Exploration of Neuroprotective Therapy

Open Exploration

Open Access Review

Natural compounds targeting glial activation in Alzheimer's disease: a review of curcumin, resveratrol, and luteolin

Nunung Yuniarti[1*], Rani Resdiani[2], Marlyn Dian Laksitorini[3], Agung Endro Nugroho[1], Yasumasa Bessho[4]

[1]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta 55281, Indonesia

[2]Master's Program of Pharmacy Science, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta 55281, Indonesia

[3]Department of Pharmaceutics, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta 55281, Indonesia

[4]Gene Regulation Research Laboratory, Division of Biological Science, Nara Institute of Science and Technology (NAIST), Nara 630-0192, Japan

***Correspondence:** Nunung Yuniarti, Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta 55281, Indonesia. nunung@mail.ugm.ac.id

Academic Editor: Claudio Viegas-Junior, Federal University of Alfenas, Brazil

Received: December 2, 2025 **Accepted:** July 27, 2026 **Published:** September 10, 2026

Cite this article: Yuniarti N, Resdiani R, Laksitorini MD, Nugroho AE, Bessho Y. Natural compounds targeting glial activation in Alzheimer's disease: a review of curcumin, resveratrol, and luteolin. Explor Neuroprot Ther. 2026;6:1004167. https://doi.org/10.37349/ent.2026.1004167

Abstract

Alzheimer's disease, a neurodegenerative disease, is caused by the accumulation of amyloid-β (Aβ) protein and hyperphosphorylation of Tau protein in the brain, resulting in decreased cognitive function and memory. Neuroinflammation, which is the body's defense mechanism in the brain, is one of the factors that can worsen the condition of Alzheimer's patients. The activity of glial cells, such as microglia and astrocytes, causes the release of proinflammatory cytokines that can damage the neurons. However, currently available therapies can only address the symptoms of Alzheimer's disease. Therefore, alternative strategies are needed that can be used to overcome Alzheimer's disease, such as the use of natural compounds that have therapeutic potential. The purpose of this article is to discuss the potential of natural substances, such as curcumin, resveratrol, and luteolin, in modulating neuroinflammation. Curcumin, a compound contained in rhizome plants, has been shown to inhibit neuroinflammation by inhibiting the activation of innate immune signalling pathways and suppressing microglia activity. Resveratrol, a polyphenol in plants, has been reported to reduce neuroinflammation by modulating the Sirtuin 1 signalling pathway and polarizing microglia. Luteolin, a plant secondary metabolite belonging to the flavonoid group, is reported to be effective in reducing the production of reactive astrocytes and inhibits the p38 MAPK pathway to reduce neuroinflammation. Overall, preclinical evidence suggests that these natural substances show potential as therapeutic candidates for Alzheimer's disease, although further clinical studies are still needed to confirm their efficacy and safety.

Keywords

neuroinflammation, microglia activation, astrocyte modulation, neuroprotective agent, therapeutic potential

Introduction

The increase in life expectancy has led to an increase in the growth of the number of Alzheimer's patients. Data show that there are currently an estimated 50 million people with Alzheimer's disease (AD) worldwide [1], and this number is expected to grow to around 152.8 million by 2050 [2]. AD is a progressive neurodegenerative disease that slowly reduces cognitive and behavioural function, causing impairments in memory, language, and thinking, so patients will have difficulty performing their daily tasks [3, 4]. Short-term memory loss is one of the most common and earliest symptoms of AD, causing patients to have difficulty remembering recent events and learning new information [5]. In addition to affecting cognitive abilities, it also causes behavioural changes such as restlessness, more frequent anxiety, and changes in sleep patterns [5].

The main markers of this disease are amyloid-β (Aβ), which accumulates due to an imbalance between the production and elimination of Aβ in the brain, and Tau protein, which undergoes hyperphosphorylation [6]. Under normal conditions, Aβ is a cell component that is naturally present in cells and can be dissolved and denatured, but under abnormal conditions, for example due to disease, Aβ production becomes excessive, and Aβ protein becomes insoluble [7]. Initially, Aβ plaques form in several parts of the brain, such as the basal, temporal, and orbitofrontal neocortex, and will develop in the hippocampus, amygdala, and basal ganglia at an advanced stage. The presence of Aβ can trigger inflammation, oxidative stress, and neuronal cell death that cause impaired cognitive function [8].

The presence of Aβ plaques also activates kinases that cause hyperphosphorylation of Tau proteins to form neurofibrillary tangles (NFTs) [8]. Tau protein plays a role in tubulin polymerization and microtubule stability, which is part of the cytoskeleton [9], so this protein is very important for maintaining the structure and stability of neurons and also plays an important role in synaptic plasticity [10]. In AD patients, Tau protein is phosphorylated [4, 9] due to increased kinase enzyme activity, which causes microtubule destabilization, impaired cytoplasmic transport, impaired synapse function and morphology, and neurodegeneration [4, 10]. In addition, this also causes the Tau protein to lose the ability to bind microtubules, undergo structural changes, and form NFTs that precipitate in the cytoplasm [10].

Other factors (Figure 1) that can increase the risk of this disease are genetic factors such as chromosome 21 trisomy and ApoE E4 [5], epigenetic factors such as histone deacetylase enzyme activity [11], illness, and unhealthy lifestyles [5]. However, aging is the most important factor in AD because it can lead to a decline in the immune system, making the elderly more susceptible to neuroinflammatory infections [12]. Neuroinflammation is one of the key components in the pathogenesis of AD because neuroinflammation can trigger the activation of microglia [13] and astrocytes [14, 15] and also increase proinflammatory cytokine production that ultimately worsens AD [13].

Although the Food and Drug Administration (FDA) has approved anti-amyloid monoclonal antibodies as a treatment for select patients with early-stage AD, the currently available treatment options still have limitations [16–18]. In addition to relatively moderate clinical benefits and the need for periodic monitoring, various pharmacological therapies are also associated with side effects. Reported side effects vary widely, ranging from gastrointestinal issues, fatigue, and muscle cramps [19] to respiratory failure, which can certainly endanger Alzheimer's patients [20], to amyloid-related imaging abnormalities (ARIA) associated with monoclonal antibody therapy [16–18]. Based on these conditions, various natural compounds have been extensively studied as therapeutic candidates for AD due to their potential to modulate the molecular mechanisms involved in the pathogenesis of this disease. Some natural ingredients with this potential include curcumin [21, 22], resveratrol [23–27], and luteolin [28–31]. These three natural ingredients are easily found because they are contained in various types of plants. For example, curcumin

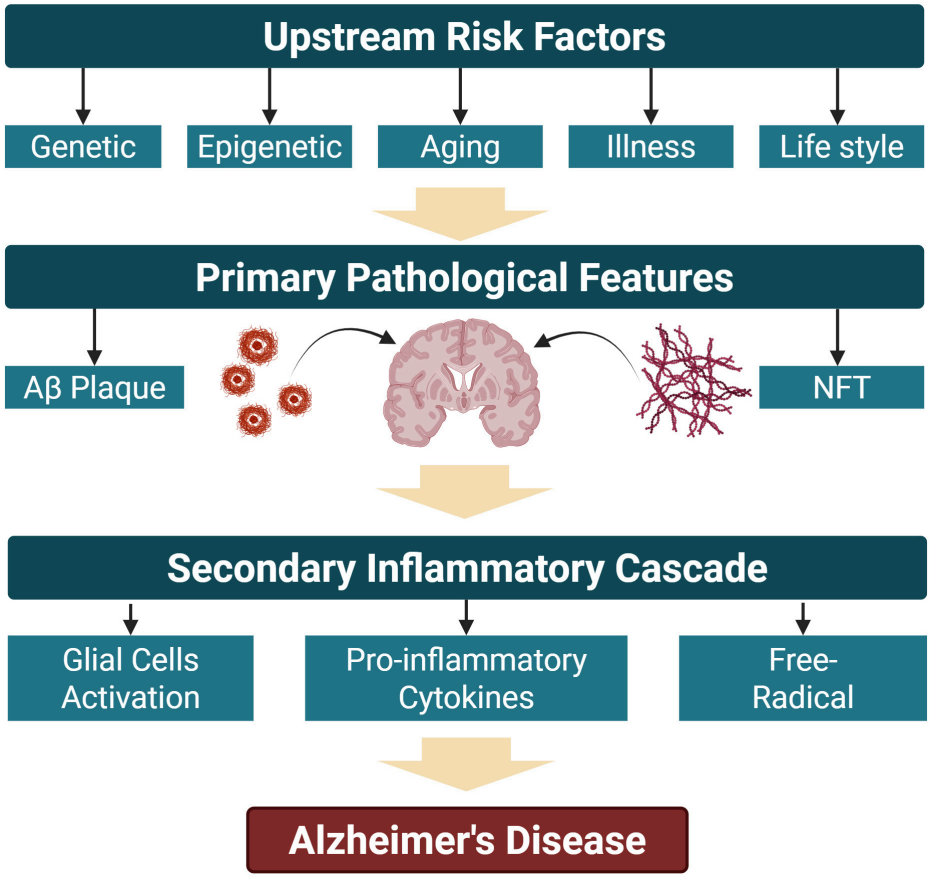

Figure 1. The multi-tiered cascade of Alzheimer's disease (AD). This diagram illustrates the sequential and interrelated events in AD. Upstream risk factors, such as genetic, epigenetic, aging, illness, and lifestyle. Primary pathological features, characterized by accumulation of Aβ plaques and NFTs. Secondary inflammation cascade, such as glial cells activation, pro-inflammatory cytokines, and free-radical. Aβ: amyloid-β; NFT: neurofibrillary tangle.

can be found in *Curcuma longa* [32–34], resveratrol can be found in berries, nuts, and eucalyptus [23–26, 35], and luteolin can be found in herbs, spices, and flowers [29–31, 36].

Curcumin, resveratrol, and luteolin can cross the blood-brain barrier (BBB) through transmembrane diffusion [37] because these compounds are low-molecular-weight, non-dissociative, and lipophilic molecules [38]. These three compounds are also polyphenols that play a role in various biological pathways and show therapeutic potential against a range of diseases, including cancer, inflammatory conditions, and neurodegenerative diseases, through the modulation of various molecular mechanisms, including the activation of glial cells in AD [39–41]. This review article aims to present research evidence on how curcumin, resveratrol, and luteolin modulate glial activation and neuroinflammatory pathways associated with AD, and to review the potential of these three compounds as candidates for natural neuroprotective agents.

Search strategy and study selection

This review article follows a literature search and selection process informed by the PRISMA guidelines to enhance the transparency and reproducibility of the article identification and selection process. The aim is to improve the transparency of the literature search and study selection process. Literature was obtained from reputable electronic databases, namely PubMed, Scopus, ScienceDirect, and ResearchGate, covering the last ten years (2015–2025), except for seminal articles that provide important scientific insights into the molecular mechanisms or biological activities of the compounds under review. The keywords used in the literature search involved the following combination of Boolean operators: ("Natural Compounds" OR "Curcumin" OR "Resveratrol" OR "Luteolin") AND ("Molecular Mechanism" OR "Glial Activation" OR "Neuroinflammation" OR "Inflammation") AND ("Alzheimer's Disease").

The literature selection process was conducted in several stages: the identification stage (collecting literature from databases, recording it, and checking for duplicate entries), the screening stage (screening titles and abstracts to eliminate irrelevant articles, while non-AD mechanistic studies are still considered if they discuss biological pathways involved in the pathogenesis of AD), the eligibility stage (reviewing the full text of the remaining articles to ensure compliance with inclusion criteria and eliminating non-compliant articles), and the inclusion stage (articles that meet all the criteria and are then synthesized narratively to explain the molecular mechanisms and evaluate the therapeutic potential of curcumin, resveratrol, and luteolin in the context of AD). This review focuses on three compounds—curcumin, resveratrol, and luteolin—because these three compounds meet the following inclusion criteria: (1) they are representative compounds of different chemical classes (curcumin: diarylheptanoids; resveratrol: stilbenes; and luteolin: flavonoids); (2) they possess consistently demonstrated bioactivity in modulating major neuroinflammatory pathways; and (3) they have comprehensive preclinical study data available, allowing for a systematic analysis of molecular mechanisms compared to other compounds.

Based on these considerations, inclusion and exclusion criteria were established to ensure that the selected literature remained relevant. Studies were included if they addressed the functions of curcumin, resveratrol, or luteolin related to glial cell activation, neuroinflammation, molecular mechanisms, or neuroprotective effects relevant to the pathogenesis of AD. In addition to studies using direct models of AD, mechanistic in vitro and in vivo studies evaluating AD-related molecular pathways (e.g., oxidative stress, microglial activation, inflammation, mitochondrial dysfunction, and apoptosis) are also considered if they provide information that supports an understanding of how these compounds work in the context of AD. English-language articles with full-text access were prioritized, including articles on experimental, preclinical, and review studies relevant to the topic. Meanwhile, articles were excluded if they did not discuss molecular mechanisms relevant to the pathogenesis of AD or did not provide information on the biological activities of curcumin, resveratrol, or luteolin related to neuroinflammation, glial cell activation, or neuroprotection. Additionally, duplicate publications, conference abstracts, and non-scientific reports were also excluded from this review. PRISMA flow diagram in Figure 2 illustrates the entire literature search and study selection process.

Neuroinflammation

Based on its etymology, inflammation, which comes from the Latin *inflammo*, means to ignite. Inflammation is a complex biological response of the immune system that arises in response to pathogens, tissue damage, toxic compounds, or radiation, and is characterized by clinical manifestations such as redness, edema, increased temperature, pain, and impaired function of the affected tissue [42]. The inflammatory response involves interactions between the lymphoid and vascular systems that play a role in protecting the body from various harmful stimuli by eliminating the cause of inflammation and initiating tissue repair processes [42, 43].

Inflammation can occur in all areas of the body, including the brain, which is called neuroinflammation. Neuroinflammation can be caused by pathological disorders such as infection, trauma, ischemia, and toxic exposure [44, 45], resulting in increased glial cell activation and the release of proinflammatory mediators in the form of cytokines [46]. Based on research conducted by Yuniarti et al. [47] (2025), neuroinflammation can also be triggered by oxidative stress due to ethanol exposure. Neuroinflammation initially serves as a natural defense mechanism when the central nervous system (CNS) experiences an acute event by limiting damage, clearing dead tissue, and initiating the healing process [48, 49]. However, in chronic conditions, persistent inflammation in the nervous system can be detrimental because it has the potential to accelerate neuron degeneration [48, 49].

The neuroinflammatory process is characterized by activation of immune responses in the CNS, involving astrocytes, microglia, BBB endothelial cells, neuronal cells, and the infiltration of peripheral immune cells into the parenchyma of the CNS [44, 49, 50]. Overactivity of glial cells, such as microglia and astrocytes, is a sign of chronic neuroinflammation. Under normal conditions, microglia act as resident immune cells in the brain that constantly monitor the brain's microenvironment and contribute to

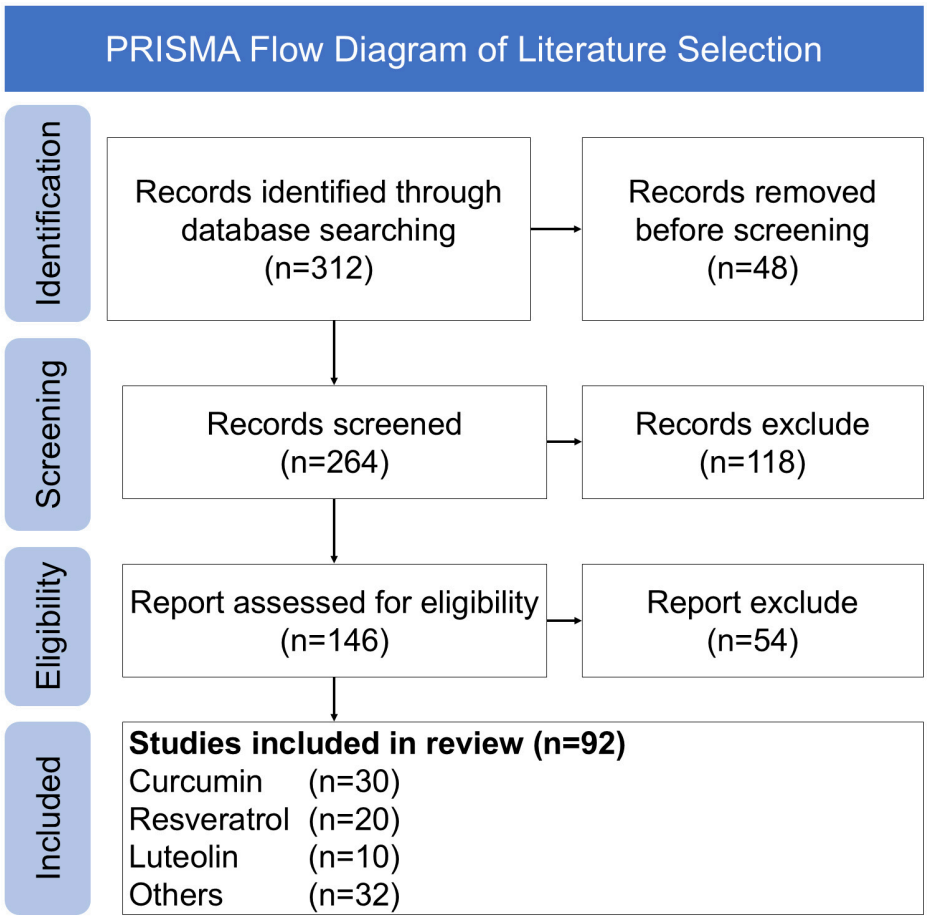

Figure 2. PRISMA flow diagram. PRISMA-based flow diagram illustrating the literature search and study selection process for articles related to curcumin, resveratrol, and luteolin in the modulation of glial activation and neuroinflammatory pathways in Alzheimer's disease. Adapted from https://www.prisma-statement.org/. Accessed May 8, 2026. © 2024-2026 the PRISMA Executive. Licensed under a CC BY 4.0.

maintaining the survival of neurons [14, 45], detect and evaluate inflammatory signals, support synaptic plasticity, and eliminate cell debris through phagocytosis [48]. When harmful stimuli are present, microglia become an activated form called disease-associated microglia (DAM). DAM can increase the expression of certain receptors, chemokines [14], and proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and IL-6, that play a role in neuroinflammation and neurodegenerative diseases such as AD [49].

Besides microglia, astrocytes may also play a role in neuroinflammation because astrocytes are responsible for maintaining brain homeostasis and providing nutrients and growth factors to neurons [14, 15] and are also involved in the formation of a unique perivascular channel in the CNS known as the glymphatic system. This system functions to eliminate neurotoxic waste products, including Aβ and Tau protein [51]. Astrocytes respond to pathological conditions, such as AD, by forming reactive astrocytes, which are characterized by cell enlargement or hypertrophy as a result of increased expression of glial fibrillary acidic protein (GFAP) [14, 42]. The formation of reactive astrocytes is induced by inflammation through the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, which then produces inflammatory mediators so that cells lose homeostatic functions and trigger apoptosis of neurons and oligodendrocytes [48, 51]. These glial cells, both microglia and astrocytes, will release various inflammatory mediators, including proinflammatory cytokines, chemokines, and reactive oxygen species (ROS), which contribute to increased neuronal damage and lead to progressive neuronal function decline, as seen in AD [48].

Neuroinflammation in Alzheimer's disease

The accumulation of Aβ plaques and hyperphosphorylation of Tau proteins lead to microglia activation. Both AD marker proteins are detected by microglia as a threat, so microglia are activated and produce cytokines such as IL-1β, IL-6, and TNF-α [13]. Aβ plaques are surrounded by microglia that will eliminate them through phagocytosis [51]. However, in chronic conditions, Aβ stimulates increased production of various neurotoxic mediators, including ROS, nitric oxide (NO), cytokines, and chemokines, which ultimately exacerbate the inflammatory response [13, 14]. In addition to microglia activation, the presence of Aβ plaques and Tau protein also triggers the activation of astrocytes into reactive astrocytes [14, 15]. Reactive astrocytes are characterized by cell hypertrophy and increased release of neurotoxic factors, which further disrupt the processing of amyloid precursor protein (APP) by astrocytes and ultimately increase the accumulation of Aβ [14].

The combination of over-activation of glial cells can disrupt the integrity of the BBB and increase its permeability, allowing peripheral immune cells, including neutrophils, B lymphocytes, T lymphocytes, and natural killer cells, to infiltrate from the bloodstream into brain tissue [13, 14]. Neutrophils activated by Aβ plaques and neuroinflammatory signals migrate across the damaged BBB, release ROS, and form neutrophil extracellular traps (NETs), which contribute to neuronal damage, BBB dysfunction, and impaired cerebral blood flow [13]. Different from neutrophil cells, T lymphocytes will interfere directly with neurons and disrupt synaptic plasticity, resulting in decreased cognitive function in Alzheimer's patients by producing proinflammatory cytokines that can increase neuroinflammation and disrupt BBB homeostasis [13]. On the other hand, B lymphocytes have a dual role, both as anti-inflammatory agents through secretion of IL-35 and IgG, and as pro-inflammatory agents through the release of TNF-α, IL-6, and activating microglia [13, 14]. Aβ plaques will also activate NK cells that will interact with microglia and release pro-inflammatory cytokines, further exacerbating neuroinflammation [13]. The mechanism underlying the involvement of glial cells in neuroinflammation in AD is illustrated in Figure 3.

Therapeutic potential of natural compounds targeting neuroinflammation

One of the challenges faced in AD therapy is the limited effectiveness of available drugs. Currently, there are two classes of therapeutic drugs used for AD therapy, which are acetylcholinesterase enzyme inhibitors and glutamate receptor antagonists [52]. The drugs used in AD therapy are not optimal because they only reduce the symptoms of AD and also have side effects such as salivation, lacrimation, urination, defecation, gastrointestinal distress, and emesis syndrome (SLUDGE syndrome) that can cause difficulty in controlling body movements and respiratory failure [20]. In recent years, disease-modifying therapies in the form of anti-amyloid monoclonal antibodies, such as lecanemab [18] and donanemab [16, 17], have been approved by the FDA for selected patients with mild cognitive impairment or mild dementia due to AD who have been confirmed to have amyloid pathology [16–18]. Although both therapies have been shown to reduce amyloid plaque burden and slow cognitive decline compared to placebo, the resulting clinical benefits remain moderate, and their use is limited to specific patient populations that meet the selection criteria. In addition, these therapies are also associated with the risk of ARIA, including cerebral edema (ARIA-E) and microhemorrhages (ARIA-H), thus requiring periodic monitoring using magnetic resonance imaging (MRI) during treatment [16–18].

Therefore, the development of alternative therapies that are safer, more effective, and applicable to a broader patient population remains a critical need in the management of AD. In this context, natural compounds are gaining increasing attention because they demonstrate promising neuroprotective activity through the modulation of various molecular pathways involved in the pathogenesis of AD. The results of research conducted by Anas et al. [53] (2024) show that natural compounds have the potential to prevent memory decline in neurotoxin-induced animal models. These findings suggest that natural compounds not only have the potential to improve symptoms but also to modulate the mechanisms underlying the development of AD. In addition, natural compounds have been extensively studied for their potential to provide neuroprotective effects through various molecular mechanisms and generally demonstrate

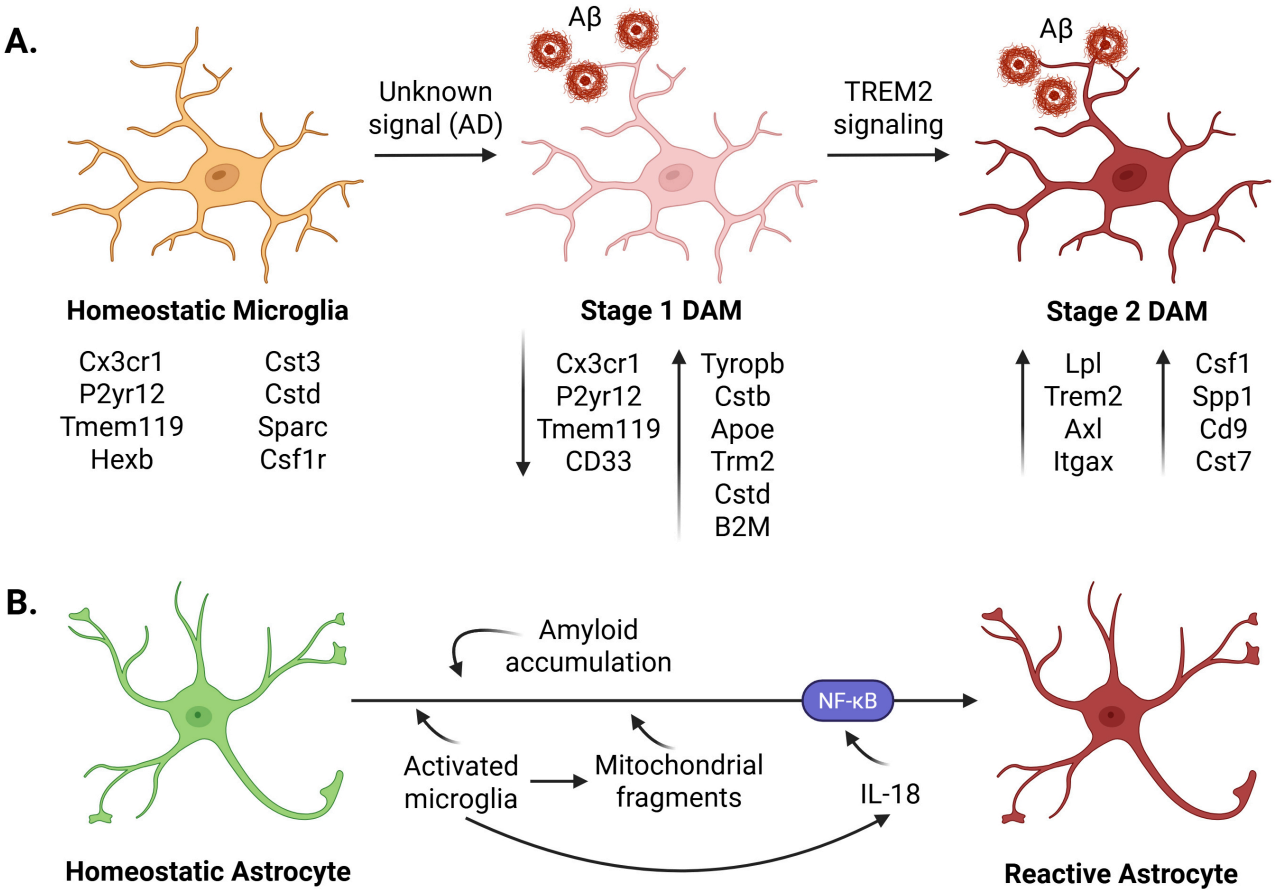

Figure 3. The mechanism by which glial cells are involved in neuroinflammation in AD. (**A**) DAM activation mechanism from homeostatic microglia is transformed into stage 1 DAM by unknown signals such as AD. Stage 1 DAM then transforms into stage 2 DAM with the presence of TREM2 signaling. (**B**) Reactive astrocyte activation from homeostatic astrocytes is mediated by several factors such as amyloid accumulation, microglia activation, mitochondrial fragments, and IL-18. AD: Alzheimer's disease; Aβ: amyloid-β; DAM: disease-associated microglia; IL-18: interleukin-18; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; TREM2: triggering receptor expressed on myeloid cells 2.

promising safety profiles in preclinical studies as well as in some clinical trials. Curcumin, resveratrol, and luteolin are natural compounds that have shown potential as anti-neuroinflammatory agents in AD [23, 28, 45]. All three compounds are reported to inhibit microglia and astrocyte activation [25, 41, 54], inhibit pro-inflammatory enzymes (e.g., COX-2, iNOS), and reduce pro-inflammatory gene expression through suppression of the NF-κB signalling pathway [26, 30, 31, 46]. On the contrary, these compounds activate anti-inflammatory signaling pathways, increase the expression of anti-inflammatory genes, and modulate multiple neuroprotective signaling pathways, including sirtuin 1 (SIRT1)/GSK3β, p38 mitogen-activated protein kinase (MAPK)/NF-κB, and triggering receptor expressed on myeloid cells 2 (TREM2)/toll-like receptor 4 (TLR4)/NF-κB [23, 31, 45]. The following is an explanation of the mechanisms of curcumin, resveratrol, and luteolin as anti-neuroinflammatory agents, as well as the studies that support them.

Curcumin

Curcumin (Figure 4) is a natural compound contained in rhizome plants such as *Curcuma longa* from the Zingiberaceae family, which has potential as a neuroprotective agent [32–34]. This plant can be found in many tropical areas, one of which is in Indonesia [32]. Curcumin has a distinctive chemical structure. Aromatic groups on curcumin play an important role in the biological activity of curcumin [55]. Based on several research results, curcumin is proven to function as an antibacterial, antihepatotoxic, antiviral, antioxidant, anticancer, and anti-inflammatory agent [21, 22, 56]. Curcumin and its analogues have been shown to act as neuroprotective agents by inhibiting HDAC2, which supports neuronal survival, synaptogenesis, and reduces neuroinflammation [47]. Curcumin is also known to be able to penetrate the BBB and is detected in the CNS [47]. This ability is closely related to its structural characteristics, especially

the presence of a methoxy group (–OCH_3), which is relatively nonpolar [55]. Curcumin has low polarity but high lipophilicity compared to its derivatives, and these physicochemical differences directly affect the pharmacokinetic profile, where the higher lipophilicity of curcumin supports BBB penetration [57].

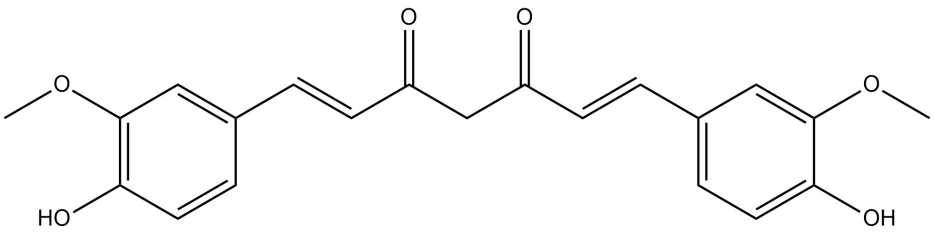

Figure 4. Structure of curcumin. Curcumin has a chemical structure of diferuloylmethane, which is a conjugated heptadiene-3,5-dione chain connecting two identical aromatic rings. (PubChem CID: 969516; 2D/3D structure: https://pubchem.ncbi.nlm.nih.gov/compound/969516).

Curcumin and its analogues have shown potential as anti-Alzheimer's agents through various multi-target mechanisms, including suppressing glial cell activity, inhibition of the NF-κB/p38 MAPK pathway, activation of nuclear factor erythroid 2-related factor 2 (Nrf2), and increased expression of neprilysin (NEP), which plays a role in Aβ degradation, as well as reducing the release of proinflammatory cytokines such as IL-1β and TNF-α [39]. In studies conducted by Iteire et al. [54] (2022) and Sorrenti et al. [46] (2018), curcumin was shown to reduce the expression of the ionized calcium-binding adapter molecule 1 (Iba1) protein, which is an important marker in microglia activation, so that microglia remain in a resting state and do not cause neuroinflammation. This decrease in Iba1 protein expression occurs because curcumin inhibits TLR4/myeloid differentiation primary response 88 (MyD88)/NF-κB pathway activation [45, 58]. TLR4, which is activated by foreign molecules such as lipopolysaccharide (LPS), activates MyD88, which then activates NF-κB, resulting in increased transcription of inflammatory genes and increased expression of Iba1 protein [58].

Curcumin specifically binds directly to the myeloid differentiation protein-2 (MD-2) co-receptor, preventing LPS from binding to TLR4. As a result, TLR4 dimerization is prevented, so that the danger signal cannot be transmitted to the MyD88 protein [59, 60]. Consequently, the downstream kinase cascade is attenuated, suppressing NF-κB activation and nuclear translocation and reducing the production of pro-inflammatory cytokines [61]. Other studies have also indicated that curcumin and its derivatives (hydroxylated monocarbonyl curcumin) can act as inducers that increase NEP enzyme activity, so it can enable the enzyme to break down and clear Aβ plaques [62]. Suppression of TLR4 expression also can increase TREM2 expression, which functions as an anti-inflammatory microglia receptor in inhibiting pro-inflammatory TLR4 signaling [45]. TREM2 activation tends to promote M2 (anti-inflammatory, neuroprotective) phenotypes, rather than M1 (pro-inflammatory) phenotypes, so that Iba1 protein expression decreases [45]. The mechanism of action of curcumin can be seen in Figure 5.

In addition to reducing Iba1 expression, curcumin can also reduce the expression of the reactive astrocyte marker, GFAP, which leads to reduced formation of reactive astrocytes that resulting in reduced neuroinflammatory response [54]. Curcumin also suppresses the expression of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 [46, 49, 63, 64] by inhibiting the activation of the TLR4/NF-κB signal transduction pathway [54]. These proinflammatory cytokines mediate the transformation of astrocytes into reactive astrocytes, so that a decrease in these cytokines prevents the formation of reactive astrocytes and reduces GFAP expression [54]. In Table 1, we can see several studies that prove that curcumin has the potential to attenuate neuroinflammation through various mechanisms.

Resveratrol

Resveratrol (Figure 6) is a polyphenol that can be found in 72 plant species spread across 31 genera and 12 families [66]. Some plants that contain resveratrol include grapes, blueberries, cranberries, nuts, and eucalyptus [23–26, 35]. The structure of resveratrol consists of two aromatic rings connected by a

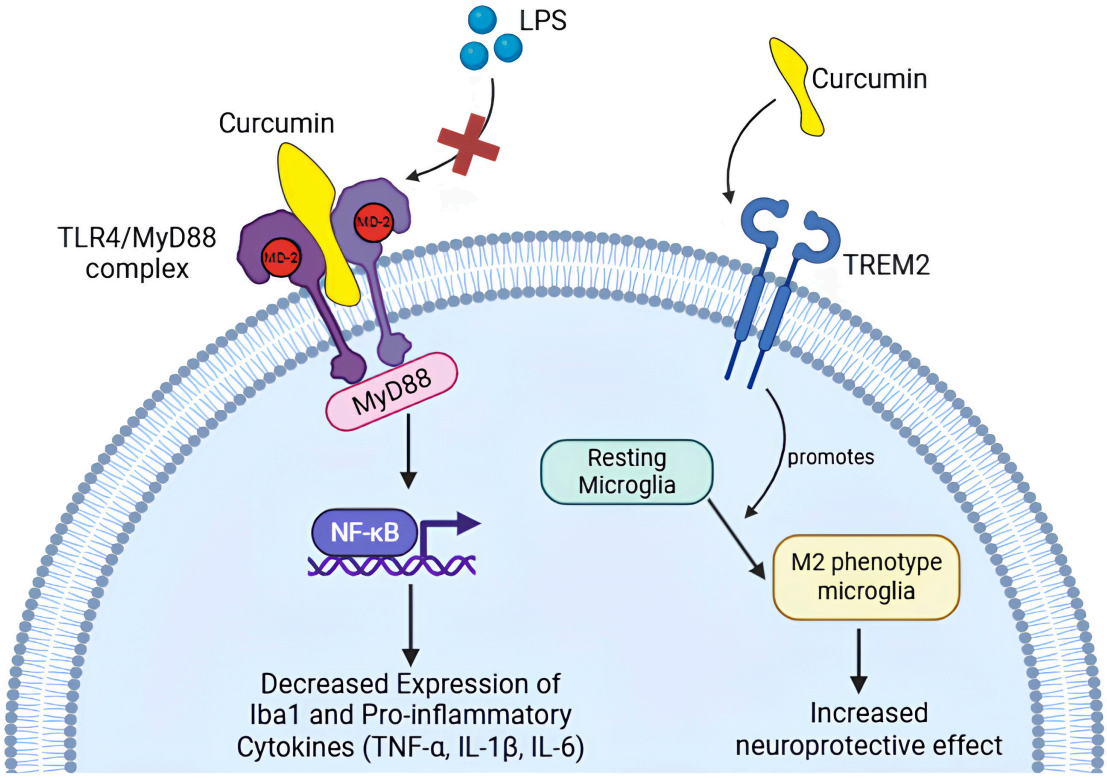

Figure 5. The mechanism of action of curcumin. Curcumin inhibits TLR4/MyD88/NF-κB pathway activation by binding to MD-2, which can cause a decrease in the expression of Iba1 protein and proinflammatory cytokines. Curcumin also increases the expression of TREM2, leading to increased anti-inflammatory activation of microglia (M2). Iba1: ionized calcium-binding adapter molecule 1; IL: interleukin; LPS: lipopolysaccharide; MD-2: myeloid differentiation protein-2; MyD88: myeloid differentiation primary response 88; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; TLR4: toll-like receptor 4; TNF-α: tumor necrosis factor-alpha; TREM2: triggering receptor expressed on myeloid cells 2.

methylene bridge [66]. Resveratrol has several biological functions such as anti-aging, anti-cancer, anti-inflammatory, antioxidant [23–27], anti-neurodegenerative [23], antiviral [25], and anti-apoptotic [25, 26]. In addition, due to its ability to penetrate the BBB, resveratrol can exert neuroprotective effects [25]. Resveratrol is lipid soluble and has a molecular weight of 228 Da, so it easily crosses the BBB via transmembrane diffusion [67]. Therefore, resveratrol may be a candidate for AD therapy [68].

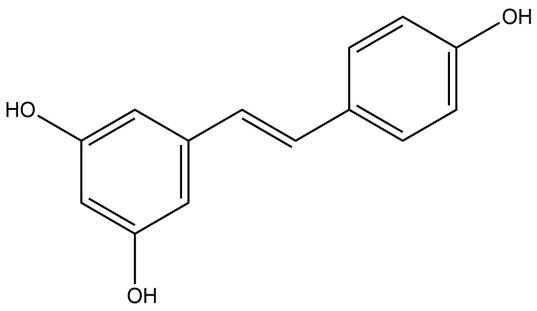

Figure 6. Structure of Resveratrol. Resveratrol has a basic structure of trans-3,5,4'-trihydroxystilbene, which consists of two aromatic rings connected by an ethylene bridge. (PubChem CID: 445154; 2D/3D structure: https://pubchem.ncbi.nlm.nih.gov/compound/445154).

Resveratrol has several mechanisms of action in reducing neuroinflammation. Based on studies performed by Chen et al. [25] (2023) and Yang et al. [40] (2017), resveratrol can reduce neuroinflammation through the mechanism of microglia polarization from M1 phenotype to M2 phenotype. It can suppress the production of M1 microglia and induce M2 microglia production, resulting in a decrease in proinflammatory cytokines and an increase in anti-inflammatory cytokines so that the brain tissue can be protected from damage due to inflammation [25]. More specifically, resveratrol activates the SIRT1/peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) pathway [23].

Table 1. Studies that prove that curcumin has the potential to overcome neuroinflammation.

Researcher and year	Model	Resveratrol dosage and duration	Parameter	Key results	Conclusion
Yu et al., 2018 [49]	Microglia BV-2 cells	5, 10, and 20 μM curcumin, 1-hour pre-incubation, then lipoteichoic acid (LTA) for 16–24 hours	1. Cell viability (MTT assay) 2. NO, PGE_2, tumor necrosis factor-alpha (TNF-α) (ELISA/Griess) 3. Expression of iNOS & COX-2 mRNA (qRT PCR) 4. Mitogen-activated protein kinase (MAPK) phosphorylation (p38, ERK, Akt) & nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) translocation 5. HO-1 & nuclear factor erythroid 2-related factor 2 (Nrf2) expression	1. No toxic effect on cell viability 2. Dose-dependent decrease in NO, PGE_2, TNF-α 3. Decreased iNOS and COX-2 mRNA expression 4. Inhibits phosphorylation of MAPK & translocation of NF-κB 5. Increases the expression of HO-1 and Nrf2; inhibition of HO-1 eliminates the anti-inflammatory effect of curcumin	Curcumin suppresses microglia activation and inflammatory mediator production by inhibiting NF-κB and MAPK pathways, as well as induction of the HO-1/Nrf2 antioxidant pathway, making curcumin a potential candidate for anti-neuroinflammatory therapy
Kharazmi et al., 2022 [65]	Wistar male rats	10 mg/kg BW curcumin, oral (gavage), 35 days pretreatment before morphine injection	1. Latency of inhibitory avoidance (IA memory) 2. Motor activity (open field) 3. Expression of p-CREB & total CREB in hippocampus 4. NOx (nitric oxide metabolite) levels in brain tissue	1. Pre-treatment with curcumin prevents latency decrease 2. No significant change in motor activity between groups 3. Increased p-CREB, supporting its protective role against memory 4. Increases NOx levels, possibly activating the NO → p-CREB → memory signaling pathway	Curcumin prevents morphine-induced memory impairment in mice, likely through increased NO and activation of downstream CREB signaling
Namgyal et al., 2020 [63]	Swiss albino mice; Cadmium (Cd) exposure	Oral curcumin (oral gavage) at various doses; Cd exposure 2.5 mg/kg BW for 60 days	1. Behavior (spontaneous alternation, elevated plus-maze) 2. Antioxidant enzyme SOD, CAT, and GSH levels and malondialdehyde (MDA) level 3. Inflammatory cytokine levels (IL-6, TNF-α, IL-10) 4. Histology of prefrontal cortex neurons	1. Working memory and anxious behavior improved in rats given curcumin 2. SOD, CAT, and GSH activities increased; MDA activity decreased 3. IL-6 and TNF-α decreased; IL-10 increased 4. Neuron morphology in the prefrontal cortex improved	Curcumin protects cognitive function and prefrontal neuron structure by reducing oxidative stress and neuroinflammation due to Cd exposure
Sorrenti et al., 2018 [46]	Young adult mice	50 mg/kg BW curcumin, orally, given 2 consecutive days before	1. Microglia activation (Iba1) 2. Proinflammatory cytokines	1. Decreased microglia activation (seen from decreased Iba1 expression and	Short-term preventive curcumin effectively suppresses LPS-induced acute neuroinflammation and reduces long-term memory consequences

Table 1. Studies that prove that curcumin has the potential to overcome neuroinflammation. (*continued*)

Researcher and year	Model	Resveratrol dosage and duration	Parameter	Key results	Conclusion
		LPS injection (5 mg/kg i.p.)	3. Physical symptoms (sickness behavior) 4. Long-term memory function (Morris Water Maze)	improved cell morphology) 2. Significant reduction in IL-1β and TNF-α expression in plasma and brain tissue 3. Reduced symptoms of sickness behavior faster than the LPS group without curcumin 4. Accelerated long-term memory recovery even though it was only given briefly	

SIRT1 is a deacetylase enzyme that has a role in oxidative stress regulation, inflammation, and cell survival [26]. Administration of resveratrol to mice with AD has been reported to increase SIRT1 expression in the hippocampus [23].

Resveratrol directly activates SIRT1, which then deacetylates the p65 subunit of NF-κB, reducing the transcription of pro-inflammatory genes [69, 70]. SIRT1, which has been activated by resveratrol, also releases the acetyl group bound to PGC-1α, activating PGC-1α and making it a transcription coactivator [69, 71]. Activation of PGC-1α can suppress the expression of the BACE1 enzyme, which plays a role in the formation of Aβ plaques, preventing the formation of Aβ plaques [72]. The mechanism of action of resveratrol can be seen in Figure 7.

Increased PGC-1α expression also may lead to decreased NF-κB activation so that transcription of M1 proinflammatory genes is reduced while transcription of M2 anti-inflammatory genes is increased. As a result, the polarization shifts from M1 to M2 [40]. Another study explained that resveratrol is capable of inducing deacetylation of p65 NF-κB and signal transducer and activator of transcription 3 (STAT3), which act as major transcription factors of proinflammatory cytokines [26]. This deacetylation process suppresses the transcription of proinflammatory genes, including TNF-α, IL-1β, and COX-2, contributing to a reduction in neuroinflammation levels [26]. In addition, resveratrol modulates downstream signaling pathways, including PI3K/Akt, and regulates GSK-3β phosphorylation, contributing to a reduction in Tau protein hyperphosphorylation [23]. Table 2 shows several studies that prove that resveratrol has the potential to attenuate neuroinflammation through various mechanisms.

Luteolin

Luteolin (Figure 8) is a flavonoid compound derived from plant secondary metabolites [36]. This compound can be found in many plant sources, including herbs such as parsley, peppermint, oregano, thyme; vegetables such as celery seeds, peppers, carrots, and broccoli; spices such as cardamom and anise/fennel; and flowers such as chrysanthemums [29–31, 36, 73]. For those plants, luteolin is used to protect against UV radiation and attract pollinators and seed dispersers [36]. Luteolin exhibits a variety of biological activities, including antioxidant, anti-inflammatory, and neuroprotective [28–31, 73]. Multiple studies have demonstrated that luteolin can inhibit the production of inflammatory cytokines in various neurological disease models, including the AD model [28–30, 73]. Due to its relatively

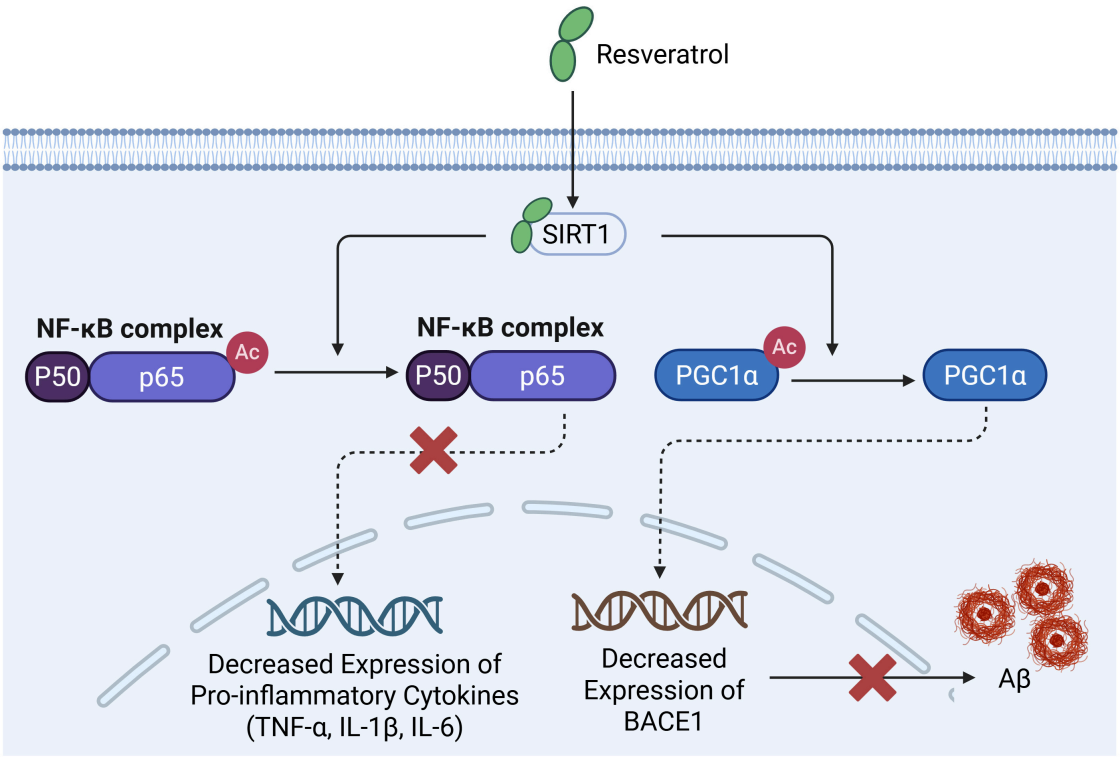

Figure 7. The mechanism of action of resveratrol. Resveratrol activates SIRT1, which then deacetylates the p65 subunit of NF-κB and reduces the expression of pro-inflammatory cytokines. Resveratrol-activated SIRT1 also enhances PGC-1α activation, reducing BACE1 expression, which leads to a decrease in Aβ plaque formation. Aβ: amyloid β; IL: interleukin; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; PGC-1α: peroxisome proliferator-activated receptor gamma coactivator-1 alpha; SIRT1: sirtuin 1; TNF-α: tumor necrosis factor-alpha.

low molecular weight (286.24 Da) [74] and moderate lipophilicity, luteolin possesses physicochemical properties that favor BBB penetration. Indeed, experimental studies have demonstrated that peripherally administered luteolin is capable of crossing the BBB and accumulating in brain tissue [75].

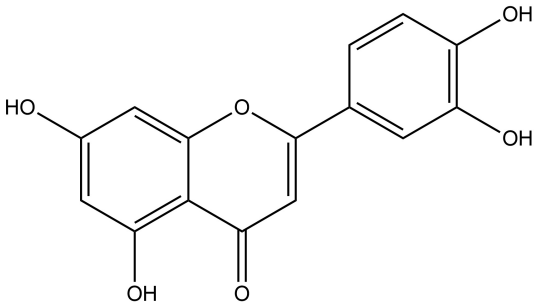

Figure 8. Structure of Luteolin. Luteolin has a basic structure of 2-(3,4-dihydroxyphenyl)-5,7-dihydroxychromen-4-one, consisting of three main rings. (PubChem CID: 5280445; 2D/3D structure: https://pubchem.ncbi.nlm.nih.gov/compound/5280445).

Luteolin may act as an anti-neuroinflammatory through several mechanisms, such as modulation of astrocytes [29, 41, 76] and suppression of proinflammatory cytokine production [28, 29, 31, 73]. In AD, the presence of Aβ and phosphorylated Tau proteins can lead to activation of the endoplasmic reticulum (ER) stress pathway characterized by GRP78 (ER stress marker), CHOP (ER stress-related pro-apoptotic protein), and phosphorylation of protein kinase RNA-activated-like ER kinase (PERK), inositol-requiring enzyme 1 alpha (IRE1α), and eukaryotic initiation factor 2 alpha (eIF-2α) [28]. Luteolin prevents the phosphorylation of PERK and eIF-2α, halting the induction of the pro-apoptotic transcription factor CHOP and ensuring that nerve cells are spared from programmed cell death [77]. Luteolin can also directly enhance IRE1α activation and lead to increased splicing of XBP1 into its active form, XBP1s [78], which enhances ER proteostasis by upregulating molecular chaperones and components of the ER-associated

Table 2. Studies that prove that resveratrol has the potential to overcome neuroinflammation.

Researcher and year	Model	Resveratrol dosage and duration	Parameter	Key results	Conclusion
Moussa et al. 2017 [68]	Mild-moderate Alzheimer's subjects (human, *N* = 119; subset analysis *N* = 19 vs. 19)	Up to 2 g per day (1 g twice daily), 52 weeks duration	1. CSF markers MMP-9, MDC, IL-4, FGF-2 2. Plasma MMP-10, IL-12P40, IL-12P70, RANTES 3. Mini-Mental Status Examination (MMSE) & AD Cooperative Study-Activity of Daily Living (ADCS-ADL) scores 4. CSF Aβ-42, Aβ-40, Tau	1. Significant decrease in CSF MMP-9 2. Increase in MDC, IL-4, FGF-2 in CSF 3. Increased plasma MMP-10; decreased IL-12P40, IL-12P70, RANTES 4. Slow decline in MMSE, ADCS-ADL, CSF Aβ-42; did not affect Tau	Resveratrol decreases neuro-inflammation, enhances adaptive immune responses, and stabilizes cognitive decline and AD biomarkers; sirtuin 1 (SIRT1) activation has potential as a therapeutic target
Abozaid et al. 2022 [23]	Wistar rats, AD model induced by $AlCl_3$ (100 mg/kg/day for 60 days)	Oral RSV-SeNPs, 200 mg/kg/day via gavage for 8 weeks (after AD formation)	1. Oxidative stress: MDA, GSH, catalase 2. AD biomarkers: Aβ-42, p-Tau 3. Neuroinflammation: IL-1β, p-STAT3 4. Cholinergic: ACh 5. Cell signaling: p-PI3K, p-GSK-3β 6. Gene expression: SIRT1, miR-134 (RT-qPCR) 7. Histopathology: hippocampus (Aβ plaques, neuronal hypoplasia vs. protection)	1. RSV-SeNPs reduce MDA, increase GSH & catalase 2. Lower Aβ-42 & p-Tau levels 3. Reduced IL-1β and p-STAT3 (decreased neuroinflammation) 4. Increased brain ACh 5. Restoring p-PI3K and p-GSK-3β to normal direction 6. Increases SIRT1 expression, suppresses miR-134 7. Histopathology: reduced Aβ plaques and neuronal degeneration in the hippocampus, as well as increased healthy neurons	RSV nano-formulation with selenium effectively ameliorated oxidative stress, neuroinflammation, cholinergic effects and AD biomarkers in Alzheimer's mouse models. Mediated through activation of the PI3K pathway/suppressing GSK-3β, modulation of SIRT1/miR-134, and decreased
Chen et al. 2023 [25]	In vivo: 6-week-old female ICR mice (Institute of Cancer Research mice); azq: primary microglia (neonatal ICR), primary neurons; PRV (pseudorabies virus)	In vivo: Res were given oral gavage pre-treatment 7 days before PRV intranasal infection, then continued 1×/day for 3 days after infection; In vitro: Res 3.75, 7.5, 15 μg/mL [incubation 24–48 h; CCK-8 (Cell Counting Kit-8): 0–60 μg/mL]	1. Blood-brain barrier (BBB)/edema: brain water content, Evans blue extravasation; IHC MMP-2, MMP-9, ZO-1, Iba1 2. Histologi: H&E, Nissl, TUNEL (neuronal apoptosis) 3. Inflamasi/sitokin: mRNA (RT-PCR) & protein (ELISA) untuk IL-6, tumor necrosis factor-alpha (TNF-α), CCL3, CXCL10, MCP-1, IL-4, IL-10, TGF-β, NGF, GDNF	1. BBB & brain edema: medium- and high-dose Res decreased brain water content; high-dose Res decreased BBB leakage; Res decreased MMP-2, MMP-9, and increased ZO-1 2. Histology & apoptosis: medium- and high-dose Res reduced neuronal damage and apoptosis 3. Cytokines & inflammation: Res decreases	Resveratrol protects against PRV-induced encephalitis in mouse models by repairing BBB integrity, suppressing pro-inflammatory responses, increasing anti-inflammatory cytokines & neurotrophic factors, and shifting microglia polarization from M1 phenotype to M2 phenotype, thereby reducing neuronal apoptosis. These results support the potential of Res as an adjuvant therapeutic agent in viral encephalitis

Table 2. Studies that prove that resveratrol has the potential to overcome neuroinflammation. (*continued*)

Researcher and year	Model	Resveratrol dosage and duration	Parameter	Key results	Conclusion
			4. M1/M2 microglia: immunofluorescence & flow cytometry (CD11b, CD86 as M1; CD206 as M2); mRNA M1 markers (CD86, TNF-α, iNOS) & M2 markers (CD206, Arg-1, Ym1) 5. Co-culture: inflamasi neuron (ELISA) & apoptosis neuron (AnnexinV/PI)	proinflammatory cytokines and increases anti-inflammatory and neurotrophic factors 4. Microglia polarization: Res decreases M1 and increases M2 5. Neuronal co-culture: Res decreases proinflammatory cytokines in neurons; Res increases anti-inflammatory cytokines in neurons; Res reduces neuronal apoptosis	

degradation (ERAD) pathway [79]. Activation of the ER stress pathway also can trigger the change of astrocytes into reactive astrocytes, resulting in increased expression of GFAP [29, 41, 76], which leads to increased production of proinflammatory cytokines such as IL-1β, IL-6, and TNF-α [28, 29, 41]. Luteolin can prevent the activation of reactive astrocytes [29, 41, 76] and also inhibit ER stress pathway activation so that the production of proinflammatory cytokines decreases [28]. The mechanism of action of luteolin can be seen in Figure 9.

In addition to modulating astrocyte activity, luteolin suppresses neuroinflammation through inhibition of p38 MAPK phosphorylation [31, 41]. In pathological conditions such as AD, activation of p38 MAPK can trigger the phosphorylation of transcription factors, which in turn increases the expression of proinflammatory cytokines and exacerbates the neuroinflammatory response [31, 41]. By inhibiting the p38 MAPK pathway, luteolin reduces the transcription of proinflammatory cytokines [31, 41]. Luteolin also reduces the expression of adhesion molecules vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), which play important roles in the leukocyte recruitment to the brain during inflammation, thereby reducing the infiltration of immune cells into the CNS [31]. In Table 3, we can see several studies that prove that luteolin has the potential to attenuate neuroinflammation through various mechanisms.

Based on the results of research that has been conducted, the three natural ingredients described above, namely curcumin, resveratrol, and luteolin, have been reported to reduce neuroinflammation. However, these three natural ingredients have different mechanisms of action in overcoming neuroinflammation. In Table 4 below, we can see the differences in the mechanisms of action of these three natural ingredients.

In addition to providing neuroprotective effects through the mechanisms described earlier, curcumin, resveratrol, and luteolin have also been reported to potentially provide neuroprotective effects through modulation of the gut-brain axis. The gut-brain axis is a highly complex two-way communication system between the CNS and the enteric nervous system [80]. This communication occurs through four pathways: the neural pathway (vagus nerve), the immune pathway, the endocrine pathway, and the metabolic pathway [81, 82]. In the gut-brain axis, the composition of the microbiota—particularly bacteria—in the gut plays a crucial role in determining whether these bacteria will act as neuroprotective agents or, conversely, as agents that increase the risk of AD [80]. In a balanced state (eubiosis), bacteria produce neuroprotective substances such as short-chain fatty acids (SCFAs) [80–82], maintain a tight intestinal barrier, and

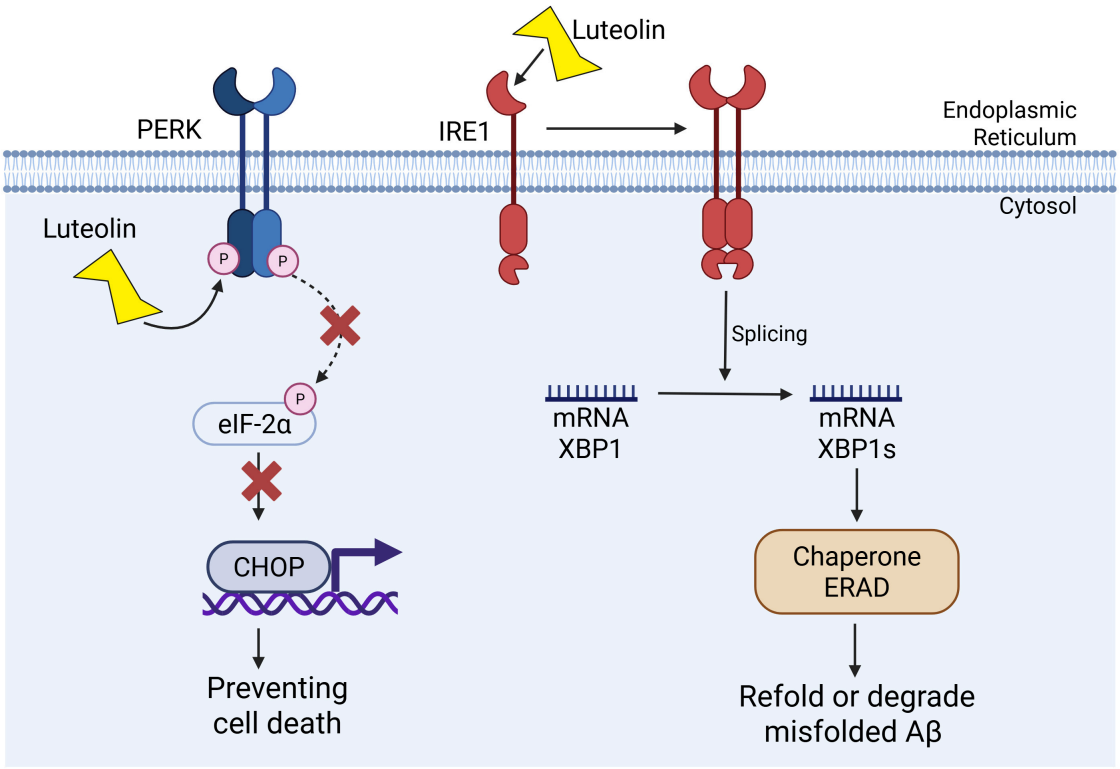

Figure 9. The mechanism of action of Luteolin. Luteolin inhibits the activation of the PERK pathway and prevents cell death. Luteolin also enhances the IRE1 activity and increases ER capacity to refold or degrade misfolded Aβ proteins. Aβ: amyloid-β; eIF-2α: eukaryotic initiation factor 2 alpha; ER: endoplasmic reticulum; IRE1: inositol-requiring enzyme 1; PERK: protein kinase RNA-activated-like ER kinase.

modulate the immune system [80]; however, in an imbalanced bacterial composition (dysbiosis), bacteria produce toxins such as LPS and bacterial amyloid that can cause the intestinal barrier to become permeable (leaky gut), allowing LPS to enter the bloodstream and trigger systemic inflammation, ultimately damaging the BBB [80–82] and inducing neuroinflammation that exacerbates amyloid plaque formation [81]. Examples of bacteria that can provide neuroprotective effects include bacteria from the class Mollicutes, genus *Ruminiclostridium 9*, genus *Clostridium innocuum*, and genus *Eggerthella*; whereas examples of bacteria that can increase the risk factors for AD include bacteria from the order Selenomonadales, family Pasteurellaceae, and genus *Methanobrevibacter* [80].

Curcumin acts as a detoxifying agent by enhancing the activation of intestinal alkaline phosphatase (IAP), allowing LPS produced by bacteria to be broken down and neutralized before it enters the bloodstream [83]. The reduction of LPS in the gut by curcumin prevents metabolic endotoxemia, which can trigger inflammation in the brain and reduce amyloid plaques [82, 83]. Additionally, curcumin works by modulating the gut microbiota composition and increasing beneficial bacteria such as *Bacteroides* and *Lactobacillus*, helping to create an anti-inflammatory gut environment [83, 84]. Meanwhile, resveratrol works by improving the physical structure of the intestinal wall through increased production of tight junction proteins, such as zonula occludens-1 (ZO-1) and occludin, which function to seal the gaps between intestinal cells, preventing leaky gut [84, 85]. Like curcumin, resveratrol also modulates gut microbiota by suppressing harmful bacteria that produce trimethylamine *N*-oxide (TMAO), which can damage brain blood vessels [86], and increasing bacteria that produce SCFAs, which can cross the BBB and act as anti-inflammatory agents [85, 86]. Furthermore, luteolin also exerts immunomodulatory effects by increasing the expression of peroxisome proliferator-activated receptor-γ (PPAR-γ), a receptor that suppresses excessive immune responses [87]. Luteolin also exerts neuroprotective effects by alleviating neuroinflammation and cognitive impairment through the inhibition of ER stress-dependent inflammatory signalling [28], as well as the TLR4/TRAF6/NF-κB and p38 MAPK-mediated NF-κB pathways. These mechanisms subsequently reduce the production of pro-inflammatory cytokines and mediators, thereby attenuating neuroinflammation in experimental models of AD and other neurological disorders [28, 30, 31].

Table 3. Studies that prove that luteolin has the potential to overcome neuroinflammation.

Researcher and year	Model	Luteolin dosage and duration	Parameter	Key results	Conclusion
Che et al., 2020 [41]	In vitro: murine astrocyte cell line (C8-D1A), activated with LPS	• Apigenin & luteolin: 30 μM and 60 μM (pretreatment 1 hour before LPS) • Evaluation at 30 minutes, 3 hours, 12 hours, and 24 hours depending on the assay	1. Cell viability 2. Astrocyte activation 3. IL-31 & IL-33 mRNA expression 4. IL-31 & IL-33 protein expression 5. IL-31 & IL-33 secretion 6. Phosphorylation of mitogen-activated protein kinase (MAPK), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), STAT3 7. Translocation & DNA-binding of NF-κB/STAT3 8. Effects of pharmacological inhibitors on signaling pathways	1. Apigenin safe ≤ 60 μM, luteolin safe ≤ 100 μM 2. Apigenin → suppresses ERK, NF-κB, STAT3; more effectively suppresses IL-33 3. Luteolin → suppresses ERK, JNK, p38, NF-κB, STAT3; more effectively suppresses IL-31 4. Both decrease IL-31 & IL-33 secretion, inhibit NF-κB/STAT3 translocation to the nucleus, and decrease DNA-binding activity. Both decrease IL-31 & IL-33 secretion, inhibit NF-κB/STAT3 translocation to the nucleus, and decrease DNA-binding activity	Apigenin and luteolin inhibited LPS-induced astrocyte activation and decreased IL-31 & IL-33 production through modulating MAPK, NF-κB, and STAT3 pathways. Both have potential as neuroprotective agents.
Ma et al., 2025 [29]	In vitro: primary cultures of neurons, astrocytes, microglia, as well as mixed cultures of neuron-glia from rat brain	• $CdCl_2$ as an inducer of neurotoxicity • Luteolin: 5–20 μM (pre-treatment) • Treatment duration varies according to test (24–48 hours)	1. Neuron viability (survival assay) 2. Neuron morphology (branching, cell body size) 3. Glia markers: glial fibrillary acidic protein (GFAP) (astrocytes), Iba1 (microglia) 4. Proinflammatory cytokines: tumor necrosis factor-alpha (TNF-α), IL-1β, IL-6 5. Neuronal apoptosis: active caspase-3	1. Luteolin increases neuron survival and maintains healthy morphology 2. Luteolin decreases GFAP expression and suppresses Iba1 expression 3. Luteolin decreases the levels of proinflammatory cytokines 4. Luteolin decreases caspase-3 expression 5. Luteolin maintains neuronal survival	Luteolin reduces Cd neurotoxicity by suppressing glial inflammation and protecting neurons from apoptosis, thus supporting neuronal survival. Potential as a neuroprotective agent.
Facchinetti et al. 2022 [76]	In vitro: co-culture primary astrocytes & oligodendrocyte precursor cells (OPCs) from the brains of Sprague-Dawley rat pups	Co-Ultramicronized Palmitoylethanolamide/Luteolin (Co-ultra PEALut) PEA: Luteolin = 10:1; 3 μM; 48 hours	1. Viability of astrocytes & OPCs (neutral red assay) 2. Protein & mRNA expression of astrocytes: GFAP, calcium-binding protein B (S100B), glutamine synthetase (GS), HMGB1, IL-6, IL-1β, NF-κB, FGF-2, TGF-β (WB, RT-qPCR) 3. Maturation of OPCs (MBP+/Olig2+ ratio) 4. Oligodendrocyte morphology	1. Co-ultra PEALut keeps viability normal 2. Co-ultra PEALut suppresses the increase of astrocyte reactivity markers; decreases the expression of proinflammatory cytokines; prevents the decrease of FGF-2, a PPAR-α-independent effect 3. Co-ultra PEALut normalizes MBP+/Olig2+ ratio 4. Co-ultra PEALut prevents cell shrinking & reduced branching	Co-ultra PEALut (PEA + luteolin) normalizes astrocyte-oligodendrocyte communication through anti-inflammatory, pro-trophic, and protective mechanisms. Part of the effect is PPAR-α mediated.

Table 3. Studies that prove that luteolin has the potential to overcome neuroinflammation. (*continued*)

Researcher and year	Model	Luteolin dosage and duration	Parameter	Key results	Conclusion
			(surface area, branching/Sholl analysis)		
Zhang et al. 2017 [31]	In vitro: human brain microvascular endothelial cells (hBMECs) as a blood-brain barrier (BBB) model	Luteolin: 10 μM, pre-treatment before fAβ1–40	1. Cell viability (MTT assay) 2. Proinflammatory cytokines (IL-1β, IL-6, TNF-α) 3. Adhesion molecules (ICAM-1, VCAM-1) 4. Activation of NF-κB (p65 nuclear translocation) 5. Activation of p38 MAPK (phosphorylation)	1. fAβ1–40 did not decrease cell viability, but increased secretion of IL-1β, IL-6, TNF-α, and expression of ICAM-1 and VCAM-1 2. fAβ1–40 activated p38 MAPK and NF-κB 3. Luteolin decreases cytokines and adhesion molecules, inhibits p38 MAPK phosphorylation, and prevents NF-κB p65 translocation to the nucleus 4. The effects of luteolin are similar to those of a p38 MAPK inhibitor	Luteolin inhibits fAβ1–40-triggered inflammation at the BBB by suppressing the p38 MAPK-NF-κB pathway, thereby decreasing proinflammatory cytokines and adhesion molecules.

These three natural compounds have been shown to act as neuroprotective agents through several mechanisms, making them potential treatments for AD, but several clinical studies have shown different results. Curcumin has been reported to be well tolerated in clinical trials (ClinicalTrials.gov Identifier: NCT00099710). However, various studies have not yet shown any significant improvement in cognitive function, behavior, or AD-related outcomes [88]. Another study (Identification number: ACTRN12611000437965) also noted that curcumin supplementation cannot prevent cognitive decline over a 12-month period [89]. The suspected cause is that curcumin has very low bioavailability, meaning it cannot be absorbed well by the body and ultimately fails to demonstrate efficacy [88]. Curcumin has very low water solubility, approximately 11 ng/mL [90]; it is unstable at physiological pH and sensitive to light, so it can degrade before it can exert a therapeutic effect [90]. Furthermore, curcumin pharmacokinetic data indicate a very short half-life; curcumin concentrations drop sharply from 1.276 μg/mL to just 0.192 μg/mL within 1.5 hours [91]. Results from another human study (Identification number: NCT03085680) indicate that even a single oral dose of 4 g fails to produce significant levels of parent curcumin in the blood (< 0.1 ng/mL) [92]. The issue of low curcumin bioavailability can be addressed through several approaches, including encapsulation techniques to protect curcumin, such as nano-complexation, gelation, and complex coacervation [90]; liposomal formulations that significantly improve the stability and biological distribution of curcumin [91]; and the use of bio-enhancers, such as piperine, to inhibit the rapid metabolism of curcumin [92].

Clinical research on resveratrol shows results that are not much different from curcumin. Resveratrol supplementation has been reported to improve psychomotor speed (ClinicalTrials.gov Identifier: NCT01126229), but does not show any improvement in more complex cognitive domains [93]. Other studies (ClinicalTrials.gov Identifier: NCT01504854) show that resveratrol exhibits a good safety and tolerability profile even when administered at high doses for one year; however, its impact on AD biomarkers and clinical outcomes remains limited and shows inconsistent results [94]. Clinical studies on resveratrol are still pilot studies, so the results shown are not yet consistent with preclinical studies. However, these pilot studies provide justification for further studies with larger designs, longer durations, or different populations to explore other effects [93].

Table 4. Comparative table summarizing the mechanisms of action of the three natural compounds.

Pathway category	Molecular targets/Signaling pathways	Curcumin	Resveratrol	Luteolin
Anti-inflammatory	Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway	Inhibits upstream activation via the toll-like receptor 4 (TLR4)/myeloid differentiation protein-2 (MD-2) complex	Deacetylation of the p65 subunit via sirtuin 1 (SIRT1) activation	Directly inhibits IKKβ kinase activity
Anti-aging	SIRT1/AMPK/peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α)	Indirect modulation	Primary activator: Increases the NAD+/NADH ratio and SIRT1 activity	Indirect activation through the reduction of oxidative stress
Glial modulation	Microglia & astrocyte phenotype	Promotes M2 polarization by increasing triggering receptor expressed on myeloid cells 2 (TREM2)	Preventing the pro-inflammatory microglial phenotype via SIRT1	Inhibits astrocyte reactivity (A1) by reducing glial fibrillary acidic protein (GFAP)
Proteostasis	Autophagy & degradation	Increasing the expression of the enzyme neprilysin (NEP) for the degradation of Aβ	Inducing autophagy through AMPK activation	Enhancing the ERAD pathway through IRE1α/XBP1s activation
Organelle stress	Endoplasmic reticulum (ER) & mitochondrial stress	Maintaining intracellular calcium homeostasis	Protecting mitochondria from oxidative damage via nuclear factor erythroid 2-related factor 2 (Nrf2)	Key regulator: Inhibits the protein kinase RNA-activated-like endoplasmic reticulum kinase (PERK)/CHOP pathway (ER stress)
Tau pathology	GSK-3β/Tau phosphorylation	Inhibits the physical aggregation of Tau filaments	Reduces Tau acetylation, which facilitates its clearance	Direct inhibitor: Binds to the ATP-binding site of GSK-3β

Unlike curcumin and resveratrol, which have begun to be studied clinically, research related to luteolin is still limited to preclinical studies. Luteolin has been shown to have potential as a neuroprotective agent [29, 31], but clinical research on this potential has not yet been widely conducted. Therefore, clinical research on luteolin is needed to support preclinical research results.

Limitations and future perspectives

Research on natural compounds with potential anti-neuroinflammatory effects in AD still faces several limitations. Most studies are confined to in vitro experiments and animal models, so evidence regarding the therapeutic effects of natural compounds in humans remains limited. Differences in glial cell morphology, disease progression, and pharmacokinetics between animal models and humans also pose challenges that ultimately hinder clinical translation.

Another challenge in using natural compounds as neuroprotective agents is their low bioavailability and rapid metabolism, which hamper absorption and make it difficult for these compounds to reach therapeutic concentrations in brain tissue. Additionally, the wide variability in research methodologies—ranging from differences in dosage, duration of administration, animal models, and measured parameters—makes direct comparison of study outcomes difficult. Existing studies have also not focused directly on glial activation, resulting in limited comprehensive mechanistic understanding.

Given these issues, future research could focus on developing nano-based formulations (such as nanoencapsulation, liposomes, and SNEDDS) to increase the bioavailability and stability of natural compounds, thereby improving their absorption and penetration across the BBB. This would subsequently increase the therapeutic concentrations of natural compounds in brain tissue. Furthermore, large-scale clinical studies must begin to evaluate safety, effectiveness, optimal dosing, and long-term therapeutic responses in Alzheimer's patients to provide more substantial evidence of the neuroprotective potential of

these natural compounds. Clinical studies may also be integrated with precision medicine approaches to account for individual genetic variations that influence responses to natural compounds.

Conclusions

Neuroinflammation has an important role in AD, which is influenced by various mechanisms such as activation of glial cells (microglia and astrocytes) and neuroinflammatory signalling pathways (NF-κB and MAPK), so that neuroinflammation can be used as a target for AD therapy. Several natural compounds, such as curcumin, resveratrol, and luteolin, have been shown to have the potential to inhibit neuroinflammation through different mechanisms. Curcumin has been reported to inhibit neuroinflammation by inhibiting the activation of the TLR4/MyD88/NF-κB pathway and suppressing microglia activity. Resveratrol has been reported to reduce neuroinflammation through modulation of the SIRT1 pathway and microglia polarization. Luteolin has been reported to suppress the activation of reactive astrocytes and inhibit p38 MAPK phosphorylation, thereby potentially reducing neuroinflammation. These three natural compounds have been reported to modulate glial cell activity and the expression of proinflammatory cytokines, thus potentially contributing to the control of neuroinflammation and providing neuroprotective effects. Therefore, further research is needed to evaluate the potential of these natural compounds as candidates for natural-based interventions in the treatment of AD.

Abbreviations

AD: Alzheimer's disease

ARIA: amyloid-related imaging abnormalities

Aβ: amyloid-β

BBB: blood-brain barrier

CNS: central nervous system

DAM: disease-associated microglia

eIF-2α: eukaryotic initiation factor 2 alpha

ER: endoplasmic reticulum

FDA: Food and Drug Administration

GFAP: glial fibrillary acidic protein

Iba1: ionized calcium-binding adapter molecule 1

ICAM-1: intercellular adhesion molecule-1

IL: interleukin

IRE1α: inositol-requiring enzyme 1 alpha

LPS: lipopolysaccharide

MAPK: mitogen-activated protein kinase

MyD88: myeloid differentiation primary response 88

NEP: neprilysin

NFTs: neurofibrillary tangles

NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells

NO: nitric oxide

Nrf2: nuclear factor erythroid 2-related factor 2

PERK: protein kinase RNA-activated-like endoplasmic reticulum kinase

PGC-1α: peroxisome proliferator-activated receptor gamma coactivator-1 alpha

ROS: reactive oxygen species

SCFAs: short-chain fatty acids

SIRT1: sirtuin 1

STAT3: signal transducer and activator of transcription 3

TLR4: toll-like receptor 4

TNF-α: tumor necrosis factor-alpha

TREM2: triggering receptor expressed on myeloid cells 2

VCAM-1: vascular cell adhesion molecule-1

Declarations

Author contributions

NY: Conceptualization, Methodology, Supervision, Writing—review & editing. RR: Writing—original draft. MDL: Supervision, Writing—review & editing. AEN: Supervision. YB: Supervision. All authors read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

This research was funded by the Research Directorate of Universitas Gadjah Mada under the 2025 Academic Excellence Improvement Program Scheme B (Contract No. 1908/UN1/DITLIT/Dit-Lit/PT.01.00/2025). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Publisher's note

References

1. Lastuka A, Bliss E, Breshock MR, Iannucci VC, Sogge W, Taylor KV, et al. Societal Costs of Dementia: 204 Countries, 2000–2019. J Alzheimers Dis. 2024;101:277–92. [DOI] [PubMed] [PMC]

2. Farina N, Jacobs R, Turana Y, Fitri FI, Schneider M, Theresia I, et al. Comprehensive measurement of the prevalence of dementia in low- and middle-income countries: STRiDE methodology and its application in Indonesia and South Africa. BJPsych Open. 2023;9:e102. [DOI] [PubMed] [PMC]
3. Khan S, Barve KH, Kumar MS. Recent Advancements in Pathogenesis, Diagnostics and Treatment of Alzheimer's Disease. Curr Neuropharmacol. 2020;18:1106–25. [DOI] [PubMed] [PMC]
4. Zhang H, Wei W, Zhao M, Ma L, Jiang X, Pei H, et al. Interaction between Aβ and Tau in the Pathogenesis of Alzheimer's Disease. Int J Biol Sci. 2021;17:2181–92. [DOI] [PubMed] [PMC]
5. Porsteinsson AP, Isaacson RS, Knox S, Sabbagh MN, Rubino I. Diagnosis of Early Alzheimer's Disease: Clinical Practice in 2021. J Prev Alzheimers Dis. 2021;8:371–86. [DOI] [PubMed] [PMC]
6. Lao K, Zhang R, Luan J, Zhang Y, Gou X. Therapeutic Strategies Targeting Amyloid-β Receptors and Transporters in Alzheimer's Disease. J Alzheimers Dis. 2021;79:1429–42. [DOI] [PubMed]
7. Lei P, Ayton S, Bush AI. The essential elements of Alzheimer's disease. J Biol Chem. 2021;296:100105. [DOI] [PubMed] [PMC]
8. Tiwari S, Atluri V, Kaushik A, Yndart A, Nair M. Alzheimer's disease: pathogenesis, diagnostics, and therapeutics. Int J Nanomedicine. 2019;14:5541–54. [DOI] [PubMed] [PMC]
9. Ossenkoppele R, van der Kant R, Hansson O. Tau biomarkers in Alzheimer's disease: towards implementation in clinical practice and trials. Lancet Neurol. 2022;21:726–34. [DOI] [PubMed]
10. Suzuki N, Hatta T, Ito M, Kusakabe KI. Anti-amyloid-β Antibodies and Anti-tau Therapies for Alzheimer's Disease: Recent Advances and Perspectives. Chem Pharm Bull (Tokyo). 2024;72:602–9. [DOI] [PubMed]
11. Yuniarti N, Juliandi B, Sanosaka T, Nakashima K. Mid-gestational exposure to histone deacetylase inhibitor suberoylanilide hydroxamic acid influence cortical interneuron and astrocyte in mouse brain. Indones J Biotechnol. 2018;22:32. [DOI]
12. Andronie-Cioara FL, Ardelean AI, Nistor-Cseppento CD, Jurcau A, Jurcau MC, Pascalau N, et al. Molecular Mechanisms of Neuroinflammation in Aging and Alzheimer's Disease Progression. Int J Mol Sci. 2023;24:1869. [DOI] [PubMed] [PMC]
13. Zhang Q, Yang G, Luo Y, Jiang L, Chi H, Tian G. Neuroinflammation in Alzheimer's disease: insights from peripheral immune cells. Immun Ageing. 2024;21:38. [DOI] [PubMed] [PMC]
14. Singh D. Astrocytic and microglial cells as the modulators of neuroinflammation in Alzheimer's disease. J Neuroinflammation. 2022;19:206. [DOI] [PubMed] [PMC]
15. Rajesh Y, Kanneganti TD. Innate Immune Cell Death in Neuroinflammation and Alzheimer's Disease. Cells. 2022;11:1885. [DOI] [PubMed] [PMC]
16. Rabinovici GD, Selkoe DJ, Schindler SE, Aisen P, Apostolova LG, Atri A, et al. Donanemab: Appropriate use recommendations. J Prev Alzheimers Dis. 2025;12:100150. [DOI] [PubMed] [PMC]
17. Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J, et al.; TRAILBLAZER-ALZ 2 Investigators. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA. 2023;330:512–27. [DOI] [PubMed] [PMC]
18. van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, et al. Lecanemab in Early Alzheimer's Disease. N Engl J Med. 2023;388:9–21. [DOI] [PubMed]
19. Briggs R, Kennelly SP, O'Neill D. Drug treatments in Alzheimer's disease. Clin Med (Lond). 2016;16: 247–53. [DOI] [PubMed] [PMC]
20. Ohbe H, Jo T, Matsui H, Fushimi K, Yasunaga H. Cholinergic Crisis Caused by Cholinesterase Inhibitors: a Retrospective Nationwide Database Study. J Med Toxicol. 2018;14:237–41. [DOI] [PubMed] [PMC]
21. Ikawati M, Septisetyani EP. Pentagamavunone-0 (PGV-0), a Curcumin Analog, Enhances Cytotoxicity of 5-Fluorouracil and Modulates Cell Cycle in WiDr Colon Cancer Cells. Indones J Cancer Chemoprevent. 2018;9:23–31. [DOI]

22. Murwanti R, Rahmadani A, Ritmaleni, Hermawan A, Ari Sudarmanto BS. Curcumin Analogs Induce Apoptosis and G2/M Arrest in 4T1 Murine Triple-Negative Breast Cancer Cells. Indonesian J Pharm. 2020;31:11–8. [DOI]
23. Abozaid OAR, Sallam MW, El-Sonbaty S, Aziza S, Emad B, Ahmed ESA. Resveratrol-Selenium Nanoparticles Alleviate Neuroinflammation and Neurotoxicity in a Rat Model of Alzheimer's Disease by Regulating Sirt1/miRNA-134/GSK3β Expression. Biol Trace Elem Res. 2022;200:5104–14. [DOI] [PubMed]
24. Chen Q, Sun KP, Huang JS, Wang ZC, Hong ZN. Resveratrol attenuates neuroinflammation after deep hypothermia with circulatory arrest in rats. Brain Res Bull. 2020;155:145–54. [DOI] [PubMed]
25. Chen X, Xue J, Zou J, Zhao X, Li L, Jia R, et al. Resveratrol alleviated neuroinflammation induced by pseudorabies virus infection through regulating microglial M1/M2 polarization. Biomed Pharmacother. 2023;160:114271. [DOI] [PubMed]
26. Cong L, Lei MY, Liu ZQ, Liu ZF, Ma Z, Liu K, et al. Resveratrol attenuates manganese-induced oxidative stress and neuroinflammation through SIRT1 signaling in mice. Food Chem Toxicol. 2021;153: 112283. [DOI] [PubMed]
27. Wang Y, Shi Y, Huang Y, Liu W, Cai G, Huang S, et al. Resveratrol mediates mechanical allodynia through modulating inflammatory response via the TREM2-autophagy axis in SNI rat model. J Neuroinflammation. 2020;17:311. [DOI] [PubMed] [PMC]
28. Kou JJ, Shi JZ, He YY, Hao JJ, Zhang HY, Luo DM, et al. Luteolin alleviates cognitive impairment in Alzheimer's disease mouse model via inhibiting endoplasmic reticulum stress-dependent neuroinflammation. Acta Pharmacol Sin. 2022;43:840–9. [DOI] [PubMed] [PMC]
29. Ma HY, Wang J, Wang J, Guo Z, Qin XY, Lan R, et al. Luteolin attenuates cadmium neurotoxicity by suppressing glial inflammation and supporting neuronal survival. Int Immunopharmacol. 2025;152: 114406. [DOI] [PubMed]
30. Yang Y, Tan X, Xu J, Wang T, Liang T, Xu X, et al. Luteolin alleviates neuroinflammation via downregulating the TLR4/TRAF6/NF-κB pathway after intracerebral hemorrhage. Biomed Pharmacother. 2020;126:110044. [DOI] [PubMed]
31. Zhang JX, Xing JG, Wang LL, Jiang HL, Guo SL, Liu R. Luteolin Inhibits Fibrillary β-Amyloid$_{1-40}$-Induced Inflammation in a Human Blood-Brain Barrier Model by Suppressing the p38 MAPK-Mediated NF-κB Signaling Pathways. Molecules. 2017;22:334. [DOI] [PubMed] [PMC]
32. Marbawati D, Umniyati SR. Effects of Curcumin and Pentagamavunon-0 Against Dengue-2 Virus Infection in Vero Cells; an in Vitro Study. Procedia Environ Sci. 2015;23:215–21. [DOI] [PubMed] [PMC]
33. Meiyanto E, Husnaa U, Kastian RF, Putri H, Larasati YA, Khumaira A, et al. The Target Differences of Anti-Tumorigenesis Potential of Curcumin and its Analogues Against HER-2 Positive and Triple-Negative Breast Cancer Cells. Adv Pharm Bull. 2021;11:188–96. [DOI] [PubMed] [PMC]
34. Ramadhan H, Forestryana D, Adisaputra GT, Muharram SR. Effect of Vanillin Quality on the Synthesis and Solid Dispersion Systems on PGV-0 Antioxidant Capacity. Int J App Pharm. 2022;14:31–6. [DOI]
35. Calado CMSDS, Manhães-de-Castro R, da Conceição Pereira S, da Silva Souza V, Barbosa LNF, Dos Santos Junior OH, et al. Resveratrol Reduces Neuroinflammation and Hippocampal Microglia Activation and Protects Against Impairment of Memory and Anxiety-Like Behavior in Experimental Cerebral Palsy. Mol Neurobiol. 2024;61:3619–40. [DOI] [PubMed]
36. Gendrisch F, Esser PR, Schempp CM, Wölfle U. Luteolin as a modulator of skin aging and inflammation. Biofactors. 2021;47:170–80. [DOI] [PubMed]
37. Banks WA, Rhea EM, Reed MJ, Erickson MA. The penetration of therapeutics across the blood-brain barrier: Classic case studies and clinical implications. Cell Rep Med. 2024;5:101760. [DOI] [PubMed] [PMC]
38. Wang F, Qi L, Zhang Z, Duan H, Wang Y, Zhang K, et al. The Mechanism and Latest Research Progress of Blood-Brain Barrier Breakthrough. Biomedicines. 2024;12:2302. [DOI] [PubMed] [PMC]

39. Anas Y, Susidarti RA, Yuniarti N, Martien R. Curcumin Analogues as Novel Anti-Alzheimer's Candidates: Synthesis Development Strategy, In vitro, Cell-Based and In vivo Studies. Indonesian J Pharm. 2022;33:493–514. [DOI]
40. Yang X, Xu S, Qian Y, Xiao Q. Resveratrol regulates microglia M1/M2 polarization via PGC-1α in conditions of neuroinflammatory injury. Brain Behav Immun. 2017;64:162–72. [DOI] [PubMed]
41. Che DN, Cho BO, Kim JS, Shin JY, Kang HJ, Jang SI. Luteolin and Apigenin Attenuate LPS-Induced Astrocyte Activation and Cytokine Production by Targeting MAPK, STAT3, and NF-κB Signaling Pathways. Inflammation. 2020;43:1716–28. [DOI] [PubMed]
42. Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget. 2017;9:7204–18. [DOI] [PubMed] [PMC]
43. Broom LJ, Kogut MH. Inflammation: friend or foe for animal production? Poult Sci. 2018;97:510–4. [DOI] [PubMed]
44. DiSabato DJ, Quan N, Godbout JP. Neuroinflammation: the devil is in the details. J Neurochem. 2016; 139 Suppl 2:136–53. [DOI] [PubMed] [PMC]
45. Zhang J, Zheng Y, Luo Y, Du Y, Zhang X, Fu J. Curcumin inhibits LPS-induced neuroinflammation by promoting microglial M2 polarization via TREM2/ TLR4/ NF-κB pathways in BV2 cells. Mol Immunol. 2019;116:29–37. [DOI] [PubMed]
46. Sorrenti V, Contarini G, Sut S, Dall'Acqua S, Confortin F, Pagetta A, et al. Curcumin Prevents Acute Neuroinflammation and Long-Term Memory Impairment Induced by Systemic Lipopolysaccharide in Mice. Front Pharmacol. 2018;9:183. [DOI] [PubMed] [PMC]
47. Yuniarti N, Wulandari F, Azizah UL, Anas Y, Murwanti R. Exposure of Histone Deacetylase-2 Inhibitor Curcumin and Its Analogues in Self-Nano Emulsifying Drug Delivery System Change Memory and Cognitive Function, Anxiety, and Social Interaction Behavior in Mouse. J Pharm Sci Community. 2025; 21:228–43. [DOI]
48. Adamu A, Li S, Gao F, Xue G. The role of neuroinflammation in neurodegenerative diseases: current understanding and future therapeutic targets. Front Aging Neurosci. 2024;16:1347987. [DOI] [PubMed] [PMC]
49. Yu Y, Shen Q, Lai Y, Park SY, Ou X, Lin D, et al. Anti-inflammatory Effects of Curcumin in Microglial Cells. Front Pharmacol. 2018;9:386. [DOI] [PubMed] [PMC]
50. Liew Y, Retinasamy T, Arulsamy A, Ali I, Jones NC, O'Brien TJ, et al. Neuroinflammation: A Common Pathway in Alzheimer's Disease and Epilepsy. J Alzheimers Dis. 2023;94:S253–65. [DOI] [PubMed] [PMC]
51. Leng F, Edison P. Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? Nat Rev Neurol. 2021;17:157–72. [DOI] [PubMed]
52. Balázs N, Bereczki D, Kovács T. Cholinesterase inhibitors and memantine for the treatment of Alzheimer and non-Alzheimer dementias. Ideggyogy Sz. 2021;74:379–87. [DOI] [PubMed]
53. Anas Y, Susidarti RA, Martien R, Yuniarti N. Effect of SNEDDS Loading Pentagamavunon-0 on Memory Impairment and Neurogenesis in Mice with Monosodium Glutamate-Induced Alzheimer's Disease-Like Symptoms. BioRxiv 594779 [Preprint]. 2024 [cited 2025 Sep 16]. Available from: https://www.biorxiv.org/content/10.1101/2024.05.17.594779v1
54. Iteire K, Uwejigho R, Okonofua G. Curcumin Attenuates Lipopolysaccharide-Induced Neuroinflammation and Memory Deficiency by Inhibiting Microglia Activation in Mice Hippocampus. Galician Med J. 2022;29:E202245. [DOI]
55. Da'I M, Suhendi A, Meiyanto E, Jenie UA, Kawaichi M. Apoptosis induction effect of curcumin and its analogs pentagamavunon-0 and pentagamavunon-1 on cancer cell lines. Asian J Pharm Clin Res. 2017; 10:373–6. [DOI]
56. Meiyanto E, Putri DD, Susidarti RA, Murwanti R, Sardjiman, Fitriasari A, et al. Curcumin and its analogues (PGV-0 and PGV-1) enhance sensitivity of resistant MCF-7 cells to doxorubicin through inhibition of HER2 and NF-kB activation. Asian Pac J Cancer Prev. 2014;15:179–84. [DOI] [PubMed]

57. Satrio Putra G, Ainur Hasan M, Ika Sulistyowaty M, Anwari F, Kesuma D. Chemical and Physical Properties, Pharmacokinetics, and Pharmacodynamics of Curcumin Derivatives. In: Kar S, editor. Health Benefits of Curcumin. London: IntechOpen; 2025. pp. 1–22. [DOI]
58. Zhu HT, Bian C, Yuan JC, Chu WH, Xiang X, Chen F, et al. Curcumin attenuates acute inflammatory injury by inhibiting the TLR4/MyD88/NF-κB signaling pathway in experimental traumatic brain injury. J Neuroinflammation. 2014;11:59. [DOI] [PubMed] [PMC]
59. Wang Z, Chen G, Chen L, Liu X, Fu W, Zhang Y, et al. Insights into the binding mode of curcumin to MD-2: studies from molecular docking, molecular dynamics simulations and experimental assessments. Mol Biosyst. 2015;11:1933–8. [DOI] [PubMed]
60. Gradisar H, Keber MM, Pristovsek P, Jerala R. MD-2 as the target of curcumin in the inhibition of response to LPS. J Leukoc Biol. 2007;82:968–74. [DOI] [PubMed]
61. Cianciulli A, Calvello R, Ruggiero M, Panaro MA. Inflammaging and Brain: Curcumin and Its Beneficial Potential as Regulator of Microglia Activation. Molecules. 2022;27:341. [DOI] [PubMed] [PMC]
62. Matiadis D, Ng ST, Chen EH, Nigianni G, Vidali VP, Canko A, et al. Synthesis and Biological Evaluation of Hydroxylated Monocarbonyl Curcumin Derivatives as Potential Inducers of Neprilysin Activity. Biomedicines. 2021;9:955. [DOI] [PubMed] [PMC]
63. Namgyal D, Ali S, Mehta R, Sarwat M. The neuroprotective effect of curcumin against Cd-induced neurotoxicity and hippocampal neurogenesis promotion through CREB-BDNF signaling pathway. Toxicology. 2020;442:152542. [DOI] [PubMed]
64. Gao Y, Zhuang Z, Lu Y, Tao T, Zhou Y, Liu G, et al. Curcumin Mitigates Neuro-Inflammation by Modulating Microglia Polarization Through Inhibiting TLR4 Axis Signaling Pathway Following Experimental Subarachnoid Hemorrhage. Front Neurosci. 2019;13:1223. [DOI] [PubMed] [PMC]
65. Kharazmi K, Alani B, Heydari A, Ardjmand A. Protection against Morphine-Induced Inhibitory Avoidance Memory Impairment in Rat by Curcumin: Possible Role of Nitric Oxide/cAMP-Response Element Binding Protein Pathway. Iran J Med Sci. 2022;47:594–602. [DOI] [PubMed] [PMC]
66. Saad NM, Sekar M, Gan SH, Lum PT, Vaijanathappa J, Ravi S. Resveratrol: Latest Scientific Evidences of its Chemical, Biological Activities and Therapeutic Potentials. Pharmacogn J. 2020;12:1779–91. [DOI]
67. Rege SD, Geetha T, Griffin GD, Broderick TL, Babu JR. Neuroprotective effects of resveratrol in Alzheimer disease pathology. Front Aging Neurosci. 2014;6:218. [DOI] [PubMed] [PMC]
68. Moussa C, Hebron M, Huang X, Ahn J, Rissman RA, Aisen PS, et al. Resveratrol regulates neuro-inflammation and induces adaptive immunity in Alzheimer's disease. J Neuroinflammation. 2017;14:1. [DOI] [PubMed] [PMC]
69. Min XL, Shi Y, Xu Y, Li YY, Dong YK, Chen FX, et al. Mechanism of Sirtuin1-Mediated Deacetylation of p65-Mediated Ferroptosis of Hippocampal Neurons in Cerebral Injury after Cardiopulmonary Resuscitation in Rats. Neurochem Res. 2025;50:66. [DOI] [PubMed]
70. Bagul PK, Deepthi N, Sultana R, Banerjee SK. Resveratrol ameliorates cardiac oxidative stress in diabetes through deacetylation of NFkB-p65 and histone 3. J Nutr Biochem. 2015;26:1298–307. [DOI] [PubMed]
71. Wu SK, Wang L, Wang F, Zhang J. Resveratrol improved mitochondrial biogenesis by activating SIRT1/PGC-1α signal pathway in SAP. Sci Rep. 2024;14:26216. [DOI] [PubMed] [PMC]
72. Mota BC, Sastre M. The Role of PGC1α in Alzheimer's Disease and Therapeutic Interventions. Int J Mol Sci. 2021;22:5769. [DOI] [PubMed] [PMC]
73. Sharma V, Mishra M, Ghosh S, Tewari R, Basu A, Seth P, et al. Modulation of interleukin-1beta mediated inflammatory response in human astrocytes by flavonoids: implications in neuroprotection. Brain Res Bull. 2007;73:55–63. [DOI] [PubMed]
74. PubChem Compound Summary for CID 5280445, Luteolin [Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; c2004 [cited 2026 Apr 24]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Luteolin

75. Sawmiller D, Li S, Shahaduzzaman M, Smith AJ, Obregon D, Giunta B, et al. Luteolin reduces Alzheimer's disease pathologies induced by traumatic brain injury. Int J Mol Sci. 2014;15:895–904. [DOI] [PubMed] [PMC]
76. Facchinetti R, Valenza M, Gomiero C, Mancini GF, Steardo L, Campolongo P, et al. Co-Ultramicronized Palmitoylethanolamide/Luteolin Restores Oligodendrocyte Homeostasis via Peroxisome Proliferator-Activated Receptor-α in an In Vitro Model of Alzheimer's Disease. Biomedicines. 2022;10:1236. [DOI] [PubMed] [PMC]
77. Hu LW, Yen JH, Shen YT, Wu KY, Wu MJ. Luteolin modulates 6-hydroxydopamine-induced transcriptional changes of stress response pathways in PC12 cells. PLoS One. 2014;9:e97880. [DOI] [PubMed] [PMC]
78. Ricci D, Marrocco I, Blumenthal D, Dibos M, Eletto D, Vargas J, et al. Clustering of IRE1α depends on sensing ER stress but not on its RNase activity. FASEB J. 2019;33:9811–27. [DOI] [PubMed] [PMC]
79. Ajoolabady A, Lindholm D, Ren J, Pratico D. ER stress and UPR in Alzheimer's disease: mechanisms, pathogenesis, treatments. Cell Death Dis. 2022;13:706. [DOI] [PubMed] [PMC]
80. Chen A, Wang Y, Hu YQ. Exploring Causal Relationships Between Gut Microbiota and Alzheimer's Disease: A Bidirectional Mendelian Randomization Study. J Alzheimers Dis Rep. 2024;8:1031–40. [DOI] [PubMed] [PMC]
81. He Y, Li B, Sun D, Chen S. Gut Microbiota: Implications in Alzheimer's Disease. J Clin Med. 2020;9:2042. [DOI] [PubMed] [PMC]
82. Jiang C, Li G, Huang P, Liu Z, Zhao B. The Gut Microbiota and Alzheimer's Disease. J Alzheimers Dis. 2017;58:1–15. [DOI] [PubMed]
83. Zhu J, He L. The Modulatory Effects of Curcumin on the Gut Microbiota: A Potential Strategy for Disease Treatment and Health Promotion. Microorganisms. 2024;12:642. [DOI] [PubMed] [PMC]
84. Gan Z, Wei W, Li Y, Wu J, Zhao Y, Zhang L, et al. Curcumin and Resveratrol Regulate Intestinal Bacteria and Alleviate Intestinal Inflammation in Weaned Piglets. Molecules. 2019;24:1220. [DOI] [PubMed] [PMC]
85. Wang P, Wang J, Li D, Ke W, Chen F, Hu X. Targeting the gut microbiota with resveratrol: a demonstration of novel evidence for the management of hepatic steatosis. J Nutr Biochem. 2020;81: 108363. [DOI] [PubMed]
86. Gostimirovic M, Rajkovic J, Bukarica A, Simanovic J, Gojkovic-Bukarica L. Resveratrol and Gut Microbiota Synergy: Preventive and Therapeutic Effects. Int J Mol Sci. 2023;24:17573. [DOI] [PubMed] [PMC]
87. Li B, Du P, Du Y, Zhao D, Cai Y, Yang Q, et al. Luteolin alleviates inflammation and modulates gut microbiota in ulcerative colitis rats. Life Sci. 2021;269:119008. [DOI] [PubMed]
88. Ringman JM, Frautschy SA, Teng E, Begum AN, Bardens J, Beigi M, et al. Oral curcumin for Alzheimer's disease: tolerability and efficacy in a 24-week randomized, double blind, placebo-controlled study. Alzheimers Res Ther. 2012;4:43. [DOI] [PubMed] [PMC]
89. Rainey-Smith SR, Brown BM, Sohrabi HR, Shah T, Goozee KG, Gupta VB, et al. Curcumin and cognition: a randomised, placebo-controlled, double-blind study of community-dwelling older adults. Br J Nutr. 2016;115:2106–13. [DOI] [PubMed]
90. Abd El-Hack ME, El-Saadony MT, Swelum AA, Arif M, Abo Ghanima MM, Shukry M, et al. Curcumin, the active substance of turmeric: its effects on health and ways to improve its bioavailability. J Sci Food Agric. 2021;101:5747–62. [DOI] [PubMed]
91. Hocking A, Tommasi S, Sordillo P, Klebe S. The Safety and Exploration of the Pharmacokinetics of Intrapleural Liposomal Curcumin. Int J Nanomedicine. 2020;15:943–52. [DOI] [PubMed] [PMC]
92. Cheng D, Li W, Wang L, Lin T, Poiani G, Wassef A, et al. Pharmacokinetics, Pharmacodynamics, and PKPD Modeling of Curcumin in Regulating Antioxidant and Epigenetic Gene Expression in Healthy Human Volunteers. Mol Pharm. 2019;16:1881–9. [DOI] [PubMed] [PMC]

93. Anton SD, Ebner N, Dzierzewski JM, Zlatar ZZ, Gurka MJ, Dotson VM, et al. Effects of 90 Days of Resveratrol Supplementation on Cognitive Function in Elders: A Pilot Study. J Altern Complement Med. 2018;24:725–32. [DOI] [PubMed] [PMC]
94. Turner RS, Thomas RG, Craft S, van Dyck CH, Mintzer J, Reynolds BA, et al. A randomized, double-blind, placebo-controlled trial of resveratrol for Alzheimer disease. Neurology. 2015;85:1383–91. [DOI] [PubMed] [PMC]