis: A study with quantitative sensory testing and laser-evoked potentials. Medicines. 2018;5(3):59.

Volume 5, Issue 2; March-April 2022; Page No 1201-1210