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Endocannabinoid-Based Interventions in Alzheimer's Disease: From Basic Mechanisms to Clinical Translation — A Systematic Review

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Abstract. In Alzheimer's disease (AD)—a progressive neurodegenerative disorder featuring cognitive impairment, synaptic loss, and neuroinflammation—the endocannabinoid system (ECS) (including CB1R/CB2R receptors, endogenous ligands AEA/2-AG, and metabolic enzymes FAAH/MAGL) acts as a key modulator of inflammatory processes, synaptic function, and neuronal resilience. Here, we present a systematic review integrating preclinical and clinical studies from the last three years (2023–2026), highlighting the multifaceted roles of the ECS in AD pathology. Both clinical and preclinical studies have identified ECS dysregulation in Alzheimer's disease—specifically, altered CB1R/CB2R expression and disturbed 2-AG/AEA signaling. Importantly, activating CB2R exerts neuroprotective and anti-inflammatory effects by controlling microglial activation, promoting autophagy, and attenuating amyloid-β (Aβ) and tau pathology. Inhibitors of MAGL and FAAH have shown promise in restoring ECS tone and reversing cognitive deficits in AD models. Phytocannabinoids such as CBD, CBG, and β-caryophyllene, as well as synthetic CB2R agonists (e.g., JWH-133), have demonstrated therapeutic potential through pathways involving PPAR-γ, NRF2, BDNF/TrkB, and NLRP3 inflammasome regulation. Clinical studies remain limited but suggest benefits for neuropsychiatric symptoms in AD. Emerging evidence also points to the retina as a potential site for early ECS-based diagnosis. Challenges such as CB1R-mediated psychotropic effects, receptor selectivity, and translational gaps remain. This review synthesizes multi-level (molecular, cellular, and systems) evidence to call for continued pursuit of ECS-targeted therapies, which represent a hopeful tactic for addressing AD.

Keywords: Endocannabinoid system; Alzheimer's disease; Neuroinflammation; CB2 receptor; Microglia; Phytocannabinoids; Cannabidiol; MAGL inhibitor; Amyloid-beta; Clinical translation.

1. Introduction

AD is a progressive, irreversible neurodegenerative disorder and the top dementia cause, featuring cognitive, memory, and behavioral decline [1]. AD hallmarks include extracellular Aβ plaques, intracellular tau tangles, synaptic dysfunction, and chronic neuroinflammation [2]. Decades of research have produced mainly symptomatic therapies with minimal disease-modifying effects, necessitating novel approaches [3]. The endocannabinoid system (ECS) critically modulates neuroinflammation, synaptic remodeling, and neuronal survival, marking it an attractive AD target [4]. ECS: CB1R/CB2R, endocannabinoids (AEA, 2-AG), and enzymes (FAAH, MAGL); all dysregulated in AD [5][6]. CB2R activation provides anti-inflammatory and neuroprotective benefits via microglial regulation and autophagy promotion [7][8]. Moreover, phytocannabinoids and synthetic cannabinoid receptor ligands have demonstrated therapeutic potential in preclinical studies [9] [10]. This systematic review synthesizes evidence from the past 3 years (Feb. 2023–Feb. 2026) to outline ECS in AD, assess translational prospects of ECS-targeted therapies, and identify challenges and future directions [11][12].

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2. Alzheimer's disease and the endogenous cannabinoid system

Alzheimer's disease manifests progressive neuronal-synaptic loss, brain atrophy, and cognitive decline. Microglia-mediated neuroinflammation has been confirmed as a key driver of AD progression. ECS and CBR expression is dysregulated in various neurodegenerative diseases, including AD. Modulating CBRs can reduce abnormal protein deposition and exert neuroprotection, pointing to natural/synthetic CBR ligands for proteinopathies [13].

CB1 receptors regulate functions from homeostasis to cognition, and recent work shows astrocytes, mediators of synaptic plasticity, are critical for cognitive learning. Most CB1 receptors are neuronal, yet cannabinoids directly regulate astrocytic energy metabolism and neuroprotection. Through tripartite synapses, astrocytes engage neurons, becoming key for synaptic plasticity and thus influencing cognition [14].

The ECS critically regulates neuron-glia communication, neurotransmission, neuroinflammation, and behavioral changes across health and disease. In addition to core dementia symptoms, AD is often accompanied by neuropsychiatric symptoms (NPS), including anxiety, agitation, apathy, hallucinations, and sleep disturbances, with an NPS incidence rate as high as 97%. Preclinical/clinical evidence positions the ECS as an NPS pathological driver and therapeutic target [15].

Owing to limited efficacy and adverse effects of current treatments, alternatives are crucial. Most cannabinoids (Δ9-THC, CBD, JWH-133, WIN55,212-2) improve memory/cognition/behavior, likely via CB1R antioxidant (e.g., BDNF/TrkB/Akt) and CB2R immunomodulatory (TLR4/NF-κB p65) pathways. Hybrid molecules combining anticholinesterase and cannabinoid features could better counter cholinergic deficits in AD, strongly supporting their clinical trial advancement [16].

2-Arachidonoylglycerol (2-AG) is the brain's predominant endocannabinoid. It regulates synaptic plasticity via CB1/CB2 and represents an endogenous termination signal that inhibits neuroinflammation and maintains brain homeostasis. Monoacylglycerol(MAGL), the main 2-AG–degrading enzyme, hydrolyzes it to arachidonic acid (AA), which then generates proinflammatory prostaglandins. Pharmacological or genetic MAGL inhibition raises 2-AG levels and lowers AA production, thereby reducing neuroinflammation, neuropathology, as well as synaptic/cognitive deficits in AD animal models. Hence, MAGL is viewed as a target for treating neurodegenerative diseases [17].

The role of neuroinflammation in amyloid toxicity in AD is further clarified by Long C et al., who found microglial activation and ensuing inflammation critically contribute to AD pathogenesis. IL-6 and TNF-α promote amyloid buildup and cellular injury. Additionally, Moreover, enhanced BBB leakage lets peripheral inflammation worsen CNS inflammation and Aβ deposition [18].

AD pathogenesis also features RNA splicing dysregulation. Our prior transcriptomic study showed that CBNR, a phytocannabinoid, protects differentiated SH-SY5Y cells from Aβ-induced viability loss and alters mRNA splicing gene expression after Aβ or CBNR pre-treatment [19]. alpha/beta-Hydrolase domain containing 6

Synaptic dysfunction critically drives AD pathogenesis. Xue Z et al. reported AAV-mediated alpha/beta-Hydrolase domain containing 6(ABHD6) knockdown in hippocampal neurons of APP/PS1 mice ameliorated synaptic and memory deficits, sparing Aβ and neuroinflammation. WWL70, an ABHD6-selective inhibitor, given intraperitoneally, also ameliorated synaptic/memory deficits in AD mice, likely via endogenous cannabinoid signaling [20].

Current acetylcholinesterase (AChE) inhibitors only alleviate symptoms and are associated with significant side effects. Drugs targeting type-2 cannabinoid receptors (CB2R) have been shown to effectively counteract neuroinflammation, and novel dual-acting hybrids targeting both CB2R and cholinesterase activity displays in vitro neuroprotection and in vivo cognitive improvement [21].

3. Alzheimer's ECS: Mechanisms, Therapies, and New Diagnostic Views

The cannabinoid signaling system is involved in various pathological processes through CB1 and CB2 receptors. CB1 primarily located on nerve terminals, linked to CNS disorders like AD; CB2 mainly expressed on immune cells, mediating immune/inflammatory responses. Clinical studies have demonstrated that CB receptors are important targets in drug development, with both agonists and antagonists showing therapeutic potential[22].

Research has highlighted the cell-specific importance of ECS enzymes in AD pathology. Joe R et al. found that APP transgenic (TG) mice with astrocyte-specific MAGL deletion (TG-aKO), but not neuron-specific deletion (TG-nKO), exhibited significantly reduced Aβ pathology, neurodegeneration, and neuroinflammation, along with preserved synaptic structure and function and improved cognitive performance. AAV-mediated silencing of astrocytic MAGL recapitulated these protective effects, whereas MAGL overexpression exacerbated neuropathology and accelerated synaptic and cognitive decline. Transcriptomic analysis revealed that dysregulated synapse-, inflammation-, and AD-related gene expression profiles were reversed in TG-aKO mice. Astrocytic MAGL was elevated in AD patients and TG mice, marking it a drug target [23]. This astrocyte-specific mechanism aligns with the broader understanding that glial cells are central to ECS dysfunction in AD.

Beyond AD, studies in other neurodegenerative models provide insights into ECS function. Di Franco N et al. observed lower CB1R in both human HD samples and HD mouse models, accompanied by alterations in synaptic structure and memory impairments. Restoring CB1R in hippocampal GABAergic interneurons via viral vectors sufficed to rescue memory deficits in HD mice, demonstrating the critical role of cell-specific CB1R signaling in cognitive function [24].

Phytocannabinoids like β-caryophyllene (BCP), cannabichromene (CBC), cannabigerol (CBG), cannabidiol (CBD), and cannabinol (CBN) possess unique abilities to modulate the ECS. AD-related ECS activation protects neurons via complex molecular cascades modulating circuitry. CB1/CB2 modulation lowers proinflammatory cytokines (IL-2, IL-6) and microglial activation, whereas natural cannabinoid enzyme inhibitors block NLRP3 inflammasome, yielding significant neuroprotection [25].

CBD, as a non-psychotropic cannabinoid, has demonstrated therapeutic potential in AD. However, its specific regulatory mechanisms on Aβ pathology and its interaction with the ECS require further investigation. In a C. elegans model, CBD alleviates pharyngeal dysfunction and attenuates weight loss through the regulation of faah-1, suggesting a conserved mechanism of action [26].

The retina is increasingly seen as a "brain window" for AD pathology. Tisi A's group noted that before the formation of hippocampal Aβ plaques and retinal degeneration, AD-like mice already exhibited gliosis and ECS dysregulation in the retina. CB2 expression was positively correlated with FAAH, DAGLα/β, and APP, while MAGL was negatively correlated with APP. UPLC-MS/MS analysis detected decreased 2-AG levels in Tg2576 retina. suggesting that retinal ECS changes may serve as an early diagnostic biomarker for AD [27].

4. Neuroprotective Mechanisms Mediated by Cannabinoids

Targeting CB2R has drawn attention for attenuating neuroinflammation, regulating mitochondrial function, and providing neurotrophic support, without CB1R-related psychotropic side effects [28]. CB2 receptors are overexpressed during inflammation, and CB2 agonists demonstrate potent anti-inflammatory effects, positioning them as therapeutic candidates for AD and related neurological disorders [29].

The neuroprotective effects of cannabinoids are mediated through complex receptor interactions. Navarro G et al. showed CB1R directly interacts with NMDAR's N1 subunit, forming receptor complexes. Bidirectional negative crosstalk: NMDA blunted CB1R cAMP inhibition; CB1R activation reduced NMDA-evoked Ca^{2+} influx and MAPK activation. These CB1R-N1 complexes

were present in neurons and microglia, with expression upregulated following Aβ1-42 treatment, suggesting a role in modulating excitotoxicity in AD [30].

Kim J et al. investigated whether cannabidiolic/tetrahydrocannabinolic acids (CBDA/THCA) can alleviate AD-like pathological features. In an Aβ1-42-treated mouse model, Treatment with CBDA/THCA lowered hippocampal Aβ/p-tau and improved cognitive performance. In primary neurons, both compounds decreased Aβ and p-tau levels, alleviated calcium dyshomeostasis, and exerted neuroprotective effects [31].

The non-psychoactive cannabinoid CBD shows antioxidant, anti-inflammatory, and neuroprotective actions in neurodegenerative diseases by inhibiting protein aggregation, scavenging radicals, and reducing neuroinflammation, making it a promising candidate for AD and Parkinson's [32]. CBD also defended mouse hippocampal neurons against Aβ toxicity, boosting cell viability while lowering lipid peroxidation and oxidative stress [33]. Furthermore, CBD's neuroprotection may involve PPAR modulation; these ligand-activated nuclear receptors suppress NF-κB expression, thereby reducing pro-inflammatory cytokine production [34].

Environmental factors can also influence ECS function. Rodríguez-Pozo M et al. found that prenatal ethanol exposure increases hippocampal astrogliosis and inflammatory responses in newborn offspring mice, accompanied by downregulated cannabinoid receptors (Cnr1 and Gpr55). This work shows that GPR55/PEA signaling in hippocampal astrocytes is influenced by maternal ethanol exposure, potentially increasing vulnerability to AD pathology [35].

5. Preclinical Evidence: Effects in AD Models

Preclinical work consistently shows ECS modulation's therapeutic promise in AD models. Zhang T et al. showed CB2R deficiency worsens cognitive impairment in AD models. Within the prefrontal cortex, microglia in CB2R-null mice exhibited enhanced immunoreactivity and altered morphology, while CB2R agonist treatment reversed this phenotypic transformation. Loss of CB2R increased pro-inflammatory cytokines and soluble Aβ40 but spared plaque deposition, suggesting CB2R modulates Aβ toxicity, not aggregation [36].

He Q et al. identified LINGO-1 modulation of CB1R signaling. Hippocampal LINGO-1 overexpression in young mice impaired spatial learning/memory and lowered CB1R protein, whereas silencing it in AD model mice reversed these effects. LINGO-1 competitively inhibited CB1R, and antagonizing LINGO-1 reversed the effects of CB1R blockade, notably reducing doublecortin, TrkB, and phosphorylated TrkB protein levels [37].

Dar NJ's group reported CBN enhanced spatial learning/memory, with greater effects in female mice. Cognitive improvements paired with sex-specific metabolic changes: increased O_2/energy use. CBN modulated MFN2/DRP1, key mitochondrial dynamics regulators, upregulated markers of mitochondrial biogenesis (TFAM, TOM20), and upregulated synaptic proteins mediating vesicle trafficking and postsynaptic signaling [38].

Dysfunctional microglia promote AD pathogenesis via proinflammatory factors including nitric oxide. Scipioni L et al. reported Aβ-exposed microglia produced 2-fold more 2-AG than normal microglia, with corresponding changes in the expression of its synthetic enzyme DAGLα and degradative enzyme MAGL. Relative to wild-type cells, Tg2576 microglia overexpressed CB2R basally, indicating a proinflammatory state. Upon inflammatory stimulation, Aβ-exposed microglia showed heightened NO production, abolished by pharmacological DAGLα blockade, highlighting the importance of the 2-AG metabolic pathway in microglial activation [39].

Sobue A et al. demonstrated that oral JWH-133 (CB2-selective agonist) ameliorated cognitive impairment in AppNL-G-F/NL-G-F mice without behavioral side effects. JWH-133 reduced reactive astrocyte markers and microglial C1q, and inhibited the expression of p-STAT3 in astrocytes. Activating microglial CB2 alleviates cognitive decline via astrocyte control and beneficial neuroinflammation [40].

6. Clinical Translational Research

6.1. Preclinical Evidence: Multi-target Effects of ECS Modulation in AD Models

The translation of ECS-targeted therapies from bench to bedside is an active area of investigation. Chronic cannabinoid receptor ligand treatment reduces anxiety and partially restores cognition in animals. Additionally, Reductions occurred in Aβ plaque count/size, cerebral glucose metabolism, and mTOR/CB2 receptor expression [41].

6.1.1. Cell Type Specificity: The Critical Role of Astrocytic CB2R in Neuroinflammation.

While much research has focused on CB2R in microglia, its role in other cell types is also critical. Zhu H et al. showed astrocytic CB2R knockdown worsened motor function in MPTP mice and triggered the NLRP3/Caspase-1/IL-1β pathway. CB2R activation eased motor deficits and reduced astrocytic NLRP3 deposition by raising autophagy and promoting NLRP3 degradation via the autophagy-lysosome pathway [42].

6.1.2. Receptor Network Interactions: Coordinated Regulation of Dopamine, Adenosine, and Cannabinoid Receptors.

The interplay between different receptor systems also offers therapeutic opportunities. Gómez-Acero L et al. found that alterations in the ratios between dopamine D2, adenosine A2A, and CB1Rs strongly associate with sensorimotor and social deficits in APP/PS1 mice. Pharmacological stimulation of A2AR and CB1R attenuated these deficits, marking these receptors as candidate targets to reverse non-cognitive AD symptoms [43].

6.1.3. Activation and Enhancement: From Exogenous CB2 Agonists to Endocannabinoid Metabolism Modulation.

Rathod SS et al. investigated the mechanism by which the CB2 agonist β-caryophyllene (BCP) counteracts rotenone-induced neurotoxicity. BCP was found to exert its effects through the GSK-3β/NRF2/HO-1 signaling axis, further supporting the neuroprotective potential of CB2 activation [44].

Enhancing endocannabinoid signaling through enzyme inhibition has also shown promise. Oddi S et al. found that enhancing AEA signaling through genetic deletion or chronic pharmacological FAAH inhibition slowed cognitive decline in AD mouse models, attenuated neuroinflammation, and reduced β-amyloid generation/deposition. This linked to lower BACE1 expression, possibly through CB1R-dependent epigenetic changes [45]. A comprehensive review by Kanwal H et al. summarizes that FAAH/MAGL inhibitors, singly or combined, reverse cognitive deficits, curb Aβ-induced neuroinflammation, oxidative stress & neuron death, slowing AD [46].

6.1.4. Beyond Major Phytocannabinoids: Phytochemical Diversity and Blood-Brain Barrier Penetration.

The therapeutic potential extends beyond the major phytocannabinoids. Cannabis produces over 120 types of phytocannabinoids, along with numerous terpenes and flavonoids that possess phenolic structures and hydrophobic nature, allowing effective the blood-brain barrier crossing. These compounds possess antioxidant, anti-inflammatory, and neuromodulatory actions, positioning them as candidates against neurodegeneration [47].

6.1.5. Sex Specificity: Differential Associations of Endocannabinoid Signaling in Brain Aging.

Sex-specific differences in ECS signaling are also emerging as an important consideration. Vered S et al. identified multiple sex-specific associations for endocannabinoids, with linoleoyl ethanolamide (LEA) levels negatively associated with hippocampal volume in men but positively associated in women. These findings point to circulating eCBs in neuro-injury and sex differences in susceptibility to fast brain aging [48].

6.2. Novel Therapeutic Strategies and Multi-Target Drug Development

Novel therapeutic approaches are also being explored. Rajkumar M's group showed GE/PEG/Mg(OH)2NCs treatment enhanced memory, attenuated cholinergic dysfunction and inflammation, and upregulated GPR55. These nanocomposites exert multi-target neuroprotective effects through GPR55 activation, representing a promising novel therapeutic candidate for AD [49].

Zhang R et al. found that RVD-hemopressin (α) inhibited scopolamine-induced oxidative stress, apoptosis, and lowered synapse-associated proteins in HT22 cells. Mediated by the BDNF/TrkB/Akt pathway and blocked by CBR1 antagonism, these effects indicate RVD is a potential therapy for conditions featuring cholinergic and oxidative stress, such as AD [50].

Given the complex and heterogeneous etiology of AD, researchers are focusing on multi-target drug candidates. Benzimidazole derivatives represent one class of multi-target drug candidates that act on various molecular targets, including CDK5, tau protein, AChE, BACE1, 5-HT4, CB2R, and GABA-A [51].

6.3. Targeting Receptor Heteromers: An Innovative Strategy

Finally, targeting receptor heteromers represents an innovative strategy. Given the extensive interactions reported between the orexin and cannabinoid systems, modulating their crosstalk has become a new research focus. Studies on microglial primary cultures from the APPSw/Ind AD mouse model have found a significant increase in CB2R-OX1R complex expression. OX1R antagonism potentiates CB2R signaling in the cAMP pathway while counteracting the neurotoxic effects of OX1R overactivation. Therefore, CB2R-OX1R heteromer targeting represents a promising AD strategy [52].

7. Perspectives, Future Outlook, and Remarks

This systematic review comprehensively summarizes ECS's multifaceted roles in Alzheimer's disease, highlighting its involvement in neuroinflammation, synaptic dysfunction, and proteinopathy. Although preclinical evidence over the past three years has robustly demonstrated the therapeutic potential of ECS modulation—particularly via CB2R activation and metabolic enzyme inhibition—clinical translation remains in its infancy, with a notable lack of large-scale, randomized controlled trials. The findings underscore the importance of ECS homeostasis in maintaining brain health and offer a compelling rationale for developing ECS-based therapies as disease-modifying strategies for AD. Future research should prioritize the development of highly selective CB2R agonists and MAGL/FAAH inhibitors with favorable safety profiles, alongside exploration of sex-specific ECS signaling and multi-target approaches (e.g., CB2R-OX1R heteromers). Additionally, leveraging the retina as a diagnostic window for early ECS dysfunction and integrating cannabinoids with existing AD therapeutics may open new avenues for early intervention and personalized treatment. Addressing these gaps will be critical to advancing ECS-targeted therapies from bench to bedside.

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