Effect of Berry-Based Supplements and Foods on cognitive function: A Systematic Review

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Abstract

In the current decade, a growing body of evidence proposes the correlation between diet and cognitive function or dementia in the ageing population. This study was designed to appraise discoveries from the randomized controlled trials (RCTs) to confirm the effects of Berry-Based supplements or foods on cognitive function in older adults. PubMed/MEDLINE, Cochrane Central Register of Controlled Trials, Web of Science, Scopus, EMBASE, Google Scholar, and ProQuest as well as SID, Magiran, and Iranmedex electronic databases were explored for human interventional studies up to March 2021. A total of 259 studies were recognized from the primary database searches, and after eliminating the duplicates, 225 studies remained. Of these, 102 were disqualified after screening the title and abstracts of studies. The lasting 17 studies were evaluated in full text and 10 studies (which include 583 participants) encountered the eligibility criteria. Of the included studies, seven were randomized parallel-group (n = 7), two were crossover (n = 2) and one was the pilot study (n = 1). In total, ten articles were identified using freeze-dried blueberries (n = 3 studies), blueberry concentrate (n = 2), beverage (n = 3), capsule (n = 1), extract and powder (n = 1). These studies were directed in older people with no recognized cognitive impairment or mild cognitive impairment (MCI). The primary outcomes included episodic memory, long-term and short-term memory, working memory, executive function, psychomotor reaction time and attention. To our knowledge, this is the first systematic review of available clinical trials on the effects of berry-based supplements and foods on cognitive performances and brain perfusion parameters in elderlies with normal cognition or MCI. Existing evidence concludes that berry-based supplements and foods have beneficial effects on resting brain perfusion, cognitive function, memory performance, executive functioning, processing speed, and attention indices.

1. Introduction

Along with the aging of the population, worldwide, cognition-related diseases are progressively rising [1]. These disorders, such as mild cognitive impairment (MCI), dementia, and Alzheimer's disease (AD), upsurge the burden of social and economic health for most communities. The total numeral of individuals with dementia is almost 35.6 million as declared by world health organization (WHO) and by 2050, the total predictable prevalence of AD is anticipated to be 13.8 million, while the percentage of expiry after AD is still growing [2].

Numerous studies have shown a relationship between lifestyle influences and cognitive function in older adults. A considerable amount of data has specified that nutrition is related to age-associated disorders and longevity. It has been shown that certain healthy dietary patterns, foods, and micronutrients, such as mediterranean diet [3], vitamin C [4], vitamin E [5], omega-3 fatty acids [6], fruit and vegetable [7], tea [8], coffee [9] and milk [10], has protective effects on the cognitive disorders and dementia.

An initial causal factor to both usual and pathological alterations in brain operative is the agglomeration of oxidative impairment attached with diminished endogenous antioxidant barricades [11,12]. The brain is principally disposed to oxidative injury because of its high amount of oxygen intake [13]. Vegetal foods, comprising vegetables, fruits, and also their juices, are human main origins of exogenous anti-inflammatory and antioxidant compounds.

Preliminary animal studies have established that antioxidant-rich dietary patterns could postpone and even reverse age-associated cognitive debility in laboratory animals [14]. Polyphenols are among the most plentiful antioxidants in the human diet. A later effort has proven that berry supplementation (i.e. blueberries and strawberries) can persuade dramatic alterations in the brains of animals besides their currently well-known antioxidant properties. Berries are not only a moral source of anthocyanins but besides; contain polyphenols such as ellagitannins that may have direct and indirect beneficial effects on metabolic markers. Additionally, berries are stable, can grow easily, have a pleasant taste, and for this reason, are known as a valued fruit source that can be easily combined into the diet.

Berry fruits and their chemical ingredients facilitate signaling paths included in cell longevity as well as increasing neuroplasticity, neurotransmission, and neuronal calcium homeostasis, all of which decrease the age-related declines in behavior [15]. A two-percent blueberry diet intake for four months improved new thing appreciation in old rats [16]. Additionally, a 2-percent blueberry diet improved motor function in old animals and led to enhanced balance and coordination [17]. However, the available indication for strawberry' improvement of motor performance in old mice and rats is less obvious[17–20].

Current clinical studies have developed the antioxidant and cognition-sparing properties of berries in humans [21–24]. Numerous clinical trials have been conducted on the effects of berry-based foods or supplements on cognitive function and memory. Elderly with MCI who expended blueberry juice (6 – 9 mL/kg/day) for 3 months exhibited improved late recall for word lists in the California Verbal Learning Test (CVLT), in relation to baseline, a tendency to improved functioning, in relation to placebo controls and better act in the Verbal Paired Acquaintances Learning Test relative to both baseline and placebo controls [25].

Due to the lack of systematic review in this regard, the present review study was planned to review recent indications for the beneficial properties of berry-based supplements and foods on cognitive components in the elderly and middle-aged healthy subjects or subjects with MCI.

2. Method

The main objective of the current systematic review was to evaluate the efficacy of whole berries or a berry-based product (e.g. smoothie, juice) or berry extract/capsule consumption in adult or old subjects with healthy cognition or MCI. The present study has been prearranged according to the guidelines and checklist in Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0) [26] and "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)" statement [27,28]. The investigation question was structured based on the PICOS (participants, interventions, comparators, outcomes, study design) criteria (Table 1) [29], is as follows: Do berry-based dietary supplements of foods affect at least one recognized cognition related outcome in the adult or old subjects with healthy cognition or MCI?

Table 1
PICOS criteria for inclusion and exclusion of studies

Parameter	Description
Population	Adult or old subjects with healthy cognition or MCI
Intervention	whole berries/ berry-based product / berry extract/ berry capsule
Comparator	Any comparator
Outcomes	1.episodic memory 2. Long-term memory 3. Short-term memory 4.working memory 5. executive function 6. psychomotor reaction time 7.attention
Study design	Randomized controlled clinical trial with a crossover or parallel design

2.1. Literature Search

Some search approaches were applied to identify the eligible studies. The online databases (MEDLINE, Web of Science, Cochrane Library, Scopus, EMBASE, Google Scholar, Clininaltrial.gov, Science direct, and ProQuest in addition to SID, Magiran, Irandoc, and Iranmedex for Persian language literature) were employed to search in the titles, abstracts and keywords of all articles for eligibility up March 2021. Duplicate studies were excluded. Additionally, a manual search of the references of the reviewed studies was applied as additional resources to identify other suitable articles that were missed by electronic search.

A web-based systematic literature exploration was executed by means of the subsequent MeSH terms: (“randomized controlled trial” OR “RCT” OR “controlled trial” OR “intervention trial” OR “intervention study”) AND (Chokeberry OR “Chokeberry extract” OR blackberry OR “blackberry extract” OR raspberry OR “raspberry extract” OR blueberry OR “blueberry extract” OR strawberry OR “strawberry extract” OR cranberry OR “cranberry extract” OR cranberry OR “cranberry extract”) AND (“memory”(all Fields) OR “cognitive”(all Fields) OR “cognition”(all Fields) OR “forgetfulness”(all Fields) AND (“older”(all Fields) OR “adult”(All Fields) OR “elderly”(all Fields) OR “older”(all Fields) NOT (animal OR mouse OR mice OR rat OR pig OR cell OR in vitro OR systematic review)). After the primary search, titles and abstracts were sent out from EndNote X8 into Microsoft Excel to be screened. All saved articles were evaluated independently by two investigators (NB and ND) regarding titles and abstracts. Any differences were considered and resolved by consensus or by a third independent investigator (YS).

2.2. Inclusion and exclusion criteria

Table 1 shows the PICOS (Participant, Intervention, Comparators, Outcomes, and Study design) criteria accepted in this systematic review of clinical trials. Articles were limited to those published in English or Persian. Inclusion criteria were intervention studies implemented in humans who examined the effects of whole berries or a berry-based product (e.g. smoothie, juice) or a berry extract/capsule supplementation on the defined cognitive-related outcomes in adults and elderlies who have been diagnosed with healthy cognition or MCI. Studies were also excluded if the participants have dementia; if the outcome of the study was not cognitive-related or if the study design was review article, semi- empirical study without a control arm, animal study, trial protocol, letter to the editor, case report, case series, observational study (cross-sectional, case-control and cohort) and unpublished trial.

2.3. Data collection

The studies’ information on the year of publication, participant characteristics, demographic details, location, study design/methodology, interventions (protocol and duration), sample size, dropout and primary outcomes were extracted for each included study by the investigators (NB, ND and YS)

2.4. Quality assessment

To assess the risk of systematic errors in the involved trials that encountered the eligibility criteria, two authors (YS and MH) independently estimated the potential risk of bias based on the Cochrane Collaboration’s tool for evaluating the risk of bias [30]. Concisely, trial quality principles comprised evaluation of: "randomization sequence generation, outcome assessment, blinding of subjects, personal and allocation concealment, imperfect outcome data, and discerning outcome reporting, as well as other sources of bias". All trials were determined for each series of bias separately, and the trials were considered to have a score of bias as “low risk,” “high risk,” or “unclear risk” if the information was insufficient (Fig. 2).

2.5. The outcome measures

The review's primary outcomes included episodic memory, Long-term memory, short-term memory, working memory, executive function, psychomotor reaction time and attention.

3. Results

3.1. Study selection process

A flowchart explaining the study selection steps is presented in Fig. 1. A total of 259 studies were recognized from the primary database searches, and after eliminating the duplicates, 225 studies remained. Of these, 102 were disqualified after screening the title and abstracts of studies. The lasting 17 studies were evaluated in full text and 10 studies encountered the eligibility criteria (Fig. 1).

3.2. *Study Characteristics*

Of the included studies, seven were randomized parallel-group (n = 7), two were crossover, one is the pilot study (n = 1) (Table 2).

Table 2
Included randomized controlled trials of berry-based food interventions on cognitive function

	Author (year)	Location	Intervention/control (sample size)	Inclusion criteria	sample size and treatment (dosage)	Sample size at the end of treatment	Design and study duration	Main outcomes
1	(Whyte et al., 2018)[34]	England	Start: 30/31/31/30 Complete: 28/29/28/27	Independently living healthy volunteers, Age: 65–80 years old, All ethnicity, Subjective self-reported memory complaints	1.WBP (500mg/ day) (n = 30) 2. WBP (1000 mg /day) (n = 31) 3.WBE (111 mg /day) (n = 31) 4.Placebo (n = 30)	1.WBP (500mg/ day) (n = 28) 2. WBP (1000 mg /day) (n = 29) 3.WBE (111 mg /day) (n = 28) 4.Placebo (n = 27)	RCT 6 months	Word recognition performance, Total number of correct sequences recalled, Working Memory, Executive Function, Mood
2	(Nilsson et al., 2017) 40	Sweden	Start:23/23 Complete:20/20	Healthy non-smoker volunteers, Age: 50–70 years old, BMI ≤ 28 kg/m2	1. Berry beverage (150g blueberries, 50g blackcurrant, 50g elderberry, 50g lingonberries, 50g strawberry, and 100g tomatoes/day) (n = 23) 2. control beverage(n = 23)	1. Berry beverage (150g blueberries, 50g blackcurrant, 50g elderberry, 50g lingonberries, 50g strawberry, and 100g tomatoes/day) (n = 20) 2. control beverage(n = 20)	RCT 5 weeks	Verbal working memory (WM-tests)
3	(Miller et al., 2018) 35	USA	Start:20/20 Complete: 19/19	Age: 60–75 years, BMI: 18.5–29.9, adequate visual acuity, > 12 months postmenopausal	1.freeze-dried blueberry (24 g/day) (n = 20) 2. Placebo (n = 20)	1.freeze-dried blueberry (24 g/day) (n = 19) 2. Placebo (n = 19)	RCT 90 Days	Executive function (TST, TMT), Long-term memory (CVLT-II), Short-term memory (DS task), Spatial cognition (VMWM), Attention (ANT), Mood (GDS, POMS)
4	(Bowtell et al., 2017) 33	England	12\14	Blueberry: (5 females, 7 males; age: 67.5 ± 3.0 y; BMI, 25.9 ± 3.3 kg·m − 2) Placebo: (8 female, 6 male; age 69.0 ± 3.3 y; BMI, 27.1 ± 4.0 kg·m − 2)	wild blueberry supplementation (30 mL\concentrate providing 387 mg anthocyanidins)	isoenergetic placebo	RCT 12weeks	Cognitive function test performance

RCT: randomized double-blind controlled trials, WBP: Wild Blueberry Powder, WBE: Wild Blueberry extract, PEGB :polyphenol-rich extract from grape and blueberry, BB: freeze-dried blueberry powder, TST: task-switching test, TMT: trail-making test, CVLT-II: California Verbal Learning Test, 2nded, DS: digit span, VMWM: virtual version of the Morris Water Maze, AN: Attention Network Task, GDS: Geriatric Depression Scale, POMS: Profile of Mood States, MCI: mild cognitive impairment ,MCDR: modified Clinical Dementia Rating, MoCA: Montreal Cognitive Assessment, CVLT: the California Verbal Learning Task, V-PAL: Verbal Paired Associate Learning Test BMI: body mass index, MMSE: a Mini Mental State Examination, BSI: the Brief Symptom Inventory

	Author (year)	Location	Intervention/control (sample size)	Inclusion criteria	sample size and treatment (dosage)	Sample size at the end of treatment	Design and study duration	Main outcomes
5	(Boespflug et al., 2018) [41]	USA	8\8	older adults with MCI age:68 – 92years according to modified Clinical Dementia Rating (MCDR), Montreal Cognitive Assessment (MoCA) and the California Verbal Learning Task (CVLT)	freeze dried, whole fruit blueberry 12.5 g per packet*2/day	placebo	RCT 16 weeks	Neural activation, working memory performance by group
6	(Krikorian et al., 2010) (25)	USA	9\7	5 men, 4 women\The mean (± SD) age of the sample was 76.2 (± 5.2) years\the mean (± SD) educational level was 15.6 (± 1.5) years	blueberry juice	placebo	Pilot trial 12 weeks	1. Memory performances for the blueberry juice sample measured by V-PAL and CVLT(Immediate Word Recognition/ Word list recall/ verbal long-term memory)
7	(Bensalem et al., 2019)[32]	France & Canada	215 male and female healthy subjects	Age: 60–70 years BMI: 20–30 26 < MMSE score ≤ 29	300 mg*2/day PEGB capsule (containing 258 mg flavonoids)	placebo	A bicentric RCT 6 month	Visuospatial learning, episodic memory test, evaluation of episodic verbal recall memory, working memory
8	(Krikorian et al., 2020)[37]	the Cincinnati, OH USA	Start: 24/23 Complete: 16/21	Age: 68 years< with MCI confirmed by MoCA	freeze-dried BB packet contained 12 g powder 2/day each placebo packet 10 g powder	placebo	RCT 16 week	Cognitive performance (semantic access and visual-spatial memory)
9	(Dodd et al., 2019)[31]	UK	18 (10 women/8 Men)	Age: 60–75 years MMSE score: ≤25, a depression index score on BSI : ≥11	a single dose flavonoid rich blueberry beverage (508 mg of antho- and 71mg procyanidins)equivalent to approximately 200g of fresh blueberries	Placebo beverage	RCT 2 hours vs 5 hours	Cognitive function,
10	(McNamara et al., 2018, McNamara et al., 2017)[38,61]	USA	Start:94 Complete:65	Age: 62–80 years-old who had mild, self-perceived cognitive decline with aging	1. FO (fish oil + Placebo capsules) :400 mg EPA and 200 mg DHA×4/day 2. BB (blueberry powder + placebo oil 3. FO + BB (fish oil + blueberry powder	PL (placebo oil + placebo powder) Placebo oil = corn oil	RCT 24 – week, follow up at week48	Neurocognitive performance

RCT: randomized double-blind controlled trials, WBP: Wild Blueberry Powder, WBE: Wild Blueberry extract, PEGB :polyphenol-rich extract from grape and blueberry, BB: freeze-dried blueberry powder, TST: task-switching test, TMT: trail-making test, CVLT-II: California Verbal Learning Test, 2nded, DS: digit span, VMWM: virtual version of the Morris Water Maze, AN: Attention Network Task, GDS: Geriatric Depression Scale, POMS: Profile of Mood States, MCI: mild cognitive impairment ,MCDR: modified Clinical Dementia Rating, MoCA: Montreal Cognitive Assessment, CVLT: the California Verbal Learning Task, V-PAL: Verbal Paired Associate Learning Test BMI: body mass index, MMSE: a Mini Mental State Examination, BSI: the Brief Symptom Inventory

3.3. Cognitive Function

3.3.1. Global cognitive performance

Dodd et al. [31] determined whether acute intake of a single dose of flavonoid-rich blueberry beverage (508mg of antho- and 71mg procyanidins) equal to 200g of fresh blueberries vs. control beverage could have favorable properties on cognitive function among 18 healthy older volunteers aged 60–75 years in a cross-over randomized controlled trial (RCT).

Cognitive function was assessed at the baseline as well as at 2 and 5 hours post-drinking the interference beverage utilizing coordinated versions of each of the cognitive functions within the test battery which were analogous in terms of function difficulty.

Pairwise comparisons exposed meaningfully worse presentation following the control drink at 2 compared to 5 hours post ingestion (mean = − 0.06 vs 0.06 correspondingly; F (1,36) = 4.60, p = 0.04) and with a deterioration in presentation relative to baseline at 2 hours, whereas there was no important difference in cognitive performance at 2 compared to 5 hours post ingesting of the blueberry drink (mean = 0.01 vs 0.02 respectively; F (1,36) = 0.05, p = 0.82). Cognitive function enhanced following the blueberry drink at both post-intervention time points.

3.3.2. Memory Outcomes

3.3.2.1. Immediate Word Recognition

In the RCT by Bensalem et al. [32], 6-month supplementation with 600 mg/day polyphenol-rich extract from grape and blueberry (PEGB) (containing 258 mg flavonoids) equal to an intake of < 200 g of fresh fruits led to the higher total number of accurate words at the immediate recall among 215 male and female 60–70 years-old healthy subjects with a BMI between 20–30 and 26 < Mini-Mental Status Exam (MMSE) score ≤ 29 in comparison with the placebo (p = 0.006). Additionally, significant impacts of the PEGB were observed on the verbal episodic, and recognition memory-free recall (VRMFR) (p = 0.014 vs placebo).

In the study of Dodd et al. [31] acute intake of a single dose of flavonoid rich blueberry beverage among healthy older volunteers resulted better performance in the immediate word recognition task compared to the control (mean = 26.71 vs 25.81 correspondingly; F(1,17.61) = 4.29, p = 0.05). Furthermore, pairwise comparisons meaningfully showed more words recognized succeeding the blueberry compared to the control drink at the 2 hours (mean = 26.77 vs 25.48 respectively; F (1,16.30) = 6.56, p = 0.02) but not the 5-hour time point (mean = 26.65 vs 26.15 respectively; F (1,27.86) = 0.60, p = 0.44).

Krikorian et al. [25] examine the efficacy of daily drinking of wild blueberry extract for 12 weeks in a sample of nine older adults with early memory changes. Blueberry juice, enhanced word list recall (p = 0.04).

3.3.2.2. International shopping list task

Bowtell et al. [33] showed that 12 weeks of daily intake of 30 milliliters of blueberry concentrate supplementation [contained 387 mg anthocyanidins (34 mg malvidin, 108 mg cyanidin, 41 mg pelargonidin, 63 mg peonidin, 86 mg delphinidin, and 55 mg petunidin)] consumed once per day in 26 healthy older adults improved International shopping list task (p = 0.002) with was no significant difference compared to the placebo.

3.3.2.3. Word list recall

Krikorian et al. [25] examined the efficacy of daily drinking of wild blueberry extract for 12 weeks in a sample of nine older adults with early memory changes. Blueberry juice, enhanced word list recall (p = 0.04).

3.3.2.4. Delayed Word Recognition

The word recognition process needs that contributors distinguish formerly provided words from a primary list whereas discounting words from another list and additional phonetically or semantically matched different interfering words. It is well recognized that episodic memory function is established to decline in older subjects [34].

In a double-blinded, placebo-controlled RCT by Whyte et al. [34], daily supplementation with purified wild blueberry extract − 111 mg (WBE111) having as low as 50 mg of polyphenols, including 7 mg anthocyanins, flavonols, proanthocyanidins, and chlorogenic acids for six months resulted in a significantly improved function in late word recognition in the Reys Auditory Verbal Learning Task (RAVLT) (mean = 0.926) in contrast with the placebo (mean = 0.871) (p = 0.038) in 65–80 years old healthy subjects (n = 122) with self-reported memory complaints. These impacts were not seen for whole wild blueberry powder at 500 mg (WBP500) and 1000 mg (WBP1000). No encouraging impacts were established for the administrative function and working memory fields in this study.

On the other hand, according to another RCT with cross-over design by Dodd et al. [31] which examined the efficacy of the intake of a single dose of flavonoid-rich blueberry beverage (508mg of antho- and 71mg procyanidins) equal to about 200g of fresh blueberries among eighteen 60–75 years old healthy older volunteers in comparison with control beverage, none of the post-drinking pairwise comparisons were important (all p > 0.05).

In the double-blind, placebo-controlled RCT by Bensalem et al. [32], 6-month supplementation with 600 mg/day polyphenol-rich extract from the grape and blueberry (PEGB) (containing 258 mg flavonoids) equal to an intake of < 200 g of fresh fruits had significant impacts on the late version of the VRMR (p = 0.005 vs the placebo) among 215 male and female 60–70 years-old healthy subjects with a BMI between 20–30 and 26 < MMSE score ≤ 29.

Miller et al.[35] showed that 3-month supplementation of 37 men and women (ages 60–75 years) with MMSE score ≥ 24 with freeze-dried blueberry (12 g, equal to 0.5 cups of fresh blueberries contains ≈ 36 mg/g total phenolic and ≈ 19.2 mg/g anthocyanins) resulted in fewer repetition faults according to CVLT, 2nd ed [36] after the end of intervention than they did at the baseline. Once group differences in physical activity were justified, the interaction remained (p = 0.032, ηp 2 = 0.128).

3.3.2.5. Verbal long-term memory

Krikorian et al. [37] did a randomized, double-blind, placebo-controlled trial for 16 weeks with 24 g per day freeze-dried blueberry (BB) fruit powder [an equal mixture (w/w) of ripe berries of the varieties 'Tifblue' (Vaccinium virgatum asheii Aiton) and 'Rubel'(Vaccinium corymbosum L.) equivalent to approximately one cup whole fruit and contained a total phenolic content of 401 gallic acid equivalents] and placebo powder supplementation in adults aged ≥ 68 years old with MCI. Despite the apparent performance increase for verbal memory (HVLT recall) favoring the BB group, 5.7 vs. 7.5, this was not a significant effect ($F(1, 33) = 2.55$, $p = 0.11$).

McNamara et al. [38] examined 24-week supplementation with daily fish oil (FO: whole daily doses of 1.6 g EPA and 0.8 g DHA) or blueberry (BB: total daily dose of whole phenolic combinations of 417 gallic acid equivalents, 269 mg cyanidin 3-glucoside equivalents of anthocyanins) or both effect in 76 elderly men and women aged 62–80 years old with mild, self-perceived cognitive deterioration in a randomized, double- blind, placebo-controlled trial. This was monitored for a further 24 weeks. There was an effect demonstrating enhanced insight in recognition memory on the HVLT for the BB-treated group, $F(1,35) = 4.24$, $p = 0.04$, Cohen's $f = 0.34$. The memory insight improvement in the BB group was not preserved at week 48 (24 weeks after cessation of the supplementation). There was no significant effect in any cognitive field for the joint FO and BB powder group.

3.3.2.6. Nonverbal long-term memory

Krikorian et al. [37] did a randomized, double- blind, placebo-controlled trial for 16 weeks with 24 g per day freeze-dried blueberry (BB) fruit powder [an equal mixture (w/w) of ripe berries of the varieties 'Tifblue' (Vaccinium virgatum asheii Aiton) and 'Rubel'(Vaccinium corymbosum L.) equivalent to approximately 1 cup whole fruit and contained a whole phenolic content of 401 gallic acid equivalents] and placebo powder supplementation in adults aged 68 years and older with MCI.

There was a substantial effect representing improved nonverbal memory performance (SPAL) for the BB group, 1.5 vs 2.6, $F(1,33) = 3.85$, $p = 0.05$, Cohen's $f = 0.33$.

Krikorian et al. [37] did a randomized, double-blind, placebo-controlled trial for 16 weeks with 24 g per day freeze-dried blueberry (BB) fruit powder [an equal mixture (w/w) of ripe berries of the varieties 'Tifblue' (Vaccinium virgatum asheii Aiton) and 'Rubel'(Vaccinium corymbosum L.) equivalent to approximately 1 cup whole fruit and contained a whole phenolic content of 401 gallic acid equivalents] and placebo powder supplementation in adults aged ≥ 68 years old with MCI.

The Trail-Making Test, part A measured psychomotor speed in a timed format so that better function was reflected in less time on task. We also detected a trend demonstrating the better psychomotor speed of processing (less time on task) for the BB group on the Trail Making Test, part A, 41.7 vs. 36.5, $F(1,33) = 3.22$, $p = 0.08$, Cohen's $f = 0.31$.

3.3.2.7. International shopping list with delayed recall

Bowtell et al. [33] showed that 12 weeks of the daily intake of 30 milliliters of blueberry concentrate supplementation [contained 387 mg anthocyanidins (34 mg malvidin, 108 mg cyanidin, 41 mg pelargonidin, 63 mg peonidin, 86 mg delphinidin, and 55 mg petunidin)] consumed once per day in 26 healthy older adults improved the international shopping list with delayed recall ($p = 0.004$) with was no significant difference compared to the placebo.

3.3.2.8. Corsi Block—Total Number of Sequences Correctly Recalled

In the study of Whyte et al. [34], 3 months of daily WBE111 supplementation caused a trend to improved visuospatial Corsi Block function (the entire number of orders properly recalled) (mean = 16.19) in contrast with the placebo (mean = 15.14) ($p = 0.069$).

3.3.2.9.Working memory (WM) test

The concept of working memory (WM) means the constructions and procedures that keep the mental illustrations presently most required for a continuing cognitive function accessible for handling [39].

Nilsson et al. [40] in a randomized crossover trial showed that 5 wk. supplementation among 46 healthy men and women between 50–70 years old with a 600 ml (~ 609 g) per day berry drink based on a combination of berries (150g blueberries, 50g blackcurrant, 50g elderberry, 50g lingonberries, 50g strawberry, and 100g tomatoes) containing 795 mg total polyphenols and 11g dietary fiber enhanced performance significantly in the WM-test at 30 min by nearly 5% in contrast to the control beverage ($F(1, 39) = 4.55$, $P = 0.039$).

Bowtell et al. [33] showed that 12 weeks of the daily intake of 30 milliliters of blueberry concentrate [contained 387 mg anthocyanidins (34 mg malvidin, 108 mg cyanidin, 41 mg pelargonidin, 63 mg peonidin, 86 mg delphinidin, and 55 mg petunidin)] consumed once per day in 26 healthy older adults improved working memory in comparison with the placebo. The percentage change in presentation of the 2-back tests showed weak evidence for upgrading in the blueberry vs. placebo group (reaction time: placebo: 0.4 ± 0.4% vs blueberry:−1.0 ± 0.7%; $p = 0.09$; accuracy: placebo: − 3.8 ± 2.5%; blueberry: 3.6 ± 2.7%; group by time interaction effect: $p = 0.05$).

3.3.3. Executive function

3.3.3.1. Task-switching test (TST)

Miller et al.[35] showed that 3-month supplementation of 37 men and women (ages 60–75 years) with MMSE score ≥ 24 with freeze-dried blueberry (12 g, equal to 0.5 cups of fresh blueberries include ≈ 36 mg/g total phenolics and ≈ 19.2 mg/g anthocyanins) resulted in a greater reduction in switch stimuli errors between follow ups [a practice visit (visit 1), a baseline visit (visit 2), and 45- and 90-day interposition visits (visits 3 and 4, correspondingly)] in comparison with control. When group differences in physical activity and computer use were measured, the interposition endured ($p = 0.044$, $\eta p\ 2 = 0.09$). Post hoc analysis shows that, within the blueberry group, performance on the baseline and 90-day intervention visits (p corrected = 0.027) as well as 45- and 90-day interposition visits (p corrected = 0.039) are meaningfully different even when the Bonferroni modification is exerted.

Dodd et al. [31] determined whether acute intake of a single dose of flavonoid-rich blueberry beverage (508mg of antho- and 71mg procyanidins) equivalent to nearly 200g of fresh blueberries vs. control beverage could have favorable properties on cognitive function among 18 healthy older volunteers aged 60–75 years in a cross-over randomized controlled trial (RCT).

Cognitive function was assessed at baseline as well as at 2 and 5 hours post-drinking the intermediation beverage utilizing coordinated versions of each of the cognitive functions within the test battery which were similar in terms of function difficulty.

The analysis showed a tendency towards lower switch cost following the blueberry (mean = 395.76) in comparison with the control (mean = 479.48) beverage at the 2-hour time point ($F (1,15.8) = 3.89$, $p = 0.066$).

3.3.4. Learning abilities

3.3.4.1. Groton maze learning task

Bowtell et al. [33] showed that 12 weeks of the daily intake of 30 milliliters of blueberry concentrate [contained 387 mg anthocyanidins (34 mg malvidin, 108 mg cyanidin, 41 mg pelargonidin, 63 mg peonidin, 86 mg delphinidin, and 55 mg petunidin)] consumed once per day in 26 healthy older adults improved the Groton maze learning role (accuracy, $p = 0.005$) with was no significant difference compared to the placebo.

3.3.4.2. Paired associate learning (PAL)

Krikorian et al. [25] inspected the efficacy of daily drinking of wild blueberry extract for 12 weeks in a sample of nine older adults with early memory changes. Blueberry juice, enhanced paired associate learning ($p = 0.009$). The memory presentations of the blueberry subjects were compared with a sample who received a placebo drink and similar consequences for paired associate learning were obtained. The discoveries of this trial propose that moderate-term supplementing with blueberry can provide a neurocognitive advantage.

In the RCT by Bensalem et al. [32] 6 monthly supplementation with 600 mg/day polyphenol-rich extract from the grape and blueberry (PEGB) (containing 258 mg flavonoids) equal to an intake of < 200 g of fresh fruits led to less paired associates learning total errors adjusted (PALTEA) among 215 male and female 60–70 years-old healthy subjects with a BMI between 20–30 and 26 < MMSE score ≤ 29 in comparison with the baseline scores. However, no important difference was seen between PEGB and placebo groups at the end of the intervention ($p = 0.798$). Fascinatingly, an important interaction was established between the PEGB effect and the baseline PALTEA score ($p < 0.001$). PEGB supplementation was established to be considerably more efficient in increasing cognitive performances among subjects with ≥ 57 errors in the baseline PALTEA (subjects with the highest cognitive impairments) ($p = 0.037$ vs. the placebo).

McNamara et al. [38] examined 24-week supplementation with daily fish oil (FO: whole daily doses of 1.6 g EPA and 0.8 g DHA) or blueberry (BB: total daily dose of entire phenolic combinations of 417 gallic acid equivalents, 269 mg cyanidin 3-glucoside equivalents of anthocyanins) or both effect in 76 elderly men and women aged 62- to 80-years-old with mild, self-perceived cognitive deterioration in a double-blind, placebo-controlled RCT. This was monitored for a further 24 weeks. The BB group described fewer cognitive signs, $F (1,35) = 3.99$, $p = 0.05$, Cohen's $f = 0.34$. Furthermore, BB powder led to improved discernment in recognition memory on the Hopkins Verbal Learning Test (HVLT), $F (1,35) = 4.24$, $p = 0.04$, Cohen's $f = 0.34$. The effect for enhanced memory discernment in the BB group was not preserved at week 48.

3.3.4.3. Lexical access

Krikorian et al. [37] did a double- blind, placebo-controlled RCT for 16 weeks with 24 g per day freeze-dried blueberry (BB) fruit powder [an equal mixture (w/w) of ripe berries of the varieties 'Tifblue' (Vaccinium virgatum asheii Aiton) and 'Rubel'(Vaccinium corymbosum L.) equivalent to approximately one cup whole fruit and contained a whole phenolic content of 401 gallic acid equivalents] and placebo powder supplementation in adults aged 68 years and older with MCI .

An effect for semantic access favoring the BB-supplemented group was observed, 14.7 vs 17.0, $F (1,33) = 6.80$, $p = 0.01$, Cohen's $f = 0.45$. This effect was specific to semantic access, as there was no between group difference for phonological access, 35.0 vs 39.6, $p = 0.79$.

3.3.5. Quantitative resting brain perfusion

Bowtell et al. [33] showed that 12 weeks of the daily intake of 30 milliliters of blueberry concentrate supplementation [contained 387 mg anthocyanidins (34 mg malvidin, 108 mg cyanidin, 41 mg pelargonidin, 63 mg peonidin, 86 mg delphinidin, and 55 mg petunidin)] consumed once per day in 26 healthy older adults resulted in significant improvements in brain activity in reaction to blueberry supplementation compared to the placebo group within Brodmann zones 4/6/10/21/40/44/45, precuneus, anterior cingulate, and insula/thalamus ($p < 0.001$) as well as important enhancements in grey matter perfusion in the parietal (5.0 ± 1.8 vs − 2.9 ± 2.4%, $p = 0.013$) and occipital (8.0 ± 2.6 vs − 0.7 ± 3.2%, $p = 0.031$) lobes.

Boespflug et al. [41] in a double-blind, placebo-controlled RCT assessed the effect of daily blueberry supplementation (freeze-dried, whole fruit blueberry powder had 417 gallic acid equivalents, of anthocyanins was 269 mg cyaniding 3-glucoside equivalents) or placebo powder for 16 weeks on blood oxygen level-dependent (BOLD) signal in sixteen 68 years and older adults with MCI.

The blueberry fruit powder was a 50%:50% mixture of blueberry cultivars V. ashei Reade 'Tifblue' and V corymbosum L 'Rubel.'

Functional MRI (fMRI) data were attained whereas contributors accomplished a consecutive letter n-back WM task planned and directed using EPrime (www.pstnet.com).

Blueberry-treated patients displayed augmented BOLD activation in the left pre-central gyrus, left middle frontal gyrus, and left inferior parietal lobe throughout working memory load situations (corrected $P < 0.01$).

4. Discussion

To our knowledge, this is the first systematic review of available clinical trials on the effects of berry-based supplements and foods on cognitive performances and brain perfusion parameters in elderlies with normal cognition or MCI. This review of 10 clinical trials provided inconsistent findings across measured outcomes. Described trials have revealed a reliable role of berry-based food interventions, in improving global cognitive performance and also memory, executive function, learning abilities, lexical access, and finally brain perfusion. These trials ranged in length from a single dose to 6 months and used different berry products (fruit powder, fruit extract, freeze-dried fruit, whole fruit, and beverage) suggesting that all these forms of delivery are efficacious. Nonetheless, establishing the involvement of berry metabolites in the recognition is puzzling, chiefly because berries have a different phytochemical profile, which can be extremely different through varieties.

Berries illustrate a variety of little red, purple, or blue fruits. The frequently consumed berries comprise the blackberry, black raspberry, blueberry, cranberry, red raspberry, and strawberries. Less frequently consumed berries comprise blackcurrant, chokeberry, and mulberries. Berries are eaten both as fresh fruit in addition to processed food products (for example beverages, extracts and freeze-dried). Generally, berries have low calories and high fiber, and comprise different natural antioxidants such as vitamins C and E, and other nutrients such as folic acid, calcium, selenium, alpha and beta carotene, and lutein. Berries are rich in polyphenols, with significant amounts of flavonoids (anthocyanins, flavonols, and flavanols), condensate tannins (proanthocyanidins), hydrolyzable tannins (ellagitannins and gallotannins), phenolic acids (hydroxybenzoic and hydroxycinnamic acids, chlorogenic acid), stilbenoids and lignans [42,43]. Anthocyanins include the major group of natural, water-soluble, pigments and provide the bright appearance to berries. Around 400 anthocyanins have been distinguished, which are mostly concentrated in the fruit external layer, particularly berries. Red berries, strawberries and cherries, have anthocyanins in their body, too [44]. The microstructure of the extract in contrast to the powders must also be considered. The extract is lacking fibers and water soluble while the full spectrum powders are very rich in insoluble fibers to which the polyphenols are bound. It is consequently likely to assume that the polyphenols in the powders were not as bio-available as in the extract, and consequently less worthwhile.

During the current decade, clinical studies have dedicated to the health profits of berries. Especially, growing interest has been intense on the impact of berries and their natural ingredients in the human gut microbiota [45], lipid metabolism[44], diabetes and diabetes-related complications [46], cardiovascular health [47], and metabolic syndrome [48].

The theory of healthy aging is concurrently intensely attractive and challenging to describe. The WHO appraised that fifty million persons are involved with dementia globally and those quantities are anticipated to increase to eighty-two million in the following decade. Recently, scientific investigators have begun to study the effect of the Western dietary pattern on various non-communicable diseases (NCD) and have established a strong favorable association between a healthy diet and cognitive decline in elderlies. For instance, harmful dietary behaviors (overeating, diets with high calories/low fiber or intake of nutrients with underneath antioxidants) and inactive lifestyle, or emotional tension, are stated as important ecological features for brain conditions [49].

When findings of the dietary intermediations systematically reviewed in this study are weighed together, it seems that there are numerous essential mechanisms whereby berries potentially may provide cognitive health properties. The brain is predominantly exposed to neuro-inflammation and oxidative stress. This susceptibility further rises with age [40]. Amplified reactive oxygen species (ROS) production or reduced antioxidant protection is described as oxidative stress, which may contribute to the increase of various disorders such as neurodegenerative diseases [50]. Several medicinal properties of berries against oxidative stress-related disorders have been associated with their great content of phenolic antioxidants, particularly anthocyanin and phenolic acids. Furthermore, berries are accepted to have acceptable content of vitamins A, vitamins C and vitamins E, which perform as antioxidants [51]. On the other hand, it has been discussed that inflammatory cytokines in the circulation can cross through the blood-brain barrier (BBB), originating a neuro-inflammatory situation, disturbing neuroendocrine performance, and neurotransmitter arrangements, finally resulting in cognitive impairment (52). Actually, numerous studies establish that berry fruits display anti-inflammatory actions. Berries shut off the initiation of nuclear factor kβ (NF- kβ) and activation of nitric oxide synthase-2, cyclooxygenase-2, interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α) in macrophages [52,53]. Berry polyphenols improve mitochondrial function in intestinal Caco-2/15 cells activated with lipopolysaccharide (LPS), which decreases intestinal inflammation [54]. Metabolites of anthocyanin imitate active agents for example the anti-inflammatory salicylic acid (2-hydroxybenzoic acid) [55] and are related with useful variations in biomarkers of inflammation in vitro models [56].

On the other hand, Phenolic compounds are shown to be extensively metabolized into simple phenolic metabolites through the action of microorganisms in the colon [57]. These compounds may modify gut microbiota by the stimulation of favorable bacteria and the deterrence of pathogenic bacteria. In healthy individuals, the gut microbiota modulations largely result in an increase in Bifidobacterium, Lactobacillus and Akkermansia, then proposing a prebiotic-like

property of the berries or their compounds [57–60]. Epidemiological explanations and studies in animal models confirm a common schema that involves the gut microbiota over the microbiome-gut-brain axis in the pathogenesis of neurodegenerative diseases, such as dementia.

The current reading has some limitations that essential to be deliberated in explaining the outcomes of this systematic review. First, despite the collective body of nutraceutical studies, the number of studies included in this explicit review after a systematic review of the scientific medical literature was less than what would have been expected. Secondly, there are two aspects like possible publication bias and the selected search terms that could have influenced the results of the review. Some unpublished abstracts and articles are not included due to their unavailability. Thirdly, we nominated only the English and Persian language due to limited resources so it makes bias. These may significantly decrease the size of our sample and therefore our capacity to explain statistically important findings. Another weakness of this review is that due to the heterogeneity of the heterogeneity of the selected studies which considered a variety of outcome events. As a final point, there may be some probable parts not considered in the current systematic review, such as the intensity of IQ, region, diet, and race. Despite the specified limitations, this systematic review is the first systematic review of clinical trials investigating the effect of berry-based dietary interventions on cognitive function.

In included trials, the highest duration of berry-based food or supplement administration was 6 months. Future investigations should attempt to clarify the potential special effects of berry-based food or supplement consumption in a prolonged period of treatment to distinguish significant enhancement in cognition. Furthermore, the safety of these interventions should be described by means of a systematic method of recording probable adverse events based on the good clinical practice.

In summary, our study suggests that intake of whole berries or berry-based products are associated with cognitive function and brain perfusion parameters in elderlies with healthy cognition or MCI.

Declarations

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Figures

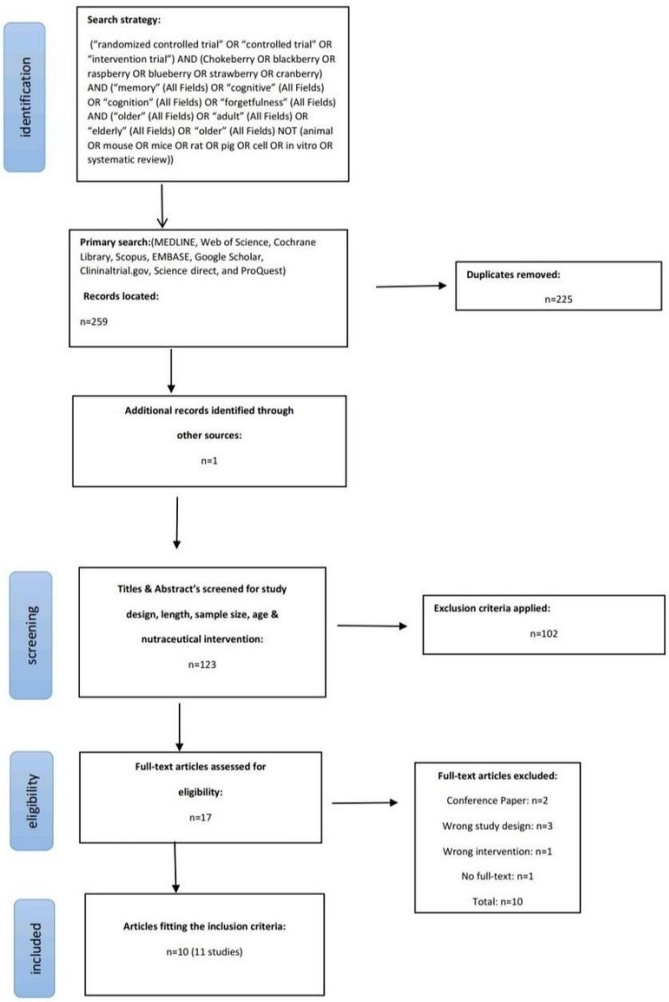

Figure 1

PRISMA flow chart summary of the systematic review search process

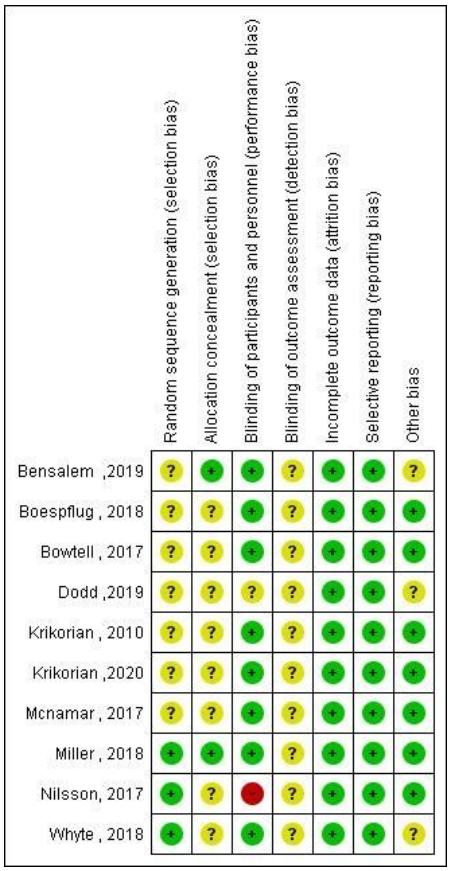

Figure 2

Risk of bias