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Neuroprotective Effects and Mechanisms of Cannabinoids in In Vitro Cell Models of Neurodegenerative Diseases: A Scoping Review

NRM Nelumdeniya
nelumdeniya@kdu.ac.lk

General Sir John Kotelawala Defence University

S Sabalingham
University of Brighton

RDN Karunathilaka
General Sir John Kotelawala Defence University

Ranga S Jayakody
University of Sri Jayewardenepura

Systematic Review

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Abstract

Background

Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and multiple sclerosis (MS) collectively affect millions of people worldwide, and none currently has a disease-modifying pharmacotherapy. Natural, semisynthetic, and synthetic cannabinoids have shown neuroprotective activity in preclinical models, but most remain at an early experimental stage, and their mechanisms of action have not been systematically mapped across disease contexts.

Objective

This scoping review maps the preclinical evidence predominantly in vitro, with select studies incorporating in vivo validation on exogenous cannabinoids, including phytocannabinoids, synthetic cannabinoid receptor agonists, and cannabinoid-active phytochemicals (e.g., β-amyrin), and their neuroprotective mechanisms across cellular models of AD, PD, HD, and MS.

Methods

This review followed JBI methodological guidance, and PRISMA-ScR reporting standards, with a protocol prospectively registered on OSF (10.17605/OSF.IO/TAQ9F). PubMed, MEDLINE, CINAHL, PsycINFO, and Web of Science were searched, yielding 8,484 records (2,844 after deduplication). Following two-stage screening in Rayyan, 194 reports were sought for full-text retrieval; 176 were assessed for eligibility, and 26 preclinical studies (2015–2025) met the inclusion criteria.

Results

Most included studies were purely in vitro (n = 18); six combined *in vitro* and *in vivo* methods, and two used *in vitro* and *in silico* or *ex vivo* components. Studies addressed AD (n = 12), PD (n = 8), general neuroinflammation models (n = 3), HD (n = 2), and MS (n = 1). Cannabidiol (CBD) was the most studied compound (n = 9), followed by the synthetic agonists JWH-133 and ACEA (n = 6 combined), THC and its analogues (n = 5), and WIN 55,212-2 (n = 4). Evidence converged on three mechanistic domains: (1) anti-neuroinflammatory signaling in microglia and astrocytes; (2) antioxidant, anti-apoptotic, and mitochondrial pathways; and (3) protein aggregate clearance, autophagy, myelination, and neurotransmitter modulation. Receptor pharmacology spanning canonical CB1R/CB2R signaling, non-canonical receptors (PPARγ, GPR55, A2AR, TRPV1), and receptor heteromerization emerged as a cross-cutting axis linking these domains rather than a fourth, parallel mechanism.

Conclusion

Cannabinoid-mediated neuroprotection in AD, PD, HD and MS cannot be explained by canonical receptor pharmacology alone; formulation effects and off-target, receptor-independent mechanisms account for a substantial share of the reported activity. Priorities for translation include systematic dose-response characterization, development of CNS-penetrating CB2R agonists, and target-deconvolution studies to establish how prevalent receptor-independent mechanisms/ direct molecular are.

1. Introduction

Increase in life expectancy worldwide carries a parallel increase of prevalence of neurodegenerative diseases (NDs) causing socio-economic impact(1) (2) (3). It represents a major health problem related to the human population, being one of the major causes of mortality and disability. Alzheimer’s disease (AD) and Parkinson’s disease (PD) are the commonest NDs, while the other forms include amyotrophic lateral sclerosis (ALS), Huntington’s disease (HD), spinal muscular atrophy, motor neuron diseases, prion diseases, and spinocerebellar ataxia. More than 55 million people have suffered from dementia globally (4), and AD is the most prevalent form. It is predicted that over 150 million individuals worldwide will be personally living with AD, an impending crisis made worse by the absence of cure therapies (5). Its neuropathological hallmarks extracellular Aβ plaques and intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau are intricately linked to chronic neuroinflammation, mitochondrial dysfunction, and oxidative stress. Parkinson's disease (PD), the second most common neurodegenerative disorder, is defined by the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc), α-synuclein aggregation into Lewy bodies, and dopaminergic nigrostriatal pathway disruption. Huntington's disease (HD) is a monogenic autosomal dominant disorder caused by cytosine-adenine-guanine (CAG) triplet expansion in the huntingtin gene, producing cytotoxic mutant huntingtin protein, striatal neurodegeneration, and progressive motor and cognitive impairment. Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS), characterized by immune-mediated destruction of myelin sheaths and progressive axonal loss.

NDs are defined by progressive alterations in neuronal morphology and function that reduce neuronal survival and increase neuronal death, ultimately manifesting as functional and mental impairment (6,7). Chronic neuroinflammation and oxidative stress are the fundamental pathological mechanism driving both onsets and the progression of the NDs (8). However, the aggregated characteristic protein may differ from disease to disease as confirmed via neuropathological evaluation at autopsy (9). Under normal conditions, neuroinflammation serves a protective role: activation and proliferation of B- and T-lymphocytes, neutrophils, macrophages, microglia, and mast cells within the brain and spinal cord clear pathogens such as viruses and bacterial

lipopolysaccharides. However, when this response becomes persistent, it drives sustained activation of microglia and astrocytes, which release neurotoxic cytokines and chemokines. The result is axonal degeneration, synaptic impairment, mitochondria dysfunction, protein degradation and apoptosis.(10)

The endocannabinoid system (ECS) regulates several physiological processes including cognition and analgesia. ECS consists of two primary G-protein-coupled receptors (GPRs) known as cannabinoid receptors 1 and 2 (CB1R and CB2R), two primary ligands/endocannabinoids namely, anandamide (AEA) and 2-arachidonoylglycerol (2AG) (11)(12) (13)and enzymes namely, fatty acid amide hydrolase (FAAH) and monoglyceride lipase (MAGL) that control the release and degradation of AEA and 2AG (14).CB1 receptors are the commonly expressed GPCRs in the CNS, distributed in glutamatergic and dopaminergic neurons, astrocytes, microglia, and oligodendrocytes, and mediate synaptic plasticity, excitotoxicity protection, and neurotransmitter modulation. Brain functions including cognition and memory, emotion, motor control, feeding, and pain perception(15)(16) are regulated by these receptors. CB2 receptors, historically regarded as peripheral immune receptors, are expressed in microglia, astrocytes, and select neuronal populations, with expression markedly upregulated under neuroinflammatory conditions (2)(17)(18)(19) a pattern directly relevant to all four disease contexts in this review. Beyond canonical CB1/CB2 pharmacology, the ECS intersects with several additional receptor systems implicated in neuroprotection: peroxisome proliferator-activated receptor gamma (PPARγ), GPR55, adenosine A2A receptor (A2AR), and transient receptor potential vanilloid 1 (TRPV1) which involved in autophagy regulation. This pharmacological breadth positions the ECS as a uniquely multi-targeted system for addressing the polypathological nature of neurodegeneration.

Since there is no cure against neurodegenerative disorders, the research effort has turned towards the discovery of new compounds that are able to exert a beneficial action against neurodegeneration, protecting neuronal cells, and being able to stop or delay the disease progression. Agents that combine anti-inflammatory and antioxidant activity are especially promising, and several phytochemicals are shown to exert protective action. Among them, cannabinoids derived from *Cannabis sativa* have drawn sustained interest over the past few decades, particularly Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (20). CBD remains the most extensively studied non-psychoactive phytocannabinoid, though cannabigerol (CBG) has also been reported to confer distinct benefits of its own (21).

Despite a growing body of preclinical literature, the existing evidence base is highly heterogeneous with respect to cannabinoid classes studied, receptor subtypes targeted, disease models employed, cellular and molecular mechanisms interrogated, and experimental endpoints used. Prior systematic reviews have focused narrowly on single compounds (CBD in AD) or single diseases (cannabinoids in PD), leaving a comprehensive multi-compound, multi-disease mechanistic mapping absent from the literature. A scoping review is the methodologically appropriate framework because: (1) the aim is to characterize the extent, range, and nature of the evidence rather than to pool effect sizes; (2) the literature spans multiple study designs, cannabinoid classes, and disease contexts; and (3) a prior mapping exercise is needed to identify priority areas before a focused systematic review or meta-analysis is warranted. This review follows the PRISMA extension for Scoping Reviews (PRISMA-ScR) and was guided by the seminal methodological framework for scoping reviews proposed by Arksey and O'Malley (2005), which provides a structured approach to identifying, selecting, charting, and synthesizing evidence from the existing literature(22). In the review; Neuroprotective effects of different cannabinoids, receptor mediated neuroprotective action, cellular and molecular mechanisms, and finally gaps in the current evidence base limit the translational potential of cannabinoids for neurodegenerative disease treatment will be discussed.

2. Methods

This scoping review followed the methodological framework originally proposed by Arksey and O'Malley (22)and further refined by subsequent methodological advancements, including recommendations in accordance with Joanna Briggs Institute (JBI) (23) and the PRISMA Extension for Scoping Reviews (PRISMA-ScR) (24) to enhance the transparency and completeness of reporting. A protocol was developed with a priori outlining the eligibility framework, search strategy, and synthesis and prospectively registered on the Open Science Framework (OSF): DOI: 10.17605/OSF.IO/TAQ9F prior to commencing the review.

The **JBI**-recommended **Population–Concept–Context (PCC)** framework is particularly suited to scoping reviews because it provides a structured approach for identifying relevant studies while ensuring that the review remains comprehensive and aligned with its research objectives. In this review, the **population** comprised **in vitro neural cell models**, including neural cells, microglial cells, astrocytes, oligodendrocytes, and differentiated neuronal cell lines. The **concept** focused on the effects of **exogenous cannabinoid compounds** administered within models of neurodegenerative diseases. These compounds included phytocannabinoids, synthetic cannabinoid receptor agonists and modulators, as well as cannabinoid-active phytochemicals (e.g., β-amyrin). Eligible studies investigated receptor-binding characteristics, intracellular signaling pathways, and neuroprotective or neurorestorative functional outcomes associated with cannabinoid exposure. The context was restricted to preclinical *in vitro* cell culture studies modelling the prespecified neurodegenerative disease contexts of Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and multiple sclerosis (MS). ALS and motor neuron disease terminology was included in the search strategy to maximize retrieval sensitivity, but these terms did not constitute eligibility in the absence of an explicitly established ALS disease context in the study. During full-text screening, generalized LPS-induced neuroinflammation or microglial activation models were identified as mechanistically relevant to the inflammatory component shared across the prespecified neurodegenerative diseases. These studies were therefore retained as a defined supplementary neuroinflammation context rather than classified as disease-specific AD, PD, HD, or MS studies. The use of a cell line or inflammatory model alone was not considered sufficient to assign a study to a specific neurodegenerative disease without an explicitly established disease context.. A publication-year cutoff of 2015 was applied as a pragmatic eligibility criterion to maintain a focused and manageable evidence base aligned with the objectives and scope of the review. This cutoff was not intended to indicate that relevant in vitro research on exogenous cannabinoids and neuroprotection commenced in 2015, as earlier studies have been reported. See Table 1.0 for detailed info.

Table 1.0
PCC Framework followed in the study

PCC Element	Specification
Population	Neural cells, microglial cells, astrocytes, oligodendrocytes, or differentiated neuronal cell lines in vitro. Includes primary cultures and established cell lines (e.g., SH-SY5Y, PC12, BV-2, N9, MC65, HOG16, and other comparable neural/glial lines).
Concept	Exogenous cannabinoid compounds; phytocannabinoids (e.g., CBD, THC, Δ8-THC, THCA, CBDA, CBG), synthetic cannabinoid receptor agonists/modulators (e.g., WIN55,212-2, CP 55,940, JWH-133, ACEA, ZCZ011, GAT211, URB597, JZL184, RO304), and cannabinoid-active phytochemicals (e.g., β-amyrin) administered in the context of neurodegenerative disease modelling. Includes receptor-binding characterization, intracellular signaling cascades, and neuroprotective functional outcomes.
Context	Preclinical settings: *in vitro* cell culture. Disease contexts included AD, PD, HD and MS. In vitro models included disease-relevant cellular/toxin/genetic paradigms; animal models such as cuprizone-induced demyelination and EAE were considered only where they occurred as complementary in vivo components of an otherwise eligible study. Other comparable disease-specific toxin, genetic, or aggregation-based models were included as proxies for inflammatory mechanisms. However, models relevant to other neurological diseases, including ALS, were not automatically classified under those diseases solely on the basis of cell-line identity unless the study explicitly established the relevant disease context. 2015 was selected as a pragmatic publication-year cutoff for this review; earlier relevant in vitro studies may therefore have been excluded; English-language publications only.

Original research articles published in peer-reviewed journals; available in full text; English language; investigating exogenous cannabinoid compounds in *In vitro* studies using neuro-relevant cell lines or primary neuronal/glial cultures (animal or human) of neurodegenerative diseases which reports outcomes of cell viability, apoptosis, neuroinflammation markers, oxidative stress, receptor expression, gene/protein expression, aggregate formation, or autophagy flux. Illustrative rather than exhaustive lists of cell lines, cannabinoid compounds, and disease models were used to guide screening, accommodating the heterogeneity of preclinical models in this literature. This refinement was made during full-text screening to accommodate mechanistic neuroinflammation models identified as relevant to the review question and was documented as a deviation from the initial eligibility specification. Studies combining eligible in vitro models with complementary in vivo, ex vivo, or in silico approaches were also included where the in vitro component constituted the principal component of the study. Clinical trials, case reports, or studies exclusively in human subjects without in vitro/in vivo neurodegeneration modelling and reviews, editorials, letters, or conference abstracts without original experimental data, studies where cannabinoid exposure is ancillary or serves solely as vehicle/comparator without neuroprotection assessment, and studies using cannabinoids solely in non-neurological contexts (cancer, metabolic disease, addiction) without neurodegeneration-relevant disease models and not available in full text were excluded.

2.1 Search Strategy

The search was performed in November 2025 across PubMed/MEDLINE, PsycINFO, CINAHL, and Web of Science. The search strategy, including all identified keywords and index terms, will be adapted for each included database and/or information source. Search strings included mesh terms “Cannabinoid” ”Neurodegenerative Diseases” “Alzheimer Disease” “Parkinson Disease” “Huntington Disease” “Amyotrophic Lateral Sclerosis” “Motor Neuron Disease” “Multiple Sclerosis” “Dementia” and key words cannabinoid*, cannabidiol, CBD, tetrahydrocannabinol, THC, endocannabinoid*, cannabis, cannabis-derived, CB1 receptor, CB2 receptor, cannabinoid receptor, cannabinoid-based, cannabinoid therapy, cannabinoid treatment, medical cannabis, cannabis extract* and neurodegenerative, neurodegenerative disorder*, motor neuron disease, ALS, Alzheimer*, Parkinson*, Huntington*, multiple sclerosis, dementia. The search strings for each database are presented in Supplementary Table S1.

2.2 Study Selection

Records retrieved from all five information sources were imported into EndNote (Version 21), duplicates were removed, and the remaining records were screened in Rayyan. Two reviewers independently screened titles and abstracts, with disagreements resolved by consensus. Full texts were subsequently assessed against the predefined PCC eligibility criteria by the reviewers, with unresolved disagreements referred to a third reviewer. Studies were eligible when they investigated exogenous cannabinoid compounds in neuro-relevant neuronal or glial cell models within the prespecified disease contexts of AD, PD, HD, or MS. Generalized LPS-induced neuroinflammation or microglial activation models retained during full-text screening were treated as a supplementary neuroinflammation context because of their relevance to inflammatory mechanisms shared across the target diseases. Eligibility was not determined solely by the presence of disease-related terminology or the identity of a cell line. Clinical trials, case reports, or studies exclusively in animal or human subjects without in vitro neurodegeneration modelling and reviews, editorials, letters, or conference abstracts without original experimental data, studies where cannabinoid exposure is ancillary or serves solely as vehicle/comparator without neuroprotection assessment, and studies using cannabinoids solely in non-neurological contexts were excluded. In total, the five databases yielded 8,484 records; after deduplication and two-stage screening, 26 studies entered the final synthesis. The full search and selection process is reported in the PRISMA flow diagram (Fig. 1.0).

2.3 Data Extraction

Data was extracted by two reviewers independently and verified by a third using a standardized nine-column charting form. Table include Year, Study Design, Cell Type, Disease Context (AD, PD, HD, MS, etc.), Main Compound Studied, Experimental Concentration/Dose, Key Molecular Targets, Primary Findings/Summary and Source.

2.4 Data analysis and presentation

Given the heterogeneity of cannabinoid compounds, disease models, receptor targets, and outcomes, a narrative thematic synthesis approach was employed. Studies were organized inductively into three thematic domains identified from the data: (1) anti-neuroinflammatory mechanisms; (2) antioxidant, anti-apoptotic, and mitochondrial pathways; (3) protein aggregate clearance, autophagy, myelination, and neurotransmitter modulation and a receptor pharmacology is presented as a cross-cutting axis (Section 3.3.4) mapping which receptor systems, and which receptor-independent mechanisms, recur

across the three functional domains. Within each domain, evidence was synthesized narratively with attention to mechanistic convergence and divergence across compounds, receptor subtypes, and disease contexts.

3. Results

3.1 Study Selection PRISMA Flow

A total of 8,484 records were identified across five electronic databases, including CINAHL (n = 623), MEDLINE (n = 2,628), PsycINFO (n = 466), PubMed (n = 2,927), and Web of Science (n = 1,840). Deduplication left 2,844 unique records, which were screened in Rayyan. Title and abstract screening excluded 2,650 records and carried 194 articles forward for full-text retrieval; of these, 18 could not be obtained in full text, leaving 176 reports assessed for eligibility. Full-text review narrowed this to the 26 studies that form the final synthesis. Exclusions at this stage comprised 20 randomized controlled trials, 9 purely computational studies, 116 animal studies, 2 studies built on the wrong phytochemicals, 2 based on in vitro chemical experiments outside scope, and 1 using irrelevant cell lines. Figure 1.0 presents the complete PRISMA flow diagram.

3.2 Characteristics of Included Studies

The 26 included studies were published between 2015 and 2025. With respect to study design, the majority employed purely in vitro experimental approaches (n = 18) (21,25–41) Six (06) studies combined in vitro and in vivo methods (26,42–46). The remaining two studies used other design combinations: in vitro with in silico modelling (n = 1)(47) and in vitro with ex vivo tissue (n = 1)(48).

Disease contexts represented included Alzheimer's disease (AD, n = 12) (26,29–32,38–43,48) Parkinson's disease (PD, n = 8) (25,26,28,33–36,47) Huntington's disease (HD, n = 2) (37,44); multiple sclerosis (MS, n = 1) (45)(Tomas-Roig et al., 2016) and general, disease-non-specific neuroinflammation models (n = 3) (21,27,46). Several studies spanned more than one disease context concurrently (e.g., combined AD/neuroinflammation and HD/neuroinflammation models) and are cited here under their primary disease focus to avoid duplicate counting. No included studies explicitly investigated amyotrophic lateral sclerosis (ALS) as a disease context. The included NSC-34 study was classified under general neuroinflammation rather than ALS because ALS was not explicitly established as the disease context by the original authors.

The most frequently studied cannabinoid was cannabidiol (CBD; n = 9 studies) (25,32–36,42,43,47), followed by the synthetic agonists JWH133 and ACEA (n = 6 combined)(26–28,35,37,49), THC and its analogues (Δ9-THC, Δ8-THC, Δ9-THCA; n = 4) (38,40,44,46), and WIN552122 (n = 4)(29,31,45,48). The remaining studies examined a broad range of additional phytocannabinoids, endocannabinoids, and synthetic cannabinoid receptor ligands/modulators (e.g., CBDA, CP55940, HU-308, JZL184, URB597, CBG), reflecting the pharmacological diversity captured within this scoping review. Summary of extracted data of included studies are shown in Table 2.0.

Table 2.0
Summary of included studies

Year	Study Design	Cell Type	Disease Context	Main Compound Studied	Experimental Concentration/Dose	Key Molecular Targets	Primary Findings/Summary	Sour
2017	*In Vitro*	Mesenchymal stem cells derived from human gingiva (GMSCs)	AD	CBD	5 μM	GSK3β, PI3K/Akt, TRPV1, BACE-1, PSEN1, PSEN2, CDK5	CBD downregulated genes involved in tau phosphorylation and Aβ production; upregulated Aβ degrading enzymes via TRPV1/PI3K/Akt signaling	(32)
2023	*In Vitro* and *In Vivo*	SH-SY5Y cells, BV2 cells	AD	CBD	2.5–25 μg/mL (In Vitro); 10–100 μg/mL (In Vivo)	Aβ40 aggregation, FAAH, CNR1, LC3, Bcl-xl, P62/SQSTM1	Combined CBD and β-asarone synergistically inhibited A β40 aggregation, reduced apoptosis, and improved behavioral deficits and learning in *in vivo C. elegans* AD models.	(42)
2021	*In Vitro* and *In Vivo*	Human SH-SY5Y cells, primary hippocampal neurons (mice)	AD	CBD	1–10 μM (In Vitro); 5 μM (C. elegans)	CB1R, FAAH, p-Akt, p-STAT3, CaMKII, PSD-95, Synaptophysin	CBD increased the expression of FAAH, CB1R and protected the reduction of dendritic spine density and rescued the activity of CaMKII It extended lifespan and improved health span (locomotion) in AD *C. elegans* models.	(43)
2025	*In Vitro* and *In Silico*	SH-SY5Y human neuroblastoma cell line	PD	CBD	1 μM	Nrf2, Keap1, PPAR γ, 8-OHdG	CBD protected against rotenone toxicity and reduced oxidative stress. It increased nuclear Nrf2 and PPAR expression, potentially interfering with Keap1-mediated Nrf2 degradation.	(47)
2023	*In Vitro* and *in silico*	Menstrual stromal cell-derived dopamine-like neurons (DALNs)	PD	CBD	100 – 10,000 nM	DJ-1,CASP3, ROS, ΔΨm,	CBD protected neurons against PQ2+/MB-induced death by binding to DJ-1 and CASP3, preventing oxidation and activation independently of CB1/CB2 receptors.	(33)
2015	*In Vitro*	PC12 (Rat) and SH-SY5Y (Human) cells	PD	CBD	1–50 μM	trkA receptors, GAP-43, Synaptophysin, Synapsin I, CASP3	CBD protected PC12 cells against MPP+ toxicity by increasing neuritogenesis via trkA activation and upregulation of synaptic proteins, independent of NGF.	(25)
2025	*In Vitro*	PC12 cell line	PD	CBD	1–10 μM	Nrf2, Bax, Bcl-2, CASP3	CBD showed neuroprotective effects against 6-OHDA toxicity by increasing cell viability and antioxidant capacity	(34)

Year	Study Design	Cell Type	Disease Context	Main Compound Studied	Experimental Concentration/Dose	Key Molecular Targets	Primary Findings/Summary	Sour
							(SOD/GSH) via upregulation of the Nrf2 and Bcl2 genes	
2025	*In Vitro*	Human SH-SY5Y cell line	PD	CBD, ACEA, GW405833, Capsaicin, AM251, AM630	CBD/ACEA: 10 μM; GW: 1–10 μM; Capsaicin: 10 μM	CB1R, CB2R, TRPV1, LC3-II, α-synuclein	CBD and ACEA induced autophagy and reduced α-synuclein levels via CB1R activation. GW405833 (CB2R) and Capsaicin (TRPV1) did not show these effects.	(35)
2024	*In Vitro*	Primary cerebellar granule cell cultures (Wistar rats)	PD	CBD (pure and formulations)	1.25 to 20 μM	GFAP, Tyr-tubulin, Mitochondrial complex I	CBD formulations (Epifractan/Xalex) attenuated rotenone-induced death. Pure CBD was toxic at 15–20 μM; MCT oil in formulations prevented this toxicity.	(36)
2022	*In Vitro*	SIM-A9 microglia; STHdhQ7/Q7 striatal neurons	HD and Neuroinflammation	ACEA, HU-308, CP55940	1.2–2.5 μM (EC90)	NO, TNF, IL-1, IL-6, iNOS, CNR1, CNR2, MAPK (ERK/JNK/p38), Akt, NF-B	Selective agonists (ACEA, HU-308) suppressed microglial release of NO and cytokines and improved neuronal survival via MAPK/Akt signaling inhibition.	(37)
2017	*In Vitro* and *In Vivo*	HEK-293T, N2a, STHdh cells; C57BL/6 mice	HD	Δ9-THCA	0.1–25 μM (In Vitro); 20 mg/kg (In Vivo)	PPAR γ, PGC-1 α, TNF- α, iNOS, IL-6, COX-2	9-THCA acted as a PPAR agonist, improved motor deficits, and attenuated neuroinflammation	(44)
2016	*In Vitro* and *In Vivo*	HOG16 cells; C57BL/6J mice	MS	WIN552122	1 μM (In Vitro); 0.5-1 mg/kg (In Vivo)	CB1, MBP, Rxra, Ngr1, MOG	Low dose (0.5 mg/kg) was neuroprotective and promoted differentiation; high dose (1 mg/kg) aggravated demyelination.	(45)
2016	*In Vitro* and *Ex Vivo*	Primary cortical astrocytes; hippocampal slices (mice)	AD	WIN552122, 2-AG, Methanandamide	5 μM	CB1, CB2, Cx43,Panx1, TNF- α, IL-1 β	Cannabinoids prevent A β-induced activation of astroglial Cx43 Panx1 channels, reducing excitotoxic glutamate/ATP release	(48)
2019	*In Vitro* and *In Vivo*	HEK-293T, murine microglia, APPSw,Ind mice	AD	Δ9-THC, JWH133	100–200 nM	cAMP, ERK1/2, -arrestin 2, Iba-1, Arg-1, iNOS, BRET, PLA	A2A and CB2 receptors form heteromers in microglia. Blockade of A2AR potentiates CB2R-mediated signaling and neuroprotection in AD models.	(49)
2023	*In Vitro*	Human SH-SY5Y cells	AD	Δ8-THC	5–20 μM	PERK, ATF6, IRE1, Bax, Bcl-2, PSMB5	Δ8-THC restored viability in A β-treated cells by modulating proteostasis and ER stress pathways, reducing Bax and promoting	(38)

Year	Study Design	Cell Type	Disease Context	Main Compound Studied	Experimental Concentration/Dose	Key Molecular Targets	Primary Findings/Summary	Sour
							misfolded protein degradation.	
2021	*In Vitro*	Human MSC-derived Cholinergic-like neurons	AD (Familial)	CP55940	1 μM	sAPPβ, p-Tau, DJ-1, ROS, ΔΨm, p53, c-Jun, PUMA, caspase-3, eAβ 42	CP55940 inhibited sA βPP βf and p-Tau aggregation and blocked apoptosis markers (p53, PUMA) mostly independent of CB1R. Stop the production od ROS dependent on CB1R.	(39)
2016	*In Vitro*	Human MC65 CNS nerve cell line	AD	THC, AEA, Q-3, AM404	50 nM to 1 μM	,IL-8, IL-1, TNF-, IFN-, P-NFB, Caspase 1/3, 5-LOX, COX-2, ROS	Cannabinoids (THC, AEA, Q-3, AM404) stimulated the removal of intraneuronal A β, blocked inflammatory responses, and prevented nerve cell death.	(40)
2022	*In Vitro*	Human SH-SY5Y neural cells	AD	CBDA, Cannabisin B, N-trans-caffeoyltyramine	8.7–59 μM (IC50)	miR-190a-5p, miR-143-3p, miR-708-5p, miR-199a-5p, miR-181a-5p, Neuregulin-1, Neuritin	modulated various miRNAs (e.g., downregulating miR-143 or miR-199a), affecting pathways related to neuronal survival and axon guidance.	(41)
2019	*In Vitro*	Human SH-SY5Y cell line	PD	ACEA, SR141716, CID1792197	100 nM – 1 μM	CB1R, GPR55, CB1R/GPR55 heteromers	CBR1 Antagonist SR141716 led protection was lost when CB1R/GPR55 heteromers were present.	(26)
2018	*In Vitro*	NSC-34 neurons and RAW 264.7 macrophages	Neuroinflammation	CBG	1–20 μM	Caspase 3, Bax, Bcl-2, IL-1 β, TNF- α, Nrf2, iNOS	CBG reduced cell death and inhibited apoptosis. It counteracted oxidative stress and inflammation by reducing cytokines and restoring Nrf2 levels.	(21)
2021	*In Vitro*	BV-2 mouse microglial cell line	General Neuroinflammation	ACEA, AM-251, CP55940, SR144528	1-300 nM	MHC-II, CIITA, IL-1 β, TNF-α	CB1R receptors primarily mediated LPS-induced MHC-II expression. ACEA and CP55940 attenuated the release of inflammatory cytokines.	(27)
2016	*In Vitro*	Human SH-SY5Y cell line	PD (Model)	JWH133	10–40 μM	CB2, Caspase	High doses of JWH133 caused a concentration-dependent decrease in cell viability not mediated by CB2R, suggesting potential neurotoxicity.	(28)
2018	Combined *In Vitro* and *In Vivo*	Sprague-Dawley rats; rat cortical astrocytes	General Neuroinflammation	THC	3 mg/kg (In Vivo); 1 μM (In Vitro)	Glutamate, Kynurenic acid (KYNA), Dopamine, GFAP, CB1R mRNA	THC increased glutamate and reduced KYNA levels via astrocytic CB1Rs and α7nAChRs; effects were	(46)

Year	Study Design	Cell Type	Disease Context	Main Compound Studied	Experimental Concentration/Dose	Key Molecular Targets	Primary Findings/Summary	Sour
							prevented by CB1R antagonism.	
2015	*In Vitro*	Primary rat cortical astrocytes	AD	WIN552122	10 μM	TNF-, IL-1, NF-B, COX-2, iNOS, PPAR-, Cu/Zn SOD, Mn SOD, MTT	WIN552122 pretreatment increased astrocyte viability and induced anti-inflammatory responses via PPAR- γ, preventing A β-induced stress.	(29)
2018	*In Vitro*	Primary mouse microglia	AD, MS, and Neuroinflammation	β-Amyrin	2–16 μM	TNF-α, IL-1β, IL-6, PGE-2, COX-2, iNOS, Arg-1, NO	β-Amyrin acted as a cannabinoid agonist, reducing pro-inflammatory factors and shifting microglia from M1 to M2 (anti-inflammatory) state.	(30)
2020	*In Vitro*	Primary rat hippocampal neurons	AD / Hyperglycemia	AEA, 2-AG, CP55940, WIN552122, URB597	1 nM to 1 μM	Nrf2, CREB, GSK3 β, ROS, SOD, iNOS	All agents prevented GLU + A βtoxicity by reducing oxidative damage and inflammation. All cannabinoid agents recruited Nrf2 signaling to protect cells	(31)

3.3 Neuroprotective mechanisms

The 26 included studies were synthesized inductively into three primary functional domains, reflecting the downstream biological processes through which neuroprotection is achieved: (1) anti-neuroinflammatory mechanisms; (2) antioxidant, anti-apoptotic, and mitochondrial pathways; and (3) protein aggregate clearance, autophagy, myelination, and neurotransmitter modulation. Because these three domains are themselves substantially initiated by upstream receptor engagement, receptor pharmacology is presented not as a fourth, parallel domain but as a cross-cutting axis (Section 3.3.4) mapping which receptor-independent mechanisms, together with additional receptor-dependent phenomena, and receptor heteromerization; that contribute onto above functional domains. Within each domain, evidence is synthesized narratively with attention to mechanistic convergence and divergence across cannabinoid compounds, receptor subtypes, and disease contexts.

3.3.1 Anti-Neuroinflammatory Mechanisms

Neuroinflammation driven by microglial and astrocytic activation is the most consistently reported target of cannabinoid action across the dataset. CB1 receptor agonism emerged as a primary anti-inflammatory mechanism in microglial cells. CB1 agonism (ACEA, CP55940) suppressed IL-1β, IL-6, TNF-α, and MHC-II/CIITA expression together with its transcriptional regulator CIITA in LPS-stimulated microglia. But these effects were fully reversed by the CB1 antagonist AM-251 but only partially by the CB2 antagonist SR144528 establishing CB1 as the dominant receptor for microglial antigen-presentation suppression (27). In Huntington's disease model, CB1/CB2 agonists (ACEA, HU-308, CP55940) suppressed microglial nitric oxide/cytokine release and improved striatal neuron survival via inhibition of ERK1/2, JNK, p38, and Akt signaling cascade(37), extending cannabinoid-mediated microglial suppression into HD. Askari et al. (2018) reported that the pentacyclic triterpenoid β-amyrin; a cannabinoid active phytochemical, dose-dependently promoted a M1-to-M2 phenotypic shift in LPS/IFN-γ-stimulated microglia (30). β-Amyrin significantly reduced the production of the pro-inflammatory mediators TNF-α, IL-1β, IL-6, PGE_2, COX-2, and iNOS, while increasing arginase-1 expression and urea production.

Aguirre-Rueda et al. (2015) extended the anti-inflammatory picture to astrocytes showing that WIN552122 pre-treatment in Aβ1-42-exposed primary cortical astrocytes prevented NF-κB p65 phosphorylation, blocked COX-2 and iNOS induction, and suppressed TNF-α/IL-1β secretion, while upregulating PPARγ and Cu/Zn superoxide dismutase (SOD) (29). These findings implicate a CB1/CB2–PPARγ axis in the suppression of astrocytic neuroinflammation. A complementary astrocyte-centered mechanism was reported by Gajardo-Gómez et al. (2017), who demonstrated that WIN552122, 2-AG, and methanandamide (a synthetic derivative of anandamide) each prevented Aβ-induced opening of astroglial connexin-43 (Cx43) hemichannels and neuronal pannexin-1 (Panx1) channels in mouse cortical astrocyte cultures through CB1, curbing glutamate/ATP release and identifying hemichannel regulation as a novel neuroinflammatory control node (48). See Fig. 2.0 for the summary of Cannabinoid-mediated modulation of neuroinflammatory signaling in microglia and astrocytes.

A2A–CB2 receptor heteromerization represented a distinct receptor-associated mechanism identified in an AD model. A2AR antagonism enhanced CB2R-mediated signaling in microglia, indicating that receptor–receptor interactions modified the anti-inflammatory response (49). Finally, Gugliandolo et al. (2018) demonstrated that pre-treatment with the non-psychoactive phytocannabinoid cannabigerol (CBG) significantly attenuated cytokine release and oxidative

stress in motor neurons exposed to inflammatory conditioned medium, restoring nuclear factor erythroid 2-related factor 2Nrf2 expression (21). It markedly reduces the pro-inflammatory cytokines IL-1β, TNF-α, and IFN-γ.

3.3.2 Antioxidant, Anti-Apoptotic, and Mitochondrial Pathways

Oxidative stress and apoptotic neuronal death, downstream consequences of mitochondrial dysfunction, are central to dopaminergic, cholinergic, and striatal neuronal vulnerability in PD, AD, and HD. CBD reduced Reactive oxygen species (ROS), restored antioxidant capacity (SOD, GSH, Nrf2), and suppressed caspase-3. In parallel, Δ8-THCsuppressed the expression of pro-apoptotic markers Bax while restoring anti-apoptotic Bcl-2 expression, indicating attenuation of mitochondrial dysfunction and inhibition of the intrinsic apoptotic pathway.

A similar antioxidant and cytoprotective effects using a CBD extracted from a *Cannabis sativa* was found on rotenone-induced SH-SY5Y neurotoxicity model. The treatment enhanced nuclear Nrf2 accumulation and increased expression of PPARγ and PPARδ, suggesting that activation of antioxidant defense pathways may involve modulation of the Keap1–Nrf2 regulatory axis and improved neuronal viability (47). CBD also protected dopamine-like neurons through direct, receptor-independent binding to DJ-1 and caspase-3, preserving mitochondrial membrane potential and restoring Ca^{2+} signaling even under CB1/CB2 blockade(33).Further, they documented CBD decreases reactive oxygen species, maintains the mitochondrial membrane potential. This suggest that CBD's antioxidant and anti-apoptotic actions can proceed through direct protein interaction rather than classical cannabinoid receptor signaling, a mechanistic pattern with important implications for structure–activity reasoning about CBD analogues.

The influence of formulation and vehicle composition on CBD-mediated antioxidant efficacy was investigated by Echeverry et al. (2024) using primary rat cerebellar granule cell cultures (36). Commercial CBD formulations (Epifractan® and Xalex®) reduced rotenone-induced mitochondrial complex I dysfunction and preserved the expression of glial fibrillary acidic protein (GFAP) and tyrosinated α-tubulin, indicating protection against mitochondrial impairment and cytoskeletal disruption. In contrast, pure CBD exhibited concentration-dependent cytotoxicity at higher concentrations (15–20 μM), an effect that was prevented when CBD was delivered within the medium-chain triglyceride (MCT) oil vehicle used in the commercial formulations. These findings highlight excipient composition as a determinant of therapeutic window. Therefore, optimization of CBD delivery systems may be critical for maximizing efficacy while minimizing concentration-related toxicity.

Beyond antioxidant activity, Santos et al. (2015) identified a distinct neurorestorative mechanism through which CBD promotes neuronal repair (25). In MPP+-treated PC12 cells CBD enhanced neurite outgrowth and increased expression of the axonal growth marker growth-associated protein 43 (GAP-43) and the synaptic proteins synaptophysin and synapsin I through activation of tropomyosin receptor kinase A (TrkA), the receptor for nerve growth factor (NGF). This effect was absent in TrkA-deficient SH-SY5Y cells, suggesting CBD-induced neurorestoration is highly dependent on cellular context and extends beyond oxidative stress regulation to include classical neurotrophic signaling pathways. Additional evidence for antioxidant modulation in glial cells was provided by Aguirre-Rueda et al. (2015), who reported CBD-induced upregulation of Cu/Zn superoxide dismutase (SOD) in astrocytes (29). Furthermore, Gugliandolo et al. (2023) demonstrated that Δ8-THC, a less extensively studied structural isomer of Δ9-THC, protected SH-SY5Y cells against Aβ-induced toxicity by modulating endoplasmic reticulum (ER) stress responses through activation of the unfolded protein response (UPR) (38). This effect involved reduction of Bax expression and increase in Bcl-2; a crucial pro-survival protein that primarily inhibits programmed cell death (apoptosis), maintains calcium balance, and regulates autophagy at the outer membrane of mitochondria. In a separate 6-OHDA PC12 model, CBD improved cell viability and lowered apoptosis rates; pretreatment reduced ROS and malondialdehyde while boosting total antioxidant capacity, SOD, and GSH. The same study reported CBD overexpressed Nrf2 and Bcl-2 genes in 6-OHDA-exposed PC12 cells and prevented the upregulation of Bax and CASP3 too (34).

Δ9-THCA is identified as more potent PPARγ agonist than its decarboxylated form Δ9-THC (44). Δ9-THCA increased mitochondrial mass and reduced striatal neurodegeneration in HD models more effectively than THC. Further, THCA-treated animals in the 3-NPA murine HD model showed significantly less striatal neurodegeneration than THC-treated animals, suggesting that acidic cannabinoids may offer superior neuroprotective efficacies. An important negative and safety-relevant finding was provided by Wojcieszak, Krzemień and Zawilska (2016): the selective CB2 agonist JWH133 at 10–40 μM induced dose-dependent cytotoxicity in SH-SY5Y cells through a mechanism that was neither CB2R-mediated nor caspase-dependent, indicating off-target toxicity at high concentrations that must be weighed against any CB2-selective therapeutic strategy (28).

The anti-inflammatory actions of CBG documented in Section 3.3.1 were paralleled by antioxidant effects in the same NSC-34 model. Gugliandolo et al. (2018) found that CBG pre-treatment reversed the rise in nitrotyrosine, SOD1, and iNOS in NSC-34 motor neurons while restoring Nrf2 levels (21). A comparable Nrf2/ARE-centered mechanism was identified by Elmazoglu et al. (2020) across a panel of cannabinoid receptor agonists (AEA, 2-AG, CP55940, WIN552122) and the FAAH inhibitor URB597 tested in primary hippocampal neurons under combined hyperglycemia and Aβ1–42 toxicity (31). All agents except URB597 recruited the Nrf2/ARE antioxidant pathway, evidenced by increased Nrf2 and CREB phosphorylation. See Fig. 3.0 for Cannabinoid-mediated antioxidant, mitochondrial, and neurorestorative mechanisms.

3.3.3 Protein Aggregate Clearance, Autophagy, Tau Inhibition, Myelination, and Neurotransmitter Modulation

Evidence for anti-aggregation efficacy was showed by Duan et al. (2023), who demonstrated synergistic effects of a combined CBD and β-asarone treatment at low doses (42). The combination inhibited Aβ40 fibril formation more effectively than either compound alone. This enhanced anti-amyloid activity translated into reduced apoptosis in APP/PS1-transfected SH-SY5Y cells and was accompanied by modulation of key autophagy-associated proteins, including increased LC3 and Bcl-xl expression together with reduced p62 accumulation, suggesting improved autophagic clearance and cell survival.

In addition to preventing protein aggregation, cannabinoids promote the clearance of pathogenic protein species through activation of autophagy. Erustes et al. (2025) demonstrated that CBD enhances autophagic flux in α-synuclein-overexpressing SH-SY5Y cells, a cellular model of PD. CBD treatment increased LC3-II accumulation and autophagosome formation, indicating enhanced autophagic activity (35). Pharmacological inhibition studies further established that

this response was mediated specifically through CB1 receptor (CB1R) activation, as it was abolished by the CB1R antagonist AM251 but remained unaffected by antagonism of CB2R or transient receptor potential vanilloid 1 (TRPV1). Supporting a related clearance mechanism, Currais et al. (2016) reported that Δ9-THC, together with anandamide, Q-3, and AM404, promoted the removal of intraneuronal Aβ in MC65 cells, thereby interrupting the downstream neuroinflammatory cascade initiated by Aβ-induced proteotoxic stress (40). Collectively, these studies indicate that cannabinoids also facilitate their intracellular clearance through receptor-dependent autophagic mechanisms.

Beyond reducing protein burden, cannabinoids may also promote structural repair within the central nervous system. Tomas-Roig et al. (2016) investigated the effects of the synthetic cannabinoid WIN552122 in the cuprizone-induced demyelination model of MS and identified a pronounced dose-dependent biphasic response (45). At a low dose (0.5 mg/kg), it promoted oligodendrocyte differentiation, increased myelinated axon density, upregulated retinoid X receptor-α (RXRα), and reduced Nogo receptor expression, consistent with active remyelination. However, doubling the dose to 1 mg/kg reversed the benefit entirely, worsening demyelination and downregulating myelin-associated genes. A modest increase was enough to flip the outcome, which emphasize how narrow the therapeutic window for remyelination-targeted cannabinoid therapy may be, and how much dose precision will matter for any clinical translation in MS.

Not every cannabinoid effect on neurotransmission was protective, though. Secci et al. (2019) found that THC-driven CB1R activation in astrocytes raised extracellular glutamate while lowering kynurenic acid; an endogenous negative allosteric modulator of α7 nicotinic acetylcholine receptors (46). These findings highlight a potential neurobiological risk associated with cannabinoid exposure, whereby excessive astrocytic CB1R activation may disturb the glutamate–kynurenine equilibrium and alter excitatory neurotransmission. Expanding the molecular mechanisms underlying cannabinoid-mediated neuroprotection, Di Palo et al. (2022) demonstrated that cannabidiolic acid (CBDA) and related hemp-derived polyphenols, including cannabisisin B and N-trans-caffeoyltyramine, exert epigenetic effects by modulating microRNA expression profiles in SH-SY5Y neuronal cells where the treatment altered the expression of AD-associated microRNAs (41). These findings suggest that non-psychoactive phytochemicals may influence neurodegenerative processes through post-transcriptional regulation of gene expression. Further, CBD pre-treatment downregulated transcription of the principal tau kinases GSK3β, CDK5, DYRK1A, CcMK IIA, and members of the MAPK family (MAPK1, MAPK12, and MAPK14) in human gingiva-derived mesenchymal stem cells, consistent with suppression of tau hyperphosphorylation and, by extension, neurofibrillary tangle formation (32).

3.3.4 Receptor Pharmacology, Heteromerization, and Receptor-Independent Mechanisms

Receptor pharmacology support the anti-neuroinflammatory, antioxidant, and clearance-related effects catalogued above, rather than a parallel category of neuroprotective outcome. The included studies provided evidence for three broad modes of cannabinoid-associated signaling: canonical CB1R/CB2R-dependent mechanisms, non-canonical receptor-associated mechanisms involving targets such as PPARγ, GPR55, A2AR, and TRPV1, and receptor-independent or direct molecular mechanisms supported by receptor-blockade or target-specific experiments. These mechanisms contributed to one or more of the three functional domains described above. Receptor heteromerization represented a further layer of pharmacological complexity rather than an independent neuroprotective outcome. In the included studies, A2A–CB2 and CB1R/GPR55 heteromers altered receptor-associated signaling in AD and PD models, respectively. These findings are therefore interpreted according to their downstream functional outcome while heteromerization is retained as a distinct feature of receptor organization.

A synaptic dimension of CB1R neuroprotection was described by Wang et al. (2021), who showed that CBD prevented Aβ-induced neurite lesions and dendritic spine loss in human SH-SY5Y cells and primary mouse hippocampal neurons (43). CB1R-dependent activation of phosphorylated Akt (p-Akt), phosphorylated STAT3 (p-STAT3), and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) preserved synaptic proteins including PSD-95 and synaptophysin. These findings were extended to a *Caenorhabditis elegans* model of Aβ pathology, where activating identical CB1R pathway extended lifespan and improved locomotor health span; a functional proof that this synaptic protection scales from cell culture to a whole organism. Notably, this is a mechanistically separate role for CB1R from the anti-inflammatory one described in Section 3.3.1: the same receptor recruits different intracellular effectors and produces a different outcome depending on which cell type expresses it.

The CB1R/GPR55 heteromer identified in a PD model provided another example of receptor–receptor modulation of cannabinoid pharmacology. The neuroprotective response differed according to whether CB1R and GPR55 were expressed individually or as a heteromeric complex (26). The A2A–CB2 heteromer described in Section 3.3.1 (49), in which A2AR antagonism potentiates rather than opposes CB2R-mediated neuroprotection, reflects the same underlying principle: within a heteromeric complex, ligand occupancy at one protomer reshapes the pharmacological behaviour of its partner, so heteromer composition, and not receptor identity in isolation, determines the direction of the neuroprotective response (interpreted further in Section 4.1).

Counterbalancing this receptor-centric picture, Soto-Mercado et al. (2021) demonstrated that CP55940 reduced the accumulation of secreted amyloid precursor protein β fragment (sAβPPβ), attenuated phosphorylated tau aggregation, and suppressed activation of the pro-apoptotic markers p53 and PUMA in cholinergic-like neurons derived from familial AD models, largely independently of CB1R activation (39). Considered alongside the CB1R/CB2R-independent DJ-1/caspase-3 pathway reported by Mendivil-Perez et al. (2023) (33) in Section 3.3.2, these findings indicate that a substantial proportion of cannabinoid-mediated neuroprotective effects cannot be attributed to classical cannabinoid receptor signaling alone. Therefore, systematic investigation of non-canonical receptor-associated mechanisms, including direct protein interactions, intracellular signaling modulation, and off-target molecular targets, is essential for a complete understanding of cannabinoid pharmacology in neurodegenerative disease, alongside rather than subordinate to receptor-centered synthesis.

To visualize the cross-cutting receptor architecture, we mapped each receptor system to its disease context(s) and downstream mechanistic domain(s) (Fig. 4.0). Three patterns are apparent. First, CB1R is the most pleiotropic receptor, engaging D1 (anti-inflammatory) in astrocytes and microglia, D3 (Aggregate Clearance / Autophagy / Myelination / Neurotransmitter & Synaptic) in PD and AD neurons demonstrating that the same receptor recruits distinct

intracellular effectors depending on cell type. Second, PPARγ-associated mechanisms were most prominently represented in D2 (Antioxidant / Anti-apoptotic / Mitochondrial), with additional involvement in anti-neuroinflammatory signaling in AD. Heteromeric complexes (A2A–CB2 in AD microglia; CB1R/GPR55 in PD neurons) are constitutes a pharmacological unit distinct from either protomer in isolation. Receptor-independent mechanisms were identified where experimental evidence supported cannabinoid activity despite inhibition of canonical cannabinoid receptors or implicated direct molecular targets.

3.4 Concentration Ranges, Formulation Effects, and Cytotoxicity Signals

The 26 included studies employed cannabinoid concentrations spanning from nanomolar(49) (100–200 nM) to high micromolar (36): up to 20 μM; (41): IC50 8.7–59 μM) (Table 2.0). Pure CBD exhibited concentration-dependent cytotoxicity at 15–20 μM in primary cerebellar granule cells, an effect abrogated by medium-chain triglyceride (MCT) oil formulation vehicles (36). Conversely, the CB2-selective agonist JWH133 induced dose-dependent cytotoxicity in SH-SY5Y cells at 10–40 μM through a non-CB2R, non-caspase-dependent mechanism (28), highlighting off-target liability at high concentrations. A biphasic dose response was observed for WIN55,212-2 in MS models, where 0.5 mg/kg promoted remyelination but 1.0 mg/kg exacerbated demyelination (45). Finally, astrocytic CB1R activation by THC at 1 μM (in vitro) / 3 mg/kg (in vivo) disrupted glutamate–kynurenine homeostasis, representing a pharmacodynamic safety signal rather than cytotoxicity (46). Collectively, these findings indicate that therapeutic windows are narrow, compound-specific, and sensitive to both formulation and cell-type-specific receptor pools. The findings also emphasize the limitations of relying primarily on cell-viability assays for assessing long-term safety. Single-endpoint *in vitro* toxicity measurements may not adequately capture delayed, pathway-specific, or cell-type-dependent adverse effects. Therefore, characterization of both beneficial and adverse responses across a range of concentrations is important when interpreting the neuroprotective potential of cannabinoids.

4. Discussion

4.1 Principal Findings

This scoping review maps a heterogeneous yet patterned evidence base spanning 26 preclinical studies (2015–2025) across four major neurodegenerative diseases. Rather than a disconnected collection of compound-specific findings, the literature reveals three mechanistic domains; (1) anti-neuroinflammatory signaling, (2) antioxidant, anti-apoptotic, and mitochondrial rescue, and (3) protein aggregate clearance, autophagy, and structural repair with receptor pharmacology functioning as the bridging geography that connects molecular engagement to functional outcomes. The evidence is overwhelmingly concentrated on CBD within vitro paradigms, with substantially less representation of in vivo validation, synthetic cannabinoid profiling, and acidic phytocannabinoid investigation. This distribution is not merely a bibliographic observation; it shapes the confidence with which mechanisms can be prioritized for translational development. The scoping methodology was essential here: the heterogeneity of compounds, disease models, cellular endpoints, and absence of common effect metrics precluded effect-size pooling, but allowed identification of the *extent, range, and nature* of mechanistic claims across the field (22)(23). What emerges is a field in an early mechanistic discovery phase, where single-compound, single-target studies dominate, and multi-target, formulation-aware, or systems-level investigations remain scarce.

At the molecular level, cannabinoid neuroprotection proceeds through both canonical receptor signaling and non-canonical direct interactions. Canonical CB1R and CB2R agonism exemplified by ACEA, CP55940, HU-308, and JWH133 consistently attenuates microglial and astrocytic inflammatory outputs (27,29,37). However, a substantial subset of neuroprotective effects operates independently of classical cannabinoid receptor engagement. CBD protects dopaminergic-like neurons through direct binding to DJ-1 and caspase-3, preserving mitochondrial membrane potential even under CB1/CB2 blockade (33). Similarly, CP55940 attenuates amyloid and tau pathology in familial AD cholinergic-like neurons largely independently of CB1R activation (39). These receptor-independent findings are not pharmacological outliers; they are consistent with CBD's low micromolar affinity for CB1R/CB2R, roughly two orders of magnitude weaker than Δ9-THC's nanomolar affinity (50), which has historically redirected mechanistic inquiry toward alternative targets including 5-HT1A, TRPV1, GPR55, and now direct intracellular protein binding. Structure–activity relationships for cannabinoid neuroprotection must be evaluated at both the receptor and whole-molecule pharmaceutical level.

At the cellular level, the most robust convergence occurs in glial regulation. CB1R and CB2R activation in microglia suppresses MAPK-associated inflammatory signaling (ERK, JNK, p38), reduces pro-inflammatory mediator expression (TNF-α, IL-1β, IL-6, NO, PGE2), and promotes M1-to-M2 phenotypic transition (30,37). This CB2R mediated Protein kinase C governed transition further confirmed in a study where they checked the Nicotine-Induced Anti-Inflammation in N9 Microglial Cells (51). In astrocytes, CB1R engagement downregulates NF-κB and prevents Aβ-induced hemichannel opening, curbing excitotoxic glutamate and ATP release (29,48). Parallel to these immunomodulatory effects, cannabinoids rescue neuronal bioenergetics: CBD, Δ9-THCA, and CBG activate the Nrf2/ARE antioxidant axis, upregulate SOD and GSH, and suppress caspase-3-dependent apoptosis (21,34,47). Autophagy represents a further cellular node, with CBD enhancing LC3-II accumulation and α-synuclein clearance via CB1R-dependent autophagic flux in PD models (35), while Δ9-THC promotes intraneuronal Aβ removal in AD models (40). A similar pathogenic tau protein removal was identified *invitro* by CBD (52). Evidence outside the present review has also reported, not only the cannabinoid derivatives but even cannabis terpenes like α-bisabolol showed antiaggregant action against β amyloid *in vitro* (53). These findings indicate that CB1R signaling differs according to cellular context, with distinct downstream effects in neurons and astrocytes. This cell-type-restricted signaling complicates any simple agonist/antagonist therapeutic logic.

At the systems level, evidence is sparser but mechanistically distinctive. CBD preserves dendritic spine density and synaptic protein expression (PSD-95, synaptophysin) through CB1R-dependent p-Akt/p-STAT3/CaMKII signaling, with functional translation to improved lifespan and healthspan in *C. elegans* AD models (43). In multiple sclerosis (MS) models, the synthetic agonist WIN55,212-2 exhibits a biphasic dose response: low dose (0.5 mg/kg) promotes oligodendrocyte differentiation and remyelination, while high dose (1 mg/kg) exacerbates demyelination (45). Conversely, astrocytic CB1R activation by THC enhances extracellular glutamate while reducing kynurenic acid, potentially disturbing excitatory neurotransmission (46). These systems-level findings reveal

that cannabinoid pharmacology is not uniformly neuroprotective; the direction of effect depends on dose, cell-type-specific receptor pools, and neural circuit context.

Receptor pharmacology functions not as a parallel mechanistic domain but as the causal substrate underlying the anti-inflammatory, antioxidant, and clearance effects described above. CB1R agonism is neuroprotective at neuronal synapses and anti-inflammatory in glia, yet excessive astrocytic CB1R activation may dysregulate glutamate and kynurenine homeostasis (46). This apparent contradiction is explained by receptor location rather than receptor identity: astrocytic CB1R couples to phospholipase-C-dependent intracellular Ca2 + mobilization, triggering non-synaptic glutamate release, whereas neuronal CB1R dampens neurotransmitter release (54–56). Thus, CB1R pharmacology becomes a question of cell-type-restricted dosing rather than a simple treatment.

CB2R activation was associated with anti-inflammatory microglial responses in several disease and neuroinflammation models. Effective immunomodulation in PD requires central rather than peripheral receptor engagement. In a study outside the present dataset showed peripherally restricted CB2R agonist RO304 failed to suppress T-cell neuroinflammation, whereas the brain-penetrant JWH133 and MAGL inhibitor JZL184 were effective (57).These findings suggest that CNS exposure may be an important determinant of CB2R-mediated effects. CB2R is expressed on both CNS-resident microglia and circulating mono lymphocytes, so peripherally restricted agonists may modulate systemic immunity without reaching parenchymal neuroinflammatory drivers. Brain-penetrant CB2R ligands, not receptor selectivity alone, are therefore the limiting design variable for neurodegenerative disease. However CB1R is constitutively expressed at low levels while the CB2R is expressed at higher levels in microglia and is modulated in relation to cell activation state (58).

Beyond canonical CB1/CB2 signaling, non-canonical targets substantially expand the therapeutic space. Δ9-THCA acts as a potent PPARγ agonist, driving mitochondrial biogenesis and striatal neuroprotection in HD models more effectively than Δ9-THC (44). The structural basis for this selectivity lies in THCA's retained carboxyl group, which is poorly accommodated by the hydrophobic CB1/CB2 orthosteric pocket but can hydrogen-bond within the PPARγ ligand-binding domain, simultaneously removing psychoactivity and redirecting pharmacology toward nuclear receptor-mediated neuroprotection.

Receptor heteromerization introduces a further layer of complexity. The CB1R/GPR55 heteromer in PD models exhibits paradoxical pharmacology where CB1R antagonist SR141716 provides neuroprotection when CB1R and GPR55 are expressed individually, but this protection is lost when the heteromer is present (26). Similarly, A2A–CB2 heteromers in microglia demonstrate that A2AR antagonism potentiates rather than opposes CB2R-mediated anti-inflammatory signaling in AD models (49). These patterns follow the general principle of GPCR heteromer pharmacology: within a heteromeric complex, ligand binding at one protomer allosterically reshapes the conformation and signaling output of its partner, so the heteromer not either receptor in isolation becomes the functional pharmacological unit (59) (60).

An important finding of this review is that cannabinoid effects were not uniformly beneficial across concentrations or dosing regimens. The dose-related findings summarized in Section 3.4 indicate that responses varied according to cannabinoid, concentration, formulation, cell type, and experimental context. This variability suggests that increasing cannabinoid exposure does not necessarily result in greater neuroprotective effects and may, under some conditions, be associated with adverse cellular responses.

The observed concentration-dependent cytotoxicity and differential responses at lower and higher doses highlight the importance of defining compound-specific exposure ranges when evaluating cannabinoid-mediated neuroprotection. Formulation may also influence the observed response, as demonstrated by the differential effects associated with CBD and its vehicle. These observations indicate that dose should be considered together with cannabinoid identity, formulation, receptor distribution, cell type, and exposure duration rather than as an independent determinant of efficacy.

Also, when comes to the astrocytic CB1R signaling: the same receptor that closes inflammatory Cx43 hemichannels (48) can, if overstimulated, trigger glutamate release and disrupt kynurenine homeostasis (46).

4.2 Disease-Context Convergence and Divergence

The transdiagnostic potential of cannabinoids is supported by mechanistic convergence: chronic neuroinflammation, oxidative stress, and protein aggregation represent common pathological denominators across AD, PD, HD, and MS, and cannabinoids modulate all three. Disease-specific mechanistic differences are nonetheless evident. In AD, the main mechanisms represented in the included studies are Aβ aggregate clearance (40), CB1R-dependent synaptic preservation (43), astroglial hemichannel regulation (48), and A2A–CB2 heteromer-mediated microglial neuroprotection (49) targets with no direct parallel in PD or HD. In PD, α-synuclein clearance via CB1R-induced autophagy (35), and receptor-independent protection of dopamine-like neurons via DJ-1/caspase-3 (33) emerge as prominent themes. The formulation-dependent toxicity profile of CBD (36) is particularly relevant here, given that clinical PD trials would likely require chronic dosing. In HD, PPARγ-driven mitochondrial biogenesis by THCA (44) is complemented by CB1/CB2 agonist suppression of microglial-to-striatal-neuron inflammatory crosstalk (37), together constituting the most extensively characterized mechanisms within the limited HD evidence identified in this review (*n* = 2 studies). In MS, the biphasic dose-response of WIN552122 on myelination (45)underscore that dosing must be empirically established.

4.3 Evidence Gaps Identified

Because this review followed scoping methodology without formal risk-of-bias assessment, the mechanistic patterns identified represent the range of reported effects rather than verified, reproducible effects (61).This is particularly important given the *in vitro* dominance of the dataset: 18 of 26 studies relied exclusively on cell-line or primary culture models, limiting extrapolation to tissue-level physiology, blood-brain barrier penetration, and organism-level pharmacokinetics. The scoping approach was methodologically appropriate, but readers should interpret the findings as a mechanistic roadmap rather than an efficacy dossier.

A major barrier to translational inference is the limited comparability of cannabinoid exposure across the included studies. Differences in concentration or dose are accompanied by variation in administration route, formulation, vehicle, cell density, exposure duration, experimental model, and endpoint selection. Consequently, numerical dose comparisons across studies may not reliably reflect equivalent pharmacological exposure. The findings further indicate that formulation and experimental context can modify the observed response. This is particularly relevant for translating *in vitro* concentrations into therapeutically meaningful exposure ranges, as nominal concentrations in culture do not necessarily correspond to free or tissue-level concentrations achievable *in vivo*. The absence of standardized exposure conditions therefore limits the establishment of consistent therapeutic windows across cannabinoids and disease models. Future studies should incorporate systematic concentration–response assessments using multiple exposure levels and complementary efficacy and toxicity endpoints. Standardized reporting of cannabinoid concentration, formulation and vehicle, exposure duration, cell density, and relevant pharmacokinetic or exposure parameters would improve cross-study comparability and strengthen the translational value of *in vitro* cannabinoid research.

A further gap concerns receptor-independent mechanism. Findings implicating DJ-1/caspase-3 signaling (33) and a largely CB1R-independent action of CP55940 (39) suggest that off-target or direct protein-binding neuroprotective mechanisms are more prevalent than the receptor-centric literature typically assumes, and this warrants systematic target-deconvolution studies. Sex and age as biological variables have likewise been neglected: no included study systematically examined sex or age differences in cannabinoid neuroprotection, despite well-established sex differences in endocannabinoid system (ECS) function and age-dependent ECS dysregulation.

Acidic cannabinoids and non-cannabinoid Cannabis constituents remain severely understudied relative to their decarboxylated counterparts. THCA demonstrates superior PPARγ affinity and neuroprotective efficacy compared to THC (44), while CBDA exhibits epigenetic miRNA modulatory capacity (41). These under-characterized chemotypes warrant expanded investigation, particularly as they offer non-psychoactive therapeutic routes. Combination pharmacology and the entourage effect are similarly underrepresented, with only Duan et al. (2023) examining cannabinoid combinations (42). Given that *Cannabis*-based medicines are typically administered as complex extracts, the single-molecule focus of the current evidence base may poorly predict clinical efficacy. Receptor heteromer pharmacology also presents a comparable gap, as A2A–CB2 and CB1/GPR55 heteromers have each been characterized in only per single study, leaving their prevalence across disease stages, developmental windows, and brain regions unexplored.

Long-term safety remains inadequately addressed. In vitro cytotoxicity assays are insufficient for chronic neurological safety profiling, and the off-target cytotoxicity observed with JWH133 highlights the need for systematic safety pharmacology studies, particularly for CB2-selective agonists intended for chronic use in neurodegenerative disease.

4.4 Implications for Research and Clinical Translation

On the basis of this evidence map, several research priorities emerge. CBD and THCA merit prioritization for further translational research in PD/AD and to a limited extent in HD respectively, given their favorable safety profile, and non-psychoactive properties. However, the formulation-dependence identified by Echeverry et al. (2024) indicates that pharmaceutical development of CBD must optimize vehicle composition alongside dose. The A2AR antagonist plus CB2R agonist combination strategy identified by Franco et al. (2019) remains a comparatively complex receptor-combination strategy identified in the included evidence and should be validated in rigorous *in vivo* studies. Given the emerging evidence for receptor-independent mechanisms, future mechanistic studies should incorporate receptor-knockout or pan-antagonist controls as standard practice to establish, rather than assume, receptor dependence. The prevalence of receptor-independent mechanisms (DJ-1, caspase-3, direct protein binding) demands systematic target-deconvolution studies using chemoproteomic approaches. Methodologically, the field must transition from single-compound, single-cell-type studies to tripartite co-culture systems (neuron-microglia-astrocyte), humanized disease models, and formal dose-response designs with toxicity endpoints. Some more computational studies may help to understand the molecular changes in receptor level. Long-term safety pharmacology studies are essential, particularly for CB2-selective agonists intended for chronic neurodegenerative indications. From a regulatory perspective, acidic cannabinoids face distinct categorization challenges compared to decarboxylated forms, which may explain their underrepresentation despite superior mechanistic profiles. Addressing these botanical and pharmaceutical regulatory barriers will be necessary to translate the PPARγ and epigenetic mechanisms of THCA and CBDA into investigational new drug pathways.

4.5 Limitations

This review is subject to the inherent limitations of scoping review methodology: heterogeneous study designs that preclude quantitative effect pooling, and the potential for publication bias favoring positive results. Restricting to English-language publications likely excluded relevant work in other languages. The use of 2015 as a pragmatic publication-year cutoff may have excluded relevant in vitro studies published before and the findings should not be interpreted as representing the complete historical body of in vitro evidence on the neuroprotective effects of cannabinoids. Additionally, most of the 26 included studies used *in vitro* designs, limiting the extent to which findings can be extrapolated to clinical populations. The inclusion of generalized LPS-induced neuroinflammation models as mechanistic proxies may also have increased heterogeneity in disease-context classification, although these studies were retained because the models address inflammatory mechanisms relevant to the target neurodegenerative disorders. Data extraction, performed by two reviewers and verified by a third in line with JBI guidance, cannot fully rule out extraction error. Finally, because the synthesis relies on data-charting summaries rather than re-analysis of primary datasets, nuanced findings from original studies may not be fully captured.

5. Conclusion

This scoping review maps a substantial and mechanistically diverse preclinical evidence base, drawn from all 26 included studies, demonstrating that cannabinoids spanning phytocannabinoids (CBD, THC, Δ8-THC, THCA, CBDA), synthetic receptor agonists (WIN552122, JWH133, ACEA, CP55940, HU-308), endocannabinoid system modulators (JZL184), and cannabinoid-active phytochemicals (β-amyrin) exert neuroprotective, anti-neuroinflammatory, antioxidant, pro-autophagic, anti-aggregative, and pro-myelinating effects across models of AD, PD, HD, and MS. Three functional domains characterize this activity: anti-neuroinflammatory mechanisms, antioxidant and anti-apoptotic pathways, and protein aggregate clearance during neuroinflammation, all

connected by a cross-cutting receptor architecture spanning synaptic preservation, receptor heteromerization, and receptor-independent mechanisms. No purely receptor-centered framework can fully account for cannabinoid neuroprotection. Pharmaceutical formulation, direct protein interaction, and off-target pharmacology must be considered alongside CB1/CB2/PPARγ/GPR55/A2AR signaling in any translational programme. Priority areas for future research include systematic dose–response characterization, validation of candidate mechanisms in physiologically relevant models, investigation of CNS exposure requirements for CB2R-targeted approaches, and systematic target-deconvolution of receptor-independent effects. These steps are needed before prioritizing specific cannabinoid candidates for clinical development.

Abbreviations

2-AG (2AG)	2-arachidonoylglycerol
3-NPA	3-nitropropionic acid
5-HT1A	serotonin (5-hydroxytryptamine) receptor 1A
5-LOX	5-lipoxygenase
6-OHDA	6-hydroxydopamine
8-OHdG	8-hydroxy-2'-deoxyguanosine
A2AR	adenosine A2A receptor
ACEA	arachidonyl-2'-chloroethylamide
AD	Alzheimer's disease
AEA	anandamide (arachidonoylethanolamide)
Akt	protein kinase B
ALS	amyotrophic lateral sclerosis
APP	amyloid precursor protein
ARG1	Arginase 1
ATF6	activating transcription factor 6
ATP	adenosine triphosphate
Aβ (Aβ40, Aβ42/Aβ1-42)	amyloid-beta (and its 40- and 42-residue isoforms)
α7nAChR	alpha-7 nicotinic acetylcholine receptor
BACE-1	beta-site amyloid precursor protein cleaving enzyme 1
Bax	Bcl-2–associated X protein
Bcl-2	An anti-apoptotic protein (first found on B-cell lymphoma 2)
BRET	bioluminescence resonance energy transfer
β-arrestin2	beta-arrestin 2
CAG	cytosine-adenine-guanine (trinucleotide repeat)
CaMKII	Ca^{2+}/calmodulin-dependent protein kinase II
cAMP	Cyclic adenosine monophosphate
CASP3	Caspase 3
CB1R (CB1)	cannabinoid receptor type 1
CB2R (CB2)	cannabinoid receptor type 2
CBD	cannabidiol
CBDA	cannabidiolic acid
CBG	cannabigerol
CDK5	cyclin-dependent kinase 5
CIITA	class II major histocompatibility complex transactivator
CNR1 / CNR2	cannabinoid receptor 1 / 2 gene
CNS	central nervous system
COX-2	cyclooxygenase-2
CREB	cAMP response element-binding protein
Cu/Zn SOD	copper/zinc superoxide dismutase
Cx43	connexin-43
DALNs	dopamine-like neurons
DJ-1	protein deglycase DJ-1 (PARK7)
DMSO	dimethyl sulfoxide
DYRK1A	dual-specificity tyrosine-phosphorylation-regulated kinase 1A

EAE	experimental autoimmune encephalomyelitis
EC90	concentration producing 90% of maximal effect
ECS	endocannabinoid system
ER	endoplasmic reticulum
ERK / ERK1/2	extracellular signal-regulated kinase
FAAH	fatty acid amide hydrolase
GAP-43	growth-associated protein 43
GFAP	glial fibrillary acidic protein
GLU	glutamate
GMSCs	gingiva-derived mesenchymal stem cells
GPCR / GPR	G-protein-coupled receptor
GPR55	G protein-coupled receptor 55
GSH	glutathione
GSK3β	glycogen synthase kinase 3 beta
HD	Huntington's disease
IC50	half-maximal inhibitory concentration
Iba-1	ionized calcium-binding adapter molecule 1
IFN-γ	interferon gamma
IL-1β	interleukin-1 beta
IL-6	interleukin-6
IL-8	interleukin-8
iNOS	inducible nitric oxide synthase
IRE1	inositol-requiring enzyme 1
JBI	Joanna Briggs Institute
JNK	c-Jun N-terminal kinase
Keap1	Kelch-like ECH-associated protein 1
KYNA	kynurenic acid
LC3 (LC3-II)	microtubule-associated protein 1A/1B-light chain 3
LOX	Lipoxygenase
LPS	lipopolysaccharide
M1 / M2	classically activated (pro-inflammatory) / alternatively activated (anti-inflammatory) microglial-macrophage phenotype
MAGL	monoacylglycerol lipase (monoglyceride lipase)
MAPK	mitogen-activated protein kinase
MBP	myelin basic protein
MCT	medium-chain triglyceride
MHC-II	major histocompatibility complex class II
miRNA	microRNA
Mn SOD	manganese superoxide dismutase
MOG (Mog)	myelin oligodendrocyte glycoprotein
mRNA	messenger RNA
MPP+	1-methyl-4-phenylpyridinium
MPTP/MPTPp	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (and its metabolite)
MS	multiple sclerosis
MSC	mesenchymal stem cell

MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (viability assay)
ND(s)	neurodegenerative disease(s)
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NFTs	neurofibrillary tangles
NGF	nerve growth factor
Ngr1	Nogo receptor 1
NO	nitric oxide
Nrf2	nuclear factor erythroid 2-related factor 2
OSF	Open Science Framework
p38	p38 mitogen-activated protein kinase
p53	tumor protein p53
p65	nuclear factor kappa B subunit (RelA)
p-Akt	phosphorylated protein kinase B
p-STAT3	phosphorylated signal transducer and activator of transcription 3
p-Tau	phosphorylated tau protein
Panx1	pannexin-1
PCC	Population–Concept–Context (framework)
PD	Parkinson's disease
PERK	(known as **EIF2AK3**)- a gene encodes an endoplasmic reticulum enzyme that senses unfolded protein stress
PGC-1α	peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PGE2 (PGE_2)	prostaglandin E2
PI3K	phosphoinositide 3-kinase
PLA	proximity ligation assay
PPARγ / PPARδ	peroxisome proliferator-activated receptor gamma / delta
PQ^{2+}	paraquat
PRISMA-ScR	Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
PSD-95	postsynaptic density protein 95
PSEN1 (PS1) / PSEN2	presenilin 1 / presenilin 2
PSMB5	proteasome subunit beta type-5
PUMA	p53 upregulated modulator of apoptosis
ROS	reactive oxygen species
RXRα (Rxra)	retinoid X receptor alpha
SNpc	substantia nigra pars compacta
SOD (SOD1)	superoxide dismutase (superoxide dismutase 1)
SQSTM1 (p62)	sequestosome 1
STAT3	signal transducer and activator of transcription 3
THC (Δ9-THC)	Δ9-tetrahydrocannabinol
Δ8-THC	Δ8-tetrahydrocannabinol
THCA (Δ9-THCA)	tetrahydrocannabinolic acid
TNF-α	tumor necrosis factor alpha
TrkA	tropomyosin receptor kinase A
TRPV1	transient receptor potential vanilloid 1
Tyr-tubulin	tyrosinated alpha-tubulin
UPR	unfolded protein response

ΔΨm	mitochondrial membrane potential

Declarations

Ethics approval and consent to participate- Not Applicable

Consent for publication-Not Applicable

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Figures

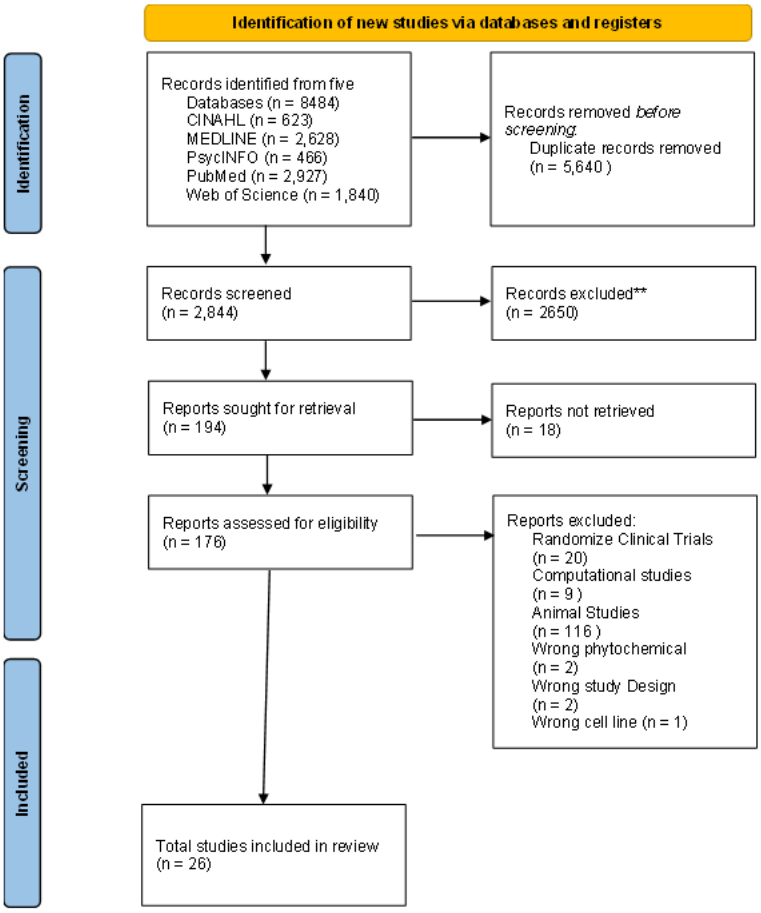


Figure 1

Prisma flow diagram of the study

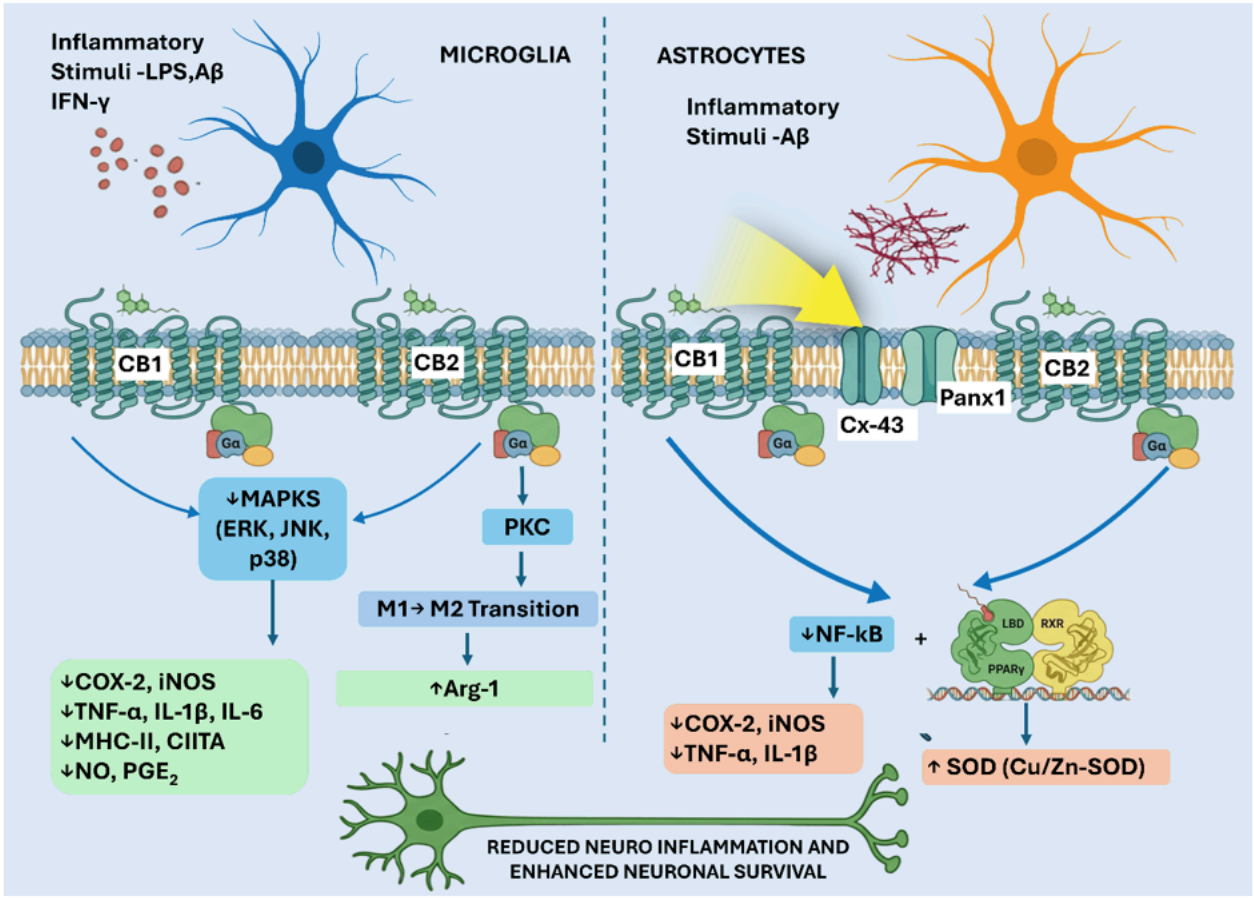


Figure 2

Cannabinoid-mediated modulation of neuroinflammatory signaling in microglia and astrocytes; The diagram illustrates CB1- and CB2-associated signaling pathways in microglia and astrocytes, including MAPK, PKC, NF-κB, and PPARγ pathways, and their relationships with inflammatory mediators, enzymes, antioxidant factors, and cellular markers. Arrows indicate proposed regulatory relationships; ↓ and ↑ denote decreased and increased activity or expression, respectively.

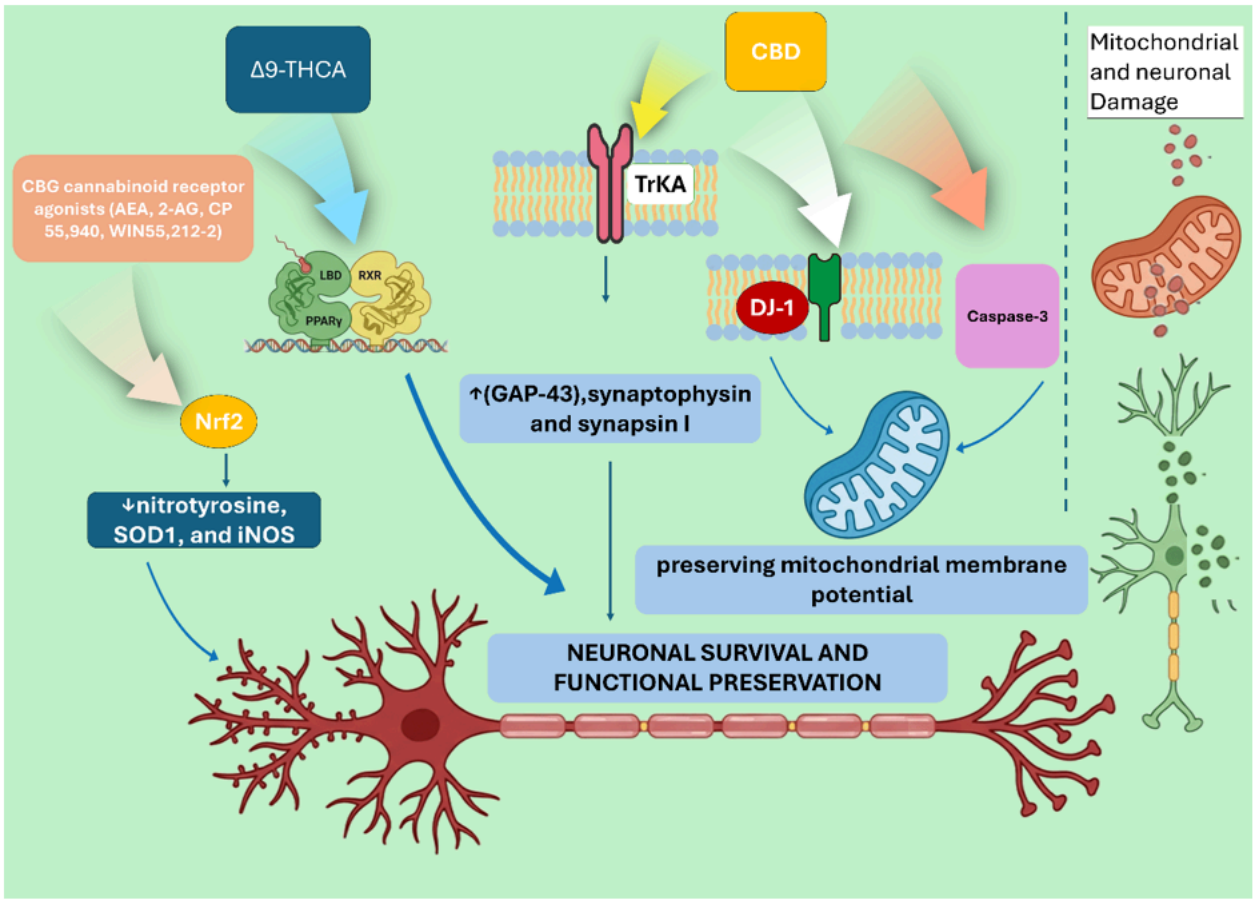


Figure 3

Cannabinoid-associated antioxidant, mitochondrial, and neurorestorative pathways; The diagram illustrates PPARγ- and Nrf2-associated signaling, TrkA signaling, and DJ-1- and caspase-3-related pathways, together with oxidative stress, mitochondrial, neuritogenic, and synaptic markers. Arrows indicate relationships depicted in the figure; ↑ and ↓ denote increased and decreased expression or activity, respectively.

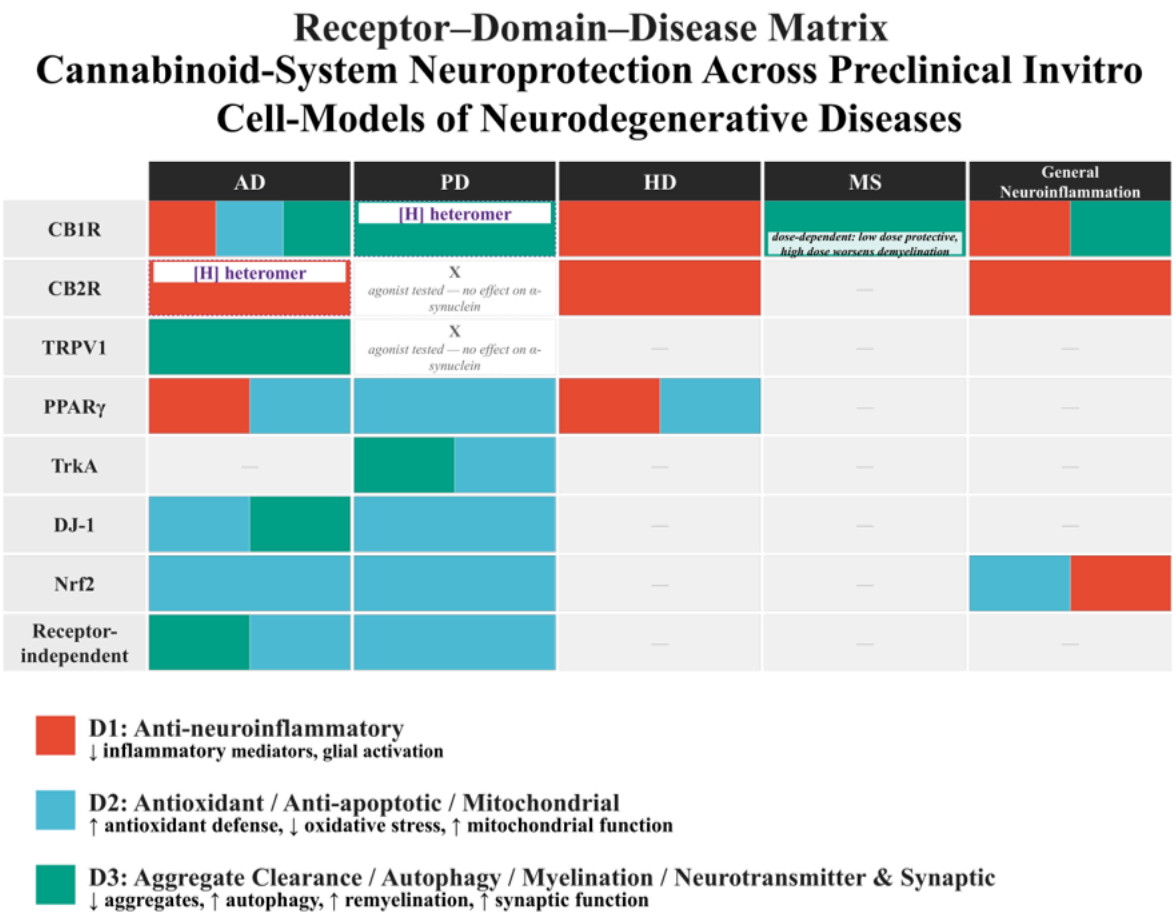


Figure 4

Receptor–mechanism–disease matrix mapping cannabinoid-associated neuroprotective mechanisms across the included studies. Rows represent receptor systems or mechanistic classes, and columns represent disease contexts. D1, D2, and D3 denote anti-neuroinflammatory; antioxidant, anti-apoptotic, and mitochondrial; and protein aggregate clearance, autophagy, myelination, and neurotransmitter-related mechanisms, respectively. Heteromeric receptor interactions are indicated separately from functional domains, and receptor-independent/direct molecular mechanisms are distinguished from receptor-mediated mechanisms. Empty cells indicate no included evidence for the corresponding receptor–disease relationship. **Cell symbols**; Split-color cell — receptor–disease pair maps to more than one functional domain (segments shown left to right); [H] heteromer (dashed purple border) — effect required a heteromeric receptor complex (e.g., A_2–CB2R in AD; CB1R/GPR55 in PD), not the receptor alone; X no effect (dashed grey box) — receptor/agonist was explicitly tested in the source study but did NOT reproduce the protective effect (e.g., CB2R/TRPV1 agonists tested for α-synuclein clearance in PD); — (light grey cell) — no evidence included in the source table for this receptor–disease pairing.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTableS1.docx