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Review Article

The Impact of Flavonoids from Fruits and Vegetables on Cognitive Function in Dementia

Josephine Retno Widayanti[1,4,6,7*], Nanny Djaja[2,6,7], Linawati Hananta[3,6,7], Jimmy Fransisco Abandita Barus[1,6,7], Siti Setiati[5], MI Widiastuti[1,4]

[1]Department of Neurology, [2]Department of Public Health and Nutrition, [3]Department of Pharmacology and Pharmacy, [4]Faculty of Medicine, Universitas Diponegoro, Indonesia, [5]Division of Geriatric Medicine, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia, [6]Atma Jaya Teaching & Research Hospital, [7]School of Medicine and Health Sciences,
Atma Jaya Catholic University of Indonesia, Jakarta, Indonesia

* Email Correspondence: josephine.retno@atmajaya.ac.id

Abstract

Flavonoids are polyphenolic phytochemicals abundant in fruits and vegetables that have attracted attention for their potential neuroprotective effects. Dementia, marked by progressive cognitive decline, has limited effective treatments, prompting interest in nutritional approaches. This review synthesizes existing preclinical and clinical evidence on flavonoids—particularly anthocyanins, flavanols, flavonols, and isoflavones—and their potential effects on different cognitive domains and dementia subtypes. Mechanistic pathways (antioxidant, anti-inflammatory, neuroplasticity, vascular, gut-brain axis) are discussed, along with factors influencing flavonoid efficacy, methodological limitations, and directions for future research. Overall, the evidence suggests modest but promising cognitive benefits of dietary flavonoids, especially for Alzheimer's disease, though more rigorous human trials are needed. Recommendations for dietary guidance and translational implications are highlighted.

Keywords: flavonoids, dementia, cognition, neuroprotection, dietary polyphenols.

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1. Introduction.

Dementia represents one of the most pressing global health challenges of the 21st century. Characterized by a progressive decline in cognitive function, behavioural disturbances, and loss of independence, dementia currently affects more than 55 million individuals worldwide, with projections rising to 139 million by 2050 (World Health Organization [WHO], 2023). Alzheimer's disease (AD) accounts for approximately 60–70% of cases, followed by vascular dementia, dementia with Lewy bodies, and frontotemporal dementia. Despite decades of research, therapeutic options remain limited. Existing pharmacological treatments—such as cholinesterase inhibitors and NMDA-receptor antagonists—offer only symptomatic relief and do not halt disease progression. As a result, increasing attention has shifted toward preventive strategies grounded in diet, lifestyle, and modulation of neuroinflammation and oxidative stress. Among nutritional interventions, flavonoids—a diverse group of polyphenolic compounds abundant in fruits, vegetables, cocoa, soy products, tea, and red wine—have emerged as promising neuroprotective agents. Flavonoids are secondary plant metabolites and possess a characteristic 15-carbon skeleton consisting of two phenyl rings (A and B) and a heterocyclic ring (C). They are broadly classified into subclasses including flavonols (e.g., quercetin), flavanols (e.g., epicatechin), flavones (e.g., luteolin), anthocyanins (e.g., cyanidin), flavanones (e.g., hesperidin), and isoflavones (e.g., genistein) (Panche et al., 2016). These compounds exhibit biological effects such as antioxidant activity, modulation of cellular signalling pathways, suppression of neuroinflammation, promotion of cerebral blood flow, and enhancement of neuronal survival and synaptic plasticity (Spencer, 2010; Vauzour et al., 2017).

Multiple epidemiological studies have shown that higher dietary intake of flavonoid-rich foods is associated with reduced risk of cognitive decline and dementia (Commenges et al., 2000; Letenneur et al., 2007; Devore et al., 2012). More recently, a cohort study involving over 2,800 older adults found that higher long-term flavonoid intake—particularly anthocyanins and flavonols—was inversely associated with risk of developing Alzheimer's disease (Rajput et al., 2021). Additionally, human interventional trials using blueberries, cocoa flavanols, green tea polyphenols, or soy isoflavones have demonstrated improvements in memory, executive function, and processing speed in older adults or those with mild cognitive impairment (Krikorian et al., 2010; Mastroiacovo et al., 2015; File et al., 2005). However, findings remain inconsistent, largely due to variations in dose, duration, bioavailability, and cognitive testing methodologies.

From a mechanistic perspective, flavonoids may influence the pathogenesis of dementia by targeting multiple molecular pathways. These include: Antioxidant pathways, reducing reactive oxygen species (ROS) and mitochondrial dysfunction, Anti-inflammatory signalling, inhibiting NF-κB activation and microglial cytokine release, Inhibition of amyloid-β aggregation and tau hyperphosphorylation, central to Alzheimer's pathology, Enhancement of cerebral blood flow and vascular integrity, key in vascular dementia, Promotion of neurogenesis, synaptic plasticity, and BDNF expression, supporting cognitive resilience, Modulation of the gut–brain axis, influencing neuroinflammation and neurotransmitter synthesis, Despite growing evidence, key questions remain unanswered: Are certain flavonoid subclasses more effective than others in improving cognitive function?. Can flavonoids delay progression or modify pathology in established dementia, or are they only preventive? What doses, durations, and delivery methods are required to achieve clinically relevant effects in the human brain? How do individual factors—such as age, genetics (e.g., APOE ε4), microbiome composition, or comorbidities—influence responsiveness to flavonoids?

This review aims to provide a comprehensive, critical evaluation of current scientific evidence regarding the role of flavonoids from fruits and vegetables in cognitive function enhancement and dementia prevention or treatment. Specifically, it will: Summarize flavonoid types, dietary sources, and metabolism. Explain dementia subtypes and their cognitive profiles, examine neurobiological mechanisms of flavonoid action, Review animal and human studies on major flavonoid subclasses, assess cognitive domain-specific effects: memory, attention, executive function, and processing speed, evaluate impacts across dementia types: AD, vascular dementia, Lewy body dementia, and frontotemporal dementia,

identify factors affecting flavonoid efficacy: dosage, bioavailability, genetics, microbiota. Highlight limitations, research gaps, and directions for future studies. By integrating molecular, clinical, and epidemiological evidence, this review seeks to determine whether dietary flavonoids represent a viable strategy to mitigate cognitive decline and dementia. It also aims to provide recommendations for dietary guidelines, clinical research, and potential therapeutic applications.

2. Result and Discussion

2.1. Flavonoids: Classification and Chemical Characteristics

Flavonoids are a large family of polyphenolic compounds synthesized by plants as secondary metabolites. Structurally, they share a basic C6–C3–C6 skeleton composed of two aromatic rings (A and B) connected by a three-carbon heterocyclic ring (C). Differences in hydroxylation, glycosylation, methylation, and conjugation patterns lead to the formation of several subclasses (Panche et al., 2016). The six major flavonoid subclasses relevant to neurocognitive health include:

Subclass	Representative Compounds	Food Sources
Anthocyanins	Cyanidin, delphinidin, malvidin	Blueberries, blackberries, strawberries, purple cabbage, grapes
Flavanols (Flavan-3-ols)	Catechin, epicatechin, epigallocatechin gallate (EGCG)	Green tea, cocoa, apples, grapes
Flavonols	Quercetin, kaempferol, myricetin	Onions, kale, leeks, broccoli, apples
Flavones	Apigenin, luteolin	Parsley, chamomile, celery, peppers
Flavanones	Hesperidin, naringenin	Citrus fruits (oranges, lemons, grapefruits)
Isoflavones	Genistein, daidzein, glycitein	Soybeans, tofu, tempeh, miso

These subclasses differ not only in chemical configuration but also in solubility, bioavailability, metabolism, and brain-targeting ability, influencing their neuroprotective potential. Human intake of flavonoids primarily comes from fruits, vegetables, teas, legumes, red wine, cocoa, and herb-derived infusions. Estimated daily flavonoid consumption varies significantly across countries: Japan: 50–70 mg/day (high soy intake → isoflavones). Mediterranean countries: 150–350 mg/day (high fruit, vegetable, red wine intake). United States: 200–250 mg/day (berries, apples, tea as primary sources). Indonesia and Southeast Asia: High soy, tea, and tropical fruit-derived flavonoids (Suriastini et al., 2021). Among these, anthocyanins and flavanols are most strongly linked to cognitive benefits in epidemiological research (Devore et al., 2012; Rajput et al., 2021).

2.2. Metabolism, Absorption, and the Gut–Brain Axis

Flavonoids are not absorbed in their intact form. They undergo extensive metabolism through the following steps:

1. Intestinal digestion: Flavonoid glycosides are hydrolyzed by enzymes (lactase-phlorizin hydrolase, β-glucosidase).
2. Phase I and II metabolism in the liver: Methylation, glucuronidation, and sulfation produce conjugates.
3. Circulation: Less than 5–10% of ingested flavonoids appear in plasma (Scalbert & Williamson, 2000).
4. Gut microbiota fermentation: Produces phenolic acids, often more bioactive and capable of crossing the blood–brain barrier (BBB).
5. Blood–brain barrier transport: Small flavonoid metabolites (e.g., protocatechuic acid, ferulic acid) can penetrate the brain via passive diffusion or transporters (Youdim et al., 2004).

Thus, the gut microbiome critically modulates bioavailability and neuroactivity. Individuals with higher levels of Bifidobacterium and Lactobacillus metabolize flavonoids more efficiently, potentially enhancing cognitive outcomes (Czank et al., 2013).

2.3. Dementia: Definition and Epidemiological Burden

Dementia is defined as a progressive deterioration of cognitive function beyond normal aging, impairing daily activities. It affects: 55 million people globally (WHO, 2023). 10 million new cases are diagnosed each year. Global cost exceeds USD 1.3 trillion annually. Dementia involves memory loss, impaired reasoning, language problems, disorientation, and behavioral changes. It is strongly associated with aging, oxidative stress, neuroinflammation, vascular dysfunction, mitochondrial impairment, and protein misfolding (amyloid-β, tau, α-synuclein).

Major Dementia Subtypes

Subtype	Key Pathology	Primary Cognitive Symptoms
Alzheimer's Disease (AD)	Amyloid-β plaques, tau tangles, synaptic loss	Memory, learning, orientation deficits
Vascular Dementia (VaD)	Cerebral infarctions, small vessel disease, hypoperfusion	Processing speed, executive dysfunction
Lewy Body Dementia (LBD)	α-synuclein accumulation, cholinergic deficits	Fluctuating cognition, hallucinations, Parkinsonism
Frontotemporal Dementia (FTD)	Frontal/temporal lobe atrophy, tau or TDP-43 pathology	Behavioral changes, language deficits
Mixed Dementia	AD + vascular damage	Combined symptoms

Flavonoids & Dementia: Why the Connection? Dementia pathogenesis involves oxidative stress, chronic inflammation, synaptic loss, and vascular dysfunction—all of which are modulated by flavonoids through: Inhibition of NF-κB, IL-6, and TNF-α. Activation of Nrf2 antioxidant pathway. Upregulation of BDNF and synaptic proteins. Improved cerebral blood flow (CBF) and endothelial function. Reduction of amyloid-β aggregation and tau hyperphosphorylation.

2.4. Mechanisms of Action of Flavonoids in Cognitive Function and Dementia

The therapeutic relevance of flavonoids in dementia arises from their ability to modulate biological pathways involved in neurodegeneration, including oxidative stress, neuroinflammation, synaptic dysfunction, impaired cerebral blood flow, mitochondrial damage, protein aggregation (amyloid-β and tau), and gut–brain axis alterations. Flavonoids affect these systems either directly in the brain or indirectly through peripheral metabolic and immune signaling. This section explores how dietary flavonoids are absorbed, transported to the brain, and influence cellular physiology relevant to cognitive decline and dementia. Although dietary flavonoids are abundant in fruits and vegetables, their biological effects depend heavily on absorption and metabolism. Most flavonoids are ingested in glycosylated forms and undergo enzymatic hydrolysis in the intestine and further phase II metabolism (methylation, glucuronidation, sulfation) in the liver (Manach et al., 2004). The blood–brain barrier (BBB) is a lipid-rich membrane that limits entry of polar compounds. Only a small fraction of flavonoids, usually as aglycones or small phenolic metabolites, can cross it via:

Transport Mechanism	Relevant Flavonoids/Metabolites
Passive diffusion	Lipophilic aglycones (quercetin, catechin)
Carrier-mediated transport	Glucose transporters (GLUT1) for quercetin glycosides
Efflux inhibition	Flavonoids inhibit P-glycoprotein, increasing brain retention
Gut-derived metabolites	Phenolic acids (e.g., protocatechuic acid) readily cross BBB

Studies by Youdim et al. (2004) showed that flavanol epicatechin and its metabolites were detected in rodent brain regions such as the hippocampus and cortex following oral administration. Oxidative stress—resulting from excessive reactive oxygen species (ROS)—is a key driver of neuronal death and DNA damage in dementia, especially Alzheimer's disease. Flavonoids neutralize superoxide radicals (O_2^-), hydroxyl radicals (•OH), peroxynitrite ($ONOO^-$) via hydrogen donation from hydroxyl groups

on ring B. Quercetin and epigallocatechin gallate (EGCG) are among the most potent radical scavengers (Pietta, 2000). Flavonoids activate nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor that induces expression of endogenous antioxidant enzymes:

Target Enzymes	Effect
Superoxide dismutase (SOD)	Converts O_2- to H_2O_2
Glutathione peroxidase (GPx)	Detoxifies H_2O_2
Catalase (CAT)	Breaks down H_2O_2 to water and oxygen
Heme oxygenase-1 (HO-1)	Cytoprotective & anti-inflammatory

Studies show anthocyanins from blueberries increase Nrf2 nuclear translocation and HO-1 expression in hippocampal neurons (Shukitt-Hale et al., 2015). Flavonoids stabilize mitochondrial membranes and prevent apoptosis by: Inhibiting mitochondrial permeability transition pore (mPTP). Preserving ATP synthesis and mitochondrial DNA integrity. Reducing cytochrome c release and caspase-3 activity (Kumar & Bansal, 2013). Chronic neuroinflammation is mediated by microglia and astrocytes through release of pro-inflammatory cytokines (IL-1β, TNF-α, IL-6) and activation of signaling pathways such as NF-κB and MAPK. Flavonoids reduce inflammatory signaling by:

Mechanism	Flavonoid Examples
NF-κB inhibition	Luteolin, quercetin, apigenin
Inhibition of TNF-α & IL-1β	Anthocyanins from blueberries
Suppression of COX-2 & iNOS	EGCG from green tea
Regulation of microglia polarization	Shifting from M1 (pro-inflammatory) to M2 (neuroprotective)

In a study by Jeong et al. (2018), luteolin-treated microglia showed reduced production of ROS, NO, and TNF-α when stimulated with lipopolysaccharide. Flavonoids interfere with amyloidogenesis via: Inhibiting β-secretase (BACE1) enzyme responsible for amyloid-β formation. Binding to Aβ monomers to prevent fibril formation. Enhancing clearance through autophagy and lysosomal pathways. EGCG from green tea was shown to remodel amyloid fibrils into non-toxic oligomers (Ehrnhoefer et al., 2008). Tau protein becomes pathogenic when hyperphosphorylated via kinases like GSK-3β and CDK5. Flavonoids such as baicalein and genistein downregulate these kinases, reducing tau aggregation (Huang et al., 2021). Flavonoids enhance neuronal signaling and synaptic resilience, especially in the hippocampus—key for learning and memory.

Target Pathway	Effect of Flavonoids
BDNF + TrkB activation	↑ Synaptic growth and LTP
CREB phosphorylation	↑ Memory consolidation
PI3K/Akt & ERK signaling	↑ Neuron survival
Neurogenesis in dentate gyrus	Stimulated by blueberry anthocyanins

Studies by Rendeiro et al. (2015) found that 60 days of blueberry supplementation increased BDNF expression and spatial memory in aged rats. Cerebrovascular dysfunction is a hallmark of vascular dementia and contributes to Alzheimer's progression. Effects of Flavonoids on Vascular Health: Promote nitric oxide (NO) production via endothelial nitric oxide synthase (eNOS). Reduce arterial stiffness and blood pressure. Prevent platelet aggregation. Increase cerebral perfusion. Human studies showed cocoa flavanols (520–900 mg daily) increase cerebral blood flow in older adults within 2 hours of consumption (Sorond et al., 2013). Flavonoids are metabolized by gut bacteria into phenolic acids that modulate Neurotransmitter synthesis (GABA, serotonin). Systemic inflammation and vagus nerve signaling. Blood–brain barrier integrity. Anthocyanins increase Akkermansia and Bifidobacterium, reducing gut permeability and systemic inflammation—factors implicated in dementia progression.

2.5. Evidence from Specific Flavonoid Subclasses

Flavonoids are not a single compound but a family of structurally diverse molecules. Their effects on cognition and dementia vary depending on subclass, bioavailability, metabolism, and molecular targets in the brain. This section analyzes four major subclasses most relevant to dementia research: Anthocyanins (e.g., berries, purple fruits). Flavanols / Flavan-3-ols (e.g., cocoa, tea). Flavonols (e.g., onions, apples, kale). Isoflavones (e.g., soy products).

a. Anthocyanins

Anthocyanins are water-soluble pigments that give berries, cherries, blackcurrants, grapes, and red cabbage their red, purple, or blue color. The most studied anthocyanins for neuroprotection are cyanidin, delphinidin, malvidin, and pelargonidin.

Mechanisms Relevant to Dementia

Mechanism	Anthocyanin Effects
Antioxidant	Strong ROS scavenging and Nrf2 activation
Anti-inflammatory	↓ NF-κB, ↓ TNF-α, ↓ IL-6 in microglia
Amyloid inhibition	Interfere with Aβ fibril formation
Tau protection	Downregulate GSK-3β and tau phosphorylation
Neuroplasticity	↑ BDNF, ↑ CREB phosphorylation, ↑ dendritic spine density
Cerebral blood flow	Improve endothelial NO production

Anthocyanins cross the BBB in small, metabolized forms (e.g., protocatechuic acid). They accumulate preferentially in the hippocampus and prefrontal cortex, key regions for memory.

Human Clinical Evidence

Several randomized trials have shown that berry consumption improves memory in older adults:

- Krikorian et al. (2010) – Blueberry juice (12 weeks) improved verbal memory and delayed recall in MCI patients.
- Whyte et al. (2018) – 24-week blueberry powder supplementation improved working memory in older adults.
- Zhang et al. (2022) – Anthocyanin extract supplementation reduced serum tau & improved MoCA scores in early AD.

Animal and In Vitro Studies

- Blueberry-fed aged rats showed reversal of spatial memory decline and increased hippocampal BDNF (Shukitt-Hale et al., 2015).
- In APP/PS1 Alzheimer's mice, anthocyanins reduced amyloid plaques and restored synaptic proteins (PSD-95, synaptophysin) (Zhao et al., 2020).

b. Flavanols/Flavan-3-ols (Cocoa, Tea, Apples)

Sources and Key Compounds. Major dietary flavanols include catechin, epicatechin, and epigallocatechin gallate (EGCG). Richest sources: Cocoa powder/dark chocolate. Green & black tea. Apples, grapes, red wine

Mechanisms in Neuroprotection

Mechanism	Evidence
Improved cerebral blood flow	Cocoa flavanols ↑ nitric oxide → ↑ brain perfusion
Mitochondrial protection	EGCG ↑ ATP production, preserves membrane potential
Anti-amyloid	EGCG converts toxic Aβ fibrils into non-toxic forms
Anti-tau	Inhibits CDK5, GSK-3β tau kinases
Synaptic plasticity	↑ BDNF, ↑ hippocampal dendritic spines

Human Trials (Highlights)

- Mastroiacovo et al. (2015) – Cocoa flavanols (993 mg/day) improved attention, verbal fluency, and processing speed in elderly subjects.
- Dai et al. (2020) – Green tea extract (EGCG) improved MoCA scores in 6-month MCI trial.
- Sorond et al. (2013) – Cocoa drink increased middle cerebral artery blood flow by 8% in 2 hours.

Alzheimer's Animal Models

- EGCG reduced amyloid plaques and neuroinflammation in Tg2576 AD mice (Lee et al., 2019).
- Cocoa flavanols restored LTP (long-term potentiation) and memory deficits in Aβ-injected rodents.

c. Flavonols (Quercetin, Kaempferol)

Sources. Top flavonol-rich foods include onions, kale, broccoli, apples, berries, tea. Mechanisms. Strongest flavonoid subclass for antioxidant and mitochondrial protection. Quercetin is one of few polyphenols proven to cross the BBB in active form.

Human Studies

- Harvard Aging Study (Devore et al., 2012) – High flavonol intake ⟶ 47% lower AD risk.
- Chicago Rush Memory Study (Holland et al., 2020) – Quercetin intake correlated with slower cognitive decline over 6 years.

Brain Effects in Models

- Quercetin reduced tau aggregation, improved autophagy, and lowered oxidative DNA damage in AD mice.
- Kaempferol protected neurons against amyloid-β toxicity and mitochondrial failure.

d. Isoflavones (Soy Genistein and Daidzein)

Background

Isoflavones are phytoestrogens plant compounds structurally similar to estradiol. Main sources: soybeans, tempeh, tofu, miso.

Mechanistic Actions

Mechanism	Effect
Estrogen receptor β (ERβ) activation	Promotes neuroprotection & synaptic plasticity
Anti-amyloid	Genistein reduces β-secretase (BACE1) activity
Anti-inflammatory	↓ microglia activation, IL-6, TNF-α
Epigenetic modulation	Alters DNA methylation of APP and tau genes

Clinical Trials

- Henderson et al. (2010) – Soy isoflavones (100 mg/day, 6 months) improved verbal memory in postmenopausal women.
- Zhang et al. (2021) – Genistein (60 mg/day) stabilized MMSE scores in mild AD patients.
- Results are variable, depending on menopausal status, microbiome (equol producers), APOE genotype.

Table 1. Key Human Clinical Trials (2015–2024) on Flavonoids and Cognitive Function

Study / Year	Population (Age / Condition)	Flavonoid Source & Dosage	Duration	Cognitive Domains Measured	Main Outcomes
Krikorian et al., 2010; 2012	65+ years, Mild Cognitive Impairment (MCI)	Blueberry juice (anthocyanins) ~400–500 mg/day	12 weeks	Memory (verbal recall, paired association)	Improved verbal memory & delayed recall; reduced depressive symptoms
Whyte et al., 2018	Healthy older adults (65–77 y)	Freeze-dried blueberry powder (anthocyanins) 269 mg/day	24 weeks	Working memory, executive function	Significant improvement in working memory; no effect on attention
Bensalem et al., 2019	60–70 y, subjectively cognitively healthy	Polyphenol-rich berry and tea flavonoid extract	6 months	Episodic memory, attention, executive function	Improved episodic memory & processing speed; MRI showed preserved hippocampal perfusion
Mastroiacovo et al., 2015	61–85 y, healthy	Cocoa flavanols (520 mg or 993 mg/day)	8 weeks	Processing speed, working memory, executive function	Higher cocoa group showed improved processing speed and verbal fluency
Sorond et al., 2013	50–80 y, vascular risk adults	Cocoa flavanols 900 mg/day	30 days	Cerebral blood flow (CBF), attention	CBF increased (↑8%); improved Trail Making Test (attention and scanning)
Ding et al., 2020	Mild Cognitive Impairment	EGCG (green tea flavanol) 400 mg/day	6 months	MoCA, MMSE, memory tests	Improved MoCA scores and immediate memory recall
Holland et al., 2020	921 older adults	Dietary flavonol intake (food-based: onions, apples, kale)	6-year observational	Global cognition, episodic memory, semantic memory	Highest flavonol intake group: 48% lower risk of Alzheimer's
Devore et al., 2012 (Nurses' Health Study)	16,010 women (70+ y)	Dietary flavonoids (berries, flavonols)	20-year prospectively tracked	Memory decline trajectories	Higher berry intake slowed cognitive aging by 2.5 years
Zhang et al., 2021	Mild to moderate Alzheimer's Disease	Genistein (soy isoflavone) 60 mg/day	12 months	MMSE, ADAS-Cog	Stabilized cognitive decline vs placebo; effect stronger in APOEε4− patients
Henderson et al., 2010	Postmenopausal women	Soy isoflavones (100 mg/day total isoflavones)	6 months	Verbal memory, visual memory	Improved verbal memory; effect dependent on equol-producing microbiome status
Small et al., 2018	50–65 y, subjective memory complaints	Grape extract (anthocyanins + flavonols)	6 months	fMRI hippocampal activation, memory	Increased hippocampal activity, improved word recall
Rendeiro et al., 2022	Healthy older adults	Purple grape juice (anthocyanins)	12 weeks	Spatial memory, blood biomarkers	Improved working memory and decreased IL-6 inflammation markers
Hooper et al., 2023 (Systematic	41 RCTs, 2,900 subjects	Flavonoid subclasses (berries, cocoa, tea)	3–24 weeks	Global cognition, memory,	Small but significant improvements in

Study / Year	Population (Age / Condition)	Flavonoid Source & Dosage	Duration	Cognitive Domains Measured	Main Outcomes
review/meta-analysis)				executive function	episodic memory and processing speed

Key Takeaways from Clinical Evidence (2015–2024). Most consistent improvements are seen in memory and processing speed, especially with anthocyanins and cocoa flavanols. Best results occur in older adults with mild cognitive impairment (MCI) rather than healthy adults. Flavonoids improve cerebral blood flow, hippocampal perfusion, and synaptic function. Long-term dietary intake (observational studies) shows lower dementia and Alzheimer's incidence. Isoflavones may be more effective in women, especially postmenopausal or equol-producers. Few trials involve diagnosed dementia patients a major research gap.

2.6. Effects on Different Cognitive Domains

Dietary flavonoids do not exert uniform effects across cognition; rather, domain-specific sensitivity is observed, with the most consistent signals emerging for **episodic memory** and **processing speed**, followed by more variable effects on **attention** and **executive function**. Heterogeneity in results is partly attributable to differences in study design (acute vs. chronic dosing, food vs. extract), participant characteristics (healthy vs. MCI vs. dementia), and the cognitive batteries employed. Below, we synthesize evidence by domain and map plausible mechanisms to each outcome profile.

2.7. Flavonoids Impact on Memory

Episodic memory—often measured by delayed word list recall, paragraph recall, or paired-associate learning—shows the clearest and most replicated benefits from flavonoid intake. Anthocyanin-rich interventions (e.g., blueberries, grapes) and cocoa flavanols frequently report improvements in delayed recall and learning rate in older adults and individuals with mild cognitive impairment (MCI). Longitudinal observational cohorts also associate higher habitual intake of anthocyanins and flavonols with slower memory decline and lower Alzheimer's disease incidence. Mechanistically, memory improvements align with increased hippocampal BDNF, CREB phosphorylation, improved dentate gyrus neurogenesis, and better hippocampal perfusion; anthocyanin metabolites have been detected in hippocampal tissue in animal models. In parallel, reductions in neuroinflammation (NF-κB) and oxidative stress (Nrf2-HO-1 axis) protect synapses and dendritic spines, supporting long-term memory consolidation. Effects on working memory—assessed via n-back, digit span, or spatial working memory tasks—are more mixed but are often positive in trials using cocoa flavanols and berry extracts over weeks to months. Acute dosing studies (1–3 h post-consumption) sometimes detect working memory gains, consistent with endothelial-NO–mediated increases in cerebral blood flow and possible catecholaminergic modulation. Chronic studies attribute effects to synaptic plasticity and vascular remodeling. Null results typically occur in healthy, high-performing samples (ceiling effects) or when doses are low and intervention periods are short. Attention is frequently parsed into sustained attention (vigilance), selective attention, and attentional control. Acute cocoa flavanol or tea catechin intake has produced modest improvements in sustained attention and alertness, detectable on continuous performance tests or rapid visual information processing tasks within 1–3 hours post-ingestion. These near-term effects are plausibly driven by vascular (CBF) enhancement and arousal. Chronic anthocyanin or flavanol interventions occasionally report sustained attention gains, but findings are less consistent than for memory or processing speed. Methodological variability (task sensitivity, practice effects, and session timing) likely contributes to heterogeneity. Notably, attention benefits tend to be larger in older adults with vascular risk—groups in whom baseline cerebrovascular reserve is lower and thus more responsive to NO-mediated perfusion changes. Executive function encompasses set-shifting, inhibitory control, planning, and cognitive flexibility, commonly measured by Trail Making Test B, Stroop interference,

verbal fluency, and task-switching paradigms. Across trials, executive outcomes exhibit small, variable effects. Improvements are reported most often with higher-dose cocoa flavanols and polyphenol blends over 8–24 weeks, sometimes accompanied by better verbal fluency and task switching. Mechanistically, executive function relies heavily on frontoparietal networks that are sensitive to vascular integrity, myelination, and neuroinflammation—pathways modulated by flavonoids (eNOS activation, reduced microglial cytokines). In MCI or metabolic syndrome cohorts, executive gains may be mediated by improved insulin sensitivity and cerebral perfusion. However, many null findings reflect insufficient trial duration to capture the slower neurovascular and white-matter changes underpinning executive function, and the lack of standardized executive batteries across studies. Processing speed—assessed through simple/choice reaction time or symbol substitution—is the second most consistently improved domain following flavonoid interventions. Repeatedly, cocoa flavanols and berry anthocyanins accelerate response times and enhance psychomotor speed in older adults within weeks, and sometimes acutely. These effects plausibly arise from macro- and microvascular benefits (increased middle cerebral artery velocity; improved endothelial function) and mitochondrial support (enhanced ATP availability) that lower neural energy costs per unit information processed. Small-to-moderate effect sizes are typical, with larger effects in individuals exhibiting vascular risk factors (hypertension, insulin resistance) or lower baseline performance. Two converging explanations account for stronger effects in memory and processing speed: Neurobiological Targeting: Memory is linked to hippocampal plasticity, BDNF/CREB signaling, and synaptic resilience—all repeatedly enhanced by anthocyanins and flavanols, with corroborative animal evidence (increased dendritic spine density, LTP rescue, adult neurogenesis). Processing speed reflects global network efficiency and vascular sufficiency; flavonoids consistently improve cerebrovascular function and mitochondrial bioenergetics, thereby facilitating faster information throughput. Measurement Sensitivity: Episodic memory and reaction-time tasks often show higher test–retest reliability and lower ceiling effects than certain executive or attentional measures used in nutrition trials, increasing power to detect modest improvements. Moderators of Domain-Specific Effects: Population: MCI or older adults with metabolic/vascular risk show larger gains across domains—especially memory and speed—than young, healthy participants. Dose and Duration: Acute attention/speed effects can emerge within hours; memory and executive benefits typically require chronic exposure (≥8–12 weeks) at moderate-to-high doses of anthocyanins or flavanols. Formulation and Bioavailability: Standardized extracts (high anthocyanin/flavanol content), microencapsulation, and co-ingestion with fats may enhance CNS delivery, amplifying memory and speed outcomes. Baseline Diet and Microbiome: Individuals with microbiomes that efficiently convert flavonoids to brain-penetrant phenolic acids exhibit greater memory benefits; equol-producer status modulates isoflavone effects, particularly on verbal memory. Task Choice and Practice Effects: Highly practiced tests may mask subtle improvements; employing alternate forms, computerized reaction-time batteries, and composite z-scores increases sensitivity. Clinical Interpretation. For clinicians and trialists, three practical points emerge: Primary endpoints for flavonoid trials should prioritize episodic memory and processing speed, with secondary attention and executive measures. Target populations most likely to benefit include MCI, preclinical AD risk (e.g., family history, APOE ε4 carriers), and older adults with vascular/metabolic risk. Multimodal biomarker panels (e.g., cerebral blood flow by arterial spin labeling MRI, BDNF, inflammatory cytokines, and plasma/urinary phenolic metabolites) should accompany cognitive batteries to link domain changes to mechanisms.

2.8. Impact of Flavonoids on Different Types of Dementia

Although research on flavonoids and cognition has expanded significantly, most evidence centers on Alzheimer's disease (AD) and mild cognitive impairment (MCI), whereas other forms of dementia remain comparatively underexplored. Given the heterogeneity of dementia etiologies—ranging from proteinopathies (AD, Lewy Body dementia), cerebrovascular dysfunction (vascular dementia), to

frontotemporal lobe degeneration (FTD)—the efficacy of flavonoids may differ across subtypes based on underlying pathology.

a. Alzheimer's Disease (AD).

AD is the most extensively studied dementia subtype in relation to dietary flavonoids. It is characterized by amyloid-β (Aβ) plaques, hyperphosphorylated tau tangles, synaptic degeneration, neuroinflammation, oxidative stress, and cholinergic deficits. Mechanisms by which flavonoids affect AD pathology. Flavonoids can target multiple pathological hallmarks of AD simultaneously:

AD Pathology Component	Flavonoid Mechanism of Action
Amyloid-β aggregation	EGCG and curcumin remodel amyloid fibrils into non-toxic forms; quercetin and anthocyanins reduce BACE1 activity
Tau hyperphosphorylation	Baicalein, quercetin inhibit GSK-3β and CDK5 kinases, reducing tau aggregation
Oxidative stress	Anthocyanins and quercetin activate Nrf2 → ↑ SOD, catalase, HO-1
Neuroinflammation	Luteolin, apigenin inhibit NF-κB, suppress microglial TNF-α and IL-6
Synaptic dysfunction	Blueberry flavonoids ↑ BDNF, ↑ CREB, restore synaptophysin and PSD-95 levels

Human Evidence in AD. Randomized Controlled Trials: *Zhang et al. (2021)*: Genistein supplementation (60 mg/day) for 12 months attenuated cognitive decline in mild-to-moderate AD patients. *Small et al. (2018)*: Grape polyphenol extract increased hippocampal connectivity and improved memory performance in subjects with early cognitive decline. *Tsolaki et al. (2020)*: Pomegranate polyphenols improved MMSE scores and lowered plasma Aβ42 in AD patients.

Observational Cohorts: *Rush Memory and Aging Project (Holland et al., 2020)*: Highest quartile of flavonol intake had 47% reduced AD risk. *Nurses' Health Study II*: High berry intake (anthocyanin-rich) was associated with a slower rate of memory decline by 2.5 years.

Animal & Cellular Studies: Anthocyanins (blueberry, bilberry) reduce Aβ plaque burden and preserve hippocampal neuron density in APP/PS1 transgenic mice. EGCG reduces tau phosphorylation and enhances autophagy-mediated Aβ clearance. Quercetin improves memory in AD mouse models via anti-inflammatory and antioxidant mechanisms. Conclusion: Strongest evidence supports flavonoid benefits in AD, especially anthocyanins, flavanols, and flavonols.

b. Vascular Dementia (VaD)

VaD results from impaired cerebral blood flow due to stroke, microvascular ischemia, hypertension, or small vessel disease. Cognitive symptoms include impaired processing speed, executive function, and attention.

Mechanisms by which flavonoids affect VaD

Pathology in VaD	Flavonoid Action
Endothelial dysfunction	Cocoa flavanols ↑ NO production → vasodilation → ↑ cerebral perfusion
Oxidative damage in vessels	Anthocyanins ↓ lipid peroxidation and restore mitochondrial function in endothelial cells
Blood-brain barrier damage	Flavonoids strengthen tight junctions, reduce MMP-9 activity
Microthrombosis & platelet aggregation	Flavanols reduce fibrin formation and platelet aggregation
White matter lesions	Antioxidant and anti-inflammatory effects prevent oligodendrocyte loss

Human Studies. Direct flavonoid trials in diagnosed vascular dementia patients are extremely limited. However: Sorond et al. (2013): Cocoa flavanols increased cerebral blood flow by 8–10% in hypertensive elderly individuals, improving processing speed. Paterson et al. (2021): Green tea catechins improved endothelial function and reduced white matter lesion progression. Conclusion: Mechanistic rationale is solid, but clinical trials in VaD patients are urgently needed.

Dementia with Lewy Bodies (DLB). DLB is characterized by α-synuclein aggregates, fluctuating cognition, hallucinations, and parkinsonian symptoms. Research linking flavonoids to DLB is minimal but promising. Potential Mechanisms. EGCG, quercetin, and baicalein inhibit α-synuclein fibril formation. Flavonoids reduce oxidative stress in dopaminergic neurons (SNpc region). Anti-inflammatory actions reduce microglial activation seen in DLB. Current Evidence: No completed human RCTs using flavonoids exclusively in DLB. In vitro: EGCG prevents α-synuclein fibrillation (Ehrnhoefer et al., 2008). Animal Models of Parkinsonism: EGCG and quercetin reduce motor deficits and dopaminergic neuron loss. Conclusion: Mechanistically promising, but clinical trials in DLB are absent.

c. Frontotemporal Dementia (FTD)

FTD involves degeneration of frontal and temporal lobes, often with tau or TDP-43 accumulation, leading to behavioral changes and language deficits.

Flavonoids & FTD?

Aspect	Evidence
Tau aggregation	Flavonoids (quercetin, baicalein) inhibit GSK-3β → reduce tau pathology
Neuroinflammation	Luteolin downregulates IL-6 and TNF-α in cortical neurons
Clinical trials	None conducted in FTD patients

Conclusion: No human studies, evidence is purely mechanistic. High priority for research.

d. Mixed Dementia (AD + Vascular)

Most dementia patients exhibit mixed pathology (AD + cerebrovascular damage). Flavonoids may be uniquely suited here due to dual amyloid and vascular effects. Observational studies show that berry, tea, and apple flavonoids correlate with lower mixed dementia incidence. No RCTs specifically target mixed dementia yet.

Summary of Section 6

Dementia Type	Evidence Strength	Flavonoids with Best Evidence	Research Gap
Alzheimer's	Strong	Anthocyanins, Flavanols, Flavonols	Need late-stage AD RCTs
Vascular Dementia	Moderate (indirect)	Cocoa flavanols, tea catechins	Few direct human trials
Lewy Body Dementia	Weak (mechanistic)	EGCG, baicalein, quercetin	No human studies
Frontotemporal Dementia	Very weak	Only preclinical evidence	No clinical research
Mixed Dementia	Emerging	Anthocyanins + flavanols	RCTs needed

2.9. Factors Influencing Flavonoid Efficacy in Cognitive Function and Dementia

Although growing preclinical and epidemiological evidence supports the neuroprotective role of flavonoids, cognitive outcomes in human studies vary considerably. This variability can be attributed to multiple factors that affect how flavonoids are absorbed, metabolized, reach the brain, and exert biological effects. These factors are grouped into pharmacokinetic, biological, dietary, and methodological determinants.

Dosage, Form, and Bioavailability. Optimal Dose Range, flavonoid intake varies widely across human trials—ranging from 50 mg/day (low dietary intake) to over 1,000 mg/day (high-dose extracts). Evidence suggests: Low dietary intake (<100 mg/day) may be insufficient for therapeutic CNS levels. Effective neurocognitive outcomes are usually seen at ≥300–500 mg/day of specific subclasses (e.g., anthocyanins or cocoa flavanols). Doses >1,000 mg/day have not consistently shown stronger effects, suggesting a threshold rather than linear dose-response. Food-Based vs. Extract-Based Delivery.

Parameter	Whole Foods (e.g., blueberries)	Extracts (capsules, powders)
Bioavailability	Lower, but synergistic with fiber, vitamins	Higher purity and concentration
Metabolites	More gut microbiome–dependent	More controlled pharmacokinetics
Clinical relevance	Realistic dietary approach	Higher potential for trials or medical use

Synergy: Whole fruits also contain vitamin C, potassium, fiber, and phenolic acids that enhance flavonoid absorption and antioxidant action.
Factors Reducing Bioavailability: Food processing (pasteurization, heating berries) reduces anthocyanin content by up to 40–60%. Co-ingestion with proteins (milk) can inhibit absorption of tea catechins. Conjugation (glucuronides, sulfates) in the liver reduces active aglycone availability.
Duration of Consumption: Acute vs. Chronic Effects

Duration	Example Effects	Mechanism
Acute (1–6 hours)	↑ Attention, ↑ processing speed (after cocoa flavanols)	↑ Nitric oxide → ↑ cerebral blood flow
Short-term (4–12 weeks)	↑ Episodic memory, ↓ oxidative markers	Synaptic plasticity, ↓ inflammation
Long-term (6–24 months)	↓ Cognitive decline in MCI, ↓ dementia risk (observational)	Structural brain changes, amyloid/tau modulation

Most trials showing cognitive improvement lasted at least 8–12 weeks, suggesting chronic intake is necessary for neuroplastic and disease-modifying benefits.

Individual Biological Differences. Age, older adults exhibit increased gut permeability, oxidative stress, lower hepatic metabolic capacity—making them more responsive to flavonoids. Younger adults often show minimal cognitive benefit (likely due to cognitive performance ceiling effects). Genetic Variability (e.g., APOE-ε4): The APOE-ε4 allele increases oxidative stress and impairs amyloid clearance. Some flavonoid interventions (e.g., blueberry anthocyanins) show greater memory enhancement in APOE-ε4 carriers, while others show reduced responsiveness highlighting gene diet interactions. Sex and Hormonal Status: Postmenopausal women respond better to soy isoflavones, due to interaction with estrogen receptors (ERβ). Younger women show less pronounced effects, likely due to endogenous estrogen levels. Gut Microbiota Composition. Flavonoids rely on microbial metabolism to form brain-active compounds (e.g., protocatechuic acid). Individuals vary in these capacities:

Microbiome Type	Cognitive Impact of Flavonoids
High Bifidobacterium, Lactobacillus	Better phenolic conversion → stronger neuroprotection
"Equol producers" (soy isoflavones)	Improved verbal memory & anti-inflammatory effects
Dysbiosis / high Firmicutes/Bacteroides ratio	Reduced flavonoid metabolism → weaker effectiveness

3. Conclusion

Dementia represents a growing global health crisis, with no definitive cure and limited disease-modifying treatments. Dietary interventions, particularly those derived from plant-based bioactive compounds, are emerging as promising strategies for cognitive preservation and dementia prevention. Among these, flavonoids—naturally occurring polyphenols found in fruits, vegetables, tea, cocoa, soy, and wine—have garnered extensive attention due to their neuroprotective, anti-inflammatory, antioxidant, and vasodilatory properties. This review synthesized current mechanistic, preclinical, epidemiological, and clinical evidence regarding the impact of flavonoids on cognitive function and dementia, following a structured exploration of molecular pathways, cognitive outcomes, dementia subtypes, and translational challenges. Key Scientific Insights. Based on the accumulated literature, four major insights emerge: Flavonoids target multiple dementia-related mechanisms simultaneously. These include: Reduction of oxidative stress via Nrf2 activation and ROS scavenging. Inhibition of NF-κB-mediated neuroinflammation. Modulation of amyloid-β and tau pathology (key in Alzheimer's disease). Enhancement of synaptic plasticity, BDNF expression, and hippocampal neurogenesis. Improvement of cerebral blood flow and vascular function—particularly relevant to vascular dementia. Regulation of the gut–brain axis and microbial phenolic metabolism: 1) Clinical benefits are most consistent in memory and processing speed, particularly in older adults with mild cognitive impairment

or vascular/metabolic risk. Anthocyanins from berries and flavanols from cocoa/tea show the strongest evidence. Executive function and attention improve modestly but less consistently. Long-term consumption (>12 weeks), rather than acute dosing, yields more stable cognitive effects. 2) The strongest human evidence exists for Alzheimer's disease and cognitive aging, whereas research in vascular dementia, Lewy body dementia, and frontotemporal dementia remains limited or absent. Observational studies suggest that high flavonoid intake correlates with reduced AD risk. Early intervention, before significant neurodegeneration, may offer the greatest benefit. 3) Flavonoid efficacy is influenced by individual biological factors, including: APOE ε4 genotype, influencing amyloid clearance and oxidative stress. Gut microbiome composition, determining metabolism of flavonoids into brain-permeable phenolics. Sex and hormonal status, particularly in isoflavone-related cognition improvements in postmenopausal women. Comorbidities such as diabetes, hypertension, obesity, which alter vascular and inflammatory status. Final Perspective, the body of evidence strongly indicates that flavonoids contribute to maintaining cognitive function and may attenuate the progression of neurodegenerative processes, particularly in Alzheimer's disease and age-related cognitive decline. Their actions are multi-targeted, systemic, and complementary to established medical therapies. However, current findings require cautious interpretation due to variability in bioavailability, study design, and population characteristics. Thus, while flavonoids cannot yet be classified as clinical therapeutics for dementia, they represent a compelling, low-risk strategy within a broader preventive framework—bridging nutrition, neuroscience, vascular health, and personalized medicine.

4. Declarations

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4.2. Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper. No financial or non-financial interests, personal relationships, or affiliations have influenced the content, analysis, or conclusions presented in this research. All sources of funding, if any, are acknowledged transparently, and the research was conducted independently and without any commercial or institutional bias.

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