Systematic Review

Effects of anthocyanin-rich supplementation on cognition of the cognitively healthy middle-aged and older adults: a systematic review and meta-analysis of randomized controlled trials

Ruo Chen Feng, Yan Hong Dong, Xian Li Hong, Ya Su, and Xi Vivien Wu

Context: *The prevalence of age-related cognitive decline has been on the rise as the global population age, putting the independence and quality of life of elderly at risk. Anthocyanin, as a subclass of dietary flavonoids, may have a beneficial impact on cognitive outcomes.* ***Objectives:*** *To examine the effects of dietary anthocyanin supplementation on cognition of the cognitively healthy middle-aged and older adults.* ***Data Sources:*** *PubMed, ScienceDirect, CINAHL, EMBASE, ProQuest and Cochrane databases were searched.* ***Data Extraction and Analysis:*** *Thirteen studies were included in this meta-analysis. Anthocyanin-rich supplementation was found to significantly improve the processing speed of the older adults (95%CI 0.08, 0.44; P = 0.004). No significant differences were observed between intervention and control groups on memory, attention, executive function and psychomotor performance. Current neuroimaging studies have found promising effects of anthocyanin supplementation on brain activation and cerebral perfusion.* ***Conclusion:*** *Anthocyanin-rich supplementation may preserve cognitive processing speed and neuro-activities in older adults, which improves their daily functioning and quality of life. This review provides useful insights to guide direction and methodological designs for future studies to explore the underlying mechanisms of anthocyanins.*
Systematic Review and Meta-analysis Registration: *PROSPERO registration No. CRD42021228007.*

INTRODUCTION

Cognitive decline is common as people age. The irreversible and disabling nature of age-related neurodegeneration has made it one of the top public health concerns worldwide[1] as it threatens the independence and quality of life of older adults. Moreover, cognitive decline caused by ageing of the brain puts older

Affiliation: *R. C. Feng* is with the High-Dependency Unit, Tan Tock Seng Hospital, National Health Group, Singapore. *Y. H. Dong* and *X. V. Wu* are with the Alice Lee Centre for Nursing Studies, Yong Loo Lin School of Medicine, National University of Singapore, Singapore. *Y.H. Dong* is with the Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore. *X. L. Hong* is with the Medical Intensive Care Unit, Tan Tock Seng Hospital, National Health Group, Singapore. *Y. Su* is with the Shanghai Jiao Tong University, School of Nursing, Shanghai, China. *Y. Su* is with the Faculty of Health Sciences, Hokkaido University, Japan. *X. V. Wu* is with the NUSMED Healthy Longevity Translational Research Programme, National University of Singapore, Singapore.

Correspondence: *Xi Vivien Wu*, Alice Lee Centre for Nursing Studies, Yong Loo Lin School of Medicine, National University of Singapore, Level 2, Clinical Research Centre, Block MD 11, 10 Medical Dr, Singapore 117597. E-mail: nurwux@nus.edu.sg.

Key words: Anthocyanin, attention, cognition, executive function, memory, middle-aged adults, neuroimaging, older adults, processing speed, psychomotor performance.

https://doi.org/10.1093/nutrit/nuac055

adults at risk of developing neurodegenerative diseases such as Alzheimer's disease.[2] The current lack of effective treatments for neurodegenerative disorders[3] has highlighted the importance of developing preventive measures to slow age-related cognitive decline even before the onset of neurodegenerative illnesses.

One of the widely held ageing theories—the free radical theory of ageing[4]—postulates that the ageing process is the accumulation of oxidative stress in cells and tissues because of excessive production of reactive oxygen species (ROS) from aerobic metabolism.[5] The brain, being a metabolically active organ, utilizes large amounts of oxygen to generate energy for neuronal activities and produces ROS in large quantities.[6] The resultant oxidative stress adversely affects cerebrovascular function, neurochemical balance and neuronal cell apoptosis in the brain.[7] To counteract such oxidative damage caused by brain ageing, building stronger antioxidant defence is the key.[8] As such, an increase in antioxidants through increasing dietary components containing anthocyanins attracts great public attention given its affordability and minimal adverse effects compared to synthetic antioxidant vitamins and other nutraceuticals which have been reported to be toxic due to overconsumption.[8,9]

Anthocyanins as a dietary supplement of a subclass of flavonoids, are found in red cabbage, aubergine skin, red onion, and tomatoes; however, anthocyanins are most abundant in fruits such as berries, grapes, and plums.[8,10] It is well known that anthocyanins can decrease the risk of various diseases because they have many antioxidants, anticarcinogenic, anti-inflammatory and cardioprotective effects, which explains the various biological effects reported for these substances.[11] Brain ageing caused by the rapid ageing of the population has led to the increased risk of dementia and other neurodegenerative diseases,[3] and the neuroprotective effect of flavonoids has also been widely proven. In addition to exerting their neuroprotective effects via the antioxidant mechanism, anthocyanins are also found to prevent the onset of neurodegenerative diseases via the anti-neuroinflammatory pathway by deactivating proinflammatory cytokines and inhibiting COX-2 enzymes.[12] Min et al. (2011) found in their study that anthocyanins may potentially reduce apoptosis of neurons as they could inhibit the release of apoptosis-inducing factors. By preserving neurons and retaining their functions, anthocyanins may counteract the loss of neurons caused by brain ageing and thus, slow age-related cognitive impairment.[13] On the micromolecular level, anthocyanins and their metabolites are absorbed by the human stomach and small intestine following ingestion.[14,15] Anthocyanin derivatives readily cross the blood–brain barrier (BBB) and are detected in different brain regions of rodents and pigs.[16,17] This has led to the postulation that anthocyanins may cross the human BBB and directly exert their antioxidant effects in the central nervous system (CNS)[18] to reduce the oxidative damage, inflammation and neuronal apoptosis inflicted during the course of normal brain ageing. Anthocyanins, hence, hold great potential to mitigate age-related cognitive decline.[19]

The positive correlation between anthocyanin intake and cognitive function has been widely demonstrated in large-scale epidemiological studies. For example, Devore et al.[20] found in their four-year study that elderly participants with a higher intake of anthocyanin-rich berries exhibited a significantly slower rate of cognitive deterioration. Similarly, another study on 3,777 older participants over a ten-year period observed that a higher intake of flavonoids—the parent class of anthocyanins—was associated with better cognitive performance and lower risks of pathological cognitive impairment.[21] In animal trials, rats that are fed an anthocyanins-rich diet have shown significant improvement in cognitive performance.[22–24] Possible explanations of such neuroprotective effects in animals are further explored by other studies and uncover that anthocyanin enhances neurological communications and brain activities in aged mice.[25–27]

Recent advancements in medical technology have inspired researchers to explore the effects of anthocyanins from new perspectives, such as neuroimaging. Neuroimaging provides direct visualization of the structure and function of the human nervous system. Boespflug et al.[28] detected a significant increase in blood oxygen level-dependent signals in participants' functional magnetic resonance imaging (fMRI) results following 16 weeks of blueberry supplementation. Such new perspectives are worth exploring in this review to gain a holistic understanding of the neuroprotective effects of anthocyanins.

While most studies explore the effects of anthocyanin supplementation on older adults, emerging evidence has suggested that age-related cognitive decline may start in middle age.[29] A longitudinal cohort study in Britain spent 10 years tracking cognitive changes in 10,308 participants aged 45 to 70 years. The data revealed significant average cognitive decline not only in elderly participants, but also in those aged 45 to 49 years.[30] Therefore, it is necessary to include middle-aged adults when exploring the effects of anthocyanin-rich supplementation on cognitive function. Moreover, existing literature have discussed the effects of dietary antioxidants on the cognition of older adults, however, they typically focus on the broad spectrum of antioxidants, namely, vitamins, carotenoids, and polyphenols.[31–34] None of the studies focused on a subclass of antioxidants and specifically explored their effects

without interference from other molecules. Hence, it is essential for this review to explore the effect of anthocyanin supplementation on cognition in both cognitively healthy middle-aged and older adults from different perspectives, namely, neuropsychological assessment and neuroimaging.

METHODS

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines,[35] and the Cochrane Handbook for Systematic Reviews of Interventions.[36] The protocol of this review has been registered on the Prospective Register of Systematic Reviews (PROSPERO) database (Registration ID: CRD42021228007).

Search strategy

A comprehensive three-step search strategy was adopted as recommended by the Cochrane Handbook for Systematic Reviews of Interventions.[37] First, a search in the six databases, namely, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Excerpta Medica database (EMBASE), PubMed, ScienceDirect, ProQuest and Cochrane databases was conducted from inception to September 2020. Keywords and index terms were used following the syntax rules of each database (see Table S1 in the Supporting Information online). Second, ongoing trials were searched in data sources such as ClinicalTrials.gov and the Cochrane Controlled Register of Trials to reduce the potential risk of publication bias.[38] Finally, the reference lists of the included studies were manually screened to retrieve relevant studies.

Eligibility criteria

Randomized controlled trials (RCTs) from inception to 17 September 2020 that met the following inclusion criteria were included: 1) participants were adults aged 40 years and above with no known diagnosis of cognitive impairment; 2) interventions included various forms of dietary products that were rich in naturally occurring anthocyanins; 3) dietary placebo or control treatments that contained negligible amounts of anthocyanins were used; 4) cognitive performance of participants was evaluated using validated neuropsychological tests or neuroimaging methods; 5) studies were published in English; 6) studies were peer-reviewed; 7) studies were required to enrol human vs. animal subjects (Table 1).

Study selection and data extraction

Two reviewers (RCF and XLH) independently screened the titles and abstracts of the papers, followed by another round of independent screening of full texts based on the detailed eligibility criteria. Two reviewers used a standardised data extraction form to extract relevant information from the included RCTs independently before verifying the results. The authors of the studies were contacted via email if there were any missing data. Any disagreements regarding study selection and data extraction were resolved through discussion with the third reviewer (XVW).

Quality assessment

The quality of each included RCT was evaluated by two reviewers independently using the first version of Cochrane's Risk of Bias (ROB) tool which consisted of selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias.[36] Every domain was graded "Low," "High" or "Unclear" risk with supporting judgement.[36] Discrepancies were resolved through discussion with the third reviewer. Cohen's kappa was calculated to assess the degree of inter-rater agreement.[39] Publication bias was assessed using Egger's regression

Table 1 **PICOS criteria for inclusion of studies**

Population	Cognitively healthy, independently living middle-aged and older adults (40 years and above) without any confirmed pathological cognitive impairment Exclude participants who had MCI or other neurodegenerative disorders either diagnosed by a professional clinician or detected by pre-trial screening
Intervention	Various forms of dietary treatments that were rich in naturally occurring anthocyanins including fresh fruits, beverages, and natural extracts Both acute (less than a day) and chronic supplementation of anthocyanin-rich fruits (one week or longer)
Comparator	Dietary placebo or control treatments which contained negligible amounts of anthocyanins
Outcome	Cognitive outcomes that were evaluated through the following means: • Validated neuropsychological tests • neuroimaging methods
Study type	Studies were peer-reviewed and written in English Animal studies were excluded

and funnel plots when there were more than ten studies in a meta-analysis.[40]

Additionally, the overall quality of evidence and strength of recommendations were evaluated using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.[41] Two reviewers independently assessed each outcome and disagreements were resolved through discussion with the third reviewer.

Data synthesis

Quantitative data extracted from the RCTs were imported into RevMan 5.4 for meta-analysis using the inverse variance method and pooling of effects with the random-effects model.[42] The pooled effect of anthocyanin-rich interventions was calculated using Z-statistics with 5% statistical significance and Cohen's d was used to indicate the magnitude.[43] RCTs that were ineligible for meta-analysis were synthesised narratively. Heterogeneity was assessed using I^2 and Chi-square (χ^2) statistics.[42]

A large variety of neuropsychological tests were used in the RCTs, which were organised into different neurocognitive domains. Such classification was based on 1) information provided by the authors, 2) a previously published systematic review[44] and 3) a well-established reference text titled "A compendium of neuropsychological tests: Administration, norms, and commentary (3rd ed.)".[45] Meta-analysis for each domain was run independently and the corresponding forest plot was produced. Under each forest plot, subgroup analysis was conducted either by subgroups of treatment duration (acute, $<$ 1 d and long-term, $\geq$ 1 wk), or by age group. Every domain and subgroup was created when there were available outcome data from two or more RCTs.[42]

RESULTS

Study selection

The search process retrieved 4781 records. A total of 60 full texts were screened for eligibility and 13 studies were included in this review. The process of study inclusion and exclusion with justifications is presented in the PRISMA flow diagram (Figure 1). Complementary searches for grey literature yielded zero results. Two of the included studies were excluded from the meta-analysis due to missing data (mean and standard difference)[46] and the use of global cognition tests.[47]

Study characteristics

The RCTs included in this review were conducted from 2014 to 2020, with sample sizes ranging from 14 to 190 subjects. A total of 871 participants were enrolled, with 149 middle-aged adults (mean age 40–55 years) and the remaining subjects were older adults (mean age above 55 years). Six of the included RCTs used blueberry-containing products,[46,48–52] two used grape-containing products,[47,53] one used the extract from both blueberry and grape[54]; one used blackcurrant extract,[55] one used chokeberry extract,[56] one used cherry concentrate,[57] and one used a beverage containing mixed berries.[58] All RCTs used placebo products as their control treatments. Two RCTs studied the effects of acute anthocyanin-rich and placebo supplementations,[49,57] while other RCTs had long-term supplementations varying from one to 24 weeks.[46–48,50–56,58] Summaries of the study and intervention characteristics are presented in Tables 2[46–58] and 3[46–58].

Neuropsychological tests were organised into the following five neurocognitive domains for synthesis: Memory, processing speed, attention, executive function and psychomotor performance (see Table S2 in the Supporting Information online). Three studies used neuroimaging methods to detect brain perfusion and brain activity.[48,56,57]

Quality assessment

ROB assessment was conducted for each included study and the ROB summary and graph are presented in Figure 2[46–58]. The overall ROB was rated "low" (68.1%). The risks of selection bias (46.2%), performance bias (15.4%), detection bias (38.5%), attrition bias (15.4%), reporting bias (30.8%) and other bias (30.8%) were rated "unclear" or "high." The Cohen's kappa statistic (K = 0.835) indicated an excellent degree of inter-rater agreement. Publication bias was not assessed since there were less than ten studies under the meta-analysis of each domain.[40] The GRADE results (see Table S3 in the Supporting Information online) showed low quality of evidence for all outcomes due to small sample sizes and variability of the interventions.

Meta-analysis results

Forest plots of the effects of anthocyanin supplementation on the processing speed and memory domains are shown in Figure 3. Four of the included RCTs reported the effects of long-term anthocyanin-rich interventions on processing speed. Participants (older adults) in three of the RCTs received a minimum of eight weeks of anthocyanin supplementation containing blueberries.[48,50,51] The pooled result was statistically significant and favoured intervention ($P = 0.004$) with a small overall effect size of 0.26 (95%CI [0.08, 0.44]). The heterogeneity among them was not statistically significant (I^2 = 0%; χ^2 = 3.81, $P = 0.87$). Seven RCTs were

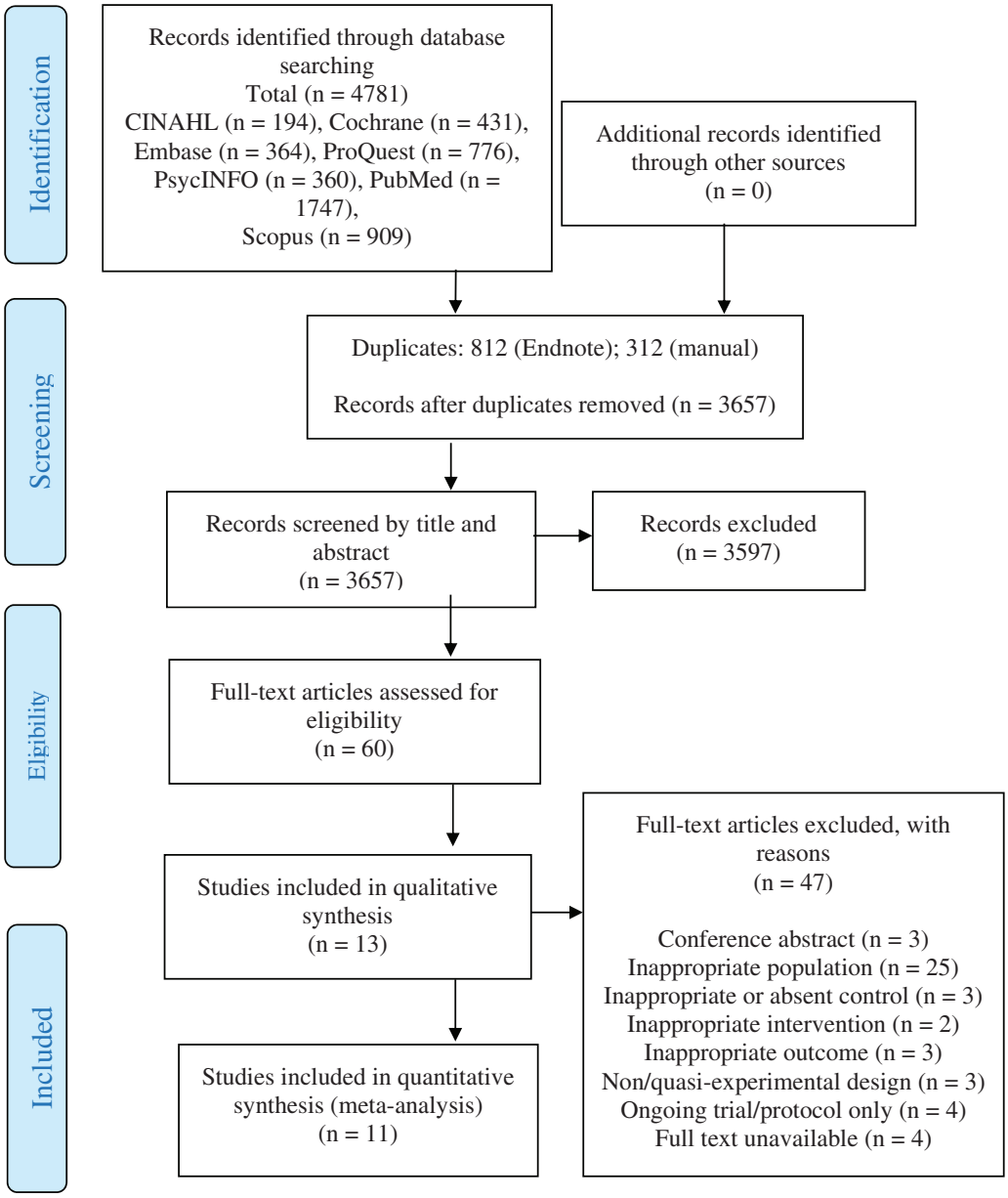


Figure 1 **PRISMA flow diagram**

included in the meta-analysis under the memory domain. No statistically significant heterogeneity (I^2 = 0%; $\chi^2 = 10.93$, $P = 0.99$) was detected. Although the effect size (d = 0.07; 95%CI [-0.03, 0.17]) was not statistically significant ($P = 0.16$), it could be observed on the forest plot to favour the intervention arm.

Non-significant effects ($P > 0.05$) with unimportant heterogeneity were found for the domains of attention (d = 0.00; $P = 0.97$; I^2 = 0%), executive function (d = 0.00; $P = 0.99$; I^2 = 0%), and psychomotor performance (d = 0.03; $P = 0.66$; I^2 = 0%), as summarized in Table 4. Subgroup analyses in terms of treatment duration (acute and long-term supplementation) and age groups (middle-aged and older adults) were conducted on attention, executive function, and psychomotor performance. The forest plots (see Figures S1–S3 in the Supporting Information online) illustrated that the RCTs with long-term anthocyanin supplementation had a relatively larger effect size which favours the intervention arm compared to the RCTs with acute supplementation. However, no significant differences or trends were observed between the middle-aged and older adults.

Narrative synthesis

The only trial that used a global cognitive test to measure participants' cognitive performance reported significant improvement in the Mini-mental State Examination (MMSE) scores ($P < 0.0001$) and

Table 2 **Characteristics of the included studies**

Study ID (Author, Year)	Publication type	Study Design/ Comparator/ Setting	Randomization Method Blinding	Population	Participants Age Range (Intervention: Mean±SD) Control: Mean±SD)	Participants Sample size N/Gender	Attrition rate	ITT/Other Missing data management (Y/N) ITT Population	Ethical Approval/ Protocol/ Registration/ Grant support (Y/N)
Ahles et al. (2020)56	Published Clinical Trial	3-arm parallel RCT Placebo-controlled	Concealed block randomization Double-blind	Cognitively intact and healthy Middle-aged adults (25≤ BMI ≤ 35 kg/m2)	40–60 90 mg group: 53 ± 1 150 mg group: 53 ± 1 Placebo group: 53 ± 1	N = 97 90 mg group: 33 150 mg group: 33 Placebo group: 31	T: 4.0% 90 mg group: 2.9% 150 mg group: 5.7% Placebo group: 3.1%	Y/N ITT population: N= 101 90 mg group: 34 150 mg group: 35 Placebo group: 32	Y/N/Y/Y
Bensalem et al. (2019)54	Published Clinical Trial	2-arm parallel RCT Placebo-controlled	NR Double-blind	Cognitively intact older adults (26 < MMSE ≤ 29) (WMS: <29 for the immediate recall score and <16 for the delayed recall score) Normal to slightly increased body mass indices (20 ≤ BMI ≤ 28 kg/m2) Cognitively intact older adults (ACE-III score ≥ 88)	60-70 I: NR C: NR	N = 190 I: 92 C: 98	T: 11.2% I: 14.0% C: 8.4%	Y/N ITT population: N = 206 I: 101 C: 105	Y/N/Y/Y
Bowtell et al. (2017)48	Published Clinical Trial	2-arm parallel RCT Placebo-controlled	Incomplete randomization Double-blind		65 and above I: 67.5 ± 0.9 C: 69.0 ± 0.9	N = 26 I: 12 C: 14	T: 0% I: 0% C: 0%	N/N	Y/N/N/Y
Calapai et al. (2017)47	Published Clinical Trial	2-arm parallel RCT Placebo-controlled	Block randomisation Double-blind	Cognitively intact older adults (MMSE ≥ 24)	55-75 I: 66.86 ± 5.3 C: 66.90 ± 5.2	N = 104 I: 54 C: 50	T: 4.6% I: 5.3% C: 3.8%	Y/N ITT population: N = 114 I: 57 C: 57	Y/Y/Y/N
Cook et al. (2020)55	Published Clinical Trial	2-arm crossover RCT Placebo-controlled	Simple randomisation Double-blind	Community dwelling, physically active independent older adults (Mini-Cog: Non-demented)	65-73 I: NR C: NR	N = 14 I: NR C: NR	T: 0.00% I: NR C: NR	N/N	Y/N/N/N
Dodd et al. (2019)49	Published Clinical Trial	2-arm crossover RCT Placebo-controlled	NR Single-blind (participants)	Cognitively intact, healthy and non-depressed older adults (MMSE > 25; BSI < 11)	60-75 I: NR C: NR	N = 18 I: 18 C: 18	T: 0% I: 0% C: 0%	N/N	Y/N/Y/Y

(continued)

Table 2 **Continued**

Study ID (Author, Year)	Publication type	Study Design/ Comparator/ Setting	Randomization Method Blinding	Population	Participants Age Range (Intervention: Mean±SD) Control: Mean±SD)	Participants Sample size N/Gender	Attrition rate	ITT/Other Missing data management (Y/N) ITT Population	Ethical Approval/ Protocol/ Registration/ Grant support (Y/N)
Keane et al. (2016)57	Published Clinical Trial	2-arm crossover RCT Placebo-controlled	NR	Healthy, middle-aged adults	45-60 I: NR C: NR	N = 27	T: 10% I: NR C: NR	N/N	Y/N/Y/Y
Lamport et al. (2016)53	Published Clinical Trial	2-arm crossover RCT Placebo-controlled Double-blind	Counterbalanced randomization schedule	Middle-aged working mothers with at least 1 child aged < 13 years; (BMI = 18–29; works ≥ 30 h/wk)	40-50 I: NR C: NR	N = 25	T: 24.0% I: NR C: NR	Y/N	Y/N/Y/N
McNamara et al. (2017)46	Published Clinical Trial	4-arm parallel RCT Placebo-controlled	NR Double-blind	Older adults with mild SCD with aging (CDR = 0; CVLT cumulative acquisition score between 1.0 SD below and 1.0 SD above the age-corrected mean; MoCA score > 25)	62-80 FO: 69 ± 1.26 BB: 68 ± 0.89 BB+FO: 68 ± 1.05 Placebo: 67 ± 1.70	N= 76 FO: 17 BB: 19 BB+FO: 20 Placebo: 20	N= 19.1% FO: 19.0% BB: 20.8% BB+FO: 23.1% Placebo: 13.0%	N/N N/N	Y/Y/Y/Y Y/Y/Y/Y
Miller et al. (2018)50	Published Clinical Trial	2-arm parallel RCT Placebo-controlled	Block randomisation Double-blind	Cognitively intact older adults (MMSE ≥ 24; BMI = 18.5–29.9)	60–75 I: 67.8 ± 4.6 C: 67.3 ± 4.8	N = 37 I: 18 C: 19	T: 11.9% I: 14.3% C: 9.5%	N/N	Y/Y/Y/Y
Nilsson et al. (2017)58	Published Clinical Trial	1-arm crossover RCT	Simple randomisation Single-blind (Outcome assessment)	Apparently healthy non-smoker older adults Normal to slightly increased body mass indices (BMI ≤ 28)	50–70	N = 40 BC: 20 CB: 21 (1 excluded in analysis)	T: 13.0% BC: 13.0% CB: 13.0%	N/Y	Y/Y/Y/Y
Small et al. (2014)51	Published Clinical Trial	2-arm parallel RCT Placebo-controlled	Block randomisation Double-blind	Cognitively intact older adults (MMSE ≥ 24)	65-85 I: 72.82 ± 5.54 C: 74.34 ± 5.48	N = 105 I: 52 C: 53	T: 7.1% I: 10.3% C: 3.6%	N/N	Y/Y/Y/Y
Whyte et al. (2018)52	Published Clinical Trial	4-arm parallel RCT Placebo-controlled	NR Double-blind	Independently living healthy older adults with subjective self-reported memory complaints, non-demented (MMSE ≥ 24)	65-80	N = 112 Placebo: 27 WBP500: 28 WBP1000: 29 WBE111: 28	T: 8.2% Placebo: 10.0 % WBP500: 6.7% WBP1000: 6.5% WBE111: 9.7%	N/N	Y/Y/N/Y

Abbreviation. ACE-III, Addenbrooke's Cognitive Examination version III; BMI, Body mass index; ITT, Intention-to-treat; MMSE, Mini-mental State Examination; N, No; NR, Not reported; RCT, Randomized controlled trial; SD, Standard deviation; WMS, Wechsler Memory Scale; Y, Yes.

Abbreviation. BMI, Body mass index; BSI, Brief Symptom Inventory; ITT, Intention-to-treat; Mini-cog, Mini cognitive scale; MMSE, Mini-mental State Examination; N, No; NR, Not reported; RCT, Randomized controlled trial; SD, Standard deviation; WMS, Wechsler Memory Scale; Y, Yes.

Abbreviations: CDR, Clinical Dementia Rating; CVLT, California Verbal Learning Test; MoCA, Montreal Cognitive Assessment; SCD, subjective cognitive decline.

Table 3 **Characteristics of interventions, comparators and outcomes of the included studies**

Study ID	Intervention			Control			Outcome	
	Description of Intervention	Daily Amount Timing & Delivery Duration	Daily Anthocyanin Intake	Description of Control	Daily Amount Timing & Delivery Duration	Daily Anthocyanin Content	Cognition-related Outcomes	Secondary outcomes reported
Ahles et al. (2020)56	Aronia melanocarpa extract (AME) capsule	90mg & 150 mg 1 capsule daily for 24 wk	90mg AME group: 16 mg 150 mg AME group: 27 mg	Placebo capsule: 150 mg Maltodextrin only	150mg 1 capsule daily for 24 wk	0mg	Stroop colour and word test Grooved pegboard test Number cross-out test	Visual analogue mood scale Double-arm blood pressure and ankle-brachial index Carotid intimamedia thickness measured by carotid ultrasound - Serum BDNF concentration
Bensalem et al. (2019)54	polyphenol-rich extract from grape and wild blueberry (PEGB capsule)	600mg 2 capsules per day for 24 wk	0.13 ± 0.04% of anthocyanins	Placebo capsule: Pure maltodextrin containing no polyphenol	600 mg 2 capsules per day for 24 wk	0mg	CANTAB	Urinary Phenolic Metabolites
Bowtell et al. (2017)48	Blueberry concentrate: Blueberry extract and sugar	30ml once per day 12 wk	387 mg anthocyanidins and 25.5 g carbohydrate	Placebo: Synthetic blackcurrant and apple cordial with sugar added to match blueberry energy content	30ml once daily for 12 wk	Negligible amount	Cognitive tests adapted from Cogstate website	MRI: Pseudo-continuous ASL & brain activity during a numerical Stroop test - Serum analysis
Calapai et al. (2017)47	Cognigrape capsule: Grape extract and maltodextrin	250mg 1 capsule daily for 12 wk	> 32.5 mg	Placebo capsule: Maltodextrin	250mg 1 capsule daily for 12 wk	0mg	MMSE & RBANS	BDI & HARS
Cook et al. (2020)55	NZBC extract capsule	600mg 2 capsules daily for a week	210mg	Placebo capsule: Microcrystalline cellulose	600mg 2 capsules daily for a week	0mg 7-d washout period	CANTAB	Blood pressure Six-minute walk test performance
Dodd et al. (2019)49	Highbush blueberry powder mixed with 300 ml of semi-skimmed milk	300ml drink containing 30.1 g blueberry powder Acute supplementation	507.79 mg	Placebo powder matched for energy, sugar, vitamin C and total ascorbic acids mixed with 300 ml of semi-skimmed milk	300ml drink containing 19.9 g of control powder mixed Acute supplementation	0mg	11 neuropsychological tests	Blood pressure Large artery stiffness index derived from a digital volume pulse measurement - Serum BDNF concentration

(continued)

Table 3 **Continued**

Study ID	Intervention			Control			Outcome	
	Description of Intervention	Daily Amount Timing & Delivery Duration	Daily Anthocyanin Intake	Description of Control	Daily Amount Timing & Delivery Duration	Daily Anthocyanin Content	Cognition-related Outcomes	Secondary outcomes reported
Keane et al. (2016)57	Montmorency tart cherries concentrate	60ml (equivalent to about 180 whole cherries) Acute supplementation	68.0 ± 0·26 mg	Placebo supplement matched for volume and macronutrient content	60ml Acute supplementation	lower than the limits of detection	3 neuropsychological tests	Visual analogue scales for mental fatigue Blood pressure Transcranial Doppler imaging to detect CBFV in the middle cerebral artery - Near-infrared spectroscopy to measure cerebral oxygenation
Lamport et al. (2016)53	Concord grape juice	355ml Daily serving for 12 wk	167 mg anthocyanins as malvidin equivalent	Placebo juice: Matched for energy, appearance, taste, volume carbohydrate content and all sugars	355ml Daily serving for 12 wk	0mg 4-wk washout period	45-min cognitive test battery comprised 7 tests	Resting blood pressure Subjective mood: Visual analogue scales Subjective stress: Perceived Stress Scale Subjective anxiety: The short State-Trait Anxiety Inventory 6-item - Driving performance test
McNamara et al. (2017)46	Blueberry powder with placebo oil	25g Blueberry powder 2 packets daily for 24 wk	362.5 ± 1.00 mg cyanidin 3-glucoside equivalents/g	placebo oil + placebo powder matched for colour, taste, and sugar content	25g Blueberry powder 2 packets daily for 24 wk	0mg	3 neuropsychological tests - The Dysexecutive Questionnaire	Serum analysis APOE genotyping - Urine anthocyanin
Miller et al. (2018)50	Tifblue blueberry powder	24g twice daily for 90 d	Estimated 921.6 mg anthocyanins	Colour-matched, isocaloric, blueberry-flavoured placebo powder, comprised of maltodextrin, fructose, artificial and natural blueberry flavour, artificial colours, and citric acid	24 g twice daily for 90 d	0mg	6 Neuropsychological tests	Mood: GDS & POMS - Mobility: Dynamic stance and gait analysis

(continued)

Table 3 **Continued**

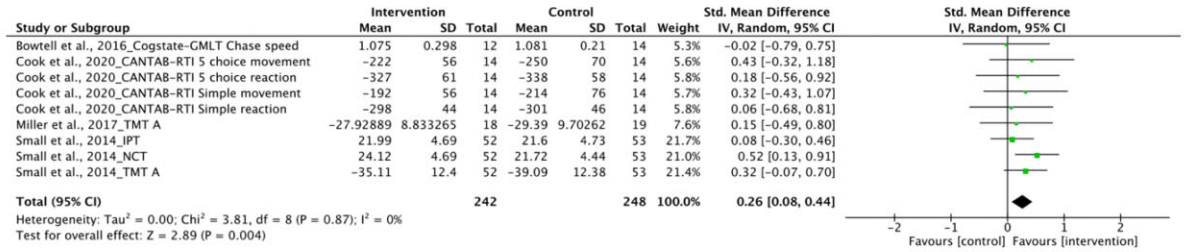
Study ID	Intervention			Control			Outcome	
	Description of Intervention	Daily Amount Timing & Delivery Duration	Daily Anthocyanin Intake	Description of Control	Daily Amount Timing & Delivery Duration	Daily Anthocyanin Content	Cognition-related Outcomes	Secondary outcomes reported
Nilsson et al. (2017)58	Berry beverage consisted of a mixture of Swedish berries	600ml 3 packages daily for 5 wk	248.52 ± 19.68 mg	Placebo beverage matched for low-molecular weight carbohydrates and pH	600 ml 3 packages daily for 5 wk	0mg 5-wk washout period	Verbal working memory test Selective attention test	Blood pressure Blood glucose monitoring - Serum analysis
Small et al. (2014)51	NT-020: A pill consisted of 900 mg proprietary formulation of blueberry, carnosine, green tea, plus 200 U vitamin D3, 40 mg Biovin Wild blueberry powder capsule	1800 mg 2 pills daily for 8 wk	225mg	A matched placebo pill	1800 mg 2 pills daily for 8 wk	Negligible amount	9 Neuropsychological tests	Nil
Whyte et al. (2018)52		500 mg (WBP500) 1000 mg (WBP1000) 111 mg (WBP111) 1 capsule daily for 24 wk	WBP500 group: 2.7 mg; WBP1000 group: 5.4 mg; - WBE111 group: 14 mg	Placebo powder: Maltodextrin and food grade artificial dye in order to be colour matched to the intervention 1000 mg/capsule	2000 mg (2 capsules) daily for 24 wk	0mg	5 Neuropsychological tests	Blood Pressure Mood: PANAS-NOW

Abbreviations: ASL, arterial spin labelling; BDI, Beck Depression Inventory; BDNF, Brain-derived neurotrophic factor; CANTAB, Cambridge Neuropsychological Test Automated Battery; fMRI, Functional magnetic resonance imaging; HARS, Hamilton anxiety rating scale; NZBC, New Zealand Blackcurrant; RBANS, Repeatable battery for the assessment of neuropsychological status.
Abbreviations: APOE, Apolipoprotein E; CBFV, Cerebral blood flow velocity.
Note. GDS = Geriatric Depression Scale; PANAS-NOW = Positive and Negative Affect Schedule (Now); POMS = Profile of Mood States; WBP = Wild blueberry powder.

Figure 2 **Risk of bias summary and graph.**

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) scores ($P < 0.0001$) of older participants after receiving 12 weeks of dietary supplementation with grapes.[47] In another trial that was excluded from the meta-analysis due to missing data, McNamara et al.[46] found a significant reduction ($P = 0.03$) in self-reported daily cognitive symptoms as measured by the Dysexecutive Questionnaire (DEX) following 24 weeks of blueberry supplementation. Significant improvements ($P = 0.04$) in recognition memory were also reported by McNamara et al.[46] but not in

Forest Plot of the Effect of Anthocyanin-rich Supplementation on Processing Speed



Forest Plot of the Effect of Anthocyanin-rich Supplementation on Memory

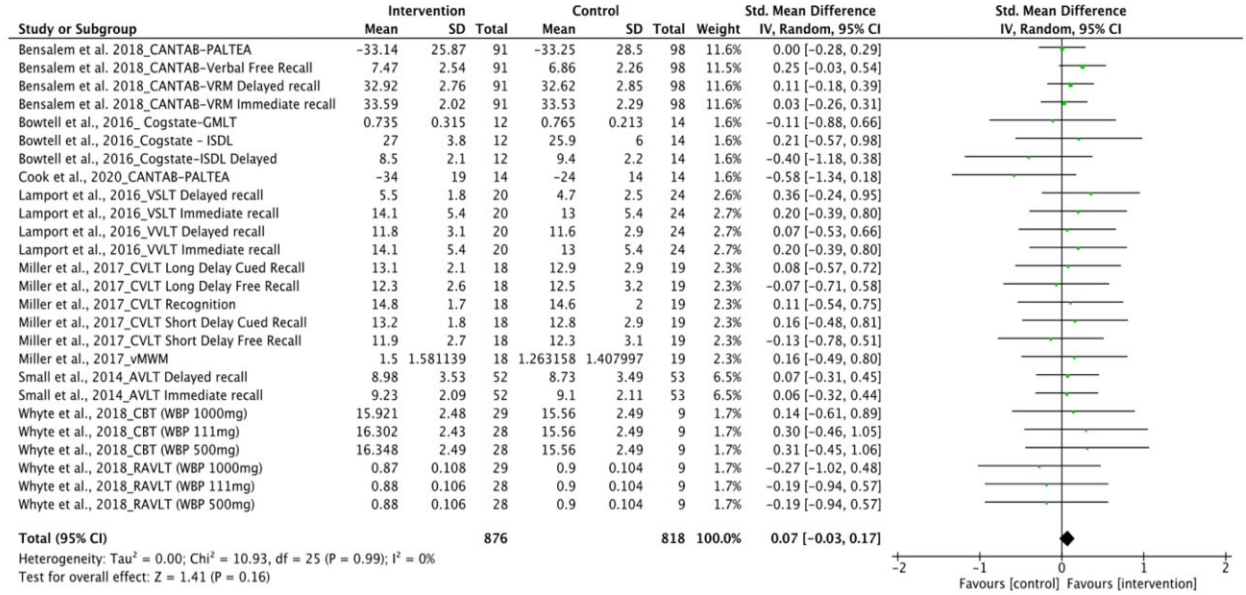


Figure 3 **Forest plot of the effect of anthocyanin-rich supplementation.**

any other cognitive domains, namely, working memory, processing speed and language.

Two studies reported outcomes measured through neuroimaging methods. Bowtell et al[48] observed a significant increase relative to baseline ($P < 0.001$) in the brain activation responses from fMRI results of the participants following the consumption of blueberries over a 12-week period. They also detected a significant elevation in cerebral blood flow to the grey matter in the parietal ($P = 0.013$) and occipital lobes ($P = 0.031$).[48] Another RCT used near-infrared spectroscopy to determine the acute effects of cherry supplementation on cerebral oxygenation, and a significant increase in the concentration of oxygenated haemoglobin was observed post-treatment but not between the intervention and placebo arms ($P = 0.029$).[57] Meanwhile, Keane et al.[57] used transcranial doppler imaging to measure cerebral blood flow velocity of the middle cerebral artery, however, no significant difference was observed.

DISCUSSION

This systematic review and meta-analysis examined the results from 13 RCTs that explored the effects of anthocyanin-rich dietary supplementation on human cognition and cerebral blood flow. Cognitive processing speed is crucial to human daily functioning, as it determines our abilities to perform instrumental activities[59] and motor tasks.[60] However, ageing can cause a decline in processing speed.[61,62] Research has found that slower processing speed is closely associated with an increased risk of falls in elderly individuals.[63] In this review, anthocyanin-rich supplementation was found to exhibit statistically significant benefits on processing speed in older adults. The majority of the RCTs used blueberry-containing products as the intervention, yet no meaningful patterns were found to inform the type and dose of supplementation due to the methodological heterogeneity among these RCTs.

Table 4 **Summary of the effect of anthocyanin-rich supplementation on attention, executive function, and psychomotor performance**

Domain	Number of RCTs	Number of participants	Heterogeneity			Pooled effect		
			χ^2	df (p)	I^2	d	95% CI	*P*
Attention	9	425	5.53	15 (0.99)	0%	0.00	[-0.15,0.14]	0.97
Executive function	11	634	16.55	29 (0.97)	0%	0.00	[-0.10, 0.10]	0.99
Psychomotor performance	6	265	6.41	11 (0.84)	0%	0.03	[-0.11, 0.18]	0.66

Meta-analysis of the memory domain suggested potential beneficial effects of anthocyanin-rich supplementation on memory, yet such effects were not statistically significant. Memory loss is one of the age-related symptoms most frequently reported by both middle-aged and older adults.[64] Memory benefits of anthocyanins have been reported in other reviews on dietary supplementation of blueberries.[65,66] Antioxidants, such as anthocyanins in blueberries, have been found to interact directly with neurons at the molecular level, initiating signalling pathways, increasing neuro-activities and stimulating neuronal regeneration.[67] The participants in these reviews are from all age groups including children whereas this current review focuses on middle-aged and older adults; the possibility could not be excluded on memory benefits of anthocyanins might be limited to the younger population when the brain and cognitive function are still at a developmental stage.[68]

This review reported statistically insignificant effects of anthocyanin supplementation on the domains of attention, executive function, and psychomotor performance. Nevertheless, evidence from existing studies supports the postulation that anthocyanins enhance attention and executive function via antioxidant mechanisms. Monoamine levels, particularly for dopamine, have been observed to rise when people perform attention and executive tasks.[69] Anthocyanins with potent antioxidant properties may increase monoamine levels by scavenging monoamine oxidase (MAO) and reducing MAO-induced oxidative stress in human brains.[70] This is supported by a RCT in which Watson et al.[71] detected significant inhibition of MAO activity in human blood following blackcurrant supplementation. The anti-neuroinflammatory and antiapoptotic mechanisms of anthocyanins, however, have only been observed in animal and in vitro studies but not in human studies. In this review, none of the included RCTs measured relevant neuro-endocrinological markers. It is possible that neuropsychological testing alone is insufficient to detect the cognitive effects of anthocyanins, and physiological changes at the molecular level should also be considered.

Subgroup analysis of acute and long-term supplementation did not detect any significant subgroup differences in attention, executive function, or psychomotor performance domains. This is likely due to the lack of sufficient acute studies. Nevertheless, it is observed from the forest plots that studies with long-term anthocyanin supplementation had relatively larger effect size than those with short-term supplementation. This might suggest that dietary anthocyanin supplementation tends to exhibit stronger neurocognitive effects in the long run, which may explain the positive correlations between anthocyanin intake and cognitive performance that were observed in long-term epidemiological studies,[20,21] but not in acute dose-timing studies.[72] Anthocyanin is a promising biologically active compound that can improve cognition and neuroprotection.[73] However, due to the differences in the study methods, such as the age of the participants, the different carriers provided for anthocyanins, and doses of anthocyanin, the conclusions of existing acute and long-term supplementation studies may require more clinical and observational studies. For example, beverages consist of a mixture of berries, which are combined with fibre, and the effect may not be attributed to anthocyanins alone, which also suggests that the carrier that provides anthocyanins is also worth considering. In addition, ageing is related to changes in the functional characteristics of the digestive system, such as delays in transit time, loss of absorption, and the impact of prescription drug use on the gut microbiota.[73] Therefore, the variation in age and genetic polymorphisms may also affect the bioavailability and metabolism of anthocyanins.[74]

This review also gathers evidence from a few neuroimaging studies that showed beneficial effects of anthocyanin-rich supplementation on neuro-activities. The underlying mechanism could be that anthocyanin molecules inhibit neuronal apoptosis by exerting their antioxidant effects in the CNS. Oxidative stress causes damage to various signalling pathways in cells, particularly the mitogen-activated protein (MAP) kinase pathways, which play an important role in mediating cell proliferation, transformation, and apoptosis.[75,76] During brain ageing, oxidative stress builds up in neuronal cells and activates pro-apoptotic signalling proteins such as c-jun amino-terminal kinase (JNK) which initiates cell apoptosis.[77] Anthocyanins with potent

antioxidant properties may thus help to inhibit neuronal apoptosis and boost neuro-activities by reducing oxidative stress in the CNS. Meanwhile, anthocyanins also help to protect the integrity of the BBB by scavenging nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOXs)—a type of ROS responsible for damaging the BBB78—from the arterial walls.[79,80] The above mechanisms explain the increase in the neuro-activities and cerebral perfusion observed in the participants' neuroimaging results following anthocyanin-rich supplementation.[48,57]

Strengths and limitations

This is the first systematic review and meta-analysis that investigated the effects of anthocyanin-specific supplementation on cognition and brain parameters in both middle-aged and older adults. Findings from this review were supported by concrete quantitative data from existing RCTs. By zooming into the subclass of anthocyanins, this review reduced potential interference from other types of dietary antioxidants, such as soy isoflavones and cocoa flavanols. In addition to the traditional neuropsychological assessment tools used to evaluate cognitive outcomes, this review added neuroimaging as an additional measure to identify relevant physiological evidence supporting the neuroprotective effects of anthocyanin interventions.

However, the limitations of this review should not be overlooked. Ten of the included RCTs had small sample sizes of less than 50 participants in each study arm. In general, 871 participants were included in this review but only 149 of them were middle-aged adults. There were only three RCTs on middle-aged adults, making it insufficient for meta-analysis to produce any meaningful results on middle-aged adults. This might result in the overall sample being unrepresentative of the target population. Moreover, this review is unable to conclude how different types and dosages of anthocyanin-rich supplementation affect cognitive outcomes due to the great heterogeneity of interventions used by the included RCTs. Most interventions used were naturally-occurring foods that may contain other micro- and macro-nutrients that could interfere with their neuroprotective effects. In addition, similar to the mixture beverage, the effect may not be attributed to anthocyanin alone, which suggests that the carrier that provides anthocyanins is also worth considering. Several compounding factors that may affect the treatment effect need to be highlighted. For example, the participants' compliance in taking the treatment products was not well monitored, especially for long-term trials. The dietary patterns of the participants were also not controlled to trace the intake of other anthocyanin-rich foods.

The diverse neuropsychological tests with different scales and scoring systems, and the difficulty level of the tasks post challenges for the meta-analysis. Mapou[81] has attempted to classify a range of integrated modalities as a framework for the assessment of cognition overall. The order of placement is not on the basis of cognitive complexity, but rather to infer those skills at the lower level are seen as fundamental to effective expression of remaining skills in the framework. According to Mapou's framework[81], attention and processing speed abilities are considered fundamental to the effective expression of other higher-level abilities, such as learning and memory. Tasks that assess higher-level abilities such as learning and memory may seem more difficult cognitively than tasks assessing fundamental abilities such as processing speed. In fact, neuropsychological assessments do not categorize cognitive outcomes based on difficulties of the tasks but focus on the performance of all cognitive domains, as cognitive domains are interconnected. Attention and processing speed abilities are essential for higher cognitive abilities. Tasks assessing higher-level abilities may seem more difficult cognitively than tasks assessing foundational-level abilities. However, this does not mean that the outcome of processing speed is less important than learning and memory. Nevertheless, this review did consider the difficulty of cognitive task, by including various level of cognitive domains, such as memory, attention, executive function, and psychomotor performance. Cognitive task difficulty is relevant for outcome measures, eg, recalling a longer wordlist [eg, >10 words, Wechsler Memory Scale used in Bensalem et al.[54]] in a verbal memory task is certainly more difficult than one with 3 words [eg, Mini-Mental State Examination used in Calapai et al[47]]. However, not all reviewed studies provide rationale for choosing the specific cognitive tests; hence, the task difficulty in relation to the study design are unable to be accounted for. Future studies should attempt to address such limitations.

Implications for future research

Based on the findings of this review, future research can focus on specific neurocognitive domains such as processing speed and memory, to minimize the heterogeneity in the neuropsychological tests used. Standardization in terms of the types, doses, and durations of anthocyanin-rich supplementations is highly encouraged to aid the conversion of research evidence into comprehensive dietary recommendations. Additionally, future trials should engage more middle-aged participants to better understand whether the effects of anthocyanin-rich supplementation on aged-

related cognitive decline can be enhanced by early intervention, with follow-up for long-term effects. Greater emphasis should be placed on applying advanced neuroimaging methods in investigating other possible underlying mechanisms of anthocyanins in the human neurological system.

CONCLUSION

This meta-analysis examined the best available quantitative evidence regarding the effects of anthocyanin-rich supplementation on the cognitive function of middle-aged and older adults. Evidence from 13 RCTs suggested that anthocyanin-rich supplementation is effective in countering the aged-related decline in cognitive processing speed and memory function of older adults. This review recommends that adults take long-term anthocyanin-rich supplementation to prevent age-related decline in their cognitive processing speed, which improves daily functioning and reduces the risk of falling. Current neuroimaging studies have also found promising effects of anthocyanin supplementation on brain activation and cerebral perfusion. This review provides useful insights to guide direction and methodological designs for future studies to explore the underlying mechanisms of anthocyanins.

Acknowledgement

Author contributions. Ms Ruochen FENG and Dr. Xi Vivien WU was involved in study conception, design, search strategy development, database searching, study selection, data extraction, collection, analysis, writing, and critical review of the manuscript. Ms Xianli HONG was involved in the quality appraisal, data extraction and critical review of the manuscript. Dr Ya SU and Dr Yanhong DONG was involved in data analysis and critical review of the manuscript.

Funding. This review is not supported by any funding or sponsorship.

Declaration of interest. The authors have no relevant interests to declare.

Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

Table S1 Search Strategy

Table S2 Classification of Neuropsychological Tests into Cognitive Domains

Table S3 Grading of Recommendations, Assessment, Development and Evaluations (GRADE) Results

Table S4 PRISMA 2009 Checklist

Figure S1.1 Forest Plots of the Effect of Anthocyanin-rich Supplementation on Attention by Subgroups of Treatment Durations

Figure S1.2 Forest Plots of the Effect of Anthocyanin-rich Supplementation on Attention by Subgroups of Age Groups

Figure S2.1 Forest Plots of the Effect of Anthocyanin-rich Supplementation on Executive Function by Subgroups of Treatment Durations

Figure S2.2 Forest Plots of the Effect of Anthocyanin-rich Supplementation on Executive Function by Subgroups of Age Groups

Figure S3.1 Forest Plots of the Effect of Anthocyanin-rich Supplementation on Psychomotor Performance by Subgroups of Treatment Durations

Figure S3.2 Forest Plots of the Effect of Anthocyanin-rich Supplementation on Psychomotor Performance by Subgroups of Age Groups

REFERENCES

1. Bishop NA, Lu T, Yankner BA. Neural mechanisms of ageing and cognitive decline. *Nature* 2010;464:529–535.
2. Yoong SQ, Lu J, Xing H, et al. The prognostic utility of CSF neurogranin in predicting future cognitive decline in the Alzheimer's disease continuum: a systematic review and meta-analysis with narrative synthesis. *Ageing Res Rev*. 2021;72:101491.
3. World Health Organization. *Dementia: A public health priority*. 2012. https://apps.who.int/iris/handle/10665/75263. Accessed February 16, 2021.
4. Harman D. Aging: a theory based on free radical and radiation chemistry. *J Gerontol*. 1956;11:298–300.
5. Wickens AP. Ageing and the free radical theory. *Respir Physiol*. 2001;128:379–391.
6. Mariani E, Polidori MC, Cherubini A, et al. Oxidative stress in brain aging, neurodegenerative and vascular diseases: an overview. *J Chromatogr B Analyt Technol Biomed Life Sci. B* 2005;827:65–75.
7. Zhang J, Wu J, Liu F, et al. Neuroprotective effects of anthocyanins and its major component cyanidin-3-O-glucoside (C3G) in the central nervous system: an outlined review. *Eur J Pharmacol*. 2019;858:172500.
8. Manach C, Scalbert A, Morand C, et al. Polyphenols: food sources and bioavailability. *Am J Clin Nutr*. 2004;79:727–747.
9. Ronis MJJ, Pedersen KB, Watt J. Adverse effects of nutraceuticals and dietary supplements. *Annu Rev Pharmacol Toxicol*. 2018;58:583–601.
10. Shukitt-Hale B, Lau FC, Joseph JA. Berry fruit supplementation and the aging brain. *J Agric Food Chem*. 2008;56:636–641.
11. Yarahmadi M, Askari G, Kargarfard M, et al. The effect of anthocyanin supplementation on body composition, exercise performance and muscle damage indices in athletes. *Int J Prev Med*. 2014;5:1594–1600.
12. Kim MJ, Rehman SU, Amin FU, et al. Enhanced neuroprotection of anthocyanin-loaded PEG-gold nanoparticles against Aβ(1-42)-induced neuroinflammation and neurodegeneration via the NF-(K)B/JNK/GSK3β signaling pathway. *Nanomedicine* 2017;13:2533–2544.
13. Min J, Yu SW, Baek SH, et al. Neuroprotective effect of cyanidin-3-O-glucoside anthocyanin in mice with focal cerebral ischemia. *Neurosci Lett*. 2011;500:157–161.
14. Bendokas V, Stanys V, Mažeikienė I, et al. Anthocyanins: from the field to the antioxidants in the body. *Antioxidants*. 2020;9:819.
15. Fang J. Bioavailability of anthocyanins. *Drug Metab Rev*. 2014;46:508–520.
16. Kalt W, Blumberg JB, McDonald JE, et al. Identification of anthocyanins in the liver, eye, and brain of blueberry-fed pigs. *J Agric Food Chem*. 2008;56:705–712.
17. Milbury PE, Kalt W. Xenobiotic metabolism and berry flavonoid transport across the blood–brain barrier. *J Agric Food Chem*. 2010;58:3950–3956.
18. Ullah R, Khan M, Shah SA, et al. Natural antioxidant anthocyanins-a hidden therapeutic candidate in metabolic disorders with major focus in neurodegeneration. *Nutrients*. 2019;11:1195.

19. Bergland AK, Soennesyn H, Dalen I, et al. Effects of anthocyanin supplementation on serum lipids, glucose, markers of inflammation and cognition in adults with increased risk of dementia – a pilot study. *Front Genet.* 2019;10.
20. Devore EE, Kang JH, Breteler MM, et al. Dietary intakes of berries and flavonoids in relation to cognitive decline. *Ann Neurol.* 2012;72:135–143.
21. Letenneur L, Proust-Lima C, Le Gouge A, et al. Flavonoid intake and cognitive decline over a 10-year period. *Am J Epidemiol.* 2007;165:1364–1371.
22. Barros D, Amaral OB, Izquierdo I, et al. Behavioral and genoprotective effects of Vaccinium berries intake in mice. *Pharmacol Biochem Behav.* 2006;84:229–234.
23. Goyarzu P, Malin DH, Lau FC, et al. Blueberry supplemented diet: Effects on object recognition memory and nuclear factor-kappa B levels in aged rats. *Nutr Neurosci.* 2004;7:75–83.
24. Williams CM, El Mohsen MA, Vauzour D, et al. Blueberry-induced changes in spatial working memory correlate with changes in hippocampal CREB phosphorylation and brain-derived neurotrophic factor (BDNF) levels. *Free Radic Biol Med.* 2008;45:295–305.
25. Galli RL, Shukitt-Hale B, Youdim KA, et al. Fruit polyphenolics and brain aging: Nutritional interventions targeting age-related neuronal and behavioral deficits. *Ann N Y Acad Sci.* 2002;959:128–132.
26. Joseph JA, Shukitt-Hale B, Casadesus G. Reversing the deleterious effects of aging on neuronal communication and behavior: Beneficial properties of fruit polyphenolic compounds. *Am J Clin Nutr.* 2005;81:313s–316s.
27. Youdim KA, Joseph JA. A possible emerging role of phytochemicals in improving age-related neurological dysfunctions: a multiplicity of effects. *Free Radic Biol Med.* 2001;30:583–594.
28. Boespflug EL, Eliassen JC, Dudley JA, et al. Enhanced neural activation with blueberry supplementation in mild cognitive impairment. *Nutr Neurosci.* 2018;21:297–305.
29. Ferreira D, Machado A, Molina Y, et al. Cognitive variability during middle-age: possible association with neurodegeneration and cognitive reserve. *Front Aging Neurosci.* 2017;9:188.
30. Singh-Manoux A, Kivimaki M, Glymour MM, et al. Timing of onset of cognitive decline: Results from Whitehall II prospective cohort study. *BMJ.* 2012;344:d7622.
31. Bell L, Lamport DJ, Butler LT, et al. A review of the cognitive effects observed in humans following acute supplementation with flavonoids, and their associated mechanisms of action. *Nutrients.* 2015;7:10290–10306.
32. D'Cunha NM, Georgousopoulou EN, Dadigamuwage L, et al. Effect of long-term nutraceutical and dietary supplement use on cognition in the elderly: a 10-year systematic review of randomised controlled trials. *Br J Nutr.* 2018;119:280–298.
33. Lamport DJ, Dye L, Wightman JD, Lawton CL. The effects of flavonoid and other polyphenol consumption on cognitive performance: a systematic research review of human experimental and epidemiological studies. *Nutr Aging.* 2012;1:5–25.
34. Willis LM, Shukitt-Hale B, Joseph JA. Recent advances in berry supplementation and age-related cognitive decline. *Curr Opin Clin Nutr Metab Care.* 2009;12:91–94.
35. Moher D, Liberati A, Tetzlaff J, et al.; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *BMJ.* 2009;339:b2535.doi:10.1136/bmj.b2535
36. Higgins JP, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of Interventions*. New Jersey: John Wiley & Sons; 2019.
37. Lefebvre C, Glanville J, Briscoe S, et al. Chapter 4: searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, et al. eds. *Cochrane Handbook for Systematic Reviews of Interventions*. 2nd ed. New Jersey: Wiley Blackwell; 2019:67–107.
38. Dalton JE, Bolen SD, Mascha EJ. Publication bias: the elephant in the review. *Anesth Analg.* 2016;123:812–813.
39. Vevea JL, Zelinsky NAM, Orwin RG. Evaluating coding decisions. In: Cooper H, Hedges LV, Valentine JC, eds. *The Handbook of Research Synthesis and Meta-Analysis*. New York: Russell Sage Foundation; 2019:173–204.
40. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. *J Clin Epidemiol.* 2000;53:1119–1129.
41. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol.* 2011;64:383–394.
42. Deeks JJ, Higgins JPT, Altman DG, et al. Chapter 10: analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. 2nd ed. 2019:241–284.
43. López-López JA, Page MJ, Lipsey MW, et al. Dealing with effect size multiplicity in systematic reviews and meta-analyses. *Res Synth Methods* 2018. doi:10.1002/jrsm.1310.
44. Connors EJ, Hauson AO, Barlet BD, et al. Neuropsychological assessment and screening in heart failure: a meta-analysis and systematic review. *Neuropsychol Rev.* 2021;31:312–330.
45. Strauss E, Sherman EMS, Spreen O, *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary*, 3rd ed. New York: Oxford University Press; 2006: xvii, 1216.
46. McNamara RK, Kalt W, Shidler MD, et al. Cognitive response to fish oil, blueberry, and combined supplementation in older adults with subjective cognitive impairment. *Neurobiol Aging.* 2018;64:147–156.
47. Calapai G, Bonina F, Bonina A, et al. A randomized, double-blinded, clinical trial on effects of a Vitis vinifera extract on cognitive function in healthy older adults. *Front Pharmacol.* 2017;8:776.doi:10.3389/fphar.2017.00776
48. Bowtell JL, Aboo-Bakkar Z, Conway ME, et al. Enhanced task-related brain activation and resting perfusion in healthy older adults after chronic blueberry supplementation. Article. *Appl Physiol Nutr Metab.* 2017;42:773-–779.
49. Dodd GF, Williams CM, Butler LT, et al. Acute effects of flavonoid-rich blueberry on cognitive and vascular function in healthy older adults. *Nutr Healthy Aging* 2019;5:119–132.
50. Miller MG, Hamilton DA, Joseph JA, et al. Dietary blueberry improves cognition among older adults in a randomized, double-blind, placebo-controlled trial. *Eur J Nutr.* 2018;57:1169–1180.
51. Small BJ, Rawson KS, Martin C, et al. Nutraceutical intervention improves older adults' cognitive functioning. *Rejuvenation Res.* 2014;17:27–32.
52. Whyte AR, Cheng N, Fromentin E, et al. A randomized, double-blinded, placebo-controlled study to compare the safety and efficacy of low dose enhanced wild blueberry powder and wild blueberry extract (ThinkBlue^{TM}) in maintenance of episodic and working memory in older adults. *Nutrients* 2018;10:660.
53. Lamport DJ, Lawton CL, Merat N, et al. Concord grape juice, cognitive function, and driving performance: a 12-wk, placebo-controlled, randomized crossover trial in mothers of preteen children. Journal Article; Randomized Controlled Trial; Research Support, Non-U.S. Gov't. *Am J Clin Nutr.* 2016;103:775–783.
54. Bensalem J, Dudonné S, Etchamendy N, et al. Polyphenols from grape and blueberry improve episodic memory in healthy elderly with lower level of memory performance: a bicentric double-blind, randomized, placebo-controlled clinical study. *J Gerontol A Biol Sci Med Sci.* 2019;74:996–1007.
55. Cook MD, Amber Kaur Sandu B, Joyce JPP. Effect of New Zealand blackcurrant on blood pressure, cognitive function and functional performance in older adults. *J Nutr Gerontol Geriatr.* 2020;39:99–113.
56. Ahles S, Stevens YR, Joris PJ, et al. The effect of long-term aronia melanocarpa extract supplementation on cognitive performance, mood, and vascular function: a randomized controlled trial in healthy, middle-aged individuals. *Nutrients.* 2020;12:2475.
57. Keane KM, Haskell-Ramsay CF, Veasey RC, et al. Montmorency Tart cherries (Prunus cerasus L.) modulate vascular function acutely, in the absence of improvement in cognitive performance. *Br J Nutr.* 2016;116:1935–1944.
58. Nilsson A, Salo I, Plaza M, et al. Effects of a mixed berry beverage on cognitive functions and cardiometabolic risk markers; A randomized cross-over study in healthy older adults. *PLoS One.* 2017;12:e0188173.
59. Owsley C, Sloane M, McGwin G Jr, et al. Timed instrumental activities of daily living tasks: Relationship to cognitive function and everyday performance assessments in older adults. *Gerontology.* 2002;48:254–265.
60. Owsley C, McGwin G Jr. Association between visual attention and mobility in older adults. *J Am Geriatr Soc.* 2004;52:1901–1906.
61. Ebaid D, Crewther SG, MacCalman K, et al. Cognitive processing speed across the lifespan: beyond the influence of motor speed. *Front Aging Neurosci.* 2017;9:62–62.
62. Salthouse TA. The processing-speed theory of adult age differences in cognition. *Psychol Rev.* 1996;103:403–428.
63. Davis JC, Best JR, Khan KM, et al. Slow processing speed predicts falls in older adults with a falls history: 1-year prospective cohort study. *J Am Geriatr Soc.* 2017;65:916–923.
64. Small GW. What we need to know about age related memory loss. *BMJ.* 2002;324:1502–1505. doi:10.1136/bmj.324.7352.1502
65. Kalt W, Cassidy A, Howard LR, et al. Recent research on the health benefits of blueberries and their anthocyanins. *Adv Nutr.* 2020;11:224–236.
66. Travica N, D'Cunha NM, Naumovski N, et al. The effect of blueberry interventions on cognitive performance and mood: a systematic review of randomized controlled trials. *Brain Behav Immun.* 2020;85:96–105.
67. Tran PHL, Tran TTD. Blueberry supplementation in neuronal health and protective technologies for efficient delivery of blueberry anthocyanins. *Biomolecules.* 2021;11:102.
68. Khalid S, Barfoot KL, May G, et al. Effects of acute blueberry flavonoids on mood in children and young adults. *Nutrients.* 2017;9:158.
69. Logue SF, Gould TJ. The neural and genetic basis of executive function: attention, cognitive flexibility, and response inhibition. *Pharmacol Biochem Behav.* 2014;123:45–54.
70. Dreiseitel A, Korte G, Schreier P, et al. Berry anthocyanins and their aglycons inhibit monoamine oxidases A and B. *Pharmacol Res.* 2009;59:306–311. doi:10.1016/j.phrs.2009.01.014
71. Watson AW, Haskell-Ramsay CF, Kennedy DO, et al. Acute supplementation with blackcurrant extracts modulates cognitive functioning and inhibits monoamine oxidase-B in healthy young adults. *J Funct Foods.* 2015;17:524–539.
72. Igwe EO, Charlton KE, Roodenrys S, et al. Anthocyanin-rich plum juice reduces ambulatory blood pressure but not acute cognitive function in younger and older adults: a pilot crossover dose-timing study. *Nutr Res.* 2017;47:28–43.
73. Kent K, Charlton KE, Netzel M, et al. Food-based anthocyanin intake and cognitive outcomes in human intervention trials: a systematic review. *J Hum Nutr Diet.* 2017;30:260–274.

74. Macready AL, Kennedy OB, Ellis JA, et al. Flavonoids and cognitive function: A review of human randomized controlled trial studies and recommendations for future studies. *Genes Nutr*. 2009;4:227–242.
75. Torres M, Forman HJ. Redox signaling and the MAP kinase pathways. *Biofactors*. 2003;17:287–296.
76. Ueda S, Masutani H, Nakamura H, et al. Redox control of cell death. *Antioxid Redox Signal*. 2002;4:405–414.
77. Kwon YW, Masutani H, Nakamura H, et al. Redox regulation of cell growth and cell death. *Biol Chem*. 2003;384:991–996.
78. Zalba G, Fortuño A, San José G, et al. Oxidative stress, endothelial dysfunction and cerebrovascular disease. *Cerebrovasc Dis*. 2007;24(suppl 1):24–29.
79. Bruce-Keller AJ, Gupta S, Parrino TE, et al. NOX activity is increased in mild cognitive impairment. *Antioxid Redox Signal*. 2010;12:1371–1382.
80. Touyz RM, Briones AM, Sedeek M, et al. NOX isoforms and reactive oxygen species in vascular health. *Mol Interv.Interv*Feb 2011;11:27–35. doi:10.1124/mi.11.1.5
81. Mapous RL, Spector J. *Clinical Neuropsychological Assessment: A Cognitive Approach*. New York: Plenum Press; 1995:362 p.