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Effect of polyphenols on inflammation related to cognitive function: a systematic review and meta-analysis of human randomized controlled trials

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Abstract.

BACKGROUND: The decline of cognitive function could in part be caused by an increase in inflammation. Polyphenols have been widely investigated due to their anti-inflammatory property which may promote therapeutic effects on the brain and cognitive performance.

OBJECTIVE: To evaluate the impact of polyphenols interventions on inflammation related to cognitive function in humans.

METHODS: Three electronic databases: PubMed/Medline, Web of Science and PsycINFO were systematically searched until 30th May 2024 to find the study that have investigated the effect of polyphenols on both inflammatory response and cognitive function in human randomized controlled trials. The outcomes were pooled and calculated using inverse variance as mean difference (MD) with 95% confidence intervals (95% CI) for the inflammatory markers and standardized mean difference (SMD) with 95% CI for cognitive domains.

RESULTS: Ten studies (451 participants, aged 20–81 years) assessed inflammatory markers and cognitive standardized tests responding to polyphenols interventions were included in this review and meta-analysis. Supplementation with polyphenols demonstrated a significant improvement of verbal memory (SMD: 0.33, 95% CI: 0.12 to 0.54, $P=0.002$), executive function (SMD: 0.38, 95% CI: 0.03 to 0.72, $P=0.03$) and attenuation in blood interleukin-6 (MD: -1.23 pg/ml, 95% CI: -2.34 , to -0.12 , $P=0.03$). No significant differences were observed in working memory (SMD: 0.13, 95% CI: -0.18 to 0.44 , $P=0.42$), attention (SMD: -0.19 , 95% CI: -0.84 to 0.46 , $P=0.57$), and psychomotor skill (SMD: 0.09, 95% CI: -0.32 to 0.50 , $P=0.66$) as well as in c-reactive protein (MD: -0.10 mg/l, 95% CI: -0.28 to 0.09 , $P=0.30$), and tumor necrosis factor- α (MD: 0.11 pg/ml, 95% CI: -1.25 to 1.47 , $P=0.87$).

CONCLUSION: Polyphenols supplementation decreases blood IL-6 as well as enhances verbal memory and executive function. Regular polyphenols consumption might prevent inflammation related to cognitive decline.

Keywords: Polyphenols, inflammation, IL-6, cognitive function, memory, executive function

1. Introduction

Inflammation, whether in the peripheral or in the brain, has been considered as an underlying mechanism of cognitive decline and neurodegenerative disorders. Previous studies demonstrated that elevated pro-inflammatory mediators have been related

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to poorer cognitive performance in various conditions, including older adults, dementia, Alzheimer's disease, mild cognitive impairment (MCI), post-operative cognitive dysfunction, diabetes, and obesity [1–5]. Even though inflammation is a protective response of the body to external and internal stimuli, the uncontrolled process or prolonged response could deteriorate the bodily functions, including the brain [6]. The up-regulated pro-inflammatory molecules in the blood, such as interleukin-6 (IL-6), IL-1 β , and tumor necrosis factor- α (TNF- α), could penetrate through the blood-brain barrier and stimulate the brain's immune cells, resulting in neuroinflammation, neuronal damage, and brain pathologies which might have a negative impact on cognitive abilities [7, 8]. Several studies demonstrated that elevated blood inflammatory markers in either acute or chronic conditions could accelerate cognitive impairments in humans, particularly in tasks involving memory, attention, processing speed, and executive function [5, 9–13]. Due to the involvement of inflammation and cognitive function, studies focusing on anti-inflammatory interventions have gained increasing interest in delaying the onset of cognitive dysfunction and the progression of neurodegenerative diseases. Non-steroidal anti-inflammatory drugs (NSAIDs) have been examined for prevention or delaying the onset of inflammatory-related neurodegenerative diseases, especially AD and MCI [14, 15]. The outcomes have been satisfied to prevent an incidence of AD and cognitive impairment in observational studies [16]. Thus, attenuating the inflammatory response might be an approach to prevent or delay the progression of cognitive decline.

Dietary and non-dietary bioactive compounds have been widely studied due to their anti-inflammatory properties, which may promote therapeutic effects on the brain and cognitive performance [17, 18]. Polyphenols, non-nutrient bioactive compounds, commonly found in fruits, vegetables, and herbs, have been demonstrated to have several health benefits [18–20]. Polyphenols can be categorized into different groups based on their fundamental structural elements and functions, including phenolic acids, coumarins, flavonoids, stilbenes, and lignans. Their chemical structures are composed of molecules sharing an analogous elementary polyphenolic structure as well as molecules with a single phenol ring such as phenolic acids [21]. A number of studies have reported that polyphenols have the potential to attenuate neuroinflammation and peripheral inflammatory mediators as well as improve cognitive performance

in animals and humans [17, 18, 22]. However, the role of polyphenols in the association between inflammation and cognitive function in humans has not been systematically elucidated. Therefore, this systematic review aims to evaluate the effect of polyphenols intervention on inflammation related to cognitive function in human randomized controlled trials to answer the question: do the polyphenols protect against cognitive decline through their potential to inhibit inflammatory processes in humans?

2. Methodology

The systematic review was performed according to The Preferred Reporting items for Systematic Reviews and Meta-Analyses guideline (PRISMA) [23]. The outcome of this systematic review is to explore the effect of polyphenols intervention on cognitive function and inflammation in human randomized controlled trials.

2.1. Search strategy

Searches were conducted using the following three electronic databases: PubMed/Medline, Web of Science and PsycINFO until 30th May 2024. The outcomes were carried out using the search terms: (neuroinflammat* OR inflammat* OR “inflammatory mediator*” OR cytokine* OR chemokine* OR “c-reactive protein” OR hsCRP) AND (cognit* OR cognition OR “cognitive function” OR “cognitive impairment” OR “cognitive decline” OR memory OR “executive function” OR “neuropsychological test*”) AND (“randomized controlled trial” OR “controlled trial” OR “cross-over stud*”).

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows:

- (i) original study with full-text papers published in English language in peer reviewed journals,
- (ii) a randomized controlled trial with a parallel or cross-over group design,
- (iii) conducted in humans aged ≥ 18 years,
- (iv) received polyphenols or polyphenols-rich food interventions,
- (v) measured both a blood/cerebrospinal fluid inflammatory marker and a standardized cognitive test at baseline and post-intervention,

Table 1

PICOS (participant, intervention, comparison, outcome, and study design) criteria for included studies

PICOS parameters	Inclusion criteria
Population	Human participants aged more than 18 years
Intervention	Polyphenols or polyphenols-rich food interventions
Comparison	Placebo or appropriate comparable intervention
Outcome	Both inflammation (i.e., CRP, IL-6, TNF- β) and cognitive function (standardized cognitive tests)
Study design	Randomized controlled trial with a parallel or cross-over group design

- (vi) outcomes were presented as mean \pm SD/SEM or median and interquartile ranges (IQR).

Exclusion criteria were as follows:

- (i) multicomponent supplementation or combined interventions,
- (ii) measured the level of inflammatory mediators by cell culture assay,
- (iii) assessed cognitive function by neuroimaging technique,
- (iv) inflammatory status or cognitive outcomes were reported separately in another publication.

The selected studies were read in full to determine eligibility in accordance with the PICO parameters as shown in Table 1.

2.3. Study selection and data extraction

The endnote programme was used to allocate all the results from the search strategy. The selected records were independently assessed for eligibility by two review authors (CM and DJL). A discussion with a third reviewer will be used to resolve any potential disagreements over the eligibility of a particular study. The data were extracted using a standardized form. The extracted information included the following: first author name and year of publication; study design; participant (condition, mean age, number of subjects); intervention (treatment, dose, and length); inflammatory marker; cognitive assessment; and main findings.

2.4. Assessment of methodological quality

Studies selected for systematic review were assessed for overall quality of methodology and the potential risk of bias by two reviewers using Cochrane Collaboration's risk of bias tool (RoB 2) [24]. For parallel randomized controlled trials, the assessed domains consisted of bias arising from randomized process, bias due to deviations from intended interventions, bias due to missing data outcome, bias in measurement outcome, bias in the selection of the reported result, and any adjustment to the overall study. The bias arising from period and carryover effects was additionally assessed in the cross-over design study. The risk of bias in each domain was rated as "low", "some concern" and "high". Any disagreements between the reviewers were resolved by discussion and a third researcher, where necessary.

2.5. Meta-analysis

Due to various types of inflammatory mediators and cognitive tests, the outcomes of inflammation were clustered into CRP, IL-6, and TNF- α . The results of cognitive function were classified based on the cognitive domains assessed in the particular studies: working memory, verbal memory, executive function, attention, and psychomotor skill. For the study measuring outcomes in different periods, the longest time point was used for analysis. Quantitative extracted data were imported into RevMan 5.4 for meta-analysis. At least three studies reported similar post-intervention outcomes as mean \pm SD both in response to polyphenols and to placebo, were pooled and calculated using inverse variance as mean difference (MD) with 95% CI for inflammatory markers because the included studies used the same measurement scales. The standardized mean difference (SMD) with 95% CI was used with cognitive tests because of the different scales of measurements [24]. In the case of outcomes reported as median, the mean and SD were calculated following the study by Hozo et al., 2005 [25]. For the studies which reported the outcomes as mean and standard error of mean, the SD value was calculated from this equation: $SEM = SD/\sqrt{N}$. The heterogeneity among the included studies will be assessed by the Cochrane Q and I^2 statistics [24]. Cochrane Q statistic with a p -value of less than 0.05 indicates statistical significance, while I^2 statistics of more than 50% indicate substantial heterogeneity among the included studies.

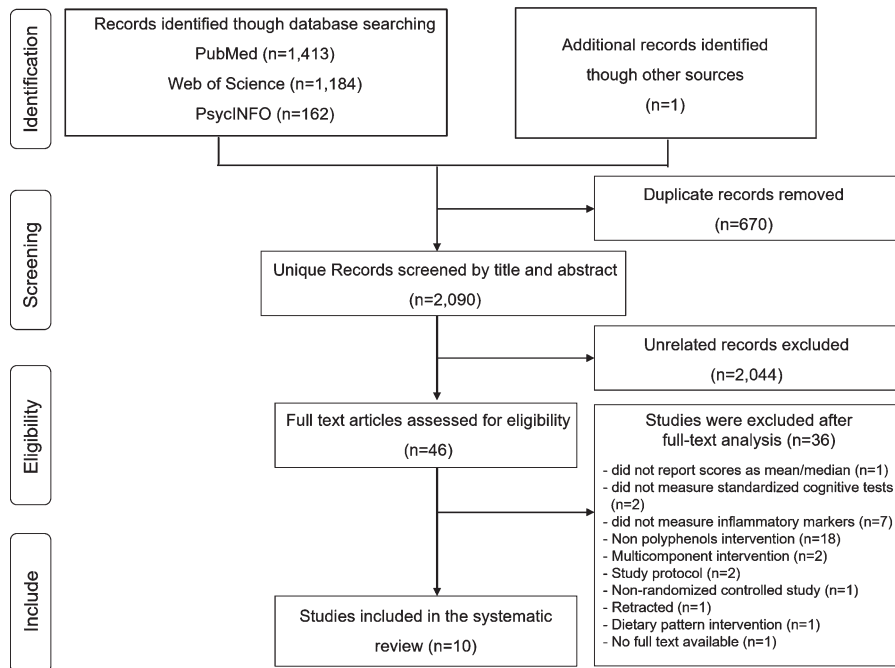


Fig. 1. Flow chart illustrating the identification of studies for the literature.

Effect size (ES) was interpreted as small ($d=0.2$), medium ($d=0.5$), and large ($d>0.8$) according to Cohen's criteria [26].

3. Results

3.1. Study identification

A total of 2,760 records were obtained after the initial search of the PubMed/Medline, Web of Science, and PsycINFO databases. 670 duplicated studies were removed, and then the titles and abstracts of 2,090 unduplicated studies were preliminary screened to identify eligibility. After that, the 46 potential eligible articles were read in full text according to the previously mentioned criteria, and 10 articles were retrieved in the systematic review and meta-analysis, respectively (Fig. 1).

3.2. The study characteristics

Ten studies met the inclusion criteria were included in a systematic review to determine the effect of polyphenols on both cognitive function and inflammation in human randomized controlled trials. Eight

studies were parallel randomized controlled trials [27–29, 32–36], and two studies were cross-over designs [30, 31]. The included studies were published between 2012 and 2024, with sample sizes ranging from 26 to 60 subjects. A total of 451 participants were enrolled, with a mean age range of 20 to 81 years. The 94 participants were grouped as young adults (age 18–40 years), and the remaining 357 participants were older adults (age ≥ 60 years). The subjects were general healthy status for five studies [27, 30, 31, 33, 34] overweight or obese for two studies [32, 35], mild cognitive impairment for two studies [28, 29], and adults with self-reported depressive symptoms for one study [36]. The polyphenols intervention was categorized into anthocyanin-rich foods (anthocyanin contents between 10 and 387 mg/day), resveratrol supplements (200 mg/day), and polyphenol-rich extracts: Brazilian green propolis extract (11 mg/day of artemillin C) and polyphenol-rich seaweed extract (polyphenols 560 mg/day). All included studies investigated the chronic effects (5 weeks to 24 months) of polyphenols supplementation on cognitive function and blood inflammatory status. The summarized characteristics and interventions of the included studies are in Table 2.

Table 2
The impact of polyphenols intervention on inflammation and cognitive function

Author	Design	Population			Intervention			Inflammatory measurement	Cognitive tests	Outcomes		Main findings
		Conditions	Mean age	Sample size	Treatment	Dose	Length			Inflammation	Cognition	
Bowtell et al. (2017) [27]	Double-blind randomized controlled trial	Healthy older adults	I: 68 C: 69	26 I: 12 C: 14	Blueberry concentrate	387 mg.day ⁻¹ anthocyanins	12 wks.	hs-CRP	The cogstate: a detection task, the Groton maze timed chase test, the Groton maze learning test with a delayed recall, international shopping list task with delayed recall, 1-2 back memory tasks	↔	↑ 2-back test	Blueberry concentrate consumption did not significantly change hsCRP levels but can improve brain activities related to working memory.
Kent et al. (2017) [28]	Double-blind randomized controlled trial	Mild-moderate dementia	I: 79 C: 81	49 I: 24 C: 25	Anthocyanin-rich cherry juice	138 mg.day ⁻¹ anthocyanins	12 wks	CRP, IL-6	RAVLT, the self-ordered pointing task (SOPT), the Boston naming test, the trail making test (TMT), digit span backwards task and category and letter verbal fluency	↔	↑ Verbal fluency, short-term long-term memory	Anthocyanin-rich juice intake improved verbal fluency and memory, as well as decreased BP. However, CRP and IL-6 levels did not alter compared to the control.

(Continued)

Table 2
(Continued)

Author	Design	Population			Intervention			Inflammatory measurement	Cognitive tests	Outcomes		Main findings
		Conditions	Mean age	Sample size	Treatment	Dose	Length			Inflammation	Cognition	
Bohn et al. (2021) [29]	Double-blind randomized controlled trial	Aged men with subjective memory impairment	I: 72 C: 71	60 I: 30 C:30	Bilberry and red grape-juice	660 ml.day ⁻¹	9 wks.	IL8, IP10, MCP, MIP-1 β , IL-4, IL-6, IL-7, IL-9, IL-10, IL-12, IL-13, IL-17, TNF- α , IFN-g	The CANTAB; Delayed matching to sample, Paired associates learning, Pattern recognition memory, Spatial recognition memory, Grooved Pegboard Test	↓ L-6, TNF- α , IL-9, IL-10, MIP-1 β	↔	Bilberry juice significantly reduced IL-6, TNF- α , IL-9, IL-10, and MIP-1 β but did not change cognitive performance.
Igwe et al. (2020) [30]	Randomized, crossover clinical trial	Healthy elderly adults	70	31	Queen garnet plum nectar	10 mg.day ⁻¹ anthocyanins	8 wks.	CRP	The Rey Auditory Verbal Learning Test (RAVLT), digit-span backwards task, stroop task, and counting span	↔	↔	Low anthocyanin queen garnet plum nectar consumption did not alter both serum CRP and cognitive function.

Nilsson et al. (2017) [31]	Randomized cross-over study	Healthy non-smoker adults	63	40	Berry beverage	795 mg/l of polyphenols, 248 mg/l of anthocyanins	5 wks.	IL-6, IL-18	Verbal working memory (WM) test, selective attention test	↔	↑ Working memory	Berry drinks improved working memory and reduced LDL cholesterol, but they did not change serum cytokine levels.
Witte et al. (2014) [32]	Double blind placebo- controlled study	Healthy overweight older adults	I: 65 C: 64	46 I: 23 C:23	Resveratrol	200 mg.day ⁻¹	26 wks.	IL-6, TNF- α , hsCRP	The auditory verbal learning task; retention, delayed recall, recognition, learning ability, fifth learning trial	↓ TNF- α	↑ Retention of word	Resveratrol intake significantly reduced TNF- α levels and increased retention of words as well as functional activity in the hippocampus.
Huhn et al. (2018) [33]	Double-blind randomized controlled trial	Healthy elderly participants	I: 69 C: 68	53 I: 27 C:26	Resveratrol	200 mg.day ⁻¹	26 wks.	IL-6, TNF- α , hsCRP	The German version of the California Verbal Learning Task (CVLT), Trail making test A& B	↑ IL-6, TNF- α , hsCRP	↔	Resveratrol supplement slightly increased serum IL-6, TNF- α , and hsCRP, but no change in cognition was found in both groups. However, the resveratrol trend preserved pattern recognition memory.

(Continued)

Table 2
(Continued)

Author	Design	Population			Intervention			Inflammatory measurement	Cognitive tests	Outcomes		Main findings
		Conditions	Mean age	Sample size	Treatment	Dose	Length			Inflammation	Cognition	
Zhu et al. (2018) [34]	Randomized, placebo-controlled double-blind	Elderly people living at high altitude	I: 72 C: 73	46 I: 30 C: 30	Brazilian green propolis extract	11 mg.day ⁻¹ Artepillin C	6,12,24 months	IL-1 β , IL-6, TNF- α , IL-10, TGF- β 1	MMSE	↓ IL-1 β , IL-6	↑ MMSE	Propolis supplements decreased plasma IL-1 β and IL-6 and improve global cognition in a time-dependent manner.
Murray et al. (2021) [35]	Double-blind, placebo-controlled, randomized parallel trial	Overweight adults	I: 34 C: 45	34 I: 17 C: 17	Polyphenol-rich seaweed (<i>F. vesiculosus</i>) extract	560 mg.day ⁻¹ of total polyphenols	12 wks.	IL-2, IL-6, IL-8, IL-10, TNF- α	The immediate word recall task, 2-back, serial three and serial seven subtraction tasks, corsi blocks, digit vigilance task, delayed word recall task, and delayed word recognition task	↔	↔	No changes were found in inflammatory markers or cognitive function between treatment and placebo after receiving seaweed extract, but an increase HDL was observed in the intervention group.
Velichkov et al. (2024) [36]	Double-blind randomized controlled trial	Adults with self-reported depressive symptoms	I: 20 C: 20	60 I: 30 C: 30	Blueberry drink	121 mg.day ⁻¹ anthocyanins, 55 mg.day ⁻¹ chlorogenic acid	2 h, 6 wks.	hs-CRP, IL-6	The task-switching paradigm	↔	↑ Task-switching at acute phase	Acute blueberry consumption enhanced executive function and mood, but long-term supplementation did not affect serum indicators or cognition.

↓: significantly reduce, ↑ significantly increase, ↔ non-significantly change, I= intervention, C: control.

3.3. Quality assessment of included studies

ROB2 was used to assess the quality of the included studies. The ROB summary and graph were demonstrated in Fig. 2A, parallel randomized controlled design, and Fig. 2B, cross-over design. The overall ROB was graded “low” for five studies [27, 29, 30, 33, 36], “some concern” for two studies [31, 32], and “high” for three studies [28, 34, 35]. The randomization process was rated “some concern” for five studies because they did not specify the process for randomization and allocation [27, 29, 31, 32, 34]. The risk of deviations from the intended intervention was assessed as “some concern” in two studies due to the fact that participants and carers might be aware of their assigned intervention [28, 34]. The “high” risk of missing data outcome was assessed in two studies because the reports did not mention the extent of missing data outcomes [28, 35]. For the risk of measurement data outcome was rated as “high” risk for one study [34] and “some concern” for two studies [32, 33] due to the assessors may not be blinded by the intervention status. The selection of the reported data was rated “some concern” for six studies because the results were likely to have been selected to be reported in the papers [28, 30, 31, 34, 35, 36]. Lastly, the risk of carryover effects was rated “low” in both cross-over design studies [30, 31].

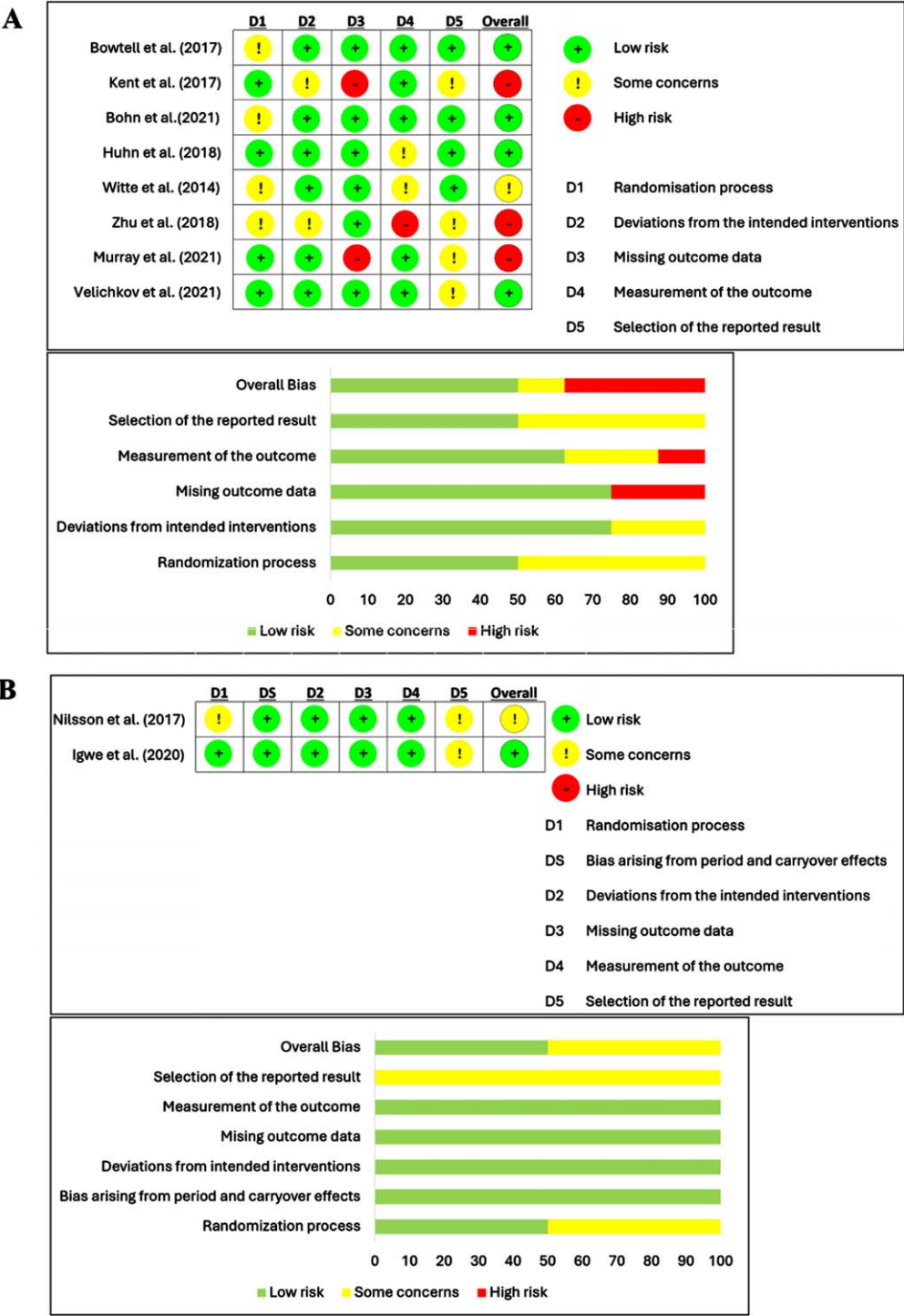
3.4. Narrative synthesis

3.4.1. Polyphenols intervention on inflammation and cognitive benefits

This systematic review includes ten studies that assessed blood inflammatory markers as well as standardized cognitive assessments in human RCTs. Eight studies were conducted with older participants, whereas the others were in a younger age group with obesity and self-reported depression symptoms. [35, 36]. Out of ten studies, three (30%) demonstrated a significant reduction of inflammatory markers, including L-6, TNF- α , IL-9, IL-10, MIP-1 β , and IL-1 β , by polyphenols interventions [29, 32, 34]. One study reported an increase in some inflammatory markers such as IL-6, TNF- α , and hs-CRP, but in both the interventional and control groups [33]. The others demonstrated no significant reduction in blood inflammatory indicators after polyphenols treatment compared to the placebo [27, 28, 30, 31, 35, 36]. Regarding cognitive outcomes, six studies (60%) demonstrated that

polyphenols supplementation significantly improved cognitive performance when compared to controls [27, 28, 31, 32, 34, 36]; however, one of these only showed a substantial improvement during the acute period (2 h) [36]. The domains of memory, especially verbal memory, and working memory were predominantly improved. In addition, one study indicated improvements in executive function and psychomotor skill [28]. However, four studies found that the polyphenols supplementation did not change cognitive function in comparison to the control [29, 30, 33, 35]. The association between inflammation and cognitive performance was summarized based on studies indicating anti-inflammatory benefits of polyphenols treatment. Three studies indicated that polyphenols significantly reduced the levels of TNF- α , IL-6 and IL-1 β mediators [29, 32, 34], and two of them identified an association with improved verbal memory and global cognition [32, 34]. Therefore, polyphenols supplementation might enhance cognitive performance underlining the anti-inflammatory processes. Four studies found that polyphenols, primarily anthocyanins, improved cognitive performance while having no effect on inflammatory responses [27, 28, 31, 36]. The improvement of cognitive functions, however, could be underlined by various mechanisms. Other putative mechanisms were highlighted in the included research, such as improving cerebral blood flow [27], activating brain regions relevant to cognitive function [27, 32], lowering blood pressure [28], and changing lipid metabolic risk indicators [31–35].

Considering the type of interventions, six studies investigated anthocyanin-rich foods [27–31, 36]; two studies demonstrated resveratrol supplementation [32, 33]; and two studies assessed polyphenol-rich extracts [34, 35]. Following anthocyanins treatment, three out of six studies reported that chronic anthocyanin consumption at concentrations of 138–387 mg/day for 5–12 weeks demonstrated a substantial improvement in cognitive performance in older adults, particularly in the domain of working memory and executive function; however, the interventions did not impact any blood inflammatory biomarkers (IL-6, CRP, and IL-18) [27, 28, 31]. Bowtell et al. (2017) reported that the consumption of blueberry concentrates (387 mg/day of anthocyanins) for 12 weeks significantly improved working memory (2-back memory test, $p=0.05$) with no change in serum CRP levels in healthy elderly compared to controls. However, they found an increase in blood perfusion to the grey matter and the activa-



+

Low risk

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Some concerns

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High risk

D1

Randomisation process

DS

Bias arising from period and carryover effects

D2

Deviations from the intended interventions

D3

Missing outcome data

D4

Measurement of the outcome

D5

Selection of the reported result

Fig. 2. Risk of bias and graph for parallel design study (A) and cross-over design study (B).

tion of some brain-related cognitive areas, including the Brodmann, anterior cingulate, precuneus, and insula/thalamus, which may result in the enhance-

ment of working memory [27]. Nilsson et al. (2017) found similarly that working memory significantly enhanced ($p<0.05$) after 5 weeks of berry beverage

consumption (248 mg/day of anthocyanins) in non-smoker healthy elderly subjects, while the serum IL-6 and IL-18 cytokines were not altered. Meanwhile, a reduction of LDL cholesterol was reported after supplementation [31]. Kent et al. (2017) reported that 12-week anthocyanin-rich juice intake (138 mg/day of anthocyanins) in elderly people with MCI significantly improved executive function ($P=0.014$), short-term memory ($P=0.014$), and long-term memory ($p\leq 0.001$), as well as reduced systolic blood pressure ($P=0.038$). However, the serum CRP and IL-6 levels were not significantly different compared to the control [28]. On the contrary, the study by Bohn et al. (2021) demonstrated that bilberry juice consumption (660 ml/day) for 9 weeks significantly reduced plasma IL-6 ($P=0.04$), TNF- α ($P=0.04$), IL-9 ($P=0.05$), IL-10 ($P=0.05$), and MIP-1 β ($P=0.02$) levels as well as plasma tissue damage biomarkers in aged men with subjective memory impairment without affecting working memory or episodic memory [29]. Another anthocyanin study by Igwe et al. (2020) found that neither serum CRP levels nor cognitive performance significantly differed after low anthocyanin queen garnet plum nectar (10 mg/day of anthocyanins) supplementation in healthy elderly compared to controls [30]. Additionally, Velichkov et al. (2024) demonstrated that six weeks of blueberry drink intake (121 mg/day of anthocyanins) had no effect on serum inflammatory markers or cognitive performance, but that acute consumption (2 h) enhanced executive function and mood in subjects with self-reported symptoms of depressive disorders [36]. To summarize, the improvement of cognitive outcomes by anthocyanin-rich food consumption, especially working memory, reported consistency in three studies with doses of 138–387 mg/day in healthy elderly participants, with non-significant changes in the makers of inflammation. The enhancement of cognitive performance by anthocyanins was unlikely to be dependent on a specific anti-inflammatory mechanism. These investigations revealed several probable underlying processes, such as increased cerebral blood flow, activation of brain regions associated with cognitive ability, and a decrease in oxidative stress indicators. In order to establish the cognitive benefits of anthocyanins supplementation, a minimum dose of at least 138 mg/day should be recommended over a long-term period (≥ 5 weeks).

The impacts of resveratrol supplementation on cognitive function and inflammatory status were evaluated in healthy older adults and older per-

sons with overweight status [32, 33]. Witte et al. (2014) found that taking 200 mg/day of resveratrol for 26 weeks significantly reduced blood TNF- α levels and improved verbal memory (word retention test, $P=0.038$) compared to a placebo in the elderly with overweight status. In addition, the enhancement of functional activity in the hippocampus, a main brain area of memory, has been reported [32]. Another study by Huhn et al. (2018) demonstrated that serum IL-6, TNF- α , and hs-CRP levels significantly increased after consuming 200 mg of resveratrol for 6 months, but in both intervention and control groups. The psychomotor skills (Trail Making Tasks A and B) were not altered in healthy elderly volunteers; however, the recognition trend to be preserved ($P=0.07$) following supplementation compared to control [33]. These studies demonstrated that prolonged resveratrol supplementation (≥ 6 months) at a dosage of 200 mg/day might maintain memory, psychomotor skills, and recognition in elderly subjects whilst additionally decreasing inflammatory mediators, particularly in overweight individuals.

Another two studies investigated the effects of polyphenol-rich extracts on inflammation and cognitive function in healthy elderly and overweight adults. Zhu et al. (2018) investigated the long-term effects of artemillin C (11 mg/day)-rich propolis extract on cognition and inflammatory mediators in elderly people living at high altitude. The chronic propolis supplementations for 6, 12, and 24 months significantly reduced serum IL-6 and IL-1 β concentrations and improved the MMSE scores in a time-dependent manner compared to the controls. Interestingly, the prolonged duration of supplementation could extend the effects of anti-inflammatory and cognitive benefits [34]. On the other hand, Murray et al. (2021) reported the negative effect of 12-weeks polyphenol-rich seaweed supplementation (560 mg/day of total polyphenols) on both cognitive function and inflammatory mediators in overweight adults. However, they reported a significant increase in HDL cholesterol after supplementation [35].

3.5. Meta-analysis results

3.5.1. The effect of polyphenols intervention on blood inflammatory markers

3.5.1.1. CRP. The effect of polyphenols intervention on serum CRP concentration (mg/l) was evaluated in seven RCTs with 356 participants. The pooled estimate demonstrated that dietary polyphe-

nols did not significantly change the level of CRP (MD: -0.10 mg/l, 95% CI: -0.28 to 0.09 , $P=0.30$). Considering I^2 index (0.0%) and Cochrane Q test ($P=0.79$), very low inter-trial heterogeneity was detected (Fig. 3A).

3.5.1.2. IL-6. Data from eight RCTs, with 436 participants, in which the effect of polyphenols interventions on serum IL-6 concentration (pg/ml) was evaluated. The pooled estimate demonstrated that dietary polyphenols significantly reduced the level of IL-6 (MD: -1.23 pg/ml, 95% CI: -2.34 to 0.12 , $P=0.03$). Considering I^2 index (94.0%) and Cochrane Q test ($P<0.00001$), substantial inter-trial heterogeneity was detected (Fig. 3B).

3.5.1.3. TNF- α . Data from five RCTs, with 249 participants, in which the effect of polyphenols interventions on serum TNF- α level (pg/ml) was assessed. The pooled estimate found that dietary polyphenols did not significantly change the level of TNF- α (MD: 0.11 pg/ml, 95% CI: -1.25 to 1.47 , $P=0.87$). Considering I^2 index (93.0%) and Cochrane Q test ($P<0.00001$), substantial inter-trial heterogeneity was detected (Fig. 3C).

3.5.2. The effect of polyphenols on cognitive performance

3.5.2.1. Verbal memory. The results from each study measuring cognitive ability in the domain of verbal memory were considered an independent study. There were eleven studies, comprising 542 participants, in which the effect of polyphenols on working memory was pooled in our meta-analysis. The pooled estimate revealed that dietary polyphenols significantly improve verbal memory. The summarized effect of the findings showed a small effect. (SMD: 0.33 , 95% CI: 0.12 to 0.54 , $P=0.002$). Considering I^2 index (34.0%) and Cochrane Q test ($P=0.13$), substantial inter-trial heterogeneity was detected (Fig. 4A).

3.5.2.2. Working memory. The results from each study measuring cognitive performance in domain of working memory were considered as an independent study. There were thirteen studies, comprising 476 participants, in which the effect of polyphenols on working memory was pooled in our meta-analysis. The pooled estimate revealed that dietary polyphenols did not significantly improve working memory. The summarized effect of the findings showed a small effect (SMD: 0.13 , 95% CI: -0.18 to 0.44 , $P=0.42$).

Considering I^2 index (62.0%) and Cochrane Q test ($P=0.002$), substantial inter-trial heterogeneity was detected (Fig. 4B).

3.5.2.3. Executive function. The results from each study measuring cognitive ability in domain of executive function were considered as an independent study. There were ten studies, comprising 486 participants, in which the effect of polyphenols on working memory was pooled in our meta-analysis. The pooled estimate revealed that dietary polyphenols significantly enhance executive function. The summarized effect of the findings showed a small effect (SMD: 0.38 , 95% CI: 0.03 to 0.72 , $P=0.03$). Considering I^2 index (71.0%) and Cochrane Q test ($P=0.0003$), substantial inter-trial heterogeneity was detected (Fig. 5).

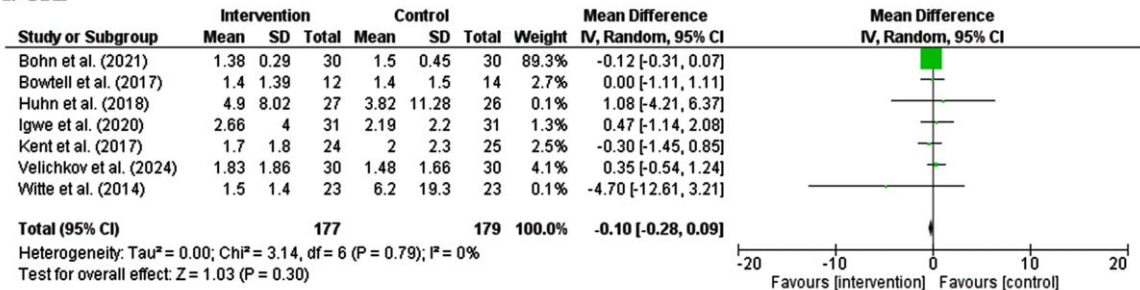
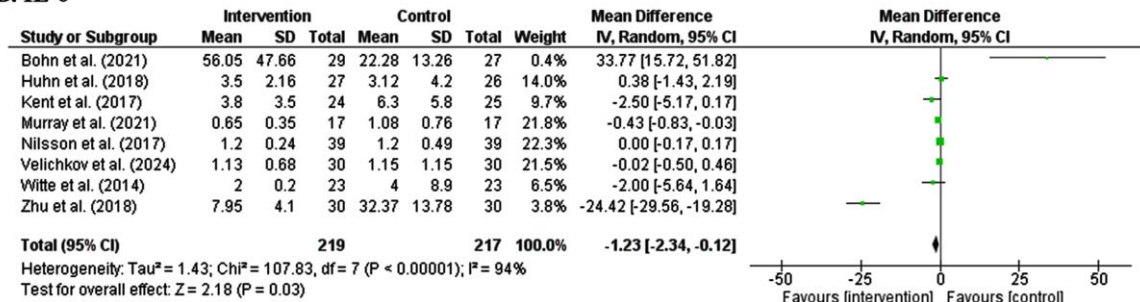
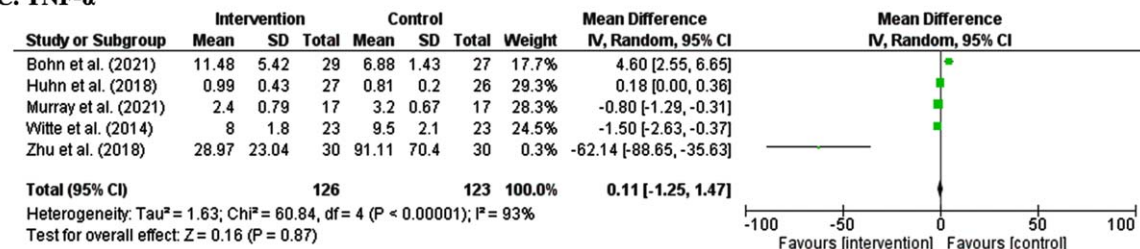
3.5.2.4. Attention. The results from each study measuring cognitive ability in domain of attention were considered as an independent study. There were four studies, comprising 150 participants, in which the effect of polyphenols on attention was pooled in our meta-analysis. The pooled estimate revealed that dietary polyphenols did not significantly enhance attentive skills. The summarized effect of the findings showed a small effect (SMD: -0.19 , 95% CI: -0.84 to 0.46 , $P=0.57$). Considering I^2 index (70.0%) and Cochrane Q test ($P=0.02$), substantial inter-trial heterogeneity was detected (Fig. 6).

3.5.3. Psychomotor skill

The results from each study measuring cognitive ability in domain of psychomotor skill were considered as an independent study. There were three studies, comprising 148 participants, in which the effect of polyphenols on psychomotor skill was pooled in our meta-analysis. The pooled estimate revealed that dietary polyphenols did not significantly increase psychomotor skill. The summarized effect of the findings showed a small effect (SMD: 0.09 , 95% CI: -0.32 to 0.50 , $P=0.66$). Considering I^2 index (37.0%) and Cochrane Q test ($P=0.21$), a low inter-trial heterogeneity was detected (Fig. 7).

4. Discussions

This comprehensive review with meta-analysis first establishes the associations between cognition and inflammation in response to polyphenols intervention in human RCTs. The included ten studies

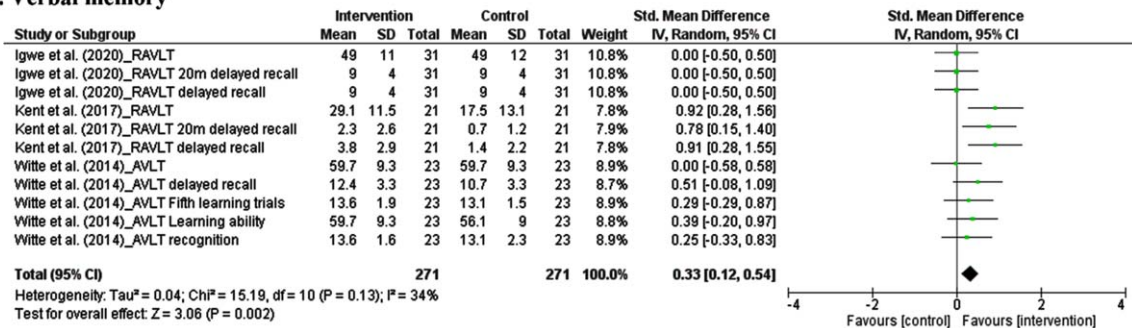
A. CRP**B. IL-6****C. TNF- α** Fig. 3. Forest plot of studies demonstration of polyphenols interventions on CRP (A), IL-6 (B) and TNF- α (C).

were primarily conducted in older age groups and supplemented anthocyanins with a daily dosage of 10–387 mg, followed by resveratrol at 200 mg, polyphenol-rich extract at 560 mg, and propolis extract containing 11 mg of artemillin C. All studies examined chronic supplementation for 5 weeks to 24 months, with one examining both acute and chronic phrases. Significant improvements were observed in verbal memory and executive function as well as an attenuation in blood IL-6 concentrations following the chronic supplementation of polyphenols. The serum TNF- α and CRP concentrations, as well as the domains of working memory, attention, and psychomotor skill, were not statistically changed (summary in Table 3).

Cognitive function refers to the mental processes involved in receiving knowledge, manipulating information, and being able to understand and think rationally, and it can be measured in a variety

of domains such as attention, memory, learning, perception, decision making, processing speed, psychomotor skill, language, and executive function [37]. In general, cognitive performance, particularly memory, deteriorates with age due to various mechanisms such as loss of brain volume and neuron cells, a decrease in synaptic plasticity, a decrease in vascular function and cerebral blood flow, as well as an increase in systemic inflammation [38]. These factors may have an impact on brain function, including cognitive performance, personality, and behavior. This meta-analysis found that polyphenols supplementation predominantly improved verbal memory and executive function, particularly in older adults. Regarding individual research, six studies reported a significant increase in cognitive performance after polyphenols supplementation compared to controls [27, 28, 31, 32, 34, 36]. The beneficial effects on domains of memory, exec-

A. Verbal memory



B. Working memory

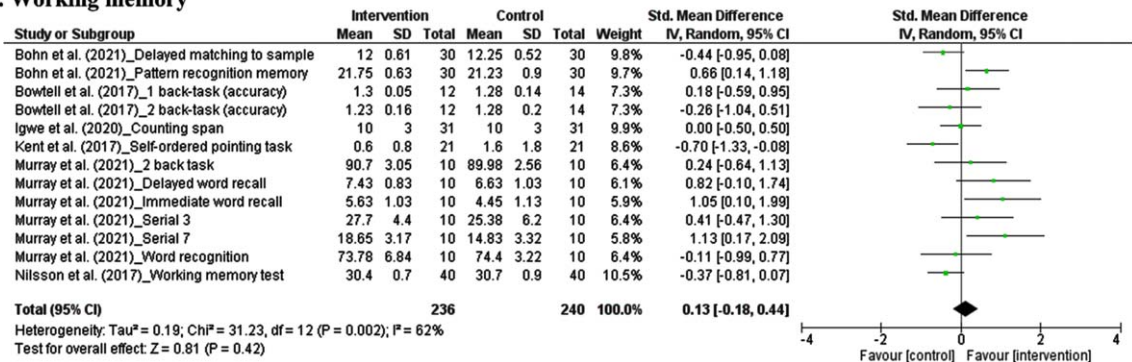


Fig. 4. Forest plot of studies demonstration of polyphenols interventions on verbal memory (A) and working memory (B).

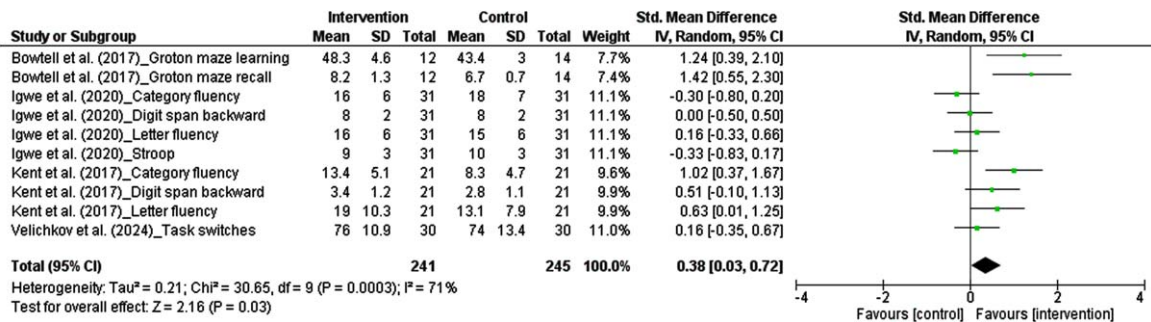


Fig. 5. Forest plot of studies demonstration of polyphenols interventions on executive function.

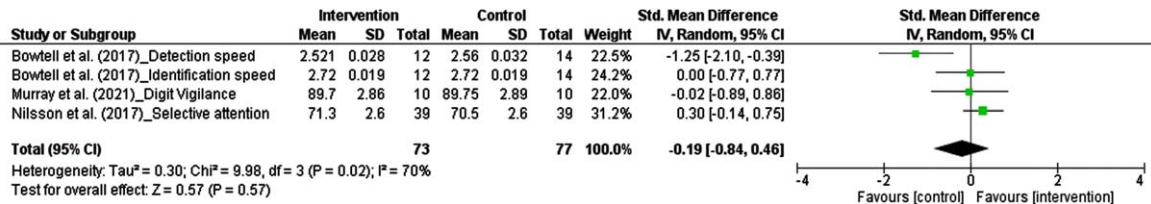


Fig. 6. Forest plot of studies demonstration of polyphenols interventions on attention.

utive function, and psychomotor skill were primarily observed in anthocyanin-rich food interventions [27, 28, 31, 36]. The supplementation with resveratrol and propolis extract demonstrated the improvement of

memory and global cognitive function, respectively [32, 34]. Consistent with a recent meta-analysis by Cheng et al. (2022), they demonstrated the positive effects of dietary flavonoids on long-term mem-

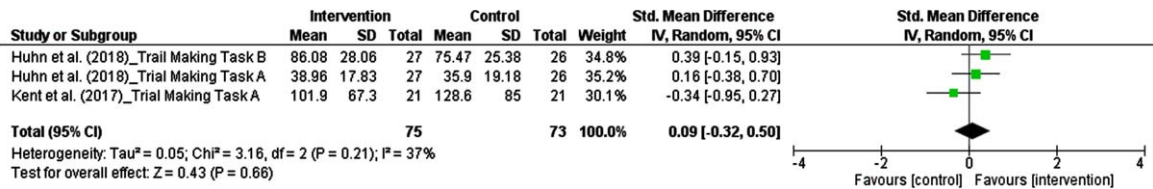


Fig. 7. Forest plot of studies demonstration of polyphenols interventions on psychomotor skill.

Table 3
Summary of the effect of polyphenols intervention on inflammation and cognitive function

Outcomes	No. of study	No. of participant	Heterogeneity			Pooled effect		
			χ^2	df (p)	I ²	d	95% CI	P
Inflammatory markers								
CRP (mg/L)	7	356	3.14	6 (0.79)	0%	−0.10	[−0.28, 0.09]	0.30
IL-6 (pg/ml)	8	436	107.83	7 (<0.000001)	94%	−1.23	[−2.34, −0.12]	0.03*
TNF- α (pg/ml)	5	249	60.84	4 (<0.000001)	93%	0.11	[−1.25, 1.47]	0.87
Cognitive domains								
Verbal Memory	11	542	15.19	10 (0.13)	34%	0.33	[0.12, 0.54]	0.002*
Working memory	13	476	31.23	12 (0.002)	62%	0.13	[−0.18, 0.44]	0.42
Executive function	10	486	30.65	9 (0.0003)	71%	0.38	[0.03, 0.72]	0.03*
Attention	4	150	9.98	3 (0.02)	70%	−0.19	[−0.84, 0.46]	0.57
Psychomotor skill	3	148	3.16	2 (0.21)	37%	0.09	[−0.32, 0.05]	0.66

*Level of significance at $P \leq 0.05$.

ory, processing speed, and mood. Chronic dietary flavonoids supplementation with a low to moderate dosage had a stronger favorable impact in middle-aged to older adults [39]. In addition, a previous meta-analysis study suggested that either acute or chronic anthocyanin supplementation could maintain cognitive processing speed in older adults [40]. The systematic review by Ahles et al. (2021) comprehensively reported the improvement of cognitive outcomes, including memory, attention, psychomotor speed, and executive function after anthocyanins supplementation. The researchers suggested that the beneficial effect of anthocyanins on cognitive function might differ depending on other factors such as the domain of cognition, the forms of products (powder, juice, or extract), and the targeted populations [41]. Furthermore, polyphenol-rich treatments have been reported to enhance cognitive function in young and middle-aged adults [42]. Another meta-analysis demonstrated that taking more than 200 mg of resveratrol per day enhanced delayed recognition and mood in adults [43]. In accordance with previous systematic reviews and meta-analyses, our findings confirm that chronic supplementation with polyphenols may improve cognitive abilities in adults and the elderly.

Regarding inflammation, IL-6, an important inflammatory cytokine, could act as both a pro-inflammatory and anti-inflammatory substance depending on conditions. IL-6 is often used as a marker for the acute phase response after tissue damage or infection [44]. The higher levels of blood IL-6 have been associated with poorer cognitive performance in either acute or chronic inflammatory responses [45–47]. Additionally, the higher blood IL-6 concentrations have been associated with poorer global cognitive performance in non-dementia older people [48–50]. Our findings demonstrated a significant difference in the reduction of IL-6 after polyphenols supplementation compared to controls. Consistent with the previous meta-analysis, dietary anthocyanins significantly decreased the levels of blood inflammatory markers such as CRP, TNF- α , IL-6, intercellular adhesion molecule-1, and vascular adhesion molecule-1 [51]. On the other hand, another meta-analysis reported that polyphenol-rich interventions did not alter the level of CRP, TNF- α , and IL-6 inflammatory markers in older adults [52]. The contradictory findings might be explained by differences in the included criteria, including the types of polyphenols and the target population. Con-

sidering our findings from individual studies, three of ten RCTs (30%) reported a significant reduction of inflammatory markers, including IL-6, TNF- α , IL-9, IL-10, MIP-1 β , and IL-1 β , following polyphenols treatment compared to controls [29, 32, 34]. Furthermore, the levels of inflammation appeared to be significantly reduced in specific population conditions, such as the elderly with overweight or obese subjects and MCI patients who might have low-grade or chronic inflammatory status.

The improvement of cognitive abilities by polyphenols could be underlined by various possible mechanistic pathways such as inhibition of inflammation, an increase in cerebral blood flow, enhancement of endothelial function, stimulation of neural synaptic plasticity, activation of brain areas related to cognitive abilities, and modulation of the gut-brain axis [53–56]. To elucidate, whether or if polyphenols protect against cognitive impairment in humans by inhibiting inflammatory processes. The quantitative findings found that the polyphenols could ameliorate verbal memory, and executive function as well as reduce blood IL-6, mainly in older participants. As a result, polyphenols' anti-inflammatory properties may contribute to enhanced cognitive function in humans, particularly in those with low-grade inflammation. Consistent with two individuals' studies, lowering blood inflammatory mediators (TNF- α , IL-1 β , and IL-6) may contribute to improved global cognitive function and verbal memory after 26 weeks and 6 months following treatments with resveratrol and propolis extract [32, 34]. Remarkably, supplementing with propolis extract for extended periods of time (12 and 24 months) may prolong the benefits of anti-inflammation and overall cognitive enhancement compared to 6 months [34]. In addition, the potential of polyphenols on inflammation related to cognition seems to be noticeable in elderly participants with obesity and MCI. This suggests that the effect of polyphenols intervention on inflammation linked to cognitive function may be more prominent over a longer period and in older people with chronic inflammatory conditions rather than in healthy individuals. However, the effects of polyphenols on the interaction between inflammation and cognitive function are complicated and vary depending on other factors such as population conditions, inflammatory status, severity of cognitive impairment, domain of cognitive function, and type and duration of polyphenols supplementation. In this review, the number of available studies reporting the properties of polyphenols

on inflammation and cognitive outcomes was limited, and most were conducted in older individuals. A number of human trials in specific subjects with ongoing chronic inflammatory status (e.g., dementia, Alzheimer's disease, MCI, stroke, diabetes, obesity, cancer, and metabolic syndrome) are required in order to clarify the effect of polyphenols intervention on the interaction between cognitive function and inflammation. Furthermore, additional variables might influence the relationship between cognition and inflammation through polyphenols intervention, such as the modulation of the gut microbiota and the blood-brain barrier, which should be further explored.

A limitation of this review is that the number of available studies which assessed both inflammatory markers and cognitive function, as well as the number of sample sizes, was rather small. In addition, the eligible studies used various types and dosages of polyphenols supplementation as well as different population conditions. So, the retrieved data from available studies was insufficient to perform the subgroup analysis, in particular the age group, subject's condition, type of polyphenols intervention, concentration, and duration. Therefore, substantial inter-trial heterogeneity was significantly detected in some parameters, including IL-6, TNF- α , working memory, executive function, and attention. These might confound the efficacy of the polyphenol's interventions on the actual outcomes.

5. Conclusion

This review provides comprehensive findings from the available evidence on the effects of polyphenol treatments on the outcomes of inflammation related to cognitive function in human randomized controlled trials. According to the findings, the reduction of IL-6 may be attributed to enhanced cognitive performance, particularly in verbal memory and executive function, following polyphenols interventions. Even though the other domains of cognition and inflammatory markers did not reach statistical significance, the findings revealed that polyphenols interventions tend to attenuate inflammatory markers as well as improve cognitive abilities. These findings shed light on the benefits of polyphenols in the link between inflammation and cognitive function, which could be promoted for the prevention of inflammatory-related cognitive dysfunction or neurodegenerative diseases.

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Conflicts of interest

The authors declare no conflicts of interest.

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