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Effects of Berry, Pomegranate, Grape and their Biophenols on Cognitive Function: A General Review

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Abstract

Background: Decline in cognitive function can be observed in normal aging, MCI, neurodegenerative disorders, cerebral hypoperfusion and post-surgery. Cognitive impairment presents with limited therapeutic options. Berries, pomegranates and grapes are polyphenol-rich fruits that have both antioxidant and anti-inflammatory effects. This review aims to explore the effects of these fruits and their biophenols on cognitive function in healthy subjects and their protective effects on cognitive deficits in normal aging, mild cognitive impairment, Alzheimer's disease (AD), cerebral hypoperfusion using both animal models and human studies.

Methods: MEDLINE® and Proquest Central data bases were searched to retrieve articles used in this general review according to specific inclusion criteria. Independently, two researchers have summarized the study characteristics and assessed quality of methodology. Meta-analysis was not possible due to the limited number of studies and marked heterogeneity, and thus results were presented as a narrative review.

Results: Biophenol-rich fruits have been shown to exert cognitive functions boosting and enhanced memory in children and healthy adults. In patients with age related cognitive decline, MCI and AD, Biophenols-rich fruits showed a marked enhancement of memory and verbal fluency with reduced dementia risk, and in artery graft and valve surgery, pomegranate protected against memory impairment. Animal studies have shown that biophenols intake enhanced cognition in AD models presumably due to a reduction of Amyloidβ plaque deposition, inflammatory cytokines, microgliosis (glial cells hypertrophy), and brain DNA protection.

Conclusions: large scale studies are urgently needed to fully evaluate the preventive and/or adjunctive therapy of biophenol-rich fruits in cognitive decline, deficit and Alzheimer disease.

Keywords: *Fruits; Polyphenols; Cognitive Disorders; Memory Impairment; Alzheimer; Dementia*

Abbreviations

AD: Alzheimer's Disease; APP: Amyloid Precursor Protein; APP/PS1: Amyloid Precursor Protein/Presenilin 1; Aβ: Amyloid β; AVLT: Auditory Verbal Learning Task; BACE1: Beta-Secretase 1; BDNF: Brain-Derived Neurotrophic Factor; CRP: C-Reactive Protein; CVLT: California Verbal Learning Test; 2CCAO: Common Carotid Arteries Occlusion; CGJ: Concord Grape Juice; Cox-2: Cycloxygenase-2; ELISA: Enzyme-linked Immunosorbent Assay; EGCG Epigallocatechin Gallate; fMRI: Functional Brain Activation; GSH: Glutathione; GSE: Grape Seed Extract; GSPE: Grape Seed Polyphenolic Extract; GDS: Geriatric Depression Scale; hsCRP: High-sensitivity C-reactive Protein; DG: Hippocampus Gyrus; iNOS: Inducible Nitric Oxide Synthase; IGF-1: Insulin-like Growth Factor-1; IL-1β: Interleukin 1 Beta; IL 2-10: Interleukin 2 - 10; LPO: Lipid peroxidation; LPS: Lipopolysaccharide Induced Neuroinflammation; LTP: Long-term Potentiation; MMSE: Minin-Mental State Examination; MCI: Mild Cognitive Impairment; MFT: Modified Flanker Task; NFT: Neuro-Fibrillary Tangles; NO: Nitric Oxide; NF-κB: Nuclear Factor-Kappa B; NFAT: Nuclear Factor of Activated T-cell; IκB: Nuclear Factor of Kappa Light Polypeptide Gene Enhancer in B-cells Inhibitor; PD: Parkinson Disease; PMT: Picture Matching Task; PE: Pomegranate Extract; PPE: Pomegranate Peel Extract; PGSE: Pomegranate Seed Extract; POCD: Postoperative Cognitive Dysfunction; PGE-2: Prostaglandin E2; PUN: Punicalagin; PGJ: Purple Grape Juice; RVIP: Rapid Visual Information Processing; RT: Reaction Time; ROS: Reactive Oxygen Species; RAVLT: Rey Auditory Verbal Learning Task; SOPT: Self-ordered Pointing Task; TNF: Tissue Necrosis Factor; TNF-α: Tissue Necrosis Factor- Alpha; TEAC: Trolox-Equivalent Antioxidant Capacity; VAD: Vascular Dementia; WBB: Wild Blueberry

Introduction

The brain is known to be highly susceptible to oxidative damage because of its high metabolic load and abundance of oxidisable endogenous substances, such as the poly-unsaturated fatty acids that form the plasma membranes of neural cells [1]. Oxidative stress usually results from an imbalance between free radicals and antioxidants. If the free radicals levels overwhelm the body's ability to regulate them, then oxidative stress ensues. Free radicals can attack DNA, proteins and lipids within the cells, which contribute to several conditions and diseases, and in particular, those related to aging including neurodegenerative diseases such as Alzheimer's disease [2,3], vascular dementia (VAD) and Parkinson's disease (PD) [4]. In addition to oxidative stress, inflammatory processes are also considered to be an important factor in the pathophysiology of neurodegenerative diseases [5,6].

Since biophenols found naturally in many fruits, vegetables and herbs have both antioxidant and anti-inflammatory effects, there is an increased interest to investigate their roles in the reduction of oxidative stress and inflammatory processes involved in cognitive deficits, and thus their potential use as neuroprotective nutrients to maintain normal cognitive function and as therapeutic agents where cognitive function actually declines [7]. Polyphenolics, or biophenols, represent one class of phytochemicals which includes thousands of uniquely identified organic structures that occur exclusively in foods of plant origin (e.g. fruits, vegetables, nuts, seeds, grains, tea, coffee, cocoa beans and wine). Polyphenols are classified according to the number of phenolic rings into: phenolic acids; stilbenes; coumarins; tannins; and flavonoids. Flavonoids found in varying concentrations in many vegetables (e.g. Broccoli, greens, onions), fruits (e.g. blueberry, blackcurrant, strawberry, cherry, grape, pomegranate, apple and orange), beverages such as green tea and red wine and in plant extracts from pine bark, *Gingko biloba* and *Pueraria lobata*. Flavonoids can be further sub-divided into the following subclasses; flavonols (e.g. quercetin rich in apple), flavones, isoflavones, flavanones (e.g. hesperidin rich in orange), anthocyanidins such as (e.g. cyanidin and delphinidin rich in berries) and flavan-3-ols (e.g. catechin rich in green tea and cocoa) [8].

Flavonoids have been well documented to elicit health benefits by reducing the risk factors associated with cardiovascular disease, diabetes and stroke [9]. Over the last decade, interest has also grown in their ability to elicit cognitive benefits. Flavonoids particularly, anthocyanidins can cross blood-brain barrier and localize in the area of learning and memory- the hippocampus [10]. Most fruits and their pure beverages contain variable levels of flavonoids. Our choice for investigating grape, blueberry, blackcurrant, cherry and strawberry stems from the fact that they are among the richest sources of flavonoids, particularly anthocyanidins such as cyanidin and delphinine (per 100g: 158 mg anthocyanidins in blackcurrants, 163.3 mg anthocyanidins in blueberries, 33.4 mg in cherry, 27 mg in strawberry and 120 mg in grapes [11]. Pomegranate has also been selected in this review due to its unique multi-biophenol contents. In addition to flavonoids such as delphinidin, cyanidin, and pelargonidin [12], pomegranate species contain a hydrolysable tannins which are known as punicalagins; these represent the largest polyphenolic antioxidants with a molecular weight of > 1000 Dalton. Following ingestion, these tannins are hydrolyzed into ellagic acid and gallagic acid that are transferred to the blood circulation. Punicalagins (alpha and beta), gallagic acid and ellagic acid account for the majority of ellagitannins found in pomegranate extract. The gut converts these ellagitannins into urolithins which are small molecules that possess antioxidant properties [4]. Pomegranate juice antioxidant power was shown to be three times higher than those of red wine and green tea [13]. Ellagic acid, gallic acid and punicalagins found in pomegranate were shown to inhibit lipopolysaccharide (LPS) induced nitric oxide (NO), prostaglandin E2 (PGE-2) and interleukin-6 (IL-6) production that is believed to be responsible for the anti-inflammatory response of pomegranate extract [4].

Aim of the Study

The aim of this review was to investigate the effect of fruits (berry, pomegranate, grape and others) supplementation and their biophenols on cognitive function as evidenced from animal and human studies:

- Healthy people defined as those with no cognitive decline "human studies".
- Decline in cognitive function due to aging and mild cognitive impairment (MCI) "animal models and human studies".
- Cognitive function deficits due to Alzheimer's disease (AD) " animal models and human studies".
- Cognitive function deficits due to cerebral ischemia and surgical operations "animal models and human studies".

Search strategy methods

MEDLINE® and Proquest Central data bases were searched to retrieve articles used in this general review of *in vivo* animal and human studies. The review preparation was completed in several steps: identification of research question, definition of inclusion criteria, literature search and selection of eligible studies. We used the following keywords: Polyphenol-rich fruits and berries and cognitive decline or memory impairment, or Alzheimer. We also searched the reference list of selected studies for more relevant research. Studies included were human randomized clinical trials or cohort studies investigating as a main outcome the link between polyphenols- rich

fruits (pomegranate and grape) and berries (e.g. blueberry, strawberry and blackcurrant) on cognitive function and memory, and placebo controlled animal studies. Epidemiological and interventional studies which investigated the effect of pomegranate and grape and their polyphenols alongside berry fruits on cognitive function in healthy subjects were also considered. Independently, two researchers have summarized each study characteristics and assessed quality of methodology. Meta-analysis was not possible due to the limited number of studies and marked heterogeneity, and thus results were presented as a narrative review.

Effect of biophenol-rich fruits on cognitive Function in healthy subjects with no cognitive decline

Grape

The effect of grape supplementation on cognition in healthy individuals with no cognitive function impairment or decline has been investigated following both chronic and acute consumption. Regarding chronic consumption, Lamport., et al. [14] conducted a study which indicated that biophenol-rich grape juice might be beneficial for cognition in healthy individuals with no apparent cognitive disorders. Healthy women (n = 25) aged 40 - 50 years, who were employed for ≥ 30 hours/week volunteered for the study. The women consumed daily either Concord grape juice (CGJ) (355 mL containing 777mg total polyphenols of which 167 mg anthocyanins and 334 mg proanthocyanidins) or matched placebo drink for 12 week with 4 weeks washout period. A marked improvement in spatial memory and driving skills were observed with no effects on measures of executive function, verbal memory and psychomotor skill. However, there was an evidence of sustained benefits in verbal recall and executive function after cessation of the CGJ supplementation [14].

Acute consumption was investigated in two further studies looking at the effect of an acute administration of grape juice on cognition and mood. Haskell-Ramsay., *et al.* [15] conducted a randomized, placebo-controlled, double-blind, crossover study which examined measures of episodic memory, working memory, attention and mood following a 20 minutes absorption period of 230 ml single serving of commercially available purple grape juice (PGJ), containing 1504 mg total phenols as gallic acid equivalent and 138 mg anthocyanin, on 20 healthy young adults (average age of 21 years) [15]. The second study conducted by Hendrickson and Mattes [16], enrolled a larger sample size with 35 young adult smokers (average age 26 years) in a randomized, placebo-controlled trial. The participants consumed either 600 mL of CGJ (containing around 2,100 total phenols as gallic acid equivalent and 580 mg anthocyanins) along with a standardized lunch or energy- matched placebo followed by assessments of mood and implicit memory [16]. Both of these studies failed to find an acute effect of grape juice supplementation on memory. However, the first study found a significant effect of acute intake of grape juice on attention and mood as measured by enhanced overall speed on attention tasks and significantly increased calm ratings. However, it is important to notice that executive function measures weren't evaluated thoroughly using these studies. Haskell-Ramsay., *et al.* [15] evaluated the measures through composite score of memory reaction time (Memory reaction time (RT) = (RT of delayed word recognition + RT delayed picture recognition + RT numeric working memory)/3). In the study conducted by Hendrickson and Mattes [16], only measure for implicit memory was utilized and thus executive memory was not evaluated. No studies have been conducted to examine the acute effect of CGJ on cognition in children.

Blueberry, cherry and blackcurrant

The Effect of berries on cognition of healthy subjects has been reviewed by Bell., *et al.* work [17]. Blueberries have different flavonoids subclasses, but they are the richest in anthocyanins. The effect of berries on cognition has been investigated only after acute consumption. For the aim of investigating the acute effect, a study by Dodd [18] has been conducted. The study had employed a randomized, controlled, double blind, crossover design of freeze dried blueberries (200g fresh equivalent containing 631 mg anthocyanidins) or energy matched control, with cognition function measured at baseline, 2 hours and 5 hours post consumption. For younger adults (n = 19), an improved accuracy on a letter memory task (measuring working memory) was observed 5 hours postprandially. No effects were observed at an earlier time of 2 hours or for other measures of executive function, memory, or mood. For a subset of participants who had consumed blueberry, blood samples taken 1 hour postprandially showed an increase in plasma levels of brain-derived neurotrophic factor (BDNF). Unfortunately, cognition was not measured after one hour and it is impossible to say whether this neurochemical change was related to any cognitive outcome. For older adults (n = 18), an improved performance on an immediate word recognition task at both 2 hours and 5 hours postprandially were observed. No improvements in measures of executive function or mood were evidenced [17]. For evaluation of the acute effect of berry consumption in children, Whyte., *et al.* [19,20] conducted two studies. The first study was a small, crossover study with only 14 children (8 - 10 years old), using fresh whole blueberries (200g containing 143 mg anthocyanins). The study found no effects at 2 hours for a range of executive function tasks, but did observe a marked improvement in delayed word recall using the Rey auditory verbal learning task (RAVLT). The second study enrolled a higher number of children (n = 21) of 7 - 10 years old in a randomized, double-blind, cross-over study with two separate blueberry doses of 15 and 30g freeze dried blueberry powder (containing 127 mg and 253 mg anthocyanins consequently).This study utilized four cognitive tests; AVLT which examined performance in learning, memory recall and recognition, modified flanker task (MFT) which examined response interference, Go-NoGo which examined response inhibition and pic-

ture matching task (PMT) which investigated both levels of processing and response interference. The effect on cognition was measured at baseline and at three post-intervention sessions (at 1.15, 3 and 6 hours). The 30g dose resulted in a significant improvement in immediate word recall after 1.25 hour and the 15g dose resulted in a trend towards significance on delayed recall. For the 15 and 30 g doses, a significant effect was seen at word recognition test 6 hours post intervention. The 30g dose showed an improved accuracy during MFT after 3h, although only for cognitively demanding incongruent trials. However, there was a no significant improvement was observed in Go-NoGo test for the 30 g dose and faster performance in Go-NoGo test in the placebo group compared with the blueberry group [19,20]. This study indicated a dose response relationship for anthocyanins; higher doses are linked to better cognitive function. Bell at al that the cognitive function domains affected by blueberry supplementation varied by age. In children and older adult, the memory function was mainly enhanced while an improvement in executive function was observed in young adults. This could be an indicative of age differences response in the capacity for particular cognitive domain improvement [17].

Blackcurrants are also considered a very rich source of anthocyanins. Watson., *et al*. [21] conducted a randomized, double-blind, controlled crossover trial using 36 healthy nonsmokers' young participants (18 - 35 years old) of two blackcurrant extracts; cold-pressed juice or freeze-dried powder or energy-matched control. The total polyphenols content of the two extracts were approximately 525 mg as gallic acid equivalent per 60 kg bodyweight. However, there was a slight difference in anthocyanin content between extracts; 483 mg/60 kg bodyweight for the powder and 467 mg/60 kg for the juice. Seven repetitions of the digit vigilance task, Stroop task and rapid visual information processing (RVIP) task were utilized in this study to examine acute blackcurrant effect on cognition. A significant improvement was observed for tests of executive functions (RVIP and to some extent vigilance). Specifically, declining accuracy on a RVIP task was attenuated after taking the powdered extract. No effects were observed for the Stroop test which evaluates inhibition and attention function. Also no enhancements in measures of mood and mental fatigue were seen [21]. The results of this study were consistent with the results of the executive function improvement seen in healthy young adults after blueberry consumption.

In addition to blueberry and blackcurrant, cherry contains a considerable concentration of anthocyanins. Caldwell., et al. [22] conducted a pilot cross-over study assessing the acute response of cherry flavonoids consumption following administration of 300 mL cherry juice approximately containing 55 mg anthocyanins to 6 younger adults (18 - 35 years) and 5 older adults (≥ 55). Three tests were utilized in this study; RAVLT which assessed verbal learning and memory, task-switching test measured higher executive function and pattern and letter comparison tasks assessed speed of processing at baseline and 6 hours postprandially. No significant differences were found for cognitive tasks with the exception of the task-switching test in older adults after consuming the single 300 ml serving [22]. Bell at al, the results of this study couldn't be adopted with high confidence, since the small sample size decreased its power dramatically, and there was also no energy matched control group. A second study administered the same juice in three separate 100 mL aliquots each consumed at 1 hour apart. No cognitive effects were observed relative to baseline following consumption of the juice in these consecutive smaller doses. It should also be noticed that the intervention dose was lower compared to some of the earlier mentioned studies. Since the concentration of anthocyanin in cherry is far lower compared to blueberry, blackcurrant and grape; 157.7 mg/100g in blackcurrants, 163.30 mg/100g in blueberries and 120 mg/100g in grapes [9], a larger volumes of cherry juice should be utilized to achieve similar anthocyanin doses consumed in other similar studies [17].

Summary and Future Recommendations

A summary of human studies conducted for the evaluation of cognition effects of grape and berry in healthy individuals with no cognitive decline is shown in table 1. There were positive effects for chronic grape supplementation on cognitive function, particularly in spatial memory. A sustained effect for executive function was also noticed after cessation of CGJ, which could mask the difference between tests groups. Future studies using chronic CGJ consumption should be conducted with longer wash out period to avoid carryover effects, or different study design. This would indicate if chronic CGJ intake produces additional benefits in executive function and verbal memory. For both berries and pomegranate, no randomized controlled studies have been performed to investigate their chronic consumption effect on healthy subjects. We would strongly justify interventional studies to be conducted very soon.

Acute blueberry and blackcurrant supplementations found to have beneficial effects on the executive function in young adults, yet no such benefits were noticed after cherry intake, and this might be due to the small sample size employed. Thus, a larger randomized control trial (RCT) using higher range of anthocyanin doses is needed to determine if cherry anthocyanins can elicit acute cognitive effects similar to those of other anthocyanin-rich fruits [23]. Acute grape intake seems to show no memory benefits (episodic or implicit). Further interventional studies to evaluate the acute effect of CGJ intake on cognition that investigate measures of executive function should be conducted to explore if anthocyanin-rich supplements (blueberry, blackcurrant and grape) produce the same benefits of executive function improvement in young healthy adults. In children and older adults, the memory functions were seen to be mainly enhanced after

blueberry supplementation. In addition, cherry intake was shown to enhance executive function in older adults. It should be noted that interventional studies of blackcurrant and grape extracts in children and older adults (older than 55 years) have not been conducted. Thus, we highly recommend such studies to be performed in order to determine if these extracts can produce similar benefits in cognitive function enhancement as those seen with blueberry consumption. This would also strengthen the evidence of anthocyanins-rich fruit intake as memory improvement supplements in children. No studies using pomegranate have been published for healthy subjects to evaluate the acute or chronic effects on memory. We suggest that further interventional studies to be conducted to study the acute and chronic effects of pomegranate intake in healthy individuals.

Effect of biophenols-rich fruits and extracts on Age-related decline in cognitive function or Mild Cognitive Impairment

Humans and animals cognitive functions start to decline during aging which thought to be related to increased susceptibility to long-term effects of oxidative stress and inflammation [23-25]. Thus, several animal and human studies have been conducted to evaluate the effects of antioxidant and/or anti-inflammatory phytochemicals on age-related cognitive decline and the possible mechanisms of their effects.

Fruit	Study design/ Duration of study *	Characteristics and N value	Dose**	Outcomes	Reference
Grape	Randomized, placebo-controlled, crossover study of either CGJ 12 weeks	25 healthy mothers, aged 40-50 years who were employed for ≥ 30	Total biophenols: 777 mg (167 mg anthocyanins as malvidin equivalent and 334 mg proanthocyanidins as catechin equivalent) /355 mL CGJ	**Memory**: ↑ Visual spatial learning test (VSLT) immediate recall (spatial memory) ↔ Visual verbal learning test (VVLT) immediate recall (verbal memory) **Executive function/working memory** ↔ Rapid visual information processing (RVIP) ↔ Tower of Hanoi **Psychomotor skill** ↔ Grooved Pegboard **↑ driving skills**	[14]
	Randomized, controlled, double-blind, crossover study of single serving of commercially available PGJ	20 healthy young adults (average age of 21 years).	Total biophenols: 504 mg (containing 138 mg anthocyanin) / 230 ml PGJ	**Attention:** ↑ Attention reaction time ↑ Attention accuracy **Memory:** ↔ Memory reaction time (composite score) ↔ Memory accuracy (Episodic memory) **Executive function/working memory** ↔ Memory reaction time (composite score) **Mood:** ↑ Bond-Lader mood scales (calm rating)	[15]
	Randomized, placebo-controlled trial of CGJ	35 young adult smokers, average age 26 years	Total biophenols: 2,100 (580 mg anthocyanins)/ 600 mL of CGJ	**Memory** ↔ implicit memory***	[16]

Blueberry	Randomized, controlled, double blind, crossover study of freeze dried whole blueberries with cognition function measured at baseline, 2 and 5 hours post drink	19 younger-healthy adults & 18 older adults	631 mg anthocyanidins /200 g fresh	**For younger adults:** **2 hours postprandial** **Memory:** ↔ Memory testing tasks **Executive function/working memory:** ↔ Executive function task **5 hours postprandial** **Memory:** ↔ Memory testing tasks **Executive function/working memory:** ↑ letter memory task ↔ other measures of executive function **For older adults:** **2 hours postprandial** **Memory:** ↑ Immediate word recognition task **Executive function/working memory:** ↔ Measures of executive function **5 hours postprandial** **Memory** ↑ working memory (immediate word recognition task) ↔ other executive function measures ↔ mood	[18]
	Randomized, crossover study of fresh whole blueberries	14 children (8-10 years old)	143 mg anthocyanins / 200g of fresh whole blueberries	**Memory:** ↑ RAVLT (delayed memory) **Executive function/working memory:** ↔ executive function	[19]
	Randomized, controlled double-blind cross-over study of either 15 or 30 g of freeze-dried blueberry powder	21 children (7- 10 years old)	15 g of freeze dried powder:127 mg anthocyanins **30g of freeze dried powder**: 253 mg anthocyanins	**30g freeze dried wild blueberry powder:** **Memory:** ↑ AVLT (immediate recall /1.5 hour post consumption) ↔ AVLT (delayed recall) **Executive function/working memory:** ↑ MFT (response interference/ 3h post consumption ↔ Go-NoGo test (nhibition) **15g freeze dried wild blueberry powder**: **Memory:** ↔ AVLT (immediate recall) ↔ AVLT (delayed recall)**** **Executive function/working memory:** ↔ MFT (response interference) ↓ Go-NoGo test (inhibition)	[20]

Black currant	Randomized, double-blind, controlled of two blackcurrant extracts; cold-pressed juice or freeze-dried powder	36 healthy nonsmokers' young participants (18-35 years old)	**Powder**: Total biophenols: 483 mg per 60 kg bodyweight **Juice:** Total biophenols: 467 mg/60 kg	**Executive function/working memory**: ↑ EVIP ↑ Digit vigilance task ↔ Stroop test (inhibition)	[21]
Cherry	Pilot cross-over study of cherry juice	Younger adults (18-35 years) and older adults (55+)	55 mg anthocyanins/ 300 mL of cherry juice	**Younger adults** **Executive function/working memory**: ↔ Task-switching test **Memory:** ↔ RAVLT (verbal memory) **Processing speed** ↔ Pattern and letter comparison tasks peed: **Older adults** **Executive function/working memory:** ↑ task-switching test **Memory:** ↔ RAVLT (verbal memory) **Processing speed**: ↔ Pattern and letter comparison tasks speed	[22]

Table 1: *Summary of human studies of the effects of grape and berries (blueberry, blackcurrant and cherry) in healthy individuals with no cognitive problems.*

**: For acute intake, no duration applicable.*

***: Doses for total biophenols expressed as gallic acid equivalent.*

****: Explicit memory and executive function weren't studied.*

*****: Trend toward significant.*

↑: Significant improvement, ↔: No significant difference, ↓: Worsening.

Animal studies

Grape

The CGJ was found to have a positive impact on both cognitive function and motor function of aged rats. A study conducted by Skukitt., *et al*. [26] showed that 10% concentrated grape fruit juice improved cognitive function in aged rats assessed through Morris water maze (Morris water maze is an age-sensitive learning paradigm that tests spatial learning and memory) and 50% concentrated grape juice produced an improvement in co-ordination motor function tests (rod walk, wire suspension, and small plank walk) [26]. The cognitive benefit was explained by improvements in oxotremorine potassium evoked release of dopamine from striatal slices. Another mechanism by which grape supplementation induced such reversal of neural and behavioral aging could be explained by Balu., *et al*. [27] work. In this study grape seed extract (GSE) showed an inhibiting effect on the accumulation of age related oxidative DNA damage both in the spinal cord and certain brain regions such as the striatum, hippocampus and cerebral cortex of aged rats [27].

Berry

Studies that investigated berry intake in aged animals showed a significant improvement in cognitive function. In a study conducted by Baros., *et al.* [28], long term memory has been significantly improved by administration of lyophilized extract of Vaccinium ashei berries for 30 days. The study suggested that the effect was due to the extract protective effect on DNA damage in the hippocampus and

cerebral cortex. This effect could be explained by the antioxidant activity of polyphenols, including anthocyanins found in the berries [28]. In addition to oxidative stress, reduction in hippocampal neurogenesis was considered to be another contributing factor for cognitive function decline during aging. One of the key modulator of hippocampal neurogenesis is Insulin-like growth factor-1 (IGF-1), a major activator of the extracellular receptor kinase pathway that plays a vital role in learning and memory processes. A study by Casadesus., *et al.* [29] showed that blueberry supplementation improved spatial memory in aged rats tested by radial arm water maze and also improved hippocampal neurogenesis, extracellular receptor kinase activation, and Insulin-like growth factor-1 (IGF-1) and IGF-1R levels, which led to enhancement of hippocampal neuronal plasticity [29].

There are also neuronal and behavioral changes that take place during the aging process in the absence of neurodegenerative disease. These changes may include decrements in calcium homeostasis [30] and sensitivity of several receptor systems, most notably adrenergic [31], dopaminergic [32], muscarinic [33,34]. Joseph., *et al*. [35] examined cognitive effects of strawberry, spinach or blueberry supplementation on aged rats and showed that strawberry and berry consumption for 8 weeks (14.8 gm and 18.6 gm daily of dried aqueous extract per kilogram of diet respectively) produced a significant enhancement in several neuronal and behavioral parameters. These include: enhancement of K+-evoked release of dopamine from striatal slices, carbachol-stimulated GTPase activity and striatal Ca^{45} buffering in striatal synaptosomes. These have presumably led to improvement in motor behavioral performance on the rod walking and accelerod tasks, and a significant enhancement of spatial learning and memory using Morris water maze. Such findings suggest the ability of biophenol-rich supplementation to reverse age related deficits [35]. Another study found that blueberry and strawberry supplementation in a model of aging rats with deteriorated motor and cognitive abilities due to exposure to whole-body irradiation, a differential effect of protection against radiation harmful effects as tested by water maze performance test [36]. Blueberry supplementation was found to improve reversal learning, which relies on intact striatal functioning, whereas strawberry supplementation appeared to show better protection against spatial deficits in the maze. This study provided some evidence that blueberry and strawberry intake could offset the irradiation-induced deficits in spatial learning and memory. Blackberry was also investigated to evaluate its efficacy in reversing age-related deficits in behavioral and neuronal function. A study by Shukitt-Hale., *et al.* [37] found that 2% of blackberry supplementation in aged rats enhanced short-term memory as assessed by the water maze test and resulted in significant improvement in motor performance of tasks that depend on balance and co-ordination [37].

Human studies

Grape

Several studies have been conducted to investigate the effect of polyphenol-rich fruits on age-related cognition decline and MCI. Individuals with MCI are usually at increased risk of developing dementia and clinical appearance of neurodegeneration which may progress to AD [38,39]. The first study conducted by Krikorian., *et al.* [40] enrolled 12 older adults with MCI supplemented with CGJ (range 444 - 621 ml/day) in a randomized, placebo-controlled study. The California verbal learning test (CVLT) was used to assess verbal memory (List acquisition performance and delayed recall), and the spatial paired associate learning test used to evaluate non-verbal memory (spatial memory). The study showed a significant improvement in verbal learning and enhancement of delayed verbal recall and spatial memory when compared to placebo [40]. The second study enrolled 21 older adults with MCI used similar dosing schedule of CGJ supplementation (range 355 - 621 ml/day containing 742 - 1298 mg total polyphenols) for 16 weeks. While the study found no difference in performance using the CVLT learning tasks and recognition memory performance, patients who consumed CGJ showed less interference errors in the recognition memory task (indicative of inhibitory control in working memory). In addition, this study assessed functional magnetic resonance imaging (fMRI) changes for participants to test potential brain activation during a working memory task, and found an increased activation in the right superior parietal cortex and right middle frontal cortex following CGJ supplementation [41]. These studies provided some evidence that grape intake might enhance memory in elderly patients with MCI and justify conducting larger trials on elderly patients with MCI or age related cognitive decline.

Berry

A small trial which investigated the effects of daily consumption of blueberry juice (444 - 621 mL containing 1056 - 1477 mg of total polyphenols) enrolled nine elderly participants with MCI who had experienced age-related memory decline such as forgetfulness and prospective memory lapses. Following 3 months of juice consumption, patients showed significant improvement in memory function as indicated by paired associate learning and word list recall tests. There was also a reduction of associated depressive symptoms. Although the sample size was relatively small, the positive effects on memory after blueberries intake may mitigate neurodegeneration. Clearly, larger randomized trials are needed to recommend the use of blueberry supplementation as preventive intervention in cognitive function deterioration [42].

Epidemiological studies have also been conducted to examine the effect of flavonoids intake on cognitive function decline. Devore., *et al.* [43] evaluated the effect of berries and other flavonoid-rich diet consumption on cognition decline in a large prospective cohort study. Female registered nurses (n = 12,1700) aged 30 - 55 years were followed up for 26 years using food frequency questionnaire updated every four years. Those women who were ≥ 70 years old and free of stroke were invited to participate in the cognitive function tests and their data have been analyzed (n = 16,010). The study calculated the intake of 31 individual flavonoids (representing six major flavonoid subclasses; anthocyanidins, flavonols, flavones, flavanones, flavan-3-ols, and polymeric flavonoids) that are commonly found in the United States diet. Blueberries and strawberries were the major foods contributing to anthocyanidin intake in this cohort, whereas tea, apples, and oranges were the major contributors to other flavonoid subclasses and total flavonoid intake. Two measures of overall cognition (global composite score averaging all tests, and the telephone interview of cognitive status) and a verbal memory composite score; averaging four tests of episodic memory were used to evaluate the cognition status. The study concluded that higher total flavonoid intake was associated with significant slower rates of cognitive decline for all of the three stated primary outcome measures. Among flavonoids, anthocyanidins were noticed to have the highest association with cognitive benefits. However, flavonols were observed to have modest association with cognitive function. Researchers specifically found that this positive effect was due to greater consumption of blueberries and strawberries, and that berry intake appeared to delay cognitive aging by up to 2.5 years. Interestingly, flavonoids intake originating from tea, onions, apples and oranges were not associated with delaying cognitive decline [43].

Pomegranate

Pomegranate juice intake by older subjects with age-associated memory complaints was investigated by Bookeimer., *et al* [44]. Participants (n = 32) were randomly assigned to drink 8 ounces (236 mL) of either pomegranate juice or a flavor-matched placebo drink for 4 weeks, and then memory tests assessed by using the Buschke-Fuld selective reminding task which evaluated verbal memory. The participants were also scanned by fMRI and blood biomarkers before and after the intervention. Following 4 weeks, only the pomegranate group showed a significant improvement in the verbal memory selective test with a significant increase in plasma trolox-equivalent antioxidant capacity (TEAC) and urolithin-A glucuronide indicating an increase in free radicals scavenging. Furthermore, the pomegranate group had increased fMRI activity during verbal and visual memory tasks compared to the placebo group. These results suggested a role for pomegranate juice in augmenting memory function through task-related increase in cerebral blood flow, which in turn facilitated memory performance. Metabolic measures did also confirm the increase in polyphenols levels among the experimental group [44].

Summary and Future Recommendations

Table 2 summarizes the animal studies on cognitive decline related to aging following grape and berries intake. There was a significant cognitive function enhancement using Morris water maze that reflected spatial learning and memory domain improvement. Proposed mechanisms for anthocyanins rich fruits beneficial effects on age related cognitive decline included: oxidative stress reduction, enhancement of neuronal signaling in brain memory centers, enhancement of hippocampal neurogenesis, increased dopamine release from striatal slices and buffering excess striatal calcium in striatal synaptosomes. No animal studies were conducted so far to investigate the effect of pomegranate extract on age related cognitive decline.

Human interventional studies of grape, berry and pomegranate showed a significant enhancement of cognitive functions in older subjects with age-related memory complaints and MCI, as evidenced by some of the memory and executive function measures assessed. In addition, an increased in the free radical scavenging effect was seen after pomegranate juice intake and an increase of fMRI activation in certain brain regions that suggested greater cerebral blood flow during memory tasks. Summary of human studies effects of grape, berry and pomegranate on cognition in patient with MCI or aged related cognition decline is shown table 3.

However, all interventional studies had a small sample size which means the data were insufficiently supported. Furthermore, epidemiological studies which evaluated the association of biophenol-rich fruit with age cognition decline related to aging are really scarce. One study showed an association of high flavonoids consumption and protection against cognitive function decline in older female nurses. However, this study didn't follow up patients who already diagnosed with MCI or patients with age-related memory complaints. We recommend future studies will assess MCI patients or those with age-related memory complaints to confirm the protective effect of biophenol-rich fruit consumption.

Fruit	Study design	Rats characteristics/ duration of study	Outcomes	Reference
Grape	Randomized, Placebo-controlled study with 10% grape juice, and 50% grape juice	Aged rats, 3 Months	**Cognitive function:** ↑ Morris water maze (the 10% grape juice) **Motor function:** ↑ Rod walk, ↑ Wire suspension, ↑ small plank walk (the 50% grape juice) ↑ Oxotremorine enhancement of K+-evoked release of dopamine from striatal slices	[26]
	Placebo-controlled study of GSE	Aged rats, 30 days	↑ Free radical levels reduction ↑ DNA strand break reduction	[27]
Berry	Placebo controlled trial of lyophilized extract of Vaccinium ashei berries	Aged rats, 30 days	**Memory:** ↑ Inhibitory avoidance task (Long term memory)	[28]
	Randomized, Placebo-controlled of blueberry extract diet	Aged rats, 8 Weeks	**Memory:** ↑ Radial Arm Water Maze (spatial memory) ↑ Hippocampal neurogenesis ↑ Extracellular receptor kinase activation, ↑ Insulin-like growth factor-1 (IGF-1) and IGF-1R levels	[29]
	Randomized, Placebo-controlled of strawberry, spinach, or blueberry	Aged rats, 8 weeks	**Memory:** ↑ Morris water maze performance (Spatial learning and memory) ↑ Oxotremorine enhancement of K^+-evoked release of dopamine from striatal slices, ↑ Carbachol-stimulated GTPase activity ↑ Striatal Ca^{45} buffering in striatal synaptosomes	[35]
	Placebo-controlled trial of 2% blueberry or strawberry extracts	Rats with irradiated-induced cognitive deficits, 8 Weeks	**Memory:** ↑ Morris water maze performance (latency measure in the strawberry) ↑ Morris water maze performance (Probe trial measures in the strawberry fed rats)	[36]
	Placebo-controlled trial of 2% blackberry supplementation	Aged rats, 8 weeks	**Memory:** ↑ Morris water maze (short-term memory) Motor performance: ↑ balance and co-ordination	[37]

Table 2*: Summary of animal studies of grape and berries effects on cognition decline related to aging and MCI.*

↑: Represents significant improvement.

	Study design/ Duration of study	Patients number and Characteristics	Dose *	Outcomes	Reference
Grape	Randomized, placebo-controlled study of CGJ 12 weeks	12 older adults with MCI	Total biophenols: 920 - 1298/444 - 621 ml/day	**Memory:** ↑ CVLT List acquisition performance (verbal memory) ↔ CVLT Delayed recall (verbal memory) ↔ Spatial paired associate learning test (spatial memory)	[40]
	Randomized, double-blinded, placebo-controlled, of CGJ 16 weeks	12 older adults with MCI	Total biophenols: 742 - 1298 mg/355 - 621ml/day	**Memory:** ↔ CVLT learning tasks and recognition (verbal memory) **Executive function/ working memory** ↑ Decreased interference on recognition memory task (inhibitory) **Mood:** ↔ Geriatric Depression Scale (GDS20) **fMRI** ↑ Activation in the right superior parietal cortex and right middle frontal cortex	[41]
Berry	Randomized, placebo-controlled of blueberry juice	9 elderly patients with MCI 3 months	Total biophenols: 1056 - 1477 mg / 444 - 621 mL	**Memory:** ↑ paired associate learning and word list recall	[42]
	Prospective cohort study of flavonoid	16,010 elderly nurses 25 years		**General (overall cognition):**** ↑ Global composite score ↑ Telephone Interview of Cognitive Status and a **Memory:** ↑ Memory composite score (verbal memory)	[43]
Pomegranate	Randomized, double-blind, placebo-controlled study of pomegranate juice	32 older subjects with age associated memory complaints	8 ounces (236 ml) of pomegranate juice 4 weeks	**Memory**: ↑ Buschke-Fuld selective reminding task (verbal memory) **Plasma biomarkers:** ↑ Plasma TEAC ↑Plasma urolithin-A glucuronide **fMRI:** ↑ Activation in visual pathways during a visual memory task ↑ Activation in in the left hemisphere (regions of the left occipital lobe and left fusiform gyrus during verbal memory task)	[44]

Table 3: *Summary of human studies of grape, berry and pomegranate effects on cognition in patient with MCI or aged related cognition decline*

**: Total polyphenols expressed as gallic acid equivalent.*

*** Anthocyanidins were noticed to have the highest association with cognitive benefits due to greater blueberry and strawberry consumption.*

↑ Significant improvement.

Effect of biophenol-rich fruits and extracts on Alzheimer Disease

Animal studies

Grape

Wang., *et al.* [45] evaluated the effect of commercially available MegaNatural grape seed polyphenolic extract (GSPE) treatment for 5 months on a transgenic mouse model with Amyloid β (Aβ) accumulation. Results showed a significant decrease in oligomerization of Aβ peptides into high molecular weight Aβ species, reduced amounts of Aβ42 and Aβ40 peptides and amyloid neuritic plaque burden compared to the matched group control animals. GSPE treated mice had marked improvement of spatial memory function compared with the control group [45]. A similar study using transgenic mice that have been supplemented with GSE for 9 months found similar findings of a reduced level of Aβ in the brain and serum in the treatment group mice. In addition, GSE intake was also found to reduce microgliosis (proliferation or hypertrophy of different types of glial cells, including astrocytes, microglia, and oligodendrocytes) in the brain of Alzheimer's mice model. GSE also decreased the levels of inflammatory cytokines: interleukin 1 beta (IL-1β), tissue necrosis factor- alpha (TNF-α) and tissue necrosis factor-gamma (IFN-γ) [46].

Tau protein phosphorylation and aggregation which lead to neurofibrillary tangles (NFT) development, may contribute to the pathophysiology of Alzheimer's disease (AD). Several studies examined the effect of polyphenol-rich fruit on tau neuropathy. A study by Wang., *et al.* [47] examined the effect of GSPE on a mouse model of AD, characterized by an age-dependent development of tau pathology in the brain, found that it effectively interfered with the assembly of tau peptides into neurotoxic aggregates. Moreover, oral administration of GSPE had attenuated the development of AD type tau neuropathology in the brain of the mouse model of AD through mechanisms associated with attenuation of extracellular receptor kinase signaling in the brain involved in tau hyperphosphorylation [47].

Berry

Amyloid precursor protein (APP) is a transmembrane protein best known as the precursor molecule whose sequential proteolysis generates Aβ protein. Therefore, APP processing could lead to Aβ production which is a key pathogenic feature of AD [48]. Several studies evaluated the effect of biohenol-rich fruit on APP processing and subsequently, the level of Aβ production and aggregation. A study by Vepsalainen., *et al*. [49] was carried out on transgenic mice with amyloid precursor protein/presenilin1, found that mice fed anthocyanin-rich bilberry or blackcurrant extract had lower APP C-terminal fragment levels in the cerebral cortex as compared to transgenic mice on the control diet. Both berry diets improved the spatial working memory deficit of aged transgenic mice compared to mice on the control diet, as evidenced by delayed Aβ protein processing. This would indicate a favorable effect of berry fruits on working memory enhancement. On another hand, both berry diets showed no changes in the expression or phosphorylation status of tau in mice. These data suggest that anthocyanin-rich bilberry and blackcurrant diets favorably modulate APP processing and alleviate behavioral abnormalities in a mouse model of AD [49].

Pomegranate

The effect of dietary supplementation of pomegranate extract (PE) on memory, anxiety, and learning skills in AD mouse model possessing double Swedish APP mutation has been examined by Subash., *et al* [50]. The study showed that the transgenic mice with APP mutation that were fed a diet containing 4% PE developed significant improvements in memory, learning, locomotors function as well as a reduction in anxiety, compared with transgenic mice fed the standard chow diet. The study suggested that pomegranates intake may slow the progression of cognitive and behavioral impairments in AD [50]. The mechanism of action was investigated by Ahmed., *et al*. [51] who used aged transgenic mice AD model to evaluate the effects of a standardized PE on spatial function of long-term and working memory, APP and Aβ levels and other biomarkers of AD in brain tissues. The study showed that PE did not improve cognitive performance of the mice, but altered levels and ratio of the Aβ40 and Aβ42 peptides that would favor a diminution in AD pathogenesis. This reversal could be due to the modification of γ-secretase enzyme activity (the enzyme involved in the generation of Aβ isoforms). These findings suggested an anti-amyloidogenic mechanism of PE in this aged AD animal model [51]. Essa., *et al*. [52] have also conducted a placebo-controlled study using dietary supplementation of pomegranates, figs and dates, and found that pomegranate significantly decreased Aβ40 levels in the cortex and hippocampus of the transgenic rats, decreased levels of inflammatory cytokines: IL-2, IL-3, IL-4, IL-5, IL-9 and IL-10, in the plasma following diet containing pomegranates. The authors concluded that reducing inflammatory cytokines during aging may represent one mechanism by which fruit supplements may exert their beneficial effects against neurodegenerative diseases such as AD [52].

The effects of Pomegranate Peel Extract (PPE) on spatial memory, biomarkers of neuroplasticity, oxidative stress and inflammation in mice with Aβ peptide deposition induced by chronic infusion of Aβ42 using mini-osmotic pumps for 35 days have been examined by Morzelle., *et al.* [53] using a placebo-controlled study. Animals consumed PPE improved the escape box Barnes maze test, which reflected an enhancement in the spatial memory, a finding that was not observed in the Aβ group that was fed chow diet. Amyloid plaque density, the activity of acetylcholinesterase enzyme and level of TNF-α were also reduced, while the expression of BDNF was increased. The effect of PE on memory in APP/PS1 transgenic mice as model of AD was also studied after 3 months supplementation and found to enhance spatial memory as evidenced by decreased path length to escape the Barnes maze compared with their initial values and their control-fed counterparts. It was also found that one month of pomegranate feeding increased spontaneous alternations, which reflected working memory improvement. Brains of the pomegranate-fed mice had significantly lower TNF-α, lower nuclear factor of activated T-cell (NFAT) transcriptional activity, attenuated microgliosis and Aβ plaque deposition. This study indicated that dietary pomegranate produced brain anti-inflammatory effects in the brain that may attenuate AD progression [54].

Human Studies

Flavonoids from various sources

Few epidemiological studies linking biophenols consumption and AD were published and some of these had evaluated the association of fruit and vegetable consumption without specifically examining the importance of biophenols contents. Cohort studies by Hughes., *et al*. [55] and Dai., *et al.* [56] showed that moderate and large fruit and vegetable consumption at midlife ages and in elderly individuals, were associated with a decreased risk of dementia [55,56]. The relationship of flavonoids with AD risk was investigated by two large prospective epidemiologic studies. In the first study, Letenneur., *et al.* [57] assessed the data of 1,640 participants for whom nutritional data were available at the 3-year visit and who completed at least one psychometric test at one of the visits. Cognitive function was assessed by 3 psychiatric tests at each visit. The mean flavonoid intake was 14.33 mg/day. The quartiles of flavonoid intake were divided into; 0 - 10.39, 10.40 - 13.59, 13.60 - 17.69, and 17.70 - 36.94 mg/day. The study estimated the prediction of flavonoid intake on the baseline and the annual rate of change in Minin-Mental State Examination (MMSE) score. The mean MMSE score at baseline was 27.1 and increased as flavonoid intake increased. The same pattern was observed for the other cognitive tests. Flavonoid intake was significantly associated with better cognitive performance at baseline and subjects in the two highest quartiles had a significantly better evolution than did subjects in the first quartile [57]. The second study (3,777 community dwellers, free from dementia at baseline, aged 65 years or older) performed by Commenges., *et al.* [58] that used a statistical method to impute a quantity of flavonoid intake for each subject based on the questionnaires analyzed the relationship between this measurement and the risk of developing dementia in a 5-year follow-up of the cohort between 1991 and 1996. Data showed that 66 incident cases of dementia were observed in 1367 patients, and flavonoid consumption did actually decrease the risk of dementia [58].

Interestingly, a recent cross sectional study was conducted also to assess the relationship of flavonoid intake with measures of cognition in 49 participants aged 65 years and older with mild to moderate AD. The study assessed measures of mood, verbal learning and memory, working memory, semantic memory, executive function and short-term memory domains with flavonoids intake. The major source of flavonoid intake was black tea (80% contribution). Other sources included green tea, berries, red wine, apples and oranges. Total flavonoid intake was significantly correlated with verbal fluency task which evaluates the executive function domain, although other measures of executive function, trial making task and self-ordered pointing task, were not improved significantly. Verbal fluency was also significantly correlated with the flavonoid subclasses; flavonols, flavan-3-ols and anthocyanins. This may be related to the consumption of black and green tea (the major sources of flavonols and flavan-3-ols) and berries (a major source of anthocyanins). Also, no other significant associations for other cognitive domains were identified. There was also a positive correlation found between depressive symptoms and flavonoids intake as assessed by geriatric depressive scale. On other hand, no significant association between flavonoids intake and cognitive measures was shown after controlling for depression. The reduction in association between verbal fluency and flavonoid intake to non-significance level when depression was controlled suggested that this relationship was confounded by the effect of depression on executive functioning. The authors suggested that previous epidemiological studies that have reported associations between flavonoid intake and cognitive outcomes, without controlling for depression, may have overestimated the strength of this relationship [59].

In contrast, two other epidemiological studies found no association between flavonoid intake and developing AD. Engelhart., *et al.* [23] analyzed the data from the Rotterdam study which followed a total of 5395 participants, who were at least 55 years old for 6 years. The study examined the effect of several antioxidants, including flavonoids on the risk of developing AD. They found a non-significant decrease in the risk of Alzheimer's disease as flavonoid intake increased [22]. Another study by Kalmijn., *et al.* [60] used 342 men and analyzed data derived from a cohort of men, aged 69 - 89 years, who were participants in the Zutphen Elderly Study for the effect of flavonoid intake on the risk of cognitive decline. Subjects classified in the medium or highest intake tertile, showed a non-significant decrease in risk of cognitive decline defined as a drop of more than two points in the MMSE over a 3-year period. The non-significant reduction was probably due to the small number of subjects included and the short period of follow-up for this sample [60].

Cherry

We have found one study that evaluated the intake of biophenol-rich fruit in patient with AD. A 12-week, randomized, controlled trial of 49 patients with mild-to-moderate dementia AD type, aged 70 years or older where cognitive outcomes were assessed after consumption of 200 mL/day of either a cherry juice (containing 138 mg of anthocyanin) or a control juice with negligible anthocyanin content. Marked improvement was seen for category verbal fluency and tasks relating to verbal learning and memory including short term and long-term memory, as evidenced by RAVLT tasks. Other measures for semantic memory and working memory or executive functions were not significantly different between the groups. Inflammation markers such as C-reactive protein remained unaltered [61].

Summary and Future Recommendations

A summary of animal studies on AD-rats model using grape, berry and pomegranate is shown in table 4. A beneficial role of grape, berry and pomegranate on cognitive and behavioral parameters in AD was observed. Most of studies targeted levels of Aβ isoforms and its disposition in the brain, modified APP processing, with the resultant decrease in the density of neuritic plaques which suggested an anti-amyloidogenic effect of the supplementation. Additionally, grape intake interfered with the assembly of tau peptides into NFTs. In fact, targeting Aβ and tau proteins showed promising results in the efforts to modify the pathological effects associated with AD. A systematic review of several trials targeted Aβ and tau proteins provided an evidence of reducing pathological outcomes during certain drugs therapy in animal models of AD that was mostly shown as an improvement in cognition [62]. Another proposed mechanism for PPE was an enhanced expression of BNDF, and presumably, the depletion of BDNF increases the progression of dementia related to AD. Thus, an increase in BDNF expression might be a potential target for the treatment of neurodegenerative diseases [63]. Interestingly, pomegranate produced an anti-inflammatory effect that was indicated by changes in inflammatory cytokines levels in blood and brain of transgenic mice and attenuation of microgliosis. Inflammation can also play an important role in AD pathophysiology as evidenced by a meta-analysis conducted by Swardfager., et al. [64] which concluded that AD cases seem to be accompanied by an inflammatory response and higher peripheral concentrations of cytokines [64]. Thus, the use of biophenol-rich fruit supplementation may have a beneficial role in AD pathogenesis.

Fruit	Study design	No. of rats / duration of study	Outcomes	Reference
Grape	Placebo-controlled study of commercially available GSPE	Transgenic mouse model with Aβ accumulation (Tg2576) 5 Months	**Memory:** ↑ Morris water maze (spatial memory) ↑ Decline in oligomerization of Aβ peptides into HMW Aβ species	[45]
	Randomized, Placebo-controlled study of GSE	APPS/PS1 transgenic mice 9 Months	↑ Aβ level reduction in the brain and serum ↑ Reduction of microglia activation ↔IL-1β and TNF-α IFN-γ	[46]
	Placebo-controlled study of GSPE	TMHT mutant tau mice 2 months	↑ Reduction in the content of insoluble tau in the brain of mice ↑ Reduction in ERK 1/2 activity (protein kinases involved in tau hyperphosphorylations)	[47]
Berry	Placebo-controlled study of bilberry or blackcurrant extract	APP/SP1 transgenic mice 9.5 months for behavioral measures and 10.5 months for other measures	**Bilberry** **Memory:** ↑ Morris swim task (Spatial memory) ↔the search bias in the probe test (spatial long-term memory) **Executive function/Working memory:** ↑ Delayed alternation task (spatial working memory)* ↑ lower APP C-terminal fragment ↔ Phosphorylation status of tau **Blackcurrant** **Memory:** ↑ Morris water task (spatial memory) ↓ Search bias in the probe test (spatial long-term memory ↔ phosphorylation status of tau	[48]

Pomegranate	Placebo-controlled study of diet containing 4% pomegranate	AD mouse model possessing double Swedish APP mutation 15 Months	**Memory and Learning:** ↑ Morris water maze (spatial memory) ↑ T maze (learning ability) Motor function: ↑ Rotarod test (Motor coordination) **Anxiety:** ↑ Elevated plus-maze test	[49]
	Placebo-controlled study of PE	Aged transgenic AD animal model 3 Weeks	**Memory:** ↑ Morris water maze (spatial long-term) Working memory: ↑ Y-maze ↑ Levels and ratio of the Aβ42 and Aβ40 peptides	[50]
	Placebo-controlled trial of pomegranates, figs and dates	Transgenic rats (APPsw/Tg2576) 15 months	↑ Reduction on plasma cytokines levels; IL-2, IL-3, IL-4, IL-5, IL-9, IL-10 ↑ Reduction on IL-1β, IL-6 and TNF- α decreased in cortex and hippocampus ↑ Reduction of levels of Aβ40 in the cortex and hippocampus	[51]
	Placebo-controlled trial of PPE	Mice chronically infused for 35 days with Aβ42	**Memory:** ↑ Barnes maze (Spatial memory) ↑ Reduction in the number of senile plaque ↑ Reduction in the activity of the acetylcholinesterase (AChE) enzyme in the cortex and hippocampus ↑ Reduction in the level of TNF-α ↑ Increased BDNF levels	[52]
	Placebo-controlled trial of PPE	APP/PS1 transgenic mice 1 or 3 Months of treatment	**Memory:** ↑ Barnes maze (Spatial memory) **Working memory:** ↑ T- Maze (spontaneous alternations ↑ Decreased NFAT activity in both the hippocampus and spleen ↑ Decreased in concentrations of TNF-α, both in the hippocampus and spleen ↑ Decreased microgliosis ↔ Astrogliosis ↑ Decreased Aβ plaque deposition	[53]

Table 4: *Summary of animal studies investigating the effects of grape, berry and pomegranate on AD.*

**: Marginally significant.*

↑: Significant improvement, ↔: No significant difference.

The association between flavonoids intake and AD risk and cognition in AD patients along with cherry effect on cognition in AD patients is summarized in table 5. As preventive supplements, most of studies conducted to evaluate the relationship of flavonoid with AD risk, found a positive correlation between flavonoid consumption and AD risk reduction. However, these studies didn't specify the benefits to a particular flavonoid subclass and we can suggest that further research exploring the effects of particular class of flavonoids such as anthocyanins on AD prevention should be performed. As therapeutic and/or adjunctive role of biophenol-rich fruit on cognitive deficit seen in AD, one cross section study of flavonoids intake and one randomized trial of cherry juice intake in patients with mild-to moderate Alzheimer's type showed a positive effect on verbal fluency and memory. However, the cherry study utilized a small dose of anthocyanins compared to other studies which examined anthocyanins-rich fruit effect on cognition. We definitely recommend RCT's of berries with varying doses to be performed that may also include further cognition measures. Also, the cross sectional study utilized a small sample

Polyphenol	Study design/ Duration of study	Patients number and Characteristics	Dose	Outcomes	Reference
Flavonoids *	Cohort prospective study 10 years	1,640 subjects aged 65 years or older, free from dementia at baseline	NA	↑ MMSE score at baseline ↑ MMSE score rate of change	[57]
	Cohort prospective study 5 years	1367 subjects aged 65 years or order, free from dementia at baseline	NA	↑ Relative risk (RR) of dementia	[58]
	Cross sectional study**	Community dwelling older adults (65+yrs) with mild to moderate Alzheimer's type dementia	NA	**Memory** ↔ Rey Auditory Verbal Learning Test (Verbal memory) ↔ The Boston Naming Task (Semantic memory) **Executive function/ working memory:** ↑ The Verbal Fluency Task ↔Trail Making Task ↔ Self Ordered Pointing Task **Memory and executive function** ↔Digit Span Backwards Task (Short-term memory storage and executive control) **Mood** ↑ The Geriatric Depression scale	[59]
	Cohort prospective study 6 years	5395 participants, aged 55 years or more, free of dementia at baseline	NA	↑ Relative risk (RR) of dementia for vitamin C and vitamin E ↔ RR for dementia for flavonoid	[60]
	Cohort prospective study 3 years	342 men, aged 69-89 years	NA	↔ MMSE score rate of change	[61]
Cherry	Randomized, placebo-controlled study of cherry juice 12 weeks	Older adults (+70 year) with mild-to moderate Alzheimer's type (n = 49)	138 mg antho cyanins/ 200 g cherry juice	**Memory**: ↑ RAVLT total (Verbal learning and memory) ↑ RAVLT delayed recall ↔ Boston naming test (Sematic memory) ↔Digit span backwards task (short-term memory) **Executive function/working memory:** ↔ Self-ordered pointing task ↔ Trail making task ↔ Category verbal fluency ↑ Letter verbal fluency ↔ Serum vitamin C, IL-6 or CRP	[62]

Table 5: *Summary of human studies of the association of flavonoids and AD risk and cognition in AD patients along with the effect of cherry on cognition in AD patients.*

↑: Significant improvement, ↔: Non-significant effect.

**: Flavonoid in general has been studies with no referral to specific subclass.*

***: Duration is not applicable and after controlling for depression no significant relationship between flavonoid and any cognitive measure was observed.*

NA: Not Available.

size and thus the identified association between cognitive function, depression and flavonoid needs to be confirmed by a larger sample size. To our knowledge, no RCT's were conducted to evaluate the effect of grape, pomegranate or other berry fruits such as blueberry and blackcurrant on cognitive deficit seen in AD. Performing these RCT's would provide an additional evidence to support the use of biophenol-rich fruit supplementation as adjunctive therapy for patients with AD cognitive deficits. In addition, it is worth mentioning that dietary microbiome intervention has the potential to improve physical and emotional wellbeing in the general population, and in particular, as a treatment option for individuals with conditions as diverse as IBS, anxiety, depression and Alzheimer's disease [65].

Effect of biophenol-rich fruits on cognitive deficit induced by cerebral ischemia

Memory deficits could also be seen in cerebral hypoperfusion or in diffuse ischemic state. Animal and human studies have been conducted to investigate the relationship between biophenols-rich fruits and cognitive deficit induced by cerebral ischemia. Unfortunately, human studies only focused on the effect of biophenols on postoperative cognitive dysfunction (POCD) without investigating other cerebral ischaemic insults causes. Reactive oxygen species generation is regarded as one of the most important factors related to neuronal death in ischemic related areas [66-68].

Animal studies

Grape

The effect of chronic oral administration of GSE on passive avoidance memory deficit and hippocampus gyrus (DG) long-term potentiating (LTP) inhibition induced by permanent bilateral common carotid arteries occlusion (2CCAO) used as an animal model of cerebral ischemia/hypoperfusion was examined by Sarkaki., et al [69]. The study showed that oral administration of GSE for 28 days could ameliorate the passive avoidance memory deficit induced by 2CCAO manifested in longer step-down latency. Moreover, GSE increased percentage of amplitude, slope, and area under curve of LTP recorded from hippocampal DG after High-frequency stimulation (HFS) compared to placebo group [69].

Pomegranate

The effect of pomegranate on memory deficits due to cerebral hypoperfusion has been studied in male adult rats. Hajipour., et al. [70] examined the effect of two weeks oral administration of pomegranate Seed Extract (PGSE) on active avoidance memory and motor coordination activities after permanent 2CCAO in rats. Those treated with PGSE showed significant improvement in impairment of memory and motor coordination. It was stated that PGSE exhibited therapeutic potential for memory and muscular coordination, most likely due to its antioxidative and free radical scavenging actions [70]. A second study by Sarkaki., *et al.* [71] aimed to evaluate the effects of PGSE on passive and active avoidance memories due to gonadal hormone deprivation in ovariectomized rats, with and without cerebral hypoperfusion after permanent 2CCAO has concluded that hormone deprivation, such as estrogen, can alter cognitive performance. Estrogen can exert positive mnemonic effects in the inhibitory avoidance task [72] and estrogen deficits in rats (ovariectomy) impaired memory [73]. This study showed that PGSE treatment has improved active and passive memories in those rats. Thus, it seemed that PGSE exhibits therapeutic potential of both active and passive avoidance memories, which is most likely related to its phytoestrogenic and antioxidative actions [71]. A third study conducted on adult female rats to evaluate the effect of two weeks oral administration of PGSE on active and passive avoidance memories after permanent 2CCAO to induce permanent cerebral ischemia found consistent results with the previous two studies [74].

Human studies

Proposed mechanisms for postoperative cognitive dysfunction (POCD) following heart surgery include general hypoperfusion of the brain (global ischemia) leading to critically low levels of oxygen and glucose throughout the brain. In addition, inhaled anesthetics have been shown to induce the formation of amyloid-beta, a potentially neurotoxic protein linked to Alzheimer's disease and acute cognitive deficits in the brain [75,76]. A pilot study was conducted by Ropacki., *et al*. [77] to investigate the effect of biophenols in pomegranate on POCD in 10 patients undergoing elective coronary artery bypass graft and/or valve surgery to examine such relationship. The patients were given either 2g of pomegranate extract/day or placebo one week before surgery to 6 weeks after surgery. The patients were also administered a battery of neuropsychological tests to assess memory function at 1 week before surgery (baseline), 2 and 6 weeks after surgery. The placebo group showed a significant deficit in post-surgery memory retention, while the pomegranate extract supplementation was shown to not only protected against postoperative cognitive dysfunction, but also actually had an improved memory retention performance for up to 6 weeks after surgery as compared to pre-surgery baseline performance. This study was the first to report that pomegranate extract improves POCD in humans and that it may provide long-lasting protection of heart surgery-induced memory retention deficits [77].

Summary and Future Recommendations

A summary of animal studies investigating the effect of grape and pomegranate on cognition deficit induced by cerebral ischemia is shown in table 6. Animal studies showed a significant enhancement of active and passive cognitive function measures. No animal studies so far were conducted to examine such benefits using berry and thus further trails would also be needed to confirm the benefits. In relation to the effect of biophenol-rich fruit on cognition impairment following surgery in humans, only a small, pilot trial was conducted using pomegranate extract to explore its effects. We highly recommend further RCT's with larger sample size to be conducted to support the notion if PE supplementation in pre and post operations settings could be beneficial. As far as we know, no RCT's have been conducted to examine the effects of grape and berry on memory impairment post operatively. We suggest RCT's to investigate grape and berry potential effect on POCD. It would also be quite important to notice that no human studies have been conducted to examine the relationship between biophenol-rich fruit supplementation and stroke induced memory dysfunction. We again recommend an RCT exploring the potential effect of grape, berry and pomegranate intake on cognitive function enhancement in stroke patients.

Fruit	Study design	Animal Characteristics/ duration of the study	Outcomes	Reference
Grape	Ranomized, placebo-controlled trail of GSE	Rats with 2CCAO 28 days	↑ Latency to step-down (passive avoidance memory) ↑ Increased hippocampal LTP(amplitude, slope, and area under curve)	[69]
Pomegranate	Placebo-controlled trail of PGSE	Rats with 2 CCAO 2 Weeks	**Memory:** ↑ Y-Maze/number of corrected conditioned responses (active avoidance memory)* **Motor function:** ↑ Rotarod (motor-coordination)	[70]
	Randomized, placebo-controlled trail of PGSE	Ovariectomised rats with and without 2 CCAO 2 weeks	**Memory:** ↑ Y-maze/ number of corrected conditioned responses (active avoidance memory)* ↑ Two--way shuttle box/step-through latency (passive avoidance memory)*	[70]
	Randomized, placebo-controlled trial of PGSE	Rats with 2CCAO	**Memory:** ↑ Y-maze/ number of corrected conditioned responses (active avoidance memory) ↑ Two--way shuttle box/step-through latency (passive avoidance memory)	[74]

Table 6: *Summary of animal studies of the effect of grape and pomegranate on cognition deficit induced by cerebral ischemia.*

Conclusion

It seems that the beneficial effects of biophenols-rich fruits on cognition of healthy subjects or cognitive deficits related to aging, MCI, AD and POCD present a safe and effective approach for memory domain improvement. It was also noticed that acute and chronic flavonoid-rich supplementations effect on cognition of healthy subjects is age, dose and subclass dependent, as we know that not all flavonoid subclasses have similar benefits on cognition. Anthocyanidins found in pomegranate, grape and berry provided such benefits. Other flavonoid subclasses investigated have shown differential effects; some (e.g. flavanones) were found to be beneficial for cognition of healthy subject. Flavanone is richest in orange juice, and studies with acute and chronic orange juice consumption indicated a marked enhancement of cognitive measures [78-80]. In contrast to the positive effect of anthocyanidins and flavanones on cognition, studies of flavonols (quercetin) and flavan-3-ols (epicatechin) rich in apple showed no observed effects on measures of attention and executive functions [81]. Also non-significant acute effects were reported for flavan-3-ol, epigallocatechin gallate (EGCG), rich in green tea on cognitive function measures [82].

Generally, the effect of grape, berry and pomegranate on cognitive deficits or decline could be examined for two main purposes - prevention and/or treatment. Due to the fact that there is no remedy for dementia so far, and we cannot predict when or if effective therapy will be developed, it would be important to consider the preventive role of biophenols-rich fruit on cognitive deficits associated with AD. Dementia has shown to have a long "pre-dementia phase", which could last for years preceding future potential AD. In this phase, patients have lower cognitive function associated with difficulties of performing instrumental activities [83]. It has been proposed that interventions initiated in individuals with pre-dementia conditions such as MCI might prevent further progression of cognitive decline, and MCI may represent the final point at which intervention can be effective [84]. Interventional studies with grape, berry and pomegranate for MCI cases showed an improvement in cognitive functions which suggests that supplementations could have a preventative role for AD if started at the MCI stage. However, these studies require larger sample size to substantiate the evidence. The treatment option of biophenol-rich fruit is scarcely studied and the conducted two studies (one RCT with cherry and one cross sectional study with flavonoids) in mild to moderate Alzheimer's type dementia, showed an enhancement of specific cognitive domains which would suggest an adjunctive role for such supplementation. A recent review exploring possible nutritional treatment of AD concluded that there is a relationship between nutrition (vitamins, curcumin and Mediterranean diet) and AD [85]. Clearly, further studies should be conducted to justify such use. An interesting aspect of grape, berry and pomegranate intake benefit was examined to study their use to improve cognitive deficit that may occur in patients with cerebral ischemia or following surgery. These studies were also limited in number and definitely further human studies should be conducted to provide clear description of the role of these fruits in cognitive deficits of those patients.

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Conflict of Interest

All authors confirm that the content of this review has no conflict of interests.

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