Plant-Based Dietary Patterns, Plant Foods, and Age-Related Cognitive Decline

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ABSTRACT

The aging population is expanding, as is the prevalence of age-related cognitive decline (ARCD). Of the several risk factors that predict the onset and progression of ARCD, 2 important modifiable risk factors are diet and physical activity. Dietary patterns that emphasize plant foods can exert neuroprotective effects. In this comprehensive review, we examine studies in humans of plant-based dietary patterns and polyphenol-rich plant foods and their role in either preventing ARCD and/or improving cognitive function. As yet, there is no direct evidence to support the benefits of a vegetarian diet in preventing cognitive decline. However, there is emerging evidence for brain-health–promoting effects of several plant foods rich in polyphenols, anti-inflammatory dietary patterns, and plant-based dietary patterns such as the Mediterranean diet that include a variety of fruits, vegetables, legumes, nuts, and whole grains. The bioactive compounds present in these dietary patterns include antioxidant vitamins, polyphenols, other phytochemicals, and unsaturated fatty acids. In animal models these nutrients and non-nutrients have been shown to enhance neurogenesis, synaptic plasticity, and neuronal survival by reducing oxidative stress and neuroinflammation. In this review, we summarize the mounting evidence in favor of plant-centered dietary patterns, inclusive of polyphenol-rich foods for cognitive well-being. Randomized clinical trials support the role of plant foods (citrus fruits, grapes, berries, cocoa, nuts, green tea, and coffee) in improving specific domains of cognition, most notably frontal executive function. We also identify knowledge gaps and recommend future studies to identify whether plant-exclusive diets have an added cognitive advantage compared with plant-centered diets with fish and/or small amounts of animal foods. *Adv Nutr* 2019;10:S422–S436.

Keywords: vegetarian diet, plant-based dietary pattern, polyphenols, berries, nuts, walnuts, cognition, cognitive decline, elderly

Introduction

With the rise in the world's aging population, there is a concomitant increase in the prevalence of age-related cognitive decline (ARCD). In 2015, 8.5% of the global population was aged >65 y (~617 million); that is expected to rise to 12% by 2030 (~1 billion), and 16.7% by 2050 (almost 1.6 billion) (1). This is paralleled by an increase in the burden of dementia, the majority of cases being of the Alzheimer type (2). There is a normal decline in cognition as we age, but an accelerated decline is seen in the setting of Alzheimer disease (AD). Full-blown disease is preceded by a long asymptomatic preclinical period lasting a decade or more, followed by mild cognitive impairment (MCI) and, ultimately, AD (3).

A continuum exists from normal cognition to dementia, the onset and progression of which is predicted by a number of risk factors including age, gender, education level, and genetic susceptibility (2, 4). Several modifiable factors increase the risk for ARCD, including midlife obesity, hypertension, diabetes, and current smoking. However, physical activity and a healthy diet appear to decrease the risk (4). According to current thinking, an accumulation of β-amyloid peptide and other abnormal proteins causes oxidative stress, inflammation, and vascular impairment leading to neuronal damage and loss (2). Unfortunately, our understanding of the pathophysiological process of cognitive dysfunction remains incomplete, and at present we lack effective methods to prevent or reverse these changes.

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Abbreviations used: AD, Alzheimer disease; AHS-2, Adventist Health Study-2; ARCD, age-related cognitive decline; BDNF, brain-derived neurotropic factor; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension Trial; DII, Dietary Inflammatory Index; EVOO, extra-virgin olive oil; MCI, mild cognitive impairment; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay; MMSE, Mini-Mental State Examination; OJ, orange juice; RCT, randomized clinical trial; WAHA, The Walnuts and Healthy Aging Study.

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Emerging evidence supports a role for antioxidant-rich foods such as fruits, vegetables, and nuts in improving cognitive health by preventing or delaying the onset of cognitive decline during aging (5–7). Dietary patterns such as the Mediterranean diet, the Dietary Approaches to Stop Hypertension Trial (DASH) diet, and the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet have also been associated with neuroprotective effects (8, 9). Additionally, cognitive decline might be slowed with diets having a low Dietary Inflammatory Index (DII) score, characterized by the presence of anti-inflammatory plant foods and phytonutrients (10). All of these dietary patterns, though not exclusively vegetarian, are plant centered, consisting of plant foods abundant in nutrients such as n−3 (ω-3) PUFAs, vitamin E, vitamin C, phytonutrients including polyphenols, and carotenoids. A significant volume of work has demonstrated that plant-based dietary patterns lower the risk for cardiovascular disease (CVD), type 2 diabetes, and other chronic diseases (11–13). Given that there could be shared pathophysiology between these chronic diseases and neurodegenerative disorders, it is biologically plausible that such dietary patterns have a role in preserving cognition.

The objective of this comprehensive review is to examine evidence that vegetarian diets prevent or delay cognitive decline in elderly adults. Given the lack of direct proof, we rely on indirect support by reviewing studies of plant-based dietary patterns and plant-food effects on cognitive well-being in the elderly. Just within the past 5 y, several reviews have been published focusing on dietary patterns, polyphenol-rich plant-foods, nutrients, and cognition in the elderly (6–20). These reviews have focused primarily on summarizing cognitive outcomes and mechanisms of action. In this review, we explore studies of plant-based dietary patterns and polyphenol-rich plant foods, including berries, fruit juices, cocoa, green tea, coffee, and nuts, in preventing ARCD, with attention to the affected cognitive domains. This review is not exhaustive, but rather an extension of previously published work in this field. We also attempt to identify knowledge gaps and opportunities for future research.

Plant-Based Dietary Patterns and Cognition

Mounting evidence supports the beneficial effects of plant-based dietary patterns in preventing ARCD and dementia. Recent reviews of epidemiological studies and intervention trials indicate that plant foods and nutrients emphasized in the Mediterranean, the DASH, and the MIND dietary patterns could play a crucial role in preventing cognitive impairment (8, 9, 14, 16, 19–24). Although these 3 dietary patterns feature a variety of plant foods, dietary patterns of geographically diverse cohorts also reveal commonalities with regard to the emphasis on certain plant foods and their overall favorable influence on cognition (25–33). These results are also broadly consistent with research investigating the DII in relation to cognitive function (10, 34–37).

The association between plant-focused dietary patterns and cognition among several Asian cohorts is reviewed in **Table 1**. Plant foods commonly consumed by Asians are green leafy and other vegetables, soy, whole grains, green tea, mushrooms, and seaweed (25–30). Consumption of diets featuring many of these plant foods is associated with reduced risk of cognitive impairment (25, 26), slower rate of cognitive decline (27, 28), better scores on logical memory (29), or higher global cognitive assessment scores (30). Elderly adults from other countries (Norway, Australia, Italy) consuming a diet plentiful in fruits, vegetables, and legumes also show improved cognitive outcomes (31–33). Interestingly, colorful vegetables, fruits, nuts, nonsoy legumes, and olive oil predominant in the Mediterranean diet and other dietary patterns are less emphasized in the Asian diets. Food preparation and processing techniques are also important considerations. In some Asian cohorts (26, 29), the diets associated with improved cognitive outcomes feature stir-fried (in oil) and fermented vegetables (pickled cabbage), which could enhance the bioavailability of phytochemicals (38, 39). Similarly, a "multigrain rice" dietary pattern (brown rice, millets, black rice, barley) compared with a "white rice and noodles" dietary pattern was shown to reduce the risk of cognitive impairment in elderly Asians (26), attributed to the higher total polyphenol content in whole grains (40). Thus, the presence of a variety of plant foods rich in bioavailable bioactive compounds rather than any 1 specific food could be important for preventing ARCD (8–24).

Assessing a diet's inflammatory potential is a relatively new concept wherein foods and nutrients are scored for their pro- or anti-inflammatory effect, that is, the DII. Diets that are proinflammatory or have a high DII score are associated with higher risk of MCI or poor cognitive outcomes (10, 34–37). Conversely, adherence to low-DII diets such as the Mediterranean diet that incorporate a variety of plant foods rich in bioactive compounds show favorable cognitive outcomes (41–44). Polyphenol-rich plant foods, a common feature of the Mediterranean, the DASH, and the MIND dietary patterns (8, 9, 19–24), as well as other geographically diverse dietary patterns (25–37), might play a critical role in conferring cognitive benefits by suppressing inflammation (9, 10, 16). Although many cohort studies support an association of plant-based dietary patterns with cognition, to date only the Mediterranean dietary pattern is supported by evidence from randomized clinical trials (RCTs). In both healthy elderly adults and in participants with high vascular risk, supplementing the Mediterranean diet with extra-virgin olive oil (EVOO) improved cognitive function in the short term (45) and favorably influenced gross global cognition (46) in the long term. Both EVOO and mixed nuts added to the Mediterranean diet produced domain-specific effects, with EVOO improving frontal function, and mixed nuts improving memory composite scores (47, 48). In these RCTs, the emphasis was not on the overall dietary pattern, but specifically on increasing the quantity of unsaturated fatty acids and phytonutrients utilizing a single food. That the effects of EVOO and walnuts were demonstrated in patients at high risk of vascular disease as well as healthy subjects speaks to the potential role of vascular risk in precipitating cognitive deficits. It could be that the neurocognitive benefits

TABLE 1 Cohort studies associating dietary patterns with cognition in healthy elderly Asian adults[1]

First author, year (ref.)	Study design, subjects	Dietary patterns/plant foods	Cognitive outcome	Findings
Chan et al., 2014 (25)	Cohort study, Chinese elderly; $n = 1926$ men, 1744 women; age >65 y	1. Vegetables-fruits pattern (green leafy vegetables, other vegetables, tomato, cruciferous vegetables, fruits, soy, legumes, mushroom). 2. Snacks-drinks-milk products pattern (condiments, coffee, nuts, potato, dairy, whole grains, sweets, beverages). 3. Meat-fish pattern	Risk of cognitive impairment	Higher vegetables-fruits pattern and Snacks-drinks-milk products pattern scores were associated with reduced risk of cognitive impairment among women
Qin et al., 2015 (26)	Prospective cohort study, Chinese elderly, $n = 1650$, age ≥55 y	1. Wheat-based diet (wheat, nuts, fruits, red meat, poultry, egg, fish, dairy, sugar, vinegar, soy sauce, plant oil). 2. Rice-pork diet	Global cognitive function	Third tertile of the wheat-based pattern was associated with slower rate of cognitive decline
Kim et al., 2015 (27)	Cross-sectional study, Korean elderly, $n = 765$, age ≥60 y	1. MFDF dietary pattern (multigrain rice, fish, dairy, fruits, fruit juices, soy, nuts, green tea). 2. WNC dietary pattern (white rice, noodles, coffee, soy)	Mini-Mental State Examination—Korean version	MFDF dietary pattern showed lower risk of cognitive impairment compared with the WNC dietary pattern
Tsai, 2015 (28)	Longitudinal study, Taiwanese elderly, $n = 4049$, age ≥60 y	1. Western dietary pattern (meat, poultry, eggs). 2. Traditional dietary pattern (≥3 servings beans/legumes, ≥7 servings fruits/vegetables, 1–5 servings fish). 3. Healthy dietary pattern (≥3 servings beans/legumes, ≥10 servings fruits/vegetables, ≥5 servings fish)	Short portable mental state questionnaire	Western dietary pattern increased the risk of cognitive decline over 8 y
Chen et al., 2017 (29)	Prospective cohort study, Chinese elderly, $n = 475$, age ≥65 y	1. Vegetable pattern (green leafy vegetables, vegetables with oil, light-colored vegetables, tuber). 2. Meat pattern. 3. Traditional pattern	Global cognition and domain-specific cognition	Vegetable dietary pattern protected against decline of logical memory; a high-score Meat dietary pattern protected against attention decline; a high-score Traditional dietary pattern protected against logical memory recall
Okubo et al., 2017 (30)	Cross-sectional, Japanese elderly, $n = 635$, age 69–71 y	1. Plant foods and fish pattern (green leafy vegetables, other vegetables, soy, seaweed, mushroom, potato, fruits, fish, green tea). 2. Rice and miso soup pattern. 3. Animal food pattern	Japanese version of the Montreal Cognitive Assessment	Plant foods and fish pattern associated with higher MoCA-J score

[1] MoCA-J, Japanese version of the Montreal Cognitive Assessment; ref., reference.

of the Mediterranean diet are mediated through a reduction in vascular disease risk (49).

Although the presence of anti-inflammatory plant foods seems to have a favorable impact on cognition, the specific cognitive domains affected remain undetermined. This is partly due to inconsistencies across studies with regard to cognitive assessments, which vary from simple determination of risk of cognitive impairment to measures of gross cognition [Mini-Mental State Examination (MMSE), Short Portable Mental State Exam], global cognition scores (Montreal Cognitive Assessment), or a comprehensive domain-specific neurocognitive battery of tests (19–33). Some of the more common cognitive assessments are related to orientation, visuospatial orientation, praxis, abstract thinking, language, executive function, and learning memory. There is some indication that dietary patterns or foods can exert domain-specific effects. In elderly Chinese adults, for example, a "vegetable" dietary pattern protected against decline in verbal memory, but increased the risk of decline in executive function (29). In the same cohort, a "meat" dietary pattern was protective against decline in attention and working memory, but increased the risk of decline in semantic fluency. Such contrasting results might reflect differential effects of dietary patterns on specific areas of cognitive function such that vegetable-rich diets have a stronger relation to mechanisms associated with memory as opposed to frontal-executive function. This highlights the importance of assessing multiple cognitive domains in future studies of diet and cognition. Furthermore, the seemingly ambiguous result in this cohort might be due to an overlap of plant foods between the "vegetable" and "meat" dietary patterns. It could be that the presence of certain plant foods more than the absence of meat is responsible for the observed neurocognitive benefits.

Whereas in Western countries intake of red meat has been associated with poor cognitive outcomes (50), among elderly Asians there seems to be either a beneficial effect on (29) or no association with (25) cognition. This could be due to the low amount of red meat consumed by Asians (35 g/d) (26) compared with Western populations (128 g/d) (51). Unlike red meat, the type of fish rather than the amount seems to matter for cognitive benefit provided the background diet includes a variety of plant-based foods (26, 27, 30). Specifically, consumption of tuna and dark-meat fish has been associated with better verbal-memory scores than consumption of light-meat fish in older women (52). However, when the background diet includes fish but places limited emphasis on plant foods, no cognitive benefits are noted (25). Other nonflesh animal foods like dairy and eggs are not associated with cognitive decline (53) or incident dementia (54). In fact, moderate egg consumption could be beneficial for cognition, attributed partly to the high lutein and zeaxanthin content of eggs. These xanthophylls could influence cognitive health of older adults by improving visual perception and decision-making (55). Whether the presence of fish, egg, or small amounts of red meat in an otherwise plant-abundant diet has a similar or greater effect on cognitive function can only be teased out if we compare vegetarian, vegan, and pesco-vegetarian cohorts sharing similar nondietary lifestyle habits, a consideration for future studies.

The plant-based dietary patterns, although emphasizing a variety of plant foods, typically also limit red meat, butter, stick margarine, whole-fat cheese, pastries, sweets, and fried/fast foods, which increase the intake of saturated fat, *trans* fat, and arachidonic acid. These unhealthy fats tend to disrupt blood–brain barrier function, increase β-amyloid plaques, and predict cognitive decline (56, 57). Using fMRI, a high–palmitic acid diet was seen to increase brain activation in the basal ganglia during the performance of working tasks, compared with diets high in oleic acid (58). In contrast, specific plant foods rich in antioxidant nutrients and phytonutrients protect the brain by reducing the oxidative burden on neuronal cells and inhibiting the deposition of β-amyloid plaques (18). In summary, the neuroprotective effects of the plant-based dietary patterns and plant foods can be mediated by a reduction in vascular and cardiometabolic risk, and by nonvascular mechanisms such as suppression of oxidative stress and inflammation (7, 11–13, 49).

Some of the common plant foods represented in these plant-based dietary patterns have been studied for their effects on cognition in the elderly, including polyphenol-rich fruit juices, berries, cherries, cocoa, green tea, coffee, and nuts. In the next sections we review these foods and identify specific cognitive domains that are most responsive to them.

Polyphenol-Rich Foods and Cognition

Fruit juices

There is substantial evidence from animal studies to support the brain-health–promoting effects of polyphenols (18), and emerging evidence to support the association of polyphenol intake with delayed cognitive decline in older adults (48). In **Table 2**, studies of polyphenol-rich fruit juices are reviewed. Fruit juices, including orange, grape, and pomegranate juice, appear to have positive effects on cognition, although the number of studies is small. High-flavanone orange juice (OJ) compared with a low-flavanone control (500 mL/d for 8 wk) in healthy older adults improved global cognition, calculated as the mean z-score of multiple tests of executive function and episodic memory (59). Notably, on tests of episodic memory, effects were observed mainly on immediate recall, which tends to reflect frontal executive aspects of attention and memory encoding. There was also a trend toward improved executive function following the high-flavanone OJ consumption. The flavanone hesperidin, the dominant polyphenol in OJ, has been shown in animal models to scavenge free radicals and reduce the oxidative burden in neuronal cells due to brain aging (60).

Pomegranate juice has the highest concentration of phenolics and exhibits the most antioxidant activity among antioxidant-rich beverages in the United States, followed by

TABLE 2 Human studies of polyphenol-rich fruit juices and cognition in elderly adults[1]

Food	Author, year (ref.)	Study design	Subjects	Duration	Results
Orange juice	Kean et al., 2015 (59)	RCT crossover design: high-flavanone (305 mg) 100% orange juice vs. low-flavanone (37 mg) placebo in 2 divided doses daily	37 healthy older adults (mean age 67 y)	8 wk. 4-wk wash-out	Global cognitive function was significantly improved with high-flavanone orange juice ($P < 0.05$)
Pomegranate juice	Bookheimer et al., 2013 (62)	RCT: POM Wonderful pomegranate juice 8 oz daily vs. placebo	32 older adults, 28 completing (mean age 63.1 ± 8.0 y) with age-related memory decline (not MCI)	4 wk	Improvement on the Buschke selective reminding test of verbal memory (total recall score $P = 0.029$, long-term retrieval score $P = 0.022$) and increased fMRI brain activation on visual and verbal memory tasks ($P = 0.05$) in the intervention group
Grape juice, grapes	Krikorian et al., 2010 (63)	RCT: 100% Concord grape juice (6 and 9 mL/kg) vs. placebo (no polyphenols) in 3 divided doses daily	12 older adults (mean age 78.2 ± 5 y) with MCI	12 wk	Improved verbal learning on the California Verbal Learning Test in the intervention group ($P = 0.04$)
	Krikorian et al., 2012 (64)	RCT: 100% Concord grape juice (6.3−7.8 mL/kg) vs. placebo (no polyphenols) in 3 divided doses daily	21 older adults (mean age 76.9 ± 6.1 y) with MCI	16 wk	No difference in learning and retention scores, but reduced semantic interference on memory tasks ($P < 0.004$), and greater activation of portions of the right hemisphere on fMRI with treatment
	Lee et al., 2017 (65)	RCT: active grape formulation with 36 g freeze-dried grape powder in H_2O vs. placebo twice daily	10 older adults (mean age 72.2 ± 4.7 y) with MCI	6 mo	Stable brain metabolism in the intervention group vs. declines in areas associated with AD in the placebo group ($P < 0.05$); no difference in neuropsychological assessments
	Calapai et al., 2017 (67)	RCT: 250 mg/d grape extract supplement vs. placebo for 12 wk	111 healthy older adults (mean age 66.9 ± 5.2 y) with MCI	12 wk	Improved cognitive performance (higher MMSE scores) after intervention and ameliorated negative neuropsychological status ($P \leq 0.0001$)

[1] AD, Alzheimer disease; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; RCT, randomized clinical trial; ref., reference.

red wine, Concord grape juice, and blueberry juice (61). The polyphenols in pomegranate juice are predominantly anthocyanins and hydrolysable tannins, including glycosides of ellagic acid. Older adults who consumed pomegranate juice [8 oz/d (225 g/d)] for 4 wk had improved encoding and retrieval on a test of verbal memory compared with the placebo group (62) accompanied by verbal and visual task-specific increases in brain activation on fMRI. Pomegranate polyphenols appeared to increase memory performance through increased task-specific cerebral blood flow.

Four small RCTs compared daily grape consumption (100% Concord grape juice or an active grape formulation of freeze-dried grape powder from California grapes) with a placebo drink in older adults. Daily Concord grape juice consumption (6.3–7.8 mL/kg body weight for 16 wk) led to improvements on the California Verbal Learning Test scores compared with placebo (63) in elderly adults with early memory decline, but not dementia. In a follow-up study (64), no difference was observed on the Verbal Learning Test after 16 wk of daily Concord grape juice, but the intervention reduced semantic interference errors in memory tasks (ability to differentiate learned material from foils), and increased activation of portions of the right cortex during a memory task with fMRI. In a longer trial (65), also in the setting of MCI, daily intake of grape extract (36 g) for 6 mo showed no differences on neuropsychological tests, but was associated with stable brain metabolism compared with declines in areas associated with AD in the placebo group. Such declines are considered a precursor to AD-related neurodegeneration and functional decline (66). Following a 12-wk intervention with a grape extract–based dietary supplement (250 mg/d), healthy elderly participants demonstrated a significant improvement in MMSE scores and domain-specific scores in attention, immediate and delayed memory, and language compared with participants given a placebo (67). Concord grape juice polyphenols include anthocyanins, hydroxycinnamic acids, procyanidins, and flavan-3-ol monomers. Flavonoids in grapes have the potential to suppress oxidative stress and influence signal transduction pathways that enhance the expression of the neurotropic factors such as brain-derived neurotropic factor (BDNF) (18).

Cherries are polyphenol-rich fruit studied for their brain health properties. No acute cognitive effects were observed with either sweet or tart cherry juice at 5 h and 6 h postconsumption in either young or older adults, with or without dementia (68, 69). However, a long-term (12 wk) intervention with cherry juice (200 mL/d) in older adults with mild to moderate Alzheimer-type dementia showed significant improvement in semantic verbal fluency and verbal learning and memory, the functions in which AD patients tend to experience the earliest and most prominent deficits (70). Improvement in systolic blood pressure was seen with both acute and longer-term treatments with cherry juice, and this could be a mediating mechanism for the prevention of cognitive decline (69).

Overall, citrus fruit juices, pomegranate juice, grape juice, and cherry juice, all with large amounts of polyphenols of different subtypes, appear to exert brain-protective effects and improve global or domain-specific cognitive function in as little as 4 wk of intervention. Based on the above studies, acute benefits after a single dose are unlikely and longer-term daily consumption could be necessary to achieve observable effects on cognition. Further, benefits might be less relevant for younger adults and more pronounced in older adults at risk for either age-related or pathological cognitive decline. Specifically, there appears to be most benefit in frontal-executive functions including attention and memory encoding and retrieval. The typical servings used in these studies are reasonable for human consumption. Additionally, polyphenols in 100% fruit juice could inhibit the absorption of some naturally occurring sugars and potentially help substitute nutrient-poor sugar-sweetened beverages. However, a recommendation to increase consumption of fruit juices should include the proviso that they be 100% fruit juice and within acceptable serving sizes. Just one serving [8 oz (225 g)] of fruit juice contains 21–37 g natural sugar depending on the type, and can inadvertently increase sugar intake. Perils of excess sugar include an increase in insulin resistance with concomitant blunting of the immune response, and an increased risk of cardiometabolic and other chronic disease outcomes (71–73). Compared with fruits and fruit juices, vegetables tend to have lower sugar content and a stronger protective effect on cognitive outcomes than fruit intake (5, 74). In fact, deeply pigmented vegetables are more anti-inflammatory and are associated with slower cognitive decline (74–76). Public health recommendations must therefore consider the risk-to-benefit ratio of phytochemical-rich vegetables compared with 100% fruit juice consumption with regards to slowing cognitive decline. Currently, there is a paucity of clinical trials exploring the chronic effects of vegetable consumption on cognition, a consideration for the future. There is also a need for epidemiological and intervention studies to consider the quantity and type of fruits and vegetables (both whole fruit and vegetable and 100% juices) in the context of cognitive functions in the elderly.

Fruits: berries

Following evidence from animal studies supporting the role of berry-rich diets in motor function, working memory, and increased neurogenesis (77, 78), human studies have supported the use of berries to improve cognitive well-being (60, 79–81). In the Nurses' Health Study, strawberries and blueberries were significantly associated with slower decline in global cognition and verbal memory among older women (61). Three RCTs evaluated the effects on cognition of supplementing various blueberry formulations, and a fourth utilized a mixed-berry drink containing blueberries, blackcurrants, elderberries, lingonberries, strawberries, and tomatoes (82–86) (**Table 3**). A freeze-dried blueberry supplement (equivalent to ∼150 g fresh blueberries) for 90 d

TABLE 3 Human studies of polyphenol-rich berries and cognition in elderly adults[1]

Author, year (ref.)	Study design	Subjects	Duration	Results
Whyte et al., 2018 (82)	RCT: whole wild blueberry powder 500 mg or 1000 mg, vs. wild blueberry extract 100 mg vs. placebo for 6 mo	122 healthy older adults, age range 65–80 y	6 mo	Wild blueberry extract facilitated better episodic memory performance at 3 mo but not 6 mo, and lower SBP at both time points compared with placebo. No significant effects with blueberry powder
Miller et al., 2018 (83)	RCT: freeze-dried blueberries 24 g/d (equivalent to 1 cup blueberries; ∼36 mg/g polyphenols, ∼19.2 mg/g anthocyanins) vs. placebo in 2 divided doses daily	37 healthy older adults aged 60–75 y Mean age: blueberry, 67.8 ± 4.6 y; placebo, 67.3 ± 4.8 y	3 mo	Fewer repetition errors on word list recall in the California Verbal Learning Test II ($P = 0.031$) and increased accuracy in task switching ($P = 0.033$) across study visits with the intervention vs. placebo. No differences in gait or balance
Bowtell et al., 2017 (84)	RCT: blueberry concentrate 30 mL (387 mg anthocyanins) vs. placebo daily	26 healthy older adults, aged ≥65 y Mean age: blueberry, 67.5 ± 0.9 y; placebo, 69.0 ± 0.9 y	12 wk	Increased resting perfusion of the brain's parietal ($P = 0.013$) and occipital lobes ($P = 0.031$) and increased task-related activation in brain areas associated with cognitive function ($P < 0.001$) with blueberry supplementation only
Nilsson et al., 2017 (85)	RCT crossover design: mixed berry beverage (150 g blueberries, 50 g each elderberry, lingonberry, strawberry, blackcurrant; 6 g tomato powder; 1% sugar; 795 mg polyphenols) vs. placebo, 600 mL in 3 divided doses daily	40 healthy adults, aged 50–70 y (mean age 63 ± 0.9 y)	5 wk + 5-wk wash-out	Modestly better working memory (5%) with the berry beverage vs. control ($P < 0.05$)
Krikorian et al., 2010 (86)	Intervention trial: wild blueberry juice 6–9 mL/kg daily (1.056–1.478 g gallic acid equivalent total phenolics, 0.428–0.598 g cyanidin-3-glucoside equivalent anthocyanins) Results were compared with a control group	Intervention group: 9 older adults with MCI (mean age 76.2 ± 5.2 y) Control group: 7 older adults with MCI from companion trial (mean age 80.2 ± 6.3 y)	12 wk	Memory function improved significantly from baseline with the intervention, as measured by the V-PAL score ($P = 0.009$) and the CVLT ($P = 0.04$). Comparing the intervention with placebo, performance was better for both assays, but significant only for the V-PAL ($P = 0.03$)

[1] CVLT, California Verbal Learning Test; MCI, mild cognitive impairment; RCT, randomized clinical trial; SBP, systolic blood pressure; V-PAL, verbal paired associate learning.

resulted in declines in both repetition errors on a verbal learning test and switching errors on a task-switching test in healthy elderly adults (83). Similarly, intake of blueberry concentrate for 3 mo improved episodic recognition memory and visual working memory performance in healthy older adults (84). In combination with other fruits and berries, blueberries improved working memory in healthy elderly subjects after just 5 wk, though no effects were observed in the areas of selective attention or psychomotor reaction time (85). Enhancement of verbal memory function with blueberry supplementation is also evident among elderly participants with early cognitive decline or more serious cognitive complaints (82, 86–88). According to fMRI, the positive impact on domains of cognition from blueberry supplementation seems to be accompanied by improved brain perfusion and activation of brain areas related to cognitive function (84).

Berries in general contain large amounts of flavonoids including the flavan-3-ols catechin and epicatechin, the flavanols kaempferol and myricetin, and the anthocyanins delphinidin and petunidin. These flavonoids are neuro protective and can slow brain aging through a number of postulated mechanisms, including suppression of microglia-mediated inflammation, and reduction of vascular risk through decrease in blood pressure and oxidative stress, facilitated in part through neuronal and inducible nitric oxide production (18, 89, 90).

Cocoa

Cocoa is another polyphenol-rich food studied for its effects on cognition (91–93). In a recent review (94) cognitive benefits were noted following acute treatment with cocoa flavanols, but conflicting results were seen in longer trials. Recent studies have shown promising results, however. A cross-sectional study in adults (aged 23–98 y) found improved cognition in subjects consuming chocolate at least once per week compared with less than once per week for global composite memory and visuospatial memory and organization (92). A prospective cohort study of cognitively healthy older adults found a significantly lower risk of gross cognitive decline (RR of 0.59) among chocolate consumers compared with nonconsumers, but only in participants consuming <1 serving size of chocolate per week (∼120 g chocolate bar or 7 g cocoa powder) and <75 mg of caffeine per day (95). Three RCTs have examined the effects of cocoa flavanols in healthy middle-aged and elderly adults over 4–12 wk (96–98). Intake of cocoa flavanols (993 mg/d) daily for 8 wk improved scores in the Trail Making tests and Verbal Fluency Test compared with placebo (96), implying that cocoa flavanols can support higher processing speeds and better executive function. Whereas a shorter intervention (4 wk) with a lower dose of cocoa flavanols (250 mg/d) did not show cognitive benefits (98), a longer exposure (12 wk) to 900 mg of cocoa flavanols per day improved cognition and blood flow to the dentate gyrus in sedentary older adults (97). The dentate gyrus is the region of the hippocampus most affected in ARCD and affects learning and consolidation of new memories.

Cocoa, from the dried and fermented seeds of *Theobroma cacao*, is a rich source of flavonoids. In particular, cocoa is rich in the flavan-3-ol epicatechin, as well as catechin and additional oligomeric procyanidins. Epicatechins are not only bioavailable in humans but appear to cross the blood–brain barrier in animals and might act directly on the brain. Flavonoids from cocoa have been implicated in enhancing neuroplasticity through increased neurogenesis, especially proliferation and survival of new hippocampal neurons, and an increase in synaptic growth by stimulation of BDNF (18, 89, 90).

Coffee and tea

Coffee and tea, well-known sources of caffeine, are also both excellent sources of polyphenols. Coffee contains large amounts of phenolic acids, notably the hydroxycinnamic acids 4-caffeoylquinic acid (19 mg/mL) and 5-caffeoylquinic acid (43 mg/mL), as well as some catechols. Green tea contains large amounts of flavanols (catechins, epicatechins, and procyanidins), and lesser amounts of phenolic acids (hydroxybenzoic and hydroxycinnamic acids; 5-caffeoylquinic acid is present at 2.3 mg/100 mL). In many countries, coffee and green teas are the most important food source of polyphenols (99, 100).

Both coffee and tea have cognitive benefits for older adults (**Table 4**) and have been associated with better cognitive outcomes or lower risk of cognitive disorders (101–105). A dose–response meta-analysis on coffee intake and risk of cognitive disorders (101) found a J-shaped relation: 1–2 cups of coffee per day compared with <1 cup significantly reduced the risk of cognitive impairment, cognitive decline, dementia, and AD, but the risk increased at higher intakes, though the difference between <1 and >3 cups/d was not significant. Most recently, in an RCT that included elderly subjects (aged 61–80 y), consumption of a cup of regular coffee (100 mg caffeine per 220 mL coffee) resulted in immediate improvement in cognitive performance, including faster reaction times and improved attention and alertness (102). A prospective cohort study of cognitively stable elderly subjects (aged 69–86 y) found that subjects in the middle tertile of coffee consumption were less likely to demonstrate deterioration on ≥2 cognitive tests over 3 y (103). In addition, cognitively stable subjects in the second and third tertiles of coffee consumption had better white matter preservation.

Epidemiological studies focused on tea consumption and AD risk have been recently reviewed (104, 105). In a meta-analysis, drinking tea (compared with not drinking or rarely drinking) was associated with a lower risk of cognitive impairment, MCI, cognitive decline (a drop in MMSE scores of 1–2), and unclassified cognitive disorder, but not with dementia or AD. An inverse association between green tea consumption and cognitive disorders including dementia was observed, but no association for black or oolong tea (106). Intakes of 100, 300, and 500 mL/d of green tea were associated with 6%, 19%, and 29% lower risk of cognitive

TABLE 4 Human studies of coffee, tea, and cognition in elderly adults[1]

Food	Author, year (ref.)	Study design	Subjects	Duration	Results
Coffee	Wu et al., 2017 (101)	Meta-analysis of 9 prospective cohort studies	34,282 men and women, baseline age ≥60 y	1.3–28 y	J-shaped association between coffee intake and incidence of AD, dementia, cognitive impairment, or cognitive decline (RR: 0.82; 95% CI: 0.71, 0.94); nadir at 1–2 cups of coffee per day
	Haskell-Ramsay et al., 2018 (102)	RCT crossover study: regular coffee (100 mg caffeine) vs. decaffeinated coffee (~5 mg caffeine) vs. placebo (2.5 g coffee flavoring)	30 healthy older adults aged 61–80 y; 29 healthy young adults aged 20–34 y	30 min	Regular coffee led to improved (faster) response times in rapid visual information processing and digit vigilance tasks compared with placebo, and better digit vigilance accuracy compared with decaffeinated coffee; cognitive effects did not differ by age or gender
	Haller et al., 2018 (103)	Prospective cohort study: data from an ongoing population-based Swiss study on healthy aging	145 healthy older adults aged 69–86 y	3 y	Moderate coffee drinkers (29–60 cups/mo) were less likely to exhibit deterioration on an extensive battery of neuropsychological tests (−0.5 SD on ≥2 tests) at both 18 and 36 mo (adjusted OR: 0.455; 95% CI: 0.208, 0.995; $P = 0.048$); moderate to heavy coffee drinkers (61–168 cups/mo) also had better MRI WM preservation ($P < 0.05$) in cognitively stable participants
Tea	Ma et al., 2016 (105)	Systematic review and meta-analysis of observational studies	52,503 participants in 26 studies	NA	Tea intake significantly lowered risk of cognitive impairment (OR: 0.52; 95% CI: 0.43, 0.62), MCI (OR: 0.64; 95% CI: 0.52, 0.76), cognitive decline (OR: 0.74; 95% CI: 0.58, 0.90), and unclassified cognitive disorder (OR: 0.76; 95% CI: 0.60, 0.91), but not of AD (OR: 0.88; 95% CI: 0.65, 1.12)
	Liu et al., 2017 (106)	Systematic review and meta-analysis of observational studies	48,435 participants in 17 studies	NA	Green tea but not black/oolong tea was inversely associated with risk of cognitive disorders (OR: 0.64; 95% CI: 0.53, 0.77). Intakes of 100, 300, and 500 mL/d were associated with 6%, 19%, and 29% lower risk

[1] AD, Alzheimer disease; MCI, mild cognitive impairment; NA, not applicable; RCT, randomized clinical trial; ref., reference; WM, white matter.

disorders. Green tea catechols such as epigallocatechin gallate in particular, but also epigallocatechin, epicatechin, rutin, and L-theanine, could be involved in reduction of amyloid formation and also amyloid-induced oxidative damage and mitochondrial dysfunction (104). Taken together, chronic intake of both coffee and tea appears to lower the risk of incident cognitive disorders, but the relation is J-shaped for coffee and linear for green tea.

Nuts

Finally, tree nuts and legumes are also rich sources of polyphenols, although few human studies have examined the role of tree nuts on cognition (**Table 5**). Studies addressing the association of nut intake and cognition in younger adults, or studies that consider postprandial effects are not part of this review.

Elderly (107, 108) and middle-aged (109) adults who consumed nuts ≥5 times per week had better global cognition and verbal memory composite scores than less frequent consumers, although significant protection from ARCD was not seen. In a cross-sectional study, younger and older adults who consumed walnuts frequently had better recall test scores, faster reaction times, and greater single-digit learning scores than nonconsumers (110). Similarly, among elderly participants from Greece, intake of legumes, nuts, and seeds was associated with improved cognition, with frequent consumers having a lower likelihood of poor MMSE scores (111). To date there have been just 2 RCTs on nuts and cognition in the elderly using either Brazil nuts or walnuts. Participants with MCI who consumed 1 Brazil nut daily for 6 mo had better verbal fluency and constructional praxis scores but showed no difference in global cognition compared with controls (112). Brazil nuts contain selenium, an antioxidant mineral utilized in selenoproteins important for brain function (113).

A dual-center RCT on walnut intake (~30–60 g/d for 2 y) and ARCD in the elderly was recently completed (114). The Walnuts and Healthy Aging (WAHA) study was conducted on 700 elderly participants in 2 geographic locations: Loma Linda, California, and Barcelona, Spain. The cognitive outcomes from this RCT are yet to be published. The neuroprotective effects of walnut bioactive compounds and the overall effect of walnut extract on motor skills and cognition have been demonstrated previously in rats (115) and formed the rationale for the WAHA study. All nuts, and walnuts in particular, have a nutrient-rich matrix consisting of polyunsaturated fats, both linoleic and α-linolenic acid (18:3n−3), and antioxidant polyphenols that might impact neuronal function and promote brain health through additive effects. In vitro, whole walnut extract protected primary neuronal cells against calcium dysregulation–induced oxidative and inflammatory stress suppressing microglial activation (116). There is also evidence to suggest that n–3 PUFAs can induce neuroprotective effects by increasing expression of neurotropic factors such as BDNF that stimulate neuronal growth and survival (117). Other bioactive compounds in walnuts such as arginine,

TABLE 5 Human studies of nuts and cognition in elderly adults[1]

Author, year (ref.)	Study design	Subjects	Duration	Results
O'Brien et al., 2014 (107)	Prospective cohort study: data from the Nurses' Health Study	15,467 female nurses aged $\geq$70 y (mean age 74 y) at time of cognitive testing	21 y	Increasing nut intakes (<1/mo, 1–3/mo, 1/wk, 2–4/wk, $\geq$5/wk) were related to better overall cognition: verbal composite score *P*-trend = 0.005, global composite score *P*-trend = 0.003, with the difference between highest and lowest intakes equivalent to ∼2 y
Koyama et al., 2015 (108)	Retrospective cohort study: data from the Health Professionals Follow-Up Study	1866 older adult men (mean age 71 y; range 63–95 y)	8 y: nut intake noted in 2006; cognitive testing in 2014	Higher nut consumption was significantly associated with better overall cognitive performance (>2 servings/wk, 1–2 servings/wk, 1–3 servings/mo, <1 serving/mo), *P*-trend = 0.02; the highest vs. lowest intakes had cognitive differences equivalent to ∼5 y
Nooyens et al., 2011 (109)	Prospective cohort study: data from the Doetinchem Cohort Study	2613 men and women aged 43–70 y (mean ages by quintile of fruit and vegetable intake: 54.3–56.0 y)	5 y (interval between cognitive tests)	Higher nut consumption was associated with better cognitive function at baseline (*P*-trend < 0.01); difference between highest and lowest quintiles equivalent to ∼5–8 y; no difference in cognitive change at 5 y
Arab et al., 2015 (110)	Cross-sectional study; 24-h recall data compared 3 groups: • Walnuts alone • Walnuts with other nuts • No nuts	NHANES 1988–1994: age 20–59 y, $n = 5662$; age $\geq$60 y, $n = 5054$ 1999–2002: age $\geq$60 y, $n = 2975$	Not applicable	Positive associations were seen between walnut consumption and cognitive function among all age groups ($P < 0.01$)
Katsiardanis et al., 2013 (111)	Cross-sectional study: population based in Velestino, Greece	557 elderly adults $\geq$65 y; 50% of men and 67% of women had MCI by MMSE	Not applicable	Intake of pulses, nuts, and seeds (assessed as a group) was associated with a lower likelihood of MCI (MMSE <24) in men only ($P = 0.04$); no food groups were associated with MCI in women
Cardoso et al., 2016 (112)	RCT: 1 brazil nut (mean 5 g, ∼288.75 μg selenium) daily vs. control	31 older adults with MCI (20 completing) (mean age 77 ± 5.3 y)	6 mo	Overall neuropsychological battery score assessing global cognition did not differ ($P = 0.138$); however, significant improvements in verbal fluency ($P = 0.007$) and constructional praxis ($P = 0.031$) subtests were seen with the intervention

[1]MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; RCT, randomized clinical trial; ref., reference.

tocopherols, folate, melatonin, and polyphenols support cognitive health by modulating several cardiovascular risk factors (118). Among nuts, walnuts contain the largest amount of free and total polyphenols, followed by Brazil nuts and almonds (61). The predominant polyphenols are proanthocyanidins, a flavan-3-ol type of flavonoid. Walnuts contain a significant amount of ellagic acid, an antioxidant phenolic acid also found in pomegranate, strawberries, and almonds. Additional studies of other nuts and cognition in both cognitively stable and cognitively impaired individuals are urgently needed. Future studies should also consider combining foods such as walnuts and blueberries that have independently demonstrated pronounced effects on cognition (78, 115). Cognitive outcomes from the WAHA study will provide some directions for future research as well.

Summary and Scope for the Future

There is growing support for consumption of 100% fruit juices, berries, cocoa, coffee, green tea, and nuts to improve cognitive function among elderly adults. However, there is less clarity on how cognitive functions are impacted by the dose, the subclasses of polyphenols, and the synergism within and between plant foods. In the Adventist Health Study-2 (AHS-2), the average dietary polyphenol intake (100) was higher among nonvegetarians (662 mg/d) compared with lacto-ovo vegetarians (504 mg/d) and vegans (498 mg/d). Adventists share a number of similar lifestyle factors (119), such as avoiding alcohol, not smoking, and consuming fewer caffeinated drinks, with low intakes of meat (28 g/d) compared with the average intake reported in Western diets (125 g/d). The high polyphenol content among nonvegetarians in the AHS-2 cohort was mainly seen among coffee drinkers. For vegans and vegetarians, polyphenols came from foods such as fruits, vegetables, nuts, legumes, and whole grains. However, unlike with the Mediterranean diet, polyphenol-rich food sources such as olive oil, red wine, and green tea are rarely or less frequently consumed among the Adventists. This highlights the need for future studies to better characterize the role of polyphenol subclasses and food sources on cognition.

Some of the foods richest in polyphenols are cocoa, berries, nuts, pomegranate juice, oranges, apples, and sweet cherries (61). These foods appear to have the most beneficial effects on memory and frontal executive functions such as attention and processing speed. Although it is premature to link polyphenol subclasses to specific cognitive domains in humans, it is plausible that multiple polyphenols work synergistically with each other and other nutrients to produce cognitive benefits. This remains a major gap in the literature and an area of interest for future studies. For example, it would be interesting to compare the cognitive effects of pomegranate, grapes, and blueberries, all of which have been shown to increase brain activation on fMRI. Identification of differential and/or synergistic effects would help us elucidate the actions of specific subclasses of polyphenols.

To further our knowledge in the area of plant-based diets, plant foods, and cognition in the elderly population, we must consider methodological aspects as well. From RCTs it appears that 8–12 wk of exposure to a single food can produce beneficial changes in cognition among healthy elderly subjects (46–48). In some studies interventions >12 wk were needed to induce significant changes in cognition (64). We must also consider the cognitive status of the study population. There is some indication that dietary interventions tend to improve brain health more in cognitively disadvantaged individuals with fewer years of education or lower socioeconomic status (120), or in elderly participants with risk for higher cognitive deficits (46–48). Additionally, cognitive function is sensitive to many factors including sleep, stress, blood pressure, and physical activity (121). Hence, where interventions affect any of these factors, they might also influence cognition. Thus, these factors must be considered when selecting study participants for RCTs, and handled as confounders in observational studies. Another consideration is the overall energy intake of plant-centered diets, which are frequently less calorie dense than Western diets (8–11, 119). Future studies should control for calorie intake and test the effect of polyphenol-rich foods in a dose-dependent manner.

Careful thought must also be given to the type of cognitive test utilized. Although studies have shown favorable outcomes with single screening tests, or tests of global cognition (21, 27, 28, 31), the use of sensitive and demanding neuropsychological tests could be more powerful (45–48). When financially feasible, including fMRI with tasks that support working memory (frontal executive function) can be useful and can corroborate the findings of neuropsychological tests. Finally, positron emission tomography scans are useful biomarkers of AD and have been linked to dietary patterns (122); they could be a valuable addition to future studies exploring the mechanisms of action for the cognitive benefits of plant foods.

Conclusions

Evidence strongly suggests that plant-based dietary patterns that are abundant in fruits, vegetables, nuts, seeds, legumes, and whole grains with less emphasis on animal foods and processed foods (11–13) are a useful and a practical approach to preventing chronic diseases. Such dietary patterns, from plant-exclusive diets to plant-centered diets, are associated with improved long-term health outcomes and a lower risk of all-cause mortality (123, 124). Given that neurodegenerative disorders share many pathophysiological mechanisms with CVD, including oxidative stress, inflammation, and vascular damage, it is reasonable to deduce that plant-based diets can ameliorate cognitive decline as well.

There is general consensus that dietary patterns centered on plant foods, such as the Mediterranean, DASH, and MIND diets, improve overall global cognitive function and prevent ARCD. Several plant foods such as polyphenol-rich berries, fruit juices, coffee, tea, cocoa, and nuts also favorably impact cognitive well-being. Polyphenols seem to exert their protective effects on specific cognitive domains, most notably frontal executive functions such as attention, processing speed, and memory encoding, consolidation, and retrieval. Possible mechanisms underlying the neuro cognitive benefits might be related to increased cerebral blood flow, reduced oxidative stress and neuroinflammation, improved neurogenesis, and neuroplasticity (121, 125, 126). Besides polyphenols, other antioxidant micronutrients and n−3 PUFAs might work synergistically to benefit cognitive wellness.

Despite protective effects noted for plant-based dietary patterns and plant foods on cognition, there is still lack of clarity on which cognitive domains are most affected. Some tests such as the screening measure of gross cognition used to screen dementia might not have sufficient sensitivity to detect subtle effects in a healthy, community-dwelling, elderly population. Further, neuroprotective effects of different foods and nutrients might be confined to specific cognitive domains. Plant-based dietary patterns and polyphenol-rich foods appear to influence the verbal memory and frontally mediated executive functions, including working memory and processing speed. Less impact has been found on other cognitive domains such as visuospatial and semantic processing. This is consistent with proposed mechanisms by which plant-based diets and plant foods protect against cognitive decline, namely through reduction of cardiovascular risk, oxidative stress, and neuroinflammation, all which have been linked to cognitive processes specifically associated with memory and executive functions (127, 128). Although there is some evidence linking polyphenol-rich foods to reduced vascular risk by preservation of cerebral blood flow and metabolism (62, 65), additional neuroimaging of small-vessel ischemic disease, infarcts, white matter integrity, and blood–brain barrier integrity could further elucidate the mechanistic relation (129–132). Other markers of oxidative stress and inflammation, such as IL-6, C-reactive protein, and serum amyloid A, would also be informative.

We should acknowledge that besides diet, other lifestyle factors such as adequate sleep, rest, and physical activity play roles in modifying the risk for cognitive decline. A comprehensive approach addressing both diet and lifestyle components known to improve cognition could be the most effective means of reducing the population risk for ARCD. In conclusion, plant-centered dietary patterns focused on polyphenol-rich foods can positively impact the cognitive well-being of the elderly population.

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