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Review Article

Apigenin-Induced Shifts in Microglial and Astrocytic Polarization: A Potential Therapeutic Strategy for Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by amyloid-β accumulation, tau pathology, synaptic failure, neurovascular dysfunction, mitochondrial injury and chronic neuroinflammation. While amyloid and tau remain central pathological features, the inflammatory state of the brain is now recognized as an active driver of disease progression rather than a secondary epiphenomenon. Microglia and astrocytes are the principal glial regulators of innate immunity, synaptic homeostasis, metabolic support and tissue repair in the central nervous system. In AD, these cells undergo heterogeneous activation states that include protective phagocytic and trophic programs as well as damaging pro-inflammatory, complement-mediated, inflammasome-driven and neurotoxic phenotypes. The historical M1/M2 and A1/A2 polarization frameworks are oversimplified, yet they remain useful shorthand for discussing inflammatory versus reparative glial tendencies. Apigenin, a naturally occurring flavone found in parsley, celery, chamomile and other plants, has emerged as a multi-target neuroprotective compound with antioxidant, anti-inflammatory, anti-amyloidogenic, neurovascular and neurotrophic properties. Preclinical studies suggest that apigenin can reduce microglial activation, suppress CD68 expression, inhibit NF-κB and ERK signaling, disrupt NLRP3 inflammasome assembly, reduce IL-1β, IL-6 and TNF-α, preserve astrocytic morphology, attenuate astrogliosis, restore neurovascular coupling, reduce amyloidogenic processing and enhance ERK/CREB/BDNF signaling. This review explored current evidence on apigenin-induced shifts in microglial and astrocytic polarization in AD-relevant models. We propose an integrated "glial state recalibration" model in which apigenin does not merely suppress inflammation but redirects glial responses away from chronic neurotoxicity toward controlled phagocytosis, trophic support, redox balance and barrier preservation. Despite promising mechanistic data, major translational barriers remain, including low bioavailability, uncertain brain exposure, limited clinical evidence, variable formulations, and incomplete understanding of dose-dependent glial effects. Finally, future development and prospective should prioritize brain-targeted delivery systems, human iPSC-derived glial models, single-cell multi-omics, biomarker-guided trials and combination strategies with disease-modifying AD therapies.

Keywords: *Apigenin, Flavonoids, Alzheimer's disease, Microglia, Astrocyte, Neuroinflammation, Glial polarization*

1. Introduction

Alzheimer's disease (AD) is the leading cause of dementia and is defined biologically by a continuum of Aβ and tau pathology that begins years before overt cognitive impairment. Yet plaques and tangles alone do not explain why neighboring synapses and neurons differ in vulnerability, why progression varies among people with comparable proteinopathy, or why reducing amyloid produces only partial clinical benefit. Contemporary models therefore place proteostasis within a broader system that includes innate immunity, vascular integrity, lipid trafficking, mitochondrial fitness, and neuron–glia metabolic coupling [1,2]. The phase 3 lecanemab and donanemab trials validated Aβ as a modifiable driver, but the modest average slowing of decline and the risk of amyloid-related imaging abnormalities also underscore the need for complementary strategies that alter how brain tissue responds to pathology [3,4].

Microglia and astrocytes are central to that response. Microglia survey the parenchyma, remodel synapses, clear debris, and organize barriers around plaques. Astrocytes regulate glutamate, ions, neurotransmitter precursors, cholesterol, energy substrates, blood–brain barrier (BBB) properties, and glymphatic flux. Under persistent Aβ, tau, cellular debris, vascular leakage, or systemic inflammation, both cell types undergo extensive transcriptional, metabolic, morphological, and epigenetic remodeling. The resulting states may be protective in one location or disease phase and harmful in another. Accordingly, expert consensus discourages equating microglia with a simple M1/M2 axis or astrocytes with an A1/A2 binary [5,6].

Apigenin is a naturally occurring flavone abundant in parsley, celery, chamomile, and several medicinal plants. Its planar 4′,5,7-trihydroxyflavone scaffold supports redox activity and interactions with kinases, transcriptional regulators, enzymes, membranes, and proteins. Reviews have catalogued antioxidant, anti-inflammatory, anti-amyloidogenic, neurotrophic, and neurovascular actions [7]. Of particular relevance, apigenin reduces activation markers in microglia and astrocytes in AD-related coculture models [8], and a recent meta-analysis of 13 animal studies reported improvement in behavioral and molecular outcomes, including lower NF-κB p65 and malondialdehyde and higher antioxidant and brain-derived neurotrophic factor (BDNF)/cAMP response element-binding protein (CREB) indices [9]. Nevertheless, "anti-inflammatory" is an imprecise therapeutic ambition. Global suppression of glia could impair plaque compaction, debris clearance, antimicrobial defense, synaptic maintenance, and repair. The sharper question is whether apigenin can redirect maladaptive glial programs while retaining beneficial functions.

This review addresses that question at three levels. First, it reframes polarization as a dynamic, multidimensional state space. Second, it integrates direct AD evidence with mechanistic evidence from related neuroinflammatory models, explicitly distinguishing demonstration from extrapolation. Third, it proposes a stage-aware "glial state-vector" development strategy in which apigenin is optimized not to silence glia, but to uncouple inflammatory amplification from aggregate containment, phagocytosis, metabolic resilience, trophic support, and barrier maintenance.

2. Narrative review approach

A structured narrative search of PubMed, publisher databases, and reference lists was conducted for peer-reviewed articles available through August 2026. Search concepts combined *apigenin* with *Alzheimer*, *amyloid*, *tau*, *microglia*, *astrocyte*, *polarization*, *neuroinflammation*, *NF-κB*, *NLRP3*, *NRF2*, *PPARγ*, *STAT*, *kynurenine*, *mitophagy*, *pharmacokinetics*, and *bioavailability*. Priority was given to primary studies using AD-relevant cells or animals, followed by mechanistic studies in other central nervous system (CNS) or immune models, human single-cell studies that refine glial-state interpretation, and recent reviews. References were cross-checked against publisher or PubMed metadata, and DOI identifiers are provided. Because the objective was conceptual synthesis rather than pooled effect estimation, selection was purposive and the review should not be interpreted as a systematic review.

3. Glial state transitions in AD

3.1. Microglia: from surveillance to containment, inflammation, and exhaustion

Homeostatic microglia express genes such as *P2RY12*, *TMEM119*, *CX3CR1*, *SALL1*, and *GPR34* and continuously sample the extracellular environment. Aβ oligomers and fibrils, tau assemblies, ATP, nucleic acids, lipids, complement, and damaged membranes activate pattern-recognition, purinergic, Fc, scavenger, and lipid-sensing receptors.

Early responses can be adaptive: migration toward plaques, TREM2-dependent survival, lysosomal activation, phagocytosis, and formation of a compact microglial barrier may limit the diffusion of toxic Aβ species. Single-cell studies transformed this field by identifying disease-associated microglia (DAM) in AD mouse models. DAM downregulate homeostatic genes and upregulate genes involved in lysosomes, phagocytosis, and lipid handling, including *APOE*, *LPL*, *CST7*, *CTSB*, *TYROBP*, and *TREM2*. A related TREM2–APOE program can drive a neurodegeneration-associated phenotype [10-12]. TREM2 also sustains mTOR-dependent energetic and biosynthetic fitness; loss of this support impairs the metabolic capacity required for a durable response to pathology [12]. Thus, neither TREM2 activation nor DAM identity is intrinsically "good" or "bad." Their impact depends on timing, aggregate species, metabolic competence, and whether phagocytosis resolves damage or becomes coupled to cytokine release and synapse ingestion [11,12].

Human data reinforce heterogeneity while warning against direct translation of mouse clusters. Single-nucleus profiling of AD prefrontal cortex revealed cell-type- and sex-dependent programs that change across pathological stages [13]. Single-cell RNA sequencing of isolated human microglia identified an AD-associated subset but also substantial interindividual diversity [14]. With chronic Aβ exposure, microglia can initially shift from oxidative phosphorylation to glycolysis through mTOR–HIF-1α, then lose metabolic flexibility and become simultaneously inflammatory and ineffective at clearance [15]. APOE4 magnifies this problem: human AD tissue and iPSC models show lipid-droplet-rich, ACSL1-positive microglia linked to inflammatory and neurotoxic outputs [16], while APOE4 produces human-specific cholesterol and matrisome abnormalities in microglia and astrocytes [17].

The conventional M1 profile, iNOS, CD86, CD68, TNF-α, IL-1β, IL-6, NO, COX-2, and NF-κB/STAT1 activity, captures a reproducible inflammatory module, and the M2 profile, arginase-1, CD206, IL-10, TGF-β, trophic factors, debris clearance, and repair, captures an alternative module. These labels remain useful experimental shorthand when the inducing stimulus and measured functions are stated (Figure 1). They become misleading when treated as mutually exclusive cell identities. A plaque-associated microglial cell can co-express phagocytic, lipid-metabolic, interferon, oxidative, and inflammatory genes. For this review, "M1-like" and "M2-like" therefore describe modules, not immutable phenotypes.

3.2. Astrocytes: homeostatic specialization and context-dependent reactivity

Astrocytes maintain synaptic and vascular homeostasis through glutamate uptake, glutamine synthesis, potassium buffering, lactate and lipid exchange, cholesterol delivery, neurotrophin production, extracellular matrix remodeling, BBB support, and aquaporin-4 organization. AD perturbs each of these functions. Astrocytes near plaques often hypertrophy and increase glial fibrillary acidic protein (GFAP), whereas astrocytes in other territories may become atrophic and lose domain organization (Figure 1). Reactive astrogliosis is therefore not synonymous with global GFAP elevation, nor does GFAP establish whether a cell is protective or toxic [6,18]. The influential A1/A2 framework arose from the finding that microglia-derived IL-1α, TNF-α, and C1q induce a neurotoxic reactive astrocyte program characterized in part by complement C3, whereas ischemia-associated astrocytes expressed a different set of potentially protective genes [18]. AD mouse and aging datasets later identified disease-associated astrocytes enriched for genes related to endocytosis, complement, and lipid metabolism; these cells emerged early and increased with pathology [19]. However, reactive astrocytes display continuous and region-specific states, and the same molecule may have different effects according to concentration and duration. Expert consensus consequently recommends defining astrocytes by multidimensional molecular and functional data rather than A1/A2 labels alone [6].

For practical purposes, an inflammatory/A1-like module includes C3, SERPING1, S100β, cytokines, NF-κB/STAT3 activity, impaired synaptogenic support, altered glutamate transport, and potentially neurotoxic secretions. A reparative/A2-like module includes S100A10, trophic support, antioxidant defense, extracellular matrix repair, and functions that promote neuronal survival (Figure 1). These are overlapping programs. A therapeutic claim of "A2 polarization" should therefore require more than reduced GFAP or increased S100A10: it should demonstrate restored glutamate handling, metabolic support, barrier function, synaptogenesis, or neuroprotection [18-20].

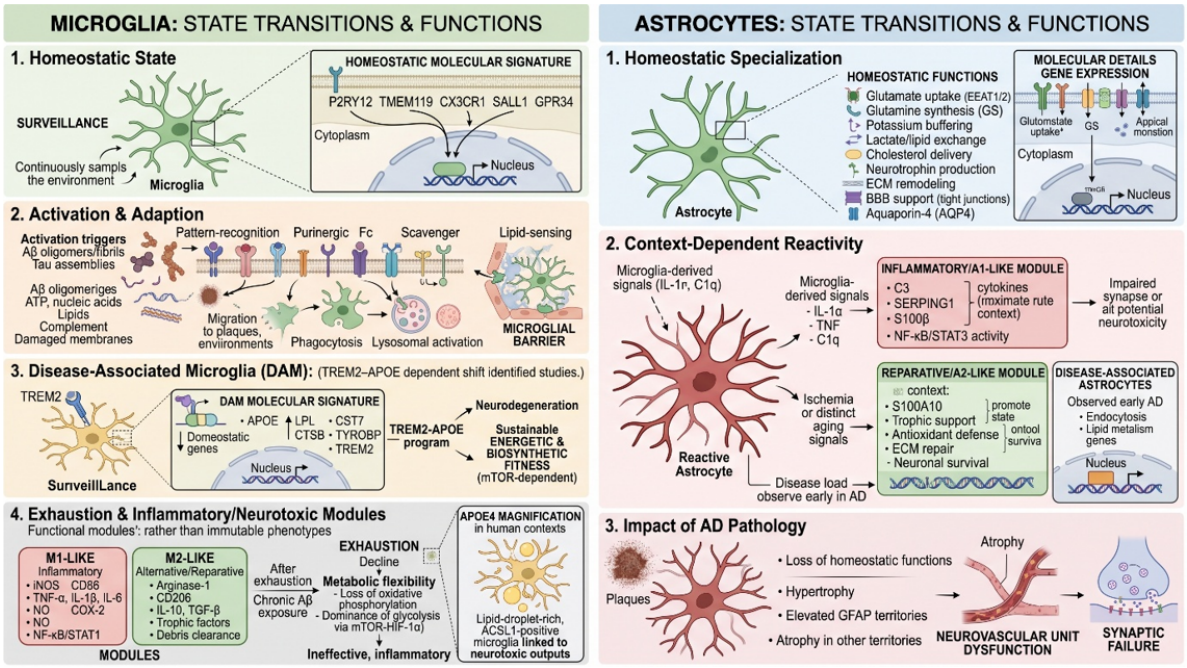

Figure 1. Microglia transition from homeostatic surveillance states toward plaque-associated adaptive states and, under persistent pathological stress, toward inflammatory/exhausted states. AD-related cues, including Aβ, tau, ATP, nucleic acids, lipids, complement, and membrane damage, engage pattern-recognition, purinergic, Fc, scavenger, and lipid-sensing receptors to drive this continuum. Adaptive plaque-associated microglia exhibit TREM2-dependent survival, lysosomal activation, phagocytosis, and DAM/TREM2–APOE-related programs, whereas chronic exposure is associated with loss of homeostatic genes, impaired clearance, metabolic inflexibility, cytokine release, and synapse ingestion. These phenotypes are shown as overlapping functional modules rather than fixed M1/M2 identities. Astrocytes shift from homeostatic states that support synaptic, metabolic, and vascular homeostasis toward context-dependent reactive states near plaques. Reactive astrocytes may display hypertrophy with GFAP induction or atrophy with loss of domain organization, and can express overlapping inflammatory A1-like and reparative A2-like modules. Microglia-derived signals, including IL-1α, TNF-α, and C1q, contribute to astrocyte reactivity, while disease-associated astrocyte states are enriched for complement, endocytic, and lipid-metabolic programs. The schematic emphasizes that astrocyte states form a multidimensional continuum and that GFAP alone does not define function.

3.3. Microglia–astrocyte crosstalk as an amplifier and a therapeutic opportunity

AD neuroinflammation is a communication disorder, not the sum of two autonomous cell reactions [20]. Microglia often sense damage first and release IL-1α, IL-1β, TNF-α, C1q, prostaglandins, ATP, reactive oxygen species (ROS), and extracellular vesicles. These signals remodel astrocytes. Reactive astrocytes then return C3, cytokines, chemokines, lipids, and metabolites that modify microglial motility, phagocytosis, and survival. Soluble Aβ can recruit complement to vulnerable synapses and drive CR3-dependent microglial engulfment before overt plaque deposition [21]. Aβ also activates astrocytic NF-κB and C3; chronic C3–C3aR signaling can impair microglial Aβ phagocytosis and aggravate amyloidosis [22,23].

The NLRP3 inflammasome provides another bridge between proteotoxicity and communication failure. In APP/PS1 mice, NLRP3 or caspase-1 deficiency improved phagocytosis, reduced amyloid burden, and preserved cognition while shifting conventional polarization markers toward a reparative profile [24]. NLRP3 also links Aβ-associated inflammation to tau phosphorylation and aggregation, although effects vary across tau models [25]. Mitochondrial damage can propagate between cells: fragmented mitochondria released by inflammatory microglia can induce neurotoxic astrocyte responses, which then transmit mitochondrial and oxidative injury to neurons [26].

Crosstalk can also be protective. Astrocyte-derived IL-3 programs TREM2-responsive microglia to migrate (Table 1), cluster around plaques, and clear Aβ and tau in mouse and human systems [27]. This example is crucial: a successful glial therapy should not simply minimize "activation." It should suppress self-sustaining injury signals while preserving or enhancing coordinated containment and clearance. This balance is the conceptual setting in which apigenin must be evaluated.

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Table 1. Working framework for glial states relevant to apigenin development.

Cell/state module	Representative markers/pathways	Potentially beneficial functions	Potentially harmful functions	Interpretation for apigenin studies
Homeostatic microglia	P2RY12, TMEM119, SALL1, CX3CR1	Surveillance, trophic support, physiological pruning	Can be lost with age/ pathology	Preservation is desirable but "return to baseline" may be impossible near plaques [10-12]
DAM/plaque-associated microglia	TREM2, APOE, LPL, CST7, TYROBP, lysosomal genes	Plaque compaction, lipid processing, aggregate uptake	Lipid overload, inflammatory signaling, functional exhaustion	Measure plaque barrier and phagocytosis as well as cytokines [10-12]
M1-like inflammatory module	NF-κB, STAT1, CD40, CD68, CD86, iNOS, TNF-α, IL-1β, IL-6, COX-2	Acute defense, recruitment, initial debris response	NLRP3 activation, ROS/NO injury, synapse loss, astrocyte toxicity	Apigenin consistently suppresses many components, but inhibition must not abolish clearance [8,20,30,34]
M2-like reparative module	PPARγ, Arg1, CD206, IL-10, TGF-β, NRF2/HO-1	Resolution, repair, antioxidant defense, phagocytosis	May be insufficient or contextually maladaptive	Demonstrate function; do not infer M2 conversion from one marker [17,26,47]
Homeostatic astrocytes	SLC1A2/EAAT2, GLUL, AQP4, metabolic and cholesterol programs	Glutamate uptake, energy and lipid support, BBB/ glymphatic regulation	Loss of function increases excitotoxic and vascular stress	Restoration of support functions is a core outcome [8,14,31,40]
Inflammatory/A1-like astrocyte module	C3, SERPING1, S100β, NF-κB, STAT3, cytokines	Short-term containment or defense in some contexts	Complement amplification, loss of synaptogenic and phagocytic support, neurotoxicity	Reduced GFAP alone is inadequate; quantify C3, transporters, metabolism, and neuronal effects [22, 28, 47, 53]
Reparative/A2-like astrocyte module	S100A10, trophic and repair-associated programs	Neuroprotection, matrix repair, trophic support	Binary label masks heterogeneity	Recent non-AD evidence supports apigenin-induced shift, requiring replication in AD models [18,20,41]

4. Apigenin as a pleiotropic glial-state modulator

Apigenin's appeal derives from pathway convergence. Rather than binding one disease-specific target with high selectivity, it modifies several regulatory nodes that jointly shape glial behavior. In macrophages and monocytes, it can reduce p65 phosphorylation, NF-κB nuclear activity, ERK-dependent cytokine expression, inflammasome assembly, and inflammatory mediator production [28,29]. In microglia it suppresses IFN-γ/STAT1-induced CD40, TNF-α, and IL-6 [30]; reduces NO and PGE2 through iNOS, COX-2, p38 (Figure 2), and JNK regulation [31]; inhibits IL-31 and IL-33 signaling outputs [32]; and activates a GSK-3β/NRF2/HO-1 antioxidant program while reducing NF-κB-dependent cytokines [33]. In astrocytes it inhibits activation and IL-31/IL-33 production through ERK, NF-κB, and STAT3 [34].

Pleiotropy is both a strength and a liability. AD involves mutually reinforcing proteinopathic, inflammatory, redox, metabolic, trophic, and vascular processes, making a network-active compound rational. Conversely, effects may be dose-, time-, and cell-dependent. Concentrations that suppress one inflammatory reporter may activate another pathway or become cytostatic. Apigenin should therefore be developed with exposure–response maps and causal target validation rather than a long unranked list of molecular associations [34]. A further distinction is essential. "Apigenin" may refer to purified aglycone, dietary glycosides, plant extracts, metabolites, salts, or nanoformulations. These preparations do not share pharmacokinetics. Studies using parenteral apigenin or high micromolar cell exposure cannot be directly equated with consuming apigenin-containing food. Translational interpretation requires chemical identity, purity, vehicle, route, free and conjugated exposure, and brain concentration.

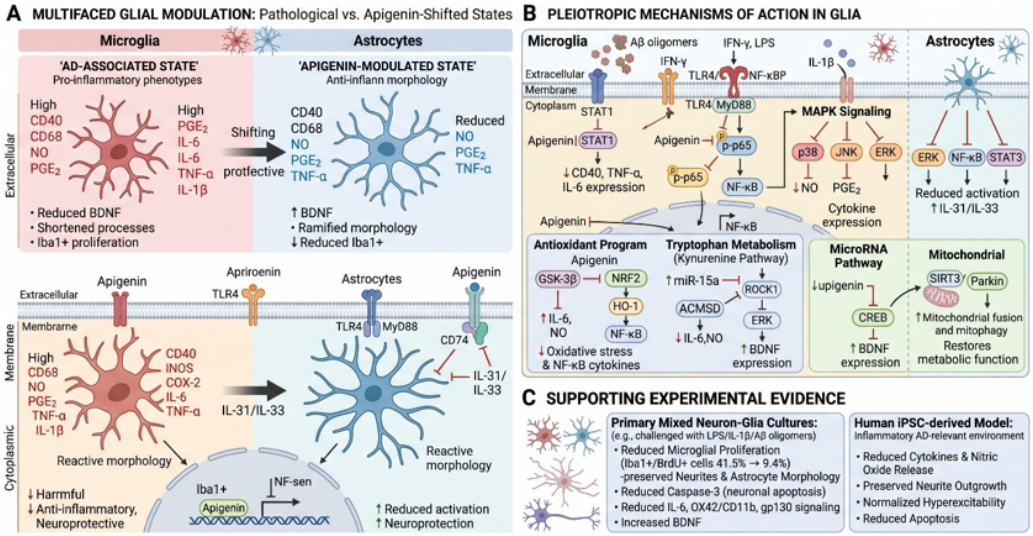

Figure 2. Apigenin is depicted as a convergent signaling hub acting across microglia, astrocytes, and peripheral innate immune-like cells, with inhibitory influence on inflammatory nodes including NF-κB/p65, p38/JNK, and CD40-associated signaling. In microglia, the schematic summarizes suppression of IFN-γ/STAT1/CD40 and TLR4/MyD88/NF-κB-driven inflammatory programs, including iNOS, COX-2, NO, PGE2, and cytokine output, together with activation of a GSK-3β/NRF2/HO-1 antioxidant module and modulation of ACMSD-linked tryptophan routing. NRF2/HO-1 activation with reciprocal attenuation of inflammatory signaling is a recurrent neuroprotective motif in glial injury models. In astrocytes and multicellular neural systems, apigenin is illustrated as reducing ERK/NF-κB/STAT3-associated activation, lowering IL-6 and related inflammatory signaling, decreasing activated/proliferating microglial populations, increasing BDNF, preserving neurite architecture, and reducing apoptosis. The biological interpretation panel emphasizes that apigenin may function as a network-active modulator of inflammatory, redox, mitochondrial, and trophic processes relevant to AD, while also acknowledging important caveats including dose-, time-, and cell-context dependence. This framing is appropriate because AD pathology integrates neuroinflammation, glial dysfunction, and mitochondrial stress rather than a single isolated pathway.

5. Evidence for apigenin-induced shifts in microglial programs

5.1. Direct AD-relevant cellular evidence

The most directly relevant study used primary mixed neuron–glia cultures from rat brain challenged with LPS, IL-1β, or Aβ1–42 oligomers. Apigenin at 1 μM, given after the insult, preserved neurites and astrocyte morphology, reduced neuronal caspase-3 activation, and decreased microglial proliferation and activation [8]. After LPS, the proportion of Iba1/BrdU-positive cells fell from 41.5% to 9.4%, and apigenin reduced Iba1- and CD68-positive populations. After Aβ, it reduced Iba1/BrdU labeling toward control levels. IL-6, OX42/CD11b, and gp130 signaling were reduced, whereas BDNF expression increased. These data demonstrate post-insult efficacy in a multicellular system and link glial modulation to neuronal survival [8,38].

The experiment does not, however, establish a complete M1-to-M2 conversion. CD68 reduction, branching morphology, and lower cytokines indicate suppression of an inflammatory module; no broad M2 functional program was mapped. Mixed cultures also prevent precise attribution of each molecular change to microglia or astrocytes. Nonetheless, the low effective concentration and use of three insults, including Aβ oligomers, make this a foundational AD-relevant result [8]. A human iPSC-derived model provided complementary evidence. Inflammatory AD-relevant cultures exposed to apigenin showed reduced cytokine and nitric oxide release, preserved neurites, normalized hyperexcitability, and reduced apoptosis [35]. Although the model was not designed to resolve microglial states at single-cell depth, it strengthens the proposition that apigenin can protect human neural networks from inflammation-associated dysfunction.

5.2. Microglial signaling studies

Earlier work in N9 and primary mouse microglia showed concentration-dependent inhibition of IFN-γ-induced CD40 and reduced TNF-α and IL-6 after CD40 ligation, mediated by reduced STAT1 phosphorylation [30]. This is relevant to AD because Aβ and IFN-γ can enhance microglial CD40, and CD40–CD40L interactions amplify antigen presentation and cytokine production. Apigenin therefore acts not only downstream at cytokines but at a state-defining transcriptional checkpoint. In primary and BV2 microglia, apigenin reduced NO, iNOS, PGE2, and COX-2 and inhibited p38/JNK activation [31]. In SIM-A9 cells, higher micromolar apigenin reduced Iba1 and LPS-induced IL-31/IL-33 through MAPK, NF-κB, and STAT3 regulation [32]. In BV2 cells, apigenin increased NRF2 and HO-1 in a GSK-3β-dependent manner; NRF2 disruption weakened suppression of cytokines and NF-κB [33]. These studies define at least three separable modules, STAT1/CD40, MAPK/eicosanoid/NO, and GSK-3β/NRF2, that converge on an inflammatory microglial phenotype. Apigenin also modified tryptophan metabolism in LPS-stimulated MG6 microglia. It increased Aminocarboxymuconate Semialdehyde Decarboxylase (ACMSD), decreased IDO, reduced IL-6 and NO, and inhibited ERK/JNK and NF-κB nuclear signaling [36]. This result links inflammatory state to kynurenine pathway routing. By favoring ACMSD, apigenin could theoretically reduce flux toward the excitotoxic metabolite quinolinic acid, although metabolite flux and AD outcomes were not directly measured [17,32,33].

5.3. In vivo evidence for microglial modulation

In GFAP–IL-6 mice, chronic apigenin-enriched chow reduced hippocampal Iba1-positive microglial numbers by approximately one-third and increased process complexity [37]. Importantly, histological improvement did not rescue spatial-memory recall in aged transgenic mice. This negative behavioral result prevents a simplistic equation between reduced microgliosis and clinical benefit. It suggests that inflammation alone, advanced age, irreversible circuit damage, insufficient brain exposure, or the specific behavioral assay can limit efficacy. In methotrexate-treated rats, apigenin reduced hippocampal microglial activation and inflammatory/oxidative injury and improved cognition through a miR-15a/ROCK1/ERK/CREB/BDNF pathway [38]. In LPS-treated mice, it restored mitochondrial fusion and mitophagy through SIRT3/PINK1/Parkin signaling and improved cognition [39]. These models are not AD, but they support the idea that glial reprogramming requires mitochondrial quality control and neurotrophic recovery, not cytokine suppression alone. Retinal microglia offer direct polarization evidence in a neural tissue. In experimental autoimmune uveitis and human HMC3 microglia, apigenin reduced CD74, iNOS, inflammatory cytokines, and migration through TLR4/MyD88 signaling [40]. Notably, arginase-1 was not significantly restored, leading the investigators to conclude that apigenin blocked M1-like polarization without fully inducing M2 conversion. This careful distinction should guide interpretation in AD [38,40].

6. Evidence for apigenin-induced shifts in astrocytic programs

Astrocyte evidence is smaller but increasingly coherent. In the AD-relevant mixed cultures described above, inflammatory and Aβ insults induced elongated, highly GFAP-reactive astrocytes, whereas 1 μM apigenin preserved polygonal morphology and GFAP patterns resembling controls [8]. Because the cultures contained microglia, the astrocytic effect could reflect direct signaling, reduced microglial cytokines, or both, precisely the network action that may matter in vivo. In purified LPS-activated astrocytes, apigenin prevented activation and reduced IL-31 and IL-33 transcription, protein expression, and secretion. Mechanistic inhibitor experiments implicated suppression of ERK, NF-κB, and STAT3, including reduced nuclear translocation and DNA binding [34]. IL-33 can be alarmin-like or homeostatic depending on context, so lower IL-33 is not automatically beneficial; nevertheless, the study directly demonstrates astrocyte target engagement at major inflammatory pathways. The strongest explicit A1/A2 evidence currently comes from outside AD.

In a 2026 rat model of fibromyalgia-like neuroinflammation, apigenin reduced spinal GFAP, C3, C1q, S100β, IDO, kynurenine, AHR, NF-κB, oxidative stress, and inflammatory mediators while increasing S100A10, an A2-associated marker [41]. This study supplies an integrated kynurenine–AHR–NF-κB mechanism and supports an A1-like-to-A2-like shift. Its anatomical site, disease trigger, and behavioral phenotype differ substantially from AD, and the finding should be considered a mechanistic bridge rather than proof of astrocyte repolarization in AD. Astrocyte benefit could also arise indirectly. Apigenin preserves BBB tight-junction proteins and suppresses TLR4-mediated inflammation after subarachnoid hemorrhage. In AD, reduced vascular leakage would lower exposure of astrocytes and microglia to fibrinogen, thrombin, peripheral cytokines, and immune cells. Thus, part of the apparent "polarization" effect may be upstream normalization of the neurovascular milieu [42].

7. An integrated mechanism: the apigenin glial state-vector model

A binary arrow from M1 to M2 and A1 to A2 is attractive but biologically inadequate. We propose that apigenin changes a glial state vector with at least seven interacting dimensions: inflammatory transcription, inflammasome activity, redox defense, immunometabolism, proteostatic clearance, trophic/synaptic support, and intercellular communication. Benefit is predicted when these dimensions move in a coordinated direction; a favorable change in one marker is insufficient [43].

7.1. Dimension 1: TLR4/MyD88/NF-κB and MAPK inflammatory transcription

TLR4 recognizes LPS but also responds to endogenous danger signals in damaged brain. Through MyD88, IKK, NF-κB, and MAPKs, TLR4 induces iNOS, COX-2, TNF-α, IL-1β, IL-6, chemokines, and inflammasome components. Aβ can amplify related pathways in both glial cell types. Apigenin reduces p65 phosphorylation and nuclear activity [28], decreases ERK-dependent cytokine mRNA stability and NF-κB activation [29], and suppresses TLR4-associated neuroinflammation in several CNS models [42,43]. In uveitis, TLR4/MyD88 inhibition accompanied selective loss of M1-like microglial markers without a full M2 program [40]. This node can reduce the initiating signal from microglia to astrocytes and the return signal from astrocytes to microglia. The risk is excessive suppression during early disease, when an acute inflammatory and glycolytic response supports migration and phagocytosis. Dose and timing should therefore be chosen to reduce sustained NF-κB output without abolishing inducible clearance.

7.2. Dimension 2: STAT1/CD40 and STAT3/gp130 state stabilization

IFN-γ/STAT1/CD40 signaling sustains inflammatory microglial interactions, whereas IL-6-family cytokines signal through gp130/JAK/STAT3 in both glia. Apigenin suppresses STAT1 phosphorylation and CD40 in microglia [30] and reduces IL-6/gp130 in mixed neuron–glia cultures [8]. In astrocytes, it inhibits STAT3 activation, translocation, and cytokine production [34]. Joint inhibition may be especially valuable because IL-6 from one glial cell can stabilize reactivity in the other. STAT3 also supports astrocyte survival and scar organization after acute injury. The aim is therefore not indiscriminate STAT3 blockade but normalization of chronic gp130/STAT3 signaling. Future studies should determine whether apigenin restores astrocytic glutamate transport and metabolic support while reducing inflammatory STAT3 targets [34,38,42].

7.3. Dimension 3: NLRP3, IL-1β, and pyroptotic amplification

NLRP3 integrates lysosomal damage, ion flux, mitochondrial ROS, and misfolded proteins. Its activation recruits ASC, cleaves caspase-1, matures IL-1β/IL-18, and can drive gasdermin-mediated pyroptosis. In AD models, NLRP3 promotes Aβ accumulation and tau pathology [24,25]. Apigenin disrupts NLRP3/ASC assembly and caspase-1 activation in macrophages [29], and upregulation of PPARγ accompanies reduced NLRP3 and IL-1β in chronically stressed rat brain [44]. More recent human monocyte/macrophage data show that apigenin inhibits NLRP3-dependent IL-1β across ATP, urate, and nigericin stimuli, apparently independently of CD38 and P2X7R and partly through calcium-flux regulation. These findings make NLRP3 a plausible high-value bridge between apigenin and AD glial reprogramming. Yet direct demonstration in human AD microglia is absent. Causal experiments should test whether NLRP3 rescue or activation reverses apigenin's effects on Aβ uptake, tau kinase/phosphatase balance, astrocytic C3, and synapse survival [45].

7.4. Dimension 4: NRF2/HO-1, GSK-3β, and PPARγ redox–resolution coupling

Oxidative stress is not merely downstream of inflammation; it helps determine glial state. NRF2 induces HO-1, glutathione synthesis, NAD(P)H-related enzymes, and detoxification programs. In BV2 cells, apigenin increased GSK-3β phosphorylation and NRF2/HO-1, and NRF2 loss weakened its anti-inflammatory effect [33]. Apigenin also activated NRF2 in aging and neuroinflammatory models and increased antioxidant indices in the animal literature summarized by the AD meta-analysis [9]. GSK-3β intersects tau phosphorylation, BACE1, NF-κB, and NRF2. In an Aβ25–35 rat model, oral apigenin lowered GSK-3β expression, BACE1, and tau hyperphosphorylation [46]. These neuronal/proteostatic effects can reduce the danger signals that drive glia, creating a virtuous loop. PPARγ coordinates lipid handling, oxidative metabolism, phagocytosis, and resolution. Apigenin directly modulated PPARγ in macrophages, reduced p65 nuclear localization, suppressed M1 genes, and enhanced M2-associated genes; PPARγ antagonism or knockdown diminished these effects [47]. Although peripheral macrophages are not microglia, the mechanism is relevant because microglial PPARγ can oppose NF-κB and improve lipid processing. In stressed rat brain, PPARγ antagonism also weakened apigenin-mediated NLRP3 inhibition [44]. A key hypothesis is therefore a PPARγ–NRF2 cooperative module that lowers inflammatory transcription while restoring the lipid and redox capacity needed for non-phlogistic phagocytosis.

7.5. Dimension 5: immunometabolism, mitochondrial quality, and kynurenine routing

Glial state is constrained by energy. Acute Aβ exposure triggers glycolysis to support microglial migration, phagocytosis, and cytokine synthesis; chronic exposure can produce combined glycolytic and mitochondrial failure [15]. Damaged mitochondria generate ROS and DNA that activate NLRP3, and exported fragments can propagate inflammatory astrocyte responses [26]. Apigenin improved SIRT3/PINK1/Parkin-dependent mitophagy and MFN2-associated fusion in LPS-treated mice [39]. The proposed consequence is not simply "more mitophagy," but removal of inflammasome-activating mitochondria while preserving ATP generation. Tryptophan metabolism adds a second metabolic layer. In microglia, apigenin reduced IDO and restored ACMSD in association with lower ERK/JNK/NF-κB, IL-6, and NO [36]. In the fibromyalgia model, suppression of KYN/AHR accompanied reduced inflammatory astrocyte markers and increased S100A10 [41]. Because kynurenine metabolites influence excitotoxicity, redox balance, and AHR-dependent glial transcription, this pathway could connect the gut–immune–brain axis to apigenin action. Direct measurements of kynurenine, quinolinic acid, kynurenic acid, and picolinic acid in AD models are needed [19,43].

7.6. Dimension 6: Aβ/tau load, phagocytosis, and trophic resilience

Apigenin reduced amyloidogenic processing and restored ERK/CREB/BDNF signaling in APP/PS1 mice given 40 mg/kg orally for 12 weeks; fibrillar deposits and insoluble Aβ were reduced and learning improved [48]. It protected neurovascular coupling after Aβ25–35 challenge [49], reduced GSK-3β/BACE1/tau pathology in Aβ-injected rats [46], and reduced mitochondrial cytochrome-c/caspase signaling [50]. In scopolamine-treated mice, it regulated BACE1/presenilins, apoptosis, and BDNF/TrkB [51]. In a transgenic Drosophila AD model, it reduced Aβ42 aggregation and acetylcholinesterase activity [52]. These actions can indirectly normalize glia by lowering the aggregate and neuronal-debris burden. Conversely, glial modulation may explain part of the reduction in Aβ. The direction of causality remains unresolved because many animal studies measured whole-tissue biomarkers after treatment. Cell-specific depletion, conditional knockouts, and in vivo phagocytosis assays are needed to determine whether apigenin decreases Aβ production, increases microglial/astrocytic clearance, changes plaque compaction, or combines these mechanisms [46]. Trophic resilience is equally important. In mixed cultures, apigenin increased BDNF after inflammatory injury [8]; in APP/PS1 mice it restored ERK/CREB/BDNF [48]. Apigenin can also bind BDNF and potentiate TrkB phosphorylation, neurite outgrowth, synaptic-protein expression, and protection against Aβ in neuronal cultures [53]. Trophic signaling may raise the threshold at which glial inflammation becomes synaptotoxic.

7.7. Dimension 7: rewiring microglia–astrocyte communication

The integrated prediction is that apigenin reduces microglial IL-1α/TNF/IL-1β/NO/ROS and STAT1/CD40 signals, thereby lowering induction of inflammatory astrocytes. Direct astrocytic NF-κB/STAT3 inhibition should reduce C3 and cytokine return signals. NRF2/PPARγ and mitochondrial repair should increase the capacity of both cell types to process lipids and debris without inflammasome activation. Reduced Aβ/tau and improved BBB integrity decrease the upstream stimulus. This model also identifies what apigenin must not suppress: TREM2-dependent energetic fitness, IL-3-directed plaque clustering, physiologic complement functions, and effective lysosomal clearance. The optimal state is neither "resting" nor uniformly "anti-inflammatory." It is an organized, metabolically competent, low-collateral-damage response [32,4048-51].

7.8. Alternative explanations, competing mechanisms, and boundary conditions

Several alternative explanations could account for the observed glial changes. First, reduced Iba1, CD68, cytokines, or GFAP may be secondary to lower neuronal injury or Aβ production rather than a primary effect on glial state. The APP/PS1 study, for example, found reduced BACE1/β-CTF and Aβ alongside restored trophic signaling [48]. If apigenin first decreases neuronal Aβ generation, glia would encounter less stimulus and appear "repolarized." This would still be therapeutically useful, but it is mechanistically distinct from direct glial reprogramming. Cell-restricted exposure, conditional target deletion, and transfer of conditioned media are required to separate these directions. Second, lower cell counts or activation markers could reflect cytostasis or selective toxicity. Apigenin is antiproliferative at sufficiently high concentrations. The 1 μM coculture study reported no toxicity and improved neuronal survival [8], whereas several microglial experiments used tens of micromolar concentrations. Each future study should report viability, proliferation, apoptosis, cell number, and unbound exposure in parallel. A reduction in inflammatory secretion is not beneficial if it is produced by eliminating metabolically active microglia.

Third, antioxidant activity can obscure a more specific signaling mechanism. Direct ROS scavenging, reduced mitochondrial ROS production, NRF2 induction, inhibition of NADPH oxidases, and lower inflammatory-cell abundance all reduce oxidative readouts but imply different dose requirements and durability. Since free apigenin concentrations in human plasma after food are generally nanomolar [54], direct stoichiometric scavenging is unlikely to explain a pharmacological CNS effect at dietary exposure. Catalytic or transcriptional mechanisms, active metabolites, tissue concentration, or formulation-enhanced delivery are more plausible and should be measured. Fourth, the same pathway may change sign across time. Acute complement and glycolysis can facilitate chemotaxis and phagocytosis, whereas chronic C3aR activation and metabolic exhaustion impair clearance [15,23]. IL-33, STAT3, and even NF-κB can support repair in specific contexts. Therefore, a lower pathway signal at one terminal time point cannot establish that the integrated trajectory improved. Dense longitudinal sampling and live imaging are preferable to endpoint-only classification. Fifth, rodent amyloid models incompletely reproduce sporadic human AD. Many develop heavy plaque burden without the full distribution of tau, vascular disease, neuronal loss, and decades-long aging found in patients. Conversely, acute Aβ injection and LPS produce abrupt inflammation unlike the slow human continuum. Concordance across transgenic, knock-in, tau, vascular, and human iPSC models should be required before clinical claims are strengthened [11,20,36,54].

8. Preclinical evidence synthesis

Taken together, the evidence supports suppression of inflammatory glial modules more strongly than it supports complete beneficial repolarization. Direct AD-relevant cellular evidence is moderate; animal evidence for cognition and core pathology is encouraging but heterogeneous; explicit astrocyte-state evidence in AD is weak; and human clinical evidence is absent. This hierarchy should be visible in claims, figures, and future grant design (Table 2).

Table 2. Key studies informing apigenin-mediated glial reprogramming.

Study/model	Apigenin exposure	Glial or related outcomes	Interpretation and limitation
N9 and primary mouse microglia; IFN-γ/CD40 challenge [30]	Up to 25 μM, short exposure	Lower STAT1 phosphorylation, CD40, TNF-α, and IL-6	Direct microglial mechanism; transformed/rodent cells and relatively high concentration
Primary/BV2 microglia and focal ischemia model [31]	1–10 μM in vitro; 20 mg/kg orally in mice	Lower NO, PGE2, iNOS, COX-2, p38/JNK; fewer OX42-positive cells	Demonstrates CNS activity but not AD or full polarization
Human iPSC AD-relevant neural model [35]	50 μM in principle inflammatory experiments	Reduced cytokine/NO release, hyperexcitability, neurite injury, and apoptosis	Human neural relevance; state-resolved microglial/astrocytic attribution limited

Table 2. Continued..

Study/model	Apigenin exposure	Glial or related outcomes	Interpretation and limitation
Primary rat neuron–glia cocultures challenged with LPS, IL-1β, or Aβ [8]	1 μM after insult	Lower Iba1/BrdU, CD68, OX42, IL-6/gp130; preserved GFAP morphology; higher BDNF and neuronal survival	Strongest direct multicellular AD-relevant evidence; no broad single-cell state map
LPS-activated astrocytes [34]	Micromolar pretreatment	Reduced astrocyte activation and IL-31/IL-33 via ERK, NF-κB, STAT3	Direct astrocyte signaling; LPS is not AD and cytokines are context-dependent
APP/PS1 mice [48]	40 mg/kg orally, 5 days/week, 12 weeks	Lower BACE1/β-CTF, Aβ deposits, oxidative stress; restored ERK/CREB/BDNF and cognition	AD transgenic efficacy; glial state not deeply profiled
GFAP–IL-6 mice [37]	Apigenin-enriched diet (~110 mg/kg/day) chronically	Fewer Iba1-positive microglia and greater ramification; no memory rescue	Valuable negative functional dissociation; model represents chronic IL-6 rather than AD proteinopathy
LPS cognitive-impairment mice [39]	40 mg/kg orally for 7 days	Improved SIRT3/PINK1/Parkin, mitochondrial fusion/mitophagy, cognition	Supports immunometabolic mechanism; non-AD insult
Methotrexate cognitive injury in rats [38]	20 mg/kg orally for 30 days	Lower microglial activation/inflammation; miR-15a/ROCK1/ERK/CREB/BDNF modulation	Connects microglia to trophic recovery; non-AD model
Autoimmune uveitis and HMC3 microglia [40]	20 mg/kg intraperitoneally; cell dose-response	TLR4/MyD88 inhibition; lower M1 markers and migration without robust Arg1 rescue	Direct human microglial-line polarization evidence; retina/autoimmunity, not AD
Fibromyalgia-like rat model [41]	Systemic apigenin; study-specific regimen	Lower GFAP, C3, C1q, S100β, KYN/AHR/NF-κB; higher S100A10	Most explicit A1/A2-like evidence; spinal cord and non-AD disease context
Human monocytes/macrophages with NLRP3 stimuli [45]	Acute micromolar exposure	Lower IL-1β, gasdermin-D cleavage, and Ca2+ flux independent of CD38	Human innate-immune mechanism; peripheral cells and supradietary exposure

9. Pharmacokinetics, delivery, and safety

9.1. Absorption and metabolism

Apigenin is poorly soluble and undergoes extensive intestinal and hepatic glucuronidation and sulfation. The circulating pool therefore consists largely of conjugates, with smaller amounts of aglycone and hydroxylated metabolites. A pharmacokinetic review concluded that oral bioavailability is limited and that tissues are exposed principally to glucuronide/sulfate conjugates or luteolin, with potential accumulation because elimination can be slow [55]. In radiolabeled rats, approximately 51% of dose-related radioactivity was recovered in urine and 12% in feces over 10 days; the long terminal signal probably reflected total labeled species rather than sustained free aglycone [56]. Human dietary data emphasize the exposure gap. Eleven volunteers consuming an unusually parsley-rich meal achieved a mean maximum plasma apigenin concentration of about 127 nmol/L, with high interindividual variation; only a small fraction of the ingested amount appeared in 24-hour urine [54]. These concentrations are below many 10–60 μM cell experiments, although the 1 μM coculture effect is closer to a potentially achievable pharmacological range. Local deconjugation, tissue accumulation, active metabolites, and repeated dosing could alter effective exposure, but these possibilities require direct measurement [53-57].

9.2. Brain penetration

Lipophilicity favors membrane permeation, yet extremely low aqueous solubility and rapid conjugation limit delivery of free apigenin. A cleavable L-lysine conjugate improved experimental brain delivery and released measurable apigenin in mouse brain [57]. Such work demonstrates feasibility but does not establish the oral brain exposure of unmodified apigenin. Claims that dietary apigenin "readily crosses" the BBB should therefore be replaced by quantitative statements specifying species, route, formulation, analyte, and time.

9.3. Formulation opportunities

Micelles, liposomes, nanosuspensions, cyclodextrins, phospholipid systems, and self-nanoemulsifying formulations can improve solubility and systemic exposure. A bioactive SNEDDS approximately doubled apigenin Cmax and area under the curve in rats compared with powder [58], and PEG-based nanosuspension strategies have improved dissolution and bioavailability. For AD, the next generation should combine solubilization with brain and cell targeting, such as transferrin-receptor or low-density lipoprotein receptor-related protein ligands, intranasal delivery, or carriers preferentially taken up by plaque-associated microglia. Delivery systems must not be presumed inert. Nanoparticles can activate complement, alter microglial phagocytosis, accumulate in liver and spleen, or release apigenin at concentrations that suppress useful immune functions [59]. Comparative studies should therefore evaluate free drug, carrier alone, non-targeted formulation, and targeted formulation with matched systemic exposure.

9.4. Safety and interactions

Apigenin-rich foods are widely consumed, but culinary exposure does not establish the safety of chronic concentrated or brain-targeted dosing in older adults. Apigenin can inhibit drug-metabolizing enzymes and transporters, creating interaction risks in a population commonly receiving anticoagulants, antiplatelets, antidepressants, antiepileptics, cardiovascular drugs, and anti-dementia agents [55]. High-dose acute exposure caused hepatotoxicity in mice in one study [60]. Sedative/GABAergic activity and endocrine effects also merit monitoring. A translational package should include chronic toxicology in aged animals, hepatic and hematologic assessment, electrocardiography, genotoxicity, cognition and motor testing, and interaction studies with cholinesterase inhibitors, memantine, anticoagulants, and anti-Aβ antibodies [59,60].

10. Translational barriers and experimental priorities

10.1. Replace marker-only polarization with functional state mapping

Many studies infer benefit from lower Iba1, GFAP, CD68, iNOS, or one "M2/A2" marker. These measures are insufficient. Iba1 and GFAP reflect structure and reactivity, not valence; CD68 can indicate useful lysosomal clearance; and arginase-1 is not a universal human microglial marker.

Future studies should combine: (i) single-cell or single-nucleus transcriptomics; (ii) spatial localization relative to plaques, tangles, vessels, and synapses; (iii) proteomics and secretomics; (iv) metabolic flux, mitochondrial respiration, glycolysis, and lipid-droplet analysis; (v) Aβ/tau uptake, degradation, and plaque compaction; (vi) complement-dependent synapse engulfment; and (vii) neuronal electrophysiology and survival. A minimal claim of beneficial microglial reprogramming should show reduced sustained inflammatory/pyroptotic output and preserved phagocytosis or plaque containment. A minimal astrocyte claim should show reduced maladaptive complement/cytokine output and restored glutamate transport, trophic/metabolic support, BBB interaction, or neuronal protection [13,33,48,56-59].

10.2. Use human, aged, multicellular, and genotype-aware models

Most evidence comes from immortalized rodent microglia, neonatal cultures, or acute LPS exposure. These systems poorly reproduce aged human microglial epigenetics, APOE4 lipid biology, chronic Aβ/tau exposure, or human astrocyte diversity. Priority models include isogenic APOE3/APOE4 iPSC-derived microglia–astrocyte–neuron tricultures, vascularized organoids, microfluidic BBB systems, directly induced aged cells, xenotransplanted human microglia, and postmortem slice cultures. Human AD-associated states identified by single-cell studies should be used as pharmacodynamic reference maps [13,14]. Sex must be designed rather than adjusted away. Human single-cell data show sex-biased AD responses [13], and apigenin has estrogen-receptor-related activity. Studies should also model diabetes, obesity, vascular disease, infection history, and microbiome-dependent metabolism, because these common modifiers alter both glial state and apigenin exposure.

10.3. Establish causality among proposed targets

Pathway convergence can become a catalogue unless tested causally. CRISPR perturbation and selective antagonists should address a hierarchy: Does PPARγ activation precede NRF2 induction? Is NLRP3 inhibition necessary for lower astrocytic C3? Does STAT1 suppression affect plaque phagocytosis? Does restored mitophagy prevent mitochondrial transfer and A1-like induction? Do IDO/ACMSD changes alter quinolinate and neuronal excitability? A target is most persuasive when genetic loss abolishes apigenin efficacy and rescue restores it at clinically plausible exposure.

10.4. Resolve stage and dose

The optimal intervention may differ across the AD continuum. In preclinical or early amyloid-positive disease, therapy should preserve TREM2/IL-3-driven microglial clustering, lysosomal activity, and plaque compaction while limiting complement-tagged synapse loss. In tau-positive symptomatic disease, stronger suppression of NLRP3, astrocytic C3, ROS, and cytokine feedback may be needed, alongside restoration of mitochondrial and trophic function. In advanced disease, reducing histological activation may not rebuild lost circuits, as the GFAP–IL-6 study illustrates [37]. Experiments should therefore use prevention and treatment paradigms, multiple ages, washout/rechallenge, and full concentration–response surfaces. Brain unbound concentration, not administered dose, should anchor cross-model comparison. Hormetic or biphasic responses should be expected for a polyphenol that interacts with redox and stress pathways.

10.5. Design biomarker-led early clinical studies

No trial has established isolated apigenin as an AD therapy. A rational first-in-human program would begin with a standardized, analytically defined, brain-penetrant formulation and quantify aglycone plus conjugates in plasma and cerebrospinal fluid. Stable-isotope microdosing or positron-emission tomography could define brain entry. Safety and interaction studies should precede efficacy testing. A biomarker-enriched phase Ib/IIa trial could recruit participants with biomarker-confirmed early AD and evidence of glial activation. Candidate outcomes include plasma/CSF GFAP, soluble TREM2, YKL-40, IL-6, inflammasome-related proteins, complement fragments, Aβ42/40, phosphorylated tau, neurofilament light, and synaptic proteins. Imaging may combine amyloid and tau PET with emerging glial or synaptic tracers. Digital cognition, sleep, and activity measures can provide sensitive longitudinal readouts. The decisive criterion should be coherent target engagement: measurable brain exposure associated with a predicted shift in glial biomarkers and preserved synaptic/cognitive function. Combination therapy is plausible but requires sequencing. Apigenin could theoretically reduce inflammatory amplification after anti-Aβ antibody-mediated plaque mobilization or lower vascular/glial contributors to ARIA. Conversely, excessive suppression might impair antibody-dependent microglial clearance. Combination studies should therefore examine Fc-mediated phagocytosis, vascular amyloid, microhemorrhage, and APOE4 genotype before clinical use.

11. A proposed research roadmap

Phase 1: Mechanistic qualification. Use isogenic human tricultures and organoids containing APOE3 or APOE4 cells. Compare free apigenin, major conjugates, and a brain-targeted formulation at measured unbound concentrations. Apply oligomeric Aβ, fibrillar Aβ, and seed-competent tau singly and sequentially. Quantify the seven state-vector dimensions and test PPARγ, NRF2, NLRP3, STAT1/3, and mitophagy causally. Phase 2: Spatial and temporal validation. In at least two complementary AD models, administer treatment before plaques, after plaques, and after tau propagation. Use spatial transcriptomics and imaging mass cytometry to determine whether apigenin preserves plaque-barrier microglia, reduces C3-positive astrocyte neighborhoods, and protects synapses. Include aged animals of both sexes, APOE-targeted replacement backgrounds, pharmacokinetics, and carrier controls. Phase 3: Translational pharmacology. Select the formulation by brain unbound exposure, not plasma total exposure alone. Establish metabolite activity, chronic safety, drug interactions, and reversibility. Develop a compact biomarker signature connecting brain tissue findings to CSF and plasma. Phase 4: Adaptive proof of mechanism. Conduct a short biomarker trial in early AD with exposure-confirmed dose escalation. Advance only if changes in glial biomarkers occur in the predicted direction without worsening amyloid clearance, edema/microhemorrhage, infection susceptibility, sedation, or cognition.

This roadmap converts the broad claim "apigenin is anti-inflammatory" into a falsifiable development program. It also permits an informative negative result: if brain exposure sufficient to change glial states cannot be achieved safely, dietary plausibility should not be mistaken for therapeutic viability.

12. Conclusion

Apigenin has a credible preclinical basis as a modulator of microglial and astrocytic responses relevant to AD. The strongest evidence supports inhibition of persistent inflammatory microglial modules, STAT1/CD40, TLR4/NF-κB/MAPK, iNOS/COX-2, and NLRP3, and attenuation of astrocytic NF-κB/STAT3 signaling and reactive morphology. NRF2/HO-1, PPARγ, mitophagy, kynurenine routing, BDNF/TrkB, BBB protection, and reduced Aβ/tau burden provide complementary routes by which a glial network could move from self-amplifying injury toward metabolically competent containment and repair. The central qualification is equally important: current evidence does not justify describing apigenin as a proven M1-to-M2 and A1-to-A2 switch in AD. Microglial and astrocytic states are continuous, mixed, and stage-dependent; explicit astrocyte polarization evidence comes largely from non-AD models; and clinical exposure, efficacy, and long-term safety remain unresolved. The most innovative and defensible therapeutic concept is therefore selective glial state-vector reprogramming. If a brain-penetrant formulation can suppress NLRP3–complement–oxidative feedback while preserving TREM2/IL-3-dependent clearance, trophic support, and neurovascular integrity, apigenin or an optimized derivative could become a useful adjunct in early, biomarker-defined AD. Achieving that goal will require human multicellular models, spatial functional pharmacology, rigorous exposure matching, and clinical trials designed around glial target engagement rather than supplement use.

List of Abbreviations

AD: Alzheimer's disease, Aβ: Amyloid-beta, APP: Amyloid precursor protein, BBB: Blood-brain barrier, BACE1: β-site amyloid precursor protein-cleaving enzyme 1, BDNF: Brain-derived neurotrophic factor, C1q/C3: Complement component 1q/complement component 3, CNS: Central nervous system, CREB: cAMP response element-binding protein, CSF: Cerebrospinal fluid, DAM: Disease-associated microglia, ERK: Extracellular signal-regulated kinase, GFAP: Glial fibrillary acidic protein, GSK-3β: Glycogen synthase kinase-3 beta, HO-1: Heme oxygenase-1, iPSC: Induced pluripotent stem cell, IL: Interleukin, ACMSD: Aminocarboxymuconate semialdehyde decarboxylase, iNOS/NOS2: Inducible nitric oxide synthase, MAPK: Mitogen-activated protein kinase, NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells, NLRP3: NOD-like receptor family pyrin domain-containing 3, Nrf2: Nuclear factor erythroid 2-related factor 2, PPAR-γ: Peroxisome proliferator-activated receptor gamma, ROS: Reactive oxygen species, STAT3: Signal transducer and activator of transcription 3, TGF-β: Transforming growth factor beta, TLR4: Toll-like receptor 4, TNF-α: Tumor necrosis factor alpha, TREM2: Triggering receptor expressed on myeloid cells 2.

Conflict of Interest

The authors declare no competing interests that may have influenced in this manuscript.

Generative AI statement

The authors declare that Gen AI and large language models (LLMs) were used in this manuscript. Generative AI items like "QuillBot" and "DeepL" were used for structural editing and improve handwriting of the text. Also, the "NOAH AI" platform was used for some parts of figures illustrations.

Author Agreement

This paper is submitted with the agreement of all its co-authors and the author list has been approved by all authors.

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Author Contribution

We agree that the author list and order is correct and complete. We understand that any changes to the author list (additions, deletions, order changes) after submission will require a formal request to the editor signed by all authors. Order list include:

ST: Conceptualization, Visualization, Writing Original Draft, Software; **FJD:** Conceptualization, Writing Original Draft; **AM:** Conceptualization, Writing Original Draft: **FN:** Conceptualization, Validation, Writing Original Draft, Reviewing and Editing, Supervision, Project Administration;

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