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Gut Microbiota–Derived Metabolites of Dietary Polyphenols in Cognitive Aging:Bioavailability, Neuroinflammation, and Precision Nutrition Implications

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Abstract: Cognitive aging, the age-related degeneration of cognitive ability, is an increasing global health issue, with diet becoming a variable to work on its course. Despite established neuroprotective properties of dietary polyphenols, most of the parent compounds have poor systemic bioavailability, prohibiting their direct action in the central nervous system (CNS). Recent studies have redirected interest to microbiota-derived catabolites; urolithins, equol, enterolignans, phenolic acids, and short-chain fatty acids (SCFAs) that are less toxic and can enter the systemic circulation and possibly cross the blood-brain barrier (BBB). This review identifies polyphenols-derived microbial metabolites as those that are generated by the gut rather than parent polyphenols. Cellular, animal, and limited human evidence implicates these metabolites in cellular neuroinflammation regulation and mitochondrial functioning in cognitive aging, albeit with varying strengths and limitations. Previous studies mainly focused on parent compounds even though most polyphenols reach the colon in their original form, where they are converted to bioactive metabolites with greater bioavailability by gut microbes. This has made these metabolites appear to be the major mediators of health benefits, and this emphasizes the need of microbial transformation processes. Nonetheless, there are still gaps, such as sparse clinical data and a high inter-individual disparity on metabolite production caused by microbiome disparities. The review also differentiates between cognitive aging, cognitive decline, and mild cognitive impairment (MCI) and marks the necessity of metabotype-based precision nutrition approaches.

Keywords: Polyphenols; Gut microbiota; Urolithin A; Cognitive aging; Neuroinflammation; Precision nutrition; Metabotype; Blood–brain barrier

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1. Introduction

Cognitive decline is one of the most significant public health challenges associated with global population aging. By 2050, dementia is estimated to affect 153 million individuals, a number that highlights the

significance of establishing modifiable risk factors that would be effective in interventions at the population level [1]. Nutrition is a scaled and accessible area of early prevention, and among various biological characteristics, dietary polyphenols have a high research interest. Polyphenols are natural secondary metabolites in plants, including fruits, vegetables, whole grains, and legumes and beverages like tea and red wine [2]. Epidemiological studies have indicated that frequent intake of polyphenol-containing foods could help prevent cognitive impairment and dementia, whereas mechanistic research has shown antioxidant, anti-inflammatory, and neuroprotective effects to be some of the primary mechanisms [3,4]. Even in increasing mechanistic insights, there are gaps. There is limited human clinical evidence and most studies are based on animal or cellular models, and personal differences in microbiome composition also play a role in metabolite production have not been studied properly [5]. The review differentiates between cognitive aging, cognitive decline, and mild cognitive impairment (MCI), and seeks to evaluate microbial biotransformation, bioavailability, mechanistic connections to neuroinflammation and implications of inter-individual variations.

2. From dietary polyphenols to microbial metabolites

Dietary polyphenols consist of various broad structural classes that possess different physicochemical characteristics according to how they act along the gastrointestinal tract. These include flavonoids (flavonols, flavones, isoflavones, and anthocyanins), phenolic acids, stilbenes, lignans, and hydrolysable tannins (ellagitannins and gallotannins) [6]. Among these, the ellagitannins, which are also present in pomegranates, walnuts and berries, are high-molecular weight compounds which, through the process of hydrolyzing in the gut, are decomposed into ellagic acid, then formed into a family of urolithin isoforms by a series of demethylation and lactonization reactions by gut bacteria, predominantly *Gordonibacter* Isoflavones, especially daidzein of soy, are converted to equol by the *Lachnospiraceae* family of bacterial consortia, which has a far higher affinity as an estrogen receptor agonist than the dietary isoflavone [7]. Colonic bacteria convert plant lignans into the mammalian enterolignans enterodiol and enterolactone while flavonoids and hydroxycinnamic acids are broken down to smaller aromatic compounds such as 3-(4-hydroxyphenyl) propionic acid and ferulic acid [8].

The biological significance of these microbial changes is mainly due to the low bioavailability of whole polyphenol molecules by the system. The presence of high molecular weight, extensive glycosylation, and high hydrophilicity limits small intestinal absorption, and the overall implication is that large proportions of the ingested polyphenols are transported to the large intestine, where microbial communities present there impart their catabolic actions [9]. The products are simpler structurally, lower molecular weight, and tend to be more lipophilic than their parents, which makes them more receptive to intestinal absorption and systemic distribution [10]. The person with insufficient bacterial populations to produce urolithin will produce insignificant levels of plasma urolithin even after consuming large amounts of ellagitannin (which explains why food intake data is not a complete and possibly misleading measure of polyphenol bioactivity) [11].

3. Bioavailability and brain relevance

During microbial catabolism in the colon, low-molecular-weight phenolic catabolites are absorbed across the colonic epithelium into the portal circulation. These are then subjected to phase II biotransformation, mainly through sulfation, glucuronidation, and O-methylation in the intestinal mucosa and liver to produce

conjugated forms, which have better aqueous solubility and are carried into the systemic circulation [10]. These conjugates can be measurably expressed in plasma: urolithin A glucuronide, such as urolithin A glucuronide, has been found at nanomolar to low-micromolar concentrations in human plasma after dietary intake of pomegranate products, and ferulic acid and protocatechuic acid have been detected in human plasma and urine after controlled diets [12].

The ability of these circulating metabolites to penetrate the blood–brain barrier (BBB) is crucial to whether they can have direct effects on the central nervous system or not. The BBB is a highly selective interface created by specialized cerebral vascular endothelial cells that express tight junction proteins and is supported by astrocytic endfeet and pericytes. Diffusion across this barrier is generally a process of moderate lipophilicity, low molecular weight (usually less than 400–500 Da), and anti-efflux transporter systems resistance [10]. Carecho et al. conducted detailed physicochemical analysis of low-molecular-weight phenolic metabolites in the frame of BBB penetration, and found compounds such as 3-(4-hydroxyphenyl) propionic acid, ferulic acid, and urolithin isoforms possessing physicochemical properties potentially consistent with passive transcytosis, yet *in silico* [10]. More recently Garay-Mayol et al. showed that urolithins themselves and their phase II conjugates can penetrate an *in vitro* BBB model and have anti-inflammatory effects in human microglial cells- results, which are encouraging in terms of mechanism though are obtained using a simplified cell-based model which does not fully replicate the complexity of the *in vivo* BBB, including active efflux systems [13]. *In vivo* confirmation of CNS penetration by these metabolites at physiologically relevant plasma concentrations in humans is not yet available. These results do indicate, however, that circulating levels of microbial metabolites, and not necessarily dietary precursor intake, may be the more useful variable to determine possible neurological effect, and that plasma or urine levels of metabolites might yield mechanistically better information than dietary intake measures alone [14].

4. Key metabolites and their relevance to cognitive aging

A summary of key gut microbiota–derived polyphenol metabolites, including their dietary precursors, major food sources, blood–brain barrier relevance, and primary mechanisms, is presented in Table 1.

Table 1. Key gut microbiota–derived polyphenol metabolites: precursors, sources, bioavailability, and mechanistic relevance

Precursor class	Major food sources	Key microbial metabolites	BBB relevance	Main mechanisms
Ellagitannins / Ellagic acid	Pomegranates, walnuts, raspberries, strawberries	Urolithins A, B, C, D	UA detected in brain tissue (preclinical); phase II conjugates cross *in vitro* BBB	Mitophagy induction (PINK1/ Parkin); NF-κB ↓; NLRP3 ↓; anti-amyloid; neuroprotection via PI3K
Isoflavones (Daidzein)	Soy, tofu, tempeh, miso	Equol (S-equol)	Moderate lipophilicity; plasma-detectable; likely BBB-permeable	ERβ modulation; anti-inflammatory; synaptic plasticity support; association with frontal lobe cognition (human observational)
Lignans	Flaxseed, sesame, whole grains, legumes	Enterodiol, enterolactone	Detected in CSF; confirmed CNS exposure	ERβ agonism; antioxidant activity; synaptic plasticity; neuroprotection

Flavonoids (Quercetin, Rutin, anthocyanins)	Onions, apples, berries, and tea	3,4-diHPP, phenolic acids, SCFAs	Phenolic acids are plasma-detectable; direct BBB data limited; SCFAs exert indirect effects.	NF-κB / MAPK ↓; microglial anti-inflammatory polarization; gut–brain axis modulation via SCFAs
Tea polyphenols (EGCG and related)	Green, black, and white tea	Gallic acid, pyrogallol, ferulic acid	Ferulic and gallic acid confirmed in CNS (preclinical)	Cholinergic support; BDNF ↑; mitochondrial biogenesis; NF-κB ↓
Stilbenes (Resveratrol)	Red grapes, red wine, berries, peanuts	Dihydroresveratrol, lunularin, piceatannol	Highly variable; some metabolites show improved stability vs. the parent compound.	Sirtuin activation; AMPK pathway; anti-amyloid effects (preclinical); production capacity microbiome-dependent

BBB = blood–brain barrier; CNS = central nervous system; CSF = cerebrospinal fluid; ERβ = oestrogen receptor-β; SCFA = short-chain fatty acid. Unless otherwise stated, mechanisms are supported by in vitro or animal evidence; human confirmation is limited.

4.1. Urolithins

Urolithins are among the most thoroughly investigated gut microbiota–derived polyphenol metabolites in relation to neurological health. Synthesized by bacterial conversion of ellagitannins, they are found as multiple isoforms (urolithin A, B, C, D), with urolithin A (UA) having been best studied [1]. In preclinical models, UA has been demonstrated to cause mitophagy, the autophagic clearance of dysfunctional mitochondria, a mechanism that might be of significance in neurodegeneration, as the mitochondrial dysfunction is a well-established phenotype in the pathology of Alzheimer's disease (AD) and Parkinson's disease. The inquiry is whether these preclinical effects of mitophagy induction can be obtained in plasma levels that can be reached by diet or supplementation in the elderly human organism.

In a cellular model of early AD, Esselun et al. demonstrated that UA normalized mitochondrial membrane potential, reduced reactive oxygen species (ROS) production, and enhanced mitophagy markers through activation of the PINK1/Parkin pathway-findings derived from an in vitro system, which limits direct extrapolation to human disease [15]. Pamoda et al. also demonstrated that UA was capable of decreasing the amyloid-β toxicity of cell-based AD models and suppressing neuroinflammatory signaling, again, offering mechanistic plausibility but not yet clinical evidence [16]. Chen et al. reported in an animal model that urolithin B reduced age-associated cognitive impairment in mice by inhibiting apoptosis through cytochrome C and enhancing neuronal survival using the PI3K signaling pathway; the applicability of the doses used to intact human plasma concentrations should be cautiously considered [17]. Wang et al. conducted a review of urolithins as potential interventions for mild cognitive impairment that showed consistent relationships between UA exposure and cognitive biomarker improvements in preclinical research [12]. In the case of human microglial cells, Madsen et al. demonstrated that UA selectively regulated innate immune defense mechanisms and cellular metabolism compared with nicotinamide riboside, indicating possible direct immunomodulatory actions at the level of brain-resident immune cells [18].

4.2. Equol and mammalian enterolignans

In a set of gut bacteria, such as *Slackia isoflavoniconvertens*, the soy isoflavone daidzein is converted to equol; however, it occurs only in a limited number of adults, approximately 25–60 percent geographically and inter-individually, and it is highly unevenly distributed [19]. The medium lipophilicity of Equol enables its systemic bioavailability and BBB penetration. According to Dominguez-Lopez et al., in a study involving human participants who conducted the observations, noted that the cognitive performance in the frontal lobe

was directly related to elevated levels of microbial phenolic compounds such as equol-related compounds in the urine, which are epidemiologically but not causally correlated with cognitive performance in older adults [20].

Enterolactone and enterodiol, mammalian enterolignans formed by colonic bacteria from the plant lignan precursors, have been found in cerebrospinal fluid, indicating the known exposure of the central nervous system [10]. Their action as estrogen receptor-β agonists might play a role in maintaining synaptic plasticity in the setting of age-related sex hormone losses, but this mechanism needs validation by suitably designed human intervention trials [4].

4.3. Phenolic acids and short-chain fatty acids

Phenolic acids such as ferulic acid, 3, (4-hydroxyphenyl) propionic acid (3, 4-diHPP), protocatechuic acid, and gallic acid are common catabolites of flavonoids and hydroxycinnamic acids in the colon [8]. Ferulic acid has also been observed in brain tissue of rodents after peripheral exposure and shown to prevent amyloid-β aggregation and dampen neuroinflammation in preclinical *in vivo* human models [14]. The controlled clinical trials that can be used to show the translation of these findings to human cognitive outcomes have not been done yet.

Fermentation of polyphenols and dietary fiber results in short-chain fatty acids (SCFA), such as butyrate and propionate, which are now increasingly considered gut-brain axis signaling molecules with anti-inflammatory and epigenetic regulatory functions in the CNS [21]. Liu et al. assessed a set of dietary polyphenol-gut microbiota-SCFA production associations and found two-way effects where microbiota controlled by polyphenol affected cognitive ability, mood, and circadian rhythmicity in human and animal groups [6]. These relations are directional and causal and are the subject of the current study.

5. Neuroinflammation and mechanistic pathways

Neuroinflammation, the ongoing activation of microglia and astrocytes, increased generation of pro-inflammatory cytokines, and impaired neural homeostasis are basic aspects of age-related cognitive decline and neurodegenerative disease [22]. Polyphenol metabolites produced by gut microbiota have been demonstrated to regulate various convergent inflammatory signaling axes, most of which are preclinical (cell-based and animal-based) models; rarely has human evidence demonstrated direct connections between these metabolites and neuroinflammatory endpoints. The pathways listed below are the most coherent mechanistic targets so far found in preclinical literature.

Schematic pathway (Figure 1) from dietary polyphenol intake through gut microbial biotransformation to the generation of circulating metabolites with potential to cross the blood–brain barrier and modulate neuroinflammatory and mitochondrial pathways relevant to cognitive aging.

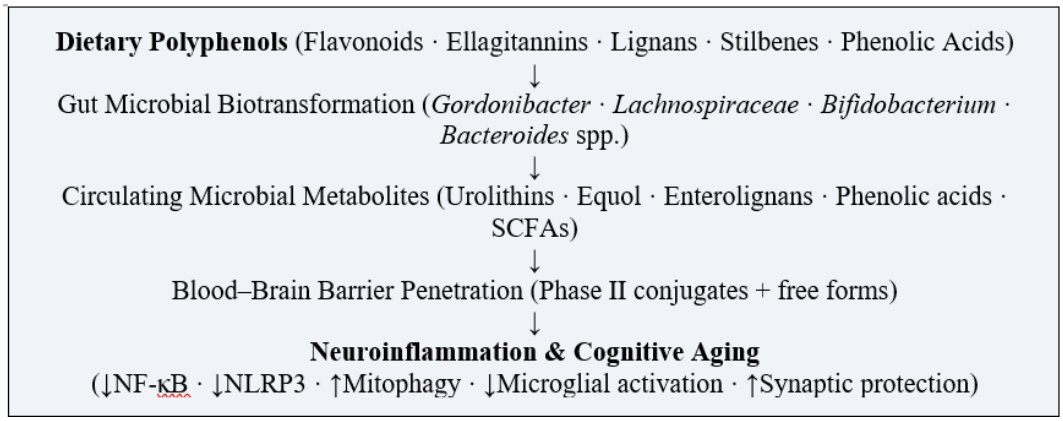

Figure 1. Conceptual framework: From dietary polyphenols to cognitive aging

BBB = blood–brain barrier; NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3 = NLR family pyrin domain-containing 3; SCFA = short-chain fatty acid.

5.1. Microglial activation and NF-κB / MAPK signaling

The main immune effector cells of the CNS is microglia. Persistent peripheral or central stimulation of the immune system, including TNF-alpha, IL-1, and IL-6, plays a role in synaptic dysfunction and neuronal death [23]. In an *in vitro* BBB model, Garay-Mayol et al. showed that urolithins and their phase II conjugates permeated the barrier, inhibited nuclear translocation of NF-kB in stimulated microglial cells, and inhibited expression of inflammatory downstream genes in a stimulus- dependent manner [13]. NF-kB signaling is upregulated by the MAPK cascade, which includes JNK and p38 kinases, and phenolic acids, such as ferulic acid, have demonstrated the ability to suppress the phosphorylation of these signaling intermediates in neuroinflammatory cell models [8]. Sarubbo et al. provide evidence of a multi-polar win of polyphenol metabolites and found microglial polarization of a pro-inflammatory (M1) to a neuroprotective (M2) phenotype as a common mechanism of action, but the applicability of this classification scheme to humans *in vivo* is still an active, controversial topic [24].

5.2. NLRP3 inflammasome regulation

The NLRP3 inflammasome is a multiprotein complex that leads to caspase-1-dependent maturation and release of IL-1 and IL-18, increasing neuroinflammatory processes. A number of microbial metabolites have been shown to inhibit NLRP3 activation in preclinical studies. Urolithin A has been shown to inhibit Mito-NLRP3-related signaling in macrophage and neuronal cell models in part by its mitophagy-activating effects because dysfunctional mitochondria are known NLRP3 activators [21]. A broad review conducted by Rakhra et al. found NLRP3 suppression to be a common response to polyphenol-microbiota-inflammation interactions across several classes of phenolic acids, but it has only limited support *in vivo* [21].

5.3. Mitochondrial dysfunction and mitophagy

Impaired mitophagy, failure to eliminate dysfunctional mitochondria drives accumulation of ROS and release of mitochondrial damage-associated molecular patterns (DAMPs), which in turn activate the NLRP3 inflammasome and perpetuate neuroinflammation. The ability of UA to induce potent mitophagy mediated

by PINK1/Parkin has been confirmed in several in vitro and in vivo experimental systems [15]. Makarov and Korkotian described UA as among the most mechanistically consistent nutritionally active inducers of mitophagy to date, and in Drosophila models, Asthana and Shravage [25,26] have shown that dietary interventions consisting of modulation of mitophagy could change phenotypes in Parkinson's disease, establishing a translational context for the mitophagy interventions.

5.4. Gut–brain axis: Indirect anti-inflammatory effects

Along with BBB-permeable metabolites, polyphenol catabolites could also act on the gut-brain axis in a series of indirect ways. The production of SCFAs by gut microbiota, specifically butyrate, regulates the maturation and activity of microglia by inhibiting histone deacetylase and altering the activity of signaling in the hypothalamic-pituitary axis [4]. Non-absorbed polyphenols have prebiotic-like effects on microbiome composition, selectively increasing anti-inflammatory taxa, including *Bifidobacterium* and *Akkermansia muciniphila*, and decreasing pro-inflammatory ones [27]. Such changes in composition favor the production of neuroprotective metabolites and inhibit gut-generated inflammatory signaling that can circulate throughout the body and affect neuroinflammatory tone [24]. Hong et al. identified the duality of the actions of tea polyphenol metabolites on neurological disorders, determining that both circulating metabolites and microbiome compositional remodeling contribute separately to brain protection, but the relative magnitude of these contributions in humans remains to be determined [8].

6. Precision nutrition implications

The inter-individual difference in the metabolism of dietary exposures to polyphenols is notable and constitutes one of the most important, yet often disregarded, aspects of the field. To be specific, the metabotype used in this review is the reproducible, individual-specific pattern of production of microbial metabolites in response to standardized exposure to polyphenols, not the number of polyphenols consumed per day (polyphenol intake) or the resultant, systemic concentration of the metabolite (circulating metabolite concentration). Iglesias-Aguirre et al. proposed a systematized definition of the concept of polyphenol metabotypes: equol-producing status and urolithin metabotype (metabotype 0, A, or B) were suggested as the most clinically relevant variables for stratification [19]. Patients with a non-equol-producing phenotype or a urolithin metabotype 0 profile (no production of urolithin) might obtain significantly less neuroprotective advantage of polyphenol-rich diets as compared to those possessing the necessary microbial communities [11].

This variability has direct implications for intervention design. Singh et al. conducted a human randomized control trial in which the direct supplementation of urolithin A, bypassing the gut microbial conversion completely, provided consistent plasma concentrations in a heterogeneous adult population, in contrast to the highly heterogeneous plasma concentrations attained following the same dosage of ellagitannin intake alone [11]. This result suggests that in low-conversion microbiomes of individuals, direct metabolite supplementation can be a more efficient approach compared to dietary enrichment of precursors. Jarrin-Orozco et al. found that baseline gut metabotype signatures correlated positively with quality of life in postmenopausal women after polyphenol exposure, in a randomized crossover trial, which suggests that metabotyping is a potentially useful stratification tool to predict intervention responsiveness [5]. Liu et al. defined precision approaches as the bridge between mechanistic discovery and population-level

implementation that they need, which, however, is especially true of the cognitively-targeted application of polyphenol research [28].

7. Limitations and future direction

A number of critical limitations limit the inferences that can be made based on the existing evidence base. Most of the mechanistic results are cell culture or animal-based, and the doses used in the preclinical trials are often higher than those that can be achieved by realistic dietary methods, so it is difficult to extrapolate them to human cognitive aging [24]. Parent polyphenol compounds have been much more extensively researched as compared to the circulating gut microbiota- derived metabolites, which are mechanistically more relevant species, and metabolite-specific human bioavailability data, which is particularly germane to phase II conjugates, are limited [29]. Most crucially, there is no direct human evidence of CNS penetration of these metabolites at nutritionally attainable concentrations, and the neuroinflammatory effects of these metabolites in cell models are not yet validated in human brain tissue or using studies of cerebrospinal fluid biomarkers. A number of structural barriers further help to broaden the translational discrepancy in preclinical mechanistic discoveries and human cognitive outcomes. Firstly, human intervention evidence regarding the polyphenol metabolites and cognitive endpoints is incredibly sparse: most of the existing trials tested surrogate biomarkers instead of validated cognitive outcomes, employed relatively short follow-ups, and were not designed to consider metabotype-stratified reactions. Second, there is a significant lack of certainty about dose equivalence between dietary exposure to polyphenols in a diet and direct supplementation of metabolites; the plasma concentrations that are obtained after food-based interventions are quite diverse and are typically lower than the concentrations used in preclinical mechanistic research. Third, inter-individual differences in gut metabotype, which are influenced by microbiome composition, age, sex, diet history, and host genetics, add a lot of noise to population-level analyses and can confound real treatment effects when analyzed unratified. Lastly, the cognitive outcome measures used in different studies are also heterogeneous, with short screening tools and elaborate neuropsychological batteries, which restrain comparability and preclude meta-analysis synthesis of metabolite-specific data, see **Table 2**.

Table 2. Representative studies on gut microbiota–derived polyphenol metabolites and cognitive or neurological outcomes

Author / Year	Model	Metabolite studied	Main findings	Key limitations
Chen et al., 2021 [17]	Animal (aging mice)	Urolithin B	Improved cognitive deficits; inhibited cytochrome C-mediated apoptosis; promoted neuronal survival via PI3K pathway	Animal model only; doses may exceed dietary relevance; no human cognitive data
Esselun et al., 2021 [15]	Cell (AD model)	Urolithin A	Normalized mitochondrial membrane potential; reduced ROS; enhanced PINK1/Parkin-mediated mitophagy markers in early AD cells	*In vitro* only; dose relevance to physiological plasma concentrations unclear
Madsen et al., 2024 [18]	Human microglial cells (*in vitro*)	Urolithin A	UA differentially regulated innate immune defense pathways and cellular metabolism vs. nicotinamide riboside; potential brain immune modulation	Cell model only; no in vivo CNS confirmation; mechanism not fully elucidated

Garay-Mayol et al., 2025 [13]	*In vitro* (BBB model + microglial cells)	Urolithins + phase II conjugates	Crossed *in vitro* BBB; exerted stimulus-dependent anti-inflammatory effects via NF-κB inhibition in human microglial cells	*In vitro* BBB model; complex metabolite mixture; in vivo BBB penetration not confirmed in humans
Domínguez-López et al., 2024 [20]	Human observational	Urinary phenolic metabolites (broad panel)	Higher urinary microbial phenolic metabolites associated with better frontal lobe cognitive performance scores	Cross-sectional; causality not established; parent compound vs. metabolite contribution not disaggregated
Godos et al., 2023 [29]	Systematic review / meta-analysis	Dietary (poly)phenols (parent compounds)	Consistent inverse association between polyphenol intake and cognitive decline across observational studies	Dietary intake assessed, not circulating metabolites; heterogeneity across studies; causality not inferable
Singh et al., 2021 [11]	Human RCT	Urolithin A (direct supplement)	Direct UA supplementation achieved consistent plasma levels across population regardless of gut microbiome variability; not achievable with ellagitannin diet alone	Short-term; cognitive outcomes not assessed; does not address dietary ellagitannin effects in high-converters
Jarrín-Orozco et al., 2025 [5]	Human RCT crossover	Gut metabolite profiles (metabotyping)	Polyphenol-related gut metabotype signatures positively correlated with quality-of-life outcomes in postmenopausal women	Female population only; quality-of-life measure not cognitive endpoint; generalizability uncertain

AD = Alzheimer's disease; BBB = blood–brain barrier; RCT = randomised controlled trial; ROS = reactive oxygen species; NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells.

The future research priority needs placebo-controlled intervention trials using well-characterized polyphenol metabolites with sensitive cognitive outcome measures; inclusion of baseline metabotyping to examine the different responses of subgroups; longitudinal biomarker studies of metabolite change with respect to cognitive aging; and mechanistic human studies involving neuroimaging or cerebrospinal fluid biomarkers. It will be critically important to establish dose-response between plasma concentrations of metabolites and cognitive outcomes, and standardize biomarker panels across studies to be able to translate the mechanistic evidence to actionable clinical advice.

8. Conclusion

The gut microbiota reshapes dietary polyphenols to produce a chemically distinct group of circulating metabolites, urolithins, equol, enterolignans, phenolic acids, and SCFAs, which are more systemically bioavailable than their dietary precursors and may have neurologically relevant effects, according to current preclinical evidence. Cell-based and animal experiments show that these metabolites have the potential to inhibit the important neuroinflammatory signaling pathways, such as NF-KB, NLRP3, and MAPK pathways, and trigger the mitophagy programs capable of suppressing the mitochondrial dysfunction typical of age-related neurodegeneration. These mechanistic findings are put into epidemiological context by human observational data to support associations between increased metabolite production and optimal cognitive performance [21]. Such associations are yet to be supported by sufficiently powered, metabolite-resolved intervention trials of validated cognitive outcomes in older adults.

Disclosure statement

The authors declare no conflict of interest.

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