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Polyphenol consumption and neurodegeneration risk: a systematic meta-analysis of randomized controlled trials bridging nutrition and cognitive health†

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Given the potential of polyphenols to mitigate neurodegenerative diseases (NDDs), this meta-analysis investigated whether clinical evidence supports the use of polyphenols for neuroprotection and as nutritional strategies in NDDs. We analyzed different polyphenol types across seven NDDs, 13 studies involving 849 participants were included. Prespecified outcomes comprised global cognition (Mini-Mental State Examination, MMSE), domain-specific cognition (Alzheimer's Disease Cooperative Study–Cognitive Subscale, ADCS-Cog), activities of daily living (Alzheimer's Disease Cooperative Study–Activities of Daily Living, ADCS-ADL), neuropsychiatric symptoms (Neuropsychiatric Inventory, NPI), and selected biomarkers (plasma amyloid-β40 and brain-derived neurotrophic factor, BDNF). Reporting followed PRISMA 2020 guidelines, methods conformed to the Cochrane Handbook, and certainty of evidence was assessed using GRADE. Overall, polyphenol supplementation was associated with improved global cognition (pooled MD in MMSE = 2.06; 95% CI 0.62–3.49). In subgroup analyses, flavonoids were associated with a modest but significant improvement in MMSE scores, whereas stilbenes produced a significant benefit in daily functioning (ADCS-ADL) without clear gains in MMSE or ADCS-Cog and no consistent effects on NPI. Anthocyanidins, phenolic acids, and lignans did not significantly affect cognitive outcomes (MMSE or ADCS-Cog), and polyphenol subclasses did not yield robust or consistent changes in NPI or biomarker endpoints (Aβ40 and BDNF). Specific polyphenol subclasses therefore appear to confer selective cognitive and functional benefits, with stilbenes primarily supporting functional outcomes and flavonoids potentially enhancing global cognition.

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Introduction

Neurodegenerative diseases (NDDs) are characterized by progressive cognitive deterioration and gradual loss of neuronal structure and function, thus representing a major global health burden. These disorders include Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), Huntington's syndrome, prion disease, frontotemporal dementia (FTD), and Lewy body dementia. As the global population ages, the prevalence of these conditions is increasing, placing substantial burdens on healthcare systems and society. Current pharmacological treatments have limited effectiveness in halting disease progression, highlighting the urgent need for alternative, preventive, and therapeutic strategies.

Diet and nutrition are essential for promoting brain health and minimizing the risk of NDDs. Polyphenols, a diverse group of plant-derived bioactive compounds, have gained significant attention for their neuroprotective potential. These compounds are prevalent in fruits, vegetables, tea, and wine. They are recognized for their potent antioxidant properties, anti-inflammatory activity, and neuro-modulatory properties,[1,2] which may contribute to their mechanism of neuroprotection. Preclinical studies have demonstrated their capacity to counteract oxidative stress, reduce neuroinflammation, and enhance synaptic plasticity, all of which are implicated in the pathogenesis of NDDs.[3] Dietary patterns rich in polyphenols, such as the Mediterranean diet, have been consistently associated with lower rates of cognitive decline and dementia.[4] However, the application of these findings in clinical practice poses several challenges. These include inconsistencies in

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study designs, variations in the bioavailability of polyphenols, and a lack of substantial clinical evidence.[5]

In this study, we aimed to clarify the role of polyphenols in advancing evidence-based nutritional strategies for the prevention and management of NDDs by integrating insights from current research trends and clinical efficacy. We have explored global research trends, hotspots, and key contributors to this rapidly evolving field using bibliometric analysis in previous studies.

We included data from 849 participants in 13 randomized controlled trials (RCTs) and employed meta-analytical techniques to integrate the findings, identify effective polyphenol types, and evaluate their impact on neurocognitive outcomes. Our study offers an in-depth evaluation of the therapeutic potential of polyphenols using a multifaceted approach.

Experimental

Meta-analyses examining the association between polyphenol intake and neurodegeneration risk were conducted through a comprehensive search of electronic databases. The search strategy was developed and peer-reviewed in collaboration with an experienced medical librarian to ensure sensitivity and precision across databases. The review process adhered strictly to the Preferred Reporting Items for Systematic Reviews and meta-Analyses (PRISMA) guidelines to ensure methodological rigor.[6] To promote transparency and reproducibility, a prespecified protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42024563383; https://www.crd.york.ac.uk/PROSPERO/view/CRD42024563383). Eligibility criteria were defined *a priori* using a Population, Intervention, Comparison, Outcomes (PICO) framework, and titles/abstracts followed by full texts were screened independently by two reviewers (YJ and ZJY). Disagreements were resolved by a third reviewer (ZJ), and inter-rater agreement (Cohen's κ) is reported.

Review structure

The review was structured using the PICO framework as follows:

- Population: individuals at risk of neurodegeneration and healthy controls without neurodegenerative conditions.
- Intervention: polyphenol consumption.
- Comparison: placebo.
- Outcomes: Mini-Mental State Examination (MMSE), Alzheimer's Disease Cooperative Study-Cognitive Subscale (ADCS-Cog), Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL), Neuropsychiatric Inventory (NPI), Plasma Amyloid-beta 40 (Aβ40), and Brain-Derived Neurotrophic Factor (BDNF).
- Study design: RCTs.

Literature search and data collection

A comprehensive literature search was conducted across four major databases—Embase, the Cochrane Library, PubMed, and Web of Science—to identify relevant studies published up to December 31, 2024. The search terms targeted three primary constructs: "neurodegeneration", "polyphenols", and "randomized controlled trials". Notably, RCT-specific screening was not applied during the initial inclusion phase for the bibliometric analysis; instead, RCT eligibility screening was performed subsequently as part of the systematic review study selection process. Studies were included if they examined any of polyphenolic compounds in relation to seven major NDDs, met predefined eligibility criteria, were peer-reviewed, and were English-written RCTs.

Eligibility criteria

An initial screening phase was conducted to evaluate the relevance of identified studies to the predefined research objectives using a systematic review approach. During this phase, the titles, abstracts, and keywords of all identified RCTs were screened. If the abstract lacked sufficient information to determine eligibility, the full text was retrieved and reviewed.

In the second screening phase, full-text articles were evaluated against all predefined inclusion criteria. Eligible studies were required to:

- Report RCT data on polyphenol intake, including specific compound types (Fig. 1).
- Assess outcomes related to NDDs across various disease types or stages.
- Report quantitative data for at least one prespecified cognitive or functional outcome, including means and standard deviations (SDs) or other statistics sufficient to calculate effect sizes.

A structured data extraction protocol was implemented to ensure accurate and consistent collection of outcome-relevant information from each included study.[7] The study selection process is summarized in Fig. 2 (PRISMA flow diagram), detailing the number of records identified, screened, included, and excluded at each stage. Duplicate records were removed prior to screening.

Exclusion criteria

Studies were excluded if they met any of the following criteria:

1. Animal or *in vitro* studies.
2. Non-original research articles (*e.g.*, editorials, commentaries, or case reports).
3. RCTs not reporting neurodegeneration-related outcomes.
4. Studies lacking quantifiable outcome measures (*e.g.*, those that did not report means and SDs or change scores).

Data extraction

Two independent reviewers (YJ and ZJY) extracted data from all eligible RCTs using a predefined extraction form. Extracted variables included study design features (methodological design, sample size, duration of follow-up, and assessment time points), population characteristics, intervention details, outcome measures, and reported effect estimates. All data were organized in a structured Microsoft Excel® spreadsheet. A third reviewer independently verified the extracted data for accuracy and consistency. The final dataset included 13 RCTs,

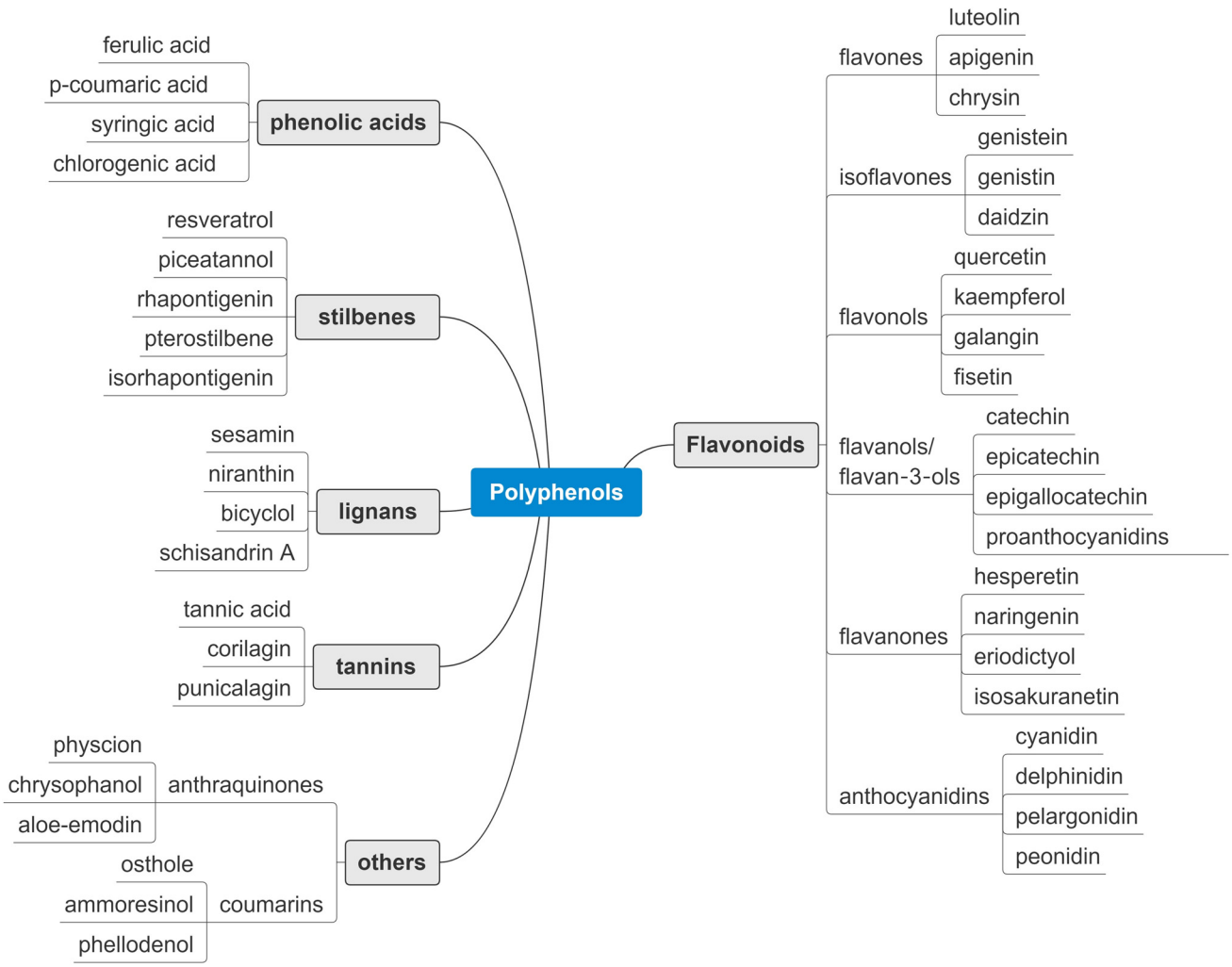

Fig. 1 Polyphenols are broadly divided into flavonoids (including flavones, isoflavones, flavonols, anthocyanidins, flavanols [flavan-3-ols], and flavanones) and non-flavonoids (including phenolic acids, tannins, lignans and stilbenes, as well as other phenolic compounds such as anthraquinones and coumarins). Representative compounds from each subclass are listed.

comprising a total of 849 participants, and captured both bibliometric and outcome-related data.

Data synthesis

Key statistical parameters, including means, SDs and confidence intervals (CIs), were recorded for all prespecified cognitive and functional outcomes (MMSE, ADCS-ADL, ADCS-Cog, and NPI) and selected biomarkers (*e.g.*, plasma Aβ40 and BDNF). When numerical data were not explicitly reported (*e.g.*, presented only in figures), graphical data extraction tools were used to estimate corresponding means and SDs. In cases of missing or unclear data, the corresponding authors were contacted for clarification. Data were extracted independently by two reviewers, and any discrepancies were resolved by discussion and consensus or by a third reviewer when needed. For continuous outcomes, mean differences (MDs) with 95% CIs were calculated and pooled using random-effects models to account for between-study heterogeneity.

Statistical analysis

This meta-analysis adhered to established methodological standards. Reference management was conducted using Review Manager (RefMan 5.3), and all statistical analyses were performed using STATA software. The quality of evidence was assessed using the grading of recommendations assessment, development, and evaluation approach, which accounts for study design, inconsistency, imprecision, indirectness, and potential publication bias. Risk of bias for individual studies was evaluated using the cochrane risk of bias tool, focusing on key domains such as random sequence generation, allocation concealment, blinding procedures, completeness of outcome data, and selective reporting. To examine the robustness of pooled estimates, sensitivity analyses were conducted by systematically excluding studies with a high risk of bias or deemed to be of low quality. When statistical heterogeneity was substantial (I^2 > 50%), random-effects models were applied. Subgroup analyses or *meta*-regression were used to

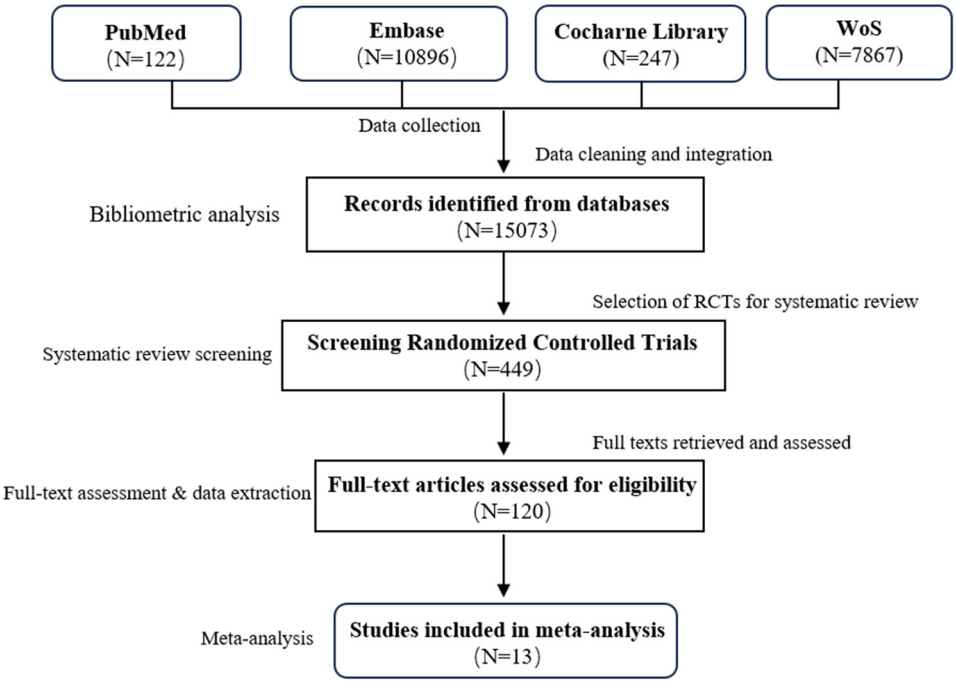

Fig. 2 PRISMA flow diagram illustrating the study process, including identification, screening, eligibility, assessment, and final inclusion. Overall, 19 132 records were identified through database searches; after initial processing (including de-duplication and preliminary screening), 15 073 unique records were screened, and 449 randomized controlled trials were assessed for eligibility. After screening and exclusions, 13 studies comprising 849 participants were included in the final meta-analysis. WOS, web of science.

explore potential sources of heterogeneity. Publication bias was assessed using funnel plots and Egger's regression test. Where bias was suspected, the "trim and fill" method was employed to adjust pooled results accordingly.

Results

Literature search

A systematic literature search was conducted by two reviewers on January 15, 2025, across four electronic databases (Embase, Cochrane Library, PubMed, and Web of Science) to identify eligible studies (Fig. 2). All databases were searched using a predefined search string, as described in the "Search Strategy" section. All retrieved records were imported into EndNote for deduplication. A total of 19 132 records were retrieved through a database search, including 10 896 from Embase, 247 from the Cochrane Library, 122 from PubMed, and 7867 from Web of Science. After automatic removal of duplicates, 15 073 unique records were retained. Only RCTs were included for screening, resulting in 449 eligible articles for title and abstract review. Three authors independently screened titles and abstracts, and discrepancies were resolved through discussion and consensus. Of the 449 articles, 120 were retained for full-text assessment and original data extraction. Additional articles were identified by manually reviewing the reference lists of the included studies and relevant reviews. During full-text evaluation, studies were further excluded owing to incomplete outcome data or failure to meet the inclusion criteria. Finally, 13 studies that evaluated polyphenol intake and its association with neurodegeneration-related outcomes were included in the final quantitative synthesis.

Systematic review of 449 RCTs

The effect of pure compounds, extracts, and composite mixtures on cognitive performance has highlighted several promising interventions, particularly in the context of AD. Among the pure compounds, resveratrol,[8–12] silymarin,[13,14] chlorogenic acid,[15] anthocyanins,[16] and catechin[17] have been studied for their potential neuroprotective effects. Polyphenol-rich substances, such as components rich in isoflavones,[18] genistein,[19] catechins,[20] sesamin,[21] epigallocatechin gallate (EGCG),[22] and anthocyanins[23,24] may have potential cognitive benefits (Table 1). Extracts of cocoa flavanols[25] olive polyphenols,[26] have also been evaluated for their role in improving brain health. Furthermore, composite mixtures such as blueberry,[27–29] cherries,[30] polyphenol-rich fruit juices,[31–33] muscadine wine,[34] and the Mediterranean-DASH Diet Intervention for Neurodegenerative Delay food[35] have been evaluated for their collective effects in mitigating cognitive decline and enhancing brain function. For Alzheimer's disease (cognitive impairment), evaluated outcome measures included cognitive function tests (*e.g.*, MMSE,[36–39] ADAS-Cog,[15,16,21] Montreal Cognitive Assessment,[8,11] Symbol Digit Modalities Test[21]) as well as daily functioning and behavioral assessments (e.g., ADCS-ADL,[8,10,12] NPI,[10–12,26] clinical dementia

Table 1 Effects of different polyphenols on various neurodegenerative diseases and their evaluated outcome measures

Disease types	Polyphenols	Outcome variable
Alzheimer's disease (cognitive impairment)	Pure compounds: Resveratrol[8–12] Silymarin[13,14] Chlorogenic acid[15] Isoflavone[18] Sesamin[21] Genistein[19] Catechins[17,20]	• Cognitive function tests: mini-mental state examination (MMSE),[8–15,23,24,29,36–39] Alzheimer's disease assessment scale – cognitive subscale,[8,10,12,15,16,21,36,37] montreal cognitive assessment,[8,11,24] stroop test,[17,21] symbol digit modalities test (SDMT),[21] CogTrack cognitive test,[23] trail making test,[15,25] complutense verbal learning test,[19] Barcelona test-revised,[19] Hopkins verbal learning test,[39] and digit symbol substitution test[17]
	Epigallocatechin gallate (EGCG)[22] Anthocyanin[16,23,24] Extracts: Cocoa flavanols[25]	• Daily functioning and behavior tests: Alzheimer's disease cooperative study–activities of daily living (ADCS-ADL),[8,10,12] neuropsychiatric inventory,[8,10–12,26] clinical dementia rating – sum of boxes,[8,14] quality of life in dementia,[19,23] and Alzheimer's disease cooperative study clinical global impression of change[40]
	Olive polyphenol extract[26] Composite mixtures: Blueberry[27,28] Grape[29] Cherries[30] Polyphenol-rich fruit juices[31–33] Muscadine wine[34] MIND Food[35]	• Amyloid and tau biomarkers: plasma Aβ40/Aβ42,[8,10,14,41] cerebrospinal fluid Aβ40/Aβ42,[8–10,14,37] and tau/phospho-tau.[10] • Neuroinflammation and oxidative stress biomarkers: neopterin, catalase, paraoxonase,[13,14,42] inflammation markers (interleukin [IL]-4, IL-6, and C-reactive protein [CRP]),[9,38] matrix metallopeptidase 9,[8,9] macrophage-derived chemokine,[9] fibroblast growth factor,[9] and urine 8-hydroxy-2′-deoxyguanosine[17] • Growth factors and neuroprotection biomarkers: brain-derived neurotrophic factor (BDNF),[38,42] insulin-like growth factor 1,[38] and LRP1[14] • Metabolic health indicators: blood pressure, blood glucose, blood lipids, body weight,[14] homocysteine, folate, and vitamin B12[32] • Oxidative stress indicators: lipid profile (triglycerides, high-density lipoprotein, total cholesterol, low-density lipoprotein), total antioxidant capacity (TAC), total oxidative status,[13,14,42] and malondialdehyde (MDA)[13,14,42] • Brain structure and volume imaging: brain volume and ventricular volume (volumetric magnetic resonance imaging [MRI]);[8,10] voxel-brain atrophy (VBM)[37] • Brain activity and connectivity imaging: hippocampal connectivity and microstructure, and structural and functional MRI[17,22] • Cerebrovascular and metabolic function imaging: amyloid beta deposition (18F-flutemetamol positron emission tomography [PET], PiB-PET),[19,37] brain metabolism (fludeoxyglucose-18 -PET),[29] neuro-metabolite ratios,[14] cerebral blood flow (transcranial Doppler ultrasound),[40] and cerebral blood volume and oxygenation[30]
Parkinson's disease/multiple system atrophy	Pure compounds: Curcumin[43] EGCG[44–46] Silymarin[47] Extracts: Polyphenol-rich extract of licorice[48]	• Motor function and disease severity scales: neurological rating scale,[52] 6-min walk test,[52] unified multiple system atrophy rating scale, Hoehn and Yahr scale,[47] and unified Parkinson's disease rating scale[48,50] • Quality of life and symptoms questionnaires: Parkinson's disease questionnaire-39, fatigue severity scale, Pittsburgh sleep quality index questionnaire,[43] and clinical global impression[44–46]
	Grape juice[49] Green tea polyphenol[50] Composite mixtures: Saffron and chamomile[51] Flavonoid-rich pure cocoa[52]	• Health indicators: blood pressure[48] • Metabolic and mineral balance: iron metabolism parameters[44–46] and electrolyte levels[48] • Neurophysiological and oxidative stress markers: BDNF levels and oxidative stress parameters[49] • Brain structure and atrophy: cerebral atrophy and iron deposition[44–46]
Amyotrophic lateral sclerosis/ multiple sclerosis	Pure compounds: Silymarin[53] EGCG[54,55] Nanocurcumin[56] Pterostilbene[57,58] Composite mixtures: Liposomed polyphenols[59]	• Functional mobility and balance: quantitative balance (Berg scale),[55] perceived balance (activities-specific balance confidence scale),[55] gait speed (10 min walk test),[55] and resistance (2 min walk test).[55] • Disease severity and functional status: expanded disability status scale[54] and functional rating scale[57,58] • Muscle function and strength: muscle strength[55] • Body composition and anthropometric measurements: waist circumference, waist-to-hip ratio, waist-to-height ratio, fat percentage, and muscle percentage[54] • Respiratory function: respiratory function and vital capacity[57] • Liver and metabolic function parameters: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, MDA, TAC, tissue transglutaminase,[53] beta-hydroxybutyrate,[54,55] albumin, paraoxonase 1, and CRP[54] • Immune function and cytokine activity: activity of Th17 and Th1 cells, T cell activity,[56] and cytokine production[56] • Metabolic regulation and cellular health: Sirtuin 1 and AMP-activated protein kinase[59] • Gut health and microbiome: intestinal microbial composition[59]

Table 1 *(Contd.)*

Disease types	Polyphenols	Outcome variable
Huntington's syndrome	Pure compounds: EGCG[60,61] Resveratrol[62]	• Cognitive function tests: stroop color-word interference test, word fluency test, and SDMT[61] • Disease-specific assessment: unified Huntington's disease rating scale[60,61] biomarkers: neurochemical markers and imaging markers[60,62]
Frontotemporal dementia	Pure compounds: Luteolin[63]	• Behavioral outcomes: clinical dementia rating dementia staging instrument plus National Alzheimer's coordinating center frontotemporal lobar degeneration, frontal assessment battery, screening for aphasia in neurodegeneration, ADCS-ADL, neuropsychiatric inventory, MMSE, Addenbrooke's cognitive examination revised, and behavioral disturbances • Biomarkers (neurochemical and blood-based): cognitive and neurophysiological assessments (multimodal approach) • Imaging/neurological assessments: cognitive and neurophysiological assessments (multimodal approach)

rating–sum of boxes,[8,14] quality of life in dementia[19,23] and Alzheimer's disease cooperative study clinical global impression of change[40]). In addition to cognitive tests, biomarkers related to amyloid and tau deposition;[9,10,14,37,41] neuroinflammation;[9,14,17] oxidative stress;[13,14,42] and growth factors, such as BDNF,[42] insulin-like growth factor (IGF-1),[38] and low-density lipoprotein receptor-related protein 1 (LRP1),[14] are critical for evaluating the efficacy of polyphenols. Neuroimaging techniques such as volumetric magnetic resonance imaging (MRI),[8,10] functional MRI,[17,22] and positron emission tomography[19,29,37] also provide insights into brain structure, activity, and metabolic function, further informing the assessment of therapeutic interventions. This multifaceted approach helps to understand the therapeutic potential of various compounds in slowing the progression of AD and other NDDs.

Research on treatments for PD and multiple system atrophy (MSA) has focused on the potential therapeutic effects of various pure compounds, extracts, and composite mixtures. Key pure compounds, such as curcumin,[43] EGCG,[44–46] and silymarin,[47] have been studied for their neuroprotective properties. Extracts such as polyphenol-rich licorice extract,[48] grape juice,[49] and green tea polyphenols[50] along with composite mixtures such as saffron-chamomile blends[51] and flavonoid-rich pure cocoa,[52] have been evaluated for their impact on disease progression. Several motor function and disease severity scales have been used to assess treatment efficacy, including the neurological rating scale,[52] Hoehn and Yahr scale,[47] and unified Parkinson's disease rating scale.[48,50] Quality of life was assessed using questionnaires, such as the Parkinson's disease questionnaire-39, fatigue severity scale, and Pittsburgh sleep quality index,[43] whereas the clinical global impression scale[44–46] was used for global symptom evaluation. In addition to clinical measures, biomarkers such as BDNF, oxidative stress parameters,[49] and iron metabolism indicators[44–46] are crucial for evaluating the biochemical effects of these treatments. Neuroimaging has been used to assess brain structure, including cerebral atrophy and iron deposition, providing additional insight into the therapeutic potential of these compounds in patients with PD and MSA.

Promising outcomes have been reported in the treatment of ALS and multiple sclerosis (MS) through the investigation of various natural compounds. Pure agents such as silymarin,[53] EGCG,[54,55] nanocurcumin,[56] and pterostilbene[57,58] have been studied for their potential to alleviate disease symptoms and slow disease progression. Additionally, composite formulations, such as liposomal polyphenol mixtures, are under evaluation for their synergistic therapeutic effects.

Functional mobility and balance in affected individuals are commonly assessed using validated tools, including the Berg balance scale, the Activities-specific Balance Confidence (ABC) Scale, and gait performance tests, such as the 10-meter walk test.[55] Disease severity and overall functional status are evaluated using standardized scales, including the expanded disability status scale[54] and the revised ALS functional rating scale.[57,58] Comprehensive assessments of muscle strength, body composition, and respiratory function are conducted to monitor clinical status, with key parameters including waist-to-hip ratio, skeletal muscle percentage, and vital capacity.[57] Hepatic and metabolic functions are evaluated using biochemical markers, including alanine aminotransferase, aspartate aminotransferase, albumin, and C-reactive protein. Immune competence and inflammatory activity are assessed through measurements of T-cell responsiveness and cytokine production.[54] Furthermore, cellular metabolism and regulatory pathways are investigated by analyzing molecular markers, such as sirtuin 1 and AMP-activated protein kinase, along with the composition of the intestinal microbiome,[59] providing a comprehensive view of how these compounds affect the overall health of patients with ALS and MS.

Concerning Huntington's disease, especially Huntington's chorea, the potential therapeutic effects of pure compounds, such as EGCG[60,61] and resveratrol,[62] have been evaluated. These compounds have been examined for their neuroprotective properties and their capacity to improve motor and cognitive functions. Cognitive performance is typically assessed using standardized tests, including the stroop color-word interference test, word fluency test, and symbol digit modalities test,[61] which measure processing speed, verbal fluency, and cognitive flexibility. Disease severity is often evaluated

with the unified Huntington's disease rating scale,[60,61] providing a comprehensive assessment of motor and non-motor symptoms. Moreover, various biomarkers, such as neurochemical indicators and neuroimaging markers,[60,61] are under investigation to better understand disease progression and to monitor responses to treatments. Together, these assessment tools and biomarkers facilitate the evaluation of the potential benefits of compounds like EGCG and resveratrol in slowing disease progression and improving patient quality of life.

Concerning FTD, the potential therapeutic effects of pure compounds, such as luteolin,[63] have been studied, which may contribute to mitigating the cognitive decline associated with this condition. To evaluate the effectiveness of the treatments, several behavioral outcomes were assessed using scales, such as the Clinical Dementia Rating Dementia Staging Instrument plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration, Frontal Assessment Battery, and Screening for Aphasia in Neurodegeneration, to measure the degree of cognitive impairment and behavioral disturbances. The ADCS-ADL and NPI have been utilized to assess daily functioning and neuropsychiatric symptoms. Additionally, the MMSE and Addenbrooke's Cognitive Examination Revised are commonly used to gauge overall cognitive function.[63] To achieve a more comprehensive understanding of disease progression in FTD, a multimodal approach incorporating biomarkers, cognitive evaluations, and neurophysiological assessments was employed. Neuroimaging techniques further contributed by providing critical insights into both structural and functional alterations in the brain, facilitating the longitudinal monitoring of neurophysiological and cognitive changes. Integrating behavioral, neurochemical, and imaging modalities is crucial for evaluating the therapeutic effects of luteolin and other investigational treatments for FTD.

Meta-analysis of the effects of polyphenols on neurocognitive impairment

Thirteen RCTs comprising a total of 849 participants were included in the quantitative analysis (Fig. 3). Relevant outcome measures included MMSE, ADCS-Cog, ADCS-ADL, and NPI for AD. Statistical heterogeneity was quantified using the I^2 statistic, and subgroup analyses were performed to identify potential sources of variability in treatment effects across studies.

The meta-analysis presented above focused on evaluating the effects of various compounds, including flavonoid extracts, anthocyanidins, phenolic acids, and stilbenes, on cognitive and behavioral outcomes in individuals, particularly those with AD and mild cognitive impairment. A breakdown of the key findings is provided below.

MMSE scores

Flavonoids were associated with a significant improvement in cognitive function ($Z = 2.03$, $P = 0.04$); however, substantial heterogeneity was observed ($I^2 = 84\%$). In contrast, anthocyanidins showed no significant effect ($Z = 1.16$, $P = 0.25$), with no heterogeneity (indicating consistency across studies). Phenolic acids similarly did not demonstrate a significant effect ($Z = 1.19$, $P = 0.24$), with very low heterogeneity ($I^2 = 0\%$). Stilbenes produced no significant effect ($Z = 0.80$, $P = 0.42$), and no heterogeneity was detected ($I^2 = 0\%$). Compound mixtures did not yield a significant effect ($Z = 0.18$, $P = 0.86$), with no observed heterogeneity.

ADCS-ADL scores

Stilbenes showed a significant improvement in daily living activities, as measured by ADCS-ADL ($Z = 3.38$, $P = 0.0007$), with no heterogeneity ($I^2 = 0\%$).

ADCS-Cog scores

Phenolic acids did not produce a significant effect on cognitive function ($Z = 1.40$, $P = 0.16$), with very low heterogeneity ($I^2 = 0\%$). Stilbenes demonstrated no significant effect on cognitive function ($Z = 0.52$, $P = 0.60$). Similarly, anthocyanidins and lignans had no significant effect on cognitive function ($Z = 0.50$ and 1.23, $P = 0.62$ and 0.22, respectively). In contrast, compound mixtures demonstrated a borderline significant improvement in cognitive function ($Z = 1.95$, $P = 0.05$), suggesting potential benefit. Flavonoids did not significantly affect ADCS-Cog scores ($Z = 0.95$, $P = 0.34$), though substantial heterogeneity was present ($I^2 = 100\%$), indicating considerable variability across studies. Stilbenes did not have a significant impact on neuropsychiatric symptoms, as measured by the NPI ($Z = 1.09$, $P = 0.27$).

Key insights

•Flavonoids and compound mixtures, particularly those containing stilbenes, demonstrated potential benefits for cognitive and daily functioning. Flavonoids were associated with a modest but significant improvement in MMSE scores.

•Stilbenes demonstrated a strong positive effect on daily functioning (ADCS-ADL) but did not yield significant improvements in cognitive assessments (ADCS-Cog and MMSE).

•Anthocyanidins, phenolic acids, and lignans did not exhibit significant effects on cognitive outcomes across the included studies.

Notably, substantial heterogeneity was observed in some comparisons—most prominently among flavonoid studies assessing ADCS-Cog—indicating variability in treatment responses across populations and studies.

Discussion

Evidence from 13 RCTs including 849 participants was synthesized in this meta-analysis to evaluate the role of polyphenols in NDDs. Our findings indicate that polyphenol supplementation, particularly flavonoids and mixed formulations containing stilbenes, is associated with improvements in cognitive outcomes, with notable benefits observed in MMSE scores.[23,27,28] Moreover, specific compounds such as resveratrol and curcumin demonstrated promising effects on cognitive and neuropsychiatric symptoms, especially in early-stage AD.[10,13] These results suggest that polyphenols may serve as a

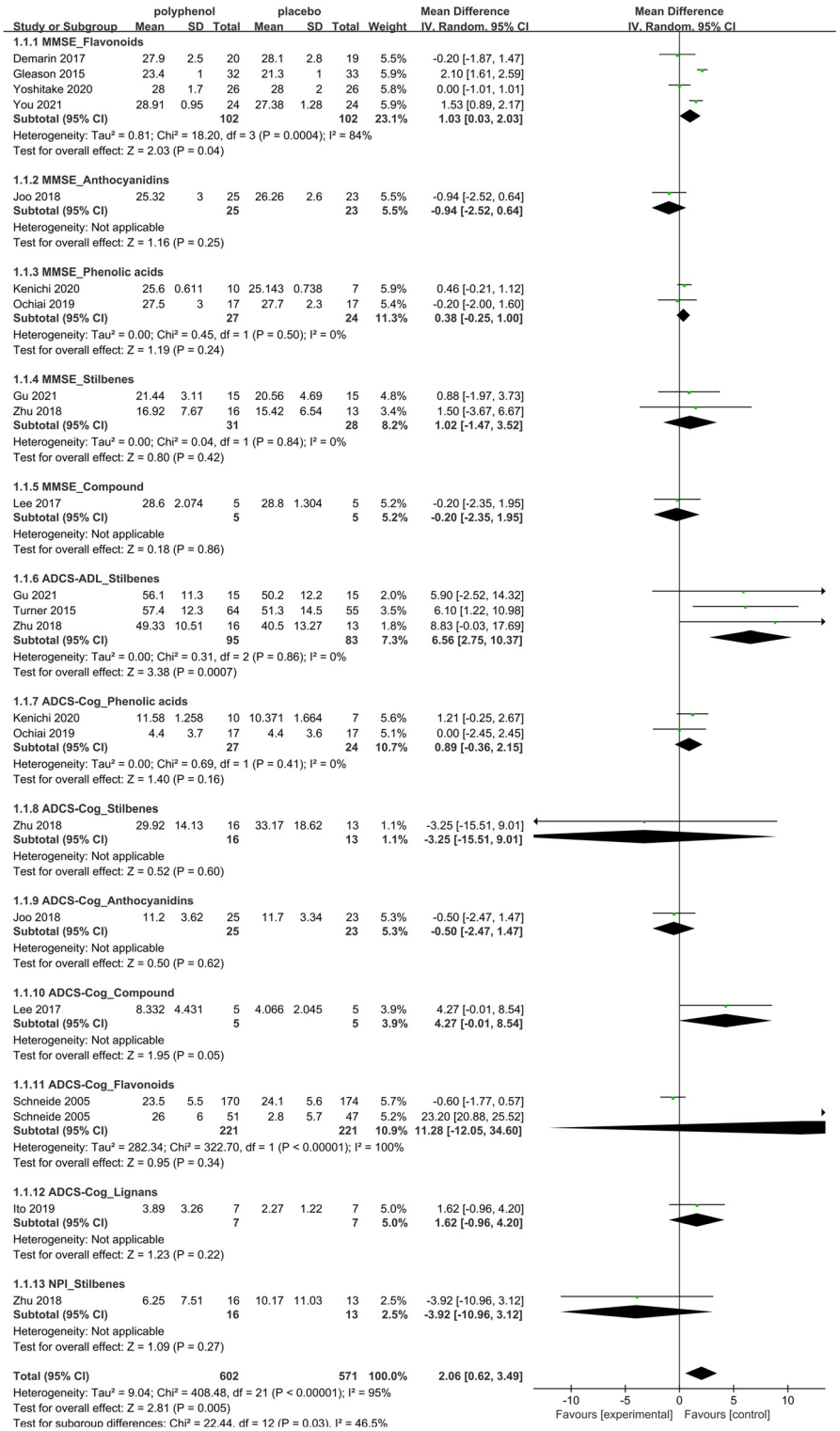

Fig. 3 Forest plot of randomized controlled trials evaluating the effects of polyphenol-based interventions on cognitive outcomes. Subgroup analyses were conducted by compound categories (flavonoid extracts, anthocyanidins, phenolic acids, stilbenes, lignans, and mixed compounds) and cognitive assessment tools (MMSE, ADCS-ADL, ADCS-Cog, and NPI). Data are presented as mean differences (MD) with 95% confidence intervals (CIs) under a random-effects model. Overall, polyphenol supplementation was associated with significant improvement in cognitive performance compared to placebo (MD = 2.06, 95% CI: 0.62–3.49, p = 0.005). SD, standard deviation.

complementary nutritional strategy in the prevention and management of NDDs. Importantly, the primary aim of the study—to clarify the clinical efficacy of polyphenols across NDDs—was met. The novelty of our study lies in its comprehensive integration of clinical trial evidence across seven NDDs, while simultaneously mapping the diversity of polyphenol types evaluated, thus offering a broad yet detailed perspective on their therapeutic potential.

The observed effects can be explained by the well-documented antioxidative and anti-inflammatory properties of polyphenols, which mitigate oxidative stress and neuroinflammation —two hallmarks of NDD pathogenesis.[12,19] Additionally, polyphenols such as flavonoids have been shown to enhance synaptic plasticity, modulate amyloid and tau pathology, and upregulate neurotrophic factors such as BDNF.[38,42] The cognitive and functional benefits observed in this analysis are consistent with mechanistic insights from preclinical studies, supporting the plausibility of polyphenols as neuroprotective agents.

Our findings align with those of prior observational and clinical research linking polyphenol-rich dietary patterns, such as the Mediterranean diet, to lower risks of cognitive decline and dementia. Notably, studies of resveratrol and curcumin in early AD have reported improvements in memory, mood, and biomarkers of amyloid pathology, consistent with our pooled analysis.[8,12,38] Similarly, trials of Ginkgo biloba extracts and cocoa flavanols have demonstrated modest but reproducible benefits in cognition and daily functioning, reinforcing the translational relevance of polyphenols from diet to clinical intervention.[36,44,64] Despite promising research being reported, there are inconsistencies that remain to be resolved. Some RCTs have reported null or limited effects, particularly for anthocyanidins and phenolic acids, reflecting variability in compound bioavailability, dosage, and study design.[23] These discrepancies likely arise from (i) variability in bioavailability and formulation (*e.g.*, standard *vs.* enhanced delivery), (ii) under-dosing or insufficient intervention duration relative to disease stage, (iii) baseline diet and lifestyle differences that obscure incremental effects, (iv) outcome-measure sensitivity (ADCS-Cog *vs.* global screens), and (v) small sample sizes limiting power to detect clinically meaningful changes. These negative or mixed findings reduce confidence and indicate that any benefits are class-specific, outcome-specific, and context-dependent rather than universal.

This review has some limitations. First, the number of high-quality RCTs remains limited, with small sample sizes and short intervention durations restricting the strength of causal inferences. Second, methodological heterogeneity across studies, such as differences in polyphenol type, dosage, formulation, and outcome measures, introduces variability and complicates direct comparisons. Third, most studies focused on AD, whereas evidence for other NDDs, such as PD, Huntington's disease, or FTD, remains sparse.[51,60,63] Finally, the potential influence of confounders such as diet, lifestyle, and genetic background was not consistently accounted for in the included trials. Despite these limitations, this study highlights important implications for practice and research. Clinically, our findings support the inclusion of polyphenol-rich foods and supplements as part of preventive and therapeutic strategies against NDDs, particularly in early disease stages.[28,33] From a research perspective, an urgent need exists for large-scale, well-controlled RCTs with standardized polyphenol interventions to validate efficacy, clarify mechanisms, and establish optimal dosing regimens.[6,7]

Conclusions

We clarified the role of polyphenols in the prevention and management of NDDs by integrating data from 13 RCTs, employing meta-analytical techniques. Our results suggest that specific polyphenol subclasses confer selective cognitive and functional benefits, with stilbenes favoring functional outcomes and flavonoids potentially enhancing cognition. However, heterogeneity in study designs, the scarcity of high-quality RCTs, and the poor bioavailability of many polyphenols hinder their clinical application. Developing standardized research protocols, improving delivery systems, and conducting larger, long-term clinical studies are essential to validate these preliminary findings. At a broad level, this work underscores the potential of nutrition-based interventions to contribute to global strategies addressing the rising burden of NDDs, aligning with precision medicine and healthy aging goals. Future studies should investigate the synergistic effects of polyphenol mixtures and their integration with existing therapeutic approaches. The value of polyphenols lies in their direct neuroprotective effects and broader role in shaping evidence-based dietary and nutritional strategies. Incorporating polyphenols into functional foods or dietary guidelines could offer a practical, accessible approach to help prevent and manage NDDs, supporting healthier aging and easing the societal burden of these conditions. Future research should focus on large-scale, multicenter trials, explore advanced technologies to improve bioavailability and targeted delivery, and investigate the combined effects of polyphenols with other therapeutic approaches. Addressing these knowledge gaps is crucial for unlocking the full therapeutic potential of polyphenols in NDD care.

Author contributions

Xiaomei Wang: conceptualization, investigation, formal analysis, visualization, writing – original draft, funding acquisition. Jiao Yang: data curation, formal analysis. Jiayuan Zhang: validation, investigation. Gaihong Yu: data curation, visualization. Jian Zhu: resources, supervision. Yingli Nie: conceptualization, supervision, project administration.

Conflicts of interest

There are no conflicts to declare.

Data availability

All data supporting the findings of this study were obtained from publicly accessible bibliographic databases: PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/), Cochrane Library (https://www.cochranelibrary.com/), and Web of Science Core Collection (https://www.webofscience.com/). Searches covered records up to 31 December 2024 and were conducted in accordance with each provider's access and usage policies. The data that support the findings of this study are available from the corresponding author, YN, upon reasonable request.

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