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Title: The effect of blueberry interventions on cognitive performance and mood: a systematic review of randomized controlled trials

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Abstract:

Blueberries are rich in polyphenols that may be beneficial to cognitive performance and mood. The aim of this systematic review was to evaluate randomized controlled trials investigating the effects of blueberries and blueberry products on measures of cognition and mood. In total, eleven articles (that included 12 studies) were identified using freeze-dried blueberries (n=9 studies), whole blueberries (n=2) and blueberry concentrate (n=1). These studies were conducted in children (n=5), young adults (n=1), and older people with either no known cognitive impairment (n=4) or indicated cognitive impairment (n=2). Eight studies reported blueberry consumption or supplementation at various doses and time lengths to improve measures of cognitive performance, particularly short- and long-term memory and spatial memory. For mood, one study reported significant between-group improvements in positive affect from blueberry products, whereas four studies reported no improvement. Low risk of bias were observed across all studies. Based on the current evidence, blueberries may improve some measures of cognitive performance when consumed for up to six months in duration. However, considerable differences in study design, dosages, and anthocyanin content hinder between-study comparison. The use of standardized blueberry interventions, consideration of placebo formulations, and consistently reported cognitive performance tools are recommended in future trials. PROSPERO registration no. CRD42018100888.

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Introduction

Polyphenols – bioactive plant compounds abundant in foods such as fruits, vegetables, spices, and teas – are a group of diverse compounds that are characterised by their phenolic structural features. Polyphenol-rich dietary patterns such as the Mediterranean diet, as well as specific polyphenol-rich foods, including berries, green tea, and cacao, have been reported in clinical and observational studies to improve measures of cognition and mood (Bell et al., 2015a; Chang et al., 2016; Donnelly et al., 2015; Hardman et al., 2016; Jacka et al., 2017; Kent et al., 2017a; Lassale et al., 2018).

Blueberries (*Vaccinium corybosum* L.) are a rich source of polyphenolic compounds, particularly anthocyanins, a sub-class of polyphenols that are responsible for the fruit's deep purple and blue colour (Li et al., 2017). These blueberry-derived polyphenols possess multiple properties that may mediate cognitive performance and neurodegeneration. In a preclinical animal model, anthocyanins have been identified in specific cerebral sites of 19-month-old male F344 rats after 8-10 weeks of receiving a blueberry-enriched diet, including the hippocampus and neocortex, regions essential for cognitive performance (Andres-Lacueva et al., 2005). Preclinical studies have also demonstrated decreased excitotoxicity relating to oxidative stress following blueberry supplementation, with its direct scavenging activity reducing the production of reactive oxygen species (ROS) (Shukitt-Hale, 2012). This antioxidant capacity may be driven via hormesis, whereby initial increases in total ROS are followed by an increased antioxidant defence (Elks et al., 2011). Blueberries have also been shown to protect against the neurodegenerative effects of beta-amyloid and tau proteins in rats through the downregulation of inflammatory responses and inhibition of pro-inflammatory molecules such as cytokines (Ebenezer et al., 2016). This is achieved via a reduction in nuclear factor kappa B (NF-κB) signalling (Goyarzu et al., 2004) and suppression of microglial activation (Zhu et al., 2008). Following blueberry consumption,

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neuroplasticity has been discovered in structures such as the hippocampus and frontal cortex through the stimulation of trophic factors including brain-derived neurotrophic factor (BDNF)(Rendeiro et al., 2013) and Insulin-like growth factor 1 (IGF-1) (Shukitt-Hale et al., 2008). In an animal model of posttraumatic stress disorder, a blueberry-enriched diet significantly increased production of neurotransmitters such as serotonin and its precursor enzymes, tyrosine hydroxylase and tryptophan hydroxylase (Ebenezer et al., 2016). As a result, blueberries appeared to enhance resiliency as indicated by reduced anxiety levels when exploring new surroundings in the elevated plus-maze. Additional modes of action include reduced lipid peroxidation and acetylcholinesterase activity (Papandreou et al., 2009), neuroprotective activity against glutamatergic excitotoxicity (Vyas et al., 2013) and suppressed expression of neuronal apoptosis (Shin et al., 2006). Furthermore, blueberries have reported to possess a range of beneficial cardiovascular properties such as antihypertension (Shaughnessy et al., 2009), hypoglycaemic (Erlund et al., 2008), and anticoagulant actions (Martineau et al., 2006) which may improve cardiovascular outcomes and provide indirect benefits to cognition by improving cerebrovascular flow,(Bowtell et al., 2017) a marker of cognitive impairment.(Kalaria Raj, 2012)

Recently, there have been numerous clinical trials that have evaluated the effect of blueberries and blueberry products (including juices, whole blueberries, and freeze-dried powders preparations) on cognition in various populations using randomized, double blind controlled study designs. However, the results of these studies have not been systematically evaluated. Therefore, this systematic review aims to examine the current evidence from randomized controlled trials to evaluate the potential effects of blueberries on cognitive performance and mood in humans.

Methods

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This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines as a methodological template (Moher et al., 2009), and was prospectively registered in an international registry of systematic reviews (PROSPERO registration no. CRD42018100888). The systematic review strategy was guided by the PICOS (population, intervention, comparator, outcomes and setting) approach. The criteria within each of these categories were as follows:

- *Population:* Human populations of any age or health status.
- *Intervention:* Original studies investigating the effects of blueberries including raw blueberries, blueberry extracts and blueberry supplements.
- *Comparator:* Human comparators were required, using a placebo or control intervention.
- *Outcomes:* Human data were analysed according to cognitive domains or mood.
- *Setting:* Any

Literature search

Electronic databases (PsychINFO, Embase, PubMed, CINAHL and the Cochrane database) were systematically searched from inception until June 2018 to identify peer-reviewed clinical trials that investigated the effects of blueberry intervention on cognitive performance and mood. The search terms used were (blueberries OR blueberry OR *Vaccinium corymbosum*) AND (cognitive OR cognition OR dementia OR Alzheimer* OR mood OR memory).

Study selection

Eligible studies met the following criteria: used a randomised controlled parallel or cross-over study design; involved human participants of any age, ethnicity or health status; and used a whole blueberry or blueberry product intervention. Observational studies, reviews,

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abstracts, conference papers, study protocols or studies that did not report relevant outcome measures were excluded. The primary outcomes of interest included validated or self-reported cognitive screening and neuropsychological measures, improvements in mood, and improvements based on informant/carer responses to validated assessment tools.

Two investigators (N.T. & N.M.D) independently conducted the searches using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). Both authors first screened for eligibility based on titles and abstracts according to the eligibility criteria. For any articles where this was unclear, the article was carried forward into the full-text review. The full text of the remaining papers was independently reviewed by both authors, and eligible studies were included. Disagreements were managed by discussion to reach consensus or by a third reviewer (W.M), where appropriate. Searches were re-run in October 2018, with one additional article located for inclusion in the systematic review (Barfoot et al., 2018).

Data extraction and quality assessment

The data was extracted into a pre-defined spreadsheet by two authors (N.T & N.M.D) and cross-checked for consistency. Data extraction was completed for study design, the details of the intervention (type, dose, & timing), descriptive statistics of the groups in the study (age & gender), the primary and secondary outcomes reported, and the results (mean change score & standard deviations). Both authors independently assessed each study for bias using the Cochrane Collaboration's tool for assessing risk of bias (Higgins et al., 2011). This tool includes criteria for assessing sequence generation, allocation concealment, blinding of participants, personnel, and outcome assessors, incomplete outcome data, and selective outcome reporting. For each criterion, studies were assessed for risk of bias as low, unclear,

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or high. Disagreements were managed by discussion and mediated by two co-authors (W.M. & E.N.G.) until consensus was reached.

Results

In total, 504 articles were identified during the initial search, with 186 omitted as duplicates. A further 296 were excluded during initial screening of the inclusion criteria, with an additional 12 excluded for reasons noted in the PRISMA flow chart (Figure 1), leaving eleven articles for inclusion in the final review. The manuscript by Khalid et al. (2017) reported results from two separate studies. Furthermore, Khalid et al. (2017) and Barfoot et al (2018) reported on separate outcomes from the same study cohort. Therefore, twelve studies from eleven cohorts are included in the analysis.

Study characteristics

The total number of participants from the included studies was 398, with study sample sizes ranging from 16 to 122 participants (Table 1). All studies were randomised controlled trials, with four studies using a cross-over design. Five studies were conducted using children (aged 7-10 years)(Barfoot et al., 2018; Khalid et al., 2017; Whyte et al., 2016, 2017; Whyte and Williams, 2015), one using young adults (aged 18-21 years)(Khalid et al., 2017), and the other six articles investigated older people (aged 60-92 years)(Boespflug et al., 2018; McNamara et al., 2018; Miller et al., 2018; Schrager et al., 2015; Whyte et al., 2018). Ten of the studies included healthy individuals. However, one study included older people with mild cognitive impairment (MCI)(Boespflug et al., 2018), and one included healthy older people with self-perceived cognitive decline (McNamara et al., 2018). The duration of the treatment ranged from acute trials (2-6 hours post-intervention) (Barfoot et al., 2018; Khalid et al., 2017; Whyte et al., 2016, 2017) to six months (Whyte et al., 2018).

Supplement and control group regimens

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The included studies used a variety of blueberry interventions and control groups. Anthocyanin content ranged from 1.55 mg/day (Whyte et al., 2018) to ~387 mg/day (Bowtell et al., 2017). Anthocyanin content of the interventions were reported in all studies except one(Schrager et al., 2015) and are presented in supplementary material. Three studies used an inert placebo as a control while nine studies used a control that was matched for some non-polyphenol components such as vitamin C, energy, and simple carbohydrates.

One study compared 30 mL of blueberry concentrate (387 mg anthocyanins) to a control which contained blackcurrant and apple cordial (Bowtell et al., 2017). Two studies used 200 g of whole blueberries compared with either carrot juice (Schrager et al., 2015), or 143 mg of anthocyanins blended with semi-skimmed milk and compared with semi-skimmed milk, matched for vitamin C, sucrose, fructose and glucose content (Whyte and Williams, 2015).

Nine studies used freeze-dried blueberry powder (12.5 g-30 g dry weight powder, 1.35 mg-387 mg anthocyanins) (Barfoot et al., 2018; Boespflug et al., 2018; Khalid et al., 2017; McNamara et al., 2018; Miller et al., 2018; Whyte et al., 2018; Whyte et al., 2016, 2017), five of which compared freeze-dried wild blueberry powder (253 mg anthocyanins) mixed with water and fruit squash with a water and fruit squash control that was matched for vitamin C, sucrose, fructose and glucose content (Barfoot et al., 2018; Khalid et al., 2017). Another freeze-dried blueberry powder study instructed participants to consume either the active product (12.5 g, 134.5 mg anthocyanins) or a colour matched, isocaloric control with water (Boespflug et al., 2018). In the study by Miller et al. (2018) participants consumed 12 g of a freeze-dried blend of Tifblue blueberries (348mg anthocyanins daily) or a colour matched isocaloric control. Similarly, two 12.5 g packets of a freeze-dried blueberry blend (269 mg anthocyanins daily) were provided per day by McNamara et al. (2018) which were colour and sugar matched with a powdered control. Both studies selected their dose to replicate the addition of one cup of whole blueberry fruit in the diet (McNamara et al., 2018; Miller et al.,

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2018). The study by Whyte et al. (2018) had four arms, comparing two capsules of a combined daily dose of 500mg (1.5 mg anthocyanins daily), 1g of wild blueberry powder (2.7 mg anthocyanins), a 111 mg purified Wild Blueberry extract (Thinkblue^{TM}; 7 mg anthocyanins) or placebo capsule consisting of sugar and dye.

Outcome measures

A wide range of cognitive measures were used across the included studies. The most common outcome measured was processing speed with three studies using the Stroop test (Bowtell et al., 2017; Whyte et al., 2018; Whyte and Williams, 2015), two studies using variations of the Trail making test (McNamara et al., 2018; Schrager et al., 2015), and one using a serial subtraction task (Whyte et al., 2018). Short-term memory was investigated in three studies using the N-back test (Boespflug et al., 2018; Bowtell et al., 2017; Whyte and Williams, 2015), Corsi blocks task (Whyte et al., 2018), and Digit span task (Miller et al., 2018). Long-term storage and retrieval were measured by three studies using the Groton maze (Bowtell et al., 2017), Auditory Verbal Learning Task (Barfoot et al., 2018; Whyte et al., 2016), and the Hopkins Verbal Learning Test (McNamara et al., 2018).

Mood was measured most commonly using the Positive and Negative Affect Schedule (Khalid et al., 2017; Whyte et al., 2018), and the Profile of Mood States (Miller et al., 2018). Positive and Negative Affect Schedule is a self-reported measure of positive and negative affect, consisting of two 10-item scales. The Profile of Mood States is also a self-reported measure that assesses 6 mood states using individual 5-point scales. Individual tests used by the included studies are displayed in Table 1.

Study results

Of the included studies, ten studies (n = 377 participants) reported cognitive outcomes. The included studies reported a wide range of cognitive improvements with the most frequently

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reported being in short- and long- term memory (4/5 trials) and spatial memory (2/6 trials) However, as reported in Table 1, there was a wide range of non-significant results reported across trials. A total of five studies assessed mood with a combined sample size of 253 participants. Of the five studies, four studies demonstrated no between-group difference in mood outcomes.

In the study by Bowtell et al. (2017), in healthy adults over 65 years, a 12-week intervention of 30 mg blueberry concentrate (387 mg anthocyanins) per day improved accuracy in the 2-back test (group by time interaction) ($p = 0.05$) but not in the 1-back test, the detection task, the Groton maze timed chase test, delayed recall task, identification task, reaction time, and the numerical Stroop test.

The study by Boespflug et al. (2018) ($n = 21$) used 12.5 g freeze-dried blueberry powder (134.5 mg anthocyanins) twice daily for 16 weeks and did not detect a significant improvement in *N*-back performance ($p = 0.08$). There was no significant difference in the Geriatric Depression Scale, and the Geriatric Anxiety Inventory scale.

The 24-week blueberry powder intervention (25 mg per day; 134.5 mg anthocyanins) by McNamara et al. (2018) ($n = 94$) improved performance in the Hopkins Verbal Learning test discrimination ($p < 0.05$) and The Dysexecutive Questionnaire ($p < 0.05$) compared to placebo. The reduction in dysexecutive behavioural symptoms as measured by The Dysexecutive Questionnaire was maintained at a 48-week follow up. No significant difference was reported for Trail making A and trail making B tasks, phonological access, semantic access, and Hopkins Verbal Learning test learning, recall, and retained domains.

The study by Miller et al. (2018) used 24 g of blueberry powder (348 mg anthocyanins daily) for 90 days in 37 healthy adults and reported improvements in executive functioning in which participants in the control group (energy and flavour matched control) made more, and

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participants in the blueberry group made fewer, repetition errors on the California Verbal Learning test ($p = 0.031$) and reduced switch cost in the task-switching test ($p = 0.033$). No significant difference was reported for the Geriatric Depression Scale and Profile of Mood States tools as well as the digit span task, virtual version of the Morris Water Maze, and the Attention Network Task.

The largest study, with 122 participants, by Whyte et al. (2018) reported improvements in a four-arm trial comparing wild blueberry powder (500 mg & 1000 mg) to a purified extract (100 mg) and placebo at 3-months follow up but not 6-months follow up. Linear mixed model analysis revealed improved word recognition on the Reys Auditory Verbal Learning Task (RAVLT) ($p = 0.038$) and Corsi Block task ($p = 0.009$) after a three month follow up. No significant difference was reported for the object recognition, Modified Attention, serial subtractions and Sternberg memory scanning tasks as well as The Positive and Negative Affect Schedule—NOW questionnaire.

One study by Schrager et al. (2015) compared flash-frozen blueberries to carrot juice over 6 weeks in 20 older adults with non-significant improvements in psychomotor reaction time and Trail Making task in both the blueberry and carrot juice groups (Schrager et al., 2015).

In a study of children aged 8 – 10 years ($n = 16$), acute improvements in delayed recall were observed two hours post-consumption of 200 g of raw blueberries (143 mg anthocyanins) mixed in skim milk compared with a control group ($p = 0.038$). Following post-hoc analysis, no difference between the groups was observed at two minutes ($p = 0.12$), but a there was a trend towards an improved delayed recall at 25 minutes in the blueberry intervention group ($p = 0.07$)(Whyte and Williams, 2015). No significant difference was reported for the following cognitive tasks: Go-NoGo, Word-colour Stroop, Visuospatial n-back, and Object location.

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Using the RAVLT, acute (2 hours post-consumption) improvements on short delay ($p = 0.04$) and memory acquisition ($p = 0.035$) were found by Barfoot et al. (2018) in 54 children aged 7 – 10 years, post-consumption of the wild blueberry drink. No significant improvements in Modified Network Attention Task or a reading efficiency task. Khalid et al (2017) reported no significant difference in the Positive and Negative Affect Scale using the same dataset.

Whyte et al also conducted two separate acute studies in 21 children aged 7-10 years old(Whyte et al., 2016, 2017). In one acute trial (outcomes measured one hour and 15 minutes, 3 hours, 6 hours and 15 minutes post-consumption), significant differences between the 30 g intervention and control were reported for final acquisition performance ($p = 0.023$), word recognition ($p = 0.016$), incongruent flanker trials at 3 hour timepoint ($p = 0.035$) as well as significant differences for the 15 g intervention in the incongruent flanker test ($p = 0.019$) (Whyte et al., 2016). No other significant differences were reported for the Auditory Verbal Learning Task, Modified Flanker Task, Go–NoGo task, and the Picture Matching Task. In the second acute study (outcomes measured two hours post-consumption), by Whyte et al, designed to assess cognitive control and executive function, participants that received the blueberry intervention were significantly faster on high visual load/congruent ($p = 0.026$), high visual load/incongruent ($p = 0.029$) and medium visual load/incongruent trials ($p = 0.021$) (Whyte et al., 2017). Response times were also significantly faster following intervention for central ($p = 0.033$) and spatial cues ($p = 0.041$).

In young adults (n= 21), a within-groups analysis revealed a significant increase in positive affect ($p < 0.001$) and a reduction in negative affect ($p < 0.001$) after consuming the blueberry drink (Khalid et al., 2017). When compared to the control group, there was a significant difference in positive affect scores post- consumption (2 hours) between the control group and blueberry drink ($p = 0.033$).

Risk of bias assessment

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The risk of bias was performed on all included studies (Figure 2) and the study by Khalid et al. (2017) was assessed as two separate studies. Overall, there was low risk of bias across all domains, particularly for selection bias. Furthermore, only the performance bias and other bias domains produced a high risk of bias on more than one study. An exception was observed for the other bias domain, with four studies presenting with a high risk of bias (Barfoot et al., 2018; Khalid et al., 2017; Whyte and Williams, 2015). Notably, three studies were observed to have a high risk for other bias. These include the study by Schrager et al. (2015) which used carrot juice as the placebo, the study by Bowtell et al. (2017) which used blackcurrant and apple cordial as the placebo and the study by Whyte et al. (2018) which used maltodextrin and food grade artificial dye as the placebo. These studies were rated as having a high risk of other bias due to the potential for the ingredients used in the placebo intervention having influence on study results. Additionally, three studies (Boespflug et al., 2018; Khalid et al., 2017; Schrager et al., 2015) produced an unclear risk of bias for sequence generation.

Discussion

The results of this systematic review suggest that various formulations of blueberry interventions can improve some aspects of cognition and mood. Eight studies reported blueberry consumption or supplementation at various doses and time lengths to improve some measures of cognitive performance, particularly short- and long- term memory and one study reported improvements in positive affect. However, as shown in Table 2, two studies did not show improvements in cognition and four studies did report improvements in mood compared to control groups. Furthermore, positive results were limited to certain cognitive (e.g. RAVLT, CVLT-II, TST), and mood (PANAS-NOW positive affect) assessment tools with no effects on others. Possible explanations for these discrepancies could be due to polyphenols providing greater benefit to brain areas related to specific cognitive domains

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such as memory. For example, previous animal studies have reported that ingested anthocyanins appear in greater concentrations in parts of the brain associated with memory (Andres-Lacueva et al., 2005). An alternative explanation is that differences could be attributed to study design features such as differences in statistical power and study length.

In trials of healthy older adults, no consistent pattern across all included studies is evident. Study lengths ranged from 12 weeks to 6 months with beneficial results observed over 12 weeks (Bowtell et al., 2017), 24 weeks (McNamara et al., 2018) and 3 months while no significant differences were reported in two studies over 6 and 16 weeks (Boespflug et al., 2018; Schrager et al., 2015). Compared to studies in older adults, the evidence for the use of blueberry products in younger populations is largely limited to acute and short-term trials. There were also no included trials with middle-aged adults. A conference abstract that did not meet the inclusion criteria for this review (no published full text manuscript identified) reported on the effect of a wild blueberry intervention on acute cognitive performance in adults aged between 45 and 60 years of age (Rahman et al., 2017). Improvements were observed in executive function in the intervention group compared to control at two hours post-consumption of a high-carbohydrate, moderate fat meal. Overall, the results suggest blueberry interventions may benefit cognitive performance in older people while further research is required to determine the continued effect of blueberry interventions on middle-aged adults and children as well as to determine the most effective length of intervention.

Similarly, the optimal whole-fruit blueberry dose for cognitive performance is yet to be established (Krikorian et al., 2010). In the included studies, blueberry intervention doses ranged from 30 mg/day of blueberry extract to 460 g/day of blueberries, with the reported amount of consumed anthocyanin content also varying from 1.35 mg to 387 mg/day between studies (Supplementary Material 1). Additionally, the flavonoid content of blueberries is known to vary widely depending on growing, processing and storage conditions (i.e. freezing,

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heating) (Michalska and Łysiak, 2015). Given that trials were conducted at various geographical locations (predominantly USA and UK), it is likely that the blueberries used came from different growers and harvests, utilising diverse breeding techniques, from diverse growing origins and exposure to different post-harvesting and management of crops (Michalska and Łysiak, 2015). Therefore, even the same blueberry dose may vary in polyphenol content as well as nutrients such as vitamin C, vitamin K and beta-carotene. This is exemplified in two studies (Dodd, 2012; Whyte and Williams, 2015) that used the same quantity of whole blueberries (200 g) but showed notable differences in polyphenolic content (631 mg and 143 mg anthocyanins per dose, respectively). In order to account for this, future studies should use standardised extracts and preferably quantify the polyphenol content, as well as the content of other relevant bioactive nutrients (e.g. vitamin C, carotenoids), using high performance liquid chromatography with mass spectrometry (HPLC-MS). The use of HPLC-MS will further assist with the identification of different polyphenolic compounds, in particular the variety and difference in anthocyanins within the extracts and variety of blueberries sourced. Furthermore, future dose-finding studies would be useful to determine optimal dosing regimens.

Given that the interventions consisted of blueberries as whole food sources, without the isolation of the anthocyanin components, the study results may be attributed to the content of other flavanols that were not reported. Alongside anthocyanins, blueberries are a rich source of flavanols including quercetin, myricetin, and kaempferol (Li et al., 2017), all of which are associated with cognitive performance and mood (Bell et al., 2015a). Concentrations of these components were not measured or reported in the trials which limits the ability to attribute benefits to polyphenols other than anthocyanins. Blueberries also contain moderate vitamin C content (Prior et al., 1998), which is linked to central nervous system function (Travica et al., 2017). Furthermore, there are a number of food-processing and compound-related factors that

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can affect the bioavailability of polyphenols including matrix sugar content, presence of dietary fat and fibre and, potentially, milk proteins.(D'Archivio et al., 2010) Several of the studies administered the blueberry intervention in conjunction with other ingredients such as semi-skimmed milk (Whyte and Williams, 2015), sucrose (Whyte and Williams, 2015) and additional vitamin C (Barfoot et al., 2018; Khalid et al., 2017), and different forms of blueberry were provided across studies (e.g. juices, powder, and whole blueberries), possibly affecting blueberry polyphenol and micronutrient bioavailability and masking the potential direct cognitive effects of the blueberry intervention itself.

Apart from limitations arising from the blueberry interventions, issues regarding the control interventions may have also influenced the results. Some studies provided control interventions that matched a number of ingredients, other than anthocyanins, present in the blueberry interventions (e.g. vitamin C, glucose and calories). However, the active comparator arms in some trials consisted of ingredients such as carrot juice (Schrager et al., 2015), and blackcurrant and apple cordial(Bowtell et al., 2017) which may also provide polyphenols and other bioactive phytochemicals (as well potential colour and taste differences). Future trials would benefit from considering the bioactivity of the placebo formulations as well as the blinding methods and assesing the adequacy of blinding procedures.

Multiple food sources are rich in bioactive compounds found in blueberries, including a variety of different polyphenols in particular, anthocyanins. These include, but are not limited to, blackcurrant, cherries, cranberry and grapes. Additionally, a variety of foods are high in other blueberry-containing bioactives and other nutrients such as glucose, vitamin C, and fibre. A number of included studies did not measure the micronutrient and polyphenol consumption and supplementation outside of the blueberry trial intervention, through food frequency questionnaires or food diaries (Balentine et al., 2015). Two included studies that

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reported on the same cohort (Barfoot et al., 2018; Khalid et al., 2017) instructed its participants to refrain from flavonoid-containing food consumption 24 hours prior to intervention, some studies instructed participants to abstain from a comprehensive list of berry fruits or high flavonoid foods and other included studies collected food diaries to monitor dietary flavonoid intake. Comprehensive dietary intake information in future trials may help control for the effects of other nutrients and polyphenol-rich foods consumed during the trial on cognitive performance and mood.

Due to the large variability in the cognitive assessments and scoring interpretations, the impact of blueberry interventions on specific cognitive domains could not be quantitatively compared across trials. Varying outcome measures used may also account for the observed variance in results between trials. An eventual meta-analysis would be possible if future studies use similar cognitive tools or tools that assess comparable cognitive domains, as per previous meta-analyses in this area (Marx et al., 2018). Similarly, the consideration of other covariates that may affect cognitive performance and mood may improve current understanding of individual responses to polyphenol interventions. Potential covariates include the number of prescribed medications, depression, exercise frequency and intensity, sleep patterns (Lucassen et al., 2010), apolipoprotein E4 genotype (Lamport et al., 2012), and estimated cognitive reserve (level of education) in the older people (Stern, 2003).

Vital physiological and biochemical covariates, some of which may be affected by blueberry intervention may also be useful to understanding possible mechanisms of action. These include the stress hormone cortisol,(Wingenfeld and Wolf, 2015) inflammatory cytokines and markers such as C-reactive protein,(Ownby, 2010) homocysteine,(McCaddon et al., 2001) blood sugar levels,(Scholey et al., 2001) mitochondrial function,(Teixeira et al., 2017) cardiovascular markers such as blood pressure and pulse wave velocity,(Elias et al., 2009) and Apolipoprotein E4 status (Schuit et al., 2001). Furthermore, it has been proposed that

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polyphenols and other bioactives found in blueberries may influence mood and cognition at least in part via the modulation of gut microbiota. Currently, there are at least three potential mechanisms that might explain how blueberry bioactives, especially polyphenols may influence cognition via gut microbiota: by direct inhibition of bacterial growth; through a bidirectional interaction with the microbiome, which enhances bioavailability and increases the availability of these compounds to the body and, finally, via bacterial moderation of polyphenols to produce novel compounds that have direct or indirect activity through the previously outlined mechanisms (Flanagan et al., 2018). Further research is required to explore these possible mechanisms of action of blueberry interventions for cognitive and mood outcomes.

The potential effect of blueberry interventions on cognitive performance has been discussed in previous systematic literature reviews which tended to focus more generally on polyphenols or specific classes of these compounds (Bell et al., 2015b; Gildawie et al., 2018; Kent et al., 2017b; Lamport et al., 2012). For example, in 2012, a systematic literature review of polyphenol-rich foods and cognitive performance identified one non-randomized, single arm trial that investigated the use of blueberry interventions for cognition (Lamport et al., 2012), which did not meet the inclusion criteria for this review. Due to the significant number of published studies in this area since the publication of prior reviews, this is the largest systematic review of blueberry intervention studies to date. Furthermore, a particular strength of the current review is that only studies with randomized controlled study designs were included, allowing for a review of studies with less risk of bias.

Conclusion

The results of this review provide preliminary evidence for the potential efficacy of blueberries as an intervention to promote cognitive performance and mood. However, due to

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the limited number of current trials in the area, with heterogenous age groups, large variation in cognitive tests between trials, relatively small sample sizes, and differing anthocyanin content in the blueberry interventions, further investigation is needed. A number of suggestions, including the use of standardized blueberry interventions, consideration of control formulations, and consistently reported cognitive performance tools, are recommended for future studies.

Competing interest statement

The authors declare no conflicts of interest.

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Figure Legend

Figure 1. PRISMA flow chart summary of the systematic review search process.

Figure 2. Risk of bias summary for included studies

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Table 1. Summary table of included studies

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Reference	Study design	Country	Sample size	Population details	Study duration & outcomes measured at:	Intervention	Cognitive outcomes	Mood outcom
Barfoot et al. (2018)	Randomised, single-blind, controlled trial	United Kingdom	54	Children (7-10 years)	2 hours Baseline, 2 hours post-intervention	30 g flavonoid-rich wild blueberry with 30 mL of low-flavonoid orange squash and 170 mL of water Placebo/Control: placebo	Rey's Auditory Verbal Learning Test (RAVLT), Modified Network Attention Task (MANT), Test of Word Recalling Efficiency 2.	Reporte Khalid (2017).

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						with vitamin C (4 mg), sugars (8.90 g fructose, 7.99 g glucose) and 30 mL orange squash and 170 mL of water.		
Boespflug et al. (2018)	Randomized, double-blind, placebo-controlled trial	USA	21	Older people with Mild Cognitive Impairment (68 - 92 years)	16 weeks Baseline, 16 weeks	12.5 g freeze-dried blueberry fruit powder. Placebo/Control: Powder containing natural blueberry	Sequential letter n-back working memory task Other: Functional MRI,	Geriatr Depres Scale, Geriatr Anxiety Invento

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						flavour, artificial purple and red colouring, maltodextrin fructose, and citric acid		
Bowtell et al. (2017)	Randomized, double-blind, placebo-controlled trial	United Kingdom	26	Healthy older volunteers (>65 years)	12 weeks Baseline, 12 weeks	30 mg Blueberry concentrate (Blueberry Active), Placebo/Control: Blackcurrant & apple cordial	Cogstate battery: detection task, the Groton maze timed chase test, delayed recall, identification task, 1-back and 2-back, reaction time, working memory, numerical Stroop test Other: Serum	None

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							glutathione, Brain-derived neurotropic factor, highly sensitive C-reactive protein, MRI.	
Khalid et al. (2017) Study 1	Randomized, double-blind, placebo-controlled, cross-over trial	United Kingdom	21	Young adults (18 – 21 years)	3 x 2 hours Baseline, 2 hours post intervention	30 g Flavonoid-rich wild blueberry with 30 mL of low-flavonoid orange squash and 220 mL of water, placebo with vitamin C (4 mg), sugars (8.90 g	None	Positive Negativ Affect Schedu NOW

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						fructose, 7.99 g glucose), 30 mL orange squash and 220 mL of water.		
Khalid et al. (2017) Study 2	Randomized, double-blind, placebo-controlled, trial	United Kingdom	52	Children (7-10 years)	2 hours Baseline, 2 hours post intervention	30 g flavonoid-rich wild blueberry with 30 mL of low-flavonoid orange squash and 170 mL of water, Placebo/Control: Formula with vitamin C	Reported in Barfoot et al. (2018).	Positive negativ affect (Childr

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						(4 mg), sugars (8.90 g fructose, 7.99 g glucose), 30 mL orange squash and 170 mL of water.		
McNamara et al. (2018)	Randomized, double-blind, placebo-controlled trial	USA	39	Healthy older people with self-perceived cognitive decline (62 – 80 years)	48 weeks Baseline, 24 weeks, 48-week follow up post intervention	25g freeze-dried blueberry, Placebo/Control: powder contained 389 calories (per 100)	Trail making A, trail making B, Hopkins Verbal Learning test (HVLT) learning, HVLT recall, HVLT discrimination, HVLT retained, phonological access, semantic	None

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						with 97.3% carbohydrate, 0.02% total fat, and <0.781% protein	access, Dysexecutive Questionnaire	
Miller et al. (2018)	Randomized, double-blind, placebo-controlled trial	USA	37	Older people (>60 years)	90 days Baseline, 45 and 90 days	2 x 12 g Freeze-dried blueberry or placebo	Task-switching test (TST), California Verbal Learning Test 2nd ed (CVLT-II), digit span task, virtual version of the Morris Water Maze, Attention Network Task	Geriatr Depres Scale, Profile Mood States
Schrager et al. (2015)	Randomized, placebo-controlled	USA	20	Older people (>60 years)	6 weeks Baseline, 6 weeks	0.46 kg flash-frozen blueberrie	Reaction time (computer-based test), Trail Making	None

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	trial					s Placebo/Control: carrot juice (control)	Test B Other: Grip strength (handheld dynamometer), adaptive gait	
Whyte et al. (2015)	Randomized, double-blind, placebo-controlled, cross-over trial	United Kingdom	16	Children aged 8 - 10	2 x 2 hours 2 hours after consumption	200 g of fresh Star variety blueberries with 100 mL of semi-skimmed milk and 8 g of sucrose, 0.02 g vitamin C powder, 8.22 g sucrose, 9.76 g glucose,	Go-NoGo, Rey's auditory-verbal learning test, Word-colour Stroop, Visuospatial n-back task, Object location task	None

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						and 9.94 g fructose Placebo/Control:100 mL of semi-skimmed milk		
Whyte et al. (2016)	Randomized, double-blind, placebo-controlled cross-over trial	United Kingdom	21	Children aged 7-10 years old	3 x 6 hours Baseline, one hour and 15 minutes, 3 hours, 6 hours and 15 minutes post-consumption	15 or 30g freeze dried wild blueberries mixed with fruit squash Placebo/Control: 30ml fruit squash	E-prime V2, Auditory Verbal Learning Task, Modified Flanker Task, Go–NoGo task, Picture Matching Task	None

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Whyte et al. (2017)	Randomized, double-blind, placebo-controlled cross-over trial	United Kingdom	21	Children aged 7-10 years old	3 x 3 hours Baseline and 3 hours post consumption during 3 test sessions over three weeks	30g freeze dried wild blueberries mixed with fruit squash Placebo/Control: 30ml fruit squash	Modified attention network task	None

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Whyte et al. (2018)	Randomized, double-blind, placebo-controlled trial	United Kingdom	122	Healthy elderly volunteers (65–80 years)	6 months Baseline, 6 months	Wild Blueberry Powder—500 mg, Wild Blueberry Powder—1000 mg, Wild Blueberry Extract 111 mg Thinkblue™,	E-prime V2, Rey's Auditory Verbal Learning Task, object recognition task, Corsi Blocks task, serial subtractions and Sternberg memory scanning, The Sternberg memory scanning task,	The Positive Negativ Affect Schedu NOW

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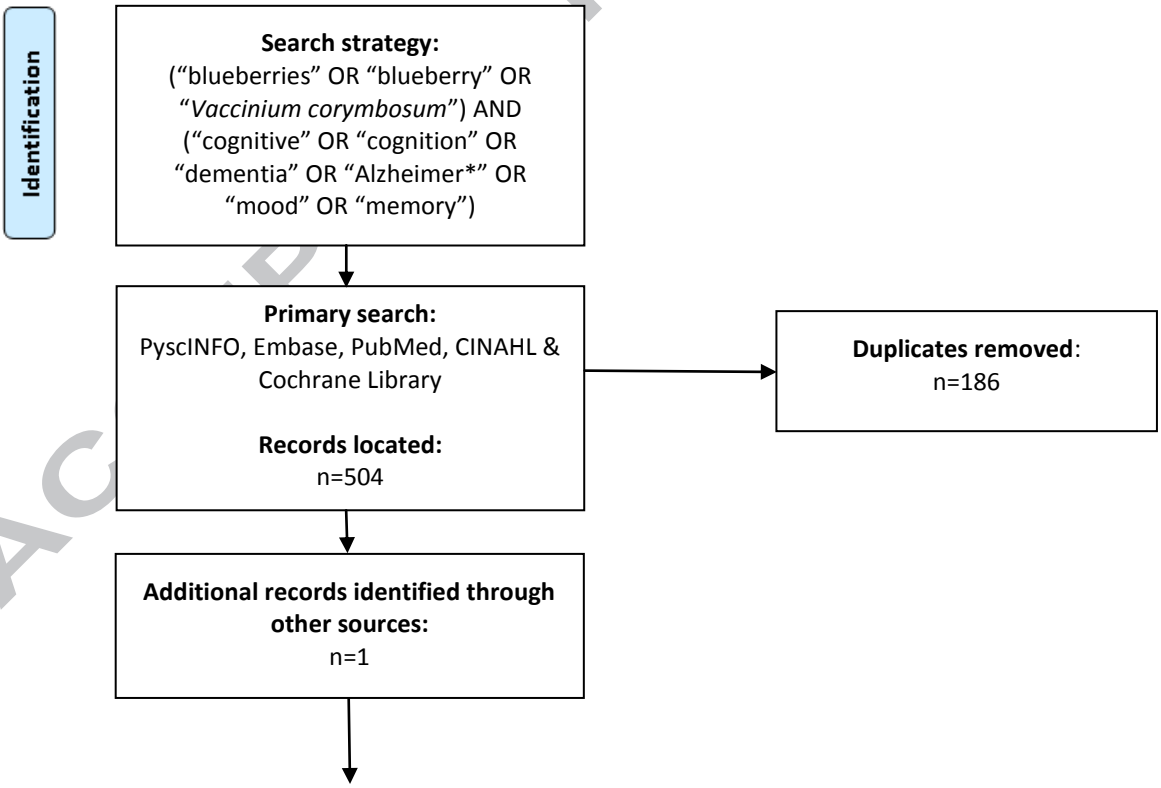
						Placebo (Maltodextrin, colouring)	Modified Attention Network Task and Stroop task Other: Blood pressure	

Figure 1. PRISMA Flow Diagram



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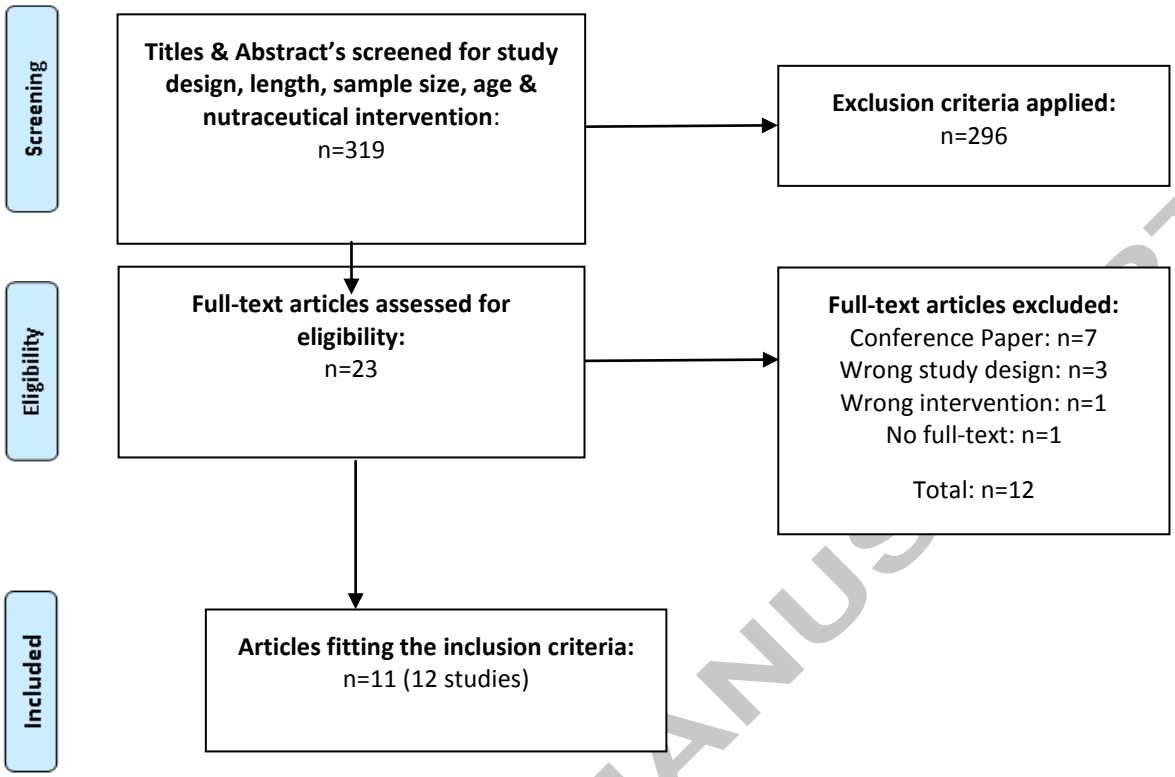

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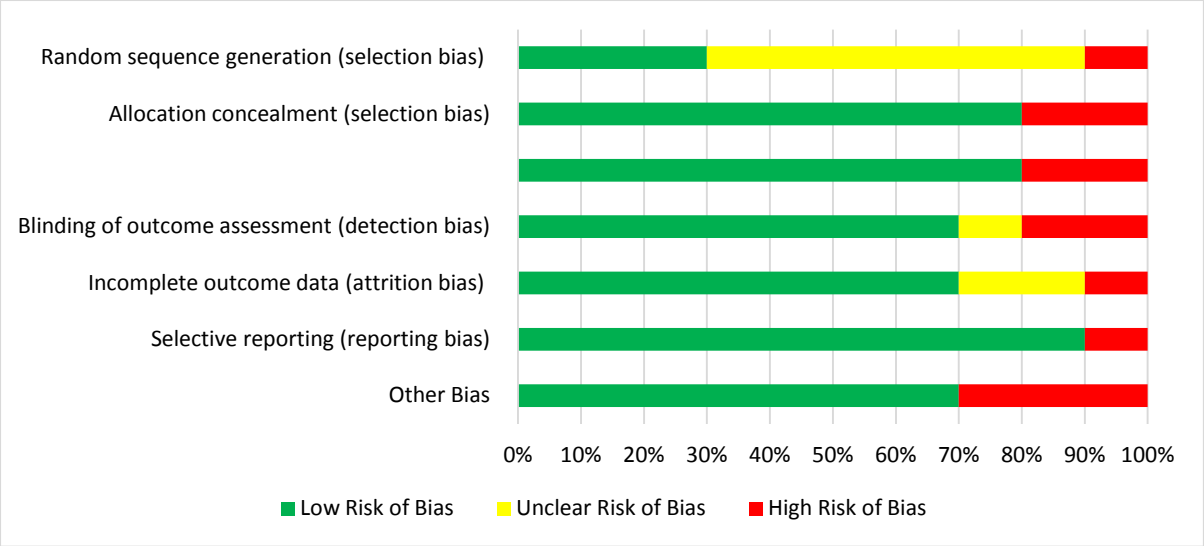
Figure 2. Risk of Bias assessment



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Highlights:

- Twelve studies, published between 2015 and 2018, investigated the effect of blueberries and blueberry products on measures of cognitive performance and mood for up to six months duration.
- Blueberry products improved measures of cognition in eight studies.
- Compared to control, blueberry products improved positive affect in one acute trial in young adults.

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