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REVIEW PAPER

Preserving Brain Function in Aging: The Anti-glycative Potential of Berry Fruit

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Abstract Advanced glycation end products (AGEs) are naturally occurring macromolecules that are formed in vivo by the non-enzymatic modification of proteins, lipids, or nucleic acids by sugar, even in the absence of hyperglycemia. In the diet, AGEs are found in animal products, and additional AGEs are produced when those foods are cooked at high temperatures. Studies have linked AGEs to various age-related physiological changes, including wrinkles, diabetic complications, and neurodegenerative disease, including Alzheimer's disease. Dietary berry fruits have been shown to reduce the severity or slow the progression of many physiological changes and disease pathologies that accompany aging. Emerging evidence has shown that the phytochemicals found in berry fruits exhibit anti-glycative activity. In this review, we briefly summarize the current evidence supporting the neuroprotective anti-glycative activity of berry fruits and their potential to preserve cognitive function during aging.

Keywords Advanced glycation end products · AGEs · Aging · Berry · Cognition · Glycation

Abbreviations

AGE	Advanced glycation end product
dAGE	Dietary AGE
AD	Alzheimer's disease
ROS	Reactive oxygen species
CML	Carboxymethyl-lysine
MG	Methylglyoxal
TCA cycle	Tricarboxylic acid cycle
T2DM	Type 2 diabetes mellitus
sMG	Serum methylglyoxal
RAGE	Receptor for AGE
BSC I	Bovine skin collagen type I
BSA	Bovine serum albumin
HSA	Human serum albumin
LTP	Long-term potentiation
STZ	Streptozotocin

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Introduction

It has been proposed that glycative modification of proteins causes changes at the cellular and tissue levels, which contribute to a variety of age-related pathologies. Glycation was first described by Louis Camille Maillard, in the beginning of the twentieth century, as the browning reaction between reactive monosaccharides and amino acids during food processing. This process was later identified as a pathway leading to the formation of advanced glycation end products (AGEs) (Henle 2005). Since then, many studies have demonstrated that Maillard browning contributes to the color, taste, and aroma of foods; furthermore, the products from this reaction also affect the nutritional and toxicological properties of food (Vlassara and Uribarri 2004). The importance of Maillard products and AGEs was not recognized by the food industry and medical community until a quarter of century later (Finot 2005; Bengmark 2007).

AGEs are a byproduct of the non-enzymatic reaction of reducing sugars with proteins, lipids, and nucleic acids.

This reaction alters their function by disrupting molecular conformation, promoting cross-linking, altering enzyme activity, reducing their clearance, and impairing receptor recognition (Stirban et al. 2013). To date, AGEs have been identified as a strong contributor to diabetic complications (Mullarkey et al. 1990; van Boekel 1991; Koschinsky et al. 1997) and neurodegenerative diseases such as Alzheimer's disease (AD) (Sasaki et al. 1998; Bengmark 2007). Unsurprisingly, hyperglycemia, a condition often associated with heightened AGE levels, is a risk factor for cognitive impairment and dementia (Biessels et al. 2006; Brands et al. 2007; Crane et al. 2013). Diets rich in fruits and vegetables are often recommended to reduce the risk of non-communicable diseases and have a positive effect on blood sugar (Sargeant et al. 2001; Slavin and Lloyd 2012; Pem and Jeewon 2015). Consumption of berry fruits has been shown to decrease inflammation (Zafra-Stone et al. 2007), improve cardiovascular health (Sayegh et al. 2014; Wightman and Heuberger 2015), protect neurons against high-energy and charged particles (Shukitt-Hale et al. 2013; Poulose et al. 2014), and improve age-related declines in cognition (Willis et al. 2009; Krikorian et al. 2010; Malin et al. 2011). The antioxidant and anti-inflammatory properties of the bioactive phytochemicals found in fruits and vegetables are believed to contribute to the observed health benefits. Interestingly, recent studies suggest that many of these phenolic phytochemicals exhibit anti-glycative activity in addition to their antioxidant activity, and these two activities may have synergistic health benefits. This review describes AGE formation and the potential role of dietary bioactives in combating their deleterious effects.

Metabolic Sources of AGEs

The formation of AGEs can occur both in vivo and ex vivo in the presence of sugars and protein. Endogenous AGEs derive from two major pathways, non-enzymatic glycosylation and auto-oxidative glycosylation. Non-enzymatic glycosylation, also known as the Maillard reaction, glycation, and the "classic" or Hodge pathway, is initiated by the addition of sugar's carbonyl group to the amino group of a protein to form Schiff's base intermediates, which then undergo further rearrangement into ketoamine Amadori products. This reaction can be divided into early (reversible) and late (irreversible) stages. In the early stage, stable Amadori products are formed from the rearrangement of glycosylamines; reversibility of the products is dependent on the concentration of the compound and incubation time. Amadori products then undergo dehydration, condensation, fragmentation, oxidation, and cyclization; these processes result in the formation of AGEs, a heterogeneous group of side-chained amino acids (Fig. 1) that are characterized by their structures, the ability to fluoresce, and the ability to initiate cross-linking (Lin 2006).

Alternatively, the oxidation of monosaccharides catalyzed by transition metals, such as copper and iron, generates dicarbonyl products that can react with proteins and lead to the formation of AGEs (Wells-Knecht et al. 1995). Therefore, this pathway is termed auto-oxidative glycosylation. The rate of reaction for both of the pathways is affected by various factors, such as temperature, pH, carbonyl/amine ratio, and time of exposure (Poulsen et al. 2013). AGE formation can occur under anaerobic conditions; however, the presence of reactive oxygen species (ROS) significantly increases the rate of formation (Baynes and Thorpe 2000). Some of the endogenous AGEs that have been well researched include N epsilon-(carboxymethyl) lysine (CML), pentosidine, pyrraline, imidazolone, and crossline (Brownlee 1995; Kikuchi et al. 2003).

Dietary Sources of AGEs

In addition to endogenous sources, AGEs are also present in our daily diet. Foods comprised of animal products contain AGEs; however, cooking accelerates the formation of AGEs in food, especially food rich in fats and proteins (Goldberg et al. 2004). Furthermore, modern cooking practices such as grilling, broiling, roasting, searing, and frying substantially accelerate the levels of AGEs (Goldberg et al. 2004). Relative dietary AGE (dAGE) content per serving in some commonly consumed foods is summarized in Table 1. It is evident that the foods which contain high amounts of fats or oils are prone to produce excessive AGEs upon processing or cooking. Fruits, whole grains, and milk are generally low in dAGEs. The harmful effects of dAGEs were largely ignored because AGEs are resistant to enzymatic digestion, and the oral bioavailability of AGEs absorbed from the gastrointestinal tract is low—approximately 10 % of total AGEs present in food (Koschinsky et al. 1997; He et al. 1999). However, recent studies have established that supplementation of AGE-rich diets in humans and animals has significantly contributed to heightened levels of endogenous AGEs (Koschinsky et al. 1997; He et al. 1999).

A comprehensive list of dAGEs and guiding food choices to reduce dAGE intake are provided in the new database for dAGEs (Uribarri et al. 2010).

Dicarbonyl intermediates of the Maillard reaction such as glyoxal and methylglyoxal (MG), as well as Amadori compound CML, play a role in aging and disease pathologies (Frye et al. 1998; Bair et al. 2010). However, exogenous MG and CML contents have been shown to vary widely

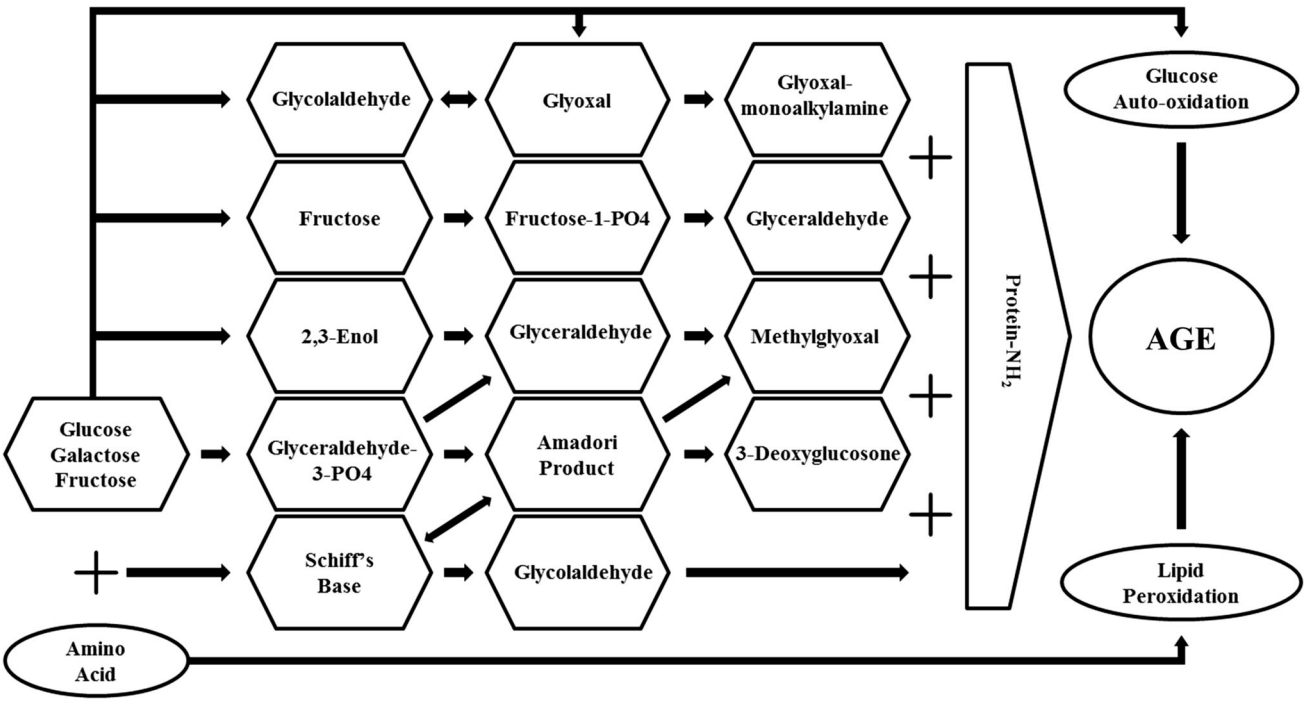

Fig. 1 Pathways for the formation of advanced glycation end products (AGEs). In the early stages of reaction, monosaccharides, such as glucose, fructose, and galactose, interact non-enzymatically with peptides, proteins, and nucleic acid via Schiff's base, to form a relatively stable Amadori product. The reactions leading up to Amadori formation are reversible depending on the concentration and incubation time. The late stage reaction, an irreversible reaction, involves dehydration, hydrolysis, condensation, fragmentation, and oxidation of Amadori product to form AGEs. Glycolytic intermediates and lipid peroxidation can contribute to the formation of AGEs in vivo

depending upon the type of cooking practice followed (Uribarri et al. 2010). For example, milk contains nearly negligible amounts of MG and CML, while butter and cheese have more than 1000-fold higher amounts of these dicarbonyl byproducts. Similarly, there is a 100-fold increase in levels of MG in pan-fried steak, compared to that of raw meat. Acidic (low pH) food constituents, such as vitamin C or vinegar marinade, has been shown to reduce the formation of AGEs by arresting the glycation process (Uribarri et al. 2010). Besides food, it has been hypothesized that AGEs are formed during the curing and aging of tobacco (Nicholl and Bucala 1998). A study by Cerami et al. (1997) demonstrated that both the aqueous extracts of tobacco and cigarette smoke contain highly reactive AGEs that readily cross cell membranes and, in the form of cigarette smoke, are absorbed through the lungs, leading to rapid induction of AGE-modified protein in vivo.

Cellular Effects of AGEs

Protein glycation promotes cellular dysfunction through multiple mechanisms. Glycation causes structural changes to protein, which can inhibit specific functions, such as those of the cytoskeleton and antioxidant enzymes (McLean et al. 1992; Ledesma et al. 1994; Yan and Harding 1997). Furthermore, changes in protein structure can also result in cross-linkage, aggregation, and precipitation of proteins (Eble et al. 1983; McPherson et al. 1988; Vlassara and Uribarri 2004; Bengmark 2006). For example, arteriosclerosis is a disease where the cytotoxicity of glycation involved in its pathogenesis is well understood. In arteriosclerosis, cross-linkage of proteins increases tissue remodeling, thickening and stiffening of the basement membranes, as well as serving as a reactive site where circulating serum proteins, such as lipoproteins, are covalently trapped, leading to decreased vessel dilation capability (Cerami et al. 1997; Singh et al. 2001). Moreover, AGE modification of ApoB prevents normal uptake, thus reducing cholesterol efflux (reviewed by Singh et al. 2001). Recent evidence has also suggested that protein glycation increases oxidative damage directly (Lee et al. 1998; Yim et al. 2001) and indirectly accelerates oxidative damage (Qian et al. 1998; Sobal et al. 2000).

Accumulation of AGEs, such as CML, has been reported in the mitochondrial matrix of aged animals (Bakala et al. 2003). It has been reported that glycation of renal mitochondrial proteins induces a significant increase in

Table 1 Dietary AGE content in commonly consumed foods, based on carboxymethyl lysine content and assessed using ELISA technique (Uribarri et al. 2010)

Food item	AGEs (kU/100 g)	AGEs (kU/serving)
Bacon, fried 5 min no added oil	91,577	11,905
Beef, broiled 450 °F, 5 min	11,270	10,143
Butter, whipped	26,480	1324
Chicken, nuggets, fast food	8627	7764
Bacon, microwaved	9023	1173
Oil, canola	9020	451
Chicken, roasted then BBQ	8802	7922
Pizza, thin crust	6825	6825
Almonds, roasted	6650	1995
Almonds, blanched slivered	5473	1642
Egg, fried, one large	2749	1237
Chips, potato	2883	865
Avocado	1577	473
Potato, white, French fries	1522	1522
Beef, ground marinated with lemon juice	1538	1384
Chicken, boiled in water, 1 h	1123	1011
Chicken, boiled with lemon	957	861
Fish, loaf, boiled 90 min	761	685
Salmon, smoked	572	515
Egg, poached, below simmer, 5 min	90	27
Apple, baked	45	45
Onion	36	36
Tomato	23	23
Potato, white, boiled 25 min	17	17
Apple, Macintosh	13	13
Rice, white, boiled 10 min	9	9
Banana	9	9
Coffee, with sugar	7.6	19
Coffee, with milk	6.8	17
Juice, cranberry	3	8
Milk, fat free	2	4
Juice, apple	2	5
Coffee, with milk and sugar	2.4	6

superoxide production (Rosca et al. 2005). Methylglyoxal (an AGE intermediate) has been shown to suppress the tricarboxylic acid cycle (TCA cycle) and electron respiratory chain (Ray et al. 1994; Rosca et al. 2002, 2005). Furthermore, a recent study by Speer et al. (2003) has suggested that MG inhibits mitochondrial permeability transition by covalently modifying the mitochondrial permeability transition pore. Thus, it is apparent that the glycation process is a potent initiator of mitochondrial dysfunction.

Furthermore, ex vivo-derived AGEs can induce cellular alterations once absorbed into cells. For example, tobacco-derived AGEs have been shown to accumulate in the lens and coronary artery vascular walls (Nicholl and Bucala 1998). Food-derived AGEs have been reported to induce ROS, suppress antioxidant reserves (e.g., GSH/GSSG ratio), and induce cytokine production in cultured endothelial cells (Cai et al. 2002). Similarly, diabetic animals fed an AGE-rich diet developed diabetic vascular or renal pathology, whereas their age-matched controls on an AGE-poor diet remained nearly free of such pathology (Zheng et al. 2002; Lin et al. 2003). These findings suggest that food-derived AGE precursors can induce significant modification of macromolecules, causing them to be toxic to target cells.

The interaction between AGEs and their receptors has been reported to activate various signaling pathways that can: (A) significantly influence cellular functions (Heidland et al. 2001; Ott et al. 2014), (B) enhance oxidative and nitrosative stress (Cai et al. 2006, 2007; Ott et al. 2014),

(C) induce cellular proliferation (Huang et al. 1999; Guh et al. 2001), (D) upregulate expression of genes involved in tissue remodeling, regeneration, and inflammatory response (reviewed by Singh et al. 2001), (E) increase production of reactive oxygen species (ROS) in macrophages, microglia, and endothelial cells (Schmidt et al. 1994; Wautier et al. 1994; Yan et al. 1994; Lander et al. 1997; Basta et al. 2005), and (F) induce apoptosis (Nitti et al. 2005). Furthermore, chronic overproduction of AGEs leads to chronic inflammatory responses and abnormal growth of certain cells (reviewed by Singh et al. 2001).

AGEs and Cognitive Function

Glucose is the brain's primary source of energy. Over time, glucose undergoes a cascade of non-enzymatic reactions with proteins, lipids, and nucleic acids and ultimately forms various types of AGEs, which accumulate in brain regions associated with learning and memory (i.e., cerebral cortex and hippocampus) (Thangthaeng et al. 2008). A hyperglycemic environment, as seen in diabetes mellitus (DM), facilitates the formation of AGEs, thus increasing the risk of cognitive impairment and dementia (Biessels et al. 2006). A cross-sectional study by Brands and colleagues comparing cognitive performance between subjects with type 2 diabetes mellitus (T2DM) to age-matched controls showed that those with T2DM performed significantly, but modestly, worse than controls on cognitive tasks, particularly on tasks that required high levels of mental efficiency (Brands et al. 2007). Moreover, longitudinal studies of subjects with T2DM showed an accelerated cognitive decline as compared to age-matched subjects without T2DM (Knopman et al. 2001; Yaffe et al. 2012). Interestingly, high peripheral AGE levels were associated with greater cognitive decline regardless of DM (Yaffe et al. 2011).

In addition to endogenous AGEs, dietary AGEs (dAGEs) have been identified as a potentially modifiable cause of cognitive decline. Cai et al. (2014) demonstrated that serum methylglyoxal (sMG) was positively correlated with dAGEs, and higher sMG levels predicted accelerated cognitive decline in older adults (Cai et al. 2014; Perrone and Grant 2015). Similarly, long-term supplementation with MG impaired psychomotor function and object recognition performance in C57/BL6 mice when compared with age-matched controls (Cai et al. 2014). Moreover, recent studies by Perrone and Grant examining the relationship between estimated dAGEs and the incidence of Alzheimer's disease (AD) reported a significant positive correlation between dAGEs and AD incidence, suggesting dietary AGEs as a risk factor for AD (Perrone and Grant 2015).

Taken together, elevated levels of endogenous AGEs or dAGEs may trigger cognitive dysfunction. For example, the glycated form of amyloid-β induced a higher degree of cognitive impairment, dendritic spine deterioration, suppression of long-term potentiation (LTP), and down-regulation of synaptic proteins when compared with its non-glycated form (Chen et al. 2014). This may be because the glycated form is a better ligand for the receptor for AGEs (RAGEs) than the non-glycated form, leading to greater neuronal death (Li et al. 2013). Not surprisingly, when an accelerated aging mouse model (SAMP 8) was treated with anti-glycation compound J147 for 7 months, these mice were found to have preserved cognitive function and restored molecular markers of synaptic function, vascular pathology, and inflammation at 10 months of age when compared with age-matched controls (Currais et al. 2015).

Anti-glycative Effects of Berries

Dietary berry fruits have been associated with healthful benefits, which are partially attributed to the antioxidant properties of the phytochemicals they contain (for further review see Miller and Shukitt-Hale 2012; Shukitt-Hale et al. 2015; Skrovankova et al. 2015). An extract of *Vaccinium vitis-idaea L.* (*V. vitis-idaea L.*, commonly known as mountain cranberry or lingonberry), an ingredient of Cree traditional herbal medicine used to treat diabetic symptoms, was shown to inhibit the formation of fluorescent AGE species and CML adducts of bovine serum albumin (CML-BSA) in vitro (Beaulieu et al. 2010). Later, other berry fruit extracts were shown to exhibit anti-glycative activity with black bearberry, crowberry, common juniper, and bog cranberry being among the most potent (Harris et al. 2014). Using in vitro systems, Liu et al. (2011) also demonstrated that cranberry phytochemicals display anti-glycative activity, especially fractions enriched with procyanidins.

Commonly consumed berries such as cranberries, strawberries, and blueberries also display anti-glycative activity. In an in vitro study conducted by Parengkuan et al. (2013), glucose incubated with either human serum albumin (HSA) or bovine skin collagen type I (BSC I) was used to test the anti-glycative activity of various fruit extracts. Both strawberry ($IC_{50\ HSA} = 0.288$ mg/ml, $IC_{50\ BSCI} = 0.607$ mg/ml) and blueberry ($IC_{50\ HSA} = 0.293$ mg/ml, $IC_{50\ BSCI} = 0.207$ mg/ml) extracts significantly inhibited glycation of albumin and collagen. The potency of strawberry and blueberry extracts was slightly lower but comparable to the positive control, aminoguanidine ($IC_{50\ HSA} = 0.0603$ mg/ml, $IC_{50\ BSCI} = 0.232$ mg/ml). The authors proposed that the bioactive phytochemicals in the berries were responsible for the anti-glycative activity observed.

Recent evidence suggests that the antioxidant activities of berry phytochemicals may mediate anti-glycative activities. For example, phenolic acids, such as ferulic acid, resveratrol, chlorogenic acid, caffeic acid, cinnamic acid and its derivatives, as well as ellagic acid have been reported to inhibit AGE formation in vitro through inhibition of the advanced stage of the glycation reaction, which involves an oxidation/reduction step (Sadowska-Bartosz et al. 2014; Sadowska-Bartosz and Bartosz 2015). However, a structural analysis study by Matsuda et al. (2003) indicated that not all antioxidants were able to prevent AGE formation. Flavonoids with strong superoxide anion radical scavenging activity more potently inhibit AGE formation as compared to those with weak superoxide anion radical scavenging activity. Furthermore, a study by Harris et al. (2011) demonstrated that the total phenolic content and free radical scavenging activity of ethanolic extracts from 17 medicinal plants were positively associated with anti-glycative activity. Wei and colleagues have also shown that phenolic compounds removed from their sugar moieties, found in blueberries, blackberries, strawberries, raspberries, cranberries, and Noble muscadine grapes, reduce the production of AGEs by scavenging bicarbonyl products, such as MG formation in vitro (Wang et al. 2011). In berries, procyanidins and catechins are constituents known to quench glyoxal and MG intermediaries (Wang et al. 2011).

Studies examining the effects of polyphenol treatment in diabetic rodent models have reported some positive effects. A study by Ciddi and colleagues treated streptozotocin (STZ)-induced diabetic rats with resveratrol (10 mg/kg) orally for 3 weeks and reported that resveratrol treatment significantly decreased AGE formation in the kidneys relative to non-treated controls (Ciddi and Dodda 2014). Like resveratrol, fisetin, a flavonol commonly found in strawberry, (~40 mg/kg/day) reduced MG-modified proteins in the cerebral cortex, blood, and kidneys of Akita mice, a type I DM mouse model, when fed for 18 weeks. Interestingly, normal C57/BL6 mice, fed with fisetin (~25 mg/kg/day) from 6 weeks of age to 24 weeks of age, also had significantly less MG-modified proteins in their cerebral cortices than age-matched controls (Maher et al. 2011). These results suggest that the anti-glycative activity of fisetin may have beneficial effects in the aging brain.

Berries are also rich in vitamin C and numerous phenolic acids that are known to inhibit the glycation of carbohydrates and proteins, thereby reducing AGE formation (Uribarri et al. 2010). Berry phytochemicals are also known to interact with numerous signaling molecules in the brain, which reduce oxidative burden and improve neuronal signaling (Poulose et al. 2012). Recent evidence also indicates that AGEs interact with amyloid-β plaques and ubiquitinated inclusion bodies, thereby increasing neurotoxicity and increasing toxic protein aggregation in the brains of AD patients (Ko et al. 2015). However, dietary berry fruits have been shown to reduce the amyloid-β burden and enhance autophagic protein homeostasis, leading to improved cognitive function, in rodent models of aging (Poulose et al. 2014, 2015; Shukitt-Hale et al. 2015).

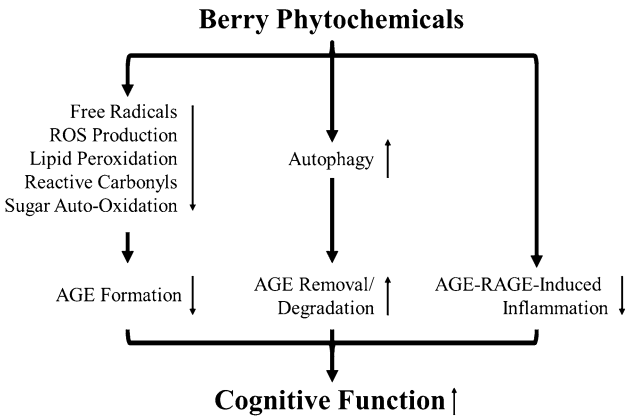

Fig. 2 Schematic representation of the possible mechanisms of berries in reducing AGEs and improving cognitive function

Conclusions

Mounting evidence indicates that AGEs may be a key contributor to pathophysiology and age-related impairment; thus, there is a need to develop potent and effective AGE inhibitors. Clinical trials studying synthetic AGE inhibitors have yielded inconsistent and unconvincing evidence of efficacy and have raised concern regarding the possible toxicity of synthetic AGE inhibitor molecules. Berry fruits phytochemicals are a potential potent natural AGE inhibitor. In vitro studies have shown that many berry fruits and their bioactive phytochemicals display a robust ability to inhibit AGE formation through their antioxidant properties. Additionally, berry fruits phytochemicals may protect AGE-induced neurotoxicity by reducing inflammation signaling, as well as enhancing AGEs degradation through autophagy. As illustrated in Fig. 2, combination of these effects is hypothesized to produce an improvement in cognitive function. Interestingly, to date, no clinical studies have examined the effect of dietary berry fruit on AGE-related mechanisms of neurodegeneration; however, preclinical data strongly suggest an association of berry fruit supplementation with cognitive improvements and prevention of age-associated neurodegeneration. Therefore, natural products with potent anti-glycative activity present a promising approach to reduce the endogenous and exogenous burden of AGE at the cellular and neuronal

level, thereby contributing to the possible cognitive improvements.

Compliance with Ethical Standards

Conflicts of interest The authors declare no financial or other conflicts of interest in the writing of this paper.

References

Bair, W. B, 3rd, Cabello, C. M., Uchida, K., Bause, A. S., & Wondrak, G. T. (2010). GLO1 overexpression in human malignant melanoma. *Melanoma Research, 20*, 85–96. doi:10.1097/CMR.0b013e3283364903.

Bakala, H., Delaval, E., Hamelin, M., Bismuth, J., Borot-Laloi, C., Corman, B., & Friguet, B. (2003). Changes in rat liver mitochondria with aging. Lon protease-like reactivity and N(epsilon)-carboxymethyllysine accumulation in the matrix. *European Journal of Biochemistry, 270*, 2295–2302.

Basta, G., Lazzerini, G., Del Turco, S., Ratto, G. M., Schmidt, A. M., & De Caterina, R. (2005). At least 2 distinct pathways generating reactive oxygen species mediate vascular cell adhesion molecule-1 induction by advanced glycation end products. *Arteriosclerosis, Thrombosis, and Vascular Biology, 25*, 1401–1407. doi:10.1161/01.ATV.0000167522.48370.5e.

Baynes, J. W., & Thorpe, S. R. (2000). Glycoxidation and lipoxidation in atherogenesis. *Free Radical Biology and Medicine, 28*, 1708–1716.

Beaulieu, L. P., Harris, C. S., Saleem, A., Cuerrier, A., Haddad, P. S., Martineau, L. C., et al. (2010). Inhibitory effect of the Cree traditional medicine wiishichimanaanh (Vaccinium vitis-idaea) on advanced glycation endproduct formation: Identification of active principles. *Phytother Res, 24*, 741–747. doi:10.1002/ptr.3025.

Bengmark, S. (2006). Impact of nutrition on ageing and disease. *Current Opinion in Clinical Nutrition and Metabolic Care, 9*, 2–7.

Bengmark, S. (2007). Advanced glycation and lipoxidation end products–amplifiers of inflammation: The role of food. *JPEN Journal of Parenteral and Enteral Nutrition, 31*, 430–440.

Biessels, G. J., Staekenborg, S., Brunner, E., Brayne, C., & Scheltens, P. (2006). Risk of dementia in diabetes mellitus: A systematic review. *Lancet Neurology, 5*, 64–74.

Brands, A. M., Van den Berg, E., Manschot, S. M., Biessels, G. J., Kappelle, L. J., De Haan, E. H., & Kessels, R. P. (2007). A detailed profile of cognitive dysfunction and its relation to psychological distress in patients with type 2 diabetes mellitus. *Journal of the International Neuropsychological Society, 13*, 288–297.

Brownlee, M. (1995). Advanced protein glycosylation in diabetes and aging. *Annual Review of Medicine, 46*, 223–234. doi:10.1146/annurev.med.46.1.223.

Cai, W., Gao, Q. D., Zhu, L., Peppa, M., He, C., & Vlassara, H. (2002). Oxidative stress-inducing carbonyl compounds from common foods: Novel mediators of cellular dysfunction. *Molecular Medicine, 8*, 337–346.

Cai, W., He, J. C., Zhu, L., Chen, X., Wallenstein, S., Striker, G. E., & Vlassara, H. (2007). Reduced oxidant stress and extended lifespan in mice exposed to a low glycotoxin diet. Association with Increased AGER1 Expression. *American Journal of Pathology, 170*, 1893–1902. doi:10.2353/ajpath.2007.061281.

Cai, W., He, J. C., Zhu, L., Lu, C., & Vlassara, H. (2006). Advanced glycation end product (AGE) receptor 1 suppresses cell oxidant stress and activation signaling via EGF receptor. *Proceedings of the National Academy of Sciences USA, 103*, 13801–13806. doi:10.1073/pnas.0600362103.

Cai, W., Uribarri, J., Zhu, L., Chen, X., Swamy, S., Zhao, Z., et al. (2014). Oral glycotoxins are a modifiable cause of dementia and the metabolic syndrome in mice and humans. *Proceedings of the National Academy of Sciences USA, 111*, 4940–4945. doi:10.1073/pnas.1316013111.

Cerami, C., Founds, H., Nicholl, I., Mitsuhashi, T., Giordano, D., Vanpatten, S., et al. (1997). Tobacco smoke is a source of toxic reactive glycation products. *Proceedings of the National Academy of Sciences USA, 94*, 13915–13920.

Chen, C., Li, X. H., Tu, Y., Sun, H. T., Liang, H. Q., Cheng, S. X., & Zhang, S. (2014). Abeta-AGE aggravates cognitive deficit in rats via RAGE pathway. *Neuroscience, 257*, 1–10. doi:10.1016/j.neuroscience.2013.10.056.

Ciddi, V., & Dodda, D. (2014). Therapeutic potential of resveratrol in diabetic complications: In vitro and in vivo studies. *Pharmacol Reports, 66*, 799–803. doi:10.1016/j.pharep.2014.04.006.

Crane, P. K., Walker, R., Hubbard, R. A., Li, G., Nathan, D. M., Zheng, H., et al. (2013). Glucose levels and risk of dementia. *New England Journal of Medicine, 369*, 540–548. doi:10.1056/NEJMoa1215740.

Currais, A., Goldberg, J., Farrokhi, C., Chang, M., Prior, M., Dargusch, R., et al. (2015). A comprehensive multiomics approach toward understanding the relationship between aging and dementia. *Aging (Albany NY), 7*, 937–955.

Eble, A. S., Thorpe, S. R., & Baynes, J. W. (1983). Nonenzymatic glucosylation and glucose-dependent cross-linking of protein. *Journal of Biological Chemistry, 258*, 9406–9412.

Finot, P. A. (2005). Historical perspective of the Maillard reaction in food science. *Annals of the New York Academy of Sciences, 1043*, 1–8. doi:10.1196/annals.1333.001.

Frye, E. B., Degenhardt, T. P., Thorpe, S. R., & Baynes, J. W. (1998). Role of the Maillard reaction in aging of tissue proteins. Advanced glycation end product-dependent increase in imidazolium cross-links in human lens proteins. *Journal of Biological Chemistry, 273*, 18714–18719.

Goldberg, T., Cai, W., Peppa, M., Dardaine, V., Baliga, B. S., Uribarri, J., & Vlassara, H. (2004). Advanced glycoxidation end products in commonly consumed foods. *Journal of the American Dietetic Association, 104*, 1287–1291.

Guh, J. Y., Huang, J. S., Chen, H. C., Hung, W. C., Lai, Y. H., & Chuang, L. Y. (2001). Advanced glycation end product-induced proliferation in NRK-49F cells is dependent on the JAK2/STAT5 pathway and cyclin D1. *American Journal of Kidney Diseases, 38*, 1096–1104.

Harris, C. S., Beaulieu, L. P., Fraser, M. H., McIntyre, K. L., Owen, P. L., Martineau, L. C., et al. (2011). Inhibition of advanced glycation end product formation by medicinal plant extracts correlates with phenolic metabolites and antioxidant activity. *Planta Medica, 77*, 196–204. doi:10.1055/s-0030-1250161.

Harris, C. S., Cuerrier, A., Lamont, E., Haddad, P. S., Arnason, J. T., Bennett, S. A., & Johns, T. (2014). Investigating wild berries as a dietary approach to reducing the formation of advanced glycation endproducts: Chemical correlates of in vitro antiglycation activity. *Plant Foods for Human Nutrition, 69*, 71–77. doi:10.1007/s11130-014-0403-3.

He, C., Sabol, J., Mitsuhashi, T., & Vlassara, H. (1999). Dietary glycotoxins: Inhibition of reactive products by aminoguanidine facilitates renal clearance and reduces tissue sequestration. *Diabetes, 48*, 1308–1315.

Heidland, A., Sebekova, K., & Schinzel, R. (2001). Advanced glycation end products and the progressive course of renal disease. *American Journal of Kidney Diseases, 38*, S100–S106.

Henle, T. (2005). Protein-bound advanced glycation endproducts (AGEs) as bioactive amino acid derivatives in foods. *Amino Acids, 29*, 313–322. doi:10.1007/s00726-005-0200-2.

Huang, J. S., Guh, J. Y., Hung, W. C., Yang, M. L., Lai, Y. H., Chen, H. C., & Chuang, L. Y. (1999). Role of the Janus kinase (JAK)/signal transducters and activators of transcription (STAT) cascade in advanced glycation end-product-induced cellular mitogenesis in NRK-49F cells. *Biochemical Journal, 342*(Pt 1), 231–238.

Kikuchi, S., Shinpo, K., Takeuchi, M., Yamagishi, S., Makita, Z., Sasaki, N., & Tashiro, K. (2003). Glycation–a sweet tempter for neuronal death. *Brain Research. Brain Research Reviews, 41*, 306–323.

Knopman, D., Boland, L. L., Mosley, T., Howard, G., Liao, D., Szklo, M., et al. (2001). Cardiovascular risk factors and cognitive decline in middle-aged adults. *Neurology, 56*, 42–48.

Ko, S. Y., Ko, H. A., Chu, K. H., Shieh, T. M., Chi, T. C., Chen, H. I., et al. (2015). The possible mechanism of advanced glycation end products (AGEs) for Alzheimer's disease. *PLoS One, 10*, e0143345. doi:10.1371/journal.pone.0143345.

Koschinsky, T., He, C. J., Mitsuhashi, T., Bucala, R., Liu, C., Buenting, C., et al. (1997). Orally absorbed reactive glycation products (glycotoxins): An environmental risk factor in diabetic nephropathy. *Proceedings of the National Academy of Sciences USA, 94*, 6474–6479.

Krikorian, R., Shidler, M. D., Nash, T. A., Kalt, W., Vinqvist-Tymchuk, M. R., Shukitt-Hale, B., & Joseph, J. A. (2010). Blueberry supplementation improves memory in older adults. *Journal of Agriculture and Food Chemistry, 58*, 3996–4000.

Lander, H. M., Tauras, J. M., Ogiste, J. S., Hori, O., Moss, R. A., & Schmidt, A. M. (1997). Activation of the receptor for advanced glycation end products triggers a p21(ras)-dependent mitogen-activated protein kinase pathway regulated by oxidant stress. *Journal of Biological Chemistry, 272*, 17810–17814.

Ledesma, M. D., Bonay, P., Colaco, C., & Avila, J. (1994). Analysis of microtubule-associated protein tau glycation in paired helical filaments. *Journal of Biological Chemistry, 269*, 21614–21619.

Lee, C., Yim, M. B., Chock, P. B., Yim, H. S., & Kang, S. O. (1998). Oxidation-reduction properties of methylglyoxal-modified protein in relation to free radical generation. *Journal of Biological Chemistry, 273*, 25272–25278.

Li, X. H., Du, L. L., Cheng, X. S., Jiang, X., Zhang, Y., Lv, B. L., et al. (2013). Glycation exacerbates the neuronal toxicity of beta-amyloid. *Cell Death and Disease, 4*, e673. doi:10.1038/cddis.2013.180.

Lin, L. (2006). RAGE on the Toll Road? *Cellular and Molecular Immunology, 3*, 351–358.

Lin, R. Y., Choudhury, R. P., Cai, W., Lu, M., Fallon, J. T., Fisher, E. A., & Vlassara, H. (2003). Dietary glycotoxins promote diabetic atherosclerosis in apolipoprotein E-deficient mice. *Atherosclerosis, 168*, 213–220.

Liu, H., Liu, H., Wang, W., Khoo, C., Taylor, J., & Gu, L. (2011). Cranberry phytochemicals inhibit glycation of human hemoglobin and serum albumin by scavenging reactive carbonyls. *Food Funct, 2*, 475–482. doi:10.1039/c1fo10087d.

Maher, P., Dargusch, R., Ehren, J. L., Okada, S., Sharma, K., & Schubert, D. (2011). Fisetin lowers methylglyoxal dependent protein glycation and limits the complications of diabetes. *PLoS One, 6*, e21226. doi:10.1371/journal.pone.0021226.

Malin, D. H., Lee, D. R., Goyarzu, P., Chang, Y. H., Ennis, L. J., Beckett, E., et al. (2011). Short-term blueberry-enriched diet prevents and reverses object recognition memory loss in aging rats. *Nutrition, 27*, 338–342. doi:10.1016/j.nut.2010.05.001.

Matsuda, H., Wang, T., Managi, H., & Yoshikawa, M. (2003). Structural requirements of flavonoids for inhibition of protein glycation and radical scavenging activities. *Bioorg Med Chem, 11*, 5317–5323.

McLean, W. G., Pekiner, C., Cullum, N. A., & Casson, I. F. (1992). Posttranslational modifications of nerve cytoskeletal proteins in experimental diabetes. *Molecular Neurobiology, 6*, 225–237.

McPherson, J. D., Shilton, B. H., & Walton, D. J. (1988). Role of fructose in glycation and cross-linking of proteins. *Biochemistry, 27*, 1901–1907.

Miller, M. G., & Shukitt-Hale, B. (2012). Berry fruit enhances beneficial signaling in the brain. *Journal of Agriculture and Food Chemistry, 60*, 5709–5715. doi:10.1021/jf2036033.

Mullarkey, C. J., Edelstein, D., & Brownlee, M. (1990). Free radical generation by early glycation products: A mechanism for accelerated atherogenesis in diabetes. *Biochem Biophys Res Commun, 173*, 932–939.

Nicholl, I. D., & Bucala, R. (1998). Advanced glycation endproducts and cigarette smoking. *Cellular and Molecular Biology, 44*, 1025–1033.

Nitti, M., d'Abramo, C., Traverso, N., Verzola, D., Garibotto, G., Poggi, A., et al. (2005). Central role of PKCdelta in glycoxidation-dependent apoptosis of human neurons. *Free Radical Biology and Medicine, 38*, 846–856. doi:10.1016/j.freeradbiomed.2004.12.002.

Ott, C., Jacobs, K., Haucke, E., Navarrete Santos, A., Grune, T., & Simm, A. (2014). Role of advanced glycation end products in cellular signaling. *Redox Biology, 2*, 411–429. doi:10.1016/j.redox.2013.12.016.

Parengkuan, L., Yagi, M., Matsushima, M., Ogura, M., Hamada, U., & Yonei, Y. (2013). Anti-glycation activity of various fruits. *J. Anti-Aging Med, 10*(3), 70–76.

Pem, D., & Jeewon, R. (2015). Fruit and vegetable intake: Benefits and progress of nutrition education interventions- narrative review article. *Iranian Journal of Public Health, 44*, 1309–1321.

Perrone, L., & Grant, W. B. (2015). Observational and ecological studies of dietary advanced glycation end products in national diets and Alzheimer's disease incidence and prevalence. *Journal of Alzheimer's Disease, 45*, 965–979. doi:10.3233/JAD-140720.

Poulose, S. M., Bielinski, D. F., Carrihill-Knoll, K. L., Rabin, B. M., & Shukitt-Hale, B. (2014). Protective effects of blueberry- and strawberry diets on neuronal stress following exposure to (56) Fe particles. *Brain Research, 1593*, 9–18. doi:10.1016/j.brainres.2014.10.028.

Poulose, S. M., Carey, A. N., & Shukitt-Hale, B. (2012). Improving brain signaling in aging: Could berries be the answer? *Expert Review of Neurotherapeutics, 12*, 887–889. doi:10.1586/ern.12.86.

Poulose, S. M., Thangthaeng, N., Miller, M. G., & Shukitt-Hale, B. (2015). Effects of pterostilbene and resveratrol on brain and behavior. *Neurochemistry International, 89*, 227–233. doi:10.1016/j.neuint.2015.07.017.

Poulsen, M. W., Hedegaard, R. V., Andersen, J. M., de Courten, B., Bugel, S., Nielsen, J., et al. (2013). Advanced glycation endproducts in food and their effects on health. *Food and Chemical Toxicology, 60*, 10–37. doi:10.1016/j.fct.2013.06.052.

Qian, M., Liu, M., & Eaton, J. W. (1998). Transition metals bind to glycated proteins forming redox active "glycochelates": Implications for the pathogenesis of certain diabetic complications. *Biochem Biophys Res Commun, 250*, 385–389. doi:10.1006/bbrc.1998.9326.

Ray, S., Dutta, S., Halder, J., & Ray, M. (1994). Inhibition of electron flow through complex I of the mitochondrial respiratory chain of Ehrlich ascites carcinoma cells by methylglyoxal. *Biochemical Journal, 303*(Pt 1), 69–72.

Rosca, M. G., Monnier, V. M., Szweda, L. I., & Weiss, M. F. (2002). Alterations in renal mitochondrial respiration in response to the reactive oxoaldehyde methylglyoxal. *American Journal of*

Physiology-Renal Physiology, 283, F52–F59. doi:10.1152/ajprenal.00302.2001.

Rosca, M. G., Mustata, T. G., Kinter, M. T., Ozdemir, A. M., Kern, T. S., Szweda, L. I., et al. (2005). Glycation of mitochondrial proteins from diabetic rat kidney is associated with excess superoxide formation. *American Journal of Physiology-Renal Physiology, 289*, F420–F430. doi:10.1152/ajprenal.00415.2004.

Sadowska-Bartosz, I., & Bartosz, G. (2015). Prevention of protein glycation by natural compounds. *Molecules, 20*, 3309–3334. doi:10.3390/molecules20023309.

Sadowska-Bartosz, I., Galiniak, S., & Bartosz, G. (2014). Polyphenols protect against protein glycoxidation. *Free Radical Biology and Medicine, 75*(Suppl 1), S47. doi:10.1016/j.freeradbiomed.2014.10.810.

Sargeant, L. A., Khaw, K. T., Bingham, S., Day, N. E., Luben, R. N., Oakes, S., et al. (2001). Fruit and vegetable intake and population glycosylated haemoglobin levels: The EPIC-Norfolk Study. *European Journal of Clinical Nutrition, 55*, 342–348. doi:10.1038/sj.ejcn.1601162.

Sasaki, N., Fukatsu, R., Tsuzuki, K., Hayashi, Y., Yoshida, T., Fujii, N., et al. (1998). Advanced glycation end products in Alzheimer's disease and other neurodegenerative diseases. *American Journal of Pathology, 153*, 1149–1155.

Sayegh, M., Miglio, C., & Ray, S. (2014). Potential cardiovascular implications of Sea Buckthorn berry consumption in humans. *International Journal of Food Sciences and Nutrition, 65*, 521–528. doi:10.3109/09637486.2014.880672.

Schmidt, A. M., Hori, O., Brett, J., Yan, S. D., Wautier, J. L., & Stern, D. (1994). Cellular receptors for advanced glycation end products. Implications for induction of oxidant stress and cellular dysfunction in the pathogenesis of vascular lesions. *Arteriosclerosis and Thrombosis, 14*, 1521–1528.

Shukitt-Hale, B., Bielinski, D. F., Lau, F. C., Willis, L. M., Carey, A. N., & Joseph, J. A. (2015). The beneficial effects of berries on cognition, motor behaviour and neuronal function in ageing. *British Journal of Nutrition, 114*(10), 1542–1549. doi:10.1017/S0007114515003451.

Shukitt-Hale, B., Lau, F. C., Cheng, V., Luskin, K., Carey, A. N., Carrihill-Knoll, K., et al. (2013). Changes in gene expression in the rat hippocampus following exposure to 56Fe particles and protection by berry diets. *Central Nervous System Agents in Medicinal Chemistry, 13*(1), 36–42.

Singh, R., Barden, A., Mori, T., & Beilin, L. (2001). Advanced glycation end-products: A review. *Diabetologia, 44*, 129–146.

Skrovankova, S., Sumczynski, D., Mlcek, J., Jurikova, T., & Sochor, J. (2015). Bioactive compounds and antioxidant activity in different types of berries. *International Journal of Molecular Sciences, 16*, 24673–24706. doi:10.3390/ijms161024673.

Slavin, J. L., & Lloyd, B. (2012). Health benefits of fruits and vegetables. *Advances in Nutrition, 3*, 506–516. doi:10.3945/an.112.002154.

Sobal, G., Menzel, J., & Sinzinger, H. (2000). Why is glycated LDL more sensitive to oxidation than native LDL? A comparative study. *Prostaglandins Leukotrienes and Essential Fatty Acids, 63*, 177–186. doi:10.1054/plef.2000.0204.

Speer, O., Morkunaite-Haimi, S., Liobikas, J., Franck, M., Hensbo, L., Linder, M. D., et al. (2003). Rapid suppression of mitochondrial permeability transition by methylglyoxal. Role of reversible arginine modification. *Journal of Biological Chemistry, 278*, 34757–34763. doi:10.1074/jbc.M301990200.

Stirban, A., Gawlowski, T., & Roden, M. (2013). Vascular effects of advanced glycation endproducts: Clinical effects and molecular mechanisms. *Mol Metab, 3*, 94–108. doi:10.1016/j.molmet.2013.11.006.

Thangthaeng, N., Sumien, N., & Forster, M. J. (2008). Dissociation of functional status from accrual of CML and RAGE in the aged mouse brain. *Experimental Gerontology, 43*, 1077–1085. doi:10.1016/j.exger.2008.08.045.

Uribarri, J., Woodruff, S., Goodman, S., Cai, W., Chen, X., Pyzik, R., et al. (2010). Advanced glycation end products in foods and a practical guide to their reduction in the diet. *Journal of the American Dietetic Association, 110*(911–16), e12. doi:10.1016/j.jada.2010.03.018.

van Boekel, M. A. (1991). The role of glycation in aging and diabetes mellitus. *Molecular Biology Reports, 15*, 57–64.

Vlassara, H., & Uribarri, J. (2004). Glycoxidation and diabetic complications: Modern lessons and a warning? *Rev Endocr Metab Disord, 5*, 181–188. doi:10.1023/B:REMD.0000032406.84813.f6.

Wang, W., Yagiz, Y., Buran, T., do Nascimento Nunes, C., & Gu, L. (2011). Phytochemicals from berries and grapes inhibited the formation of advanced glycation end-products by scavenging reactive carbonyls. *Food Research International, 44*, 2666–2673.

Wautier, J. L., Wautier, M. P., Schmidt, A. M., Anderson, G. M., Hori, O., Zoukourian, C., et al. (1994). Advanced glycation end products (AGEs) on the surface of diabetic erythrocytes bind to the vessel wall via a specific receptor inducing oxidant stress in the vasculature: A link between surface-associated AGEs and diabetic complications. *Proceedings of the National Academy of Sciences USA, 91*, 7742–7746.

Wells-Knecht, K. J., Zyzak, D. V., Litchfield, J. E., Thorpe, S. R., & Baynes, J. W. (1995). Mechanism of autoxidative glycosylation: identification of glyoxal and arabinose as intermediates in the autoxidative modification of proteins by glucose. *Biochemistry, 34*, 3702–3709.

Wightman, J. D., & Heuberger, R. A. (2015). Effect of grape and other berries on cardiovascular health. *Journal of the Science of Food and Agriculture, 95*, 1584–1597. doi:10.1002/jsfa.6890.

Willis, L. M., Shukitt-Hale, B., & Joseph, J. A. (2009). Recent advances in berry supplementation and age-related cognitive decline. *Current Opinion in Clinical Nutrition and Metabolic Care, 12*, 91–94. doi:10.1097/MCO.0b013e32831b9c6e.

Yaffe, K., Falvey, C., Hamilton, N., Schwartz, A. V., Simonsick, E. M., Satterfield, S., et al. (2012). Diabetes, glucose control, and 9-year cognitive decline among older adults without dementia. *Archives of Neurology, 69*, 1170–1175. doi:10.1001/archneurol.2012.1117.

Yaffe, K., Lindquist, K., Schwartz, A. V., Vitartas, C., Vittinghoff, E., Satterfield, S., et al. (2011). Advanced glycation end product level, diabetes, and accelerated cognitive aging. *Neurology, 77*, 1351–1356. doi:10.1212/WNL.0b013e3182315a56.

Yan, H., & Harding, J. J. (1997). Glycation-induced inactivation and loss of antigenicity of catalase and superoxide dismutase. *Biochemical Journal, 328*(Pt 2), 599–605.

Yan, S. D., Schmidt, A. M., Anderson, G. M., Zhang, J., Brett, J., Zou, Y. S., et al. (1994). Enhanced cellular oxidant stress by the interaction of advanced glycation end products with their receptors/binding proteins. *Journal of Biological Chemistry, 269*, 9889–9897.

Yim, M. B., Yim, H. S., Lee, C., Kang, S. O., & Chock, P. B. (2001). Protein glycation: Creation of catalytic sites for free radical generation. *Annals of the New York Academy of Sciences, 928*, 48–53.

Zafra-Stone, S., Yasmin, T., Bagchi, M., Chatterjee, A., Vinson, J. A., & Bagchi, D. (2007). Berry anthocyanins as novel antioxidants in human health and disease prevention. *Molecular Nutrition and Food Research, 51*, 675–683. doi:10.1002/mnfr.200700002.

Zheng, F., He, C., Cai, W., Hattori, M., Steffes, M., & Vlassara, H. (2002). Prevention of diabetic nephropathy in mice by a diet low in glycoxidation products. *Diabetes/Metabolism Research and Reviews, 18*, 224–237. doi:10.1002/dmrr.283.