International Journal of Scientific Research and Engineering Development-– Volume 4 Issue 5, Sep- Oct 2021

Available at www.ijsred.com

RESEARCH ARTICLE OPEN ACCESS

Medical Potential of Cannabis and Endocannabinoid System Against Alzheimer's Disease

PassaraVajanavinit*

*Ekamai International School, Sukhumvit, Vadhana, Bangkok, Thailand 10110

Email: pattjung5051@gmail.com

----------**********----------

Abstract:

Alzheimer's disease (AD) is one of the most seen progressive neurodegenerative disorders characterized by the aggregation of amyloid plaques and neurofibrillary tangles. Damaged and dead neurons in AD brains cause signal transmission to break down, thus resulting in cognitive dysfunction and progressive loss of memory. The limited effectiveness of existing AD treatments signifies that AD is currently one of the largest unmet medical needs in neurology and that more research efforts are highly essential. In this regard, targeting the endocannabinoid system (ECS) and focusing on cannabinoid interventions have interestingly emerged as a potential medical approach in treating Alzheimer's neuropathological changes and pain. The ECS is a complex cell-signaling system composed of endocannabinoids, or retrograde neurotransmitters that bind to at least two receptors known as CB1 and CB2 receptors. Here we present a review on findings that show how activation of these two receptors may potentially reduce β-amyloid and misfolded tau protein levels. Furthermore, several studies have demonstrated that endocannabinoid signaling may have a considerable impact on the progression of AD through regulating different pathological processes, for instance, neuroinflammation, malfunction in mitochondria, excessive oxidative stress, excitotoxicity, and neurotransmission. Taken together, the endocannabinoid system could be a promising therapeutic candidate for AD, thus highlighting that more clinical research effort is necessary.

Keywords **—Alzheimer's disease, Cannabis, CB1 and CB2 receptors, Neuroinflammation, Endocannabinoid system**

----------**********----------

I. INTRODUCTION

Alzheimer's Disease (AD) is known to be a progressive neurologic disorder that depends on aging. The disease itself is characterized by the accumulation of senile plagues, which are primarily composed of amyloid-β (Aβ), and the accumulation of neurofibrillary tangles (NFTs), which contains various isoforms of hyperphosphorylated tau protein that once has the function of stabilizing microtubules(1, 2). It is suggested that the presence of β-amyloid is the basis leading to plaque development, tau protein hyperphosphorylation, and the disease progression of AD(3). β-amyloid is the result of abnormal cleavage of Aβ precursor protein (APP) by two particular enzymes: β- and γ-secretases(4, 5).This may take place in early-onset patients, rooting back to the mutations happening in PSEN-1 and PSEN-2 coding genes or the similar mutations happening with Down syndrome patients(6). For late-onset patients, tau hyperphosphorylation precedes Aβ deposition around different cerebral regions(7, 8). The time length of AD progression starting from the early, silent stage to the symptomatic, striking phases might proceed in a slow manner, however, once

cognitive decline and dementia manifest, such illness then progresses considerably faster(9).Therefore, it can be concluded that AD may progress slowly until the limits are surpassed(10). These findings underline the urgent necessity for therapy and medication that can efficiently target specific origins during the silent, mild period of the disease, focusing on slowing and halting the disease progression before it becomes too severe(11).In recent years, the endocannabinoid system (ECS) has significantly originated as an excellent candidate for AD promising treatment. Signaling of endocannabinoid system has been shown to have an influence on the major pathogenic events that take place in the midst of the obscure stage of AD progression, such as during the protein misfolding activity, neuroinflammatory responses, free radicals outnumbering antioxidants, excitotoxicity, and mitochondrial dysfunction(11). The current study covers the investigations that demonstrate the multifarious characteristics of cannabinoids and endocannabinoid systems in relation to the treatment of AD.

II. ENDOCANNABINOID SYSTEM ALTERATIONS IN BRAINS WITH ALZHEIMER'S DISEASE

After examining post-mortem human brain samples, it was discovered that some changes in the ECS composition and signalling were present in AD patients' brains, regardless of how the role of these changes is still under investigation(12). The modifications to cannabinoid 1 (CB1) receptors described in AD are unsettled(13). While some researchers revealed that CB1 receptors levels were reduced significantly in cortical regions and neurons distant from senile plagues, other authors concluded to no difference in terms of cortex and hippocampus activities or allocation and availability of the CB1 receptors between healthy and AD brains (14). Surprisingly, there was little to no correlation found between the activity of CB1 receptor levels and AD markers such as Aβ and tau levels (15). Contrarily, the increased work rate of CB2 receptors is shown to be related to Aβ42 peptide levels and formations of plaques, but not associated with cognitive condition (14). This now further indicates that the AD harmful events increase the stimulation of CB2 receptors(12, 14, 16).

Several studies examined additional ECS components within the brains of AD patients. Through the findings, it was discovered that the two critical endocannabinoids so far are anandamide (AEA) and 2-arachidonoylglycerol (2-AG)(17). The first study did not reveal any difference in the concentration of these two endocannabinoids when comparing healthy controls to AD brains (18). On the contrary, an up-to-date analysis of brain autopsy samples from AD patients showed significantly lower AEA levels in the mid frontal and temporal cortices when set side by side to the healthy controls. Such a finding indicates that AEA deterioration can be explained by the increase of Aβ42 peptide levels(19).Additionally, alterations in the content level and activation of enzymes involved in the endocannabinoid system have been observed in brains of AD patients. In AD brains, an endocannabinoid system-related enzyme called FAAH, or fatty acid amide hydrolase, is overexpressed, near both neuritic plaque-associated glia and other immune cells (20). This overexpression of such an enzyme may notably have two unfavorable effects on Alzeimer's disease advancement: (i) a drop in the availability of AEA in neurons and (ii) a rise in the stimulation of pro-inflammatory molecules (21). According to a study, late-stage AD patients have altered 2-AG signaling as a result of poor MAGL recruitment and elevated DAGL levels, which triggers the AD silent synapses stage (16, 22, 23).

III.CLINICAL AND PRECLINICAL EFFICACY OF CANNABINOIDS ON ALZHEIMER'S DISEASE

The majority of research supporting cannabis' medicinal ability in treating AD is based on cell cultures and animal studies that implicate changes

similar to AD in the human brain. It is worth considering that the limited clinical trial at hand still does support the therapeutic benefits of cannabis drugs in treating some behavioral symptoms that are seen in patients with AD(24). Throughout all the cases studied, Delta-9-tetrahydrocannabinol (Δ9-THC), including both synthetic dronabinol and nabilone, was observed. Importantly, following after 6 weeks of dronabinol therapy, a clinical trial including a total of 15A AD patients showed a reduction in the levels of aberrant, abnormal behavior and also a rise in body weight of patients who were at one time rejecting meals. The only side effects linked with cannabis treatment were euphoria, somnolence, and fatigue, which however did not necessitate therapy cessation(25, 26). On the same hand, two pilot trials involving 8 dementia patients indicated that the application of synthetic dronabinol reduced agitation during sleep, and also did not show any unfavorable side effects (27, 28). Accordingly, the administration of synthetic nabilone was associated with immediate and significant reduction in the extreme agitation and aggression seen in a progressive AD patient who, importantly, was not responding to anxiolytic and antipsychotic medicines (29). Regardless of how limited the trials were, both in terms of numbers and in terms of how cognitive or neurodegenerative markers were not considered, the therapeutic behavioral outcomes of the patients are still very encouraging, especially given that there has been no other significant detrimental side effects.

IV. CANNABINOIDS AND ENDOCANNABINOIDS RECEPTORS FOR PAIN Cannabinoids and Endocannabinoid Receptors for ALZHEIMER'S DISEASEPAIN

Numerous investigations in AD patients have found that their sensory, emotional, and behavioral reactions to painful stimuli are either diminished, increased, or normal (30-32). According to a study, the lateral pain system that controls the location, intensity, and pain quality is found to be less damaged by the pathology of AD(33-35). The medial pain system responsible for the emotional aspects of pain, on the other hand, is considerably disrupted by AD harmful stimuli and neurodegenerative changes, which then leads to patients' negative, emotional response(36-39). Protein attributes for CB1 receptors in humans are the 472 amino acids that make up the cannabinoid receptor 1 gene (CNR1)(13, 40-42). In addition, mice and rats have 97% to 99% similar amino acid sequence identification when compared to humans, containing one more extra amino acid. Studies discovered that certain *CNR1* variants were linked to Cannabis usage(43, 44). Together with the *CNR1* is the cannabinoid receptor 2 gene (CNR2), which is responsible for administering the CB2 receptors, consisting of 360 amino acids in humans(45-48). When comparing CB1 to CB2 receptors, it was discovered that both show a sequence homology of up to 44% and are binded by many natural cannabinoid molecules. Not only that, but CB2 receptors also exhibit greater species diversity across rodents and humans than CB1 receptors, with an amino acid sequence homology, compared to rodents, of over 80%(49-51). It is discovered that there are two forms of CB2 receptor polymorphism (52-54). Moreover, the expression of CB1 receptors can be detected both in the brain and the peripheral nervous system(55-59). CB2 receptors, however, are more often expressed around the body's immune cells, gastrointestinal system, and spleen (57, 60, 61). Surprisingly, both CB1 receptors and CB2 receptor expressions have been found near the human placenta and both are involved in regulating the transportation of serotonin(57, 62).

Predictably, endocannabinoids and their functions have been discovered as a result of the findings of CB1 and CB2 receptors (12). Both centrally and peripherally positioned CB1 receptors were shown to be widely linked with nociception in preclinical and clinical studies (63, 64). Mainly found in immune system cells, CB2 receptors are also known to take part in pain reduction since they are widely associated with the activity of suppressing inflammatory responses (65-68). In addition, it is known that cerebral stress-mediated analgesia has

been extensively affected by the endocannabinoid system(43). Such exogenous cannabinoid like THC has also been recognized as a potential treatment for inflammatory responses due to its strong influence on opioid, glutamatergic, and serotonergic receptors(69-71). All these receptors are now involved with the management of neuropathic pain in neurodegenerative disorders. As a result, while endocannabinoids produced by human bodies may be necessary for pain homeostasis, exogenous cannabinoids derived from cannabis may have medicinal promise for the treatment of AD-related pain(71, 72).

The first use of cannabis in medicine is to alleviate pain. Cannabis, like endocannabinoids (Donvito et al., 2018), has been shown to have analgesic properties in a number of pain types, as well as the ability to suppress discomfort from inflammation (Fine and Rosenfeld, 2013; Donvito et al., 2018).

Apart from CB1 receptors, studies have suggested that the association of TRPV1, or transient receptor potential vanilloid-, with CB2 receptors can lead to pain modulation (Jhaveri et al., 2007; Akopian et al., 2009). Exogenous cannabinoids such as CBD, which interacts with CB2 receptors, has been documented to have the medical potential for treatment of chronic pain (63). However, it should be clearly understood that pain is a very subjective metric in a therapeutic context. It is difficult to quantify and define pain in patients with Alzeimer'sdisease and dementia because speech is usually impaired together with how many other symptoms are shown all at once.

V.CANNABINOIDS THERAPEUTIC PROPERTIESAGAINST NEUROINFLAMMATION

Neuroinflammation initiated by microglia in the brain has been found to speed up cell impairment and neuronal death (73-75). According to the findings, CB2 receptor appears to be involved in the suppression of microglia-induced neurotoxicity and inflammation of the nervous tissue(76). Furthermore, in several animal models, activating CB2 receptors significantly reduces the neuroinflammatory response to Aβ(76-78). Several investigations have demonstrated that CB2 receptor agonists, both selective and mixed, dramatically decreased microglial proliferation and proinflammatory mediator production in animal brains associated with Aβ(79). Similarly, in APP Tg models, selective CB2 receptor agonists has been shown to reduce the concentration of microglial cells near to the areas affected by Aβ and proinflammatory cytokines (80, 81). Referring to an animal study characterized by misfolded tau proteins, Sativex® is also capable of dampening microglial activity, however, there was no indication that CB2 receptors or other receptors were involved. Furthermore, in APP/PS1 Tg mice, prolonged therapy with the CB1 receptor agonist ACEA demonstrated a reduction in astrocytic reactivation and interferon expression (82, 83). Surprisingly, an exogenous cannabinoid known as CBD, despite its little binding ability to cannabinoid receptors, exhibited the potential to lessen inflammation in laboratory mice associated with AD (Esposito et al., 2006a; Martin-Moreno et al., 2011). Although the location of CBD's beneficial actions is uncertain, some evidence suggests that CBD interacts specifically with peroxisome proliferator-activated receptors that regulate glucose and lipid homeostasis (84).

Degradation of AEA and 2-AG through enzymes may possibly be associated with the regulation of inflammation in AD. A great example would be fatty acid amide hydrolase (FAAH), a membrane-bound enzyme that is found in neurons and astrocytes. FAAH was shown to be overexpressed in astrocytes and to be considerably maintained during the neuroinflammatory process, indicating that it may help buffer the negative effects of toxic insults produced by a reduction in the overall state of the endocannabinoid system(85). Based on the rise of cytokine release and cell death, it can be concluded that FAAH-deficient astrocytes were more active in Aβ astrocytes compared to wildtype astrocytes and also displayed a more pro-

inflammatory phenotype. Extracellular signal-regulated protein kinases 1/2 (ERK1/2) that are responsible for regulating cell proliferation and survival are likely the cause for such an event. The same thing happens with p38 mitogen-activated protein kinases (MAPK1/2)(86). These mechanisms, according to the researchers, are linked to PPAR-, PPAR-, and TRPV1 receptors rather than CB1 or CB2 receptors. Inhibition of FAAH has thus far failed to induce the proinflammatory phenotype in astrocytes. This suggests that the rise in N-acylethanolamines might have been the reason causing a compensatory alteration, such as the effect seen in astrocytes missing FAAH. The research suggests that extremely long-term endocannabinoid tone extension may have negative repercussions. In an AD animal model, blocking MAGL, an enzyme concerned with the hydrolysis of endocannabinoids and the control of arachidonic acid release, reduced Aβ levels and reduced neuroinflammation (87-89). Hence, pharmacological MAGL inhibitor confirmed anti-inflammatory cytokine-lowering effects via reduced prostaglandin production.

VI. CONCLUSIONS

Cannabinoids work by addressing various signalling pathways, including pain, aberrant Aβ and tau protein formation, neuroinflammation, malfunction in mitochondria, excessive oxidative stress, excitotoxicity, and neurotransmission. Additionally, cannabinoids are beneficial in the treatment of behavioural and cognitive disorders. In reference to the medical applications and trials on cannabinoids, it can be inferred that using cannabis and the ECS to produce an effective AD therapy is a viable and promising method. Cannabinoids may also promise for a low-cost, safe, and effective therapy with only few side effects. However, further study is needed in a clinical trial environment to determine the efficacy of cannabis in treating AD.

REFERENCES

1. Masters CL, Selkoe DJ. Biochemistry of amyloid β-protein and amyloid deposits in Alzheimer disease. Cold Spring Harbor perspectives in medicine. 2012;2(6):a006262.
2. Panza F, Lozupone M, Logroscino G, Imbimbo BP. A critical appraisal of amyloid-β-targeting therapies for Alzheimer disease. Nature Reviews Neurology. 2019;15(2):73-88.
3. Small SA, Duff K. Linking Aβ and tau in late-onset Alzheimer's disease: a dual pathway hypothesis. Neuron. 2008;60(4):534-42.
4. Lessard CB, Cottrell BA, Maruyama H, Suresh S, Golde TE, Koo EH. γ-Secretase Modulators and APH1 Isoforms Modulate γ-Secretase Cleavage but Not Position of ε-Cleavage of the Amyloid Precursor Protein (APP). PLoS One. 2015;10(12):e0144758.
5. Sarasija S, Norman KR. A γ-Secretase Independent Role for Presenilin in Calcium Homeostasis Impacts Mitochondrial Function and Morphology in Caenorhabditis elegans. Genetics. 2015;201(4):1453-66.
6. Raut S, Patel R, Al-Ahmad AJ. Presence of a mutation in PSEN1 or PSEN2 gene is associated with an impaired brain endothelial cell phenotype in vitro. Fluids Barriers CNS. 2021;18(1):3.
7. Xia D, Watanabe H, Wu B, Lee SH, Li Y, Tsvetkov E, et al. Presenilin-1 knockin mice reveal loss-of-function mechanism for familial Alzheimer's disease. Neuron. 2015;85(5):967-81.
8. Belbin O, Beaumont H, Warden D, Smith AD, Kalsheker N, Morgan K. PSEN1 polymorphisms alter the rate of cognitive decline in sporadic Alzheimer's disease patients. Neurobiol Aging. 2009;30(12):1992-9.
9. Kabir MT, Uddin MS, Setu JR, Ashraf GM, Bin-Jumah MN, Abdel-Daim MM. Exploring the Role of PSEN Mutations in the Pathogenesis of Alzheimer's Disease. Neurotox Res. 2020;38(4):833-49.
10. de Tommaso M, Kunz M, Valeriani M. Therapeutic approach to pain in neurodegenerative diseases: current evidence and perspectives. Expert Rev Neurother. 2017;17(2):143-53.
11. Navarro E, De Andrés C, Guerrero C, Giménez-Roldán S. Corticobasal Syndrome in a Family with Early-Onset Alzheimer's Disease Linked to a Presenilin-1 Gene Mutation. Mov Disord Clin Pract. 2015;2(4):388-94.
12. Gowran A, Noonan J, Campbell VA. The multiplicity of action of cannabinoids: implications for treating neurodegeneration. CNS Neurosci Ther. 2011;17(6):637-44.
13. Bonini SA, Premoli M, Tambaro S, Kumar A, Maccarinelli G, Memo M, et al. Cannabis sativa: A comprehensive ethnopharmacological review of a medicinal plant with a long history. J Ethnopharmacol. 2018;227:300-15.
14. Mastinu A, Premoli M, Ferrari-Toninelli G, Tambaro S, Maccarinelli G, Memo M, et al. Cannabinoids in health and disease: pharmacological potential in metabolic syndrome and neuroinflammation. Horm Mol Biol Clin Investig. 2018;36(2).
15. Narayanan SE, Sekhar N, Rajamma RG, Marathakam A, Al Mamun A, Uddin MS, et al. Exploring the Role of Aggregated Proteomes in the Pathogenesis of Alzheimer's Disease. Curr Protein Pept Sci. 2020;21(12):1164-73.
16. Ledesma JC, Rodríguez-Arias M, Gavito AL, Sánchez-Pérez AM, Viña J, Medina Vera D, et al. Adolescent binge-ethanol accelerates cognitive impairment and β-amyloid production and dysregulates endocannabinoid signaling in the hippocampus of APP/PSE mice. Addict Biol. 2021;26(1):e12883.
17. Abate G, Uberti D, Tambaro S. Potential and Limits of Cannabinoids in Alzheimer's Disease Therapy. Biology (Basel). 2021;10(6).
18. 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. Mol Neurobiol. 2020;57(11):4878-90.
19. Potter R, Patterson BW, Elbert DL, Ovod V, Kasten T, Sigurdson W, et al. Increased in vivo amyloid-β42 production, exchange, and loss in presenilin mutation carriers. Sci Transl Med. 2013;5(189):189ra77.
20. Shepherd C, McCann H, Halliday GM. Variations in the neuropathology of familial Alzheimer's disease. Acta Neuropathol. 2009;118(1):37-52.
21. Russo R, Cristiano C, Avagliano C, De Caro C, La Rana G, Raso GM, et al. Gut-brain Axis: Role of Lipids in the Regulation of Inflammation, Pain and CNS Diseases. Curr Med Chem. 2018;25(32):3930-52.
22. Armstrong RA. What causes alzheimer's disease? Folia Neuropathol. 2013;51(3):169-88.
23. Cruchaga C, Chakraverty S, Mayo K, Vallania FLM, Mitra RD, Faber K, et al. Rare variants in APP, PSEN1 and PSEN2 increase risk for AD in late-onset Alzheimer's disease families. PloS one. 2012;7(2):e31039.
24. Solimini R, Rotolo MC, Pichini S, Pacifici R. Neurological Disorders in Medical Use of Cannabis: An Update. CNS Neurol Disord Drug Targets. 2017;16(5):527-33.
25. Volicer L, Stelly M, Morris J, McLaughlin J, Volicer BJ. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. International journal of geriatric psychiatry. 1997;12(9):913-9.
26. Mücke M, Carter C, Cuhls H, Prüß M, Radbruch L, Häuser W. [Cannabinoids in palliative care: Systematic review and meta-analysis of efficacy, tolerability and safety]. Schmerz. 2016;30(1):25-36.
27. Charernboon T, Lerthattasilp T, Supasitthumrong T. Effectiveness of cannabinoids for treatment of dementia: a systematic review of randomized controlled trials. Clinical gerontologist. 2021;44(1):16-24.
28. Walther S, Schüpbach B, Seifritz E, Homan P, Strik W. Randomized, controlled crossover trial of dronabinol, 2.5 mg, for agitation in 2 patients with dementia. Journal of clinical psychopharmacology. 2011;31(2):256-8.
29. Morris PE, Goad A, Thompson C, Taylor K, Harry B, Passmore L, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. Critical care medicine. 2008;36(8):2238-43.
30. Mograbi DC, Brown RG, Salas C, Morris RG. Emotional reactivity and awareness of task performance in Alzheimer's disease. Neuropsychologia. 2012;50(8):2075-84.
31. Hoefer M, Allison SC, Schauer GF, Neuhaus JM, Hall J, Dang JN, et al. Fear conditioning in frontotemporal lobar degeneration and Alzheimer's disease. Brain. 2008;131(6):1646-57.
32. Goto S, Kamal N, Puzio H, Kobylarz F, Herrup K. Differential responses of individuals with late-stage dementia to two novel environments: A multimedia room and an interior garden. Journal of Alzheimer's Disease. 2014;42(3):985-98.
33. Scherder EJA. Low use of analgesics in Alzheimer's disease: possible mechanisms. Psychiatry. 2000;63(1):1-12.
34. Scherder EJ, Bouma A. Is decreased use of analgesics in Alzheimer disease due to a change in the affective component of pain? Alzheimer disease and associated disorders. 1997;11(3):171-4.
35. Scherder EJA, Bouma A. Visual analogue scales for pain assessment in Alzheimer's disease. Gerontology. 2000;46(1):47-53.
36. Kalenzaga S, Piolino P, Clarys D. The emotional memory effect in Alzheimer's disease: Emotional words enhance recollective experience similarly in patients and control participants. Cognition and Emotion. 2015;29(2):342-50.
37. Bungener C, Jouvent R. Depression as an emotional response in Alzheimer disease. Alzheimer Disease & Associated Disorders. 2004;18(3):176.
38. Halpin SN, Dillard RL, Puentes WJ. Socio-emotional adaptation theory: charting the emotional process of Alzheimer's disease. The Gerontologist. 2017;57(4):696-706.
39. Grande MRL, Murphy BM, Higgins RO, Worcester MUC, Parkinson A, Brown SL, et al. Physical activity and negative emotional response after percutaneous coronary intervention. European Journal of Preventive Cardiology. 2006;13(2):254-60.
40. Hay EA, McEwan A, Wilson D, Barrett P, D'Agostino G, Pertwee RG, et al. Disruption of an enhancer associated with addictive behaviour within the cannabinoid receptor-1 gene suggests a possible role in alcohol intake, cannabinoid response and anxiety-related behaviour. Psychoneuroendocrinology. 2019;109:104407.
41. Siniscalco D, Sapone A, Giordano C, Cirillo A, de Magistris L, Rossi F, et al. Cannabinoid receptor type 2, but not type 1, is up-regulated in peripheral blood mononuclear cells of children affected by autistic disorders. Journal of autism and developmental disorders. 2013;43(11):2686-95.
42. Marcos M, Pastor I, de la Calle C, Barrio‐Real L, Laso FJ, Gonz ález‐Sarmiento R. Cannabinoid receptor 1 gene is associated with alcohol

dependence. Alcoholism: Clinical and Experimental Research. 2012;36(2):267-71.
43. Smith DR, Stanley CM, Foss T, Boles RG, McKernan K. Rare genetic variants in the endocannabinoid system genes CNR1 and DAGLA are associated with neurological phenotypes in humans. PLoS One. 2017;12(11):e0187926.
44. Krebs MO, Morvan Y, Jay T, Gaillard R, Kebir O. Psychotomimetic effects at initiation of cannabis use are associated with cannabinoid receptor 1 (CNR1) variants in healthy students. Molecular psychiatry. 2014;19(4):402-3.
45. Rom S, Persidsky Y. Cannabinoid receptor 2: potential role in immunomodulation and neuroinflammation. Journal of Neuroimmune Pharmacology. 2013;8(3):608-20.
46. Karsak M, Cohen-Solal M, Freudenberg J, Ostertag A, Morieux C, Kornak U, et al. Cannabinoid receptor type 2 gene is associated with human osteoporosis. Human molecular genetics. 2005;14(22):3389-96.
47. Coppola N, Zampino R, Bellini G, Macera M, Marrone A, Pisaturo M, et al. Association between a polymorphism in cannabinoid receptor 2 and severe necroinflammation in patients with chronic hepatitis C. Clinical Gastroenterology and Hepatology. 2014;12(2):334-40.
48. Liu QR, Pan CH, Hishimoto A, Li CY, Xi ZX, Llorente‐Berzal A, et al. Species differences in cannabinoid receptor 2 (CNR2 gene): identification of novel human and rodent CB2 isoforms, differential tissue expression and regulation by cannabinoid receptor ligands. Genes, Brain and Behavior. 2009;8(5):519-30.
49. Muller C, Reggio PH. An analysis of the putative CBD binding site in the ionotropic cannabinoid receptors. Frontiers in cellular neuroscience. 2020;14:435.
50. Geiger J, Sexton R, Al-Sahouri Z, Lee M-Y, Chun E, Harikumar KG, et al. Evidence that specific interactions play a role in the cholesterol sensitivity of G protein-coupled receptors. Biochimica et Biophysica Acta (BBA)-Biomembranes. 2021:183557.
51. Neumann A, Engel V, Mahardhika AB, Schoeder CT, Namasivayam V, Kieć-Kononowicz K, et al. Computational investigations on the binding mode of ligands for the cannabinoid-activated G protein-coupled receptor GPR18. Biomolecules. 2020;10(5):686.
52. Sipe JC, Arbour N, Gerber A, Beutler E. Reduced endocannabinoid immune modulation by a common cannabinoid 2 (CB2) receptor gene polymorphism: possible risk for autoimmune disorders. Journal of leukocyte biology. 2005;78(1):231-8.
53. Minocci D, Massei J, Martino A, Milianti M, Piz L, Di Bello D, et al. Genetic association between bipolar disorder and 524A> C (Leu133Ile) polymorphism of CNR2 gene, encoding for CB2 cannabinoid receptor. Journal of affective disorders. 2011;134(1-3):427-30.
54. Howlett AC, Abood ME. CB1 and CB2 receptor pharmacology. Advances in Pharmacology. 2017;80:169-206.
55. Pertwee RG. Central & Peripheral Nervous Systems: Cannabinoid receptor ligands: clinical and neuropharmacological considerations relevant to future drug discovery and development. Expert Opinion on Investigational Drugs. 1996;5(10):1245-53.
56. Ishac EJN, Jiang L, Lake KD, Varga K, Abood ME, Kunos G. Inhibition of exocytotic noradrenaline release by presynaptic cannabinoid CB 1 receptors on peripheral sympathetic nerves. British journal of pharmacology. 1996;118(8):2023-8.
57. Santoro A, Mele E, Marino M, Viggiano A, Nori SL, Meccariello R. The complex interplay between Endocannabinoid System and the Estrogen System in Central Nervous System and periphery. International Journal of Molecular Sciences. 2021;22(2):972.
58. Huang S, Xiao P, Sun J. Structural basis of signaling of cannabinoids receptors: paving a way for rational drug design in controling mutiple neurological and immune diseases. Signal Transduction and Targeted Therapy. 2020;5(1):1-2.
59. Freundt-Revilla J, Kegler K, Baumgärtner W, Tipold A. Spatial distribution of cannabinoid receptor type 1 (CB1) in normal canine central and peripheral nervous system. PLoS One. 2017;12(7):e0181064.
60. Yonker LM, Barrios J, Mou H, Hurley BP. Untapped potential: Therapeutically targeting eicosanoids and endocannabinoids in the lung. Clinical Pharmacology & Therapeutics. 2021.
61. Joshi N, Onaivi ES. Endocannabinoid system components: overview and tissue distribution. Recent Advances in Cannabinoid Physiology and Pathology. 2019:1-12.
62. Fantegrossi WE, Wilson CD, Berquist MD. Pro-psychotic effects of synthetic cannabinoids: interactions with central dopamine, serotonin, and glutamate systems. Drug metabolism reviews. 2018;50(1):65-73.
63. Urits I, Gress K, Charipova K, Habib K, Lee D, Lee C, et al. Use of cannabidiol (CBD) for the treatment of chronic pain. Best Practice & Research Clinical Anaesthesiology. 2020.
64. Urits I, Borchart M, Hasegawa M, Kochanski J, Orhurhu V, Viswanath O. An update of current cannabis-based pharmaceuticals in pain medicine. Pain and therapy. 2019;8(1):41-51.
65. Navarrete F, García-Gutiérrez MS, Aracil-Fernández A, Lanciego JL, Manzanares J. Cannabinoid CB1 and CB2 receptors, and monoacylglycerol lipase gene expression alterations in the basal ganglia of patients with Parkinson's disease. Neurotherapeutics. 2018;15(2):459-69.
66. Udoh M, Santiago M, Devenish S, McGregor IS, Connor M. Cannabichromene is a cannabinoid CB2 receptor agonist. British journal of pharmacology. 2019;176(23):4537-47.
67. Ward SJ, Castelli F, Reichenbach ZW, Tuma RF. Surprising outcomes in cannabinoid CB1/CB2 receptor double knockout mice in two models of ischemia. Life sciences. 2018;195:1-5.
68. Kita M, Ano Y, Inoue A, Aoki J. Identification of P2Y receptors involved in oleamide-suppressing inflammatory responses in murine microglia and human dendritic cells. Scientific reports. 2019;9(1):1-10.
69. Milligan AL, Szabo-Pardi TA, Burton MD. Cannabinoid receptor type 1 and its role as an analgesic: an opioid alternative? Journal of dual diagnosis. 2020;16(1):106-19.
70. Manzanares J, Julian MD, Carrascosa A. Role of the cannabinoid system in pain control and therapeutic implications for the management of acute and chronic pain episodes. Current neuropharmacology. 2006;4(3):239-57.
71. Baron EP, Lucas P, Eades J, Hogue O. Patterns of medicinal cannabis use, strain analysis, and substitution effect among patients with migraine, headache, arthritis, and chronic pain in a medicinal cannabis cohort. The journal of headache and pain. 2018;19(1):1-28.
72. Alves P, Amaral C, Teixeira N, Correia-da-Silva G. Cannabis sativa: Much more beyond Δ9-tetrahydrocannabinol. Pharmacological research. 2020;157:104822.
73. Friedland RP, McMillan JD, Kurlawala Z. What Are the Molecular Mechanisms by Which Functional Bacterial Amyloids Influence Amyloid Beta Deposition and Neuroinflammation in Neurodegenerative Disorders? Int J Mol Sci. 2020;21(5).
74. Xiong X-Y, Liu L, Yang Q-W. Functions and mechanisms of microglia/macrophages in neuroinflammation and neurogenesis after stroke. Progress in neurobiology. 2016;142:23-44.
75. Okunuki Y, Mukai R, Nakao T, Tabor SJ, Butovsky O, Dana R, et al. Retinal microglia initiate neuroinflammation in ocular autoimmunity. Proceedings of the National Academy of Sciences. 2019;116(20):9989-98.
76. Wu J, Hocevar M, Bie B, Foss JF, Naguib M. Cannabinoid type 2 receptor system modulates paclitaxel-induced microglial dysregulation and central sensitization in rats. The Journal of Pain. 2019;20(5):501-14.
77. Docagne F, Mestre L, Loria F, Hernangomez M, Correa F, Guaza C. Therapeutic potential of CB2 targeting in multiple sclerosis. Expert opinion on therapeutic targets. 2008;12(2):185-95.
78. Aso E, Ferrer I. CB2 cannabinoid receptor as potential target against Alzheimer's disease. Frontiers in neuroscience. 2016;10:243.
79. Whiteside GT, Lee GP, Valenzano KJ. The role of the cannabinoid CB2 receptor in pain transmission and therapeutic potential of small molecule CB2 receptor agonists. Current medicinal chemistry. 2007;14(8):917-36.
80. Janefjord E, Mååg JLV, Harvey BS, Smid SD. Cannabinoid effects on β amyloid fibril and aggregate formation, neuronal and microglial-activated neurotoxicity in vitro. Cellular and molecular neurobiology. 2014;34(1):31-42.
81. Pascual AC, Martín-Moreno AM, Giusto NM, De Ceballos ML, Pasquaré SJ. Normal aging in rats and pathological aging in human Alzheimer's disease decrease FAAH activity: modulation by cannabinoid agonists. Experimental gerontology. 2014;60:92-9.
82. Casarejos MJ, Perucho J, Gomez A, Munoz MP, Fernandez-Estevez M, Sagredo O, et al. Natural cannabinoids improve dopamine

neurotransmission and tau and amyloid pathology in a mouse model of tauopathy. Journal of Alzheimer's Disease. 2013;35(3):525-39.
83. Watt G, Karl T. In vivo evidence for therapeutic properties of cannabidiol (CBD) for Alzheimer's disease. Frontiers in pharmacology. 2017;8:20.
84. Esposito G, Scuderi C, Valenza M, Togna GI, Latina V, De Filippis D, et al. Cannabidiol reduces Aβ-induced neuroinflammation and promotes hippocampal neurogenesis through PPARγ involvement. PloS one. 2011;6(12):e28668.
85. Benito C, Núñez E, Tolón RM, Carrier EJ, Rábano A, Hillard CJ, et al. Cannabinoid CB2 receptors and fatty acid amide hydrolase are selectively overexpressed in neuritic plaque-associated glia in Alzheimer's disease brains. Journal of Neuroscience. 2003;23(35):11136-41.
86. Benito C, Tolón RM, Castillo AI, Ruiz‐Valdepeñas L, Martínez‐Orgado JA, Fernández‐Sánchez FJ, et al. β–Amyloid exacerbates inflammation in astrocytes lacking fatty acid amide hydrolase through a mechanism involving PPAR‐α, PPAR‐γ and TRPV1, but not CB1 or CB2 receptors. British journal of pharmacology. 2012;166(4):1474-89.
87. Nomura DK, Morrison BE, Blankman JL, Long JZ, Kinsey SG, Marcondes MCG, et al. Endocannabinoid hydrolysis generates brain prostaglandins that promote neuroinflammation. Science. 2011;334(6057):809-13.
88. Nomura DK, Lombardi DP, Chang JW, Niessen S, Ward AM, Long JZ, et al. Monoacylglycerol lipase exerts dual control over endocannabinoid and fatty acid pathways to support prostate cancer. Chemistry & biology. 2011;18(7):846-56.
89. Piro JR, Benjamin DI, Duerr JM, Pi Y, Gonzales C, Wood KM, et al. A dysregulated endocannabinoid-eicosanoid network supports pathogenesis in a mouse model of Alzheimer's disease. Cell reports. 2012;1(6):617-23.

