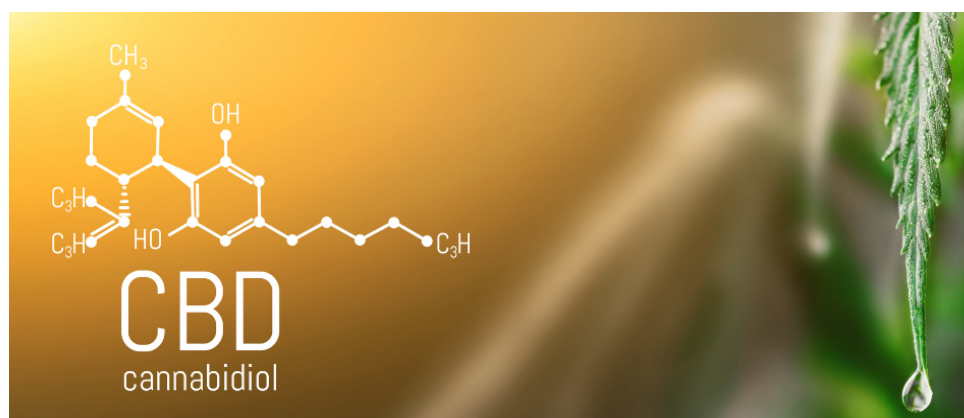# The Therapeutic Potential of Synthetic and Natural Cannabinoids in Treating Alzheimer's Disease

By: Nidhi Kanchumarthi, Avigail Rockland, Thejaswini Vembar, Elaine Liu, Rithvik Kanaad, Erick Torres Hinojosa, Kira Tiv, Benjamin Chen, Shira Hao, Sri Guttikonda, and Ramiro Garza

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Abstract

Alzheimer's disease (AD) is one of the most prevalent and debilitating neurodegenerative diseases in the world, highlighting the need for research on novel treatments and therapies. Previous studies have found that the body's endocannabinoid system (ECS) interacts closely with its neural system, making it a potential avenue for the treatment of neurological disorders. One hallmark of AD is the accumulation of amyloid-beta (Aβ) in the brain and its potentially detrimental effects on cognitive function. Cannabis-based drugs have been observed to regulate Aβ modifications and inhibit AD progression. Furthermore, cannabinoids have been noted to reduce inflammation and neurotoxicity. Synthetic cannabinoids were able to rescue memory deficits and neurodegeneration, and reduce immunoreactivity. Similarly, natural cannabinoids like Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) demonstrate therapeutic potential by interacting with the cholinergic system, and reversing the symptoms of AD. Although further research and testing are needed, it is evident that the use of cannabinoids shows promise for future treatment in AD patients.

I. Introduction

Previous studies have concluded that the endocannabinoid system (ECS) is disrupted by many neurodegenerative disorders (Di Marzo et al., 2015; Fagan, 2014; Paloczi et al., 2018). The goal of this paper is to comprehensively review and outline the most recent data around the pathophysiology of the ECS as it relates to Alzheimer's Disease (AD), as well as to investigate the efficacy of natural and synthetic cannabinoids as a therapeutic option. Even as medicine advances and life expectancy increases, AD is still a prevalent issue.

With increased prevalence comes the need for new and effective therapies. The endocannabinoid system shows promise, serving as both a neuromodulator and immunomodulator. Cannabis sativa has been studied for its potential neuroprotective qualities and its role in attenuating nociception in several medical contexts, including cancer, psychiatric disorders, and epilepsy. Its primary active components, Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD), interact with the endocannabinoid signaling system through the endocannabinoid CB1 and CB2 receptors. Stimulation of these receptors by various agonists has also successfully reduced the chronic neuroinflammation associated with AD by interfering with the different neural pathways. Our goal has been to identify the mechanisms by which the reduction in neuroinflammation is accomplished.

Accumulation of Aβ peptide and hyperphosphorylated tau protein in the brain play an important role in the onset and progression of Alzheimer's disease (AD) (Farkhondeh et al., 2020). However, recent research has suggested that Aβ is no longer considered the primary cause, which was the accepted belief for many years (Cubinkova et al., 2018). Nevertheless, the ECS offers many therapeutic possibilities for targeting these Aβ deposits. Many studies support the finding that elevated levels of the endocannabinoid 2AG, coupled with the modulation of the common cannabinoid receptor CB2, could reduce Aβ plaque accumulation (Paloczi, 2018). While Aβ may not be the primary cause of AD, studies have shown that these deposits are detrimental to healthy synapses (Shankar et al., 2008), decreasing long-term potentiation and increasing long-term depression. Sometimes, this neural damage is permanent, but the use of cannabinoids to stimulate the ECS has shown some success in preventing this kind of damage.

Pathology of the cholinergic system is also associated with AD and thus has been further investigated as a therapeutic target. Many cholinergic pathways function in conscious awareness, attention, and working memory, which are areas commonly found to be damaged or dysfunctional in those who suffer from AD. Research by K.J. Thompson suggests that interacting signals between the endocannabinoid and cholinergic systems may be a way to improve cholinergic signaling and repair synaptic plasticity that is damaged as a result of AD (Thompson et al., 2020). We then investigate the inhibitory activity of various receptor agonists of the ECS, both natural and synthetic. This section looks at CBD and THC as receptor agonists and concludes that CBD plays a role in the inhibition of neural apoptosis while THC is active in the inhibition of acetylcholinesterase (AChE), which serves to improve the reduced cholinergic signalling associated with AD. Both agonists seem to play a part in the reduction of Aβ build-up, but the exact pathways still need to be elucidated.

Some of the most effective and well-researched synthetic agonists of the ECS include Dronabinol, Nabilone, WIN55,212-2, and JWH-015. Dronabinol and Nabilone were found to be particularly effective in treating the neuropsychiatric symptoms (NPS) associated with AD, while the others primarily function in reducing Aβ plaques and neuroinflammation. Our review presents published research that supports the efficacy of both natural and synthetic cannabinoids as a potential treatment for AD. This introduces a potential bias, as studies which conclude positive results and relationships are more likely to be published than those with negative results. Nevertheless, this research highlights the potential benefits that cannabinoid therapy could provide and recommends that it be studied further.

II. Neural Pathway
A. Amyloidogenic Pathway
Accumulation of Aβ peptide and hyperphosphorylated tau protein in the brain are the leading sources of the onset and progression of AD (Farkhondeh et al., 2020). When amyloid precursor protein (APP) is activated, it is cleaved by other proteins, which leads to the production of small Aβ fragments. This induces an increased production and aggregation of Aβ peptide in limbic and association cortices. As a result, the altered neuronal homeostasis and oxidative injury provoke neurofibrillary tangle formation. These tangles are a characteristic trait of AD brains and lead to

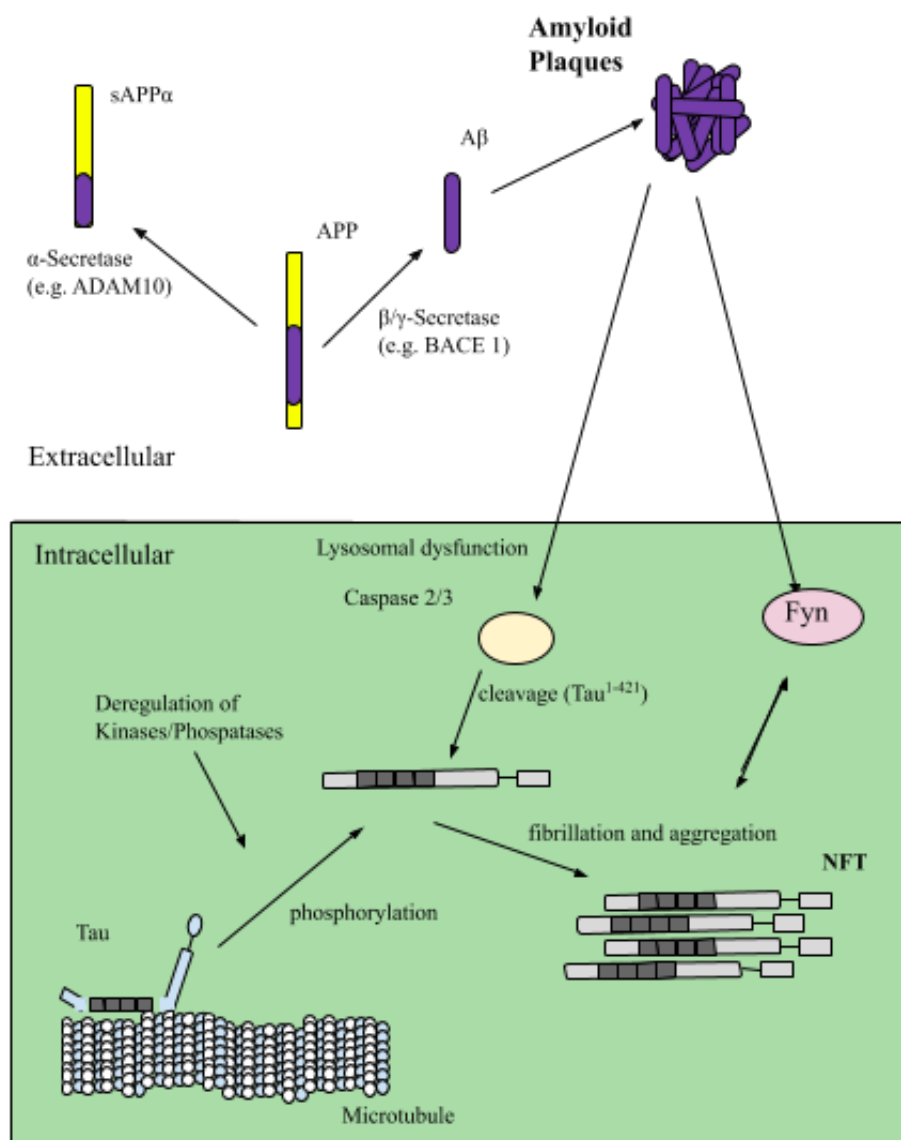neuronal loss and cognitive impairment (Hall et al., 2001; Nelson et al., 2012).

Fig. 1: The process of neurofibrillary tangle formation induced by amyloid plaque buildup. As the amyloid precursor protein (APP) is activated, amounts of Aβ are produced. This excess Aβ leads the neurofibrillary tangle formation, as seen in AD affected patients.

CBD, a Cannabis derivative devoid of psychotropic effects, has been shown to interfere with several Aβ-triggered neurodegenerative pathways (Scuderi et al., 2014). Studies found that CBD led to the downregulation of genes linked to AD, including genes coding for the kinases responsible for tau phosphorylation and for the secretases involved in Aβ generation. Pre-treatment with CBD prevented the expression of proteins potentially involved in tau phosphorylation and Aβ production in gingiva-derived

mesenchymal stem cells (GMSCs) (Librое al., 2016). In one study, the role of CBD was investigated as a modulating compound of APP processing in SHSY5Y(APP+) neurons. In addition, the putative involvement of PPARγ was explored as a candidate molecular site responsible for CBD actions. The results indicated that CBD is capable of inducing the ubiquitination —the degradation —of APP protein, leading to a decrease in APP full length protein levels in SHSY5Y(APP+) and a consequent decrease in Aβ production. CBD also promoted an increased survival of SHSY5Y(APP+) neurons by reducing their long-term apoptotic rate (Scuderi et al., 2014). In conclusion, research indicates that cannabis-based drugs inhibited the progression of AD by regulating Aβ modifications (Farkhondeh et al., 2020).

While the aggregation of Aβ plaques has been the leading hypothesis in the onset ofAD for several years, recent research has suggested alternative hypotheses. A number of drugs targeting Aβ, such as Aducanumab — an antibody drug that binds to insoluble and soluble Aβ plaques to reduce its levels in the brain — were successful in slowing the rate of cognitive function decline in patients with mild AD, but not in treating the root cause. One hypothesis suggests that AD is a synaptic disease. It has been argued that synaptic impairment is an early event in neurodegenerative processes during AD and that synaptic loss and failure corresponds with cognitive decline in AD as well (Cubinkova et al., 2018). Recently, it was shown that impaired synapses in AD brains released tau protein in response to potassium chloride (KCl) stimulation, suggesting that it may be involved in the progression of tau in the brain (Cubinkovaet al., 2018). In addition to the synaptic hypothesis, some researchers believe that alpha-synuclein acts as a pathogenic modulator in AD. Alpha-synuclein is a protein that localizes to the nerve terminal and regulates neurotransmitter release in the presynaptic neuron. It was found that levels of soluble alpha-synuclein are about two-fold higher in the brains of AD patients than in control brains and correlate better with cognitive impairment (Cubinkova et al.,2018), suggesting that overexpression of the alpha-synuclein protein may play a role in the onset of AD. Even in light of these alternative hypotheses, most research focuses on the effects that cannabinoids have on the production of Aβ plaques as a measure of treating AD.

B. Endocannabinoid Signaling

The endocannabinoid system regulates brain function as well as immune system activity, thus allowing it to serve as a therapeutic strategy for AD. Its dual ability as a neuromodulator and immunomodulator is due to the specific locations in which cannabinoid receptors type 1 (CB1) and type 2 (CB2) gather (Bonnet & Marchant, 2015). The components of the endocannabinoid system primarily include two endocannabinoid signaling molecules, 2-arachidonoyl glycerol (2AG) and anandamide (AEA), and their G-protein coupled receptors, cannabinoid receptor type 1 and cannabinoid receptor type 2 (Fagan & Campbell, 2014). The endocannabinoid system works specifically in both the regulation of neuroinflammation as well as neurogenesis.Studies show that the endocannabinoid system is able to reduce chronic neuroinflammation, a major mediator in neurodegeneration in Alzheimer's patients. PPARγ is a key component involved in the cannabinoid anti-inflammatory effect. This protein consists of a group of hormone receptors involved in gene expression and inflammation. The use of cannabinoids increases PPARγtranscriptional activity in adult rats, thus decreasing neuroinflammation (Fagan & Campbell, 2014).
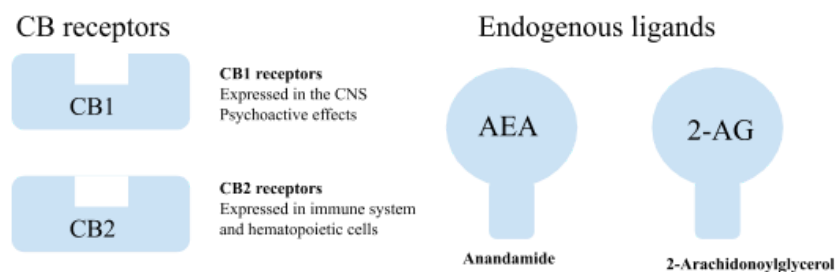

Fig. 2: Illustration and description of CB1 & CB2 receptors, and the endocannabinoid signaling molecules, anandamide (AEA) and 2-arachidonoyl glycerol (2AG).

An elevation of the 2AG endocannabinoid signaling molecule, coupled with a modulation of the CB2 specific cannabinoid receptor, could combat aggregated Aβ neuritic plaques (Paloczi et al., 2018). The cannabinoid receptors play a vital role in allowing the formation of new neurons and neuronal connections to sustain neuronal function. The proliferation of neural precursor cells, both neural stem cells and neural progenitor cells, has been proven to activate CB1 receptors; the proliferation of neural

progenitor cells has been seen to activate both CB1 and CB2 receptors, allowing the production and survival of new neurons (Fagan & Campbell, 2014). This activation of neurogenesis offers promising potential within the endocannabinoid system in reducing brain atrophy in Alzheimer patients (Fagan & Campbell, 2014).

A potential therapeutic component of the endocannabinoid system involves the cannabinoid receptors CB1 and CB2. CB1 receptors, the most abundant cannabinoid receptors,are mainly located in the neurons of the central nervous system and work to regulate cognition and memory, motor control, feeding, and pain perception — allowing the endocannabinoid system to serve as a neuromodulator. Studies on CB1 receptors have yielded inconsistent results,preventing a correlation between CB1 presence in AD patients and in control patients from being observed (Ahmad et al., 2014). A more recent study has indicated a reduction in the number of CB1 receptors in the frontal cortex while no change was observed in the hippocampus. CB2 receptors, on the other hand, are expressed mostly in immune cells and to some extent, in the peripheral system of the brain — allowing the endocannabinoid system to serve as an immunomodulator. As such, CB2 is highly involved in the research regarding the neuroinflammatory response associated with AD (Atakan, 2012). Within the endocannabinoid system in an Alzheimer's patient's brain, studies found an increase in CB2 receptor expression in microglia, phagocytic cells in the brain and spinal cord. This increase correlates with Aβ levels and plaque accumulation, suggesting that the activation of CB2 receptors plays a role in stimulating Aβ removal (Talarico et al., 2019). The use of CB2 receptors has shown to be a promising medium for both a therapeutic treatment and as a marker for the advancement of Alzheimer's disease. In addition, CB2 receptors have continuously been co-localized with Aβ plaque buildup (Ahmad et al., 2016). Despite this, there have been findings that demonstrated CB2 receptor concentration is highly expressed within microglia cells surrounding senile plaques — extracellular deposits of Aβ — within post-mortem brainsdiagnosed with AD (Aso & Ferrer, 2016). Conversely, studies demonstrated that CB2 receptors may not be the most accurate biomarker for tracking AD advancement, as they are also found on neuronal cells. However, this does not necessarily eliminate them as targets for treatment as they remain largely expressed within immune cells (Ahmad et al., 2016). As such, the significant presence of CB2 receptors in microglia cells in brains of AD patients allows for selective activation(stimulating certain CB2 receptors to decrease inflammatory cell generation) in affected

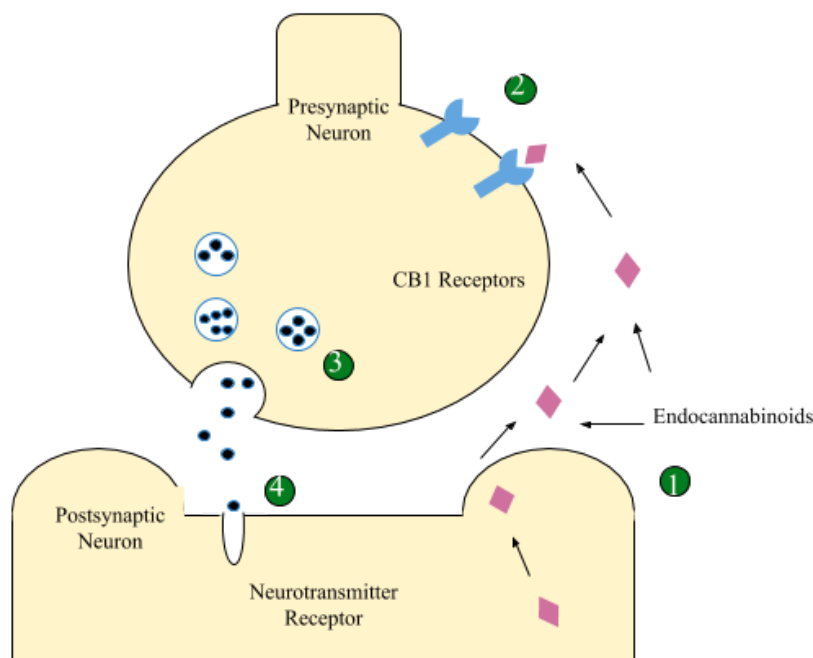tissues,therefore decreasing the risk of harmful effects (Ramírez et al., 2005).

Fig. 3: Illustration of the interaction between endocannabinoids and the cannabinoid receptors, CB1 and CB2. Endocannabinoids from the postsynaptic neuron travel through the synaptic cleft to the presynaptic neuron, thus attaching to the Cannabinoid Type 1 receptor. The binding of these two molecules results in a suppression of neurotransmitters altering the neuronal firing in the postsynaptic cell, thus allowing it to work as a regulator.

One avenue of therapeutic treatment is the usage of CB2 activity against inflammation. Within microglia cells, CB2 receptors inhibit neurotoxicity caused by microglia by substantially reducing the production of pro-inflammatory molecules and by manipulating macrophage migration(Aso& Ferrer, 2016). "This was supported by experiments utilizing receptor agonists within in vitro experiments containing different species of toxic Aβs, such as JWH-015, JWH-133, HU-308, WIN55,212-2, and HU-210, which observed a reduction of inflammatory molecules" (Aso & Ferrer, 2016). It has been postulated that these CB2 receptor agonists aid in inhibiting microglial activation through decreasing intracellular calcium concentration (Martín-Moreno et al., 2011). In essence, the utilization and subsequent exploitation of the endocannabinoid system provides an essential medium for the therapeutic treatment of Alzheimer's disease.

The endocannabinoid system has shown to reduce inflammatory response through thePPARγ protein as well as facilitate neurogenesis through the activation of both the cannabinoid receptors, when neural stem cells and neural progenitor cells are proliferated. The self-renewal capability and multipotency of stem cells is supported through the complex microenvironment provided through the action of the endocannabinoid system, specifically cannabinoid receptors CB1 and CB2 (Rodrigues et al., 2019). The prospect of neural stem cells as regenerative therapies is very promising, leading to a possible personalized and effective approach (Rodrigueset al., 2019). Moreover, the various cannabinoid actions on neural stem cells open paths of research to uncover the mechanisms responsible behind cannabinoid effects. New avenues of research could provide new knowledge, leading to the development of refined therapeutic strategies to alleviate Alzheimer's effects.

C. Synaptic Plasticity

Among the neural pathways negatively impacted by AD are those involved in synaptic plasticity. The brain's circuitry is heavily affected by numerous daily activities ranging from learning new information to engaging in social interactions. These exposures to the environment have the potential to modify the brain's neural organization and influence its activity. Synaptic plasticity is the phenomenon that describes these changes in the neural circuits' structure and function, which result from modifications to synaptic transmission. Although synaptic plasticity may allow a damaged brain to restrengthen synaptic connections and reverse damage, AD is known to impair this plasticity and leave permanent damage. Research has demonstrated that Aβdeposition, a widely recognized hallmark of AD pathophysiology, is detrimental to healthy synapses (Shankar et al., 2008). Soluble dimeric Aβ assemblies were found to be strong inhibitors of long-term potentiation —the strengthening of synaptic communication by repeated stimulation (Shankar et al., 2008). The soluble Aβ assemblies were also found to augment long-term depression causing a decrease in dendritic spine density. Dendritic spine density has been found to strongly correlate to the degree of dementia for patients with AD. Specifically,the research showed that AD brain samples had a 47% decrease in spine density when compared to a control (Shankar et al., 2008). The researchers localized various receptors, includingN-methyl-D-aspartate receptors (NMDAR), metabotropic glutamate receptors (mGluR), and nicotinic acetylcholine receptors(nAChR) as among those impacted by Aβ and negatively affecting

synaptic plasticity in diseased brains. Studies confirmed that the introduction of soluble Aβ dimers into rats interrupted their ability to recall learned behaviors, further implicating Aβ as the primary culprit responsible for impaired synapse remodeling and plasticity (Shankar et al., 2008).
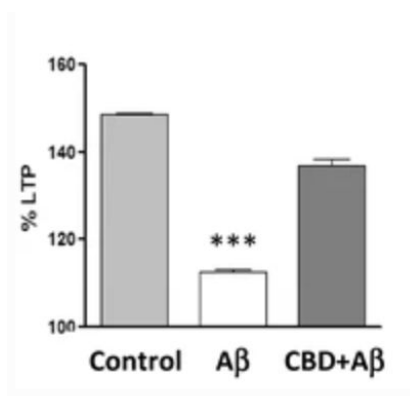

Fig. 4: In a research study conducted by Hughes and Herron, effects of long-term potentiation (LTP) of CBD was investigated in the hippocampus. Treatment of slices with CBD attenuated the Aβ-mediated deficit in LTP. LTP was significantly attenuated in the presence of Aβ1–42 (500nM) (112.6±2.9%;n=23) compared to control (148.6±2.4%; n=59; AandC). B Application of CBD to slices 30 minutes prior to addition of Aβ attenuated theAβ-mediated deficit in LTP (136.9±5.9%; n=15, p≤0.001) compared to Aβ alone. LTP in the presence of CBD and Aβ was similar to control (p>0.05).
Citation: Cannabidiol reverses deficits in hippocampal LTP in a model of Alzheimer's disease. (n.d.). NeurochemicalResearch. https://link.springer.com/article/10.1007/s11064-018-2513-z

Synaptic plasticity can be modulated through the interaction between CBD and the endocannabinoid system. While the exact mechanism must still be elucidated, it is clear that CBD influences and interacts with endocannabinoid receptors. Various studies have arrived at different conclusions on the actions of CBD, some stating that there is no affinity between CBD and the CB1/CB2 receptors (McPartland, 2007). Others state CBD binds as a weak antagonist (Thomas, 2007), and yet more that claim CBD functions as a negative allosteric modulator for the endocannabinoids 2-AG and delta-9-THC (Hughes et al., 2019). CBD enhances neuroprotection by different signal transduction pathways that are controlled indirectly by cannabinoid receptors (Li et al., 2020). Similarly, CBD treatment enhanced synaptic transmission in mouse models, most likely acting in conjunction with CB1 and CB2 receptors to decrease neurotoxicity and cell death that was the result of Aβ deposits. CBD has shown its capability in reversing and preventing cognitive damage due to AD (Watt et al., 2017) and precluding the suppression of long-term

potentiation (Hughes et al., 2019). Therefore,modulation of the agonists and antagonists which bind to CB1 and CB2 receptors, such as CBD, has an effect on synaptic plasticity in the brain. AD-induced dysfunction of the endocannabinoid receptors negatively influences synaptic plasticity.
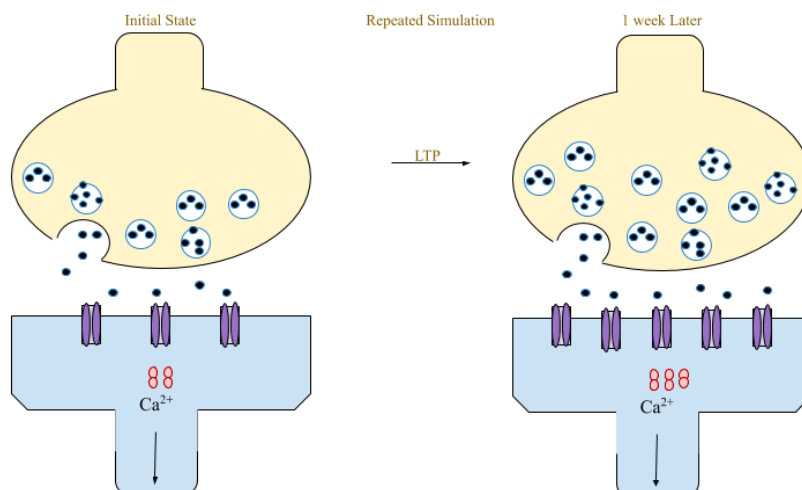

Fig. 5: Illustration of synaptic plasticity and long-term potentiation. After repeated simulation and long-term potentiation, there is an increase in the number of neurotransmitters in the presynaptic neuron and an increase in the number of receptors in the postsynaptic neuron. This results in a stronger response.

Pathology of the cholinergic system is also associated with AD. Many cholinergic pathways are commonly found to be damaged or dysfunctional in those who suffer from AD, impairing synaptic plasticity. AD has been correlated with decreased cholinergic transmission, especially in the hippocampus where new memories are formed. Studies have found 'crosstalk' — signals within one system that produce changes in another system — between the cholinergic signaling and the endocannabinoid signaling systems (Thompson et al., 2020). Past studies specifically investigated this communication between the systems in AD. This research found that α-7 nAChR are of particular concern because they are highly expressed in the hippocampus and play a significant role in the development of memory and learning abilities (Thompson et al., 2020). Elevated levels of α-7 nAChR have been found to disrupt normal signaling and negatively impact synaptic plasticity (Thompson et al., 2020). Interestingly, Aβ deposition also seems to increase in α-7 nAChR rich regions (Thompson et al., 2020). While their research did not corroborate a definite 'cross-talk' between the ECS and α-7 nAChR specifically, they did find that α-5 nAChR and α-6 nAChR correlated to THC addiction and withdrawal (Thompson et al., 2020), which are known to involve the pathways of the

ECS. The researchers concluded that the ECS seemingly plays a role in cholinergic signaling, although not specific to the α-7 nAChR.This research suggests that indirect crosstalk between the endocannabinoid and cholinergic systems and its modulation may be a way to improve cholinergic signaling and repair synaptic plasticity that is damaged as a result of AD (Thompson et al., 2020).

III. Receptor Agonists
A. Inhibitory Activity by Receptor Agonists

Many studies have investigated the variety of proposed therapeutic treatments mediated by endocannabinoid receptor agonists, specifically the inhibitory activity of receptor agonists in Alzheimer's disease. One of the primary focuses of cannabinoid receptor agonists is their ability to inhibit neuroinflammation, a specific characteristic signaled by the dysfunction of microglia. Cannabinoid agonists increase endocannabinoid availability, which allows activation of receptor agonists to prevent Aβ-induced cognitive deficits (Martín-Moreno et al., 2011). The synthetic cannabinoid, WIN 5512-2, inhibits neuroinflammation induced by Aβ through the CB1 and CB2 receptors. In primary cultures, a laboratory procedure in which cell extracts are grown under controlled conditions, WIN5512-2's inflammatory response specifically prevented cell death in astrocytes — specialized glial cells that aid in a variety of neurological functions such as water homeostasis and oxidative stress defense (Sofroniew, 2010). Mice studies have effectively demonstrated this by reducing the levels of the proinflammatory molecules interleukin-1 beta (IL-1beta), TNF-alpha, COX-2, and inducible nitric oxide synthase (iNOS) (Aguirre-Rueda, 2015) within their system. Additionally, two proinflammatory cytokines, TNF-alpha and IL-6, were measured in the cerebral cortex of mice treated with CBD and WIN5512-2 (Martín-Moreno et al., 2011). The initial 6-fold increase of IL-6 from the Aβ was decreased by both cannabinoid agonists, and WIN5512-2 partially reduced TNF-alpha gene expression (Martín-Moreno et al., 2011). In a similar experiment, Aβ injected mice subject to subchronic administration of WIN5512-2 or CBD showed better performance in the Morris water maze task, an experiment in which a mouse is placed within a circular pool of water and must escape from the water onto a hidden platform whose location is discerned through the use of spatial memory (Martín-Moreno et al., 2011).

CBD is a CB2 receptor agonist that also prevents Aβ neurodegeneration by reducing microglial activation responsible for the release of toxic molecules like nitric oxide (NO) and proinflammatory cytokines (Martín-Moreno et al., 2011). By inhibiting calcium responses in glial cells, cannabinoid agonists are similarly able to prevent microglial activation.
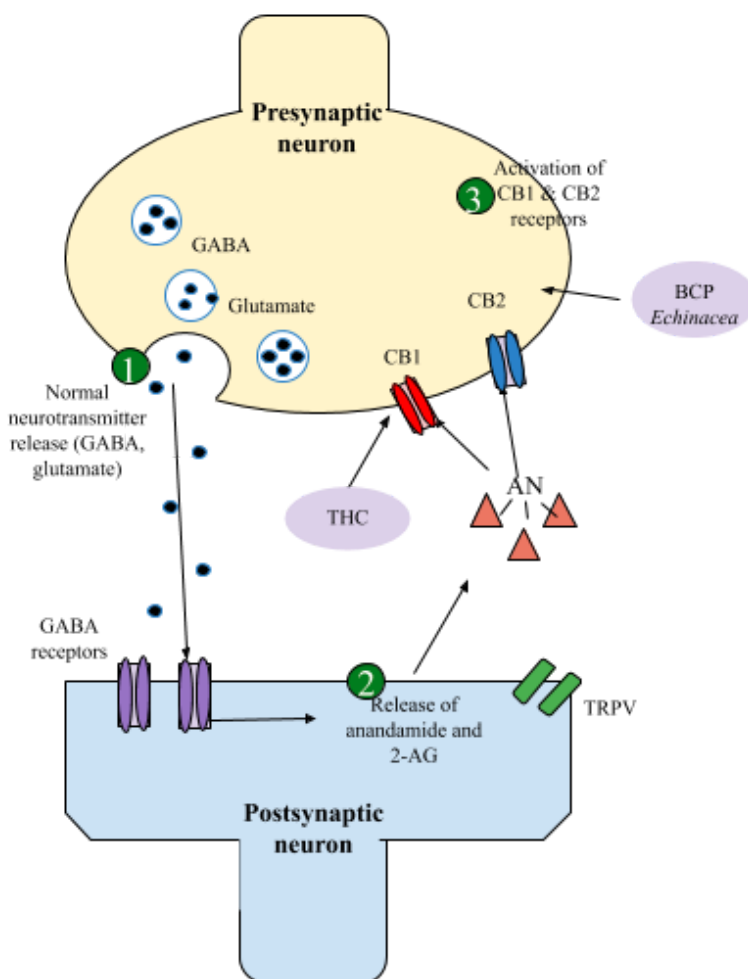
Fig. 6: Illustration of inhibitory activity by receptor agonists.

Additionally, CB1 receptor activation causes migration of the N13 (nitrogen-13) microglial cells and primary microglial cells (Martín-Morenoetal., 2011). Migration is a cellular mechanism that ultimately allows for the removal of deposit Aβ protein. In a study conducted in Aβ injected mice, those that did not receive the CBD treatment of WIN5512-2 showed significant reduction in their ability to reach a hidden platform (Martín-Moreno et al., 2011). Another strength

pertaining to the inhibitory activity of receptor agonists is the suppression of Aβ plaque buildup. Aspreviously mentioned, AD has been largely characterized by its substantial aggregation of beta amyloid peptide clusters; thus, focusing further investigation towards the wingless-related integration site (Wnt) pathway as it becomes largely impacted due to aforementioned clusters (Esposito, 2006). Normally, Wnt activation triggers the "...inhibition of glycogen synthase kinase-3beta (GSK-3β), a multifunctional phosphorylating serine/threonine kinase and relative accumulation of [unphosphorylated] β-catenin in the cytoplasm" (Esposito, 2006). This Aggregation allows for the expression of genes that code for homeostasis and neuronal survival (Esposito, 2006). Within neurons exposed to Aβ peptides, however, GSK-3ß is activated through phosphorylation; therefore, Wnt signaling experienced significant reduction (Esposito, 2006). Furthermore, these phosphorylated GSK-3ß lead to the neurofibrillary tangles and significant tau protein hyperphosphorylation witnessed in the brains of patients with AD (Esposito, 2006). CBD serves as a rescue of the Wnt signaling pathway as it promptly reduces the accumulation of phosphorylated GSK-3ß, consequently inhibiting the rise of neurofibrillary tangles and tau protein hyperphosphorylation (Esposito, 2006). Furthermore, CBD indirectly inhibits neural apoptosis due to its rescue of the Wnt signaling pathway (Esposito, 2006).

Δ9-Tetrahydrocannabinol (THC) is another viable receptor agonist in combating the advancement of Alzheimer's disease via competitive inhibition. THC, the active component of marijuana, competitively inhibits acetylcholinesterase (AChE) in addition to preventing acetylcholinesterase-induced Aβ plaque buildup (Eubanks, 2006). One study, conducted by Eubanks et al., demonstrated through computational modeling of THC-AChE interaction that THC binds to AChE in a critical region involved in amyloid synthesis, ultimately serving an inhibitory function (Eubanks, 2006). THC and analogous compounds were found to augment acetylcholine levels by inhibiting Aβ aggregation and reducing neurotransmitter degradation(Eubanks, 2006).This study proposes a possible mechanism by which THC molecules directly impact the pathogenesis of Alzheimer's disease (Eubanks, 2006). Through focusing on the cholinergic system, THC was found to be a promising receptor agonist as its potential AChE inhibition might be implicated in AD treatment (Campbell et al., 2007). Multiple drugs — donepezil, edrophonium, galantamine, etc. — inhibit AChE for the purpose of increasing acetylcholine (ACh) levels in the synapse and increasing cholinergic

transmission. In an investigation of cannabinoids as potential inhibitors of AChE, Δ-9-THC was found to be a competitive inhibitor for AChE, which has the added effect of inhibiting Aβaggregation (AChE has been found to accelerate the aggregation of Aβpeptides into complexes, increasing their neurotoxicity) (Campbell et al., 2007).

Nonetheless, more research is needed in order to understand the efficacies of CBD and THC in the treatment of Alzheimer's disease. As therapeutic treatments for Alzheimer's disease continue to be explored, CBD is a promising candidate. A handful of studies show that THC is a more effective inhibitor than CBD in regards to amyloid plaque buildup. While the general consensus of the present community is built upon the effects of cannabidiol, the efficacy of Δ9-Tetrahydrocannabinol should also be considered as a viable method of treatment for Alzheimer's. It is nearly impossible to ignore the therapeutic potential of receptor agonists within the endocannabinoid system against the advancement of Alzheimer's Disease.

B. Synthetic Cannabinoid Receptor Agonists

Synthetic cannabinoid receptor agonists target the degenerative effects of Alzheimer's through the CB1 and CB2 receptors of the ECS. These receptor agonists can reduce the density of neuritic plaques by inhibiting acetylcholinesterase activity, or increasing expression of neprilysin, an enzyme in the Aβ degradation cascade (Fernández-Ruiz et al., 2015). The syntheticcannabinoids also function as a treatment that blocks the activation of the microglial clustercaused by the deposition of Aβ at the senile plaque. This deposition is typically responsible for the prolonged damaging effects of the disease, and the presence of cannabinoids alleviates neurodegeneration (Ramírez et al., 2005).

Since these potential neuroprotective effects have been discovered, extensive research is being dedicated towards studying the endocannabinoid system. Researchers have already found That dysfunction of CB1 and CB2 receptors and in endocannabinoid signaling plays a specific role in the pathophysiology of AD (Liu et al., 2015). One study investigated the specific benefits that synthetic cannabinoids could have on neuropsychiatric symptoms (NPS) associated with AD. The researchers studied two synthetic analogs of Δ-9-THC, Dronabinol and Nabilone, and their interactions with receptors in the ECS. Nabilone and Dronabinol were

found to be more potent analogs to THC that act on both CB1 and CB2 receptors and reduced overall agitation in AD patients (Liu et al., 2015). Participants receiving Nabilone experienced no adverse side effects. In the Dronabinol study, the researchers measured disturbed behavior in study participants using the Cohen-Mansfield Agitation Inventory (CMAI), a scale which systematically assesses patient agitation. They found that with administration of the synthetic cannabinoid, disturbed behavior dropped among the participants over the course of the 6-week test period (Liu et al., 2015). Stimulation of the CB2 receptor by these synthetic cannabinoids increases the removal of Aβ deposits by enhancing macrophage activity, thus explaining the improvements in NPS seen in study participants. Another studyinvestigating the efficacy of Nabilone as a potential treatment for the NPS of AD similarly found an overall decrease in agitation, and sometimes aggression as well (Ruthirakuhan et al., 2019). The synthetic cannabinoid receptor agonists WIN55,212-2 and arachidonyl-2-chloroethylamide were also found to decrease aggressive behavior associated with AD and reduce tau hyperphosphorylation and the neurofibrillary tangles (Liu et al., 2015). WIN55,212-2 along with JWH-133 were also found to assist in the removal of Aβ deposits, one of the most common pathophysiology associated with Alzheimer's. WIN55,212-2's ability to stimulate neurogenesis makes it a great contender as a therapeutic agent. Although there are positive outcomes of such drugs on reversing AD-related amnesia, they must be used with caution as there is a risk of exacerbating the neurodegeneration associated with AD (Liu et al., 2015).

Agonists that specifically target CB2 activate responses that reduce both inflammatory and Aβ plaque buildup. The CB2 agonist JWH-015 was used to further investigate the function of CB2 with tests done on AD human tissue. These tests demonstrated that JWH-015 was able to reduce plaque buildup dramatically in THP-1 macrophage cells (Tolón et al., 2009). However, the U373 astrocytoma cells, which are from the astrocytoma cancer cell line in the human brain, were immune to the effects (Tolónet al., 2009). Thus, the CB2 agonist induced plaque removal was only effective in certain cells (the human macrophages). This finding shows some limits of CB2 agonist use in alleviating symptoms, while narrowing down a line of cells to focus on. CB2 receptors' primary role in plaque removal, with in vitro injection of the antagonist SR144528, showed partial reversal of the JWH-015 Aβ removal (Tolón et al., 2009), which highlights other factors at play in plaque reduction. These results indicate that JWH-015 can be used

as a specific target treatment for AD, however it is not the only option. CB2 receptor agonists have a preventative function in suppressing neuroinflammation (Ehrhart et al., 2005). Irregularly stimulated CD40 receptor expression by the signaling pathway IFN-γ is prominent in patients with AD and is known to increase inflammation (Ehrhart et al., 2005). CD40 induction produces inflammatory cytokines and is correlated with the inflammation and Aβ peptide increase in AD. Using the JWH-015 agonists, stimulation of CB2 diminishes IFN-γ-induced CD40 expression in microglial cells (Ehrhart et al., 2005). This occurs by the intervention of the JAK/STAT1pathway (Ehrhart et al., 2005), which is a pathway that is involved with immune system response and ultimately decreases IFN-γ-induced CD40 expression. There is further evidence to show thatCB2 agonists have the potential to inhibit inflammation. JWH-133, a CB2 agonist, was found to rescue spatial memory deficits in rats injected with Okadaic acid (OKA), which induces spatial memory impairment and neurodegeneration (Çakır et al., 2019). Rats injected with OKA were found to have higher numbers of degenerative neurons in the cortex and hippocampus, but the addition of JWH-133 ameliorated this damage (Çakır et al., 2019). JWH-133 application was found to reduce the level of immunoreactivity caused by OKA. Caspase-3, Aβ, and IL-1β immunoreactivity were reduced in both the hippocampus and the cortex, while TNF-αimmunoreactivity was reduced in only the hippocampus (Çakır et al., 2019).

1-((3-benzyl-3-methyl-2,3-dihydro-1-benzofuran-6-yl) carbonyl) piperidine (MDA7), a highly-selective CB2 agonist, was found to have a neuroprotective effect in in vivo and in vitro models (Wu et al., 2012). MDA7 administration in Aβ1–4-induced mice was found to lower immunoreactivity in the hippocampus (Wu et al., 2012). The Morris water maze test (Wu et al., 2012) showed MDA7 rescued amyloid fibril-impaired performance. While progress has been made in the development of drugs targeting these receptors, the ones currently available to patients come with many unwanted side effects such as nausea, vomiting, and weight loss (Wattet al., 2017). While there are bound to be side effects to most drugs, synthetic cannabinoids offer the added benefit of producing effects similar to that which natural Cannabis derivatives cause but without the psychoactive side effects (Campbell et al., 2007). Due to the complexity of AD and the pathology of many different pathways involved, it is unlikely that just one drug will suffice to treat the progression of the disease. Rather,

it is more likely that multiple drugs will be needed to treat the multifaceted symptoms of Alzheimer's.

IV. Potential and Effective Therapies
A. Natural Therapies

Cannabinoids possess great potential as effective natural therapies for AD. Previous studies indicate that Cannabis use diminishes symptoms associated with AD (Suryadevara et al., 2017). When administered in patients with similar neurodegenerative conditions, Cannabis use is shown to decrease pain and spasticity in people with multiple sclerosis, decrease tremor, rigidity, and pain in people with Parkinson's disease, and improve the quality of life of amyotrophic lateral sclerosis (ALS) patients by improving appetite and decreasing pain and spasticity (Suryadevara et al., 2017). Interestingly, a large portion of the negative side effects from Cannabis administration in these diseases is absent in Alzheimer's patients (Suryadevara et al., 2017). Cannabis has been used to alleviate pain and muscular contractions to target the inflamed pathways of the brain in Alzheimer's patients. The perception of pain is atypical in that Alzheimer's patients are more prone to oxidative stress, which is an imbalance between free radicals and the body's ability to detoxify them. However, studies demonstrate a positive relationship between stress reduction in dementia and medical Cannabisuse (Aso et al., 2014). The anti-inflammatory and anti-neurotoxicity properties of cannabinoids help mediate the neuroinflammation caused by microglia activation, which is characteristic of chronic pain in Alzheimer's patients. In addition, further studies have shown that with the use of cannabinoids, Alzheimer's patients have experienced a decrease in altered cognitive ability (Aso et al., 2014). Research indicates that a "coadministration of CBD and Δ9-THC" is necessary in order to deliver the beneficial elements of Cannabiswhile attempting to reduce certain side effects of Δ9-THC in Alzheimer'spatients (Giacoppo et al., 2014). CBD and THC, natural components in cannabinoids, provide encouraging results for possible use in Alzheimer's patients. The phytocannabinoid component of Cannabis, a naturally occurring component found in the trichomes of this plant, is seen to be particularly beneficial in the treatment of Alzheimer's Disease as it lacks psychoactive properties and does not risk further cognitive impairment damage in Alzheimer's patients (Karlet al., 2017). In fact, Cannabis can can actually help restore cognitive dysfunctions characteristic of Alzheimer's disease (Uddin et al., 2020). Cannabis is a promising agent with numerous

therapeutic properties that hinder the progression of AD, leading to the investigation of cannabidiol (CBD) therapies. Current CBD therapies are seen to bring "very modest symptomatic relief" (Karl et al., 2017). CBD treatment is described as being a preventative, multimodal drug strategy targeting the wide variety of symptoms, making it a viable candidate for AD therapy (Karl et al., 2017).

V. Conclusion

The features of AD, which consist of inflammation (Atakan, 2012), amyloid-beta plaque buildup (Farkhondehet al., 2020), and neurofibrillary tangles (Hall et al., 2001; Nelson et al.,2012), lead to life-altering cognitive deficits and other extensive effects that impact a significant population of individuals. It is one of the most heavily researched diseases, yet there is still no method to stop its progression. Therefore, the injection of cannabinoids provides one promising revenue for scientists to counter the damage. The connection between AD and cannabinoids has been made apparent through many recent studies. Investigations into the efficacy of the ECS as well as natural and synthetic cannabinoids have developed in regards to the treatment and management of AD and its varying pathologies. Cannabinoid agonists have presented researchers with neuroprotective qualities as well as the ability to manage the chronic psychiatric pathology associated with AD. This is due to the inherent physiology of the endocannabinoid system. ECS receptors exist both in the brain and parts of the immune system pathways, as a result, controlling its function through cannabinoid agonists and ECS ligands can serve both as a neuromodulator and an immunomodulator. Therapeutic use of the ECS and cannabinoids in relation to AD include elevated activation of endocannabinoid receptors to bolster neurogenesis and thus reduce the neurodegenerative effects of AD (Fagan & Campbell, 2014). This process occurs through the stimulation of CB1 receptors by the endocannabinoid signaling molecules and external agonists. CB2 receptors are mainly targeted for their anti-inflammation properties (Tolón et al., 2009); their modulation using receptor agonists — such as JWH-015 (Tolón et al., 2009) and JWH-133 (Çakır et al., 2019) — indicates a reduction of proinflammatory molecules,which block proper neurofunction, that are normally present in AD. Endocannabinoid-specific agonists also inhibit the effects of AD by blocking harmful processes in the brain; these processes are microglia activation (Martín-Moreno et al., 2011), neurofibrillary tangles, and tau protein phosphorylation (Esposito, 2006). Experimentation with the

synthetic agonist has been seen to further suppress symptoms due to their structural similarity to the natural cannabinoids and have even stronger receptor activation. Mice study results identify the synthetic agonists according to what they prevent in the AD injured brain: WIN55,212-2 is correlated to nerve development (Liu et al., 2015), JWH-133 binds to CB2 to reduce rapid inflammation (Çakır et al., 2019), and Dronabinol and Nabilone treat mostly neuropsychiatric symptoms (Liu et al.,2015). In dealing with the synapse, long term potentiation was regained in tests with mice who had amyloid-beta plaque buildup in combination with CBD dosages (Hughes et al., 2019). As The major finding is the revival of neuron activity, restoration of the cholinergic signaling system alleviates AND effects (Thompson et al., 2020). While commonly used as a relief drug, natural cannabinoids THC and CBD derived from the Cannabis Plant are used in tandem to manage cognitive deficits (Giacoppo et al., 2014). CBD acts as a modulator to THC intoxication and together effectively reduces oxidative stress and inflammation associated with AD (Giacoppo etal., 2014). While more studies and clinical trials are required before making any definitive statements,the associations discovered thus far indicate necessary future research and possible implementations of this form of therapy.

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