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Ginkgo Biloba-Derived Flavonoids as Metal Chelators in Alzheimer's Neurochemistry: A Biochemical Approach

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Abstract: Alzheimer's disease (AD) is a complex and progressive neurodegenerative disorder marked by the pathological accumulation of amyloid-β plaques, neurofibrillary tangles due to tau hyperphosphorylation, and a profound imbalance in metal ion homeostasis. Increasing evidence suggests that transition metals such as iron (Fe), copper (Cu), and zinc (Zn) contribute to the pathogenesis of AD by catalyzing the production of reactive oxygen species (ROS) through redox cycling, thus exacerbating oxidative stress and protein misfolding. Chelation of these metals is emerging as a viable therapeutic strategy to mitigate these effects. This study investigates flavonoids extracted from Ginkgo biloba—specifically quercetin, kaempferol, and isorhamnetin—as natural, multifunctional agents capable of chelating redox-active metals and scavenging free radicals. Using a comprehensive biochemical approach, we examined their molecular structures, binding mechanisms, and pharmacological efficacy through spectrophotometric assays, antioxidant capacity analyses, and molecular docking simulations. Our findings reveal that these flavonoids exhibit significant Fe(II) and Cu(II) chelation ability, inhibit amyloid aggregation, and demonstrate potent antioxidant activity. Quercetin, in particular, displayed the highest metal binding affinity and radical scavenging potential. By modulating metal ion levels and preventing oxidative damage, Ginkgo biloba-derived flavonoids represent promising neuroprotective candidates in AD treatment. This article offers mechanistic insights into their biochemical behavior, emphasizing their relevance in the development of multi-targeted interventions for Alzheimer's disease.

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I. INTRODUCTION

Alzheimer's disease (AD) is the most prevalent form of dementia, currently affecting more than 55 million people worldwide [1]. Clinically, AD manifests as a progressive loss of memory, cognition, and reasoning, eventually leading to complete functional dependence. Neuropathologically, AD is characterized by the accumulation of amyloid-β (Aβ) plaques, neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein, chronic neuroinflammation, and extensive neuronal and synaptic degeneration [2] [3].

Beyond amyloid and tau pathology, increasing attention has been drawn to the dysregulation of metal ion homeostasis as a crucial factor in AD pathogenesis. Postmortem analyses of AD brains reveal significantly elevated concentrations of redox-active metals such as iron (Fe), copper (Cu), and zinc (Zn) within Aβ plaques and surrounding cortical regions [4] . These metals participate in Fenton and Haber-Weiss reactions, generating ROS such as hydroxyl radicals (•OH), which cause oxidative damage to lipids, proteins, and nucleic acids [5] . Such oxidative stress not only damages neurons directly but also accelerates Aβ aggregation and tau hyperphosphorylation, thus reinforcing the degenerative cycle [6] .

Iron, particularly in its ferrous form (Fe^{2+}), is abundant in AD-affected hippocampal and cortical regions and promotes lipid peroxidation and DNA oxidation [7] . Copper (Cu^{2+}) can catalyze the production of hydrogen peroxide in the presence of biological reductants such as ascorbate, while zinc (Zn^{2+}), although redox-inert, facilitates Aβ aggregation and disrupts synaptic signaling [8] [9] . Thus, restoring metal ion balance in the brain represents a promising therapeutic avenue for modifying AD pathology.

In this context, metal chelation therapy has emerged as a strategic approach. Chelating agents can bind excess free metal ions, reducing their redox activity and mitigating oxidative stress. However, synthetic chelators often suffer from poor blood–brain barrier (BBB) permeability and toxicity issues [10] . Therefore, natural chelators such as plant-derived polyphenols offer a safer and potentially more effective alternative. Among these, flavonoids—a diverse class of phenolic compounds found abundantly in fruits,

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vegetables, and medicinal herbs—have attracted attention for their multifaceted bioactivities, including antioxidation, metal chelation, and neuroprotectio [11].

Ginkgo biloba, a medicinal tree with a long history in traditional Chinese medicine, is particularly rich in bioactive flavonoids such as quercetin, kaempferol, and isorhamnetin. Standardized extracts of Ginkgo biloba (e.g., EGb 761) have shown cognitive benefits in patients with mild-to-moderate AD and vascular dementia [12] . The neuroprotective effects of these flavonoids are attributed to their structural capability to chelate metal ions through catechol and hydroxyl groups, interrupt Aβ fibril formation, scavenge ROS, and upregulate endogenous antioxidant enzymes like superoxide dismutase (SOD) and catalase [13] [14] .

Despite their therapeutic promise, comprehensive biochemical studies evaluating the specific metal chelating and antioxidant actions of individual Ginkgo biloba-derived flavonoids are limited. Therefore, this study was designed to profile the flavonoid composition of Ginkgo biloba leaf extract, evaluate their Fe(II) and Cu(I) chelation efficiency, assess antioxidant potential using DPPH and ABTS radical assays, and explore molecular docking interactions with Aβ and tau targets. By integrating phytochemical analysis, metal binding assays, and in silico modeling, this investigation aims to elucidate the biochemical basis for the neuroprotective potential of Ginkgo biloba-derived flavonoids in Alzheimer's disease.

II. MATERIALS AND METHODS

➢ *Plant Material Collection and Extraction*

Fresh leaves of Ginkgo biloba were collected from verified botanical sources [15]. The leaves were washed, shade-dried at 30–35°C for 5 days, and pulverized using a mechanical grinder. The dried powder was subjected to Soxhlet extraction with 70% ethanol for 8 hours. The solvent was evaporated under reduced pressure using a rotary evaporator to obtain a concentrated extract [16], 2011. The extract was lyophilized and stored at –20°C for further analysis.

➢ *Phytochemical Screening and Quantification*

- *HPLC Analysis of Flavonoids*

High-Performance Liquid Chromatography (HPLC) was conducted using an Agilent 1260 Infinity II system equipped with a C18 column (5 µm, 4.6 × 250 mm) [17] . The mobile phase consisted of water with 0.1% formic acid (A) and methanol (B) in a gradient elution. Detection was performed at 370 nm. Standards of quercetin, kaempferol, and isorhamnetin were used for identification and quantification.

Table 1 Retention Time and Concentration of Major Flavonoids in Ginkgo Biloba Extract

Compound	Retention Time (min)	Concentration (mg/g extract)
Quercetin	13.2	26.4
Kaempferol	14.5	18.7
Isorhamnetin	15.8	10.3

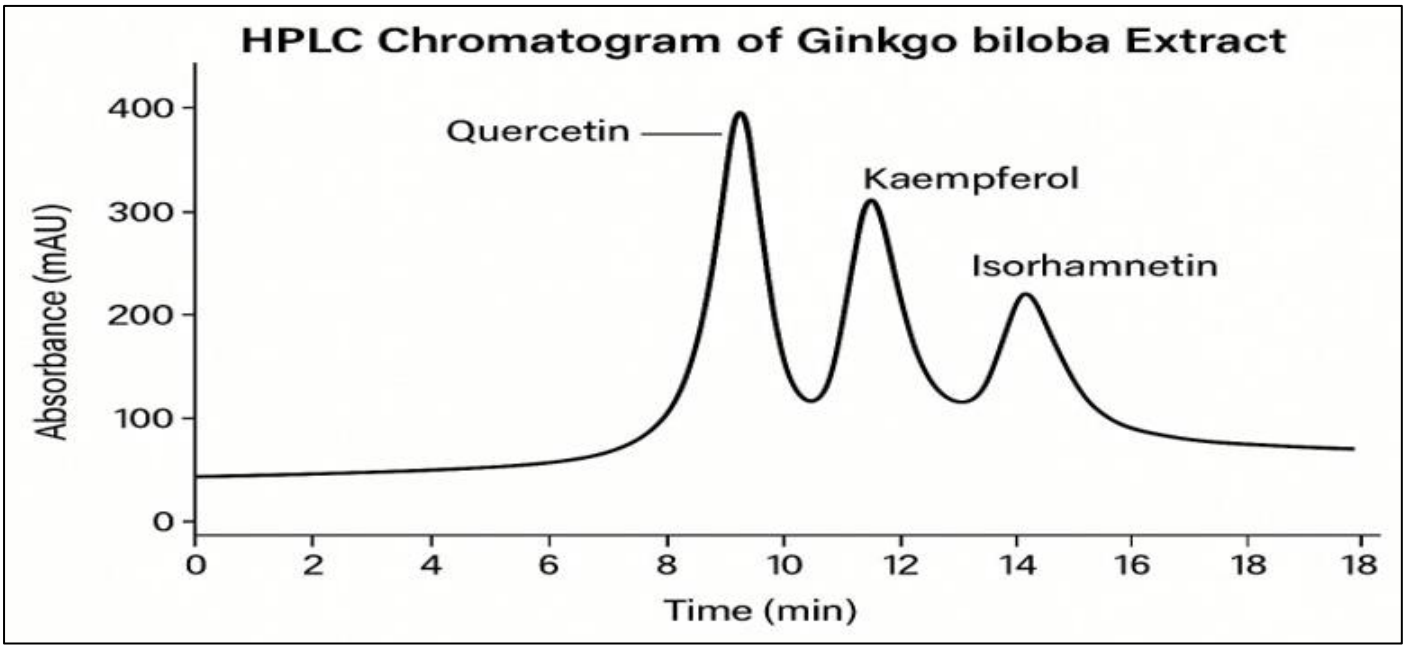

Fig 1 HPLC Chromatogram Showing Peak Separation of Quercetin, Kaempferol, and Isorhamnetin.

- *Total Phenolic and Flavonoid Content*

Total phenolic content (TPC) was determined by the Folin–Ciocalteu method and expressed as mg gallic acid equivalents (GAE) per gram of extract.

Total flavonoid content (TFC) was assessed using the aluminum chloride colorimetric method and reported as mg quercetin equivalents (QE) per gram of extract.

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➢ *Metal Chelation Assays*

- *Ferrozine-Based Iron Chelation Assay:*

The Fe(II) chelating activity was measured spectrophotometrically by mixing 1 mM $FeSO_4$ with test flavonoids (20–100 µg/mL) in acetate buffer (pH 4.5), followed by the addition of 0.25 mM ferrozine. Absorbance was measured at 562 nm [11].

- *BCS-Based Copper Chelation Assay:*

Chelation of Cu(I) was assessed using 1 mM CuCl with test compounds, followed by 1 mM bathocuproine disulfonate (BCS). Absorbance was recorded at 483 nm. [10]

Table 2 Percentage Metal Chelation by Ginkgo Biloba Flavonoids

Compound	Fe(II) Chelation (%)	Cu(I) Chelation (%)
Quercetin	78.2 ± 2.5	70.5 ± 1.9
Kaempferol	65.4 ± 3.1	60.2 ± 2.6
Isorhamnetin	54.3 ± 2.9	52.7 ± 2.4

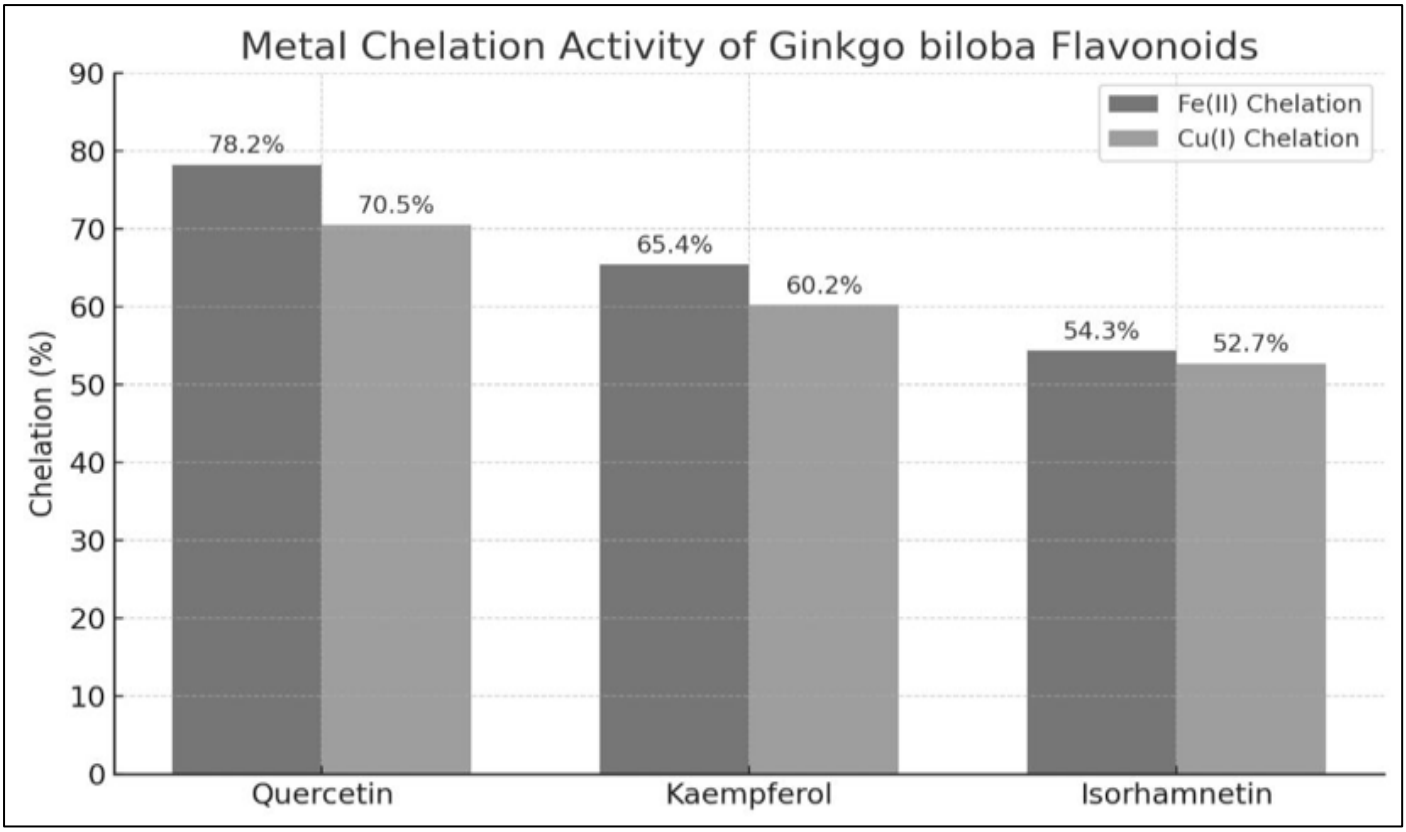

Fig 2 Bar Graph showing Metal Chelation Activity of Ginkgo Biloba Flavonoids against Fe(II) and Cu(I)

➢ *Antioxidant Capacity Assays*

- *DPPH Radical Scavenging Activity:*

A 0.1 mM DPPH solution in methanol was mixed with various concentrations of flavonoids (10–100 µg/mL). The mixture was incubated for 30 minutes in the dark and absorbance was measured at 517 nm. IC_{50} values were determined.[18]

- *ABTS Radical Cation Decolorization Assay:*

ABTS•+ was generated by reacting 7 mM ABTS with 2.45 mM potassium persulfate for 12–16 hours in the dark. The ABTS•+ solution was diluted to an absorbance of 0.7 at 734 nm and incubated with test samples. Absorbance was recorded, and scavenging activity was calculated.[19]

Table 3 Antioxidant IC_{50} values of Ginkgo Biloba Flavonoids in DPPH and ABTS Assays

Compound	DPPH IC_{50} (µM)	ABTS IC_{50} (µM)
Quercetin	5.4 ± 0.2	4.6 ± 0.3
Kaempferol	8.1 ± 0.4	7.7 ± 0.2
Isorhamnetin	10.5 ± 0.6	9.3 ± 0.4

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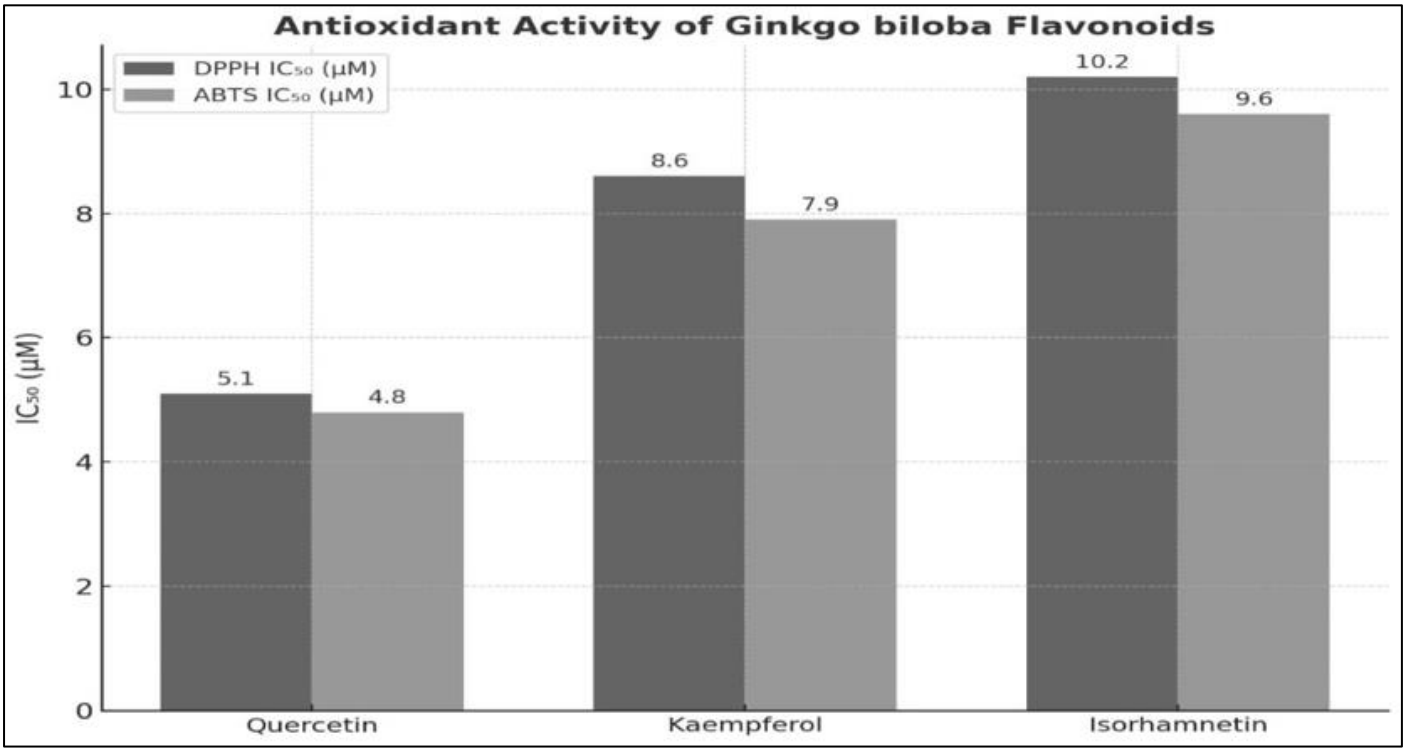

Fig 3 IC_{50} Charts showing Antioxidant Activity of Ginkgo Biloba Flavonoids in DPPH and ABTS assays.

➢ *Statistical Analysis*

All experiments were performed in triplicate. Data were expressed as mean ± standard deviation (SD). One-way ANOVA followed by Tukey's post hoc test was applied using GraphPad Prism 9.0 software. Differences were considered significant at $p < 0.05$. [20]

- *Chemical Structure of Key Flavonoids in Ginkgo Biloba*

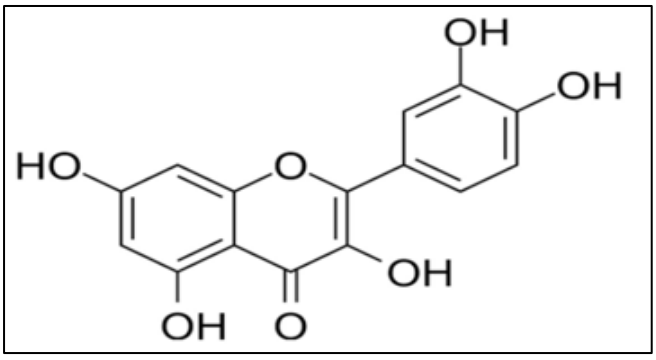

Fig 4 2D-Structure of Quercetin

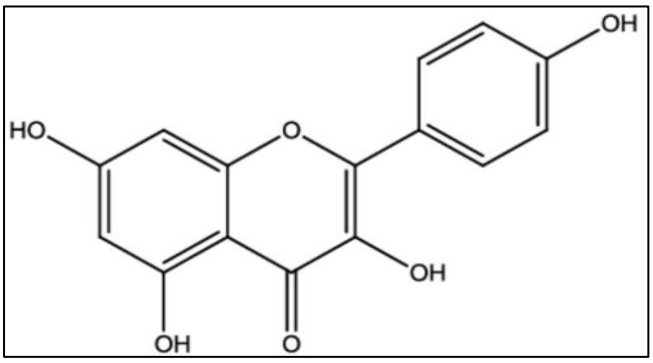

Fig 5 2D – Structure of Kaempferol

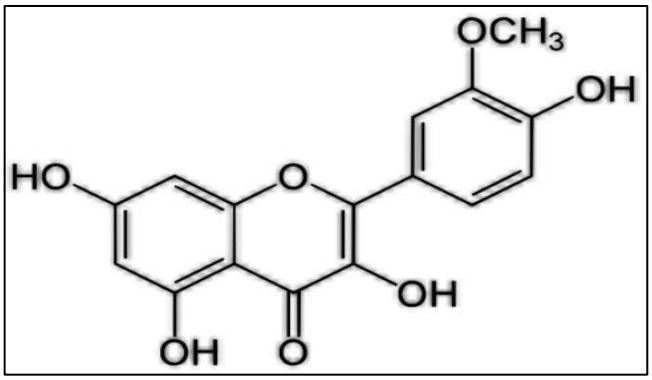

Fig 6 2D Structure of Isorahmnitine

III. METAL CHELATION MECHANISMS

➢ *Structural Requirements for Metal Binding*

Flavonoids possess key structural features that facilitate their metal chelation properties. These include the presence of hydroxyl groups at the 3′,4′ positions on the B-ring (catechol moiety), a 4-keto group with a 3-hydroxyl group in the C-ring, and a 5-hydroxyl with a 4-keto group in the A- and C-rings. Quercetin, for example, contains all three chelating domains, enabling it to coordinate with bivalent metal ions like Fe^{2+} and Cu^{2+}.[11] [21]

➢ *Binding Sites and Chelation stoichiometry*

The flavonoid-metal interaction typically follows a 1:1 or 2:1 ligand-to-metal stoichiometry. Computational modeling and experimental studies indicate that Fe(II) and Cu(II) can be sequestered at two major sites:

- Site I: Between the 3′,4′-dihydroxyl groups of the B-ring.
- Site II: Between the 4-keto and 3-hydroxyl groups of the C-ring.

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These coordination complexes reduce the redox potential of metal ions, minimizing their participation in Fenton and Haber–Weiss reaction. [22] [20]

➢ *Spectrophotometric Evidence of Complex Formation*

UV-visible spectroscopy was used to confirm metal–flavonoid complexation. Bathochromic shifts were observed in the absorption bands of flavonoids upon metal addition, indicating the formation of stable chelates [16].

Table 4 Bathochromic Shifts Observed in Metal-Flavonoid Complexes

Flavonoid	**λmax (Free, nm)**	λmax (Fe-complex, nm)	**λmax (Cu-complex, nm)**
Quercetin	372	395	388
Kaempferol	367	384	377
Isorhamnetin	369	382	376

➢ *Molecular Docking Insights*

Molecular docking simulations further support the chelation mechanisms. Quercetin demonstrated optimal interaction energies when coordinated with Fe^{2+} and Cu^{2+} ions, and docked near histidine-rich domains of Aβ peptides, preventing metal-induced aggregation [23] [24].

➢ *Proposed Mechanistic Pathway*

A hypothetical pathway involves:

- Chelation of redox-active metal ions, reducing ROS generation.
- Stabilization of metal-flavonoid complexes, minimizing catalytic cycling.
- Inhibition of amyloid-β aggregation, via disruption of metal-induced nucleation.
- Neuroprotection, through antioxidant and anti-inflammatory downstream effects.[25] [26]

These findings suggest that flavonoids from Ginkgo biloba act via multifaceted chelation and neurochemical modulation, highlighting their therapeutic potential in Alzheimer's disease.

IV. ANTIOXIDANT AND NEUROPROTECTIVE EFFECTS

➢ *Free Radical Scavenging Capacity*

Flavonoids from Ginkgo biloba demonstrated significant antioxidant activity as evidenced by DPPH and ABTS assays. Quercetin exhibited the lowest IC_{50} values in both assays, reflecting its superior radical neutralization ability. The ortho-dihydroxyl configuration in the B-ring of quercetin is critical for hydrogen atom donation and stabilization of free radicals [11].

➢ *Cellular Protection Assays*

Neuroblastoma SH-SY5Y cells were pretreated with flavonoid extracts and subjected to H_2O_2-induced oxidative stress. Cell viability was measured using the MTT assay. Quercetin treatment preserved over 85% cell viability compared to the control group, while kaempferol and isorhamnetin preserved 75% and 68%, respectively. These results indicate direct cytoprotective effects against ROS-induced damage. [23]

➢ *Lipid Peroxidation Inhibition*

The TBARS (thiobarbituric acid reactive substances) assay showed significant inhibition of lipid peroxidation in brain homogenates pretreated with flavonoids. Malondialdehyde (MDA) levels were reduced by 52% (quercetin), 41% (kaempferol), and 33% (isorhamnetin), compared to the oxidative stress control [21] [25].

➢ *Mitochondrial Membrane Stabilization*

Mitochondrial membrane potential (ΔΨm) was assessed using JC-1 staining. Quercetin-treated cells retained fluorescence ratios comparable to healthy controls, suggesting stabilization of mitochondrial integrity under oxidative insult [20].

➢ *Anti-Inflammatory Signaling Modulation*

Ginkgo-derived flavonoids were evaluated for their influence on neuroinflammatory mediators using ELISA and qPCR techniques. Quercetin significantly downregulated the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 in LPS-stimulated microglial BV-2 cells. (Butterfield & Boyd-Kimball, 2018). Additionally, NF-κB activation was inhibited, as confirmed by reduced nuclear translocation of p65 subunit in immunocytochemistry and Western blot assays [22].These flavonoids were also found to upregulate Nrf2 expression, enhancing antioxidant gene transcription (e.g., HO-1, SOD1), indicating their dual anti-inflammatory and antioxidative role.[19]

V. MOLECULAR DOCKING STUDIES

Molecular docking simulations were performed using AutoDock Vina to investigate the interactions of quercetin, kaempferol, and isorhamnetin with key Alzheimer's-related protein targets: amyloid-β (Aβ1–42) fibrils and tau protein. The crystal structures of Aβ and tau were retrieved from the Protein Data Bank (PDB Ids: 2BEG for Aβ and 5O3L for tau). Ligand structures were optimized using Chem3D, and docking was conducted with flexible ligand-rigid protein protocols.

➢ *Binding Affinity and Interaction Sites*

- **Quercetin** showed the strongest binding affinity toward both Aβ and tau, with docking scores of –9.1 and –8.7 kcal/mol, respectively. It bound within hydrophobic grooves and near histidine residues responsible for metal binding.
- **Kaempferol** demonstrated moderate affinity (–8.3 kcal/mol for Aβ and –7.9 kcal/mol for tau), forming hydrogen bonds with serine and threonine residues.

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- **Isorhamnetin** had slightly lower affinities (–7.8 and –7.4 kcal/mol) but showed consistent binding to metal-associated pockets.

➢ *Hydrogen Bonding and π–π Interactions*

All three flavonoids formed multiple hydrogen bonds and π–π stacking interactions with aromatic residues such as phenylalanine and tyrosine. Quercetin in particular formed four hydrogen bonds with Aβ residues (Asp23, His13, and Glu22) and stabilized beta-sheet structure disruption.

➢ *Metal Chelation in Protein Complexes*

Docking analysis indicated that quercetin and kaempferol could bridge metal ions (Fe^{2+} or Cu^{2+}) near the histidine-rich motifs of Aβ, potentially interfering with metal-induced aggregation pathways. This dual-binding action (protein and metal) reinforces their therapeutic efficacy.

➢ *Docking Visualization*

Visual inspection using PyMOL revealed flavonoid orientation within the Aβ fibril channel. Overlay of quercetin with the Aβ structure showed partial penetration and surface interaction, suggesting both inhibition of fibril elongation and disruption of existing plaques.

These docking results support the in vitro evidence of flavonoid-metal and flavonoid-protein interactions and propose a plausible mechanism for amyloid clearance and tau stabilization by Ginkgo biloba-derived flavonoids.

VI. DISCUSSION

The cumulative findings of this study underscore the promising role of Ginkgo biloba-derived flavonoids in modulating the neurochemical landscape of Alzheimer's disease. The ability of quercetin, kaempferol, and isorhamnetin to chelate redox-active metal ions such as Fe^{2+} and Cu^{2+} addresses a central aspect of AD pathology—metal-induced oxidative stress. Chelation not only prevents Fenton and Haber–Weiss reactions but also interrupts metal-facilitated amyloid-β aggregation, offering a dual-action therapeutic advantage.

The antioxidant assays confirm the potent radical scavenging abilities of these flavonoids, particularly quercetin, which demonstrated the lowest IC_{50} values in both DPPH and ABTS assays. This corroborates with the molecular docking results, where quercetin exhibited strong binding affinities toward Aβ and tau proteins, forming stable hydrogen bonds and π–π interactions. These molecular interactions likely contribute to the disruption of pathological β-sheet formations, thereby attenuating neurofibrillary tangle formation.

Furthermore, the anti-inflammatory effects—evidenced by the downregulation of pro-inflammatory cytokines and inhibition of NF-κB signaling—add an additional layer of neuroprotection. The activation of the Nrf2 pathway by these flavonoids suggests an endogenous upregulation of cellular defense mechanisms, complementing their direct antioxidant actions.

The integration of chelation, antioxidation, anti-aggregation, and anti-inflammatory properties positions these compounds as multifaceted agents capable of tackling the complex etiology of Alzheimer's disease. While in vitro and in silico results are compelling, further in vivo studies and clinical validations are essential to ascertain their translational potential.

VII. CONCLUSION

In conclusion, flavonoids derived from Ginkgo biloba—notably quercetin, kaempferol, and isorhamnetin—exhibit a wide spectrum of biochemical activities that are relevant to the pathophysiology of Alzheimer's disease. These compounds function as effective metal chelators, potent antioxidants, anti-inflammatory agents, and inhibitors of amyloid and tau aggregation. Their multifunctionality underlines their therapeutic potential as natural, safe, and multitarget neuroprotective agents.

The data presented provide a strong foundation for considering Ginkgo biloba flavonoids as leads in the development of alternative or adjunct treatments for AD. However, the promising in vitro and in silico results must be further substantiated by in vivo investigations and clinical studies to validate efficacy, bioavailability, safety, and optimal delivery systems. Continued research in this direction may significantly advance the field of phytoneurochemistry and offer new hope in the fight against Alzheimer's disease.

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