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Review

Low Brain Levels of Dietary Polyphenols and Their Conjugates: Reassessing Mechanisms of Alzheimer's Disease Prevention

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Abstract

Dietary polyphenols such as quercetin, resveratrol, and (−)-epigallocatechin-3-gallate (EGCG) have shown neuroprotective effects in epidemiologic and experimental studies of Alzheimer's disease (AD), although clinical evidence remains limited. This review highlights the importance of investigating glucuronide and sulfate conjugates of these polyphenols, as well as their intestinal microbial metabolites, at bioavailable low nanomolar concentrations, particularly those capable of reaching the brain. Although many in vitro studies use micromolar concentrations of aglycones, the relevance of such concentrations to neuroprotection remains uncertain. While polyphenols are redox-sensitive, their direct antioxidant or prooxidant effects may be limited at nanomolar concentrations. Instead, their neuroprotective actions appear to be mediated through high-affinity interactions with molecular targets such as the 67-kDa laminin receptor (67LR). This receptor binds both aglycones and conjugates at low nanomolar concentrations through a peptide G region containing glycosaminoglycan- and palindromic sequence-related motifs. The same region also binds the prion–amyloid-β complex, suggesting that polyphenols may antagonize amyloid-β binding and thereby prevent its neurotoxicity. The peptide G region may also function as a redox sensor. Binding of polyphenols to 67LR activates cAMP signaling and downstream neuroprotective pathways involving CREB, SIRT1, and protein phosphatase 2A. In addition, nanomolar concentrations of resveratrol and quercetin inhibit quinone reductase 2, an enzyme associated with cognitive decline and reported to be elevated in AD. Given their low bioavailability in the brain and their distinct molecular targets, combining multiple polyphenols at low doses may produce additive or synergistic effects, enhance efficacy, and minimize potential toxicity in the prevention of AD.

Keywords: Alzheimer's disease; amyloid-β; cAMP; epigallocatechin-3-gallate; glucuronide metabolites; laminin receptor; polyphenols; quercetin; quinone reductase 2; resveratrol

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1. Introduction

Alzheimer's disease (AD) is a major global health challenge and the most common age-related neurodegenerative disease. In 2021, an estimated 57 million people worldwide were living with dementia, with AD accounting for 60–70% of cases; nearly 10 million new dementia cases occur each year [1]. Based on current demographic trends, the global number of people living with dementia is projected to increase to 152.8 million by 2050 [2]. In the United States, an estimated 7.2 million adults aged 65 years and older are living with Alzheimer's dementia in 2025, representing about 1 in 9 older adults (approximately 11%) [3].

Importantly, AD unfolds over a prolonged prodromal period, characterized by biological and cognitive alterations that precede clinical dementia by years [4]. During this trajectory, many individuals progress through amnestic mild cognitive impairment (aMCI), a transitional state carrying a 10–20% annual risk of conversion to AD [5]. This extended pre-dementia phase offers a critical therapeutic window for early interventions, notably lifestyle and dietary modifications [6]. Consequently, to develop effective preventative strategies, it is imperative to elucidate the mechanistic pathways through which dietary polyphenols exert their neuroprotective effects and inhibit AD pathogenesis.

1.1. Unique Focus of the Review

Given the clinical importance of AD, several reviews have addressed the relationship between polyphenols and AD from multiple perspectives [7–16]. This review focuses on the unique features of dietary polyphenols that limit their bioavailability, specifically, their rapid conjugation to glucuronide and sulfate metabolites, and the resulting low nanomolar concentrations reached in the brain. We emphasize the functional roles of these glucuronide and sulfate conjugates, as well as intestinal microbial metabolites. We also discuss the limitations of direct antioxidant and prooxidant mechanisms, highlighting instead the importance of high-affinity, redox-sensitive molecular targets for polyphenols. Although the human diet contains hundreds of polyphenols, this review focuses on quercetin, resveratrol, and (−)-epigallocatechin-3-gallate (EGCG), which have demonstrated consistent, reproducible neuroprotective effects in animal models of AD.

1.2. Multifactorial AD Pathogenesis

The β-amyloid (Aβ) hypothesis has long been a central framework for AD, proposing that abnormal amyloid precursor protein (APP) processing leads to the accumulation of pathogenic Aβ species [17–19]. Within this view, soluble Aβ oligomers are considered particularly toxic: they impair synaptic plasticity and memory-related signaling and can initiate downstream cascades that include tau dysregulation, neuroinflammation, and, ultimately, synaptic and neuronal loss [20,21]. Strong genetic support comes from autosomal-dominant (familial) AD, in which pathogenic variants in APP and presenilins alter Aβ generation and promote amyloid pathology [22]. Despite this biological rationale, translating Aβ-lowering into meaningful clinical benefit has proven difficult, with several approaches failing in symptomatic disease. More recently, however, anti-amyloid antibodies such as lecanemab and donanemab have produced a statistically significant, albeit modest, slowing of cognitive decline in early symptomatic AD. This supports Aβ as a valid target while also implying that timing (earlier intervention) and/or multi-target strategies may be necessary for larger clinical effects [23].

Currently, there is increasing emphasis on the multifactorial nature of AD. In addition to the important role of Aβ, other frameworks highlight contributions from tau pathology, chronic neuroinflammation, metabolic and mitochondrial dysfunction, dysregulated Ca^{2+} homeostasis, iron dyshomeostasis, and cerebrovascular or blood–brain barrier (BBB) impairment during disease initiation and progression [24–29]. This broader perspective has increased interest in combination and multi-target approaches that engage multiple disease mechanisms rather than focusing on a single pathway [24,30]. Within this context, dietary polyphenols have attracted attention because they can modulate several AD-relevant processes (e.g., Aβ- and tau-related pathways, inflammatory and oxidative signaling, and metabolic stress responses) across experimental systems [7,15].

1.3. Intervention of AD with Dietary Polyphenols

Epidemiological studies suggest that diets rich in plant-based foods are associated with slower cognitive decline [31], with several specific plant products shown to enhance mem-

ory [32,33]. Notably, the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet is consistently linked to a lower risk of AD and related dementias [34–38]. This diet features foods high in polyphenols, such as fruits, vegetables, olive oil, and tea, alongside moderate amounts of red wine. Furthermore, several epidemiological studies have reported a lower incidence of dementia and AD specifically associated with green tea consumption [39,40]. In preclinical research, *trans*-resveratrol has been shown to attenuate AD pathology in various animal models [41–46], a protective effect similarly reported for quercetin in AD mouse models [47–52] (Figure 1). Resveratrol also protects isolated neurons from amyloid-β-induced toxicity and other harmful insults in vitro [53–56]. Finally, EGCG has demonstrated robust neuroprotective effects across multiple experimental models of AD [34,57,58].

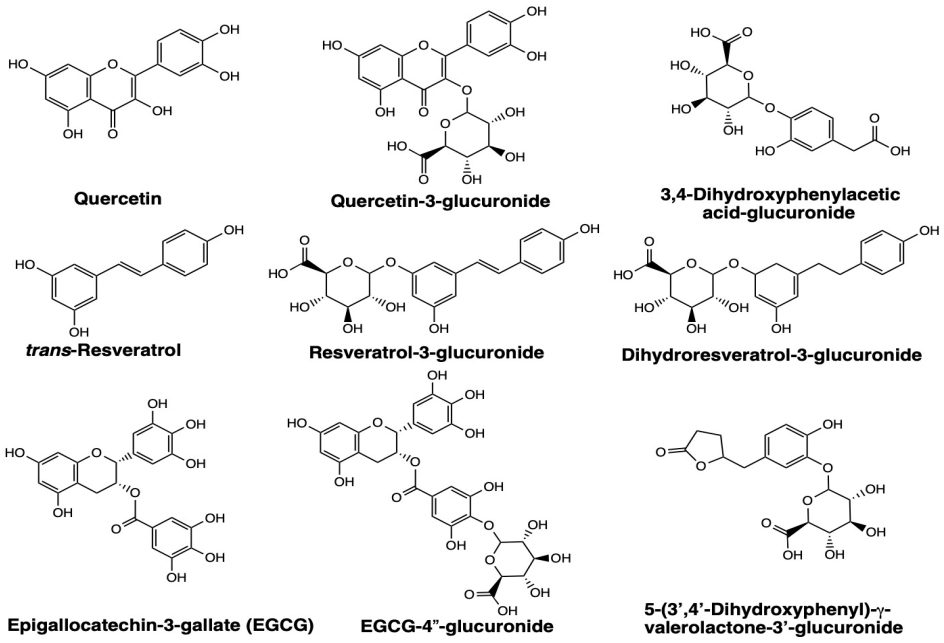


Figure 1. Structures of polyphenol aglycones (**left three**), glucuronide conjugates of polyphenols (**middle three**), and glucuronide conjugates of intestinal microbial metabolites (**right three**).

1.4. Challenges in Understanding the Role of Dietary Polyphenols in AD Prevention

As extensively reviewed elsewhere, quercetin, resveratrol, and EGCG exert neuroprotective effects in vitro against Aβ toxicity and oxidative stress in neuronal cells; however, these effects often require 10 to 100 μM concentrations [59–62]. In contrast, these compounds reach only low nanomolar concentrations in the brain. These dietary polyphenols are absorbed to a limited extent and undergo rapid phase II metabolism to form glucuronide and sulfate conjugates [63–65]. Consequently, the parent (aglycone) compounds are present at very low concentrations in the plasma. Furthermore, both the parent compounds and their metabolites are extensively bound to plasma proteins [66–68]. As a result, only small amounts of aglycones and conjugates, often in the low nanomolar range, cross the BBB. This discrepancy is a critically important consideration when designing experiments to elucidate the mechanisms underlying their neuroprotective effects in vivo.

2. Absorption, Distribution, Metabolism, and Excretion of Polyphenols (ADME)

First, we reviewed the general ADME aspects of dietary polyphenols. We then examined these features for specific compounds, quercetin, resveratrol, and EGCG, summarizing the findings in Table 1. Finally, we explored polyphenol accumulation in

the brain during prolonged supplementation, highlighting species-related differences in detected concentrations.

2.1. General Pharmacokinetic Aspects of Polyphenols

Dietary polyphenols exhibit limited and highly variable absorption; their bioavailability depends strongly on chemical structure, the food matrix, intestinal processing, and host factors [69–73]. In the small intestine, some low-molecular-weight aglycones and certain glycosides can be absorbed after hydrolysis. However, many larger, esterified, glycosylated, or polymerized polyphenols are poorly absorbed proximally. These compounds pass instead to the colon, where they undergo extensive microbial catabolism into smaller, absorbable phenolic metabolites [69–72]. During and after absorption, polyphenols undergo substantial first-pass metabolism in enterocytes and the liver. Glucuronidation, sulfation, and O-methylation produce the major circulating forms, meaning plasma typically contains conjugated metabolites rather than the parent aglycones [69–73]. Intestinal handling also involves efflux back into the lumen and interactions with carrier-mediated transport. Once in circulation, polyphenols are largely bound to plasma proteins, which influence their distribution, tissue uptake, and elimination [69,71,73]. Consequently, circulating concentrations of intact parent compounds remain low, transient, and far below those commonly used in vitro. Instead, conjugated and microbiota-derived metabolites constitute the principal forms that reach tissues and drive biological effects [70–73].

Table 1. Distribution of quercetin, resveratrol, EGCG and their metabolites in plasma and brain.

Parameters	Quercetin	Resveratrol	EGCG
Present in plants as	Glycoside form	Glycoside form	Aglycone
Absorption	Aglycone 20% [74] Onion quercetin glucosides 60–80% [63]	75% [75]	Poorly absorbed [76]
Bioavailability	2% [74]	<1% [75]	0.1–0.3% [76]
Plasma concentration	Humans [64] Quercetin glycoside (equivalent to 100 mg aglycone) administered. Aglycone, N.D. Q-3-G, 500 nM Q-3-S, 300 nM Methylated-Q, 75 nM	Humans [77]: 25 mg *trans*-resveratrol Aglycone, <0.02 μM Conjugates all, 2 μM	Humans [78]: Catechin mixture containing 135 mg EGCG. Aglycone, 230 nM EGCG-4″-S, 170 nM EGCG-4″-G, 75 nM
Plasma protein binding	Humans [66]: Aglycone: 99%	Humans [67,79]: Aglycone: 98% Conjugates: 50%	Humans [68]: Aglycone: 90%
BBB permeability	Model: Rat endothelial/glioma cell co-culture [80] Permeability coefficient 0.5–1.1 (10^{-6} cm/s) Transport ratio 2.1 to 2.5%	Model: Human brain microvascular endothelial cells [81] High passive permeability Transport ratio: >2%	Model: Co-cultures of endothelial cells, pericytes, astrocytes [82] Permeability coefficient 9.32 ± 0.32 (10^{-6} cm/s) Transport ratio: 2.82%
Brain concentration	Rats [83]: Red wine polyphenol mixture 150 mg was administered. Aglycone, N.D. Q-3-G, 1 nM	Rats [84]: Trans-resveratrol (15 mg/kg) by i.v. Aglycone, 0.17 nmol/g Mice [85]: Trans-resveratrol (150 mg/kg) by gavage R-3-G, 1.06 nmol/g R-3-S, 0.44 nmol/g	Rats [86]: EGCG 50 mg/kg administered. EGCG, 10 nM Rats [87]: High dose (500 mg/kg): EGCG, 0.5 nmol/g Mice [88]: EGCG, N.D.

Table 1. *Cont.*

Parameters	Quercetin	Resveratrol	EGCG
CSF concentration	Sheep [89]: Powdered dry onion skin administered via intraluminal intubation Aglycone, 0.3 nM Conjugates, N.D.	Humans [90]: Escalating resveratrol doses (500 mg/day to 2 g/day) were administered for 52 weeks. Aglycone, 2 nM R-3-G, 20 nM R-4′-G, 27 nM R-3-S, 39 nM	Humans [91]: MS patients were given 250 mL green tea (5.8 g tea leaves) Analyzed after 2 h. EGCG, N.D. (LOD: 10 nM)

Note: Treatments consisted of a single oral dose unless otherwise specified. Exceptions include human CSF measurements (daily dosing for 52 weeks) [90], resveratrol in rat brains (intravenous administration) [84], and powdered dry onion skin in sheep (intraluminal intubation) [89]. N.D., not detectable; Q-3-G, quercetin-3-glucuronide; Q-3-S, quercetin-3-sulfate; R-3-G, resveratrol-3-glucuronide; R-3-S, resveratrol-3-sulfate, LOD, limit of detection.

2.2. Quercetin

Quercetin is a flavonol-type flavonoid found predominantly in vegetables and fruits in the form of glycosides [92]. These glycosides are hydrolyzed by intestinal bacteria and by intestinal enzymes, such as lactase-phlorizin hydrolase and cytosolic β-glucosidase, to release the quercetin aglycone, which is then absorbed in the intestine [93]. Up to 20% of administered quercetin is absorbed, but its bioavailability is only 2% [74]. In the liver, quercetin is rapidly metabolized by phase II enzymes to form glucuronides, sulfates, mixed glucuronide-sulfate conjugates, and methylated glucuronides [64]. In plasma, only these conjugated metabolites are detected at nanomolar to low micromolar concentrations, depending on the dose of quercetin or quercetin glycosides administered to animals or humans; quercetin aglycone itself is not detectable [64]. In sheep administered dried onion skin, quercetin was detected in cerebrospinal fluid (CSF) at a concentration of 0.30 nM, whereas quercetin-3-O-glucuronide (Q-3-G) and other conjugated metabolites were not detectable [89] (Table 1). In contrast, Pasinetti and colleagues quantified Q-3-G in rat brain at concentrations as low as 1 nM following oral administration of a red wine polyphenol mixture [83].

Pharmacokinetic studies in humans receiving quercetin (500 mg, three times daily) indicate an average terminal plasma half-life of 3.5 h [94], while the elimination half-lives of its major conjugated metabolites range from 1.7 to 5.3 h [95]. Urinary excretion of intact quercetin metabolites accounts for only ~5% of the administered dose [95]. Instead, a significant portion of the compound undergoes extensive degradation, exhibiting an extended 'biological half-life' of 20 to 72 h, and is primarily recovered as expired CO_2 [96].

2.3. Resveratrol

Resveratrol (3,5,4′-trihydroxystilbene) is a non-flavonoid polyphenol found in red wine, grapes, berries, and peanuts [97,98]. The *trans* isomer is the predominant and more stable form compared to its *cis* counterpart. In plant sources, resveratrol exists primarily in glycosylated forms. Upon ingestion, these glycosides are hydrolyzed by intestinal microbial glycosidases to release the absorbable aglycone [97,98]. Although nearly 75% of an oral dose is absorbed in the intestine, extensive first-pass metabolism reduces its absolute bioavailability to less than 1% [75]. Following the consumption of resveratrol-containing red wine or moderate doses of the purified compound (e.g., 25 mg) in humans, rapid metabolism renders the circulating aglycone largely undetectable; instead, glucuronide and sulfate conjugates are present at low concentrations [65,75,99]. Conversely, high pharmacological doses (100–5000 mg) yield detectable plasma levels of the free aglycone, albeit only in the nanomolar to low-micromolar range, with conjugate concentrations

remaining significantly higher [75]. Because resveratrol crosses the BBB in vitro only to a limited extent [81], the parent compound and its metabolites achieve merely low nanomolar concentrations or remain undetectable in the brain and CSF [85].

Human studies indicate the plasma half-life of *trans*-resveratrol is approximately 1–3 h, whereas its conjugated metabolites exhibit a much longer half-life of about 9 h [100]. Consequently, while the parent compound is cleared rapidly, the pool of conjugates persists for an extended period [100]. Ultimately, most of the administered dose is recovered in the urine, predominantly as glucuronide and sulfate conjugates alongside microbiota-derived metabolites [75].

2.4. EGCG

EGCG is the most abundant catechin flavonoid in green tea, co-occurring with other catechins such as epicatechin, epigallocatechin, and epicatechin-3-gallate. Unlike polyphenols such as quercetin and resveratrol, which naturally occur primarily as glycosides, green tea catechins exist predominantly in the unconjugated (aglycone) form [101]. Following oral administration in humans and rodents, the systemic bioavailability of EGCG remains remarkably low, estimated at 0.1–0.3% [76]. However, its metabolic profile differs notably from other dietary polyphenols. When a green tea catechin mixture is administered to humans, a substantial fraction of EGCG (~45% or higher) circulates in the plasma as the intact aglycone, with the remainder present as conjugated metabolites, primarily EGCG-sulfate and EGCG-glucuronide [78]. Thus, compared to quercetin and resveratrol, EGCG undergoes relatively less extensive phase II conjugation, allowing a significant proportion to persist in its aglycone form in systemic circulation [78].

The extent to which EGCG and its metabolites penetrate the brain following green tea consumption or oral supplementation remains controversial. In one study, orally administered ^{3}H-labeled EGCG produced measurable radioactivity in brain tissue, suggesting central nervous system (CNS) uptake; however, the specific chemical forms and absolute concentrations were not determined [102]. Subsequent mouse models found that while EGCG distributed to several peripheral tissues after standard oral dosing, it remained undetectable in the brain [88]. In rats given 50 mg/kg of EGCG, brain concentrations of roughly 10 nM were reported [88]; yet, it is unclear whether residual blood contamination was adequately controlled for in this analysis. Conversely, another study achieved detectable brain EGCG levels of approximately 0.5 nmol/g in rats, but only following a very high pharmacological dose (500 mg/kg) [87].

In vitro models suggest limited BBB permeability for EGCG (Table 1). For context, human consumption of two cups of green tea yields a peak plasma EGCG concentration of approximately 0.2 μM [103]. Utilizing an in vitro system, Pervin et al. reported a BBB permeability rate of 5.6% for EGCG over a 1-h period, leading to an estimated delivery of nearly 10 nM to the brain parenchyma [82]. However, such in vitro models possess inherent limitations when predicting in vivo brain uptake. Highlighting this translational gap, clinical studies have found that neither EGCG nor its conjugates are detectable in human CSF following oral green tea consumption [91].

Pharmacokinetically, EGCG exhibits a plasma half-life of 3.4 h in humans following the ingestion of green tea or purified extracts [103]. Furthermore, only trace amounts of EGCG are excreted in the urine. Instead, elimination occurs predominantly via biliary secretion and fecal excretion, accompanied by extensive biotransformation into microbial metabolites within the gut [104].

2.5. Plasma Protein Binding and the "Free" Polyphenol Fraction

In plasma, these polyphenol aglycones are highly protein-bound: quercetin binding can reach 99% [66], resveratrol is nearly 98% bound (with ~50% binding for its conjugates) [67,79], and EGCG is 80–90% bound [68]. As demonstrated with numerous drugs and steroid hormones, extensive protein binding reduces the unbound (free) fraction, thereby limiting tissue availability and narrowing the range of accessible molecular targets. However, protein binding exists in a dynamic equilibrium; the bound pool serves as a reservoir that can replenish the free fraction as the unbound compound is distributed, metabolized, or excreted. Furthermore, binding to plasma proteins can slow glomerular filtration, thereby extending the compound's half-life, and may stabilize polyphenols against auto-oxidation. Despite these pharmacokinetic benefits, extensive protein binding significantly restricts free polyphenol levels in tissues and further limits their penetration across the BBB. Consequently, brain exposure may remain low, compounding the separate permeation constraints already imposed by molecular size and polarity. Methodologically, it is also important to note that polyphenols and their metabolites are typically extracted from plasma using organic solvents, a process that yields total (bound plus unbound) concentrations rather than isolating the biologically active free fraction. Therefore, protein binding must be critically considered when interpreting in vivo exposure measurements and when designing translationally relevant in vitro experiments to elucidate mechanisms of action.

2.6. Polyphenol Accumulation in the Brain with Chronic Administration

While prolonged supplementation can enhance the brain accumulation of quercetin, resveratrol, and EGCG, the resulting concentrations remain low, and the strength of the evidence varies considerably among the three compounds [62,76,105–108]. In the case of quercetin, repeated oral dosing in rats yields a measurable accumulation of conjugated metabolites in the brain, though the parent aglycone remains undetectable [105]. Specifically, feeding rats a purified diet containing 1% (*w*/*w*) quercetin aglycone (equivalent to a 213 mg intake) produced tissue concentrations of nearly 20 pmol/g after one hour, doubling to approximately 40 pmol/g after one month of feeding [105]. Similarly, animal models indicate that repeated administration of EGCG increases its cerebral accumulation; however, absolute levels remain low and may partially represent EGCG-derived metabolites rather than intact parent molecules [62,76]. Conversely, while prolonged resveratrol supplementation elicits sustained neurobiological effects, direct evidence for the progressive accumulation of the parent compound in brain tissue is less robust. This is largely due to its rapid metabolism and the inherently low brain availability associated with conventional systemic dosing [107,108].

2.7. Species-Dependent Variation in the Accumulation of Polyphenols in the Brain

Species-dependent differences significantly influence the brain accumulation of quercetin, resveratrol, and EGCG. In the case of quercetin, while rats, mice, and humans all circulate predominantly conjugated metabolites rather than the free aglycone, the specific proportions of glucuronidated, sulfated, and methylated forms vary across species, potentially impacting brain penetrance and retention [71,109]. Similarly, although resveratrol undergoes extensive first-pass metabolism across all three species, marked differences in glucuronidation, sulfation, clearance rates, and half-lives suggest that rodents are not strictly interchangeable models for predicting human CNS exposure [71,109]. Regarding EGCG, mice appear to achieve higher systemic exposure than rats and may more closely mirror human bioavailability, indicating that rat models could underestimate actual exposure levels [76,88]. Because direct data on human brain tissue are inherently limited, these

interspecies comparisons rely heavily on plasma pharmacokinetics, circulating metabolite profiles, and the concentrations of polyphenols and their specific metabolites in the CSF [71,110].

3. Polyphenol Aglycone Actions at Micromolar Concentrations

Collectively, pharmacokinetic studies suggest that polyphenols, such as quercetin, resveratrol, and EGCG, or their conjugates, may reach the brain at low nanomolar concentrations, often falling below detection limits. Nonetheless, many in vitro studies demonstrating the beneficial effects of these polyphenols (including antioxidant and prooxidant activities, as well as the inhibition of β-amyloid aggregation) rely on much higher micromolar concentrations. While these observations provide valuable mechanistic insights, further research is required to determine whether such effects are achievable in the brain at physiologically bioavailable concentrations and in relevant chemical forms.

3.1. Antioxidants—Limitations

Although dietary polyphenols can, in principle, quench reactive oxygen species (ROS) through direct chemical scavenging, their contribution to antioxidant defense in vivo, particularly in the brain, is thought to be limited because their physiological concentrations typically remain in the low-nanomolar range [111–114]. In addition, polyphenol glucuronide and sulfate conjugates generally exhibit weaker radical-scavenging activity than their corresponding aglycones [92,115]. Instead, polyphenols such as quercetin, resveratrol, and EGCG, whether as aglycones or as glucuronide/sulfate metabolites, can modulate redox-sensitive signaling pathways that upregulate the expression of endogenous antioxidant enzymes [116–118]. Compounds acting primarily through this mechanism are termed "indirect antioxidants": rather than directly scavenging ROS, they enhance intrinsic antioxidant defenses, conferring protection that may persist even after the compound has been cleared from the tissues [119,120].

3.2. Prooxidants—Limitations

Conversely, several studies have described how quercetin, resveratrol, and EGCG can act as prooxidants under conditions that favor their oxidation or transition-metal redox cycling, leading to net ROS generation rather than ROS quenching. For example, copper complexes of quercetin and resveratrol can promote ROS formation and oxidative DNA damage [121,122]. However, at lower, non-toxic exposures, this prooxidant activity may function as a mild oxidative stimulus that engages adaptive defenses (e.g., Nrf2-dependent gene expression), consistent with a hormetic mechanism [123]. Notably, H_2O_2 generated via EGCG autoxidation has been reported to be protective in human keratinocytes [124]. The prooxidant actions of EGCG have thus been proposed as a potential contributor to its health benefits, though they may also mediate adverse effects under certain conditions [125]. Furthermore, Forman and colleagues have detailed how electrophiles derived from dietary polyphenols can increase nucleophilic tone by activating Nrf2 [126], and Shah et al. demonstrated the critical role of Nrf2 and heme oxygenase-1 in flavanol-mediated neuroprotection [127].

Halliwell and colleagues have cautioned that cell culture media can generate artifacts, as iron-dependent oxidation can produce reactive species such as H_2O_2 and quinones or semiquinones [128]. They also noted that the potential prooxidant activities of polyphenols in humans, particularly at the low concentrations achieved through diet, remain to be clearly established in vivo [129]. While quinone metabolites of these polyphenols have not been isolated from animals consuming typical dietary amounts, they may form transiently and react rapidly with low-molecular-weight thiols. Furthermore, although EGCG, quercetin,

and resveratrol form adducts with protein thiols in vitro, these specific adducts have not been observed in vivo at typical dietary intakes [130,131]. In contrast, EGCG-quinone-cysteine thiol adducts have been isolated from the urine of mice administered high, toxic doses of EGCG, but not following lower, dietary-relevant doses [132]. However, minor amounts of a quercetin-glutathione adduct have been identified in human plasma following the consumption of quercetin-rich foods [133]. Rapid conjugation by phase II enzymes likely limits quinone formation, thereby minimizing the potential for toxicity often observed in vitro. Nevertheless, the trace amounts of quinones that do form may react with signal transduction enzymes, oxidize vicinal thiols, and subsequently revert to their phenolic states. Consequently, these transiently formed quinones could play a functional role in cellular signaling.

3.3. Inhibition of Protein Kinases and Other Enzymes—Limitations

Previous reviews have detailed resveratrol's capacity to inhibit multiple enzymes—including cyclooxygenase, lipoxygenase, PKCs, ERK1, JNK1, p38, Src, ribonucleotide reductase, DNA polymerases, PKD, and aromatase—typically exhibiting IC_{50} values in the 10–60 μM range [134]. Similarly, EGCG has been shown to inhibit various receptor tyrosine kinases at effective concentrations generally ranging from 5 to 100 μM [135], as well as cyclooxygenase-1 and -2 with IC_{50} values of 17–28 μM [136]. However, given that polyphenol aglycones are present at substantially lower concentrations in plasma and tissues, the physiological relevance of these high-dose in vitro findings remains uncertain.

3.4. Inhibition of Aβ Aggregation—Limitations

In vitro, several dietary polyphenols can directly interfere with Aβ self-assembly. For instance, quercetin inhibits Aβ fibril formation and can promote the disaggregation of preformed fibrils, at least in peptide/fibril model systems [137]. Resveratrol inhibits Aβ42 fibril formation and reduces Aβ-associated cytotoxicity, although it may not completely prevent oligomer formation [138]. Furthermore, EGCG can bind natively unfolded Aβ, redirecting its aggregation away from β-sheet-rich fibrils and toward unstructured, off-pathway oligomers [139]. However, these inhibitory effects are typically observed at micromolar concentrations of the parent aglycones. It remains to be determined whether comparable Aβ-polyphenol interactions occur within the brain at the low nanomolar concentrations achievable in vivo, either for the aglycones or their conjugated metabolites.

4. Polyphenol Metabolites Formed by Gut Microbiota, Gut–Brain Axis

Given that parent polyphenol aglycones circulate at very low levels, attention has shifted to the gut microbiota's role in their metabolism to help explain their health benefits. Because many polyphenols are poorly absorbed in the small intestine, a substantial fraction reaches the colon, where the microbiota converts them into smaller, more readily absorbable molecules [140]. Specifically, quercetin is degraded via C-ring fission and side-chain modifications into more absorbable phenolic acids, such as 3,4-dihydroxyphenylacetic acid [141,142]. Similarly, gut microbes reduce resveratrol to dihydroresveratrol and, depending on the individual's microbiota, can further convert it to dehydroxylated products like lunularin [143,144]. For EGCG, microbial esterases first catalyze its degalloylation, yielding epigallocatechin and gallic acid [145–147]. Epigallocatechin is subsequently metabolized into downstream products, including valerolactone-type metabolites [145–147], while gallic acid can be converted into smaller phenolics like pyrogallol, which notably induces Nrf2-associated gene expression more potently than its parent compound, EGCG [148]. Ultimately, metabolite profiles and yields vary substantially among individuals, reflecting interindividual differences in microbiota composition and metabolic capacity.

Growing evidence suggests that these microbial metabolites contribute significantly to the health benefits associated with dietary polyphenols. However, many of these gut-derived products are themselves phenolic compounds that undergo extensive phase II metabolism in the liver to form glucuronide and sulfate conjugates. This metabolic reality reiterates the fundamental question of how these specific conjugates and intestinal microbial metabolites exert their biological effects. Consequently, defining the mechanisms by which microbiota-derived metabolites and their conjugates support neuroprotection via the gut–brain axis in AD remains a critical research priority.

5. Glucuronide and Sulfate Conjugates as Active Metabolites

Given the low circulating concentrations of parent polyphenols compared to the relatively higher levels of their conjugates, researchers increasingly propose that glucuronide and sulfate metabolites may mediate at least a portion of the biological actions attributed to the parent compounds [149]. Traditionally, drug conjugates were viewed merely as inactive excretory products; however, this paradigm is shifting as a growing number of compounds are shown to retain or gain biological activity in their conjugated forms. For instance, morphine is activated via glucuronidation, while the antihypertensive drug minoxidil is activated by sulfation [150,151]. Notably, morphine-6-glucuronide is actively transported across the BBB and can also be synthesized locally within the brain, where it directly contributes to analgesia [152,153].

While direct evidence indicates that glucuronide conjugates of both resveratrol and quercetin can reach CNS compartments, their net brain exposure remains generally low. Because these glucuronides are polar anions, they do not readily cross the BBB via passive diffusion. Consequently, when these metabolites are detected in the CSF or brain tissue, their presence is presumed to reflect carrier-mediated transport processes at brain barrier sites [154]. Furthermore, a fraction of circulating polyphenol glucuronides may be taken up by BBB-associated cells and locally deconjugated into aglycones. Since brain tissue also expresses UDP-glucuronosyltransferases and sulfotransferases, these aglycones can subsequently undergo local reconjugation within the neural environment [155–158].

An alternative hypothesis posits that polyphenol glucuronides and sulfates function primarily as circulating reservoirs. In this model, these conjugates are locally hydrolyzed by β-glucuronidase and sulfatase enzymes, regenerating the corresponding aglycones within target tissues to exert their biological effects [159,160]. This targeted deconjugation may occur more readily at sites of inflammation, which are characterized by an increased cellular release of these hydrolases [161,162]. Nevertheless, this process would still yield only minute quantities of free aglycones, raising the critical question of how such low local concentrations can mediate significant biological outcomes.

6. Direct Protective Actions of Polyphenols on Neurons—Binding to High-Affinity Receptors and Relevance to AD Prevention

Although oral administration yields only low nanomolar concentrations of polyphenols in the brain, these compounds may still exert neuroprotective effects by acting directly on neurons via high-affinity receptor binding. Two relevant molecular targets are the 67-kDa laminin receptor (67LR) and quinone reductase 2 (QR2). Both respond to polyphenols at these low concentrations and may contribute to the prevention of AD.

6.1. Neuroprotective Actions of Polyphenols Mediated by 67LR

6.1.1. 67LR as an Evolutionarily Conserved Multifunctional Protein: Friend or Foe

The 67LR is a cell-surface laminin receptor originally implicated in tumor cell adhesion, invasion, and metastasis [163–168]. Evolutionarily conserved, this receptor is initially syn-

thesized as a 37-kDa precursor (37LRP), also known as ribosomal protein SA (RPSA), which plays an essential role in ribosomal biogenesis and protein synthesis [167,169]. Through mechanisms that remain incompletely understood, this 37-kDa precursor converts into the mature 67-kDa cell-surface form, functioning as a high-affinity laminin receptor [166–168]. Furthermore, 67LR mediates the internalization of diverse pathogenic bacteria and viruses, as well as cellular and infectious prion proteins [166–168]. Crucially, it also serves as a coreceptor for the Aβ-prion protein complex, facilitating Aβ internalization and inducing neuronal death, a critical step in the pathogenesis of AD [170,171]. Collectively, these findings indicate that 67LR plays multiple pathological roles.

The widespread tissue distribution of 67LR, particularly within the brain [172], suggests its involvement in essential cellular processes far beyond cancer metastasis and infections. Indeed, we and others have demonstrated that 67LR mediates several beneficial physiological functions, including neuritogenesis, neuroprotection, and the maintenance of BBB integrity [173–176]. Recent studies further highlight its importance in the axonal growth of dorsal root ganglion neurons [177], while other research indicates it mediates pigment epithelium-derived factor-induced morphogenesis in cortical neurons [178]. Furthermore, gene knockout studies show that the homozygous deletion of *Rpsa* (which encodes 37LRP) results in embryonic lethality, underscoring its indispensable role in early development [166]. Ultimately, 67LR can exert either pathological or protective effects depending strictly on the specific ligands it binds or internalizes.

6.1.2. 67LR as a High-Affinity Target for Dietary Polyphenols and Their Metabolites

Tachibana and colleagues identified the high-affinity binding of EGCG (Kd = 40 nM) to 67LR, demonstrating that this receptor mediates cancer cell death at low micromolar concentrations of EGCG [179,180]. This discovery stemmed from an unbiased screening strategy designed to identify proteins upregulated by retinoic acid that sensitize cancer cells to EGCG-induced apoptosis [181]. Strikingly, in contrast to the apoptotic effects observed at micromolar levels, EGCG promotes neuroprotection and neuritogenesis at low nanomolar concentrations, also in a strictly 67LR-dependent manner [173,174,181,182].

Research from our laboratory and others demonstrates that EGCG binds to two distinct sites on 67LR, notably within the peptide G region [182,183]. Molecular docking studies indicate that the "A" site binds EGCG and other polyphenols with higher affinity. This site is primarily composed of the second half of the peptide G region, which features a hydrophobic palindromic sequence encompassing Trp175 and Trp176 (Figure 2, Table 2). Indeed, assays using synthetic peptide G show that EGCG binds this palindrome with high affinity (1.95 nM) [182]. In contrast, the "B" site involves residues from the first half of the peptide G region (outside the palindrome) and exhibits lower polyphenol binding affinity. Notably, other dietary polyphenols, including resveratrol and quercetin, also interact with 67LR via this region [181,182]. Furthermore, α-tocopherol and α-tocotrienol interact with 67LR through Trp176, reinforcing the role of the peptide G sequence as a shared binding motif [184,185]. A variety of other polyphenols, such as thearubigin, theaflavin, rutin, epicatechin-3-gallate, epigallocatechin, and procyanidin C1, also bind 67LR with high affinity to elicit cellular responses [186,187]. Together, these findings suggest that 67LR serves as a common receptor for a diverse array of dietary polyphenols.

Interestingly, the glucuronide and sulfate conjugates of these polyphenols exhibit higher binding affinity for peptide G than their aglycone forms [181–183]. Furthermore, molecular docking studies indicate that intestinal microbial metabolites of quercetin (3,4-dihydroxyphenylacetic acid), *trans*-resveratrol (dihydroresveratrol), and EGCG [5-(3′,4′-dihydroxyphenyl)-γ-valerolactone] also bind to 67LR, albeit generally with lower affinity than their corresponding polyphenol aglycones (Table 2). However, upon conjugation,

the glucuronide forms of these microbial metabolites dock with higher affinity than their unconjugated counterparts. Notably, binding assays using isolated peptide G revealed a specific exception: dihydroresveratrol binds with higher affinity than its parent compound, *trans*-resveratrol [182]. Much like *trans*-resveratrol, dihydroresveratrol also induces elevations in intracellular cAMP via a strictly 67LR-dependent mechanism [182].

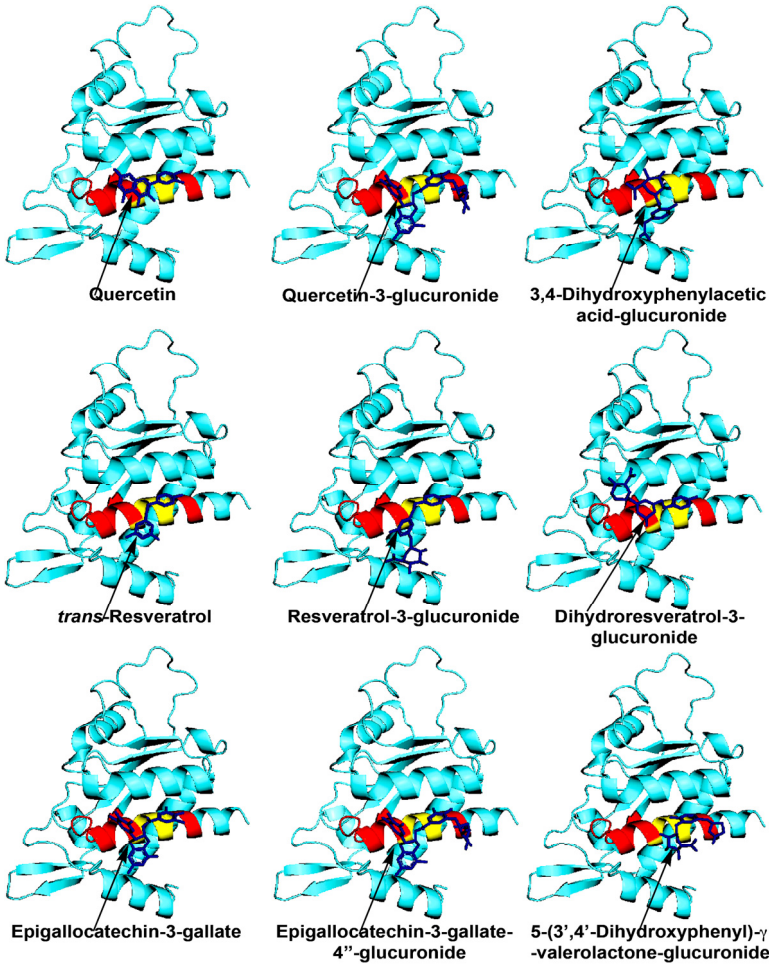


Figure 2. Molecular docking of polyphenols and their metabolites to truncated 37LRP. PyMOL (version 2.5.4)-generated models showing the crystal structure of truncated 37LRP (cyan) docked with polyphenols and their glucuronide metabolites. The peptide G region is highlighted in red, the palindromic sequence in yellow, and the bound ligands in blue. The docked ligands are grouped as follows: polyphenol aglycones (**left three**), glucuronide conjugates of polyphenols (**middle three**), and glucuronide conjugates of intestinal microbial metabolites (**right three**).

Many dietary polyphenols accumulate inside cells only to a limited extent because they are relatively polar and are subject to active efflux by membrane transporters [188]. Glucuronide and sulfate conjugates are even more hydrophilic organic anions; consequently, their cellular entry is often transporter-dependent, while efflux transporters can further restrict their intracellular exposure [189]. In this context, a cell-surface binding protein like 67LR is ideally positioned to sense extracellular polyphenols without requiring substantial intracellular accumulation. Collectively, these findings support the concept that 67LR serves as a common receptor for structurally diverse dietary polyphenol aglycones, their glucuronide conjugates, and intestinal microbial metabolites, thereby potentially mediating their broad biological and chemopreventive actions.

Table 2. Binding energies of polyphenol aglycones and their intestinal microbial metabolites to 37LRP, along with the predicted amino acids involved in ligand binding. Three-dimensional structures of all compounds were generated using ChemDraw (version 22.2.0) and converted to PDB format with Avogadro. Molecular docking was performed using the crystal structure of truncated 37LRP (PDB ID: 3BCH; amino acid residues 9–183) with AutoDock Vina (version 1.2.5) and AutoDockTools (version 1.5.7). Ligand-binding amino acid residues on 37LRP were identified using Discovery Studio (version 24.1). All glucuronide conjugates are primarily formed in the liver.

Polyphenol Aglycones or Their Metabolites	Binding Energy (kcal/mol)	Amino Acids Involved in the Ligand Binding to "A" Site in 37LRP (A Precursor Protein for 67LR)
Quercetin	−8.34	Thr82, Arg85, Ala86, Lys89, Trp175, Trp176, Ala179 # (Phe90, Ala93, Ala168, His169, Gly172, Leu173)
Quercetin-3-glucuronide	−8.43	Arg85, Ala86, Lys89, Gly172, Trp175, Trp176 (Asn81, Thr82, Phe90, Ala93, His169, Leu173, Ala179)
* 3,4-Dihydroxyphenylacetic acid	−5.06	Ala86, Lys89, Gly172 (Arg85, Phe90, Leu173, Trp175, Trp176, Ala179)
3,4-Dihydroxyphenylacetic acid-glucuronide	−7.11	Ala86, Ala168, His169, Leu173, Trp176 (Lys17, Ala20, Ala21, Arg85, Lys89, Gly172)
trans-Resveratrol	−6.65	Ala86, Lys89, His169, Gly172, Trp175, Trp176, Ala179 (Phe90, Ala93, Leu173)
Resveratrol-3-glucuronide	−7.78	Ala86, Lys89, His169, Trp175, Trp176, Ala 179 (Lys17, Ala20, Ala21, Phe90, Ala93, Gly172, Leu173)
* Dihydroresveratrol	−6.38	Ala86, Lys89, His169, Trp175, Trp176, Ala179 (Phe90, Ala93, Gly172, Leu173)
Dihydroresveratrol-3-glucuronide	−8.18	Thr82, Arg85, Ala86, Lys89, Trp175, Trp176, Ala179 (Asn81, Gln84, Phe90, Ala93, Ala168, Gly172)
Epigallocatechin-3-gallate	−9.31	Thr82, Arg85, Lys89, Gly172, Leu173, Trp176 (Lys17, Ala20, Ala21, Ala86, Phe90, Ala93, Ala168, His169, Trp175, Ala179)
Epigallocatechin-3-gallate-4″-glucuronide	−9.96	Ala21, Thr82, Arg85, Lys89, Ala168, Leu173, Trp176 (Lys17, Ala20, Ala86, Phe90, Ala93, His169, Gly172, Trp175, Ala179, Arg180, Leu183)
* 5-(3′,4′-Dihydroxyphenyl)-γ-valerolactone	−5.99	Ala86, Lys89, Trp175 (Arg85, Phe90, Gly172, Trp176, Ala179)
5-(3′,4′-Dihydroxyphenyl)-γ-valerolactone-3′-glucuronide	−6.84	Lys 89, Gly172, Trp176, Ala179 (Ala86, Phe90, Ala93, Leu173, Trp175, Leu183)

* Denotes intestinal microbial metabolites. # Amino acid residues contributing to van der Waals interactions are indicated in parentheses.

6.1.3. 67LR Structural Basis for Binding of Polyphenol Glucuronide/Sulfate Conjugates

Glucuronide and sulfate conjugates of polyphenols are highly water-soluble and are thus generally expected to bind weakly to receptors. However, contrary to this long-held view, these polyphenol conjugates bind to 67LR with even higher affinity than their aglycones [181–183]. While the mechanisms by which other conjugates, such as morphine-6-glucuronide and minoxidil sulfate, bind their receptors with high affinity and exert enhanced biological activity remain unclear [150,151], 67LR possesses unique structural features that explain this phenomenon. Specifically, 67LR interacts with heparan sulfate proteoglycans, a class of glycosaminoglycans (GAGs) rich in uronic acids (D-glucuronic and L-iduronic acid) and sulfate residues [190]. GAG-binding motifs, typically following the consensus sequences X-B-B-X-B-X or X-B-B-B-X-X-B-X (where B is a basic amino acid and X is a hydropathic residue), are well-documented in other proteins [191,192]. The

peptide G region of 67LR contains one such GAG-binding motif, which likely provides the additional interaction coordinates necessary to facilitate the high-affinity binding of polyphenol conjugates at both the A and B sites (Figure 3).

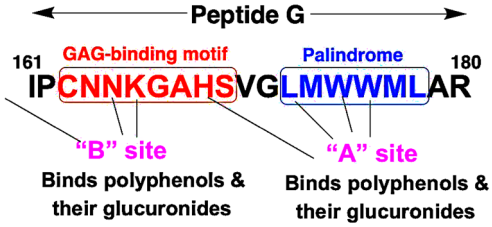


Figure 3. Binding sites "A" and "B" for polyphenols and their glucuronides within the peptide G region of 67LR. The peptide G region contains a palindromic sequence (blue) and a GAG-binding motif (red). The high-affinity "A" site mediates the binding of polyphenols and their glucuronides, primarily utilizing Leu173, Trp175, and Trp176 within the palindrome, alongside His169 from the GAG-binding motif and other residues. Conversely, the "B" site comprises Asn165 and Lys166 within the GAG-binding motif, along with additional amino acids, to facilitate ligand binding.

While our primary focus is the binding of polyphenols to mature, cell-surface 67LR, crystallographic data for this specific form remain unavailable. Instead, existing structural data are restricted to the bacterial recombinant precursor, 37LRP. We acknowledge that the conformation of mature 67LR may differ from that of 37LRP, which could potentially alter its binding affinity for polyphenols. Furthermore, while other groups have utilized surface plasmon resonance to measure the affinity of EGCG for the receptor [179], our study employed a synthetic peptide G in binding assays [181,182]. Nevertheless, our conclusion that polyphenols bind cell-surface 67LR with high affinity is strongly supported by the observation that 67LR-blocking antibodies inhibit the cellular effects of these compounds and their metabolites at low nanomolar concentrations. Ultimately, future studies directly investigating polyphenol binding to the intact 67LR protein are warranted.

6.1.4. 67LR as a Coreceptor for the Aβ-Prion Complex—Neuronal Cell Death

Paradoxically, while 67LR serves as a common receptor for a diverse array of neuroprotective dietary polyphenols, it also functions as a co-receptor for neurotoxic amyloid-beta (Aβ) oligomers. Aβ neurotoxicity is largely driven by the high-affinity binding of these Aβ oligomers (AβOs) to neuronal cell-surface receptors [193,194]. Strittmatter and colleagues identified that the lipid raft-associated cellular prion protein (PrP^C) is a major high-affinity receptor for AβOs [195,196]. This AβO-PrP^C complex can subsequently interact with various co-receptors to mediate neuronal toxicity [193,194]. Building on this, Weiss and colleagues identified 67LR, which also localizes to lipid rafts, as a specific co-receptor for the AβO-PrP^C complex [170,171]. Although PrP^C is known to bind 67LR directly via the peptide G region [191], the direct binding of the intact AβO-PrPC complex to 67LR remains unconfirmed. Functionally, 67LR facilitates the internalization of this neurotoxic complex, driving intracellular Aβ accumulation and subsequent neuronal cell death [170,171]. Consequently, 67LR presents a promising therapeutic target, as evidenced by reduced neurodegeneration in AD transgenic mice following the intranasal administration of a 67LR-blocking antibody [197].

The binding of Aβ oligomers to cell-surface receptors triggers their internalization, leading to increased ROS generation, synaptic toxicity, and neuronal death [193,194,198]. Therefore, elucidating why polyphenol-induced signaling diverges from this pathway, and how it effectively counteracts these detrimental effects, represents a critical area of ongoing research.

6.1.5. 67LR-Mediated cAMP Signaling and Downstream Events for AD Prevention by Dietary Polyphenols

We previously reported a rapid, several-fold increase in intracellular cAMP levels within neuronal cells treated with low nanomolar concentrations of resveratrol, EGCG, and quercetin [181,182]. This elevation was prevented by a 67LR-blocking antibody, indicating that 67LR mediates cAMP induction by these polyphenols [182]. Because 67LR is not a G-protein-coupled receptor, it cannot directly activate adenylyl cyclase (AC) [167]. Although resveratrol has been reported to inhibit phosphodiesterases (PDEs), a mechanism that could elevate intracellular cAMP levels, this effect requires relatively high concentrations (20–40 μM) [199]. Consistent with this, we did not observe the inhibition of PDE4B or PDE4D at low nanomolar concentrations of these polyphenols.

Compared with healthy age-matched controls, patients with AD and AD mouse models exhibit markedly reduced levels of cAMP, AC, and PKA in the hippocampus [200]. The cAMP-elevating neuroprotective peptide, pituitary adenylyl cyclase-activating polypeptide (PACAP), protects neurons from Aβ oligomer (AβO)-induced cell death [201]; however, PACAP levels are reduced in AD patients relative to age-matched controls [202]. Furthermore, the administration of PACAP improves cognitive performance in AD transgenic mice [203]. Phosphodiesterase (PDE) inhibitors are currently under clinical investigation for AD treatment [204]; yet, chronic, non-physiological activation of cAMP signaling by these agents can lead to cognitive impairment, hyperexcitability, and hyperalgesia [205]. In contrast, dietary polyphenols induce modest, localized increases in intracellular cAMP, potentially avoiding the adverse effects associated with synthetic PDE inhibitors. However, the precise mechanisms by which 67LR binding enhances cAMP generation remain unclear.

As illustrated in Figure 4, cAMP levels rise in response to dietary polyphenols and activate protein kinase A (PKA). PKA then phosphorylates the transcription factor cAMP-response element-binding protein (CREB) at Ser133, which increases the expression of brain-derived neurotrophic factor (BDNF), a neurotrophin essential for neuronal survival [206–208]. Consistent with this, enhanced CREB activation has been reported in neurons treated with low concentrations of quercetin-3-glucuronide [83]. Furthermore, cAMP signaling enhances the activity of sirtuin 1 (SIRT1), an NAD^+-dependent deacetylase [209]. The cAMP/CREB pathway upregulates nicotinamide phosphoribosyltransferase (NAMPT), thereby raising the intracellular NAD^+ levels required for optimal SIRT1 activity [210]. Once activated, SIRT1 deacetylates and stimulates key transcriptional regulators, including PGC-1α (involved in mitochondrial biogenesis and antioxidant defense) and FOXO3 (which regulates oxidative stress responses and longevity) [211,212]. SIRT1 also deacetylates and inhibits NF-κB to reduce inflammation, an effect that may benefit cognitive function [213]. Resveratrol is widely documented to increase SIRT1 expression and activity, protecting against Aβ toxicity in experimental AD models [214,215]; quercetin and EGCG reportedly share this SIRT1-activating capacity [216,217]. However, it remains to be determined whether the low concentrations of polyphenol aglycones and conjugates actually achieved in the brain are sufficient to activate neuronal SIRT1 in vivo. Ultimately, both BDNF and SIRT1 protect neurons from Aβ-induced toxicity while enhancing synaptic plasticity and cognitive function [54,218]. Because aging naturally dysregulates cAMP-PKA signaling [219], polyphenol-induced enhancement of this pathway offers a highly beneficial countermeasure.

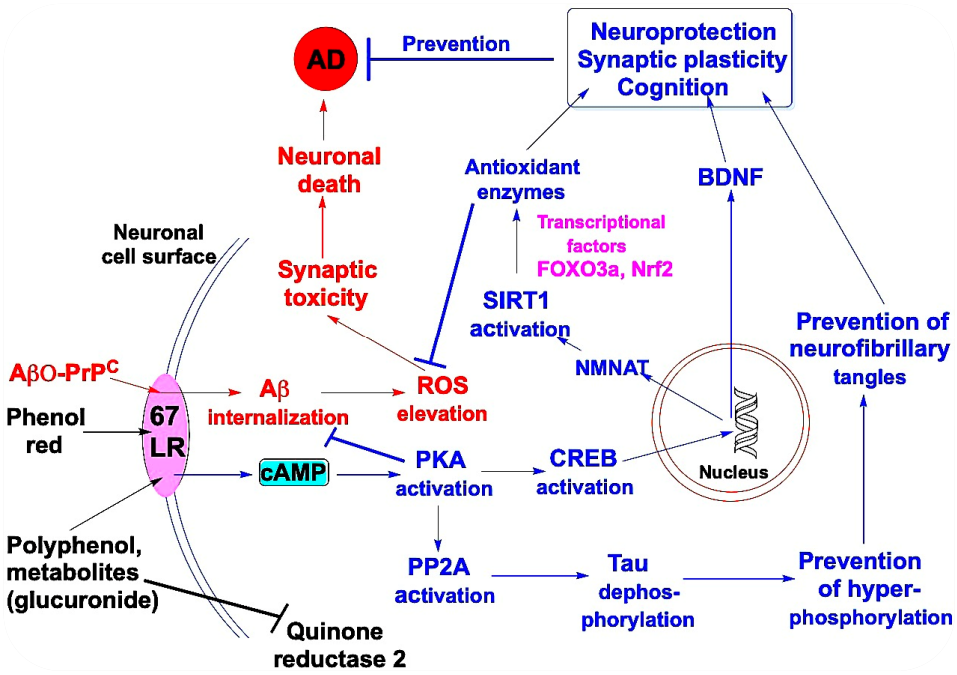


Figure 4. The Aβ-PrP^C complex binds to 67LR to trigger signaling that promotes neuronal death, whereas polyphenols and their glucuronide metabolites compete for the same receptor to activate neuroprotective pathways. Binding of the Aβ-PrP^C complex to 67LR promotes Aβ internalization, elevates reactive oxygen species (ROS), induces synaptic toxicity, and ultimately drives neuronal death and Alzheimer's disease (AD) progression (events shown in red). In contrast, polyphenols and their conjugates bind to 67LR and increase intracellular cAMP, thereby activating PKA and subsequently phosphorylating CREB. Activated CREB promotes the transcription of BDNF and NMNAT (nicotinamide mononucleotide adenylyl transferase). NMNAT then supports SIRT1 activation, which deacetylates transcription factors such as FOXO3a and Nrf2, inducing antioxidant enzymes that reduce ROS levels. Additionally, PKA activates protein phosphatase 2A (PP2A), which dephosphorylates tau to limit its hyperphosphorylation and the formation of neurofibrillary tangles. Together, these events (shown in blue) promote neuroprotection and neuroplasticity, improve cognition, and may slow AD progression. Furthermore, polyphenols such as resveratrol and quercetin inhibit quinone reductase 2 (QR2), an enzyme elevated in AD and linked to cognitive decline.

Once activated by polyphenol treatment, the cAMP/PKA pathway phosphorylates and activates protein phosphatase 2A (PP2A), a key serine/threonine phosphatase [220,221]. This step is critical, as PP2A is the primary enzyme responsible for dephosphorylating the neuronal microtubule-associated protein tau [222]. By preventing tau hyperphosphorylation, PP2A activation inhibits the formation of neurofibrillary tangles and subsequent neuronal death. This mechanism is especially relevant to AD, given that PP2A activity is markedly reduced in the brains of AD patients [223]. Consequently, the activation of cAMP signaling by polyphenols via the 67LR receptor may represent a central mechanism driving their neuroprotective effects and their capacity to mitigate AD pathology.

6.1.6. Potential Antagonism Between AβO-PrP^C and Dietary Polyphenols at 67LR

Because the AβO-PrP^C complex, as well as polyphenols and their metabolites, bind to the same peptide G region of 67LR [181,182,190], they likely compete for this site. Consequently, polyphenols may antagonize AβO-PrP^C binding, thereby preventing Aβ internalization and reducing neurotoxicity. Furthermore, polyphenol binding to 67LR induces cAMP/PKA signaling, which activates CREB, SIRT1, and PP2A. As illustrated in Figure 4, this cascade elevates the activity of antioxidant enzymes to promote neuroprotection and synaptic plasticity. Additionally, elevated cAMP has been shown to independently reduce

Aβ internalization [198]. Consistent with this mechanism, other studies have demonstrated that cAMP protects cortical neurons from AβO-induced cell death [224].

6.1.7. Phenol Red Binds to 67LR and Interferes with Polyphenol and Aβ-PrP^C Interactions

Phenol red, a widely used pH indicator in cell culture media, binds with high affinity to the peptide G region of 67LR. Because polyphenols and the Aβ-PrP^C complex target this exact site, phenol red can significantly interfere with their binding. Standard culture media, such as DMEM, RPMI 1640, and Neurobasal, contain phenol red at concentrations as high as 42, 14, and 21 μM, respectively. Consequently, these high background concentrations necessitate artificially high polyphenol doses to achieve neuroprotective effects in vitro. Initially unaware of this interference, we found that high nanomolar concentrations of EGCG were required to elicit neuritogenic and neuroprotective effects in phenol red-containing media [173,174]. However, after culturing cells in phenol red-free medium for two to three passages, we demonstrated that as little as 5 nM EGCG was sufficient to produce neuroprotection [182]. Similarly, we previously observed that omitting phenol red decreased the concentration of Aβ required to induce neuronal cell death [198]. Although direct competition between phenol red and Aβ oligomers at the 67LR receptor warrants further experimental verification, these collective findings underscore a critical methodological point: phenolic compounds like phenol red must be avoided in culture media when investigating the in vitro effects of polyphenols and Aβ at physiologically relevant, low concentrations.

6.1.8. 67LR as a Redox Sensor

Although polyphenols and their metabolites physically bind to 67LR via their phenolic groups, their inherent redox sensitivity may also play a crucial role in cellular regulation. Previous studies have established that 67LR can function as a redox sensor [225]. Specifically, H_2O_2 induces the oxidation of redox-active cysteine thiols within the receptor; one of these cysteine residues is located directly within peptide G, while another lies in close proximity [225]. Additionally, the peptide G region features a Met–Trp–Trp–Met motif within its palindromic sequence. Because studies using artificial model proteins have demonstrated that methionine-flanked tryptophan residues can participate in electron transfer reactions [226], we postulate that this evolutionarily conserved motif in 67LR may support localized charge-transfer or redox interactions, particularly under oxidative conditions. Furthermore, 67LR has been reported to exhibit sulfhydryl oxidase-like activity [227]. It remains unclear whether transiently oxidized polyphenol species, such as semiquinone or quinone intermediates, interact with these redox-active vicinal sulfhydryls before being reduced back to their original phenolic states. Finally, EGCG binding to 67LR induces a modest, sublethal elevation in H_2O_2, a molecule increasingly recognized as an essential mediator of cellular signaling [228].

6.2. Neuroprotective Actions of Polyphenols by Inhibiting QR2

Resveratrol and quercetin inhibit QR2 with high affinity (Kd = 35 and 50 nM, respectively), and this inhibition leads to upregulation of antioxidant enzyme expression [229]. QR2 is overexpressed during aging and is particularly abundant in the hippocampus of patients with AD, where it likely contributes to metabolic stress and cognitive deficits [230,231]. Because specific QR2 inhibitors have been shown to reduce metabolic burden and reverse AD phenotypes in mouse models [230], inhibition of QR2 by polyphenols such as resveratrol and quercetin may improve cognitive function and offer therapeutic benefit in AD.

The exact physiological function of QR2 remains unclear; whether it primarily catalyzes quinone reduction or functions in cell signaling is still under investigation [232]. Unlike typical reductases, QR2 cannot use NAD(P)H as a reducing cofactor. Instead, it

retains a functional FAD cofactor and cycles between oxidized and reduced states. These unique characteristics suggest that QR2 may act as a redox sensor and regulator rather than a traditional detoxifying enzyme for electrophilic quinones [232]. Finally, given the low concentrations of polyphenol aglycones achieved in the brain, it remains to be determined whether their more prevalent glucuronide and sulfate conjugates or their oxidative metabolites retain the ability to interact with and inhibit QR2 in vivo.

7. Indirect Neuroprotective Actions of Polyphenols—AD Prevention

7.1. Actions on Glial Cells in the CNS

The neuroprotective effects of polyphenols may also arise indirectly through the modulation of glial cell function. Aβ accumulation activates microglia and induces the production of proinflammatory cytokines, driving a chronic state of neuroinflammation [233]. Polyphenols effectively counter this cascade: resveratrol, for example, inhibits prostaglandin E2 (PGE2) production and free radical formation in activated microglia by modulating the cyclooxygenase/PGE2 signaling pathway [234]. Furthermore, resveratrol suppresses NF-κB transcriptional activation, thereby reducing cytokine secretion from both Aβ-activated astrocytes and microglia [235]. Similarly, EGCG exerts broad anti-inflammatory effects by transcriptionally downregulating cytokine release [236]. Notably, both resveratrol and EGCG activate SIRT1, which markedly attenuates Aβ-induced NF-κB signaling to confer strong neuroprotection [237]. Quercetin complements these actions by mitigating microglial inflammatory responses via activation of the Nrf2/heme oxygenase-1 pathway [238].

Despite these promising findings, most in vitro demonstrations of these anti-inflammatory effects have relied on micromolar concentrations of polyphenol aglycones. It remains to be determined whether the low nanomolar concentrations of their biologically relevant glucuronide and sulfate conjugates can elicit comparable responses. Additionally, while the PEDF peptide is known to mediate anti-inflammatory actions via 67LR in astrocytes [239], future studies must clarify whether polyphenols similarly leverage this receptor to exert their anti-inflammatory effects in glial cells.

7.2. Peripheral Actions

Although brain exposure to dietary quercetin, resveratrol, and EGCG is limited, these polyphenols may indirectly promote resilience to AD by attenuating systemic drivers of neurodegeneration through peripheral actions. Chronic elevations in circulating cytokines and sustained immune-cell activation are known to exacerbate cerebrovascular dysfunction and amplify neuroinflammation in AD [240,241]. In vivo, quercetin demonstrates robust systemic anti-inflammatory activity and improves vascular risk factors, such as blood pressure, which may translate into protection against cognitive decline [242,243]. Similarly, resveratrol ameliorates peripheral metabolic dysregulation (e.g., insulin resistance) via pathways involving SIRT1.

BBB integrity is compromised in AD, allowing blood-derived plasma proteins, such as fibrinogen, to extravasate into the brain parenchyma and promote neuronal degeneration [244–246]. EGCG has been shown to attenuate this serum extravasation by acting via 67LR [175]. Resveratrol also supports endothelial nitric oxide bioavailability and overall vascular function, which may indirectly protect the brain by improving cerebral perfusion and preserving BBB integrity [247,248]. Furthermore, in vitro studies report that micromolar concentrations of quercetin attenuate Aβ-induced cytotoxicity in human brain microvascular endothelial cells [249]. Because QR2 is expressed in endothelial cells and generates reactive ROS that can weaken the BBB [232], its inhibition by resveratrol and quercetin likely provides an additional mechanism for preserving barrier function. However, mechanistic evidence remains limited, and it is still unclear whether these protective

effects are mediated in vivo by the parent aglycones or by their bioavailable glucuronide and sulfate conjugates acting through 67LR and QR2.

Furthermore, EGCG exerts significant gut-mediated systemic effects. Although extensively metabolized in the gut, EGCG can reshape the local microbiota and fortify intestinal barrier function. This fortification reduces the systemic translocation of pro-inflammatory microbial products, such as lipopolysaccharide (LPS), which are known to drive BBB impairment and neuroinflammatory signaling [250]. Collectively, these peripheral anti-inflammatory, metabolic, vasoprotective, and gut-restoring actions provide a cohesive mechanism by which quercetin, resveratrol, and EGCG can mitigate AD pathobiology, despite their low concentrations in the brain.

8. Combining Low-Dose Polyphenols for the Prevention of AD

When dietary polyphenols are consumed at standard, well-tolerated doses, only low nanomolar concentrations of the parent compounds and their conjugates reach the brain (Table 1). Crucially, these physiological concentrations fall below the in vitro binding affinities (Kd) required to effectively engage 67LR. For example, consuming two cups of green tea yields an estimated brain EGCG concentration of just 10 nM [82], whereas its observed Kd for 67LR is 40 nM [179]. Similarly, dietary quercetin-3-glucuronide reaches brain concentrations of approximately 1 nM [83], yet its binding affinity for the receptor's peptide G region is 4 nM [181]. Because our model indicates that the Aβ-PrP^C complex targets this exact region of 67LR, effective competition would require significantly higher brain concentrations than diet alone can provide. Consequently, at these low dietary levels, 67LR occupancy by polyphenols is likely suboptimal, yielding limited direct neuroprotection.

While escalating the dose of these polyphenols might intuitively seem like a strategy to enhance their efficacy for AD prevention, this approach carries a significant risk of peripheral toxicity. Although higher dosing may improve systemic exposure and CNS delivery, it is frequently accompanied by severe adverse effects. For instance, high-dose EGCG (or green tea extract) has been linked to hepatocellular injury in humans and produces marked hepatotoxicity in preclinical models [251]. Similarly, escalating the doses of resveratrol and quercetin has been associated with renal toxicity in animal studies [252,253] and adverse drug interactions [254], respectively. Most concerningly, an unexpected finding from a randomized, placebo-controlled trial in patients with mild-to-moderate AD revealed that high-dose resveratrol administration was actually associated with greater brain volume loss on MRI compared to placebo [90].

An alternative strategy is to administer a combination of three or four well-characterized dietary polyphenols at low doses. Even if each compound achieves only low brain concentrations individually, agents converging on the same pathway (e.g., 67LR-mediated signaling) could produce additive effects that approximate the impact of a high-dose monotherapy. Moreover, because these polyphenols differ structurally, EGCG is a galloylated flavan-3-ol (catechin), quercetin circulates largely as glucuronide and sulfate conjugates, and resveratrol is a stilbene, they may engage complementary mechanisms that enable synergistic interactions. However, such combinations must also be carefully evaluated for potential receptor antagonism. Overall, supplementation with a limited set of structurally diverse, low-dose polyphenols represents a practical strategy to promote additive or synergistic neuroprotection for AD prevention while minimizing the risk of toxicity.

9. Conclusions and Perspectives

Given that AD develops over decades, its extended prodromal phase provides a realistic window for prevention. Because AD is multifactorial, however, meaningful risk

reduction will likely require interventions that engage multiple, distinct pathways. Dietary polyphenols are highly appealing in this context because of their ability to influence several AD-relevant mechanisms simultaneously.

A central constraint in translating these benefits is pharmacokinetics. Most polyphenols are rapidly converted to glucuronide and sulfate conjugates and are extensively protein-bound, leaving only a small unbound fraction available for tissue distribution. Consequently, both parent aglycones and their conjugated metabolites typically reach the brain at only low nanomolar concentrations after limited passage across the BBB. Microbiota-derived metabolites follow a similar pattern: they are absorbed, rapidly conjugated, and circulate predominantly in these modified forms. Traditionally, these conjugates have been viewed merely as inactive excretory products or temporary reservoirs for regenerating aglycones. An important unresolved issue is whether these conjugated metabolites possess intrinsic biological activity, particularly through engagement of high-affinity targets, and therefore contribute directly to neuroprotection.

Although polyphenols can scavenge ROS, their direct antioxidant effects in vivo, especially in the brain, are likely negligible because of these low tissue concentrations and the generally weaker radical-scavenging capacity of conjugates compared with their parent aglycones. A more plausible mechanism is an "indirect antioxidant" action, whereby quercetin, resveratrol, EGCG, and their metabolites activate redox-responsive signaling pathways that upregulate endogenous cytoprotective enzymes. Such pathway-level reinforcement can persist even after the compounds themselves are cleared, providing a biologically credible route to sustained protection.

Two targets emphasized in this review are particularly relevant to AD pathogenesis and illustrate how ligands present at low concentrations can still produce meaningful effects. First, 67LR binds the AβO-PrP^C complex, promoting Aβ internalization and triggering downstream neurotoxic signaling. Quercetin, resveratrol, EGCG, and their conjugated metabolites bind this same 67LR site, competitively antagonizing AβO-PrP^C binding and activating neuroprotective cascades. Second, QR2 is an enzyme elevated in AD and associated with cognitive decline; resveratrol and quercetin bind QR2 with high affinity, inhibit its activity, and improve cognition in experimental settings. Notably, both 67LR and QR2 may function as redox sensors that react with oxidized polyphenol species, suggesting that redox-dependent chemistry contributes even within a receptor-based framework. Moving forward, it will be critical to determine whether other newly identified polyphenol receptors contain structural features that enable redox sensing, thereby clarifying when physical-binding targets and redox-sensing targets are distinct entities and when they are one and the same.

The ability of steroid hormones and catecholamines to act at low nanomolar or subnanomolar concentrations provides a highly relevant analogy: selective binding to a limited set of receptors enables substantial signal amplification through downstream transduction pathways. Polyphenols and their conjugates may similarly exert biological effects at low concentrations by engaging high-affinity targets that initiate defined signaling cascades. One illustrative mechanism is receptor-mediated elevation of cAMP, a second messenger whose amplification can drive broad transcriptional and functional responses despite minimal initial ligand exposure.

Ultimately, achieving therapeutically meaningful CNS exposure remains a major translational hurdle. Simply escalating doses to raise brain concentrations is not a viable solution, as higher intake increases the risk of peripheral toxicity, such as the hepatotoxicity reported with high EGCG exposure, raises the likelihood of adverse drug-nutrient interactions, and introduces safety concerns for long-term use.

A more practical strategy is low-dose combination supplementation using three or four well-characterized polyphenols. Even if each compound achieves only limited brain penetration individually, agents converging on the same protective node, such as 67LR-mediated signaling, could produce additive or synergistic effects that rival high-dose monotherapy while minimizing toxicity risks. Overall, defining which circulating conjugates and microbiota-derived metabolites are active, identifying their high-affinity targets, and delineating how redox-dependent processes intersect with receptor signaling will be essential for translating dietary polyphenols into an evidence-based clinical approach for AD prevention.

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Abbreviations

The following abbreviations are used in this manuscript.

aMCI	Amnestic mild cognitive impairment
Aβ	Amyloid-β
AβO	Amyloid-β oligomers
AD	Alzheimer's disease
BBB	Blood–brain barrier
BDNF	Brain-derived neurotrophic factor
CNS	Central nervous system
CREB	cAMP response element-binding protein
CSF	Cerebrospinal fluid
EGCG	(−)-Epigallocatechin-3-gallate
GAG	Glycosaminoglycan
67LR	67-kDa laminin receptor
NMNAT	Nicotinamide mononucleotide adenylyltransferase
PDE	Phosphodiesterase
PKA	Protein kinase A
PP2A	Protein phosphatase 2A
PrP^C	Cellular prion protein
Q-3-G	Quercetin-3-O-glucuronide
R-3-G	Resveratrol-3-O-glucuronide
ROS	Reactive oxygen species
SIRT1	Sirtuin 1 (NAD^+-dependent deacetylase)

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