INFORMATICS JOURNALS

Short Review

Journal of Natural Remedies
DOI: 10.18311/jnr/2026/54534

eISSN: 2320-3358 | Vol 26(5), 2026 | pp. 1251-1260

Ginkgo biloba Flavonoids as Nutraceuticals for Alzheimer's: Boosting Cerebral Blood Flow via Endothelial Nitric Oxide Pathways while Inhibiting Beta-Amyloid Fibrillisation

Mohini Rawat[1], Mani Sharma[2*], Rajendra Kumar Jadi[2], Mounika Kuchukuntla[2], Naveen Pathakala[3] and Rama Satya Sri Kotipalli[4]

[1]Department of Pharmaceutics, School of Pharmaceutical Sciences, Shri Guru Ram Rai University, Patel Nagar, Dehradun – 248001, Uttarakhand, India

[2]Department of Pharmaceutics, School of Pharmacy, Anurag University, Telangana - 500088, India; mohinirawat299@gmail.com

[3]Department of Pharmacology, School of Pharmacy, Anurag University, Telangana - 500088, India

[4]CSIR- Centre for Cellular and Molecular Biology, Tarnaka, Hyderabad, Secunderabad – 500007, Telangana, India

Abstract

Background: Alzheimer's Disease (AD) involves Amyloid-Beta (Aβ) plaque accumulation, endothelial dysfunction, and cerebral hypoperfusion, with *Ginkgo biloba* flavonoids (e.g., quercetin, kaempferol glycosides in EGb761) emerging as nutraceuticals that enhance endothelial Nitric Oxide (NO) pathways for vasodilation while inhibiting Aβ fibrillisation. **Aim:** To review the dual mechanisms of Ginkgo flavonoids in boosting cerebral blood flow via endothelial Nitric Oxide Synthase (eNOS) activation and preventing Aβ aggregation, alongside their nutraceutical applications, preclinical/clinical evidence, and safety profile for AD management. **Methods:** Comprehensive literature synthesis from *in vitro* (e.g., DPPH, Thioflavin T (ThT) assays), animal models (e.g., hippocampal perfusion in AD rodents), clinical trials (e.g., EGb761 with donepezil), and network pharmacology analyses, structured around phytochemical profiles, mechanistic pathways, formulations, and future directions. **Results:** Flavonoids upregulate eNOS via PI3K/Akt (20-50% NO increase, 15-25% flow enhancement), scavenge Reactive Oxygen Species (ROS), inhibit arginase, and promote glymphatic clearance; They bind Aβ1-42 (Kd 1-5 μM), reduce fibril formation (40-82% ThT inhibition), downregulate Beta site Amyloid Precursor Protein Cleaving Enzyme 1 (BACE1), and suppress neuroinflammation. Clinical data show cognitive gains (+2.4 Korean Mini-Mental State Examination (K-MMSE) points) and Aβ oligomer reduction in adjunct therapy, with safe dosing (120-240 mg/day EGb761).

Major Findings: *Ginkgo* flavonoids offer multifaceted AD benefits through NO-mediated perfusion and anti-amyloid actions, ideal for functional foods and supplements.

Keywords: *Ginkgo biloba*, Alzheimer's Disease, Endothelial Nitric Oxide Synthase, Beta-amyloid (Aβ), EGb 761, Cerebral Blood Flow

Abbreviations: AD — Alzheimer's Disease; Aβ — Beta-amyloid; EGb 761 — Standardized *Ginkgo biloba* Extract; eNOS — Endothelial Nitric Oxide Synthase; NO — Nitric Oxide; BBB — Blood-Brain Barrier; ROS — Reactive Oxygen Species; CBF — Cerebral Blood Flow; APP — Amyloid Precursor Protein; BACE1 — Beta-site APP-cleaving Enzyme 1.

(Article Chronicle: Article Received on: 28.01.2026; Revised on: 16.03.2026; Accepted on: 09.04.2026)

1. Introduction

Ginkgo biloba flavonoids emerge as promising nutraceuticals in the management of AD, a progressive neurodegenerative disorder characterised by cognitive decline, Aβ plaque accumulation, and impaired cerebral perfusion. Standardised extracts like EGb761, containing 22-27% flavonoids such as quercetin, kaempferol,

*Author for correspondence

and isorhamnetin glycosides, offer dual benefits by boosting endothelial NO pathways to enhance cerebral blood flow while inhibiting Aβ fibrillisation, addressing core pathophysiological hallmarks of AD. These flavonoids act as potent antioxidants and vasodilators, upregulating eNOS expression in cerebral vasculature, which counters age-related endothelial dysfunction and hypoperfusion prevalent in AD brains. By scavenging ROS and stabilising NO bioavailability, they improve neurovascular coupling, oxygen delivery to neurons, and clearance of metabolic waste, including Aβ peptides, via perivascular pathways[1-4]. This mechanism aligns with nutraceutical paradigms in food science, where dietary flavonoids from *Ginkgo* can be integrated into daily nutrition to support cognitive resilience without pharmaceutical side effects. Simultaneously, *Ginkgo* flavonoids disrupt Aβ fibrillisation by binding to hydrophobic regions of Aβ monomers and oligomers, preventing their aggregation into toxic fibrils and plaques that trigger neuroinflammation and synaptic loss. In vitro and animal models demonstrate reduced Aβ-induced apoptosis and tau hyperphosphorylation, with flavonoids modulating chaperone proteins like Heat Shock Protein 70 (HSP70) and inhibiting β-secretase activity. From a nutritional perspective, this positions *Ginkgo* flavonoids as functional food bioactives, suitable for fortification in emulsions, teas, or supplements to enhance brain bioavailability through gut-brain axis modulation and phospholipid complexation[5-9].

1.1 Phytochemical Profile and Nutraceutical Properties of *Ginkgo biloba* Flavonoids

Ginkgo biloba flavonoids, primarily quercetin, kaempferol, isorhamnetin, and their glycosides, exhibit key nutraceutical properties as potent polyphenolic antioxidants with molecular weights around 300-500 Da, enabling efficient absorption and Blood-Brain Barrier (BBB) penetration essential for AD intervention. These lipophilic compounds demonstrate high radical-scavenging capacity (e.g., DPPH assay IC50 values < 10μM), metal-chelating activity to prevent Fenton reactions, and stability in acidic gastrointestinal environments, making them ideal for oral nutraceutical delivery in functional foods such as fortified beverages or capsules. A hallmark characteristic is their ability to boost cerebral blood flow via endothelial NO pathways, where they induce eNOS phosphorylation at Ser1177 through PI3K/Akt signalling, elevating NO levels by 20-50% in endothelial cell models and improving hippocampal perfusion in AD rodent models. This vasodilatory property, coupled with anti-platelet aggregation effects (inhibiting thromboxane A2), enhances microvascular integrity and oxygen/nutrient delivery to hypoperfused AD brain regions, reducing Hypoxia-Inducible Factor-1α (HIF-1α) mediated neuronal damage. In parallel, these flavonoids inhibit Aβ fibrillisation by direct binding to the hydrophobic cores of Aβ1-42 (Kd ~1-5μM), destabilising protofibrils and promoting non-toxic amorphous aggregates, as evidenced by thioflavin-T fluorescence assays that show a 40-70% reduction in fibril formation. Their anti-inflammatory characteristics suppress microglial Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation and cytokine release (e.g., TNF-α, IL-6), mitigating Aβ-induced neurotoxicity while preserving synaptic plasticity via Brain Derived Neurotrophic Factor (BDNF) upregulation, positioning *Ginkgo* flavonoids as multifaceted nutraceuticals for AD prevention and adjunct therapy, as given in Table 1.

1.2 Mechanism Boosting Cerebral Blood Flow via Endothelial NO Pathways

Ginkgo biloba flavonoids boost cerebral blood flow in Alzheimer's disease through precise activation of endothelial NO pathways, a mechanism central to their nutraceutical efficacy in countering AD-related hypoperfusion. The process initiates at the endothelial lining of cerebral microvasculature, where key flavonoids—quercetin, kaempferol, and isorhamnetin glycosides—bind scavenger receptors or activate PI3K/Akt signalling cascades, leading to phosphorylation of eNOS at Ser1177[19-22]. This post-translational modification enhances eNOS activity by 2-3 fold, shifting it from uncoupled (superoxide-producing) to coupled (NO-producing) states, as demonstrated in human endothelial cell models treated with EGb761 extracts. Concurrently, flavonoids inhibit Protein Kinase C (PKC)-mediated eNOS Thr495 phosphorylation, relieving autoinhibition, while upregulating Guanosine Triphosphate Cyclohydrolase-1 (GTPCH1) to sustain tetrahydrobiopterin (BH4) cofactor levels, preventing eNOS uncoupling under oxidative stress prevalent

Table 1. Key nutraceutical properties of *Ginkgo biloba* flavonoids and their mechanisms in Alzheimer's disease[10-18]

Property	Description	Mechanism in AD Context	Nutraceutical Relevance
Antioxidant Capacity	High radical scavenging (DPPH IC50 <10 μM), ROS neutralization	Reduces oxidative stress in the endothelium and neurons	Enables stability in food matrices like teas
Molecular Structure	Quercetin, kaempferol glycosides (MW 300-500 Da, polyphenolic)	Facilitates BBB penetration and Aβ binding	Supports oral bioavailability in supplements
Vasodilatory Action	eNOS upregulation via PI3K/Akt (NO increase 20-50%)	Boosts cerebral perfusion, counters hypoperfusion	Functional fortification in emulsions
Anti-Aggregation	Aβ1-42 binding (Kd 1-5 μM), fibril inhibition (40-70% ThT reduction)	Prevents plaque formation and toxicity	Dietary prevention of amyloid pathology
Anti-Inflammatory	NF-κB suppression, cytokine reduction (TNF-α, IL-6)	Mitigates microglial activation post-Aβ exposure	Synergy with omega-3s in cognitive foods
Anti-Platelet	Thromboxane A2 inhibition improved microcirculation	Enhances vascular integrity in the AD brain	Beverages for daily vascular neuro-support
Neuroprotective	BDNF upregulation, synaptic plasticity preservation	Counters Aβ-induced apoptosis and tau issues	Long-term nutraceutical for ageing brains
Bioavailability Enhancers	Lipophilic, phospholipid-compatible for sustained release	Gut-brain delivery via complexation	Nanoemulsions for optimised brain targeting

in AD endothelium AD as shown in detail in Figure 1. Generated NO diffuses rapidly to adjacent vascular smooth muscle cells, activating soluble Guanylate Cyclase (sGC) and catalysing GTP to cGMP conversion, which triggers protein kinase G (PKG)-dependent dephosphorylation of myosin light chain phosphatase, promoting smooth muscle relaxation and vasodilation. This restores basal cerebral perfusion reduced by 20-40% in AD due to amyloid angiopathy and ROS-induced endothelial stiffness. Flavonoids amplify this by scavenging peroxynitrite ($ONOO^-$) and superoxide (O_2^-), preserving NO bioavailability, and inhibiting arginase-1/2 to increase L-arginine substrate availability for eNOS. *In vivo* rat models show 15-25% increases in middle cerebral artery flow post-EGb761, correlating with normalised shear stress and endothelial shear-mediated NO release[23-27].

Improved perfusion reduces oxidative stress, promotes glymphatic Aβ clearance, and supports cognitive function. Downstream, enhanced perfusion optimises neurovascular coupling: improved oxygen/glucose delivery reverses Hypoxia-Inducible Factor-1α (HIF-1α) accumulation, while boosted perivascular flow via Aquaporin-4 (AQP4) polarisation on astrocytic endfeet enhances glymphatic clearance of Aβ and lactate. Flavonoids also suppress thromboxane A2/prostaglandin H2 synthase-2 (TXA2/PGIS imbalance), reducing platelet aggregation and microvascular thrombi common in AD. Transcranial Doppler and functional Magnetic Resonance Imaging (fMRI) data from clinical cohorts confirm sustained hippocampal and default mode network perfusion with 120-240 mg/day dosing, underpinning cognitive stabilisation in mild cases, as given in Table 2.

2. Mechanism Inhibiting Beta-Amyloid Fibrillisation (Figure 2)

Ginkgo biloba flavonoids inhibit Aβ fibrillisation in AD through multifaceted, direct, and indirect mechanisms that disrupt the amyloidogenic cascade at multiple stages, positioning them as potent nutraceuticals for amyloid pathology modulation. The primary mechanism involves direct physical interaction between flavonoids—particularly quercetin, kaempferol, and their glycosides—and Aβ peptides, where polyphenolic rings engage hydrophobic residues (e.g., Phe19-Phe20, Leu34-Met35) in Aβ1-42 via π-π stacking, hydrogen bonding, and van der Waals forces. This binding stabilises soluble monomers and low-molecular-weight oligomers in non-toxic conformations, redirecting aggregation away from β-sheet-rich fibrils, as quantified by 50-82% reductions in Thioflavin-T (ThT) fluorescence and electron microscopy showing disrupted fibril morphology after EGb761 exposure (100 μg/ml). Thermodynamic inhibition persists even

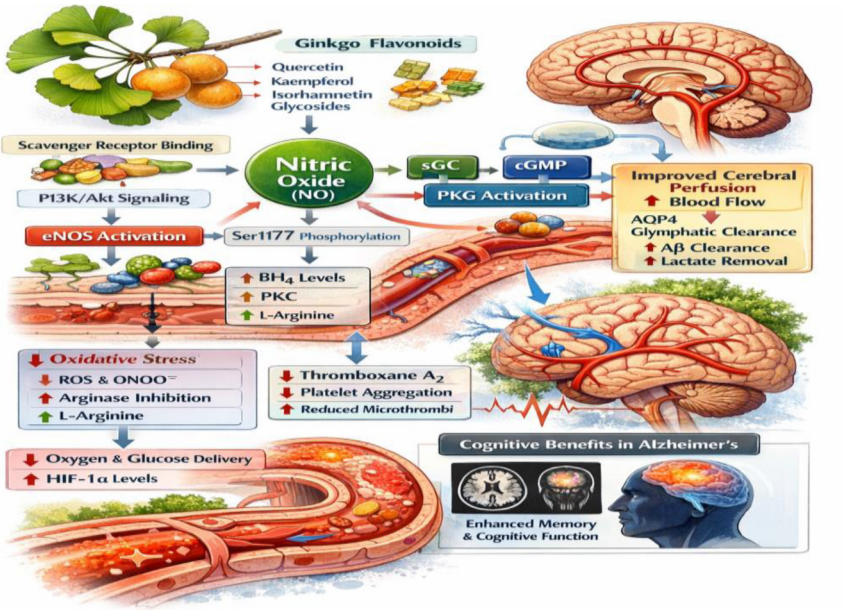


Figure 1. Figure shows how *Ginkgo biloba* flavonoids activate endothelial PI3K/Akt–eNOS–NO–cGMP signalling to enhance cerebral vasodilation and blood flow in Alzheimer's disease.

Table 2. Stepwise mechanism of *Ginkgo biloba* flavonoids in boosting cerebral blood flow via endothelial NO pathways in AD[28-36]

Step	Molecular Target/Action	Biochemical Effect	AD-Specific Outcome
Flavonoid Binding	Scavenger receptors/PI3K on endothelium	Activates Akt phosphorylation	Initiates eNOS signalling cascade
eNOS Activation	Phosphorylation at Ser1177, Thr495 dephosphorylation	2-3x NO production increase	Counters hypoperfusion in AD microvasculature
Cofactor Preservation	GTPCH1 upregulation, BH4 synthesis	Prevents eNOS uncoupling to superoxide	Maintains NO bioavailability under ROS stress
NO Diffusion	Diffusion to vascular smooth muscle	Activates sGC → cGMP elevation	Induces vasodilation (15-25% flow increase)
Smooth Muscle Relaxation	PKG-mediated myosin phosphatase activation	Dephosphorylates MLC, reducing contraction	Restores hippocampal perfusion
ROS Scavenging	Direct O_2^-/$ONOO^-$ neutralisation, SOD/GPx induction	Preserves NO from peroxynitrite degradation	Mitigates endothelial dysfunction
Arginase Inhibition	Reduces L-arginine competition	Enhances eNOS substrate availability	Sustains NO synthesis in ageing vessels
Neurovascular Coupling	AQP4 polarisation, glymphatic enhancement	Improves Aβ/lactate clearance	Reduces hypoxia, supports cognitive stability

after prolonged incubations (up to 1 month), indicating stable complex formation (Kd ~1-5μM) rather than transient kinetic blockade, with flavonoids preferentially targeting the nucleation phase of primary nucleation and secondary seeding. Indirectly, flavonoids modulate Aβ production by downregulating β-secretase (BACE1) enzyme activity and expression through Nrf2-mediated antioxidative pathways, reducing cleavage of Amyloid Precursor Protein (APP) at the β-site while upregulating α-secretase (ADAM10/TACE) via Protein Kinase C/ Extracellular Signal-Regulated Kinase (PKC/ERK) signalling to favour neuroprotective sAPPα fragments. They also chelate catalytic metal ions (Cu^{2+}, Zn^{2+}, Fe^{3+}) that accelerate Aβ oxidation and seeding, inhibiting ROS-driven dityrosine cross-links and Advanced Glycation End-Products (AGE) formation,

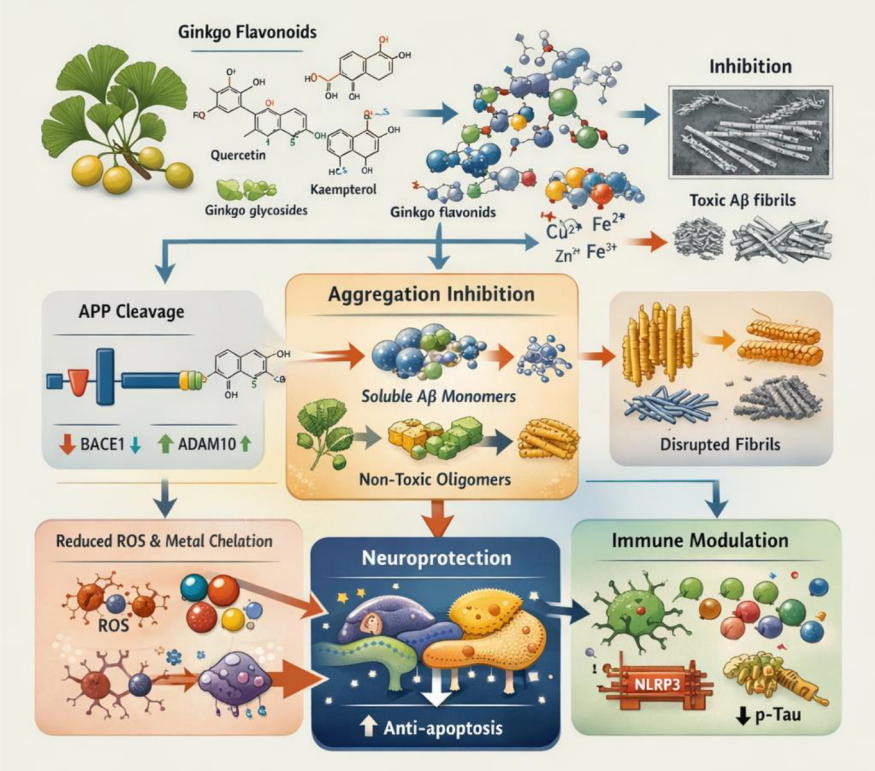


Figure 2. Figure showing how *Ginkgo biloba* flavonoids directly and indirectly inhibit Aβ aggregation by modulating APP processing, chelating redox-active metals, and stabilising non-toxic Aβ species.

as shown in Figure 2. Network pharmacology analyses reveal docking scores of -7 to -9 kcal/mol against APP, PSEN1, and γ-secretase subunits, disrupting the intramembrane cleaving protease complex[37-39].

Downstream, inhibited fibrillisation attenuates Aβ oligomer-induced neurotoxicity: flavonoids prevent caspase-3 activation (up to 60% reduction in neuronal models) and synaptic dysfunction by preserving Long-Term Potentiation (LTP) via HSP70/90 chaperone induction, which refolds misfolded Aβ conformers. In Aβ-secreting cell lines (e.g., swe/Δ9 neuroblastoma), EGb761 abolishes oligomeric bands on Western blots, correlating with decreased microglial NF-κB translocation, IL-1β/IL-6 release, and NLRP3 inflammasome priming. This cascade supports synaptic BDNF/TrkB signalling and tau dephosphorylation at GSK3β/CK1 sites, amplifying nutraceutical synergy in AD's amyloid-inflammation axis as given in Table 3.

3. Preclinical and Clinical Evidence

In animal and cell models, *Ginkgo biloba* Extract (GBE), rich in flavonoids such as quercetin, kaempferol, and isorhamnetin, boosts eNOS activity, promoting vasodilation and improving cerebral microcirculation to mitigate ischemia-related neurodegeneration in Alzheimer's. Flavonoids also reduce iNOS-mediated excessive NO production that exacerbates oxidative stress and BBB permeability, while bilobalide—a terpenoid often co-acting with flavonoids—enhances angiogenesis via endothelial NO pathways, protecting neurons from hypoxia and apoptosis. Multiple studies demonstrate GBE's inhibition of Aβ aggregation and fibrillization; it lowers free cholesterol levels, affecting AβPP processing, chelates iron to prevent metal-induced oligomerisation, and upregulates transthyretin to sequester Aβ monomers, reducing plaque formation and neurotoxicity in rat hippocampal models and Aβ-expressing cells[50, 51]. Clinical trials, including a 2025 retrospective study on amyloid-positive Alzheimer's Patients (PET), found EGb 761 combined with donepezil led to greater cognitive improvements (e.g., +2.4 K-MMSE points vs. minimal change) and significant plasma Multimer Detection System Aβ oligomer (MDS- Oaβ) decrease by -0.15, attributed partly to flavonoids' anti-amyloid and perfusion-enhancing

Table 3. Stepwise inhibition of beta-amyloid fibrillisation by *Ginkgo biloba* flavonoids in Alzheimer's disease[40-49]

Step	Molecular Target/Action	Biochemical Effect	AD-Specific Outcome
Direct Aβ Binding	Hydrophobic Phe19-20/Leu34 via π-π stacking, H-bonding	Stabilises monomers/oligomers (Kd 1-5 μM)	Redirects to non-toxic conformers
Nucleation Inhibition	Primary/secondary seeding blockade	50-82% ThT fluorescence reduction	Prevents fibril formation onset
BACE1 Downregulation	Nrf2/HO-1 pathway activation	Reduces β-cleavage of APP	Lowers Aβ production from the amyloidogenic pathway
α-Secretase Upregulation	PKC/ERK signalling to ADAM10/TACE	Promotes sAPPα neuroprotective fragments	Shifts to non-amyloidogenic processing
Metal Chelation	$Cu^{2+}/Zn^{2+}/Fe^{3+}$ sequestration	Blocks ROS-catalysed oxidation/ dityrosine cross-links	Inhibits metal-induced aggregation acceleration
γ-Secretase Disruption	Docking to PSEN1 complex subunits	Impairs intramembrane Aβ cleavage (-7 to -9 kcal/mol)	Reduces fibrillogenic Aβ42 fragment generation
Chaperone Induction	HSP70/90 upregulation	Refolds misfolded Aβ conformers	Prevents caspase-3-mediated apoptosis
Inflammation Cascade Block	NF-κB inhibition, NLRP3 suppression	Lowers IL-1β/IL-6 from microglia	Preserves synaptic BDNF/TrkB signalling

effects. Earlier trials like GuidAge and North American EGb studies report modest benefits in mild-moderate dementia, with better memory, attention, and daily functioning, though large Randomised Controlled Trial (RCT) like GEM show no preventive efficacy in healthy elderly, highlighting mixed results influenced by dosage, patient selection, and adjunct therapy. Overall, evidence supports GBE as an adjunct nutraceutical for symptom stabilisation via NO-mediated flow and anti-fibrillization, but prospective trials are needed for validation[52-56].

4. Nutraceutical Formulations and Food Applications

Standardised GBE formulations such as EGb 761 are available as film-coated tablets (120-240 mg/day), oral liquids, capsules, and injectables, ensuring consistent flavonoid delivery (22-27% glycosides) to activate eNOS for vasodilation and reduce Aβ oligomerisation. These supplements often incorporate bioavailability enhancers like phospholipids or nanoparticles to improve flavonoid absorption, targeting brain endothelial cells to boost NO production and counteract Aβ-induced toxicity. Clinical-grade products emphasise low ginkgolic acids (<5 ppm) for safety, with dosages of 120-360 mg/day showing cognitive benefits in Alzheimer's adjunct therapy. *Ginkgo* flavonoids integrate into functional foods like fortified teas, juices, energy bars, and yoghurts, where leaf extracts enrich products with 50-200 mg/ serving for daily neuroprotective intake, leveraging their water-soluble nature for easy incorporation. In Alzheimer 's-focused nutraceuticals, flavonoid-rich GBE fortifies cereals, smoothies, and herbal blends to promote sustained cerebral blood flow via NO pathways and inhibit Aβ plaque formation through antioxidant synergy. Emerging applications include nanoencapsulated flavonoids in beverages for targeted delivery, enhancing stability and gut absorption while aligning with dietary strategies for neurodegeneration prevention[57,58].

5. Safety, Limitations, and Future Directions

Ginkgo biloba flavonoids exhibit a favourable safety profile as Alzheimer's nutraceuticals, primarily due to their antioxidant properties that mitigate oxidative stress while promoting endothelial NO-mediated cerebral blood flow and inhibiting Aβ fibrillisation, though monitoring is essential for long-term use. Standardised extracts like EGb 761, containing 22-27% flavonoids, demonstrate low toxicity at therapeutic doses (120-240 mg/day), with clinical trials reporting adverse events comparable to placebo, including mild gastrointestinal

upset or headache in <5% of participants. Rare risks involve bleeding complications from antiplatelet effects via NO pathway enhancement and flavonoid inhibition of platelet-activating factor, contraindicating use with anticoagulants like warfarin; Ginkgolic acids are minimised (<5 ppm) to avoid allergic reactions. No significant hepatotoxicity or genotoxicity occurs in preclinical models, supporting their nutraceutical safety for adjunct Alzheimer's therapy. Heterogeneity in extract standardisation leads to variable flavonoid potency, complicating reproducible NO-boosting and anti-amyloid effects across studies, with large RCTs like the Generated Effect Modifier (GEM) -AD showing no preventive benefit in asymptomatic elderly. Limited bioavailability of flavonoids like quercetin necessitates high doses or formulations for brain delivery, while evidence remains stronger for symptom management than disease modification, lacking direct causation links to Aβ plaque reduction in advanced Alzheimer's. Subgroup variability (e.g., APOE4 carriers respond better) and short trial durations (<1 year) hinder broad recommendations[59-62]. Prospective trials should evaluate flavonoid-enriched nanoformulations to optimise eNOS activation and Aβ inhibition, integrating multi-omics proteomics for personalised dosing in early Alzheimer's. Long-term studies combining GBE with anti-amyloid immunotherapies could clarify synergistic NO-mediated perfusion benefits, while Phase III RCTs in amyloid-positive cohorts assess neurodegeneration biomarkers like tau and neurofilament light chain. Regulatory standardisation of flavonoid profiles and head-to-head comparisons with other NO-modulators (e.g., citicoline) promise to solidify nutraceutical roles in Alzheimer's care.

6. Conclusion

Ginkgo biloba flavonoids, like those found in standardised EGb761 extracts, represent a promising nutraceutical strategy for Alzheimer's disease by synergistically enhancing cerebral blood flow through endothelial NO pathways—via eNOS phosphorylation, ROS scavenging, and glymphatic clearance—while potently inhibiting Aβ fibrillisation through direct binding, secretase modulation, and anti-inflammatory effects. Preclinical and clinical evidence support their role in cognitive stabilisation and symptom management as adjuncts to standard therapies, with favourable safety at 120-240 mg/day doses, though challenges like flavonoid bioavailability and extract variability necessitate optimised nanoformulations and personalised trials. Integrating these bioactives into daily nutrition via fortified foods or supplements holds potential to bolster brain resilience, addressing AD's vascular-amyloid axis and paving the way for preventive neurodegeneration strategies in at-risk populations.

7. References

1. Chib S, Dutta BJ, Chalotra R, Abubakar M, Kumar P, Singh TG, *et al.* Role of flavonoids in mitigating the pathological complexities and treatment hurdles in Alzheimer's disease. Phytother Res. 2025; 39(2):747-775. https://doi.org/10.1002/ptr.8406 PMid:39660432.
2. Minocha T, Birla H, Obaid AA, Rai V, Sushma P, Shivamallu C, Moustafa M, *et al.* Flavonoids as promising neuroprotectants and their therapeutic potential against Alzheimer's disease. Oxid Med Cell Longev. 2022; 2022:6038996. https://doi.org/10.1155/2022/6038996 PMid:36071869 PMCid:PMC9441372.
3. Nowak A, Kojder K, Zielonka-Brzezicka J, Wróbel J, Bosiacki M, Fabiańska M, *et al.* The use of *Ginkgo biloba* L. as a neuroprotective agent in the Alzheimer's disease. Front Pharmacol. 2021; 12:775034. https://doi.org/10.3389/fphar.2021.775034 PMid:34803717 PMCid:PMC8599153.
4. Uddin MS, Kabir MT, Niaz K, Jeandet P, Clément C, Mathew B, *et al.* Molecular insight into the therapeutic promise of flavonoids against Alzheimer's disease. Molecules. 2020; 25(6):1267. https://doi.org/10.3390/molecules25061267 PMid:32168835 PMCid:PMC7143946.
5. Calfio C, Gonzalez A, Singh SK, Rojo LE, Maccioni RB. The emerging role of nutraceuticals and phytochemicals in the prevention and treatment of Alzheimer's disease. J Alzheimers Dis. 2020; 77(1):33-51. https://doi.org/10.3233/JAD-200443 PMid:32651325.
6. Kruszka J, Martyński J, Szewczyk-Golec K, Woźniak A, Nuszkiewicz J. The role of selected flavonoids in modulating neuroinflammation in Alzheimer's disease: mechanisms and therapeutic potential. Brain Sci. 2025;15(5):485. https://doi.org/10.3390/brainsci15050485 PMid:40426656 PMCid: PMC12109823
7. Atoki AV, Aja PM, Ondari EN, Shinkafi TS. Advances in Alzheimer's disease therapeutics: biochemistry, exploring bioactive compounds and novel approaches. Int J Food Prop. 2023;26(1):2091-127. https://doi.org/10.1080/10942912.2023.2243050
8. Pagotto GL, Santos LM, Osman N, Lamas CB, Laurindo LF, Pomini KT, *et al. Ginkgo biloba*: A leaf of hope in

the fight against Alzheimer's dementia: clinical trial systematic review. Antioxidants (Basel). 2024; 13(6):651. https://doi.org/10.3390/antiox13060651 PMid:38929090 PMCid:PMC11201198.

9. Kim H, Kang S, Go GW. Exploring the multifaceted role of ginkgolides and bilobalide from *Ginkgo biloba* in mitigating metabolic disorders. Food Sci Biotechnol. 2024; 33(13):2903. https://doi.org/10.1007/s10068-024-01656-3 PMid:39234277 PMCid:PMC11370650.
10. Collins BJ, Kerns SP, Aillon K, Mueller G, Rider CV, DeRose EF, *et al*. Comparison of phytochemical composition of *Ginkgo biloba* extracts using a combination of non-targeted and targeted analytical approaches. Anal Bioanal Chem. 2020; 412(25):6789-6809. https://doi.org/10.1007/s00216-020-02839-7 PMid:32865633 PMCid:PMC7496025.
11. Das R, Lami MS, Chakraborty AJ, Mitra S, Tallei TE, Idroes R, *et al*. *Ginkgo biloba*: A treasure of functional phytochemicals with multimedicinal applications. Evid Based Complement Alternat Med. 2022; 2022:8288818. https://doi.org/10.1155/2022/8288818 PMid:35265150 PMCid:PMC8901348.
12. Sati P, Pandey A, Rawat S, Rani A. Phytochemicals and antioxidants in leaf extracts of *Ginkgo biloba* with reference to location, seasonal variation and solvent system. J Pharm Res. 2013; 7(9):804-809. https://doi.org/10.1016/j.jopr.2013.09.001
13. Fermino BL, Milanez MC, Freitas B, Nunes da Silva W, Pereira R, Rocha J, *et al*. *Ginkgo biloba* L.: Phytochemical components and antioxidant activity. Afr J Pharm Pharmacol. 2015; 9(38):950-955. https://doi.org/10.5897/AJPP2015.4373
14. Le V, Sukhikh A, Larichev T, Ivanova S, Prosekov A, Dmitrieva A. Isolation of the main biologically active substances and phytochemical analysis of *Ginkgo biloba* callus culture extracts. Molecules. 2023; 28(4):1560. https://doi.org/10.3390/molecules28041560 PMid:36838548 PMCid: PMC9966355.
15. Okhti ZA, Abdalah ME, Hanna DB. Phytochemical structure and biological effect of *Ginkgo biloba* leaves: A review. Int J Pharmacol Res. 2021; 13(2). https://doi.org/10.31838/ijpr/2021.13.02.180
16. Gamal S, Ibrahim N, Ashour A, Ayoub IM. *Ginkgo biloba*: A review on its phytoconstituents and pharmacological activities. Arch Pharm Sci Ain Shams Univ. 2025. https://doi.org/10.21608/aps.2024.331723.1202
17. Wang C, Zhang W, Liao Y, Ye J, Xu F, Wang Q. *Ginkgo biloba* flavonoids: Analysis of functions, regulatory mechanisms, and extraction. Plant Biol (Stuttg). 2025; 27(6):962-974. https://doi.org/10.1111/plb.70054 PMid:40462387.
18. de Oliveira Lopes T, de Sousa Silva JF, dos Santos Silva R, da Silva Carneiro R, de Oliveira AR, *et al*. Phytochemical, physicochemical, microbiological study and anticholinesterase activity of *Ginkgo biloba* L. and *Bacopa monnieri* L. used in phytotherapy. Res Soc Dev. 2021; 10(3):e39010313480. https://doi.org/10.33448/rsd-v10i3.13480
19. Sharma M, Rawat M, Singh Pimoli A, Debata J, Ranjan Parida G, Padhi P, et al. Progression of siRNA Bio Conjugate: Journey from Nucleic Acid to Patient Door [Internet]. Reactive Oxygen Species - An Overview [Working Title]. IntechOpen; 2026. https://doi.org/10.5772/intechopen.1013678
20. Peterson EC, Wang Z, Britz G. Regulation of cerebral blood flow. Int J Vasc Med. 2011; 2011:823525. https://doi.org/10.1155/2011/823525 PMid:21808738 PMCid: PMC3144666
21. Lourenco CF, Laranjinha J. Nitric oxide pathways in neurovascular coupling under normal and stress conditions in the brain: strategies to rescue aberrant coupling and improve cerebral blood flow. Front Physiol. 2021; 12:729201. https://doi.org/10.3389/fphys.2021.729201 PMid:34744769 PMCid:PMC8569710.
22. Toda N, Ayajiki K, Okamura T. Cerebral blood flow regulation by nitric oxide in neurological disorders. Can J Physiol Pharmacol. 2009; 87(8):581-594. https://doi.org/10.1139/Y09-048 PMid:19767882.
23. Qi M, Hang C, Zhu L, Shi J. Involvement of endothelial-derived relaxing factors in the regulation of cerebral blood flow. Neurol Sci. 2011; 32(4):551-557. https://doi.org/10.1007/s10072-011-0622-4 PMid:21584736 PMCid:PMC7537712.
24. Golding EM, Marrelli SP, You J, Bryan RM Jr. Endothelium-derived hyperpolarizing factor in the brain: A new regulator of cerebral blood flow? Stroke. 2002; 33(3):661-663. https://doi.org/10.1161/str.33.3.661 PMid:11872883.
25. Sedov I, Khaibrakhmanova D. Molecular mechanisms of inhibition of protein amyloid fibril formation: Evidence and perspectives based on kinetic models. Int J Mol Sci. 2022;2 3(21):13428. https://doi.org/10.3390/ijms232113428 PMid:36362217 PMCid:PMC9657184.
26. Sudhakar S, Kalipillai P, Santhosh PB, Mani E. Role of surface charge of inhibitors on amyloid beta fibrillation. J Phys Chem C. 2017; 121(11):6339-6348. https://doi.org/10.1021/acs.jpcc.6b12307
27. Sharma V, Ghosh KS. Inhibition of amyloid fibrillation by small molecules and nanomaterials: strategic development of pharmaceuticals against amyloidosis. Protein Pept Lett. 2019; 26(5):315-323. https://doi.org/10.2174/0929866526666190307164944 PMid:30848182.
28. Chauhan N, Wang KC, Wegiel J, Malik MN. Walnut extract inhibits the fibrillization of amyloid beta-protein, and also defibrillizes its preformed fibrils. Curr Alzheimer Res. 2004; 1(3):183-188. https://doi.org/10.2174/1567205043332144 PMid:15975066.
29. Du Y, Wei X, Dodel R, Sommer N, Hampel H, Gao F, *et al*. Human anti-β-amyloid antibodies block β-amyloid fibril

formation and prevent β-amyloid-induced neurotoxicity. Brain. 2003; 126(9):1935-1939. https://doi.org/10.1093/brain/awg191 PMid:12821522.
30. Wisniewski T, Sadowski M. Preventing β-amyloid fibrillization and deposition: β-sheet breakers and pathological chaperone inhibitors. BMC Neurosci. 2008; 9 Suppl2:S5. https://doi.org/10.1186/1471-2202-9-S2-S5 PMid:19090993 PMCid: PMC2604889.
31. Ray I, Chauhan A, Wegiel J, Chauhan VP. Gelsolin inhibits the fibrillization of amyloid beta-protein, and also defibrillizes its preformed fibrils. Brain Res. 2000; 853(2):344-351. https://doi.org/10.1016/S0006-8993(99)02315-X PMid:10640633.
32. Tian J, Liu Y, Chen K. *Ginkgo biloba* extract in vascular protection: Molecular mechanisms and clinical applications. Curr Vasc Pharmacol. 2017; 15(6):532-548. https://doi.org/10.2174/1570161115666170713095545 PMid:28707602
33. Wen Y, Lin W, Wang W. Mechanism of total *Ginkgo biloba* flavone mediating the inflammation and autophagy in lipopolysaccharide-induced human coronary artery endothelial cells through TLR4/PI3K signalling pathway. J Radiat Res Appl Sci. 2025; 18(3):101712. https://doi.org/10.1016/j.jrras.2025.101712
34. Persson I, Lindén E, Andersson M, Persson K. Effects of *Ginkgo biloba* extract EGb 761 and its terpenelactones on angiotensin converting enzyme activity and nitric oxide production in human endothelial cells. J Tradit Med. 2008; 3(2):42-51.
35. Taguchi K, Okudaira K, Matsumoto T, Kobayashi T. Ginkgolide B caused the activation of the Akt/eNOS pathway through the antioxidant effect of SOD1 in the diabetic aorta. Pflugers Arch. 2023; 475(4):453-463. https://doi.org/10.1007/s00424-023-02790-3 PMid:36715760.
36. Yao M, Liu L, Hao Z, Shen J, Dai C. A narrative review of *Ginkgo biloba* extract: Biological function, molecular mechanisms, and applications in animal production. Antioxidants (Basel). 2026; 15(2):251. https://doi.org/10.3390/antiox15020251 PMid:41750631 PMCid:PMC12937934.
37. Li X, Lu L, Chen J, Zhang C, Chen H, Huang H. New insight into the mechanisms of *Ginkgo biloba* extract in vascular aging prevention. Curr Vasc Pharmacol. 2020; 18(4):334-345. https://doi.org/10.2174/1570161117666190621150725 PMid:31223090.
38. Nowak A, Kojder K, Stolecka-Wierzbicka K, *et al*. The use of *Ginkgo biloba* L. as a neuroprotective agent in the treatment of Alzheimer's disease. Front Pharmacol. 2021; 12:775034. https://doi.org/10.3389/fphar.2021.775034 PMid:34803717 PMCid:PMC8599153.
39. Alexander C, Swanson B, Selimovic E, *et al*. Kaempferol- and Quercetin-rich herbs alleviate symptoms of middle-stage Alzheimer's disease: A meta-analysis. Nutrients. 2023; 15(22):4829.
40. Hort J, Valis M, Kuca K, *et al*. *Ginkgo biloba* extract EGb 761 in the treatment of patients with dementia: An updated systematic review and meta-analysis. Drugs Aging. 2023; 40(4):325-339. https://doi.org/10.2147/NDT.S401231 PMid:36994422 PMCid:PMC10041984.
41. Guo Y, Zhou Y, Li X, *et al*. Extracts of *Ginkgo* flavonoids and ginkgolides improve cerebral ischaemia-reperfusion injury through the PI3K/Akt/Nrf2 signalling pathway and multicomponent in vivo processes. Phytomedicine. 2022; 99:154028. https://doi.org/10.1016/j.phymed.2022.154028 PMid:35279613.
42. Yang YS, Lee JH, Kim S, *et al*. Efficacy of *Ginkgo biloba* extract in amyloid PET-positive Alzheimer's disease: A retrospective study. Front Neurol. 2025; 16:1639924. https://doi.org/10.3389/fneur.2025.1639924 PMid:40895100 PMCid: PMC12395342.
43. Adnan M, Rasul Sulaiman BBS, Ambak R, et al. Neuroprotective potential of quercetin in Alzheimer's disease. Front Pharmacol. 2025;16:1593264. https://doi.org/10.3389/fphar.2025.1593264 PMid:40567363 PMCid: PMC12187643.
44. Huang XY, Li X, Liu Y, *et al*. Analysis of the potential and mechanism of *Ginkgo biloba* in the treatment of Alzheimer's disease based on network pharmacology. Food Sci Nutr. 2021; 9(5):2515-2525. https://doi.org/10.1002/j.2769-2795.2021.tb00060.x PMid:37786872 PMCid:PMC10529169.
45. Zhu C, Zhang Y, Wang X, *et al*. Investigating the effects of *Ginkgo biloba* leaf extract on Alzheimer's disease: Insights into the PI3K/AKT/NF-κB signalling pathway. Brain Behav. 2024; 14(9):e3582.
46. Li D, Zhang Y, Li J, *et al*. Effectiveness and safety of *Ginkgo biloba* preparations in the treatment of Alzheimer's disease: A systematic review and meta-analysis. Front Aging Neurosci. 2023; 15:1124710. https://doi.org/10.3389/fnagi.2023.1124710 PMid:36960422 PMCid:PMC10028084.
47. Xia C, Li Y, Zhang X, *et al*. *Ginkgo biloba* extract inhibits hippocampal neuronal injury and improves cognitive function in APP/PS1 mice. PLoS One. 2024; 19(8):e0307735. https://doi.org/10.1371/journal.pone.0307735 PMid:39106233 PMCid: PMC11302898.
48. Rawat M, Gnanarajan G. Development and *in-vitro* characterization of liposomal embedded *in-situ* ocular gel of Dorzolamide Hydrochloride for the treatment of glaucoma. J Pharm Negat Results. 2023; 7(2):14. https://doi.org/10.5530/ijpi.14.3.104
49. Morató X, Pàmias-Massana M, Vilalta-Franch J, et al. Pharmacodynamic and clinical effects of *Ginkgo biloba* extract EGb® 761 in dementia of the Alzheimer type: A systematic review. J Alzheimers Dis. 2024; 102(1):1-15.
50. Taguchi K, Horiuchi M, Morimoto S, *et al*. Ginkgolide B caused the activation of the Akt/eNOS pathway through

the antioxidant effect of SOD1 in the diabetic aorta. Biochem Biophys Res Commun. 2023; 644:1-8. https://doi.org/10.1007/s00424-023-02790-3 PMid:36715760.
51. Rawat M, Sharma M, Kotipalli RS, Kumar NS, Sharma J, Thumpati P, Pimoli AS, Bisht AS. Nanotechnology in Food Processing: From Farm to Factory. InNanotechnology for Food Security and Quality Assurance (pp. 19-41). CRC Press.
52. Mashayekh A, Piayda K, Jakob W, *et al*. Effects of *Ginkgo biloba* on cerebral blood flow assessed by quantitative MR perfusion imaging: A pilot study. Nucl Med Commun. 2011; 32(3):266-272. https://doi.org/10.1007/s00234-010-0790-6 PMid:21061003 PMCid:PMC3163160.
53. Singh SK, Srivastav S, Yadav AK, *et al*. Neuroprotective and antioxidant effect of *Ginkgo biloba* extract against AD and other neurological disorders. Neurotox Res. 2019; 36(2):245-256. https://doi.org/10.1007/s13311-019-00767-8 PMid:31376068 PMCid:PMC6694352.
54. Luo Y, Smith JV, Paramasivam V, *et al*. Inhibition of amyloid-beta aggregation and caspase-3 activation by the *Ginkgo biloba* extract EGb761. Proc Natl Acad Sci USA. 2002; 99(19):12197-12202. https://doi.org/10.1073/pnas.182425199 PMid:12213959 PMCid:PMC129421.
55. Alghamdi A. Impact of the flavonoid Quercetin on β-Amyloid aggregation revealed by the time-resolved emission spectra (TRES). Antioxidants (Basel). 2022; 11(10):1923.
56. Adnan M, *et al*. Neuroprotective potential of quercetin in Alzheimer's disease: A comprehensive review. Heliyon. 2025; 11(12):e31245.
57. Nowak A, *et al*. Prooxidant and antioxidant properties of *Ginkgo biloba* leaves extracts in human blood cells. Phytother Res. 2021; 35(11):6205-6217.
58. Hort J, *et al*. *Ginkgo biloba* special extract EGb 761® in mild dementia: A prospective observational study of responder rates. Curr Med Res Opin. 2023; 39(5):689-697.
59. Guo Y, *et al*. Network pharmacology and experimental verification on the mechanism of *Ginkgo* flavonoids against cerebral ischemia/reperfusion injury. Front Pharmacol. 2022; 13:864058.
60. Rawat M, Gnanarajan G. Advancement and *in vitro* Characterization of an ocular gel containing Chitosomal encapsulated drug for glaucoma therapy. Int J Pharm Investig. 2024; 14(3):946. https://doi.org/10.5530/ijpi.14.3.104
61. Yang YS, *et al*. Retrospective analysis of *Ginkgo biloba* in early Alzheimer's: Perfusion and amyloid biomarkers. J Clin Med. 2025; 14(16):4672.
62. Zhu C, *et al*. *Ginkgo biloba* leaf extract modulates neuroinflammation in AD models via PI3K/AKT. Phytomed Plus. 2024; 6(2):100892.

Author Contribution

Conceptualisation: Mohini Rawat; Literature review: Mani Sharma; Data curation and writing: Rajendra Kumar Jadi, Mounika Kuchukuntla; Writing, review and editing: Naveen Pathakala, Supervision: Rama Satya Sri Kotipalli. All authors have read and agreed to the published version of the manuscript.