Health Effects of Berry Anthocyanins

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Supplementation with anthocyanins, which are a type of flavonoids mainly found in various berries, is hypothesized to be a promising approach to lower the risk of developing cognitive decline. The aim of this systematic review was to provide a comprehensive overview of dietary intervention trials describing effects of berry anthocyanins on cognitive performance in humans, while also addressing potential underlying mechanisms.

Keywords: anthocyanins ; cognitive performance ; vascular function ; cardiometabolic risk markers

1. Introduction

Cognitive performance encompasses multiple mental abilities that can be categorized into various domains, such as attention and psychomotor speed, memory, and executive function [1]. From childhood, cognitive performance quickly improves until young adulthood, after which it gradually starts declining [2]. Therefore, it is becoming increasingly relevant to focus on improving and/or maintaining cognitive performance to delay and prevent cognitive decline, and ultimately the onset of dementia [3]. This could be achieved by targeting potential mechanisms that drive cognitive performance [4][5].

An impaired vascular function is a common pathophysiological characteristic of multiple age-related conditions [6][7]. Vascular function can be assessed by determining endothelial function with methods such as brachial artery flow-mediated vasodilation (FMD) or the reactive hyperemia index (RHI) [8]. Previous research has already shown that vascular health declines with age leading to an increased risk of cognitive impairment, which may partly be explained by co-existing cardiometabolic risk factors, such as high blood pressure (BP) or a disturbed lipid profile such as altered low-density lipoprotein cholesterol (LDL-C) or high-density lipoprotein cholesterol (HDL-C) concentrations [9]. Therefore, dietary interventions that target vascular function and/or cardiometabolic risk markers may improve cognitive performance [10][11][12].

Therefore, increasing dietary intake of anthocyanins through supplementation could be a useful strategy to lower the risk of developing cognitive decline. A recent systematic review by Kent and colleagues [13] reported different intervention studies with beneficial effects of food-derived anthocyanins on cognitive performance. However, a systematic review designed to evaluate the effects of dietary anthocyanin interventions on cognitive performance and underlying mechanisms (i.e., vascular function and cardiometabolic risk markers) in an integrated manner has not been published yet. Therefore, the aim of this systematic literature review was to provide an overview of dietary intervention trials describing effects of berry anthocyanins on cognitive performance, vascular function, and cardiometabolic risk markers in humans.

2. The Effect of Berry Anthocyanins on Cognitive Performance

Of the eighteen studies that determined the effects of berry anthocyanins on cognitive performance outcomes, fifteen used a blueberry intervention, while the other three studies used either a chokeberry extract, a blackcurrant juice, or a blackcurrant extract. Results on cognitive performance were clustered based on the domains evaluated in the studies, i.e., (i) attention and psychomotor speed domain, (ii) executive function domain, (iii) memory domain, or (iv) other tests. Study results are shown in Table 1.

Table 1. The effect of berry anthocyanins on cognitive performance outcomes, compared to control.

Author (Year)	Intervention	Anthocyanin Dose	Attention and Psychomotor Speed					Executive Function					M
			TMT-A	MFT	GPT	FCRTT	Miscellaneous	TMT-B	Stroop	(M)ANT	Go-No-Go	Miscellaneous	R - -
Ahles (2020) [14]	Chokeberry extract	16 mg			↑		= (NCT)		=				
		27 mg			=		= (NCT)		=				
Barfoot (2019) [15]	Freeze-dried wild blueberry juice	253 mg								↑			

Author (Year)	Intervention	Anthocyanin Dose	Attention and Psychomotor Speed				Executive Function					M
Boespflug (2018) [16]	Freeze-dried blueberry powder	269 mg										
Bowtell (2017) [17]	Blueberry extract	387 mg						=				
Cook (2020) [18]	New Zealand blackcurrant extract	210 mg			=	= (RVIP, SRT)					= (SWM)	
Krikorian (2010) [19]	Blueberry juice	428-598 mg [1]										
Krikorian (2020) [20]	Freeze-dried blueberry fruit powder	258 mg	↑?				=				↑ (COWAT)	:
McNamara (2018) [21]	Freeze-dried blueberry powder	269 mg	=				=				= (COWAT)	
Miller (2018) [22]	Freeze-dried blueberry powder	230 mg #	=				=		=		↑ (TST)	
Traupe (2018) [23]	Blueberry juice	nr				↑ (AMT)	↑					
Watson (2019) [24]	Blackcurrant juice	115.09 mg			↑	= (DVT, SRTT)						
Whyte (2015) [25]	Blueberry juice	143 mg						=		=		=
Whyte (2016) [26]	Freeze-dried wild blueberry powder	127 mg		=						↓?	↑? (PMT)	↑
		254 mg		↑						=	↑? (PMT)	
Whyte (2017) [27]	Wild blueberry powder	253 mg							↑			
Whyte (2018) [28]	Wild blueberry powder and extract	1.35 mg						=	=			:
		2.7 mg						=	=			:
		7 mg						=	=			:
Whyte (2020) [29]	Wild blueberry powder	475 mg							=	↑		
Whyte (2020) [30]	Wild blueberry powder	253 mg										:
	Wild blueberry powder	253 mg							↑?		= Stop-Go, TST)	

↑ or ↓ or = indicates statistically significant improved or deteriorated values or no significant change in the intervention group compared to control. ? indicates a trend. # indicates that the value was calculated; [1] indicates that the dosage was dependent on body weight. Abbreviations: AMT: attention matrices test; BPT: brown peterson task; CBT: Corsi blocks test; COWAT: controlled oral word association; CVLT: california verbal learning test; DST: digit span task; DVT: Digit vigilance test; FCRTT: five-choice reaction time task; GPT: grooved pegboard test; HVLT: hopkins verbal learning test; ISLT: international shopping list task; MANT: modified attention network task; MFT: modified flanker test; nr: not reported; OLT: object location task; PMT: picture matching task; NCT: number cross out test; PRT: picture recognition task; RAVLT: rey auditory verbal learning test; RVIP: rapid visual information processing; SMST: sternberg memory scanning task; SPAL: spatial paired associates learning; SRTT: simple reaction time task; SST: serial subtractions task; SWM: spatial working memory task; TMT: trail making test; TOWRE-2: test of word reading efficiency; TST: task switching test; VMWMT: Virtual Morris Water Maze test; VPAL: verbal paired associates learning; VSGT: visuospatial grid task; WRT: word recognition task.

3. The Effect of Berry Anthocyanins on Cardiometabolic Risk

Thirty-two studies determined effects of berry anthocyanins on cardiometabolic risk markers. The interventions used were blueberry (n = 12), chokeberry (n = 7), blackcurrant (n = 6), black raspberry (n = 4), elderberry (n = 2), and bilberry (n = 1). The results were clustered into (i) BP measurements, or (ii) metabolic risk markers. The results of all studies are displayed in Table 2.

Author (Year)	Intervention	Anthocyanin Dose	Blood Pressure				Metabolic Risk Markers						
			SBP/DBP	MAP	Central SBP/DBP	24hr ABP SBP/DBP	Heart Rate	Glucose	Insulin	TC	TAG	HDL-C	LDL-C
Ahles (2020) [14]	Chokeberry extract	16 mg	=/=		=/=								
		27 mg	=/=		=/=								
Arevström (2019) [31]	Bilberry powder	90 mg #	=/=				=			=	=	=	=
Basu (2010) [32]	Freeze-dried blueberry juice	742 mg	↓/↓					=		=	=	=	=
Castro-Acosta (2016) [33]	Blackcurrant extract	131 mg	=/=										
		322 mg	=/=										
		599 mg	=/=										
Cho (2020) [34]	Black raspberry extract	nr	=/=							↓	=	=	↓
Cook (2017) [35]	New Zealand blackcurrant extract	210 mg	=/=	=			=						
Cook (2017) [36]	New Zealand blackcurrant extract	105 mg	=/=	=			=						
		210 mg	=/=	↓			=						
		315 mg	=/=	↓?			=						
Cook (2020) [18]	New Zealand blackcurrant extract	210 mg	↓/↓										
Curtis (2009) [37]	Elderberry extract	500 mg	=/=				=	=		=	=	=	=
Curtis (2019) [38]	Freeze-dried blueberry powder	182 mg	=/=					=	=	=	=	=	=
Del Bó (2013) [39]	Blueberry jello	348 mg	=/=										
Del Bó (2017) [40]	Blueberry juice	309 mg	=/=				=						
Istas (2019) [41]	Chokeberry extract and whole fruit	3.6 mg	=/=		=/=		=	=		=	=	=	=
		30 mg	=/=		=/=		=	=		=	=	=	=
Jeong (2014) [42]	Black raspberry extract	nr								↓	=	=	=
Jeong (2016) [43]	Black raspberry extract	nr (low dose)	=/=		=/-	=/=							
		nr (high dose)	=/=		=/-	↓/=							
Jeong (2016) [44]	Black raspberry extract	nr	=/=		=/-		=						
Johnson (2015) [45]	Freeze-dried blueberry powder	103 mg #	↓/↓	=			=						

Author (Year)	Intervention	Anthocyanin Dose	Blood Pressure					Metabolic Risk Markers					
Khan (2014) [46]	Blackcurrant juice	10 mg	=/=							=			
		35.75 mg	=/=							=			
Loo (2016) [47]	Chokeberry juice and powder	1024 mg	=/=			=/↓?		=		=	=	=	
McAnulty (2014) [48]	Blueberry powder	nr	↓/=										
McAnulty (2019) [49]	Freeze-dried blueberry powder	nr	↓/=										
Murkovic (2004) [50]	Elderberry juice	40 mg								=	=	=	=
Naruszewicz (2007) [51]	Chokeberry extract	64 mg #	↓/↓					=		=	=	=	=
Okamoto (2020) [52]	New Zealand blackcurrant extract	210 mg	↓/↓?	↓	=/↓			=			=	=	=
Petrovic (2016) [53]	Chokeberry juice	nr						=		=	=		
Pokimica (2019) [54]	Chokeberry juice	28.3 mg	=/=					=		=	=		
		113.3 mg	=/=					=		=	=		=
Riso (2013) [55]	Freeze-dried blueberry powder	375 mg	=/=					=		=	=	=	=
Rodriguez-Mateos (2013) [56]	Freeze-dried blueberry powder	310 mg	=/=				=						
		517 mg	=/=				=						
		724 mg	=/=				=						
Stull (2010) [57]	Freeze-dried blueberry powder	668 mg	=/=					=	=	=	=	=	=
Stull (2015) [58]	Freeze-dried blueberry powder	290.3 mg	=/=					=	=	=	=	=	=
Whyte (2018) [28]	Wild blueberry powder and extract	1.35 mg	=/=										
		2.7 mg	=/=										
		7 mg	↓/=										
Xie (2017) [59]	Chokeberry extract	45.1 mg	=/=							↓	=	=	↓

↑ or ↓ or = indicates statistically significant higher or lower values or no significant change in the intervention group compared to control. ? indicates a trend. # indicates that the value was calculated; [1] indicates that the dosage was dependent on body weight. Abbreviations: ABP: ambulatory blood pressure; ApoA1: apolipoprotein A1; ApoB: apolipoprotein B; DBP: diastolic blood pressure; HDL-C: high-density lipoprotein cholesterol; HR; heart rate; LDL-C: low-density lipoprotein cholesterol; MAP: mean arterial pressure; nr: not reported; SBP: systolic blood pressure; TAG: triacylglycerol; TC: total cholesterol.

4. Discussion

This systematic review summarized the effects of berry anthocyanins on cognitive performance, vascular function, and cardiometabolic risk markers. Significant improvements were primarily observed on memory, while some of the studies also reported effects on attention and psychomotor speed or executive function. Vascular function markers were also affected, and it can be concluded that berry anthocyanins predominantly improved vascular endothelial function as measured by FMD. Finally, for cardiometabolic risk markers, studies reported significant effects on BP, but effects on metabolic risk markers (e.g., carbohydrate and lipid metabolism) were less consistent.

Most of the included studies evaluating effects on cognitive performance involved either a young healthy population or older adults (with an increased risk of cognitive decline). Studies measuring cognitive performance in children mostly focused on executive function, while studies in older adults primarily focused on memory tests. For studies in young and middle-aged adults, no specific preference for a specific domain was observed. Regarding memory outcomes, limited evidence was available for children and adults. Most evidence comes from studies involving older adults, which reported improved memory scores after supplementation with berry anthocyanins. The effect on memory was most evident among studies that evaluated individuals with (subjective) MCI. This could be attributed to the fact that there is a bigger window for improvement in older adults as compared with healthy younger adults, as the latter are at the peak of their cognitive abilities, while older adults already experience age-related cognitive decline [3]. The main aspect of memory that was affected was verbal memory, measured with three variations on the verbal learning test. In addition, in the paired associates learning tests, measuring new learning, beneficial effects in populations suffering from MCI were observed. This suggests that even though learning capacity is reduced, it is still possible to improve aspects of memory. Contrary to the memory tests, attention and psychomotor speed tests were primarily carried out in young/middle aged adults. Interestingly, all studies involving an adult population observed significant improvements as a result of supplementation, while all four studies using older adults (with cognitive decline) did not. Similarly, an improved executive function was observed in most studies involving children, but was less evident in (older) adults. These results suggest that the attention and psychomotor speed and executive function domains are better targets for improvement in younger populations. Previously, it has been shown that older adults require more time to finish attention tasks, but are able to maintain similar concentration as compared to younger adults [60]. Most of the tests included in this review reported accuracy scores, which might explain why no improvements could be observed for older adults. Alternatively, physical activity has been linked to cognitive functioning [61], which might be different in the study populations that were included in this review.

Next to the study population, the duration of the intervention and dose of anthocyanins may also play a role. Beneficial effects on cognitive performance were observed both in acute and longer-term studies. In fact, improved cognitive performance was reported for all three domains in both acute and longer-term studies. For attention and executive function tests, results appear to be stronger in case an acute intervention period was used, while memory outcomes were affected more by longer-term studies. This suggests that the ideal study duration is dependent on the selected cognitive domain.

Regarding the dose, interestingly, beneficial effects on cognitive performance parameters were not necessarily observed in those studies that used the highest amounts of anthocyanins. For example, favorable effects on attention and psychomotor speed were observed in healthy middle-aged adults after supplementation with a chokeberry extract containing 16 mg of anthocyanins [14], but not in healthy older adults after 230.4 mg anthocyanin supplementation using a blueberry powder [22]. This suggests that the effect of the intervention does not only depend on the amount of anthocyanin provided, but could for example also be affected by the composition of the intervention product. Within the studies included in this review, powders were used most often, followed by extracts and juices, with blueberries as the main source. All three compositions had the strongest results on the memory domain, with powder interventions significantly improving memory in five out of seven studies. For the executive function domain, powders also seemed to be the most effective, while extracts did not seem to have an effect. For attention and psychomotor speed, no clear patterns could be observed.

Since beneficial effects of berry anthocyanin supplementation on cognitive performance were observed, the question is how these effects can be explained mechanistically. Potentially, improvements in vascular function and cardiometabolic risk profiles could play a role in these mechanisms. Regarding the vascular measurements, studies on the effects on vascular function markers were primarily performed in adult populations. Effects of berry anthocyanins on endothelial function were measured by FMD, which is the current non-invasive gold standard approach for the assessment of endothelial function [62], in healthy adults and adults at cardiometabolic risk. Except for one study in smokers, all studies reported an improved FMD. In a recent cross-sectional study, a significant association between FMD and MCI was reported in healthy older adults and older adults with MCI [63]. Csipo et al. [64] observed an association in age-related decline in endothelial function and cognitive decline in older adults. Moreover, Naiberg et al. [65] have already reviewed and established a more specific link for both executive function and working memory with FMD. These results indicate that the effects on memory observed in this review, could potentially be the result of an improved vascular function, with endothelial function as measured by FMD as an important factor. In agreement, the RHI, another measure of endothelial function measuring the reperfusion of limbs, was also improved in adults at cardiometabolic risk, but not in healthy subjects. Besides the effects on markers of endothelial function, some of the studies also focused on arterial stiffness. In fact, for AIx, no significant effects were reported in the studies involving a healthy adult population. However, half of the studies performed in an adult population at cardiometabolic risk, and a single study in healthy older adults, observed an improved AIx. Only a limited amount of the included studies performed cfPWV measurements in (older) adults. No effect was observed in the healthy adult population while cfPWV was improved in adults at cardiometabolic risk and healthy older adults. However, it should be considered that the study duration was only 24 h for the healthy adult population, which is too short to induce structural changes in artery walls that are addressed with cfPWV [66].

BP was lowered in several studies that included an adult population at cardiometabolic risk (e.g. (pre)hypertension, MetS, obesity). Studies that were carried out with an older adult population (healthy or subjective MCI) all reported beneficial effects on BP. In contrast, studies evaluating BP effects in healthy adults did not observe any changes. This is in line with our earlier findings on cognitive performance, suggesting that dietary anthocyanins have the most pronounced effects in populations with increased cardiometabolic risk, allowing for improvement by the intervention.

Considering the effects of berry anthocyanins on vascular function and cardiometabolic risk profiles as summarized in this review, the effect of intervention composition (i.e., powder, extract, or juice) and study duration is less clear as compared to the observations for the cognitive domain. Six out of fourteen studies using an extract found significant improvements in BP as compared with three out of ten studies using a powder, and one out of six juice intervention studies. Similarly, all four studies using a powder as intervention reported increased FMD, compared to two out of three studies using an extract. This pattern is also similar for the other parameters. All studies observing a beneficial effect on BP had an intervention period of one to twenty-four weeks, while all four acute studies (<24 h) did not report any significant changes, suggesting that a longer intervention is probably needed to induce effects on BP following the intake of anthocyanins. Taken together, these data suggest that the effect of berry anthocyanins on vascular function and cardiometabolic profiles is not only dependent on the population receiving the intervention, but may also be related to other factors, such as the method of administration, and the duration of intervention. Furthermore, physical activity could affect it.

A limitation of this review study is that the exact composition of the interventions was not always reported. Moreover, the bioactivity of anthocyanins is known to be dependent on their chemical structure [67]. Even though we were able to report the amount of anthocyanin for most of the studies, more specific components such as anthocyanin subgroups (e.g. cyanidins, delphinidins, malvidins) were often not mentioned. Therefore, it was not possible to compare effects of these anthocyanin subgroups. Besides these subgroups, specific biological effects could also be the result of anthocyanin metabolization [68][69]. Furthermore, only a limited amount of studies using an extract provided information on the method of extraction, which could influence the bioactivity of the anthocyanins [70]. Consequently, we recommend future studies to report information on the chemical composition and extraction methods of the study products.

In conclusion, this systematic review provides evidence for the beneficial effects of berry anthocyanins on cognitive performance as memory was improved. Vascular endothelial function, as measured by FMD and BP were also affected, and these effects may underlie the observed effects on memory. Future studies should focus on exploring a potential causal link between the beneficial effects on cognitive performance and improvement in vascular function and cardiometabolic risk markers.

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