

Special bioactive compounds and functional foods may exhibit neuroprotective effects in patients with dementia (Review)

MUTSUMI MURAKAMI*, YUKA IKEDA, YUKIE NAKAGAWA, AI TSUJI,
YASUKO KITAGISHI and SATORU MATSUDA*

Department of Food Science and Nutrition, Nara Women's University, Kita-Uoya Nishimachi, Nara 630-8506, Japan

Received March 18, 2019; Accepted May 7, 2020

DOI: 10.3892/br.2020.1310

Abstract. Dementia is a failure of cognitive ability characterized by severe neurodegeneration in select neural systems, and Alzheimer's disease (AD) is the most common type of neurodegenerative disease. Although numerous studies have provided insights into the pathogenesis of AD, the underlying signaling and molecular pathways mediating the progressive decline of cognitive function remain poorly understood. Recent progress in molecular biology has provided an improved understanding of the importance of molecular pathogenesis of AD, and has proposed an association between DNA repair mechanisms and AD. In particular, the fundamental roles of phosphatase and tensin homologue deleted on chromosome 10 (PTEN) and breast cancer gene 1 (BRCA1) tumor suppressors have been shown to regulate the pathogenesis of neurodegeneration. Consequently, onset of neurodegenerative diseases may be deferred with the use of dietary neuroprotective agents which alter the signaling mediated by the aforementioned tumor suppressors. In a healthy neuron, homeostasis of key intracellular molecules is of great importance, and preventing neuronal apoptosis is one of the primary goals of treatments designed for dementia-associated diseases. In the present review, progress into the understanding of dietary regulation for preventing

or limiting development of dementia is discussed with a focus on the modulatory roles of PTEN and BRCA1 signaling.

Contents

1. Introduction
2. Role of ROS in the pathogenesis of dementia
3. PTEN and BRCA1 tumor suppressors participate in DNA repair initiated by oxidative DNA damage
4. Certain dietary compounds exhibit neuroprotective effects by modulating PTEN and/or BRCA1 activity
5. Dietary nutrients may reduce oxidative stress
6. Conclusion

1. Introduction

Dementia is a failure of cognitive abilities characterized by severe neurodegeneration in selective neural systems, and the incidence of dementia is predicted to increase significantly within 20 years (1). Dementia is one of the most significant health burdens, and, at present, there are no suitable disease-modifying agents for treatment of progressive dementia. Alzheimer's disease (AD) is the most common form of dementia, and is the most significant health-concern worldwide (2). Pathologically, AD is a slowly progressing neurodegenerative disorder categorized by severe damage of neurons and synapses (3). Aberrations of amyloid- β peptide may be responsible for the neuro-synaptic malfunctions leading to cognitive deficits in AD (4). Genetic factors account for ~80% of the risk contributing to AD, while modifiable factors associated with lifestyle may also be involved (5). Epidemiological studies have suggested that nutrition is one of the most important yet modifiable risk factors of AD (6). Risk factors for vascular dementia, the second most common cause of dementia, include hypertension and metabolic syndrome, which are also modifiable lifestyle factors. Managing these non-genetic risk factors may provide effective opportunities to prevent the progressive cognitive decline.

Studies have shown that oxidative stress represents a major risk factor associated with the pathology of dementia (7,8). Substantial evidence has established that oxidative stress as an aspect in AD is associated with neuronal apoptosis and brain

Correspondence to: Professor Satoru Matsuda, Department of Food Science and Nutrition, Nara Women's University, Kita-Uoya Nishimachi, Nara 630-8506, Japan
E-mail: smatsuda@cc.nara-wu.ac.jp

*Contributed equally

Abbreviations: AD, Alzheimer's disease; ATM, ataxia telangiectasia-mutated; ATP, adenosine triphosphate; BRCA1, breast cancer gene 1; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; PIP3, phosphatidylinositol 3,4,5-triphosphate; PI3K, phosphoinositide-3 kinase; PPAR, peroxisome proliferator-activated receptor; PPRE, PPAR response element; PTEN, phosphatase and tensin homologue deleted on chromosome 10; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; SOD, superoxide dismutase

Key words: PTEN, BRCA1, tumor suppressor, Alzheimer's disease, reactive oxygen species, DNA damage, DNA repair, cell signaling

dysfunction (9). Particularly, mitochondrial dysfunction is a conspicuous feature observed during neurodegeneration (10), which is of importance in the formation of reactive oxygen species (ROS) and thus DNA damage. ROS are a group of oxygen-containing molecules which contribute to increased oxidative stress, and are formed as a result of oxygen metabolism in cells. Thus, increased oxidative stress may result in increased DNA damage, and subsequently apoptosis, which contributes to the degeneration of neuronal tissue. Detoxification of ROS and/or reduction of ROS levels may protect neurons from DNA damage and apoptosis. Since metabolic processes physiologically produce ROS, any means used to reduce ROS levels may assist in decreasing the prevalence and incidence of dementia. Cells possess machinery to retain genomic integrity in response to genotoxic damage. There is increasing evidence which supports the use of different antioxidants as a treatment for AD (11), including vitamins (12). In addition, dietary and nutritional approaches are of significant importance in the management of AD. Improving and altering nutrient intake may reduce the progression of chronic neurodegenerative diseases, an area which has recently been gaining increased interest (13), and nutritional plans are progressively being integrated into public health strategies (14). In the present review, the functions of key intra-cellular signaling molecules involved in oxidative genotoxic stress and DNA repair in neurons are summarized, offering a clarification on the molecular mechanisms for the treatment of dementia. Specific attention is placed on the mechanisms underlying the neuroprotective effects of specific nutrients against dementia in reducing brain damage, which may be used as an efficient therapeutic intervention.

2. Role of ROS in the pathogenesis of dementia

In AD, significant molecular and biochemical changes result in an increase in amyloid- β substance, which is modified by ROS into a toxic product that promotes apoptosis of neurons (15), suggesting a link between progression of AD and oxidative stress. In cells, metabolic processes physiologically produce ROS that cause oxidative damage to DNA (16), and this physiological production of ROS is associated with aging of the brain and neurodegeneration. Under physiological conditions, ROS may act as a second messenger in cells (17). ROS controls several physiological processes, such as the hypoxic response and inflammation, as well as the regulation of growth factor signaling (18). Abnormal accumulation of amyloid- β inhibits long-term potentiation in neurons which is prevented by treatment with antioxidants (19). Therefore, decreasing oxidative damage in the brain may inhibit or reduce the damage to neurons. ROS may exert its effects on cells through the regulation of several target molecules, including PI3K/AKT/PTEN (20). Interactions of ROS with amyloid- β have been shown to prevent mitochondrial respiration (21). In addition, increased levels of ROS within the mitochondria of neurons may disturb synaptic plasticity, and thus memory formation/retention (22). Therefore, ensuring that ROS levels are maintained within physiological ranges may improve outcomes in patients with AD by preventing/reducing damage to neurons. Neurons exhibit considerably high levels of metabolic activity and use distinct oxidative damage-repair mechanisms to reverse

DNA damage (23). Therefore, malfunctions of the DNA repair system in the brain may result in neurological dysfunction. Damaged DNA can be repaired by the DNA repair machinery, which consists of ataxia telangiectasia-mutated (ATM) and ATR, BRCA1, PTEN and others (24). Abnormalities in these molecules are often observed in patients with neurodegenerative diseases (25).

ROS are free radicals under physiological conditions. Hyperglycemia exacerbates the accumulation of ROS in neurons leading to increased apoptosis (26). Several environmental and lifestyle associated factors, including tobacco smoking, alcohol consumption, exposure to ionizing radiation, infections, inflammation and even the aging process may result in increased oxidative stress (27). In addition, in population studies, obese patients have been shown to possess significantly higher serum levels of ROS, suggesting that obesity may increase oxidative stress (28). High-intensity exercise increases oxidative damage and induces disruption of the blood-brain barrier (28). Exercising may upregulate the expression of endogenous antioxidants and thus reduce oxidative damage; however, vigorous exercise may result in the accumulation of ROS (29). Consistent exposure to oxidative stress is an initiator of various chronic diseases including degenerative disorders, diabetes, cardiovascular diseases and cancer. In general however, cells are able to correct damage to DNA as a result of oxidative stress to a certain extent.

3. PTEN and BRCA1 tumor suppressors participate in DNA repair initiated by oxidative DNA damage

PTEN is a tumor suppressor with dual-specificity phosphatase activity; protein phosphatase activity and lipid phosphatase activity, and antagonizes the activity of PI3K (30). Cells lacking PTEN have higher levels of PIP3 which activates downstream targets of PI3K/AKT. The PI3K/AKT signal regulates a variety of cellular events including proliferation, survival and apoptosis of cells (Fig. 1). PTEN is associated with the apoptotic cascade, which may be a result of its effect on decreasing PI3K/AKT signaling (31). In part, neuronal cell death may be attributed to the differences in PTEN expression (32). Inhibition of PTEN protects synaptic function and thus cognition in animal models of AD (33). Suppressing PTEN and/or increasing the activity of AKT reduces the levels of oxidative stress, and thus decreases cell death, suggesting that AKT activation may be required for neuroprotection. Thus, PTEN contributes to the defense mechanisms against severe oxidative damage in the brain. It has been shown that PTEN insufficiency results in an increase in mitochondrial activity, consistent with the activation of the AKT signaling pathway (34), and thus may increase the levels of ROS.

In addition to PTEN, BRCA1 serves an important role in the response to DNA damage (35). The PI3K/AKT signaling pathway has been shown to be constitutively activated in BRCA1-defective cells (35). BRCA1, is one of the best studied and prominent suppressors of breast cancer, mutations of which are associated with breast and/or ovarian cancer risk in addition to genetic susceptibility (36). BRCA1 exerts several effects on the DNA repair system (37). BRCA1-related hereditary cancer is a type of cancer with functional defects

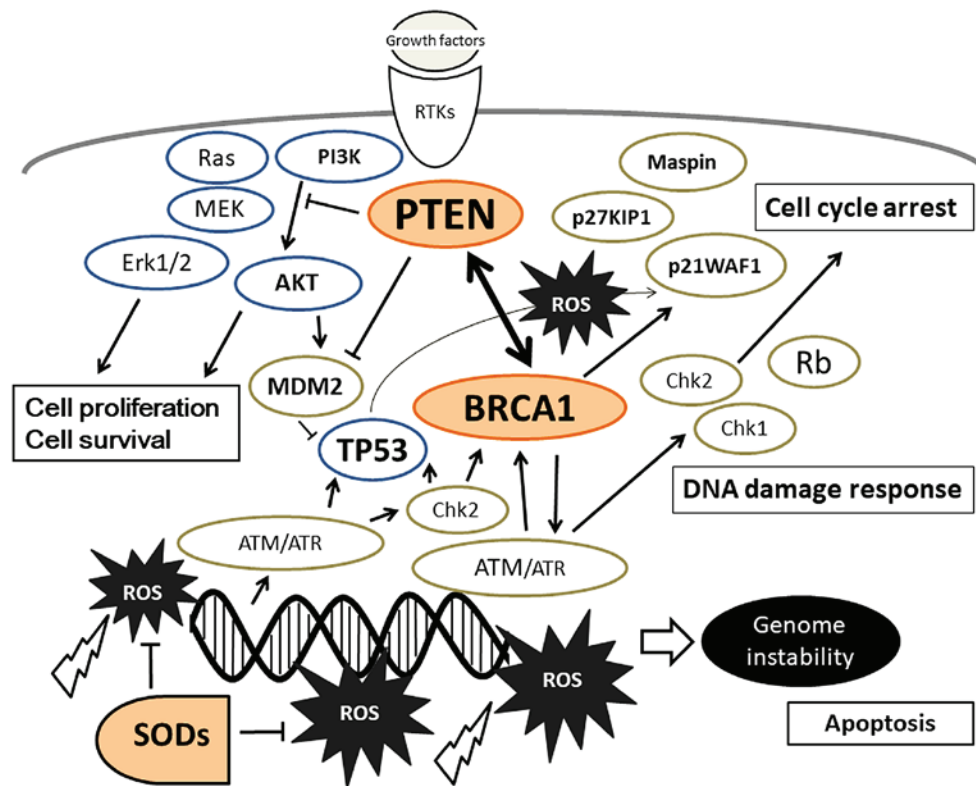


Figure 1. Schematic illustration of PTEN and BRCA1 signaling pathways. Examples of molecules involved in Alzheimer's disease known to affect cell survival, apoptosis and DNA repair are presented. Some critical pathways have been omitted for clarity and brevity. BRCA1, breast cancer gene 1; PTEN, phosphatase and tensin homologue deleted on chromosome 10; PI3K, PI3K, phosphoinositide-3 kinase.

in the DNA repair mechanisms (38). Mutations of the BRCA1 gene are associated with increased genomic instability (30,31), which may increase the rate of accumulation of genetic mutations. The primary recognition molecule for DNA damage is ATM, which is the checkpoint kinase that phosphorylates a number of proteins including BRCA1 in response to DNA damage (39). Reduced levels of BRCA1 expression have been observed in the brains of patients with AD (40). Knocking down neuronal expression of BRCA1 results in an increased rate of DNA double-stranded breaks, synaptic plasticity impairments and memory deficits (40). Therefore, BRCA1 may support neuronal integrity and cognitive function by protecting the neuronal genome, and depletion of neuronal BRCA1 may result in cognitive deficits. Activation of the DNA repair system to protect neurons may occur during the early stages of neurodegeneration, as the impairment of BRCA1 accelerates disease progression (41). Oxidative damage to the DNA of neurons has been demonstrated to be a significant contributing factor in the development of dementia. BRCA1 reduces the production of ROS (42), which in-turn, results in decreased oxidative damage to the DNA (35). BRCA1 also supports the telomere, alterations of which may result in neurodegeneration (43). BRCA1 serves an important role in telomere maintenance, although the exact mechanisms remain unknown (43). Telomere length insufficiency is a typical feature of degenerating neurons in the brains of patients with dementia (44). Additionally, there may be an indirect association between PTEN and BRCA1 gene function (45). PTEN inhibition represses nuclear translocation of BRCA1, which impairs DNA repair resulting in an accumulation of DNA damage (46).

4. Certain dietary compounds exhibit neuroprotective effects by modulating PTEN and/or BRCA1 activity

Due to a lack of reliable treatment options, brain dysfunction and/or dementia is an increasing public health concern. A number of disease-protective factors, such as physical activity, sleep and dietary patterns, have been proposed by epidemiological research (47). Among these factors, dietary choices may exhibit certain neuroprotective effects. In particular, dietary choices may result in alterations to AKT/PTEN as well as BRCA1 signaling, and may prevent neurodegenerative diseases or reduce progression. Several plants and fruits are promising candidates for reducing the progression or risk of dementia diseases. An ingredient derived from the root of *Curcuma longa*, curcumin, present in culinary turmeric, may reverse the effects of dementia on memory (48). The neuroprotective effects of curcumin may be mediated through modification of the PI3K/AKT signaling pathway (49). Kaempferol is a flavanol present in several plants, including grapefruit and edible berries, which has been shown to demonstrate neuroprotective effects in a rat animal model (50), and Kaempferol protects neurons through activation of AKT signaling (51). A neuroprotective ingredient of a Chinese medicinal herb, *Herba epimedii*, Icariin, reduces PTEN expression following activation of PI3K/AKT signaling (52). Furthermore, certain components of rosemary herb prevent the expression of PTEN in K562 myeloid cells (53). In contrast to this, the expression levels of PTEN are increased following treatment with Ginsenoside (54).

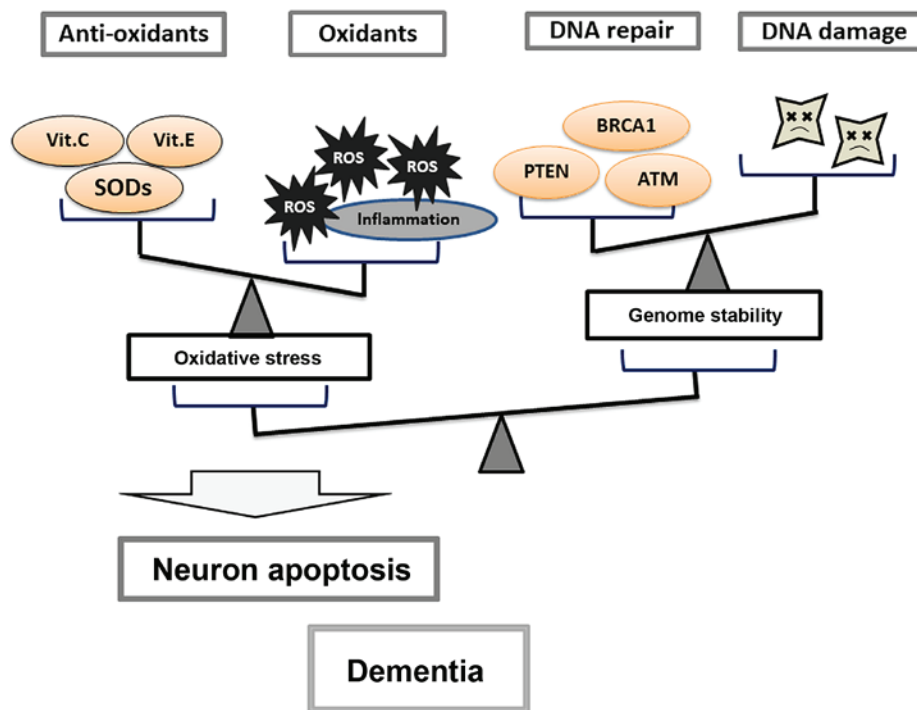


Figure 2. Imbalances in the activities between oxidants and antioxidants and/or between DNA repair and DNA damage contribute to the pathogenesis of dementia as a result of neuronal cell death. SOD, superoxide dismutase; BRCA1, breast cancer gene 1; PTEN, phosphatase and tensin homologue deleted on chromosome 10; Vit., vitamin; ATM, ataxia telangiectasia-mutated.

Fat soluble lycopene is a carotenoid with a red pigment found in several fruits and vegetables such as tomatoes. Treatment with the lycopene increased the mRNA expression levels of BRCA1 (55). In addition, lycopene increases phosphorylation of BRCA1 in breast cancer cells (56). Treatment with phytoestrogens result in higher expression levels of BRCA1 by reversing DNA hypermethylation (57), and individuals with phytoestrogen-rich diets possessed increased expression levels of BRCA1 mRNA (58). Rats exposed to genistein showed higher expression levels of BRCA1 in the mammary glands (59). Genistein and indole-3-carbinol are biochemicals derived from soy and green vegetables, respectively. These phytoestrogens have been shown to reduce the risk of AD progression (60). Furthermore, gallic acid, a phenolic compound present in natural plants, increases the phosphorylation of BRCA1 (61).

The aforementioned potential compounds found in foodstuffs which may exhibit neuroprotective effects, predominantly do so by exerting some sort of influence on tumor suppressor molecules, such as PTEN and BRCA1. Thus, PTEN and BRCA1 functions may be important for individual brain health (Fig. 2). As mentioned above, imbalances in the activity between PTEN and AKT may contribute to the pathogenesis of dementia. Therefore, appropriate activation and/or inhibition for maintaining the balance of kinases may be important (31). Certain food and/or dietary components may aid in maintaining the balance of these signaling molecules by modulating their functional activities (Fig. 3). Thus, future studies should focus on determining the most appropriate method of using these neuroprotective compounds identified in *in vitro* studies and animal models, and translating them to bedside therapeutics.

5. Dietary nutrients may reduce oxidative stress

Superoxide dismutases (SODs) exhibit robust antioxidant activity characterized by their ability to scavenge ROS (61). SODs catalyze the reaction of superoxide to hydrogen peroxide (62). As aberrantly increased ROS levels results in extensive oxidative DNA damage, SODs have been suggested to serve as a principal defense system against oxidative stress. There are three types of SODs that have been identified in humans, SOD1-3. Cytosolic SOD1 may serve a role in conjunction with $\text{Cu}^{2+}/\text{Zn}^{2+}$ ions in the prevention of central nervous system damage (63). Several mutations in the SOD1 gene are responsible for mitochondrial impairments, leading to progressive neurodegenerative diseases including familial amyotrophic lateral sclerosis (64). SOD1-null animals also develop other seemingly unrelated diseases, such as muscle atrophy (65). SOD2 is a functional tumor suppressor, and SOD2 expression has been reported to be significantly reduced in several tumors (65). SOD2 and Mn^{2+} ions are present in the matrix of the mitochondria, the primary site of free radical formation from the electron transport chain. ATP production in mitochondria is impaired in patients with AD (66). Therefore, the primary function of SOD2 may be to protect the mitochondria against oxidative damage. SOD3 and $\text{Cu}^{2+}/\text{Zn}^{2+}$ are secreted into the extracellular matrix and contribute to metabolic regulation of neurons by altering the rate of blood flow (67), and may be induced by chemical antioxidants such as vitamin C (68). Dietary intake of Cu^{2+} stabilizes SOD activity, indicating a potential therapeutic benefit (69). It has been suggested that inhibition of ROS by SODs decreases neuronal cell apoptosis, microglial cell activation, and disruption of the blood brain barrier, thus maintaining brain health (70). Active

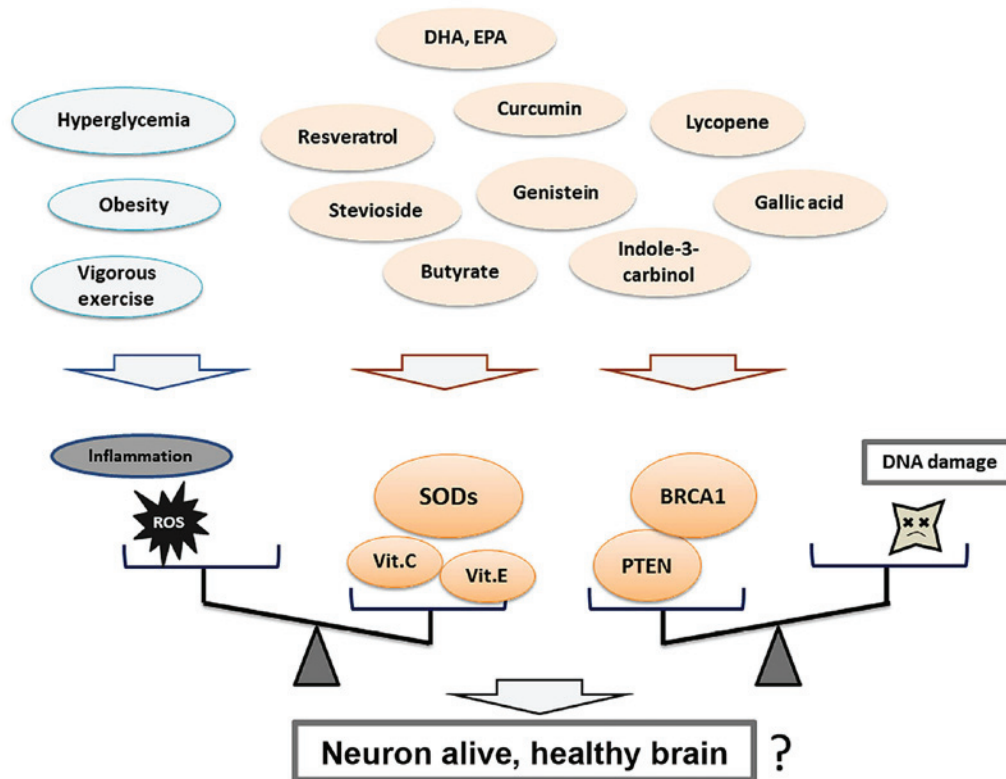


Figure 3. Several food ingredients and/or dietary components may improve the balance of oxidants/antioxidants, reducing neuronal cell death and thus maintaining a healthy brain. SOD, superoxide dismutase; BRCA1, breast cancer gene 1; PTEN, phosphatase and tensin homologue deleted on chromosome 10; Vit., vitamin; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.

aglycone-genistein inhibits ROS production by activating SODs (71). Lycopene also inhibits neuronal apoptosis by reducing ROS levels, and by improving mitochondrial function (72). Expression of SODs is dependent on the activity of peroxisome proliferator-activated receptors (73). Therefore, resveratrol analogs, which activates peroxisome proliferator-activated receptors, may increase the mRNA and protein expression levels of SODs (74). Furthermore, increased expression of SOD2 has been observed following administration of grape juice (75). The polyphenolic antioxidant, resveratrol, and calorie restriction may promote human longevity. Stevioside, a natural sweetener, may also increase the expression of SOD1-3 (76). In addition, butyrate, a short-chain fatty acid, increases the expression of SODs (77).

Antioxidant supplements may reduce cognitive decline. Vitamin C, vitamin E and the vitamin-like substance coenzyme Q10 have been used to treat patients with dementia with some efficacy (78), and the plasma levels of vitamin C have been found to be considerably lower in patients with AD (79). Decreased levels of plasma vitamin E are associated with an increased risk of neurodegenerative disorders (80). Vitamin E acts as a scavenger of free radicals (81), and thus, may exhibit a neuroprotective effect by scavenging ROS. In addition, ingestion of vitamin E is associated with an increase in the levels of SODs (80). Dietary omega-3 polyunsaturated fatty acid (PUFA) has been demonstrated to improve memory and learning processes (82). Long-term diets rich in omega-3 PUFA may lead to lower levels of DNA damage caused by oxidative stress (83). *Perilla frutescens* is a good source of the omega-3 PUFA. The perilla-diet promotes

neuronal signaling and alters synaptic plasticity, improving learning and memory (84), possibly by enhancing intracellular SOD activity (85). Together, these studies support the hypothesis that SODs, as well as antioxidant vitamins, offer a certain degree of neural protection against dementia progression. However, the association between neuroprotection and nutrient consumption is a complex matter of study. Difficulties in the variabilities of human-diets makes this a challenging subject to research.

6. Conclusion

To maintain physiological cellular function, cells prevent against oxidative damage through the use of antioxidants. In neurons, excess oxidative stress may result in neuronal cell death and potentially dementia. In dementia, genomic DNA damage is a feature of the pathogenesis of neurodegeneration; however, DNA damage may be additionally explained by a lack of or improper DNA repair mechanisms. Therefore, increased production of ROS and/or alterations in BRCA1 and PTEN function concurrently suggest a neurodegenerative stimulus present in dementia. Several compounds in naturally occurring foodstuffs may exhibit neuroprotective effects, which may facilitate DNA repair or reduce ROS-production, and some of these neuroprotective compounds may form the basis of future potential therapeutic options for preventing or limiting the progression of dementia. Future therapeutic strategies should utilize the observation that defects in the key processes required for neuronal homeostasis, which results in unfavorable neuronal conditions, and this should represent a basis for the

development of dietary treatments for dementia. One aspect to consider is the difference between psychiatric illnesses and dementia. For treatment of psychiatric illnesses, it is important to maintain the levels of key intracellular molecules balanced (31). For dementia, it is also imperative to limit or prevent neuronal apoptosis (Fig. 3). However, both these aspects are important for keeping the brain functioning healthily.

Numerous neuroprotective factors have been suggested as potential targets for preventing or limiting neuronal apoptosis. For example, phytoestrogens may rescue neurons and glial cells from cell apoptosis by preventing oxidative stress. However, despite experimental interpretations based on *in vitro* and *in vivo* studies, the translational value of the neuroprotective compounds in the clinical setting remains to be determined. The potential therapeutic effects for preventing dementia should be more cautiously considered in clinical research (86). It may also be possible to use these compounds found in natural foodstuffs as an adjuvant alongside established treatment modalities. Further mechanistic studies are required to understand the detailed molecular mechanisms underlying the neuroprotective effects of the compounds highlighted in the present review. Additionally, clinical studies are required to determine their efficacy in humans.

In conclusion, ROS as well as PTEN and BRCA1 tumor suppressors may be involved in the pathogenesis of dementia and neuroprotective compounds found in certain diets may reduce or prevent dementia by reducing oxidative DNA damage.

Acknowledgements

Not applicable.

Funding

This work was supported in part by JSPS KAKENHI (grant no. JP18K17964) and a grant from Nara Women's University in Japan.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

MM and SM conceived the subject of the review. MM, YI, YN, AT, YK and SM participated in writing and revising the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

- Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H and Tuomilehto J: Risk score for the prediction of dementia risk in 20 years among middle aged people: A longitudinal, population-based study. *Lancet Neurol* 5: 735-741, 2006.
- Finneran DJ and Nash KR: Neuroinflammation and fractal-kine signaling in Alzheimer's disease. *J Neuroinflammation* 16: 30, 2019.
- Trujillo-Estrada L, Dávila JC, Sánchez-Mejías E, Sánchez-Varo R, Gomez-Arboledas A, Vizuete M, Vitorica J and Gutiérrez A: Early neuronal loss and axonal/presynaptic damage is associated with accelerated amyloid- β accumulation in A β PP/PS1 Alzheimer's disease mice subiculum. *J Alzheimers Dis* 42: 521-541, 2014.
- Zhao J, Gao W, Yang Z, Li H and Gao Z: Nitration of amyloid- β peptide (1-42) as a protective mechanism for the amyloid- β peptide (1-42) against copper ion toxicity. *J Inorg Biochem* 190: 15-23, 2019.
- Tanzi RE: The genetics of Alzheimer disease. *Cold Spring Harb Perspect Med* 2: a006296, 2012.
- Ravi SK, Narasingappa RB and Vincent B: Neuro-nutrients as anti-Alzheimer's disease agents: A critical review. *Crit Rev Food Sci Nutr* 59: 2999-3018, 2019.
- Barus R, Béné J, Deguil J, Gautier S and Bordet R: Drug interactions with dementia-related pathophysiological pathways worsen or prevent dementia. *Br J Pharmacol* 176: 3413-3434, 2019.
- Butterfield DA and Halliwell B: Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease. *Nat Rev Neurosci* 20: 148-160, 2019.
- Tian JS, Zhai QJ, Zhao Y, Chen R and Zhao LD: 2-(2-benzofuranyl)-2-imidazoline (2-BFI) improved the impairments in AD rat models by inhibiting oxidative stress, inflammation and apoptosis. *J Integr Neurosci* 16: 385-400, 2017.
- Perez Ortiz JM and Swerdlow RH: Mitochondrial dysfunction in Alzheimer's disease: Role in pathogenesis and novel therapeutic opportunities. *Br J Pharmacol* 176: 3489-3507, 2019.
- Chang KH, Cheng ML, Chiang MC and Chen CM: Lipophilic antioxidants in neurodegenerative diseases. *Clin Chim Acta* 485: 79-87, 2018.
- Gugliandolo A, Bramanti P and Mazzon E: Role of Vitamin E in the treatment of Alzheimer's disease: Evidence from animal models. *Int J Mol Sci* 18: E2504, 2017.
- Yu J, Zhu H, Taheri S, Mondy W, Perry S and Kindy MS: Impact of nutrition on inflammation, tauopathy, and behavioral outcomes from chronic traumatic encephalopathy. *J Neuroinflammation* 15: 277, 2018.
- Tako E, Bar H and Glahn RP: The combined application of the Caco-2 cell bioassay coupled with *in vivo* (*Gallus gallus*) feeding trial represents an effective approach to predicting Fe bioavailability in humans. *Nutrients* 8: E732, 2016.
- Jazvinšćak Jembrek M, Hof PR and Šimić G: Ceramides in Alzheimer's disease: Key mediators of neuronal apoptosis induced by oxidative stress and A β accumulation. *Oxid Med Cell Longev* 2015: 346783, 2015.
- Mitra J, Guerrero EN, Hegde PM, Wang H, Boldogh I, Rao KS, Mitra S and Hegde ML: New perspectives on oxidized genome damage and repair inhibition by pro-oxidant metals in neurological diseases. *Biomolecules* 4: 678-703, 2014.
- Zhou DR, Eid R, Miller KA, Boucher E, Mandato CA and Greenwood MT: Intracellular second messengers mediate stress inducible hormesis and programmed cell death: A review. *Biochim Biophys Acta Mol Cell Res* 1866: 773-792, 2019.
- Görlach A, Dimova EY, Petry A, Martínez-Ruiz A, Hernansanz-Agustín P, Rolo AP, Palmeira CM and Kietzmann T: Reactive oxygen species, nutrition, hypoxia and diseases: Problems solved? *Redox Biol* 6: 372-385, 2015.
- Freund RK, Gibson ES, Potter H and Dell'Acqua ML: Inhibition of the Motor protein Eg5/Kinesin-5 in amyloid β -mediated impairment of hippocampal long-term potentiation and dendritic spine loss. *Mol Pharmacol* 89: 552-559, 2016.
- Ikeda Y, Murakami M, Nakagawa Y, Tsuji A, Kitagishi Y and Matsuda S: Diet induces hepatocyte protection in fatty liver disease via modulation of PTEN signaling. *Biomed Rep* 12: 295-302, 2020.
- Schaefer PM, von Einem B, Walther P, Calzia E and von Arnim CA: Metabolic characterization of intact cells reveals intracellular amyloid beta but not its precursor protein to reduce mitochondrial respiration. *PLoS One* 11: e0168157, 2016.

22. Richetin K, Moulis M, Millet A, Arrázola MS, Andraini T, Hua J, Davezac N, Roybon L, Belenguer P, Miquel MC and Rampon C: Amplifying mitochondrial function rescues adult neurogenesis in a mouse model of Alzheimer's disease. *Neurobiol Dis* 102: 113-124, 2017.
23. Canugovi C, Misiak M, Ferrarelli LK, Croteau DL and Bohr VA: The role of DNA repair in brain related disease pathology. *DNA Repair (Amst)* 12: 578-587, 2013.
24. Ali R, Rakha EA, Madhusudan S and Bryant HE: DNA damage repair in breast cancer and its therapeutic implications. *Pathology* 49: 156-165, 2017.
25. Tokarz P, Kaarniranta K and Blasiak J: Role of the cell cycle Re-initiation in DNA damage response of post-mitotic cells and its implication in the pathogenesis of neurodegenerative diseases. *Rejuvenation Res* 19: 131-139, 2016.
26. Li WA, Moore-Langston S, Chakraborty T, Rafols JA, Conti AC and Ding Y: Hyperglycemia in stroke and possible treatments. *Neurol Res* 35: 479-491, 2013.
27. Mena S, Ortega A and Estrela JM: Oxidative stress in environmental-induced carcinogenesis. *Mutat Res* 674: 36-44, 2009.
28. Roh HT, Cho SY and So WY: Obesity promotes oxidative stress and exacerbates blood-brain barrier disruption after high-intensity exercise. *J Sport Health Sci* 6: 225-230, 2017.
29. Thirupathi A and Pinho RA: Effects of reactive oxygen species and interplay of antioxidants during physical exercise in skeletal muscles. *J Physiol Biochem* 74: 359-367, 2018.
30. Tsai CY, Wu JCC, Fang C and Chang AYW: PTEN, a negative regulator of PI3K/Akt signaling, sustains brain stem cardiovascular regulation during mevinphos intoxication. *Neuropharmacology* 123: 175-185, 2017.
31. Matsuda S, Ikeda Y, Murakami M, Nakagawa Y, Tsuji A and Kitagishi Y: Roles of PI3K/AKT/GSK3 pathway involved in psychiatric illnesses. *Diseases* 7: pii: E22, 2019.
32. Ogino M, Ichimura M, Nakano N, Minami A, Kitagishi Y and Matsuda S: Roles of PTEN with DNA repair in Parkinson's disease. *Int J Mol Sci* 17: pii: E954, 2016.
33. Knafo S, Sánchez-Puelles C, Palomer E, Delgado I, Draffin JE, Mingo J, Wahle T, Kaleka K, Mou L, Pereda-Perez I, *et al*: PTEN recruitment controls synaptic and cognitive function in Alzheimer's models. *Nat Neurosci* 19: 443-453, 2016.
34. Chen CY, Chen J, He L and Stiles BL: PTEN: Tumor suppressor and metabolic regulator. *Front Endocrinol (Lausanne)* 9: 338, 2018.
35. Yi YW, Kang HJ, Kim HJ, Hwang JS, Wang A and Bae I: Inhibition of constitutively activated phosphoinositide 3-kinase/AKT pathway enhances antitumor activity of chemotherapeutic agents in breast cancer susceptibility gene 1-defective breast cancer cells. *Mol Carcinog* 52: 667-675, 2013.
36. Krivokuca A, Boljevic I, Jovandic S, Magic Z, Mandic A, Tomasevic Z and Brankovic-Magic M: Germline mutations in cancer susceptibility genes in high grade serous ovarian cancer in Serbia. *J Hum Genet* 64: 281-290, 2019.
37. Yoshino Y, Endo S, Chen Z, Qi H, Watanabe G and Chiba N: Evaluation of site-specific homologous recombination activity of BRCA1 by direct quantitation of gene editing efficiency. *Sci Rep* 9: 1644, 2019.
38. Savage KI and Harkin DP: BRCA1, a 'complex' protein involved in the maintenance of genomic stability. *FEBS J* 282: 630-646, 2015.
39. Fernandes N, Sun Y, Chen S, Paul P, Shaw RJ, Cantley LC and Price BD: DNA damage-induced association of ATM with its target proteins requires a protein interaction domain in the N terminus of ATM. *J Biol Chem* 280: 15158-15164, 2005.
40. Suberbielle E, Djukic B, Evans M, Kim DH, Taneja P, Wang X, Finucane M, Knox J, Ho K, Devidze N, *et al*: DNA repair factor BRCA1 depletion occurs in Alzheimer brains and impairs cognitive function in mice. *Nat Commun* 6: 8897, 2015.
41. Moruno-Manchon JF, Koellhoffer EC, Gopakumar J, Hambarde S, Kim N, McCullough LD and Tsvetkov AS: The G-quadruplex DNA stabilizing drug pyridostatin promotes DNA damage and downregulates transcription of Brcal in neurons. *Aging (Albany NY)* 9: 1957-1970, 2017.
42. So EY and Ouchi T: BRAT1 deficiency causes increased glucose metabolism and mitochondrial malfunction. *BMC Cancer* 14: 548, 2014.
43. Tanaka H, Phipps EA, Wei T, Wu X, Goswami C, Liu Y, Sledge GW Jr, Mina L and Herbert BS: Altered expression of telomere-associated genes in leukocytes among BRCA1 and BRCA2 carriers. *Mol Carcinog* 57: 567-575, 2018.
44. Zhan Y and Hägg S: Telomere length shortening in Alzheimer's disease: Procedures for a causal investigation using single nucleotide polymorphisms in a mendelian randomization study. *Methods Mol Biol* 1750: 293-306, 2018.
45. Minami A, Nakanishi A, Ogura Y, Kitagishi Y and Matsuda S: Connection between Tumor Suppressor BRCA1 and PTEN in damaged DNA repair. *Front Oncol* 4: 318, 2014.
46. Maidarti M, Clarkson YL, McLaughlin M, Anderson RA and Telfer EE: Inhibition of PTEN activates bovine non-growing follicles in vitro but increases DNA damage and reduces DNA repair response. *Hum Reprod* 34: 297-307, 2019.
47. A. Zhao C, Noble JM, Marder K, Hartman JS, Gu Y and Scarmeas N: Dietary patterns, physical activity, sleep, and risk for dementia and cognitive decline. *Curr Nutr Rep* 7: 335-345, 2018.
48. Liu D, Wang Z, Gao Z, Xie K, Zhang Q, Jiang H and Pang Q: Effects of curcumin on learning and memory deficits, BDNF, and ERK protein expression in rats exposed to chronic unpredictable stress. *Behav Brain Res* 271: 116-121, 2014.
49. Sang Q, Sun D, Chen Z and Zhao W: GF and PI3K/Akt signaling participate in the ventral motor neuronal protection of curcumin in sciatic nerve injury rat models. *Biomed Pharmacother* 103: 1146-1153, 2018.
50. Hussein RM, Mohamed WR and Omar HA: A neuroprotective role of kaempferol against chlorpyrifos-induced oxidative stress and memory deficits in rats via GSK3 β -Nrf2 signaling pathway. *Pestic Biochem Physiol* 152: 29-37, 2018.
51. Wu B, Luo H, Zhou X, Cheng CY, Lin L, Liu BL, Liu K, Li P and Yang H: Succinate-induced neuronal mitochondrial fission and hexokinase II malfunction in ischemic stroke: Therapeutical effects of kaempferol. *Biochim Biophys Acta Mol Basis Dis* 1863: 2307-2318, 2017.
52. Shen R and Wang JH: The effect of Icarin on immunity and its potential application. *Am J Clin Exp Immunol* 7: 50-56, 2018.
53. Yoshida H, Okumura N, Kitagishi Y, Nishimura Y and Matsuda S: Ethanol extract of Rosemary repressed PTEN expression in K562 culture cells. *Int J App Biol Pharmaceutical* 2: 316-322, 2011.
54. Lu M, Fei Z and Zhang G: Synergistic anticancer activity of 20(S)-Ginsenoside Rg3 and Sorafenib in hepatocellular carcinoma by modulating PTEN/Akt signaling pathway. *Biomed Pharmacother* 97: 1282-1288, 2018.
55. Chalabi N, Le Corre L, Maurizis JC, Bignon YJ and Bernard-Gallon DJ: The effects of lycopene on the proliferation of human breast cells and BRCA1 and BRCA2 gene expression. *Eur J Cancer* 40: 1768-1775, 2004.
56. Chalabi N, Maurizis JC, Le Corre L, Delort L, Bignon YJ and Bernard-Gallon DJ: Quantification by affinity perfusion chromatography of phosphorylated BRCA1 and BRCA2 proteins from tumor cells after lycopene treatment. *J Chromatogr B Analyt Technol Biomed Life Sci* 821: 188-193, 2005.
57. Bosviel R, Dumollard E, Déchelotte P, Bignon YJ and Bernard-Gallon D: Can soy phytoestrogens decrease DNA methylation in BRCA1 and BRCA2 oncosuppressor genes in breast cancer? *OMICS* 16: 235-244, 2012.
58. Vissac-Sabatier C, Coxam V, Déchelotte P, Picherit C, Horcajada MN, Davicco MJ, Lebecque P, Bignon YJ and Bernard-Gallon D: Phytoestrogen-rich diets modulate expression of Brcal and Brc2 tumor suppressor genes in mammary glands of female Wistar rats. *Cancer Res* 63: 6607-6612, 2003.
59. Cabanes A, Wang M, Olivo S, DeAssis S, Gustafsson JA, Khan G and Hilakivi-Clarke L: Prepubertal estradiol and genistein exposures up-regulate BRCA1 mRNA and reduce mammary tumorigenesis. *Carcinogenesis* 25: 741-748, 2004.
60. Soni M, Rahardjo TB, Soekardi R, Sulistyowati Y, Lestariningsih, Yesufu-Udechuku A, Irsan A and Hogervorst E: Phytoestrogens and cognitive function: A review. *Maturitas* 77: 209-220, 2014.
61. Weng SW, Hsu SC, Liu HC, Ji BC, Lien JC, Yu FS, Liu KC, Lai KC, Lin JP and Chung JG: Gallic acid induces DNA damage and inhibits DNA repair-associated protein expression in human oral cancer SCC-4 cells. *Anticancer Res* 35: 2077-2084, 2015.
62. Taysi S, Tascan AS, Ugur MG and Demir M: Radicals, oxidative/nitrosative stress and preeclampsia. *Mini Rev Med Chem* 19: 178-193, 2019.
63. Vehviläinen P, Koistinaho J and Gundars G: Mechanisms of mutant SOD1 induced mitochondrial toxicity in amyotrophic lateral sclerosis. *Front Cell Neurosci* 8: 126, 2014.
64. Sakellariou GK, Davis CS, Shi Y, Ivannikov MV, Zhang Y, Vasilaki A, Macleod GT, Richardson A, Van Remmen H, Jackson MJ, *et al*: Neuron-specific expression of CuZnSOD prevents the loss of muscle mass and function that occurs in homozygous CuZnSOD-knockout mice. *FASEB J* 28: 1666-1681, 2014.

65. Bravard A, Sabatier L, Hoffschir F, Ricoul M, Luccioni C and Dutrillaux B: SOD2: A new type of tumor-suppressor gene? *Int J Cancer* 51: 476-480, 1992.
66. Dixit S, Fessel JP and Harrison FE: Mitochondrial dysfunction in the APP/PSEN1 mouse model of Alzheimer's disease and a novel protective role for ascorbate. *Free Radic Biol Med* 112: 515-523, 2017.
67. Demchenko IT, Gutsaeva DR, Moskvina AN and Zhilyaev SY: Involvement of extracellular superoxide dismutase in regulating brain blood flow. *Neurosci Behav Physiol* 40: 173-178, 2010.
68. Singh B and Bhat HK: Superoxide dismutase 3 is induced by antioxidants, inhibits oxidative DNA damage and is associated with inhibition of estrogen-induced breast cancer. *Carcinogenesis* 33: 2601-2610, 2012.
69. Natarajan G, Perriotte-Olson C, Casey CA, Donohue TM Jr, Talmon GA, Harris EN, Kabanov AV and Saraswathi V: Effect of nanoformulated copper/zinc superoxide dismutase on chronic ethanol-induced alterations in liver and adipose tissue. *Alcohol* 79: 71-79, 2019.
70. Janyou A, Wicha P, Jittiwat J, Suksamrarn A, Tocharus C and Tocharus J: Dihydrocapsaicin attenuates blood brain barrier and cerebral damage in focal cerebral ischemia/reperfusion via oxidative stress and inflammatory. *Sci Rep* 7: 10556, 2017.
71. Lee SH, Kim JK and Jang HD: Genistein inhibits osteoclastic differentiation of RAW 264.7 cells via regulation of ROS production and scavenging. *Int J Mol Sci* 15: 10605-10621, 2014.
72. Sheriff SA, Shaik Ibrahim S, Devaki T, Chakraborty S, Agarwal S and Pérez-Sánchez H: Lycopene prevents mitochondrial dysfunction during d-galactosamine/lipopolysaccharide-induced fulminant hepatic failure in albino rats. *J Proteome Res* 16: 3190-3199, 2017.
73. Desjardins F, Sekkali B, Verreth W, Pelat M, De Keyser D, Mertens A, Smith G, Herregods MC, Holvoet P and Balligand JL: Rosuvastatin increases vascular endothelial PPARgamma expression and corrects blood pressure variability in obese dyslipidaemic mice. *Eur Heart J* 29: 128-137, 2008.
74. Chatterjee A, Ronghe A, Padhye SB, Spade DA, Bhat NK and Bhat HK: Antioxidant activities of novel resveratrol analogs in breast cancer. *J Biochem Mol Toxicol* 32: e21925 2018.
75. Ribeiro CCD, Silva RM, Campanholo VMLP, Ribeiro DA, Ribeiro Paiotti AP and Forones NM: Effects of Grape Juice in superoxide dismutase and catalase in colorectal cancer carcinogenesis induced by Azoxymethane. *Asian Pac J Cancer Prev* 19: 2839-2844, 2018.
76. Geeraert B, Crombé F, Hulsmans M, Benhabiles N, Geuns JM and Holvoet P: Stevioside inhibits atherosclerosis by improving insulin signaling and antioxidant defense in obese insulin-resistant mice. *Int J Obes (Lond)* 34: 569-577, 2010.
77. Ma N, Abaker JA, Bilal MS, Dai H and Shen X: Sodium butyrate improves antioxidant stability in sub-acute ruminal acidosis in dairy goats. *BMC Vet Res* 14: 275, 2018.
78. von Arnim CA, Herbolzheimer F, Nikolaus T, Peter R, Biesalski HK, Ludolph AC, Riepe M and Nagel G; ActiFE Ulm Study Group: Dietary antioxidants and dementia in a population-based case-control study among older people in South Germany. *J Alzheimers Dis* 31: 717-724, 2012.
79. de Oliveira BF, Veloso CA, Nogueira-Machado JA, de Moraes EN, dos Santos RR, Cintra MT and Chaves MM: Ascorbic acid, alpha-tocopherol, and beta-carotene reduce oxidative stress and proinflammatory cytokines in mononuclear cells of Alzheimer's disease patients. *Nutr Neurosci* 15: 244-251, 2012.
80. Ghanbari AA, Shabani K and Mohammad Nejad D: Protective effects of Vitamin E consumption against 3MT electromagnetic field effects on oxidative parameters in Substantia Nigra in Rats. *Basic Clin Neurosci* 7: 315-322, 2016.
81. Thiriot C, Durand P, Jasseron MP, Kergonou JF and Ducouso R: Radiosensitive antioxidant membrane-bound factors in rat liver microsomes: I. The roles of glutathione and vitamin E. *Biochem Int* 14: 1-8, 1987.
82. Vinot N, Jouin M, Lhomme-Duchadeuil A, Guesnet P, Alessandri JM, Aujard F and Pifferi F: Omega-3 fatty acids from fish oil lower anxiety, improve cognitive functions and reduce spontaneous locomotor activity in a non-human primate. *PLoS One* 6: e20491, 2011.
83. Ray SD, Parmar M, Syed I, Rathod J, Zinkovskiy D, Bulku E, Gigliotti J, Hackman RM and Stohs SJ: Long term exposure effect of a unique metabolic nutrition system containing a diverse group of phytochemicals on serum chemistry and genomic and non-genomic changes in the liver of female B6C3F1 mice. *Phytother Res* 22: 458-71, 2008.
84. Lee J, Park S, Lee JY, Yeo YK, Kim JS and Lim J: Improved spatial learning and memory by perilla diet is correlated with immunoreactivities to neurofilament and α -synuclein in hilus of dentate gyrus. *Proteome Sci* 10: 72, 2012.
85. Byun EB, Cho EJ, Kim YE, Kim WS and Byun EH: Neuroprotective effect of polysaccharide separated from *Perilla frutescens* Britton var. *acuta* Kudo against H₂O₂-induced oxidative stress in HT22 hippocampus cells. *Biosci Biotechnol Biochem* 82: 1344-1358, 2018.
86. Vallés SL, Borrás C, Gambini J, Furriol J, Ortega A, Sastre J, Pallardó FV and Viña J: Oestradiol or genistein rescues neurons from amyloid beta-induced cell death by inhibiting activation of p38. *Aging Cell* 7: 112-118, 2008.



This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.