



Review Article

A berry thought-provoking idea: the potential role of plant polyphenols in the treatment of age-related cognitive disorders

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Abstract

Today, tens of millions of elderly individuals worldwide suffer from dementia. While the pathogenesis of dementia is complex and incompletely understood, it may be, at least to a certain extent, the consequence of systemic vascular pathology. The metabolic syndrome and its individual components induce a proinflammatory state that damages blood vessels. This condition of chronic inflammation may damage the vasculature of the brain or be directly neurotoxic. Associations have been established between the metabolic syndrome, its constituents and dementia. A relationship has also been observed between certain dietary factors, such as constituents of the ‘Mediterranean diet’, and the metabolic syndrome; similar associations have been noted between these dietary factors and dementia. Fruit juices and extracts are under investigation as treatments for cognitive impairment. Blueberry, strawberry, blackberry, grape and plum juices or extracts have been successfully tested in cognitively impaired rodents. Published trials of the benefits of grape and blueberry juice in the treatment of small numbers of cognitively impaired persons have recently appeared. The benefits of fruit products are thought to be a result of its polyphenol content. A grape polyphenol found in grapes, resveratrol, now being studied in humans, and one in grapes and blueberries, pterostilbene, have been found to improve cognition in rodents. In the design of future human trials, one ought to consider the poor bioavailability of these products, the possible need to initiate the experimental therapy long before the onset of symptoms, and currently limited knowledge about the appropriate form (e.g. juice, powder or individual polyphenol) of treatment.

Key words: Fruits: Polyphenols: Cognition: Ageing

The pathogenesis of dementia and nutrition

While slowing of cognition and some short-term memory loss occur with normal ageing, there is also an increase in a pathological cognitive condition, dementia, with age^(1,2). The condition affects globally over 35 million people, and will more than triple in the USA in the next four decades⁽³⁾. Dementia is defined by its symptomatology. Demented patients have chronic functional difficulty with memory, in addition to one of the following abnormalities: deficits in executive function (problem-solving, organising a plan to carry out a multi-step activity), agnosia (naming people or objects), aphasia (perception) or apraxia (executing speech or movement)^(4–6). Those with some cognitive impairment but that does not meet the definition of ‘dementia’ are considered to have ‘mild cognitive impairment’⁽⁴⁾.

The most common form of dementia, which occurs in more than half of all cases, is Alzheimer’s disease, which is characterised pathologically by amyloid plaques and neurofibrillary tangles⁽³⁾. A significant minority of cases of dementia, having radiological evidence of infarction, can be referred to as having vascular or multi-infarct dementia. However, vascular pathology may also be present in Alzheimer’s disease, and the term ‘mixed dementia’ is sometimes referred to patients who have features of both Alzheimer’s and vascular dementia⁽⁷⁾. Together, these conditions account for more than 80% of all cases of dementia. Parkinson’s disease and alcohol are the other causes of dementia; and rarer dementias also have their distinctive pathologies.

The pathogenesis of Alzheimer’s disease is a complex, much studied, but yet incompletely understood topic, the totality of

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which cannot be addressed fully in this paper. Abnormal processing of amyloid peptides whose function is not well understood, occurs as a result of both genetic and other factors, in which mitochondrial failure, formation of neurofibrillary tangles involving mutations of the tau protein, and reduction of the number of synapses in the hippocampus are all involved⁽³⁾. Defective epigenetic DNA repair has also been implicated^(8–10).

The effect of vascular disease on the brain may contribute to at least some of these pathological processes. Vascular pathology is present in autopsy specimens of 60–90% of all patients with Alzheimer's disease⁽³⁾. As previously mentioned, Alzheimer's disease and vascular dementia can coexist.

A proinflammatory state, which is characteristic of the metabolic syndrome (a syndrome defined by central adiposity and two or more of the following: (1) high fasting plasma glucose, (2) low-HDL cholesterol, (3) high blood pressure or (4) high TAG⁽¹¹⁾), has also been found to be related to dementia and systemic vascular disease^(12,13). Individual components of the metabolic syndrome – hypertension, hyperlipidaemia, diabetes and high BMI – have also been associated with the incidence of dementia⁽¹²⁾. Amyloid precursor protein, a protein whose misprocessing is one of the important neuronal cellular abnormalities observed in Alzheimer's disease, is itself a proinflammatory cytokine that is also present in adipocytes⁽¹²⁾. There is a relationship between the production of amyloid precursor protein and other proinflammatory cytokines, such as IL-1 β , IL-6 and IL-8⁽¹²⁾.

Dietary factors may be related to the development of the metabolic syndrome. Persons who consume a 'Mediterranean-style diet', less fat, especially saturated fat, meat, and more fruits and vegetables, are less likely to develop this condition⁽¹⁴⁾. Both animal and human investigations of the roles of individual components of this diet show that many of its constituents, such as plant polyphenols, may have a beneficial effect on the components of the metabolic syndrome^(15–20,21). Among these, berry polyphenols are under active study as treatments. Grape seed compounds prevent the differentiation of adipocytes *in vitro*, lower blood pressure in humans and reduce ischaemic damage in animal models of myocardial infarction^(21–23). Resveratrol, a polyphenol found in numerous fruits including grapes, is being currently investigated as a treatment for the metabolic syndrome in a clinical trial^(24,25).

Much research has also suggested a relationship between nutrition and dementia. Several epidemiological studies have implied an association between fruits and vegetables and dementia^(26,27). One investigation found a relationship between consumption of a variety of foods: fruits, dark, green leafy and cruciferous vegetables, tomatoes, fish, nuts, poultry and salad dressings, with Alzheimer's disease⁽²⁶⁾. Closer adherence to a Mediterranean diet was also correlated with a lowered risk of dementia⁽²⁸⁾.

Polyphenols and their mechanism of action on cognitive illness

Polyphenols are being considered as a potential treatment or preventive agent for dementia. Polyphenols may have multiple physiological effects that serve to protect the brain from the pathogenic

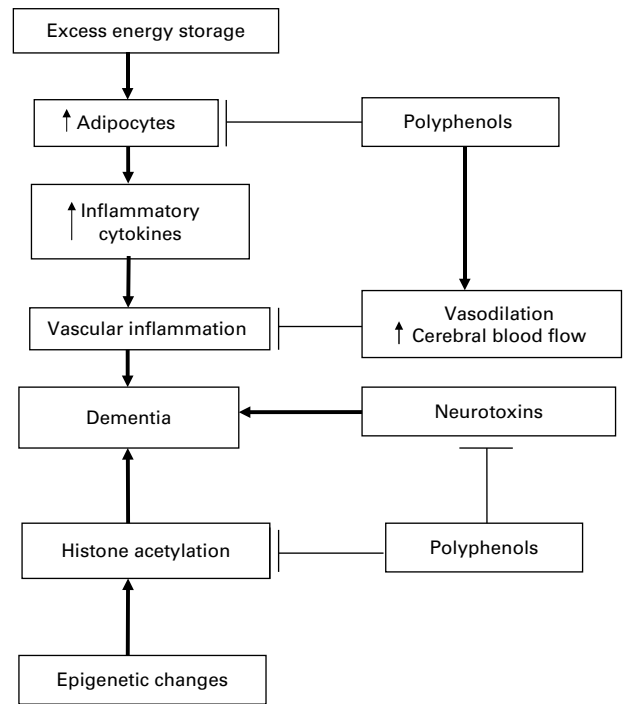


Fig. 1. Potential mechanisms for polyphenol activity against dementing illness.

mechanism underlying dementia. One effect may be a systemic anti-inflammatory action (Fig. 1). Polyphenols retard systemic vascular inflammation by reducing the production of adipocyte-generated inflammatory cytokines through the regulation of adipocyte development. More than fifteen polyphenols have been found to regulate the adipocyte lifecycle, causing anti-proliferative changes such as preventing adipocyte maturation, retarding lipid storage and inducing adipocyte apoptosis⁽²⁹⁾. The best-studied fruit polyphenol, resveratrol, interacts at the cellular level with a gene called Sirtuin 1 (*SIRT1*)⁽³⁰⁾. Activation of *SIRT1* heightens insulin release and sensitivity, and promotes the differentiation of many types of cells, but arrests the development of adipocytes⁽³¹⁾.

Several polyphenols, including resveratrol and quercetin, lower inflammatory cytokine levels, improve insulin sensitivity and glucose and insulin levels, and reduce blood pressure in animal models and preliminary human trials⁽³²⁾. In one investigation, mice that ingested a high-fructose diet and high-cholesterol diet with added resveratrol had a heightened glucose tolerance, insulin sensitivity and lower cholesterol than mice that did not consume resveratrol⁽³³⁾. In another study on mice, rodents that ingested resveratrol had lower amounts of visceral fat, and reduced levels of glucose, TAG, cholesterol, and the inflammatory cytokines monocyte chemoattractant protein-1 (MCP-1) and TNF- α ⁽³⁴⁾. Rats consuming resveratrol for 4 weeks had decreased levels of lipids and serum glucose⁽³⁵⁾. In a study, ten overweight older subjects (average age of 72 years) with reduced glucose tolerance who ingested resveratrol for 4 weeks augmented their insulin sensitivity⁽³⁶⁾.

Quercetin is another polyphenol with anti-inflammatory activity. The polyphenol reduces the output of the proinflammatory cytokines IL-8 and TNF- α *in vitro*⁽³⁷⁾. Individuals with

the metabolic syndrome who consumed quercetin achieved small reductions in blood pressure⁽³⁸⁾.

Polyphenols may be beneficial in the treatment of cognitive disorders by protecting the brain vasculature against the proinflammatory state induced by the metabolic syndrome. Diabetic rats that received resveratrol showed a significantly better performance on memory tests (rats were placed in a device where they learned to avoid foot shocks) than those that received a placebo⁽³⁹⁾.

Polyphenols, especially cocoa flavonols, may also preserve cognition by causing other beneficial changes in the cerebral vasculature (Fig. 1). These include enhancing cerebral blood flow, local endothelial repair mechanisms, and retarding platelet aggregation and augmenting vasodilation through increasing nitric oxide levels⁽⁴⁰⁾. Resveratrol promotes the production of nitrous oxide⁽³¹⁾. This preservation of the cerebral vasculature may allow the maintenance of hippocampal neurons, the loss of which may be an important feature in dementing illness⁽⁴⁰⁾.

In addition, polyphenols may have direct neuroprotective effects on neurons. Resveratrol averts neuronal loss in several animal models in which neurons are exposed to toxic agents.

Resveratrol protected mouse neurons *in vitro* when exposed to toxins⁽⁴¹⁾. In newborn rats, resveratrol reduced neuronal loss after traumatic brain injury⁽⁴²⁾. Rats with dementia caused through injections of streptozocin had improved memory and learning (tested by maze negotiation and avoidance of foot shocks) after being given resveratrol⁽⁴³⁾. In another rat dementia model, in which rats were injected with colchicine, resveratrol again alleviated the deficit in cognitive function measured by the water maze test⁽⁴⁴⁾. Elderly rats fed pterostilbene, another polyphenol found in grapes and blueberries, had better performances on the water maze test than those fed a control substance, and pterostilbene provided even greater *in vitro* protection in a chemical-induced neurotoxicity model than resveratrol⁽³²⁾.

While the mechanism of this neuroprotective effect has not been fully elucidated, there are many possible hypotheses. Polyphenols activate the neurotransmitter on neurons that facilitate neuronal and microglial growth gene pathways⁽⁴⁰⁾. A polyphenol subtype, flavonoids, which include resveratrol, quercetin and epigallocatechin gallate, in animal models modulate the synthesis, processing and disposal of amyloid peptides that may be important in the pathogenesis of dementia⁽⁴⁰⁾.

Polyphenols may induce epigenetic changes that are neuroprotective (Fig. 1). Histone acetylation may be implicated in the pathogenesis of several dementing illnesses, including Alzheimer's disease and Parkinson's disease^(45,46). SIRT1, which may be a target of resveratrol action, also codes for an enzyme known as histone deacetylase⁽⁴⁷⁾. This enzyme causes conformational changes in histones about which DNA is wrapped, that reveal the DNA to prepare it for transcription by RNA polymerases⁽⁴⁸⁾. Mice engineered with a defect in histone acetylation show greater memory deficits in old age⁽⁴⁹⁾.

Clinical trials on the use of resveratrol in combination with other substances in the treatment of dementia are now underway. At the Bronx, New York, United States Department of Veterans Affairs Medical Center, an investigation is underway

in which sixty subjects with Alzheimer's disease are being given grape juice supplemented with resveratrol, malate and glucose, or a placebo drink for 1 year⁽⁵⁰⁾. At the Medical College of Wisconsin, another placebo-controlled trial is taking place in which fifty subjects with Alzheimer's disease are taking one 215 mg tablet a day for 1 year of Longevinex, a dietary supplement that contains resveratrol, quercetin (another grape polyphenol), rice bran, ferulic acid and 1200 IU of vitamin D₃⁽⁵¹⁾.

Fruit juices and extracts

Polyphenols occur naturally in fruits and plants, which can be synthesised into fruit juices and extracts. The polyphenols in these compounds may act individually or synergistically to protect cognition through the same mechanisms as do individual polyphenols.

Consumption of fruit extracts and juices may preserve neurons and improve cognition in aged rodents^(52,53). Blueberry products are among the most well-studied in this context. Blueberry supplements increase the levels of neuroprotective heat shock proteins in aged rats⁽⁵⁴⁾. In a study, 6-month-old (young) rats that were fed blueberry extracts for 8 months (until old age) had better performances on a water maze test (a test of recall and spatial learning in which rats are placed in water and given cues to find a hidden platform to allow it to leave the water)⁽⁵⁵⁾ than those fed a placebo⁽⁵⁶⁾. Addition of a blueberry supplement to 15-month-old (elderly) rats significantly enhanced their ability on an object recognition test⁽⁵⁷⁾. In another trial, old rats that ate a blueberry extract for 2 months had significantly better balanced walking across a wire or rotating rod and negotiated the water maze more quickly than at baseline, which control rats fed a placebo supplement did not⁽⁵⁸⁾. However, in a similar trial in which the rats were given a blueberry supplement for an extra month, the rodents demonstrated improved motor function as demonstrated by the ability to hang on to a tilted screen, but did not have improved cognitive function in water maze tests⁽⁵⁹⁾. Rats that had cognitive impairment induced by injection of a neurotoxic agent (kainic acid) and consumed over 2 months a blueberry extract had a better maze performance than those that did not⁽⁶⁰⁾. When transgenic mice engineered to create an Alzheimer's disease model of dementia were given a blueberry supplement, they maintained better coordination, strength, muscle tone and balance, but did not have fewer amyloid plaques in their brains⁽⁶¹⁾. Blueberry extracts also preserved neurogenesis in the hippocampus of elderly rats⁽⁶²⁾.

An investigation of the benefit of blueberry juice in the treatment of people with cognitive impairment has been published⁽⁶³⁾. A total of nine subjects, mean age 76.2, drank 6–9 ml/kg of commercially manufactured blueberry juice a day for 3 months. In the study, seven other subjects consumed a placebo drink. At the end of 3 months, those who consumed blueberry juice had a 41% improvement on the Verbal Paired Associate Learning Test (a test of the associations between two unrelated words, 13.2 *v.* 9.3 on a 0-to-20 word pair scoring scale; *P*=0.009) and a 33% improvement on the California Verbal Learning Test (a test of list learning and recall, 9.6 *v.* 7.2 on a 0-to-16 word scoring scale; *P*=0.04). In addition, on the

Verbal Paired Associate Learning Test, those who consumed blueberry juice had 86% higher scores as compared to those who consumed the placebo drink (13 *v.* 7; $P=0.03$), but there was not a significant difference between groups in scores on the California Verbal Learning Test.

Grape products are also being actively investigated. Grape seed extract has been observed to increase antioxidant enzyme levels in rodent brains⁽⁶⁴⁾. Mixtures of grape polyphenols inhibit the formation of amyloid plaques in mouse dementia models^(65,66). Young mice genetically engineered to become demented that consumed a grape polyphenol extract performed better on the water maze test than those given water instead⁽⁶⁶⁾.

The first published human trial showing the benefit of a grape-derived product on cognition was recently published. In this trial, twelve subjects with mild cognitive impairment drank 6–9 ml/kg of Concord grape juice or a placebo for 3 months⁽⁶⁷⁾. Subjects who drank grape juice had a 20% improvement in their score (38 *v.* 33 items) on a 44-item California Verbal Learning Test ($P=0.04$) from baseline.

At the University of Oslo, Norway, a trial has recently been completed in which elderly individuals who are not demented but had a 'gradual subjective memory decline' were given 9 weeks of a 50% bilberry (European blueberry), 50% red grape juice mixture in a double-blinded, placebo-controlled trial⁽⁶⁸⁾. The results of the trial have not yet appeared in print.

Other fruit juices have improved cognition in animal models, and some have been used in human trials. In a previously mentioned trial which included a blueberry extract, a strawberry supplement also enhanced rats' speed at completing a water maze and ability to cross a wire⁽⁵⁸⁾. In another trial involving blueberry juice, a cranberry extract enhanced the ability of rats to cling to a wire, but did not affect cognition⁽⁵⁹⁾. In a study, fifty normal elderly individuals drank 32 ounces a day of a drink containing 27% cranberry juice or a placebo⁽⁶⁹⁾. However, there were no differences in neuropsychological testing between subjects in the two groups at the end of this 6-week study. Elderly rats that drank blackberry juice completed the water maze test in less time and were able to balance on a rotating rod for longer than those given a placebo⁽⁷⁰⁾. Old rats that drank plum juice for 2 months negotiated the water maze more quickly, but those that consumed a plum powder had no benefit⁽⁷¹⁾. Apple juice prevented cognitive impairment and increased amyloid- β in aged mice caused by dietary folate or apoE deficiency^(72–74). In an open-label trial, twenty-one elderly persons with Alzheimer's disease drank two four-ounce glasses of apple juice daily for 30 d. The institutional caregivers of these subjects described a 27% improvement in behavioural symptoms, although there was no change in cognition⁽⁷⁵⁾.

Future considerations

Thus far, the research on the use of fruit polyphenols in the treatment of cognitive impairment appears promising. However, there are many further considerations that need to be addressed in the design of more definitive studies.

First, one important consideration is the optimum age for the initiation of therapy. The pathogenic progress resulting in

dementia, which might be the consequence of a systemic inflammatory process on the vasculature, might occur years before the onset of symptoms. If this is the case, the optimum time for the initiation of therapy might be in young or middle age, long before symptoms occur. In rodent trials, starting treatments in middle age, which might occur after more than a year in a 2-year lifespan, is not a great difficulty. However, in a human trial, one might have to give the supplement for decades to observe the optimum effect, making the study unfeasible.

In addition, the bioavailability of polyphenols consumed from supplements has been called into question^(76–78). The bioavailability of most polyphenols, especially those of higher molecular weight is quite limited^(76,77,79–82). They are poorly absorbed and extensively metabolised first in the intestine, where they are conjugated through glucuronidation, methylation or sulphation⁽⁸¹⁾. They are then transported to the liver, where they undergo further metabolism⁽⁸¹⁾. Finally, they are readily excreted in the urine or in the bile, resulting in low serum levels for most polyphenols^(79,81,82). Pharmacokinetic studies in humans have confirmed this pattern for resveratrol and quercetin, which have been analysed both in single- and multiple-dose administration. However, many of the investigation of the bioavailability of other polyphenols have relied upon the ingestion of single doses of substances. There is controversy involving the accuracy of the assays used to detect the levels of polyphenols and their metabolites, resulting in additional uncertainty about possible error^(79,80). Studies of resveratrol pharmacokinetics may have underestimated serum resveratrol plasma levels due to technical problems in quantification⁽⁸²⁾.

Furthermore, it is unclear how readily the small quantities that enter the blood stream cross the blood–brain barrier⁽⁷⁸⁾. If the effect of polyphenols on the brain is primarily mediated through its systemic effect on the vasculature, the latter concern is less important. Furthermore, the concern about bioavailability is based on studies of the pharmacokinetics of certain individual polyphenols, particularly resveratrol, which may be less applicable for other polyphenols and mixtures. In fact, the effects of polyphenols might be mediated through the active metabolites of ingested polyphenols, or through the synergism of multiple polyphenols in a compound, such as that occurring in fruit extracts or juices^(76,82).

A related consideration is the form in which polyphenols are consumed. Polyphenols may be given naturally as a fruit, processed into juices, extracts and tablets, or given as individual polyphenols. At present, there is not much evidence about which form is the best to administer.

In a previously mentioned study on the effect of plum extract on rat cognition, the greater effect caused by plum juice than plum powder was postulated to be either the result of a greater polyphenol content of the juice, changes in the form, differences in the amounts and bioavailability of different polyphenols, or caused by differences in the manufacture and storing of juice and powder from the fruit⁽⁷¹⁾. Further chemical and pharmacokinetic studies may be necessary to fully resolve these issues.

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