# Cannabinoid pharmacology and its therapeutic uses in Alzheimer's disease

**Kadja Luana Chagas Monteiro, Marcone Gomes dos Santos Alcântara, Thiago Mendonça de Aquino, Edeildo Ferreira da Silva-Júnior***

Alzheimer's disease (AD) is a chronic neurodegenerative disease, which is difficult to diagnose in its early stages. It is associated with aging and consists of a decline in cognitive functions, memory, and other mental activities. Some pathophysiological markers are associated with AD progression and worsening, such as the deposition and intracellular accumulation of senile plaques containing amyloid-β (Aβ) peptides, and tau protein hyperphosphorylation, leading to the formation of neurofibrillary tangles. Normally, this process leads to neuronal death and impaired inter-neuronal communication. *Cannabis sativa* is one of the oldest and well-known medicinal plants from the *Cannabaceae* family. More than 500 different compounds have been reported in their composition, in which cannabinoids stand out as compounds pharmacologically relevant for several pathologies (Premoli et al., 2019; Li et al., 2020). In this context, cannabidiol (CBD) is one of the most well-known phytocannabinoid used in the treatment of AD. In general, it presents low-toxicity, poor systemic absorption via oral administration of capsules or aqueous emulsions by humans and animals, and good bioavailability after feeding. Although several studies have highlighted the potential of THC ($\Delta^9$-tetrahydrocannabinol, or $\Delta^9$-THC), CBD targeting AD has been investigated recently. CBD and other cannabinoids are studied toward other psychiatric diseases, such as epilepsy, psychotic disorders, Parkinson's disease, anxiety disorders, and depression. Among its various pharmacological applications, it also demonstrates anticonvulsive, antipsychotic, anti-nausea, anti-inflammatory, and anti-rheumatoid arthritis properties. The endocannabinoid system is an endogenous system responsible for regulating physiological processes by endogenous cannabinoids, such as anandamide (AEA), 2-arachidonylglycerol (2-AG), and 2-arachidonyl glyceryl ether (2-AGE or noladin ether). The endocannabinoid system has two main receptors, CB1, which is present in the central nervous system and is responsible for memory, emotional processing, and appetite regulation; while CB2 is present in the peripheral nervous system and central nervous system, in cells from the immune system, which is responsible for immune responses modulation, such as inflammation. During AD, the endocannabinoid system undergoes some changes, where the progress of the disease may be related to the CB1 levels, in addition to the alteration of the CB2 expression, which starts to be expressed only in microglial cells. Thereafter, it is also observed the decreased AEA levels in cortical areas from the brain, which is related to the loss of cognitive ability. The potential neuroprotective ability of natural cannabinoids, such as CBD and THC, has increased the interest of research groups in studies targeting endocannabinoids. The neuroprotective functions of AEA and noladin ether in Aβ-mediated neurotoxicity have been proven. The AM251, a CB1 receptor antagonist, prevented the protective effects of endocannabinoids. Notwithstanding this fact, an inhibitor of the mitogen-activated protein kinase pathway, PD98059, was also able to inhibit the protective effects of AEA and noladin ether, suggesting a probable role of mitogen-activated protein kinase in Aβ-induced neurodegeneration. The endocannabinoid 2-AG exhibits anti-inflammatory and neuroprotective effects by interacting with the CB1 receptor, which has led to an interest in the exogenous application of 2-AG. Thus, in a culture of Aβ neurodegeneration- and apoptosis-induced was observed significant protection of neurons in the hippocampus. The role of the receptor was assessed by blocking the neuroprotective effect via a selective CB1R antagonist, SR14171A, in contrast to the results observed for the CB2R selective antagonist, SR144528. Moreover, two selective inhibitors of monoacylglycerol lipase, an enzyme responsible for 2-AG hydrolysis, have been used as promising agents. Then, it was expected that monoacylglycerol lipase inhibition could increase 2-AG levels and consequently reduce neurodegeneration and apoptosis. As hypothesized, these effects were noted by the authors and it was also observed that its neuroprotective effects are mediated by 2-AG upregulation (Chen et al., 2011).

Deeming the observed low- or very-low affinities of CBD forwards CB1 and CB2 receptors, the neuroprotective role of cannabinoids has been widely studied. Using a glutamate-induced toxicity model, CBD and THC can antagonize the neurotoxic effects of the neurotransmitter by neutralizing the calcium influx. Somewhat, the antioxidant effects of CBD and other cannabinoids may prevent oxidative damage. Regarding this information, Eposito et al. (2006) demonstrated the effects of CBD on the toxicity induced by Aβ-peptides. The treatment prior to PC12 cell exposure to Aβ-peptides increased cell survival, and led to the reduction of reactive oxygen species, decreasing lipid peroxidation. Additionally, the reduction of the apoptosis process has been observed in different studies. Besides, CBD was reported to inhibit the hyperphosphorylation of tau protein, one of the pathological features observed in AD. The rescue of the Wnt/β-catenin pathway was identified as responsible for the CBD effect (Esposito et al., 2006a). Posteriorly, anti-inflammatory effects related to inhibition of inducible nitric oxide synthase and the production of nitrite Aβ-induced were reported. The effect of CBD was observed along with a reduction in the phosphorylated form of p38 MAP kinase and activation of the nuclear transcription factor-κB. The relationship between the peroxisome proliferator-activated receptor (PPARγ) and AD has also been studied in rat models showing Aβ-induced neurotoxicity. Blocking PPARγ reduced the effects of CBD on reactive gliosis and neuronal damage. There was also a stimulus to the neurogenesis of the hippocampus after exposure to Aβ. These results lead to the conclusion that the effects of CBD were dependent on the selective stimulation of PPARγ (Esposito et al., 2011). Another important pathological hallmark of AD is the glial activation. The neuroprotective function of cannabinoids stands out by preventing this activation. The microglial function was modulated by CBD and other cannabinoid agonists by reducing the intracellular calcium ATP-induced in N13 microglial cells and the primary microglia of rats (Martín-Moreno et al., 2011). Besides, encouraging effects in reducing gliosis and NO (nitric oxide) production was also demonstrated by mixing CBD with THC. This combination also revealed an important role in the phosphorylation of tau protein by reducing the formation of neurofibrillary tangles and free radicals (Casarejos et al., 2013). Recently, CBD has also been shown to down-regulate AD-linked genes, such as genes encoding kinases that regulate tau phosphorylation and Aβ generation. Also, it was revealed the inhibition of GSK3β expression (Libro et al. 2017). Although most of the studies involving cannabinoids are related to CBD, further studies to explain their neuroprotective *in vivo* and *in vitro* mechanisms need to be performed. CBD demonstrates the ability to reduce reactive gliosis and neuroinflammatory response, in addition to neurogenesis promoting. A combination of studies involving CBD and THC demonstrates that CBD could antagonize the psychoactive effects of THC, along with improving therapeutic effects. Promising results are demonstrated in studies involving cognitive deficits, which encourage researches with this cannabinoid.

Neuroprotective effects of THC are also frequently studied, although in some cases their psychotic effects are prominent. In general, THC is well-tolerated in patients with dementia symptoms, the total lack of significant adverse effects allows higher dosages. The active component from

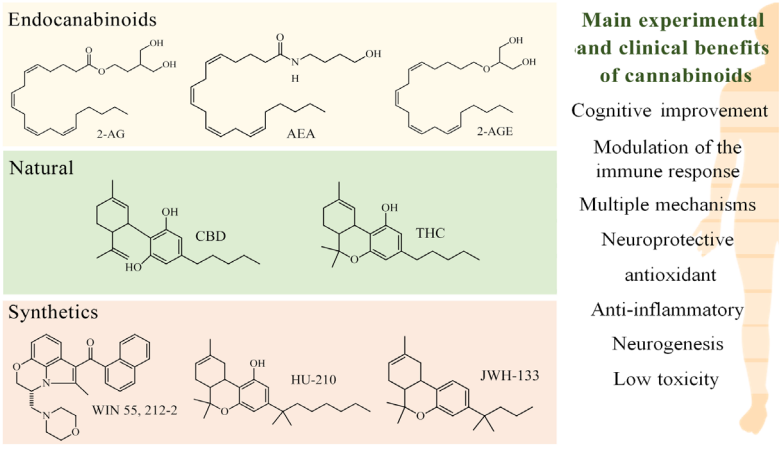


**Figure 1** | **Anti-AD cannabinoids categorized as endogenous, natural, and synthetic, as well as the main activities related to them.**
2-AG: 2-Arachidonylglycerol; 2-AGE: 2-arachidonyl glyceryl ether; AD: Alzheimer's disease; AEA: anandamide; CBD: cannabidiol; THC: $\Delta^9$-tetrahydrocannabinol.

marijuana has been shown to competitively inhibit the enzyme acetylcholinesterase and prevent Aβ-aggregation. This result is interesting since the current anti-AD drugs are acetylcholinesterase and N-methyl D-aspartate inhibitors. It was observed that THC binds to the anionic region from this enzyme, a critical region for amyloidogenesis. Subsequently, it was shown that THC interacts with the Aβ peptide, inhibiting its aggregation. Further, THC promoted the reduction of GSK3β levels (Cao et al., 2014). In parallel, the meaningful emphasis has been given to synthetic agonists of cannabinoid receptors. Based on this, a study described the intracerebroventricular administration of WIN55,212-2. This remarkable study showed the prevention of Aβ-induced microglial activation, improvement in cognitive impairment, and loss of neuronal markers (Ramírez et al., 2005). Considering this information, the cannabinoids HU-210 and JWH-133 blocked indeed Aβ-induced activation of microglial cells. It is important to note that these effects seem to be independent of the antioxidant activity induced by cannabinoids. Glial stimulation has also been studied for WIN 55,212-2 via NO production, important in the tau hyperphosphorylation. Similarly, ACEA (arachidonoyl-2'-chloroethylamide/ N-(2-chloroethyl)-5Z,8Z,11Z,14Z-eicosatetraenamide), WIN 55,212-2 inhibited tau hyperphosphorylation by negative regulation of inducible nitric oxide synthase protein expression and Aβ-stimulated NO production in cells (Esposito et al., 2006a, b). Afterward, WIN 55,212-2 and JWH-133 promoted the reduction of intracellular calcium in N13 microglial cells in an ATP-induced manner (Martín-Moreno et al., 2011). Recently, a study involving WIN 55, 212-2 demonstrated that the increase in neuronal viability after exposure to Aβ was related to the microglial modification in response to the LPS-induced pro-inflammatory mediator (Janefjord et al., 2014).

Considering the extensive potential of natural, endogenous, and synthetic cannabinoids, few studies have been carried out to explore their role in AD (**Figure 1**). The frequent indication that the mechanism related to neuroprotective effects of cannabinoids is associated with their properties as disease-modifying agents further encourages the development of new studies that could assess theirs *in vivo* and *in vitro* activities. Current studies reveal that cannabinoids could exert their effects by different mechanisms. In particular, the modulation of pathways related to the production of endogenous cannabinoids seems to be a promising alternative for the production of new drugs. Finally, benefits associated with the cognitive deficit, social recognition, anxiety, and associative learning should be more explored in order to recognize new and potential effects of anti-AD cannabinoids.

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