

# Cognition: the new frontier for nuts and berries<sup>1–3</sup>

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## ABSTRACT

The inclusion of nuts in the diet is associated with a decreased risk of coronary artery disease, hypertension, gallstones, diabetes, cancer, metabolic syndrome, and visceral obesity. Frequent consumption of berries seems to be associated with improved cardiovascular and cancer outcomes, improved immune function, and decreased recurrence of urinary tract infections; the consumption of nuts and berries is associated with reduction in oxidative damage, inflammation, vascular reactivity, and platelet aggregation, and improvement in immune functions. However, only recently have the effects of nut and berry consumption on the brain, different neural systems, and cognition been studied. There is growing evidence that the synergy and interaction of all of the nutrients and other bioactive components in nuts and berries can have a beneficial effect on the brain and cognition. Regular nut consumption, berry consumption, or both could possibly be used as an adjunctive therapeutic strategy in the treatment and prevention of several neurodegenerative diseases and age-related brain dysfunction. A number of animal and a growing number of human studies show that moderate-duration dietary supplementation with nuts, berry fruit, or both is capable of altering cognitive performance in humans, perhaps forestalling or reversing the effects of neurodegeneration in aging. *Am J Clin Nutr* 2014;100(suppl):347S–52S.

## INTRODUCTION

There are very few foods that have experienced such vindication and renaissance as tree nuts and berries. Twenty years ago they were overlooked, considered only as a snack or a seasonal delight, by nutrition experts and the general public. However, recently they have risen to prominence as superior healthy foods that can significantly benefit people's well-being. Studies conducted in animals and humans have shown that frequent (preferably daily) inclusion of nuts in the diet is associated with decreased risk of coronary artery disease, hypertension, gallstones, diabetes, cancer, metabolic syndrome, and visceral obesity; protection against aging; and improved semen quality (1–9). The frequent consumption of berries seems to be associated with improved cardiovascular and cancer outcomes, improved immune functions, and decreased recurrence of urinary tract infections (10). In addition, the consumption of nuts and berries seems to be beneficial with regard to oxidative damage, inflammation, vascular reactivity, platelet aggregation, and immune functions (11–15). Nevertheless, there is only a limited amount of research that is focused on the health benefits of nuts and berries on the human brain, different neural systems, and cognition.

The most commonly consumed tree nuts are almonds (*Prunus dulcis*), cashews (*Anacardium occidentale*), hazelnuts (*Corylus colurna*), macadamias (*Macadamia integrifolia* and *tetraphylla*),

pistachios (*Pistacia vera*), pecans (*Carya illinoensis*), and walnuts (*Juglans regia*). Peanuts (*Arachis hypogaea*), although botanically legumes, have a very similar nutrient profile to tree nuts; therefore, they are included in this review.

Nuts are energy-dense foods that are particularly rich in fat, mostly MUFAs and PUFAs. They also contain a substantial amount of plant protein (source of tryptophan, arginine, lysine), vitamins (folate, riboflavin, and  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\delta$ -tocopherols), minerals (calcium, phosphorus, magnesium, potassium, and sodium), trace elements (zinc, copper, and selenium), soluble fiber (raffinose and stachyose), and a number of other potentially neuroprotective compounds such as melatonin and numerous polyphenols (**Table 1**) (16).

The most commonly consumed berries are blackberries, black raspberries, blueberries, cranberries, red raspberries, and strawberries. Included in this review are also studies on grapes because of their similar nutrient profile to berries. Contrary to nuts, they are low in energy and high in moisture and soluble fiber. They contain natural antioxidants (ascorbic acid,  $\alpha$ - and  $\beta$ -carotene, lutein, zeaxanthin, and  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\delta$ -tocopherols), vitamins (niacin and folate), minerals/trace elements (potassium, calcium, and selenium), and polyphenols, particularly flavonoids (anthocyanin and ellagitannins) (**Table 2**) (16).

There are several pathologic bases for the decline in cognitive and motor performance associated with aging and neurodegenerative diseases. First, poor vascular health contributes to age-related decline in the brain and in cognition (17, 18). Second, oxidative stress and inflammation are at the center of age-related neuronal dysfunction and neurodegenerative diseases (19). Nutrients contained in nuts and berries seem to promote vascular health and mediate oxidative stress and inflammation and consequently have the potential to advance better cognitive health.

In this review, we summarized the recent knowledge on the expanding area of nuts and berries on cognition. The effects of nuts or berries directly on cognition, as well as related indirect

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**TABLE 1**  
Energy, fatty acid, phenolic, and sterol composition of an average portion of nuts<sup>1</sup>

Nut (28 g)	Energy	Fat	SFA	MUFA	PUFA	LA	ALA	TPs	PSs	Folate	Vitamin E
	<i>kcal</i>	<i>g</i>	<i>g</i>	<i>g</i>	<i>g</i>	<i>g</i>	<i>g</i>	<i>mg</i> GAE	<i>mg</i>	<i>μg</i> DFE	<i>mg</i>
Almonds	162	14.2	1.1	9.0	3.4	3.4	0.0	117	33.6	14	7.4
Cashews	154	13.0	2.6	7.6	2.2	2.2	0.0	76	44.2	7	0.3
Hazelnuts	176	17.0	1.3	12.8	2.2	2.2	0.0	82	26.2	32	4.3
Macadamias	201	21.2	3.4	16.5	0.4	0.4	0.1	45	32.5	3	0.2
Pecans	193	20.2	1.7	11.4	6.0	5.8	0.3	464	28.6	6	0.4
Pistachios	156	12.4	1.5	6.5	3.8	3.7	0.1	565	59.9	14	0.7
Walnuts	183	18.3	1.7	2.5	13.2	10.7	2.5	436	20.2	28	0.2
Peanuts	149	13.8	1.9	6.8	4.4	4.4	0.0	117	61.6	68	2.4

<sup>1</sup> Values presented are for raw nuts. Data are from reference 16. ALA,  $\alpha$ -linolenic acid; DFE, dietary folate equivalents; GAE, gallic acid equivalents; LA, linoleic acid; PS, plant sterol; TP, total phenol.

outcomes (presence or absence of substances influencing cognition and cognitive performance), will be addressed.

## COGNITION

Cognition is a group of mental processes that includes attention, producing and understanding language, learning, reasoning, problem solving, and decision making (20). Cognition can also be defined broadly by aggregated concepts such as intelligence, memory, or mood (affect). Most of the research on the relation between nutrition and cognitive function has been conducted by using animal or pathologic populations, with a limited number of human studies.

### Nuts and cognition

#### Animal and cell studies

The first landmark study to show the beneficial effect of tree nut consumption on cognitive abilities was published in 2008. The study reported the potential benefit of walnuts on cognitive behavior in aged rats (21). In this study, 19-mo-old Fischer (F344) rats were fed diets containing 0%, 2%, 6%, or 9% ground walnuts with skins for 8 wk. The animals were tested by using 5 age-sensitive tests of psychomotor behavior (rod walking, wire suspension, plank walking, inclined screen, and accelerating rotarod) and the Morris water maze (MWM)<sup>4</sup> for reference memory (acquisition trial) and working memory (retrieval trial). The 2% and 6% walnut-supplemented diets improved performance on motor tests that rely on balance, coordination, and strength, whereas the 9% walnut diet actually impaired performance. All of the walnut diets improved working memory in the MWM, although the 9% diet showed impaired reference memory. Whereas too many walnuts were disadvantageous, the most positive effect was reported at the 6% amount, which is in line with US Food and Drug Administration recommendations for nut consumption for humans (22). A 6% walnut diet is approximately equivalent to a human eating 28 g (1 oz) walnuts daily. The 6% amount of dietary supplementation with walnuts was determined on the basis of studies reporting a reduction in LDL cholesterol in human subjects who consumed walnuts (21).

<sup>4</sup> Abbreviations used: A $\beta$ , amyloid  $\beta$  protein; BDNF, brain-derived neurotrophic factor; MWM, Morris water maze; NF- $\kappa$ B, nuclear transcription factor  $\kappa$ B; PREDIMED, Prevención con Dieta Mediterránea.

The brains of aged rats fed walnuts were evaluated for polyubiquitinated proteins (23). An increase in the aggregation of misfolded/damaged polyubiquitinated proteins is the hallmark of many age-related neurodegenerative diseases. The accumulation of these potentially toxic proteins in the brain increases with age, in part the result of increased oxidative and inflammatory stresses. It was found that rats fed the 6% and 9% walnut diets showed significantly reduced aggregation of polyubiquitinated proteins and activation of autophagy, a neuronal housekeeping function in the striatum and hippocampus. Walnut-fed animals exhibited upregulation of autophagy through inhibiting phosphorylation of rapamycin (mTOR), upregulation of *ATG7* and *Beclin 1* genes, and turnover of microtubule-associated protein 1 light chain 3 (MAP1B-LC3) proteins. The clearance of polyubiquitinated protein aggregates such as sequestosome (p62/SQSTM1) was more profound in the hippocampus, a critical region in the brain involved in memory and cognitive performance (24).

In another recent study (25), rats were fed 80 mg of finely crushed walnuts for 28 d mixed with water (the equivalent human dose would be 27 g of walnuts for a 60-kg person). A significant improvement in learning and memory was observed as measured by elevated-plus and radial arm mazes. Walnuts are a rich source of tryptophan, which is the precursor for serotonin. Increases in brain serotonin concentrations may protect against depression and anxiety, as well as enhance memory functions. Walnuts also contain several other neuroprotective compounds such as vitamin E, folate, melatonin,  $\alpha$ -linolenic acid (18:3n-3) and numerous polyphenolic components. It seems that walnuts could be effective in slowing down age-related cognitive decline and enhance memory functions.

Almonds have been studied as possible supplemental therapy in cognitive dysfunctions such as dementia in Alzheimer disease (26). Male albino rats were fed 150, 300, or 600 mg almond paste/kg daily for 7–14 d. The dose amounts were selected by the conversion of conventional human doses into animal doses; the human dose of almonds would be 5 to 6 nuts daily (6 g). The almond-fed rats showed significant reversal of scopolamine-induced cognitive impairment as tested in the elevated-plus maze and in the passive shock-avoidance paradigm. The memory-improving activity of almonds may be attributed to their anticholinesterase, procholinergic, and cholesterol-reducing properties.

Three *in vitro* studies with walnuts extracts have shown that walnuts might counteract oxidative damage and cell death as observed in patients with Alzheimer disease. Fibrillar amyloid  $\beta$  protein (A $\beta$ ) is the principal component of amyloid plaques in



**TABLE 2**  
Nutrient and phytochemical composition of selected berries and grapes<sup>1</sup>

Fruit (100 g)	Energy	Fiber	Vitamin C	Vitamin E	Total flavonols <sup>2</sup>	Total anthocyanidins <sup>3</sup>
	<i>kcal</i>	<i>g</i>	<i>mg</i>	<i>mg</i>	<i>mg</i>	<i>mg</i>
Blackberries	43	5.3	21	1.2	2.5	90.5
Raspberries	52	6.5	26.2	0.9	1.3	38.7
Blueberries	57	2.4	9.7	0.6	9.7	163.5
Cranberries	46	4.6	13.3	1.2	20.8	133.0
Strawberries	32	2.0	58.5	0.3	1.6	33.6
Grapes	69	0.9	3.2	0.19	2.39	67.6

<sup>1</sup> Values presented are for raw fruit. Data are from reference 16.

<sup>2</sup> Total flavonols (kaempferol, myricetin, quercetin).

<sup>3</sup> Total anthocyanidins (cyanidin, delphinidin, peonidin, petunidin).

the brains of Alzheimer patients. After 2–3 d of incubation with 5 mL methanolic walnut extract, researchers observed the inhibition of the A $\beta$  formation and defibrillation of A $\beta$  preformed fibrils. It is not clear whether this antiamyloidogenic activity of walnuts is attributable to the antioxidative properties of their constituents such as flavonoids and ellagic acid or to their direct interaction with A $\beta$  (27). In another study, lyophilized powder of walnut extract dissolved in 7.4-pH Tris-HCL buffer solution reduced A $\beta$ -mediated cell death, DNA damage, and generation of reactive oxygen species in a concentration-dependent manner. This effect of walnut extract may be attributable to the active compounds present in walnuts, which increase the capacity of endogenous antioxidant defenses and modulate the cellular redox state (28). A recent study (29) assessed if pretreatment of primary hippocampal neurons with walnut extract or PUFAs would protect cells against dopamine- and LPS-mediated cell death and calcium dysregulation. Results indicated that walnut extract,  $\alpha$ -linolenic acid, and DHA provided substantial protection against cell death and calcium dysregulation. It seems that walnut extract may protect against age-related cellular dysfunction. The direct applicability of in vitro studies might be limited, but they do suggest that diets rich in walnuts could possibly reduce A $\beta$ -mediated toxicity, cell death, formation of plaques, and age-related dysfunction.

#### Human studies

Nuts are a traditional component of the Mediterranean diet. Two recent publications (30, 31) from the Prevención con Dieta Mediterránea (PREDIMED) study found that nut consumption could help individuals with depression and counteract age-related cognitive decline. PREDIMED is a large parallel-group, multicenter, randomized controlled clinical trial designed to ascertain the effects of a Mediterranean diet on primary prevention of cardiovascular disease. Participants in the study were randomly assigned to 3 intervention arms: a Mediterranean diet supplemented with virgin olive oil (1 L/wk), a Mediterranean diet supplemented with 30 g of mixed nuts/d (15 g walnuts, 7.5 g almonds, 7.5 g hazelnuts), or a low-fat control diet (32). The study started in 2003 and was completed in 2011, with an average follow-up of 5 y.

Three years into the clinical trial, researchers were able to show that adherence to a Mediterranean dietary pattern supplemented with nuts seemed to improve plasma brain-derived neurotrophic factor (BDNF) concentrations, specifically among

patients with depression (30). BDNF is related to such actions as synaptic plasticity, neuronal survival and differentiation, axonal elongation, and neurotransmitter release (33). Low concentrations have been associated with neurodegenerative disorders such as epilepsy, Alzheimer disease, Huntington disease, autism, schizophrenia, and major depression, whereas higher concentrations are associated with the prevention of memory loss and cognitive impairment (34, 35).

PREDIMED participants from the Barcelona sample underwent neuropsychological testing to assess their cognitive function (31). Researchers found that dietary habits associated with higher intakes of both total olive oil and virgin olive oil, coffee, walnuts, and wine were associated with better memory function and global cognition. Walnut, but not other nut, consumption was specifically associated with better working memory scores. The common characteristic of all of these foods that are associated with improved cognition is their high polyphenol content.

In the latest PREDIMED report (18) the relative risk of stroke was significantly reduced by 46% by the Mediterranean diet supplemented with nuts. These findings are of great significance because stroke is at the center of the vascular mediation of cognitive deterioration associated with aging.

A recent study was designed to investigate the effect of dietary walnut supplementation on cognitive performance in young adults (36). In a double-blind, randomized, placebo-controlled crossover design, students were assigned to consume banana bread for 8 wk with or without 60 g walnuts, with a 6-wk washout period in between. Data were collected for nonverbal and verbal reasoning, memory, and mood. In this short-term supplementation study, there was no effect on memory, mood, or nonverbal reasoning; however, a significant increase in inferential verbal reasoning was observed. Small improvements attributable to walnut consumption in healthy, cognitively intact young adults could translate into important outcomes in aging populations (24).

As was recently reported in the Doetinchem Cohort Study (37), higher intakes of nuts were associated with significantly elevated cognitive functions (memory, speed, cognitive flexibility, and global cognitive function) at baseline. The difference in cognitive functions between the lowest and the highest quintile of nut consumption was equivalent to a 5- to 8-y difference in age. However, there was no significant change observed in cognitive function at the second testing after 5 y.

All of these studies provide substantial support for the hypothesis that the synergy and interaction of all of the nutrients and

other bioactive components in nuts might have a beneficial effect on the brain and cognition. Regular nut consumption may be used as an adjunctive therapeutic strategy in the treatment of several neurodegenerative diseases as well as in the treatment of age-related brain dysfunction.

## Berries and cognition

### Animal studies

The first study to show the beneficial effect of berry consumption on cognitive abilities was published in 1999, almost a decade earlier than the first nut study (38). In this study, aged 19-month-old F344 male inbred albino rats whose diet contained 1.86% lyophilized blueberry or 1.48% lyophilized strawberry (matched according to antioxidant activity) showed improved performance in a working memory version of the MWM relative to rats fed a control diet (AIN-93, a casein-based purified diet; American Institute of Nutrition). In addition, blueberry-fed animals showed enhanced balance on the rod-walking and rotarod tests relative to controls. A subsequent study found that the beneficial effects of 2% blueberry supplementation were also discernible in an already well-balanced diet (a modified NIH-31 diet, a natural ingredient, cereal-based diet) because balance, coordination, working, and reference memory were still protected (39).

Anthocyanin compounds in blueberries were found to cross the blood-brain barrier and enter the brain (40). In fact, the amount of total anthocyanins found in the cortex and hippocampus correlated significantly with MWM behavior, in that rats with higher cortical anthocyanin concentrations had shorter latencies on reversal learning and rats with higher hippocampal anthocyanin concentrations exhibited enhanced spatial learning on the probe trial, indicated by increased crossings of the previous location of the platform. These findings show that, once consumed, dietary polyphenols from blueberries are both neuroavailable and localize in various brain regions that are important for learning and memory.

Novel object testing is also improved by blueberry supplementation (41). In a study designed to test possible mechanisms for the beneficial effects of blueberry supplementation in aged organisms, F344 rats explored 2 identical objects placed within an arena. After a 30-s or a 60-min delay, the animals were returned to the arena in which there was one familiar and one novel object. Rodents that remember the familiar object will explore a novel object more than they will a familiar one. In the 60-min delay condition only, aged (19-month-old) 2% blueberry-fed (for 4 mo) animals spent more time with the novel object, compared with age-matched controls, which was not different from young (4-month-old) rats, indicating improved memory. Furthermore, aged rats fed the control diet showed significantly higher nuclear transcription factor  $\kappa$ B (NF- $\kappa$ B) concentrations than did young rats in all brain regions; however, aged blueberry-fed rats showed attenuated NF- $\kappa$ B concentrations in the frontal cortex, hippocampus, striatum, and cerebellum, which were similar to those of the young rats. In addition, a significant negative correlation was found among the aged rats between the percentage of time spent investigating the novel object and the amount of NF- $\kappa$ B proteins, averaged across the brain regions. This study suggests that blueberry supplementation attenuates age-related object recognition memory impairment through reduction in aging-induced oxidative stress and inflammation, as measured by NF- $\kappa$ B concentrations in the brain.

The time course of dietary blueberry's effects was investigated in another study in this laboratory (42). In aging F344 rats, age-related object memory decline was reversed and prevented by maintenance for 1 mo on a 2% blueberry-enriched diet. However, feeding rats a blueberry-enriched diet for 2 mo resulted in a more prolonged benefit after diet termination in that they showed no decline in performance after 2 or 4 wk with the control diet. Conversely, rats that were only fed the blueberry diet for 1 mo showed a decline in performance after 2 wk and were not significantly different from the age-matched controls after 4 wk with the control diet. An additional experiment showed that 19-month-old rats with age-related memory declines in object memory performance that were subsequently placed on a blueberry diet for 1 mo had significant improvements in object memory recognition; no improvements were seen in the control group. These findings show that deficits in cognition are reversed in aged rats with as little as 1 mo of dietary supplementation with blueberry; however, at least 2 mo of supplementation are required to maintain the benefit long term.

Supplementation with a 2% blueberry diet (2% wt:wt) for 12 wk improved, within 3 wk, the performance of aged outbred hooded Lister rats in a spatial working memory task by decreasing errors and latencies in a modified food-motivated plus maze (43). In addition, possible mechanisms for these beneficial effects were examined when memory performance correlated with the activation of cAMP-response element-binding protein (CREB) and increases in both precursor and mature concentrations of BDNF in the hippocampus, which were accompanied by increases in the phosphorylation state of extracellular signal-related kinase (ERK). These results suggest that blueberry supplementation may invoke changes in spatial working memory in aged animals that are linked to the ERK-CREB-BDNF pathway.

To study the genoprotective effects of blueberries, cognitive performance was investigated in mice by using step-down inhibitory avoidance, open-field habituation, and elevated plus-maze tasks (44). Feeding blueberry extract containing either a low ( $0.6\text{--}1\text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ ) or a high ( $2.6\text{--}3.2\text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ ) concentration of anthocyanin significantly enhanced long-term memory in the inhibitory avoidance task, induced an increase in the number of crossings during open-field habituation, and had an anxiolytic effect in the elevated plus-maze task. Moreover, the extract reduced oxidative DNA damage in brain tissue *in vitro*, possibly a result of the antioxidant activity of the blueberry polyphenols.

Other berry fruit has also shown age-related improvements in brain and behavioral function, including blackberries. After 2 mo, aged (19-month-old) F344 rats whose diet contained 2% blackberry showed improved motor performance on 3 tasks that rely on balance and coordination (the accelerating rotarod, wire suspension, and the small plank walk) and greater working, or short-term, memory performance in the MWM relative to aged matched rats fed a control diet (45).

In another study (46), aged F344 rats were fed a control diet or diets containing either 2% blueberry, 2% cranberry, 2% blackcurrant, or 2% boysenberry for 2 mo. The blackcurrant and cranberry diets enhanced neuronal signal transduction as measured by striatal dopamine release, whereas the blueberry and cranberry diets were effective in ameliorating deficits in inclined screen performance, suggesting increased muscle tone and control, and hippocampal heat shock protein 70 neuroprotection; the changes in heat shock protein 70 were positively correlated





with performance on the inclined screen, suggesting another possible mechanism of action for berry fruit.

In another study, aged F344 rats (19-mo-old) were fed 10% or 50% Concord grape juice (identical to juice that humans consume) or an isocaloric placebo for a period of 2 mo (47). Rats that drank the 10% grape juice had improvements in oxotremorine enhancement of K<sup>+</sup>-evoked release of dopamine from striatal slices and in cognitive performance on the MWM. Rats that consumed the 50% grape juice exhibited improvements in motor function, specifically enhanced balance on the rod and plank walking tasks, as well as increased forelimb strength on a wire suspension task relative to rats that consumed placebo.

In a model of vascular dementia, orally administered mulberry fruit extract (2, 10, and 50 mg/kg) was studied for its protective effects and possible mechanisms of action on memory impairment and brain damage (48). Rats fed mulberry (particularly the 10-mg/kg dose) before and after the occlusion of the right middle cerebral artery showed enhanced memory, decreased oxidative stress, increased densities of neurons and cholinergic neurons in the hippocampus, and enhanced densities of Bcl-2-immunopositive neurons together with the suppression of acetylcholinesterase in the hippocampus. The authors attributed the neuroprotective effect of mulberry to increased cholinergic function via decreased oxidative stress and apoptosis.

In the past 10 y, studies have examined the possible mechanisms of action behind the neuronal and behavioral improvements with berries, such as anti-inflammatory activities or changes in neuronal signaling capability. These studies were reviewed in the *Journal of Agriculture and Food Chemistry* in 2008 (49) and recently updated in the same journal (50). Briefly, the possible mechanisms include the following: direct effects on signaling to enhance neuronal communication, the ability to buffer against excess calcium, increased neurogenesis, alterations in neuronal morphology, enhancement of neuroprotective stress shock proteins, alteration of inflammatory gene expression and protection against neurodegeneration after excitotoxic stress, and reduction in stress signals such as NF- $\kappa$ B (47, 48).

#### Human studies

Recent clinical trials have extended these effects on cognition to humans. Daily supplementation of between 6 and 9 mL blueberry juice/kg for 12 wk among older individuals with mild cognitive impairment ( $n = 9$ ) improved cognitive function, particularly with respect to improved paired-associate learning, word list recall, and reduced depressive symptoms (51). To explore the effect of grape juice on cognition, participants with early memory decline consumed either Concord grape juice (6–9 mL/kg;  $n = 5$ ) or an isocaloric placebo ( $n = 7$ ) in addition to their normal diet for 3 mo (52). Grape juice intake significantly improved the acquisition of word lists on the California Verbal Learning Test II and showed trends toward improvements in delayed verbal recall and spatial memory, as measured by the spatial paired-associate test, relative to participants who consumed the placebo beverage. These studies show that moderate-duration dietary supplementation with berry fruit is capable of altering cognitive performance in humans, perhaps forestalling or reversing the effects of neurodegeneration in aging.

Furthermore, a recent epidemiologic study from the Nurse's Health Study showed that greater intakes of blueberries and

strawberries were associated with slower rates of cognitive decline in an analytic sample consisting of 16,010 women >70 y of age, as were greater intakes of anthocyanidins and total flavonoids (53). The authors concluded that berry intake delayed cognitive aging by up to 2.5 y.

#### CONCLUSIONS AND FUTURE RESEARCH

In the past 20 y, nutritional neuroscience has emerged as a recognized discipline with the potential to make significant contributions to our understating of the relation between nutrition and cognitive functions (54). Animal studies indicate that different neural systems and cognition can be affected by short- and long-term supplementation with nuts, berries, or both. The evidence from human trials, although limited, suggests potential positive effects, particularly among older patients, on memory function, global cognition, and depression.

Future research should focus on epidemiologic and short- and long-term clinical studies because the evidence from human studies is limited and equivocal. Short-term clinical trials could focus on cognitive disorders such as depression, seasonal disorder, and attention-deficit hyperactivity disorder, whereas long-term trials could focus on prevention and treatment of neurodegenerative diseases and age-related brain dysfunction. In conclusion, there is growing evidence that the inclusion of nuts and berries in the diet can provide a significant beneficial effect on the brain and cognition.

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#### REFERENCES

1. Ros E. Health benefits of nut consumption. *Nutrients* 2010;2:652–82.
2. Sabaté J, Salas-Salvadó J, Ros E, eds. Nuts: nutrition and health outcomes. *Br J Nutr* 2006;96:S1–2.
3. Ros E, Tapsell LC, Sabaté J. Nuts and berries for heart health. *Curr Atheroscler Rep* 2010;12:397–406.
4. Estruch R, Ros E, Salas-Salvadó J, Covas M, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutierrez V, Fiol M, Lapetra J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013;368:1279–90.
5. Pan A, Sun Q, Manson JE, Willett WC, Hu FB. Walnut consumption is associated with lower risk of type 2 diabetes in women. *J Nutr* 2013;143:512–8.
6. Davis PA, Vasu VT, Gohil K, Kim H, Khan IH, Cross CE, Yokoyama W. A high-fat diet containing whole walnuts (*Juglans regia*) reduces tumour size and growth along with plasma insulin-like growth factor 1 in the transgenic adenocarcinoma of the mouse prostate model. *Br J Nutr* 2012;108:1764–72.
7. Hardman WE, Ion G, Akinsete JA, Witte TR. Dietary walnut suppressed mammary gland tumorigenesis in the C(3)1 TAG mouse. *Nutr Cancer* 2011;63:960–70.
8. Parker ED, Harnack LJ, Folsom AR. Nut consumption and risk of type 2 diabetes. *JAMA* 2003;290:38–9.
9. Robbins WA, Lin X, FitzGerald LZ, Esquerra S, Henning SM, Carpenter CL. Walnuts improve semen quality in men consuming a Western-style diet: randomized control dietary intervention trial. *Biol Reprod* 2012;87:101.
10. Beattie J, Crozier A, Duthie GG. Potential health benefits of berries. *Curr Nutr Food Sci* 2005;1:71–86.
11. López-Urriarte P, Bulló M, Casas-Agustench P, Babio N, Salas-Salvadó J. Nuts and oxidation, a systematic review. *Nutr Rev* 2009;67:497–508.
12. Cortés B, Núñez I, Cofán M, Gilbert R, Pérez-Heras A, Casals E, Deulofeu R, Ros E. Acute effects of high-fat meals enriched with

- walnuts or olive oil on postprandial endothelial function in healthy subjects and patients with hypercholesterolemia. *J Am Coll Cardiol* 2006;48:1666–71.
13. Ros E, Núñez I, Pérez-Heras A, Serra M, Gilibert R, Casals E, Deulofeu R. A walnut diet improves endothelial function in hypercholesterolemic subjects. *Circulation* 2004;109:1609–14.
  14. López-Uriarte P, Nogués R, Saez G, Bulló M, Romeu M, Masana L, Tormos C, Casas-Agustench P, Salas-Salvadó J. Effect of nut consumption on oxidative stress and the endothelial function in metabolic syndrome. *Clin Nutr* 2010;29:373–80.
  15. Basu A, Rhone M, Lyons TJ. Berries: emerging impact on cardiovascular health. *Nutr Rev* 2010;68:168–77.
  16. USDA. Nutrient database. Available from: <http://ndb.nal.usda.gov/ndb> (cited 22 April 2013).
  17. Raz N, Rodrigue KM, Kennedy KM, Acker JD. Vascular health and longitudinal changes in brain and cognition in middle-aged and older adults. *Neuropsychology* 2007;21:149–57.
  18. Breteler MM. Vascular involvement in cognitive decline and dementia. Epidemiologic evidence from the Rotterdam Study and the Rotterdam Scan Study. *Ann N Y Acad Sci* 2000;903:457–65.
  19. Leyse-Wallace R. Nutrition and mental health. Hoboken, NJ: Taylor and Francis, 2013. Available from: <http://www.eblib.com> (cited 14 October 2013).
  20. Sattler JM. Assessment of children: cognitive applications. 5th ed. San Diego, CA: Jerome M Sattler Publishers, 2008.
  21. Willis LM, Shukitt-Hale B, Cheng V, Joseph JA. Dose-dependent effects of walnuts on motor and cognitive function in aged rats. *Br J Nutr* 2009;101:1140–4.
  22. USDA; US Department of Health and Human Services. Dietary guidelines for Americans 2010. Available from: <http://www.dietaryguidelines.gov> (cited 24 April 2013).
  23. Poulouse SM, Bielinski DF, Shukitt-Hale B. Walnut diet reduces accumulation of polyubiquitinated proteins and inflammation in the brain of aged rats. *J Nutr Biochem* 2013;24:912–9.
  24. Carey AN, Poulouse SM, Shukitt-Hale B. The beneficial effect of tree nuts on aging brain. *Nutr Aging* 2012;1:55–67.
  25. Haider S, Batool Z, Tabassum S, Perveen T, Saleem S, Naqvi F, Javed H, Haleem DJ. Effects of walnuts (*Juglans regia*) on learning and memory functions. *Plant Foods Hum Nutr* 2011;66:335–40.
  26. Kulkarni KS, Kasture SB, Mengi SA. Efficacy study of *Prunus amygdalus* (almond) nuts in scopolamine-induced amnesia in rats. *Indian J Pharmacol* 2010;42:168–73.
  27. Chauhan N, Wang KC, Wegiel J, Malik MN. Walnut extract inhibits the fibrillization of amyloid beta-protein, and also defibrillizes its preformed fibrils. *Curr Alzheimer Res* 2004;1:183–8.
  28. Muthaiyah B, Essa MM, Chauhan V, Chauhan A. Protective effects of walnut extract against amyloid beta peptide-induced cell death and oxidative stress in PC12 cells. *Neurochem Res* 2011;36:2096–103.
  29. Carey AN, Fisher DR, Joseph JA, Shukitt-Hale B. The ability of walnut extract and fatty acids to protect against the deleterious effects of oxidative stress and inflammation in hippocampal cells. *Nutr Neurosci* 2013;16:13–20.
  30. Sánchez-Villegas A, Galbete C, Martínez-González MA, Martínez JA, Razquin C, Salas-Salvadó J, Estruch R, Buil-Cosiales P, Martí A. The effect of the Mediterranean diet on plasma brain-derived neurotrophic factor (BDNF) levels: the PREDIMED-NAVARRA randomized trial. *Nutr Neurosci* 2011;14:195–201.
  31. Valls-Pedret C, Lamuela-Raventós RM, Medina-Remón A, Quintana M, Corella D, Pintó X, Martínez-González MA, Estruch R, Ros E. Polyphenol-rich foods in the Mediterranean diet are associated with better cognitive function in elderly subjects at high cardiovascular risk. *J Alzheimers Dis* 2012;29:773–82.
  32. Estruch R, Martínez-González MA, Corella D, Salas-Salvadó J, Ruiz-Gutiérrez V, Covas MI, Fiol M, Gomez-Gracia E, Lopez-Sabater MC, Vinyoles E, et al. Effects of a Mediterranean style diet on cardiovascular risk factors: a randomized trial. *Ann Intern Med* 2006;145:1–11.
  33. Karege F, Schwald M, Cisse M. Postnatal developmental profile of brain-derived neurotrophic factor in rat brain and platelets. *Neurosci Lett* 2002;328:261–4.
  34. Hashimoto K, Iwata Y, Nakamura K, Tsujii M, Tsuchiya KJ, Sekine Y, Suzuki K, Minabe Y, Takei N, Lyo M, et al. Reduced serum levels of brain-derived neurotrophic factor in adult male patients with autism. *Prog Neuropsychopharmacol Biol Psychiatry* 2006;30:1529–31.
  35. Huang TL. Effects of antipsychotics on the BDNF in schizophrenia. *Curr Med Chem* 2013;20:345–50.
  36. Pribis P, Bailey RN, Russell AA, Kilsby MA, Hernandez M, Craig WJ, Grajales T, Shavlik DJ, Sabatè J. Effects of walnut consumption on cognitive performance in young adults. *Br J Nutr* 2012;107:1393–401.
  37. Nooyens AC, Bueno-de-Mesquita HB, van Boxtel MP, van Gelder BM, Verhagen H, Verschuren WM. Fruit and vegetable intake and cognitive decline in middle-aged men and women: the Doetinchem Cohort Study. *Br J Nutr* 2011;106:752–61.
  38. Joseph JA, Shukitt-Hale B, Denisova NA, Bielinski D, Martin A, McEwen JJ, Bickford PC. Reversals of age-related declines in neuronal signal transduction, cognitive, and motor behavioral deficits with blueberry, spinach, or strawberry dietary supplementation. *J Neurosci* 1999;19:8114–21.
  39. Youdim KA, Shukitt-Hale B, Martin A, Wang H, Denisova N, Bickford PC, Joseph JA. Short-term dietary supplementation of blueberry polyphenolics: Beneficial effects on aging brain performance and peripheral tissue function. *Nutr Neurosci* 2000;3:383–97.
  40. Andres-Lacueva C, Shukitt-Hale B, Galli RL, Jauregui O, Lamuela-Raventós RM, Joseph JA. Anthocyanins in aged blueberry-fed rats are found centrally and may enhance memory. *Nutr Neurosci* 2005;8:111–20.
  41. Goyarzu P, Malin DH, Lau FC, Tagliamonte G, Moon WD, Jennings R, Moy E, Moy D, Lippold S, Shukitt-Hale B, et al. Blueberry supplemented diet: Effects on object recognition memory and nuclear factor-kappa B levels in aged rats. *Nutr Neurosci* 2004;7:75–83.
  42. Malin DH, Lee DR, Goyarzu P, Chang YH, Ennis LJ, Beckett E, Shukitt-Hale B, Joseph JA. Short-term blueberry-enriched diet prevents and reverses object recognition memory loss in aging rats. *Nutrition* 2011;27:338–42.
  43. Williams CM, El Mohsen MA, Vauzour D, Rendeiro C, Butler LT, Ellis JA, Whiteman M, Spencer JP. Blueberry-induced changes in spatial working memory correlate with changes in hippocampal CREB phosphorylation and brain-derived neurotrophic factor (BDNF) levels. *Free Radic Biol Med* 2008;45:295–305.
  44. Barros D, Amaral OB, Izquierdo I, Geracitano L, do Carmo Bassols Raseira M, Henriques AT, Ramirez MR. Behavioral and genoprotective effects of vaccinium berries intake in mice. *Pharmacol Biochem Behav* 2006;84:229–34.
  45. Shukitt-Hale B, Cheng V, Joseph JA. Effects of blackberries on motor and cognitive function in aged rats. *Nutr Neurosci* 2009;12:135–40.
  46. Shukitt-Hale B, Galli R, Meterko V, Carey A, Bielinski D, McGhie T, Joseph JA. Dietary supplementation with fruit polyphenolics ameliorates age-related deficits in behavior and neuronal markers of inflammation and oxidative stress. *Age (Dordr)* 2005;27:49–57.
  47. Shukitt-Hale B, Carey A, Simon L, Mark D, Joseph JA. Effects of concord grape juice on cognitive and motor deficits in aging. *Nutrition* 2006;22:295–302.
  48. Kaewkaen P, Tong-Un T, Wattanathorn J, Muchimapura S, Kaewrueng W, Wongcharoenwanakit S. Mulberry fruit extract protects against memory impairment and hippocampal damage in animal model of vascular dementia. *Evid Based Complement Alternat Med* 2012;2012:263520.
  49. Shukitt-Hale B, Lau FC, Joseph JA. Berry fruit supplementation and the aging brain. *J Agric Food Chem* 2008;56:636–41.
  50. Miller MG, Shukitt-Hale B. Berry fruit enhances beneficial signaling in the brain. *J Agric Food Chem* 2012;60:5709–15.
  51. Krikorian R, Shidler MR, Nahs TA, Kalt W, Vinqvist-Tymchuk MR, Shukitt-Hale B, Joseph JA. Blueberry supplementation improves memory in older adults. *J Agric Food Chem* 2010;58:3996–4000.
  52. Krikorian R, Nash TA, Shidler MD, Shukitt-Hale B, Joseph JA. Concord grape juice supplementation improves memory function in older adults with mild cognitive impairment. *Br J Nutr* 2010;103:730–4.
  53. Devore EE, Kang JH, Breteler MM, Grodstein F. Dietary intakes of berries and flavonoids in relation to cognitive decline. *Ann Neurol* 2012;72:135–43.
  54. Gillette Guyonnet S, Abellan Van Kan G, Andrieu S, Barberger Gateau P, Berr C, Bonnefoy M, Dartigues JF, de Groot L, Ferry M, Galan P, et al. IANA task force on nutrition and cognitive decline with aging. *J Nutr Health Aging* 2007;11:132–52.

