Article:
Ellis, L.R. orcid.org/0000-0002-0750-7248, Boesch, C. orcid.org/0000-0001-6705-5709 and Dye, L. orcid.org/0000-0002-2331-4227 (2024) Effects of anthocyanins on cognition and vascular function: a systematic review. Molecular Nutrition & Food Research, 68 (13). 2300502. ISSN 1613-4125

https://doi.org/10.1002/mnfr.202300502

Molecular Nutrition & Food Research
www.mnf-journal.com

Effects of Anthocyanins on Cognition and Vascular Function: A Systematic Review

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Scope: Good vascular function is crucial for cerebral blood flow and cognitive performance. Diets high in anthocyanins have been shown to improve vascular function and are associated with improvements in cognition. This systematic review investigates randomized controlled trials examining the impact of anthocyanin intake on both cognition and vascular function.
Methods and results: Of the 1486 studies identified through searching Ovid Medline and AMED, PsychInfo, Web of Science, and Scopus, 20 studies are selected which measured cognitive and vascular function. Overall, positive effects on verbal and working memory are observed, which are supported by studies using functional magnetic resonance imaging to demonstrate increased blood flow in brain regions related to these cognitive domains. However, effects of anthocyanins on blood pressure and markers of endothelial function are inconsistent.
Conclusion: This systematic review provides evidence for a positive effect of anthocyanins on cognition and insight into the relevance of endothelial function. Anthocyanins are widely available and can be easily consumed in a range of different fruits, vegetables, and other products. Further studies should establish the optimal daily intake of anthocyanins for cardiovascular and cognitive health.

1. Introduction

Cognition is defined as the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses.[1] Some cognitive abilities such as vocabulary are resilient to brain aging; however, abilities such as memory and processing speed gradually decline with increasing age.[2] It is becoming clearer that risk factors for cardiovascular disease (CVD), such as high blood pressure (HBP), diabetes and obesity are associated with deleterious effects on cognitive function,[3] brain structure,[4] and increase the risk of cognitive decline and dementia.[5] Studies have identified reductions in brain flow to the prefrontal cortex,[6] hippocampus,[7] inferior temporal cortex, and inferior parietal lobule[8] in hypertensive individuals compared to normotensives. Worse performance on working memory tasks, executive function, and speed of processing has also been observed in hypertensive individuals[9]; and individuals with metabolic syndrome showed impaired performance on attention and visual memory tasks.[10] Precise mechanisms that precipitate loss of cognitive function due to CVD risk factors remain to be discerned; however, it is proposed that long-term effects of inflammation and oxidative stress,[11] endothelial dysfunction,[12] and disruption of the blood brain barrier (BBB)[13] are involved. Cerebral blood flow (CBF) to meet the needs of active brain areas depends upon microvascular endothelial function and disruptions may lead to impairment of cognitive function.[14] Emerging evidence suggests that consumption of bioactive compounds is associated with reduced age- or disease-related cognitive decline, enhanced cognitive function, and improved vascular function.[15]

Anthocyanins comprise one of the flavonoid subgroup and impart the red, purple, and blue colors to many fruits and vegetables.[16] A large body of evidence has accumulated which reports benefits of anthocyanin consumption for human health. The Iowa Women's Health Study examined the dietary intake of 34 489 postmenopausal women and monitored diagnoses in CVD, coronary heart disease (CHD), stroke, and total mortality over 16 years.[17] Multivariate analysis suggested that a diet rich in anthocyanidins, specifically from grapefruit, strawberries, apples, and pears was associated with lowest risk of all-cause mortality, CHD, and CVD. Higher intake of fruits and vegetables rich in anthocyanins was associated with an overall reduced risk of cognitive decline.[18] Outcomes from the Framingham Offspring Cohort demonstrate that individuals with highest intakes (>60th percentile) of anthocyanins and flavonoid polymers had a lower risk of developing Alzheimer's disease or other forms of

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DOI: 10.1002/mnfr.202300502

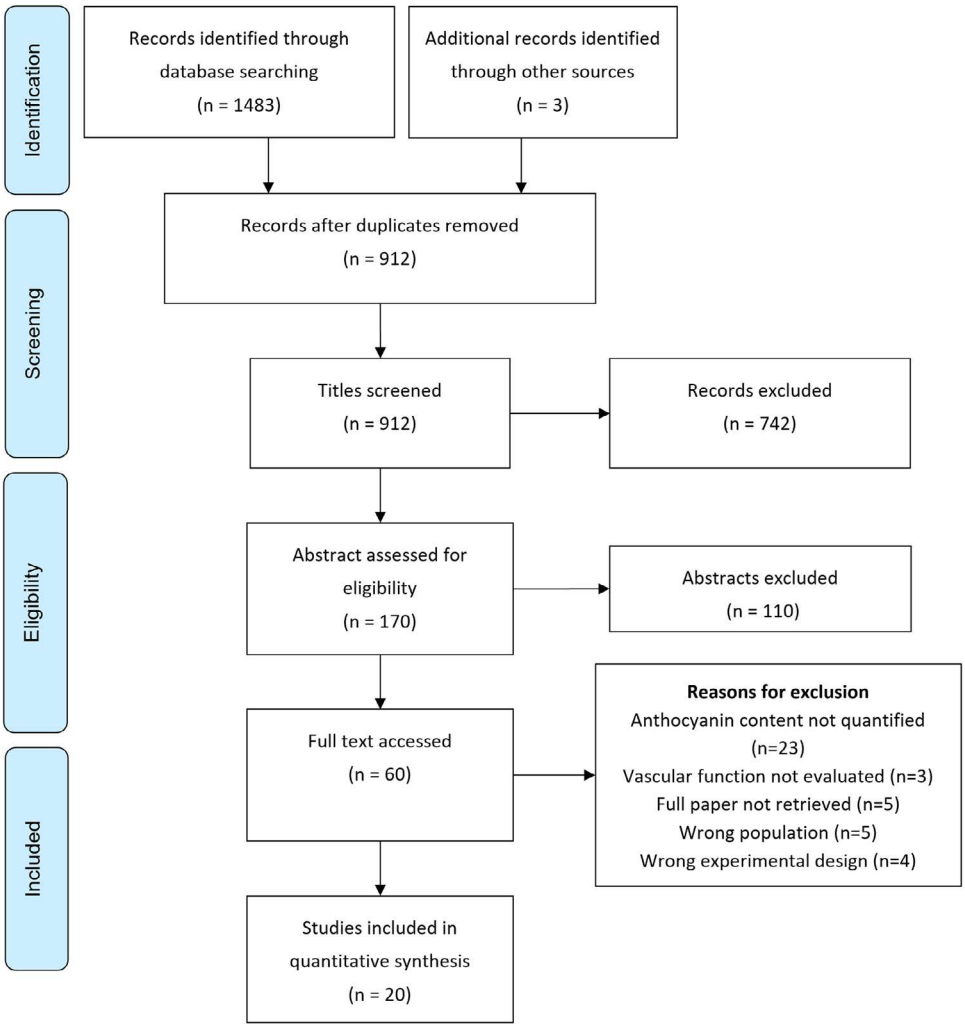

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

dementia compared to individuals with low intake (≤15th percentile) of anthocyanins during the 19-year follow-up.[19]

The consumption of anthocyanins has been suggested to impact cognition in a multifactorial way. Firstly, anthocyanins modulate the vascular system by enhancing the production of nitric oxide (NO) in endothelial cells and subsequently increasing CBF.[20] Secondly, anthocyanins facilitate neuronal signaling along brain derived neurotrophic factor (BDNF), ERK, and phosphatidylinositol-3 (PI3) kinase/protein kinase B (Akt) signaling pathways[21] and appear able to trigger neurogenesis.[22] Lastly, the antioxidant and anti-inflammatory effects of anthocyanins may confer neuroprotection.[23]

Previous systematic reviews have reported the efficacy of anthocyanins to improve blood flow,[24] decrease blood pressure (BP),[25] and modulate cognitive processes.[26,27] These reviews indicated that anthocyanin intake may reduce age related cognitive decline or mitigate some risk factors of CVD. The current review aims to address two key questions. The first aim is to outline the cognitive effects following both acute and chronic intervention with anthocyanin-containing foods or extracts. The second aim is to examine studies which concurrently included tests of vascular function or brain activity in an attempt to explicate the relationship between cognition and blood flow.

2. Results

2.1. Study Descriptions

Initial searches returned 1486 studies of which, 20 studies were eligible for inclusion (**Figure 1**). The characteristics and relevant information of each study are described in **Table 1**. Publication dates ranged from 2010 to 2023. Abbreviations for the cognitive tests included within this review can be found in **Table 2**. Of the 20 studies included, 4 were acute studies (**Table 3**) and 16 were chronic studies (**Table 4**). Randomization was performed in 19 studies[28–46] with one study being a counterbalanced pilot study, where randomization is assumed although it was not stipulated.[47] Eight studies used a crossover design,[32,33,36,40,43–45,47] and 12 studies used a parallel design.[28–31,34,35,37–39,41,42,46] Blinding was not performed in one study,[40] three studies used single blinding,[33,35,45] and the other 16 studies were double-blind.[28–32,34,36–39,41–44,46,47] In total, one

Table 1. Characteristics of the studies included within this systematic review.

Reference and study design	Study duration	Anthocyanin source, VOA, dose [mg dose]	Control	Participant characteristics (sample size – mean age years (SD): mean BMI (kg/m^2) (SD)	Cognitive tests	Secondary outcomes
Bell 2019: DB, 4-arm CO[47]	Acute measured at 90 min post drink (1-week washout)	Haskap Berry (Drink) 100, 200, 400 mg (mixed with 30 mL lemon squash and 220 mL water)	Fructose, glucose (10 g each) with 30 mL lemon squash and 220 mL water	Healthy older adults (N = 20 – 70.50 ± 5.49: 24.94 ± 4.54)	AVLT Serial 3s and 7s subtraction MANT	BP
Dodd 2019: R, PC, SB, 2-arm CO[45]	Acute measured at 2- and 5-h post drink Wash out not stated	Blueberry (drink) 579 mg of antho- and pro-cyanidins (508 and 71 mg, respectively)	Color and flavor matched powder	Healthy older adults (N = 18 – 68.72 ± 3.30: 25.89 ± 4.46)	Go-NoGo Stroop Digit Switch Continuous performance task Digit symbol substitution test Random word generation Three-word sets N-back Letter memory Location task Immediate and delayed recall and recognition	BP Digit Volume Pulse BDNF
Keane 2016: R, DB, PC, 2-arm CO[43]	Acute measured at 1-, 2-, 3-, and 5-h post drink (14-day washout)	Tart cherry (drink) 4 mg C3G equivalent	Cordial with whey protein isolate and maltodextrin (match energy content of tart cherry drink)	Healthy middle-aged adults (N = 30 – 50 ± 6: 26.1 ± 4.9)	RVIP Digit Vigilance Stroop	BP Transcranial Doppler NIRS
Watson 2019: R, DB, PC, 2-arm CO[44]	Acute measured at 75-min post drink (5-day washout)	Blackcurrant (drink) 115 mg	Blackcurrant cordial	Healthy young adults (N = 9 – 23: 23.5)	Choice reaction time Simple reaction time Digit vigilance	EEG
Ahles 2020: R, DB, PC, 2-arm PG[30]	24 weeks	Aronia Melanocarp (capsule) 16 mg, 27 mg daily	150 mg maltodextrin	Healthy older adults 90 mg aronia (N = 34 – 53 ± 1: 29.5 ± 0.4) 150 mg aronia (N = 35 – 53 ± 1: 29.4 ± 0.5) Placebo (N = 32 – 53 ± 1: 29.3 ± 0.5)	Grooved pegboard Stroop color and word Number cross-out test	BP Ankle brachial index Carotid artery intima media thickness BDNF
Boesfplug 2018: R, DB, PC, 2-arm PG[38]	16 weeks	Blueberry (drink) 269 mg daily	Maltodextrin, fructose (12 g)	Older adults with MCI Blueberry (N = 8 – 80.4 ± 7.3: 26.2 ± 3.6) Placebo (N = 8 – 75.5 ± 4.8: 26.4 ± 2.4)	N-back test MoCA CVLT	fMRI
Bowtell 2017: R, DB, PC, 2-arm PG[39]	12 weeks	Blueberry (drink) 387 mg anthocyanidins daily	Synthetic apple and blackcurrant cordial	Healthy older adults Blueberry (N = 12 – 67.5 ± 0.9: 25.9 ± 1.1) Placebo (N = 14 – 69.0 ± 0.9: 27.1 ± 1.7)	N-back Detection task Groton maze timed test (and delayed) Identification task	fMRI Glutathione
Cheatham 2022: R, DB, PC, 3-arm PG[28]	6 months	Blueberry (powder) 35 g a day 412.25 mg daily	Maltodextrin, fructose powder (35 g)	Older adults with MCI Blueberry (N = 45 – 72.2 ± 4.2: 27.2 ± 3.5) Placebo (N = 42 – 72.5 ± 4.4: 28.1 ± 4.0) Reference group (N = 44 – 72.0 ± 4.5: 27.0 ± 4.0)	Reaction Time Spatial Working memory PAL RVIP	EEG

(*Continued*)

Table 1. (Continued)

Reference and study design	Study duration	Anthocyanin source, VOA, dose [mg dose]	Control	Participant characteristics (sample size – mean age years (SD): mean BMI (kg/m^2) (SD)	Cognitive tests	Secondary outcomes
Cook 2020: R, DB, PC, 2-arm CO[32]	1 week (1-week washout)	Blackcurrant (capsules) 105 mg twice daily	Microcrystalline cellulose (300 mg twice per day)	Healthy older adults (N = 14 – 69)	RVIP Reaction time Vi-PAL Spatial working memory test	BP
Flanagan 2022: R, DB, PC, 2-arm PG[42]	12 weeks	Cranberry (freeze dried powder) 59 mg daily	Maltodextrin, fructose (color flavor match)	Healthy older adults Cranberry (N = 29 – 65.86 ± 5.51: 24.9 ± 4.0) Placebo (N = 31 – 65.32 ± 4.91: 25.0 ± 5.9)	ACE-III, TMT, Digit Span, Rey Complex Figure Test	BP fMRI BDNF
Garcia-Cordero 2022: R, DB, 3-arm PG[41]	12 weeks	Red berries (redcurrant, blackcurrant, raspberries, blueberries) 100 mg daily	Cocoa flavanols (200 mg flavanols) Combined (cocoa and mixed berries)	Healthy older adults Red berries (N = 20 – 56.4 ± 4.14: 25.24 ± 2.61) Placebo (N = 20 – 59.15 ± 9.08: 26.33 + 4.44) Combined (N = 19 – 57.84 ± 6.76: 25.91 ± 3.38)	TAVEC Stroop Tower of London WAIS-IV symbol digit search WAIS-III number key ADAS-COG WAIS-III digits	BP BDNF NGF-R
Igwe 2020: R, SB, PC, 2-arm CO[33]	8 weeks (4-week washout)	Queen garnet plum (drink) 7.4–10.6 mg C3G equivalent daily	Raspberry cordial	Healthy older adults (N = 31 – 70 ± 10)	RAVLT Verbal Fluency Digit Span Stroop Task Counting Span	BP Mean arterial pressure BDNF
Joo 2019: R, DB, PC, 2-arm PG[31]	12 weeks	Black rice (C3G extract) (capsule) 6 capsules daily (19 mg)	100% crystalline cellulose	Older adults with SMI Black rice (N = 25 – 64.96 ± 8.2) Placebo (N = 23 – 62.70 ± 6.84)	ADAS-COG CERAD-K (verbal fluency, Boston naming test, MMSE, word list memory, constructional praxis, word list recall, word list recognition, constructional recall, TMT A) SMCQ	BP
Kent 2015: R, SB, PC, 2-arm PG[48]	12 weeks	Cherry (drink) 69 mg daily	100 mL apple juice	Older adults with dementia Cherry (N = 24 – 78.9 ± 5.2: 25.7 ± 3.4) Placebo (N = 25 – 78.9 ± 5.2: 25.7 ± 3.4)	Category and letter verbal fluency RAVLT TMT Self-ordered pointing task	BP
Kimble 2022: R, DB, PC, 2-arm PG[34]	12 weeks	Montmorency cherry juice (drink) 22.2 mg daily	Flavored koolaid, dextrose and fructose	Healthy middle-aged adults Cherry (N = 28 – 49 ± 6: 27.3 ± 3.8) Placebo (N = 27 – 47 ± 6: 27.5 ± 3.8)	Digit vigilance RVIP N-back Bond-lader VAS	NIRS
Krikorian 2012: R, DB, PC, 2-arm PG[37]	16 weeks	Concord Grape (drink) 226 mg daily	Placebo juice	Older adults with MCI Concord Grape (N = 10 – 78 ± 5) Placebo (N = 11 – 75 ± 6)	CVLT N-back	BP fMRI
Lamport 2016: R, DB, PC, 2-arm CO[36]	12 weeks (4-week washout)	Concord grape (drink) 167 mg daily	Energy and taste matched placebo	Healthy middle age (N = 25 – 43.2 ± 0.6: 24.6 ± 0.5)	VVLT VSLT Tower of Hanoi RVIP Grooved pegboard	BP

(*Continued*)

Table 1. (Continued)

Reference and study design	Study duration	Anthocyanin source, VOA, dose [mg dose]	Control	Participant characteristics (sample size – mean age years (SD): mean BMI (kg/m^2) (SD)	Cognitive tests	Secondary outcomes
Nilsson 2017: R, PC, 2-arm CO[40]	5 weeks (1-week wash out)	Mixed berry (blueberry, elderberry, lingonberry, strawberry) (drink) 414 mg daily	Carbohydrate matched beverage	Healthy older adults (N = 23 – 63.0 ± 0.9: 24.4 ± 0.4)	Verbal working memory test Selective attention test	BP
Whyte 2018: R, DB, PC, 4-arm PG[29]	6 months	Blueberry (capsules) 1.35, 2.7, 7 mg daily	1000 mg maltodextrin	Older adults with MCI (N = 122 – 70.8 ± 3.88)	Corsi block task Object recognition task MANT	BP
Wood 2023: R, DB, PC, 2-arm PG[46]	12 weeks	Blueberry (powder) 26 g a day 302 mg daily	Carbohydrate matched beverage	Healthy older adults Intervention (N = 32 – 69.44 ± 3.48: 24.57 ± 2.7) Control (N = 29 – 70.76 ± 3.81: 23.16 ± 2.59)	AVLT Corsi Block Serial 3s Serial 7s Task Switching Task	BP FMD Arterial Stiffness Transcranial Doppler

CO, crossover; DB, double-blind; PC, placebo-controlled; PG, parallel group; R, randomized; SB, single-blind; VOA, vehicle of administration.

study recruited healthy young adults aged between 18 and 25,[44] three studies included adults aged between 30 and 55,[34,36,43] and ten studies healthy adults over the age of 55[30,32,33,39–42,45–47] while six studies recruited older adults with some form of cognitive impairment.[28,29,31,37,38,48] In total, 14 intervention arms included healthy participants (n = 490), four included older adults with mild cognitive impairment (MCI) (n = 290), one study included people with dementia (n = 49), and one study included participants with subjective memory impairment (SMI) (n = 48). Study duration ranged from acute measuring at 75 min study[44] to a max of 5 h postconsumption, and the longest study was 24 weeks.[30]

Table 2. Abbreviation of the cognitive tests used in studies included within this systematic review.

Abbreviation	Cognitive test
ADAS-COG	Alzheimer's Disease Assessment Scale-Cognitive Subscale
AVLT	Auditory verbal Learning Test (RAVLT)
CVLT	California Verbal Learning Test
MANT	Modified Attention Network Task
MMSE	Mini Mental State Examination
PAL	Paired Associate Learning Test
RVIP	Rapid Visual Information Processing
SMCQ	Subjective Memory Complaints Questionnaire
TAVEC	Verbal Learning Spain Complutense
TMT	Trail Making Test (A/B)
TST	Task Switching Task
VAS	Visual Analogue Scale
Vi-Pal	Visual Paired Associate Learning Test
VSLT	Visual-Spatial Learning Test
VVLT	Visual-Verbal Learning Test
WAIS	Weschler Adult Intelligent Scale

2.2. Risk of Bias Assessment

Risk of bias (ROB) assessment was conducted for each included study. The ROB graph is presented in **Figure 2**. The overall ROB was rated as low.

2.3. Intervention Descriptions

In four of the included studies, the anthocyanins were administered in capsule form,[29–32] seven studies used a preformulated juice drink,[33,35–37,40,44,47] six studies used a freeze-dried powder in either juice or food,[28,38,41,42,45,46] and three studies used a concentrate.[34,39,43] Different anthocyanin interventions were used: blueberries (n = 6 [28,29,38,39,45,46]), cherry juice (n = 3[34,43,48]), blackcurrant juice (n = 2[32,44]), berry mix (n = 2[40,41]), Concord grape juice (CGJ, n = 2[36,37]), Queen Garnet Plum Juice (n = 1[33]), and n = 1 of the following: black rice capsules,[31] Aronia Melanocarp capsules,[30] Haskap berry,[47] and cranberry.[42] The anthocyanin content of the interventions ranged from 22 mg to 508 mg per day. In three studies, the intervention dose was calculated as the monomeric anthocyanidin cyanidin-3-glucoside (C3G) with doses ranging from 7.4 to 27 mg daily.

2.4. Cognitive Tests

Across the 20 included studies, a total of 47 separate cognitive performance measures were employed. These comprised 24 different memory tests, nine tests of executive function, seven attention tasks, seven global functions (which included language,

Table 3. Studies reporting acute effects of anthocyanin intervention on cognitive performance and vascular function parameters.

Reference	Significant cognitive effects (Cohen's *d* effect size)	Significant effects on secondary outcomes
Bell 2019[47]	AVLT recognition (total) 400 mg[a] ($d = 3.3$) AVLT Recognition (recall 5) 200 mg higher than 100 mg and 400 mg[c] (NM) AVLT Recognition (List B) 400 mg lower than 100 mg and 200 mg[c] (NM) AVLT Proactive Interference lower in 200 mg compared to 400 mg[c] (NM) Serial 3s 200 mg[a,c] ($d = 4.13$) Serial 7s 100 mg[a] ($d = 4.31$) (400 mg increased errors on serial 7s)[a]	DBP[a] (400 mg)
Dodd 2019[45]	Word recognition task[a] ($d = 0.5$) Delayed recognition[a] ($d = 0.45$) Digit switch task[a] ($d = 0.47$)	Trend – SBP Trend BDNF
Keane 2016[43]		SBP[b] Near-IR[b]
Watson 2019[44]	Choice reaction time[a] ($d = 0.89$) – negative effect	EEG (increase in delta and theta brain waves)

AVLT, Auditory Verbal Learning Test; BDNF, brain derived neurotrophic factor; DBP, diastolic blood pressure; EEG, electroencephalography; NM, not measurable effect size; SBP, systolic blood pressure. [a] Significant difference from placebo; [b] Significant difference from baseline; [c] A significant difference compared to another dose.

intelligence, or used to assess cognitive suitability for studies in older adults). Immediate and delayed recall or recognition for the same task were counted as a single memory task. The frequently used cognitive tests were the Stroop ($n = 5$), RVIP ($n = 5$), n-back test ($n = 5$), RAVLT ($n = 4$), and digit vigilance ($n = 3$). In total, 15 studies detected a positive effect on at least one cognitive test after anthocyanin supplementation.

2.5. Overview of Vascular Function

Within the 20 included studies, 15 evaluated the effect of anthocyanins on BP using a non-invasive method such as a BP cuff.[29–33,35–37,40–43,45–47] In seven of these studies, no effect on BP was observed,[31,33,36,37,40–42,45] four studies found significant reductions of systolic blood pressure (SBP),[29,35,43,46] two studies reported significant reduction of diastolic blood pressure (DBP),[30,47] and one study reported a significant reduction of both SBP and DBP.[32] One study also measured endothelial function using flow mediated dilation (FMD).[46]

The effects of anthocyanins on cerebrovascular function were evaluated in eight studies using different techniques that included functional magnetic resonance imaging (fMRI) ($n = 4$[37–39,42]), transcranial Doppler ($n = 2$[43,46]), or near-infrared spectroscopy (NIRS) ($n = 2$[34,43]). Brain activity was assessed using electroencephalography (EEG) in one acute study[44] and in one chronic study.[28]

Finally, the effects of anthocyanins on neuronal proteins were determined in six studies. BDNF was measured in five studies.[30,33,41,42,45] Nerve growth factor (NGF) was measured in one study.[41]

Results were clustered based on study duration of acute or chronic. Acute studies were those with a single dose and testing duration of less than 24 h, whereas studies were considered chronic with repeated supplementation and testing duration of more than 24 h.

2.6. Acute Studies

In four crossover studies, the acute effects of anthocyanins on cognition and vascular function were examined. In a study which recruited healthy older adults, intake of 200 g of blueberries (508 mg anthocyanins) significantly improved verbal memory and a nonsignificant trend for reduced switch cost in the digit switch task was observed.[45] The blueberry drink also mitigated the decline in BDNF and increased SBP compared to the control group, although these effects were not statistically significant. No impact on arterial stiffness index was observed. Bell and Williams[47] found that different doses of anthocyanins from a Haskap berry drink resulted in lower errors on Serial 3s following the 200 mg dose and lower errors on Serial 7s following the 100 mg dose, compared to the control group. The 400 mg dose improved DBP, word recall, and word recognition in an episodic memory task but was also associated with increased errors on the Serial 7s task. Keane et al.[43] reported that cherry concentrate (4 mg C3G) acutely reduced SBP and increased total hemoglobin in the frontal cortex as measured by NIRS. However, cognitive performance did not significantly differ between conditions. Interestingly, Watson et al.[44] found that after participants consumed the blackcurrant intervention (115 mg anthocyanins), they exhibited longer reaction times during the choice reaction test. These effects co-occurred with increased delta and theta (δ and θ) waves on EEG, which the authors interpreted as anxiolytic effects of the blackcurrant drink.

2.7. Chronic Studies

Sixteen studies examined the chronic effects of anthocyanins on cognition. In four of these, healthy middle-aged adults were recruited.[29,30,34,36] In a 12-week, crossover trial, spatial memory, executive function, and enduring verbal memory improvements were observed after consuming 167 mg of anthocyanins from CGJ. However, participants in the placebo arm showed faster completion times on the grooved pegboard task. CGJ consumption did not affect BP.[36] Kimble et al.[34] observed significant improvements in accuracy and reductions in false alarms on an attention task; however, no effects on hemoglobin levels using NIRS were observed after 3-months consumption of cherry juice (22.2 mg anthocyanins). Episodic memory and a significant reduction in BP was shown after 3 and 6 months of supplementation using a wild blueberry extract with 7 mg anthocyanins.[29]

Table 4. Studies reporting the chronic effects of anthocyanin intervention on cognitive performance and vascular function parameters.

Reference	Significant cognitive effect (Cohen's *d* effect size)	Significant effects on secondary outcomes
Ahles, 2020[30]	Grooved pegboard 16 mg[a] (NM)	DBP[c]
Boesfplug, 2018[38]		fMRI (left-central gyrus, left middle gyrus, and left parietal lobe)
Bowtell, 2017[39]	N-back (speed and accuracy)[a] (NM)	fMRI (Brodmann area, precuneus, anterior cingulate, insula, and thalamus)
Cheatham, 2022[28]	RVIP mean latency[a] (NM)	EEG (frontal, central, and midline clusters)
Cook, 2020[32]		SBP[a], DBP[a]
Flanagan, 2022[42]	RCF delayed recall score ($d = 0.19$)	fMRI (right caudate, right accumbens area, right entorhinal cortex)
Garcia-Cordero, 2022[41]	In red berries and cocoa group only Time to start TOL[b] (NM) Duration of TOL[b] (NM) TAVEC[b] (NM)	
Igwe, 2020[33]	No effects	
Joo, 2019[31]	SMCQ[b] ($d = 0.20$)	
Kent, 2015[48]	Category verbal fluency[b] ($d = 1.04$) RAVLT[b] ($d = 0.89$ave)	SBP[b]
Kimble, 2022[34]	Digit vigilance (accuracy $d = 0.62$ and false alarms $d = 0.84$)[a]	
Krikorian, 2012[37]	CVLT interference[a] ($d = 0.50$)	fMRI (right middle frontal cortex, superior parietal cortex)
Lamport, 2016[36]	VSLT (immediate)[a] (NM) VVLT[a] (NM) Tower of Hanoi[a] (NM)	
Nilsson, 2017[40]	Working memory task[a] ($d = 0.69$)	
Whyte, 2018[29]	RAVLT[a] (NM) Corsi Block[a] (NM) (7mg dose only)	SBP (7 mg)[a]
Wood, 2023[46]	AVLT (immediate recall)[a] ($d = 0.40$) Placebo = improved delayed recall ($d = 0.43$) TST[a] ($d = 0.44$)	FMD[a] SBP[a]

AVLT, Auditory Verbal Learning Test (RAVLT); BDNF, brain derived neurotrophic factor; CVLT, California Verbal Learning Task; DBP, diastolic blood pressure; EEG, electroencephalography; FMD, flow mediated dilation; fMRI, functional magnetic resonance imaging; NM, not measurable effect size; RCF, Rey Complex Figure Task; RVIP, Rapid Visual Information Processing; SBP, systolic blood pressure; SMCQ, Subjective Memory Complaints Questionnaire; TAVEC, Verbal Learning Spain Complutense; TOL, Tower of London; TST, Task Switching Task; VSLT, Visuo Spatial Learning Test; VVLT,Visual Verbal Learning Test; [a] Significant difference from placebo; [b] Significant difference from baseline; [c] A significant difference compared to another dose.

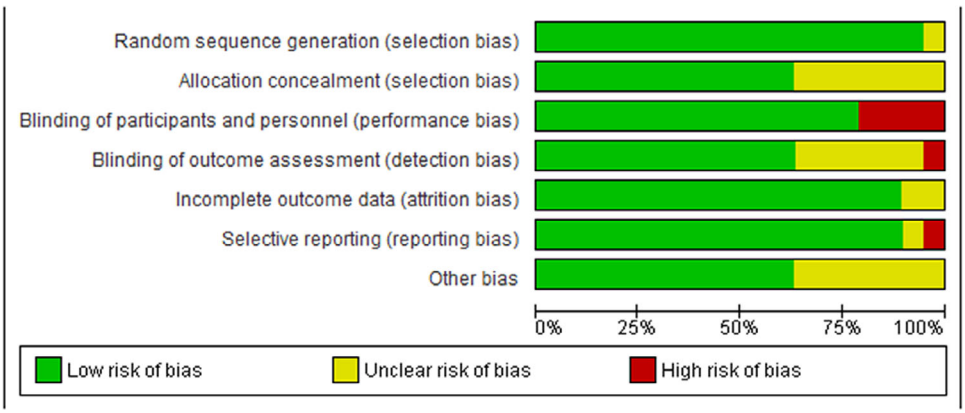

Figure 2. Risk of bias (ROB) graph according to the RoB2 tool.

Using two doses of chokeberry extract, psychomotor speed was improved after supplementation with the lower dose (16 mg anthocyanins) and DBP was significantly decreased after the higher dose (27 mg anthocyanins). No effects on ankle brachial index, carotid elasticity, and carotid intima media thickness were observed.[30]

In studies with healthy older adults,[41] observed a significant decrease in the time taken to start and finish the Tower of London task when participants consumed a mix of red berries (100 mg anthocyanins) and cocoa flavanols (200 mg flavanols) for 12 weeks. No differences were found in BP, BDNF, or NGF among intervention groups. Significantly more words were recalled on the AVLT after healthy older adults consumed blueberry (302 mg anthocyanins) daily for 12 weeks. Additionally, an improvement in accuracy on task switching task was observed. These effects were associated with a significant decrease in SBP and a significant improvement in FMD. However, the placebo group showed improved delayed recall scores on the AVLT.[46] Another study showed a modest improvement in working memory test performance with no effect on BP after 5 weeks of mixed berry consumption with 414 mg anthocyanins.[40] Intake of Queen Garnet plum juice (dosed between 7.4–10.6 mg C3G equivalent to body weight) had no impact on cognition or BP.[33] Lastly, Cook et al.[32] found a significant lowering of BP after a 1 week intake of New Zealand blackcurrant extract (105 mg anthocyanins) in the absence of cognitive improvements.

Three studies examined effects of anthocyanins on older adults with memory impairment.[28,31,35] After 6 months supplementation with blueberries containing 412.25 mg anthocyanins, participants had significantly decreased scores on RVIP latency and better performance under cognitively fatiguing circumstances compared to placebo.[28] Given the known decline of neuronal function with aging, analyses of ERP were conducted with age group included as an additional factor (65–69, 70–74, and 75–80 years).[28] In this analysis, participants aged 75–80 who consumed blueberries, outperformed the placebo group, with the frontal, midline, and central clusters showing greatest effects. Improvements in verbal fluency, RAVLT, and a significant reduction in SBP were evident in participants with mild dementia who consumed cherry juice (69 mg anthocyanins) for 12 weeks.[35] Joo et al.[31] reported improvements in subjective memory tests and a trend toward lower BP in older adults with SMI after 12 weeks of daily consumption of a purified extract from black rice with low anthocyanin content (19 mg). In a study involving older adults with MCI, reduced semantic interference during the CVLT and greater activation in the anterior and posterior regions of the right hemisphere were observed after 16 weeks of grape juice consumption (226 mg anthocyanins).[37] However, there were no significant effects on BP.

Finally, the impact of anthocyanins on cerebrovascular function as measured by fMRI was investigated in four studies which identified positive effects in brain regions associated with the cognitive test employed (Table 4).[37–39,42] In three of the studies, significant positive effects were found on cognitive tasks for episodic memory performance,[42] verbal memory,[37] and working memory.[39]

3. Discussion

The current systematic review was conducted to provide an up-to-date insight into research exploring the cognitive and vascular effects of anthocyanin supplementation. In agreement with previous reviews,[49,50] the cognitive domains that appear to be sensitive to acute anthocyanin consumption are episodic/working memory (verbal memory) whereas memory and executive function appear to be impacted in chronic studies. The cognitive impacts associated with anthocyanins can be systematically stratified based on the age of the participants enlisted in the study. Notably, there is a discernible paucity of investigations focusing on the cognitive and vascular effects of anthocyanins within cohorts of healthy middle-aged (n = 3) and healthy young adult (n = 1) populations. Within the scope of the present systematic review, discernible outcomes were identified in healthy adults (18–45 years) on tasks pertaining to executive function. Conversely, in the cohort of healthy older adults (over 50 years old), favorable outcomes were observed specifically on tasks related to working memory. For cognitively impaired adults, the effects of anthocyanins were most evident on verbal memory, with greatest test sensitivity shown on the verbal learning test and its variants (RAVLT, AVLT, and VVLT).

Existing research indicates that anthocyanins can improve vascular function by reducing BP.[51,52] The current systematic review identified 8/15 studies which found a BP lowering effect following anthocyanin supplementation. Within these results, three acute studies reported positive effects following anthocyanin consumption with 400 mg of a haskap berry drink,[47] 508 mg blueberry drink,[45] or 4 mg (C3G equivalent) cherry drink.[43] Conversely, the chronic studies identified significant effects using capsules (7 mg,[29] 16 mg,[30] and 105 mg[32]) and drink (69 mg[48]) with what is considered to be a low anthocyanin dose. In 6/7 studies where an effect on BP was not observed, these studies were conducted on older adults.[31,33,37,40–42] In the other study which did not observe reductions in BP, the adult participants did not have HBP at baseline and therefore the potential to improve from supplementation was low.[36]

3.1. Mechanisms of Anthocyanins

The effects of anthocyanins on cognition can be attributed to both direct and indirect mechanisms of action. Previous in vivo and in vitro research has outlined that acute anthocyanin intervention can positively influence the ERK-CREB-BDNF signaling pathway related to memory formation.[53] This direct mechanism on cognition relies on the ability of bioactive compounds to cross the BBB. Recent evidence for interactions via gut–brain axis has demonstrated that gut microbial metabolites produced during intestinal processing of anthocyanins may modulate cognitive processes as they are able to cross the BBB.[54] Notably, anthocyanins and their metabolites have been detected in different brain regions in animal studies, affirming their ability to cross the BBB.[55] In addition, chronic intake of anthocyanins can reduce oxidative stress and inflammation in the brain, enhance neuronal growth, and induce BDNF promoting genes.[21]

Anthocyanin consumption can also modulate cognitive function through peripheral mechanisms. Indirectly, anthocyanins

can impact hyperglycemia,[56] reduce BP, and ameliorate dyslipidemia.[57] Anthocyanins positive modulation of endothelial function through the upregulation of NO is well documented.[58] The production of NO is dependent on the activities of endothelial nitric oxide synthase (eNOS) and neuronal NO synthase. Acute decreases in BP can be attributed to the increased expression of eNOS and subsequent NO release, while chronic reductions may result from adaptations leading to enhanced vasculature efficiency. Assessment of vasculature efficiency involves techniques such as FMD. Notably, only one study included in this review reported a significant improvement in FMD after a 12-week daily supplementation of 302 mg of blueberry anthocyanins.[46] This finding aligns with previous research which also reported a positive effect of anthocyanin consumption on FMD but did not include cognitive measures so was not included in this review.[59]

Furthermore, the relationship between cognitive processes and vascular dynamics is underscored by the reliance of active brain regions on an adequate supply of CBF, a process contingent upon the release of NO from cerebral endothelial cells.[20,60] Increased CBF not only provides acute increases in energy substrates to improve cognition, but over time may also promote angiogenesis and neurogenesis.[22] Beyond its role in vasodilation and blood flow, NO has been implicated in regulation of transcription factor CREB which is important for neuron survival and plasticity.[61] An increase in CBF is detectable in studies using brain imaging such as fMRI. A small number of studies in this systematic review ($n = 4$)[37–39,42] measured the vasoactive properties of anthocyanins by transcranial doppler and fMRI. All these studies found a significant increase in brain activity or blood flow following anthocyanin consumption in areas of the brain associated with the cognitive functions measured. However, the small sample sizes of these studies presents a limitation for the reliability of the significant effects. Reporting biases affect fMRI studies where small sample sizes combined with a large number of detectable foci can increase false-positive outcomes.[62]

3.2. Factors which Moderate Cognitive and Vascular Effects

3.2.1. Age Effects

Variations in cognitive effects across different age groups may reflect age-related disparities in neuronal structures and their capacity for improvement. Although there is no singular age at which humans reach peak overall cognitive performance, evidence suggests that distinct cognitive domains may peak at different ages.[63] According to an age of peak performance analysis, analyses of vocabulary, visual memory, verbal memory, and processing speed peaked at different age groups. For example, verbal memory (using forward digit span) was shown to peak around 30–35 years old whereas vocabulary peaked around 66 years.[63] Performance on tasks related to fluid intelligence peak in mid-life and decline with age whereas performance on crystallized intelligence can continue to develop.[64]

The frontal regions of the brain, which are associated with executive function processes, are particularly sensitive in adulthood[65] which could partially explain the findings from this systematic review. In healthy older adults, working memory was highlighted as a sensitive domain to anthocyanin intervention, although no particular cognitive task stood out. Even though the learning capacity of older adults may be reduced particularly in tasks of increasing cognitive demand, there is evidence that older adults can recruit multiple brain regions to compensate for the lack of regional specialization.[66] Such compensatory mechanisms mean that there is still a potential to improve cognition.

The current review predominantly included older adults ($n = 16$) who varied in terms of cognitive health (such as MCI, SMI, dementia, or healthy). Heightened vulnerability of the brain to oxidative stress and inflammation during aging[67] is associated with poorer cognitive function.[68] Additionally, age-related decline in endothelial function increases the risk of HBP, reduced CBF[69] and cognitive impairment.[70] The aging process also impacts mechanisms critical for memory formation such as long-term potentiation[71] and NMDA receptor plasticity[72] which may lead to the assumption that there is a greater potential to improve cognition and that this would be detectable using sensitive cognitive tests. Indeed, the current systematic review highlights that anthocyanin supplementation attenuates declines in verbal memory among older adults with cognitive impairment.[29,31,35,37] In some of the fMRI studies included, activation of foci were independent of any effect on cognition which could be due to lack of sensitivity of the cognitive test employed. For example, Boespflug[38] found no improvement in the n-back working memory test in older adults with MCI. However, Bowtell et al.[39] demonstrated significant improvements in the n-back working memory test in healthy older adults. Whilst the n-back test has been previously used to detect MCI in patients living with Parkinson's disease,[73] it has also been shown that MCI patients perform worse than healthy controls on the n-back test.[74] This implies that the n-back test may not be sensitive for adults with MCI. It is important that future studies utilize cognitive tests which have been shown to be sensitive to anthocyanin supplementation and relevant to the population being studied, such as those proposed by de Jager and colleagues in their review.[75]

3.2.2. Dose and Duration Effects

Cognitive and vascular effects have been systematically observed across various durations and doses in studies included in this review, precluding the definitive establishment of a dose- or duration-dependent response. However, insights into the bioavailability of anthocyanins offer some guidance for recommendations regarding dosage in acute and chronic experimental designs. Following anthocyanin consumption, studies have consistently reported a minimal retrieval of parent anthocyanins from circulation, usually less than 2%.[76] Current understanding indicates that anthocyanins undergo hydrolysis in the small intestine and then extensive metabolism by gut bacteria in the colon, resulting in the production of diverse low-molecular-weight catabolites responsible for the health-promoting properties of anthocyanins.[77] Individuals who habitually consume anthocyanins are likely to foster a gut microbiota specialized in anthocyanin metabolism.[78] Consequently, it can be postulated that a higher dose is a requisite to evoke health or cognitive effects following acute ingestion, whilst a lower dose may contribute to a cumulative effect over time. Additionally, existing literature

suggests that intake of at least 6 weeks is required for the manifestation of cognitive benefits.[79]

3.2.3. Sources of Anthocyanins

Variations in the cognitive and vascular responses to anthocyanin supplementation may stem from differences in the intervention delivery or vehicles utilized within studies included in this systematic review. Intervention vehicles such as fresh fruit drinks, preformulated beverages, concentrates, freeze-dried powders, or capsule extracts have been employed. However, it is known that foods contain multiple bioactive compounds concurrently that have distinct bioactive properties. For example, berries contain high amounts of anthocyanins, but they are also an important source of flavanols (with blueberries containing 330 mg/100 g and strawberries containing 148 mg/100 g).[80] The diverse structural characteristics of polyphenols potentially lead to synergistic effects on bioactivity or bioavailability. Factors such as the presence of fiber,[81,82] chlorogenic acid, and flavanol oligomers[83] in polyphenol-rich foods may influence cognitive function.

3.3. Limitations

This review has highlighted a lack of consistency across the included studies with respect to the cognitive outcomes measured, study designs and the health status and age of participants which precludes definitive conclusions. Developing an understanding of methods and conditions under which anthocyanins elicit cognitive benefits should be a key aim for future research. There is, however, a paucity of studies which recruit ostensibly healthy adults aged between 18 and 50 years old who have some cardiovascular risk factors such as raised BP or overweight/obesity. Identifying nutritional interventions which can reduce risk in those with risk factors for vascular problems could be key toward reducing the probability of cognitive decline in later life.[70]

A concerning finding in the present review is that researchers use cognitive tests that appear to have very little sensitivity or specificity to anthocyanin (or polyphenol) supplementation. For example, the Stroop test was used in five different studies and did not demonstrate any significant effects in any study. In addition, the n-back test was employed four times and detected a significant difference between active and placebo treatment in only one study.[39] Cognitive tests must be chosen based upon the available evidence for the compound being tested, the characteristics of the participants, and sensitivity and specificity of the chosen test.[75] Applying multiple cognitive tests could cause fatigue which then affects the validity of the study outcomes and order in the test battery may affect outcomes too but these influences are also difficult to disentangle.[84]

Multiple studies did not report upon or did not include standardized meals before the cognitive tests. Including standardized meals prior to and on the test day is extremely important because background diet, differences in glycogen stores, as well as common foods such as caffeine or sugar are known to impact cognitive function testing.[85]

3.4. Potential for Pooling Data

Despite substantial interest in the health benefits of anthocyanins, there remains a lack of experimental studies in humans with sufficiently large sample sizes and consistent methodologies to pool data for quantitative (meta) analysis of specific cognitive domains. A recent meta-analysis of dietary flavonoid interventions combined studies using separate cognitive tests into domains classified under the Cattel–Horn–Carroll classification.[79,86] Results outlined a positive effect on global cognition for all combined flavonoid studies ($g = 0.148$) and for the berry subgroup analysis ($g = 0.149$) using z-scores derived from a range of different cognitive tests. Analysis of cognitive domains revealed significant effects of flavonoids on long term memory and processing speed but domain specific discrimination for the berry subgroup was not possible.[79] Future research should aim to identify tasks that are reliable in their sensitivity to anthocyanin intervention in similar populations and replicate studies with larger sample sizes.

4. Concluding Remarks

This systematic review underscores the findings that anthocyanins can have positive effects on cognitive function, particularly on verbal and working memory and executive function. However, the influence of anthocyanins on peripheral vascular function parameters (e.g., BP) is not as clear. Vascular control of CBF across the lifespan is critical for maintaining cognitive function with a clear association between vascular dysfunction and cognitive impairment. Recommendations for intake of anthocyanins from foods and beverages could promote public health benefits for CVD prevention and cognitive function although more research is needed to help determine specific recommendations for intake of those foods and beverages.

5. Experimental Section

Protocol: The recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[87] were adopted to conduct this systematic review (see PRISMA checklist in Supporting Information Table S1).

Search Strategy: A systematic search was conducted using Ovid (MEDLINE, AMED), PsychInfo, Web of Science, and Scopus databases up to January 2024. Briefly, search terms were (anthocyanin* OR individual fruits such as blueberries) AND (cognition or truncations such as cogni$). A full list of search terms can be found in Supporting Information Table S2. In addition, a manual search of the reference list of included studies was conducted to determine any references not included in the searched databases.

Eligibility Criteria: Studies were eligible for inclusion if they met the following inclusion criteria: randomized or non-randomized trials (including cross-over trials), published in the English language, population aged over 18 years who were healthy or at an increased risk of CVD, or who reported cognitive decline or dementia (as diagnosed by care facilities or a hospital). Only studies that objectively measured the anthocyanin content of the intervention, used validated cognitive tests, and measured vascular function were included. Studies were excluded if the anthocyanin content was estimated from habitual diet. Due to the confounding effects of alcohol, studies which investigated anthocyanin consumption exclusively from alcoholic beverages (e.g., wine) were excluded. Identified records were exported from the databases and managed in Endnote x4.

Data Extraction and Assessment of Study Quality: Two reviewers (L.E. and L.D.) separately assessed the results and any disagreements were resolved by a third reviewer (C.B.). For included studies, a standardized data extraction form was created in Excel. The form captured relevant summary data following the structure format suggested by Population, Intervention/Comparison, Outcome (PICO) guidelines.[88] Further information including study design, cognitive tests, and vascular tests employed were also included.

The quality of the included studies was assessed using the "Revised Cochrane risk-of-bias tool" (RoB 2) as described in the Cochrane Handbook of systematic reviews of interventions.[89] The following methodological assessment points were considered: adequacy of sequence generation, allocation concealment, blinding, drop-out rates (incomplete outcome data), means to address incomplete outcome data, selective outcome reporting, and other potential sources of bias.

Data Synthesis: Where possible, Cohen's d was calculated to provide an effect size for statistically significant outcomes for cognition according to a method previously published by Lipsey and Wilson.[90] A value equal to 0.2, 0.5, or 0.8 corresponds to a small, medium, or large effect size.[91]

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

Acknowledgements

Lucy Ellis was supported by a Emma and Leslie Reid PhD scholarship from University of Leeds.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

L.E. was involved in design, search strategy development, database searching, study selection, data extraction, analysis, and writing of the manuscript. L.D. and C.B. were involved in design, secondary study selection, quality appraisal, and critical review of the manuscript.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords

anthocyanins, blood pressure, cognition, endothelial function

Received: July 16, 2023
Revised: March 6, 2024
Published online:

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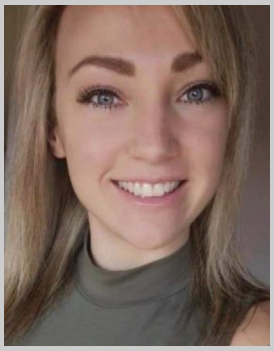

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