Diet and Nutrition in Alzheimer's Disease and Healthy Aging

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Abstract

According to UN report of the world aging, older people are those 60 years of age and over, though others defined those over 85 as "oldest old." Aging is a complex and gradual process which involves degeneration of cells mainly due to cellular redox reactions that result in detrimental biochemical and genetic alterations. Studies have related the risk of age-related diseases with increased level of oxidants. Dietary polyphenols like flavonoids are strong antioxidant that acts through interacting with reactive oxygen species producing reactive metals.

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All organisms need organic and inorganic nutrients such as proteins, carbohydrates, lipids, vitamins, minerals, and water. These nutrients have a significant role in regular biological activities like metabolism, growth, and repair. Protein is the most essential among the three macronutrients (i.e. carbohydrates, protein, and fat) responsible for aging. Moreover, bioactive chemicals from plants are important, though not essential, and they have been referred to as "life span essential," since they have beneficial effect in healthy aging. Therefore, dietary interventions along with avoiding risk factors will reduce the risk of age-related degenerative diseases and increase healthy life span among the elderly.

Keywords
Alzheimer disease · Aging · Nutrition · Protein · Minerals · Vitamins · Omega fatty acids

3.1 Introduction

Basically, along with the chronological aging process, aging is a result of both biological and environmental factors, and there is no clear definition of aged and elderly. The United Nations report of the world aging mentioned that older people are those 60 years of age and over, while some studies defined those over 85 as "oldest old." This classification varies widely in different countries around the world in relation to the varying life expectancies (Clements and Carding 2018). Yet, in the year 2050, the estimated population of older adults in world is 2 billion, which is almost 21% of the total population and more than double of the 841 million aged populations in 2013. The number of those aged over 80 will also increase three fold between 2013 and 2050 becoming 392 million (Shlisky et al. 2017). In elderly people, a reduced muscle and body mass, increasing volume of extracellular fluid, as well as decline in body cell mass are widely observed. The cognitive and physical functional status, nutritional and endocrine status, quality of life, and comorbidity in elderly people must be well defined. These changes shall not be perceived as simple imbalance between energy intake-expenditure process, since they are results of complex metabolic processes that also include hormones like growth and sex hormones (Baumgartner 2000; Balagopal et al. 1997).

Alzheimer's disease (AD) is a very prevalent form of dementia that has affected more than 5.4 million people only in the USA. Production and accumulation of the β amyloid (βA) senile plaque is the pathological hallmark of AD. Although various therapeutic approaches have been tested against the production and deposition of βA in the past 20+ years, their clinical efficacy is not promising (Solfrizzi et al. 2017). To date, none of the therapeutic interventions succeeded in averting the onset or progression of AD. On the contrary, optimal use of essential nutrients that aid proper functioning of the brain is considered vital for neuronal health and its normal functioning (Mohajeri et al. 2015). Hence, nutritional approaches are currently the promising options toward managing AD risk factors. In this regard, nutritional

pattern like the Mediterranean diet that comprise good proportion of vegetables, fruits, whole grain, legumes, nuts, or n-3 PUFA is the most recommended (Alles et al. 2012). Diet is an important factor among the flexible environmental factors; however, the experimental data from literatures on the impact of individual food item or nutrient on AD is not consistent. This is due to the complex nature of human dietary approach where combination of nutrients and food items are consumed at once (Gu et al. 2010). Alternatively, mechanistic studies, epidemiologic analyses, and randomized controlled trials have laid foundation underlining the neuronal health-promoting effect of docosahexaenoic acid (DHA) and micronutrients such as the vitamin B family and vitamins E, C, and D, during aging. In addition to being essential, these nutrients are cheap, are easy to obtain, and have lesser side effects. Besides, they have established mode of actions and are widely accepted by the public (Mohajeri et al. 2015).

3.2 Overview of Health and Aging

Aging is a complex and gradual process which involves degeneration of cells mainly due to cellular redox reactions that result in detrimental biochemical and genetic alterations. The cellular metabolic reactions produce reactive oxygen species (ROS) and reactive nitrogen species (RNS) that act through oxidative stress (OS) and are known to destroy cellular biomolecules such as proteins, lipids, carbohydrates, and nucleic acids. Therefore, cellular OS is responsible for aging and chronic diseases including diabetes, cardiovascular disease (CVD), cancer, AD, Parkinson's diseases (PD), and other age-related diseases (Shlisky et al. 2017; Thapa and Carroll 2017). The increasing aged population of the world is becoming a major public health burden. One of the age-related public health challenge due to increased life span is a sharp increase of age-related chronic diseases worldwide (Rajaram et al. 2017). A decreased appetite in relation to aging leads to energy imbalance between the physiological energy demands and energy expenditure in older adults. As compared to younger adults of similar level of activity, height, and weight, older adults consume lesser food items (energy), although the body's demand for micronutrients remained high (Mohajeri et al. 2015). The resulting malnutrition is associated with impaired muscle function, immune dysfunction, poor wound healing, anemia, delayed recovering from surgery, impaired muscle function, decreased bone mass, reduced cognitive function, higher hospital and readmission rate, and mortality. Currently, malnutrition is rising among the older population being 16% in those aged 65 and over and 2% among the 85 years and older (Ahmed and Haboubi 2010).

The energy consumed and body weight have impact on the quality and span of old age. Despite the controversies on humans, caloric restriction positively affects life span in different animal species. On the contrary, however, some researchers have suggested mild and excess obesity is associated with lower risk of mortality in older adults. Hence, this debatable topic needs further research to clearly state the impact of energy intake and weight on the age/mortality/among the olds (Shlisky et al. 2017). Mitochondrial functions have significant role in aging and age-related

chronic ailments such as AD, and thus it is an important therapeutic target to focus on during intervention. As a result of the process of aging, OS and the level of oxidized molecules rise, and the energy balance in the brain becomes impaired. In this process of aging, mitochondria plays a major role as they are the center of energy production and hence springs ROS in the cells and promotes age-related diseases. Accordingly, various animal model studies on aging and aging studies on human skeletal muscles have reported mitochondrial dysfunction in the brain (Gu et al. 2010). In addition, certain actions that control cellular metabolism are integrated with the molecular mechanisms regulating synaptic functions. For instance, mitochondrial metabolic activities can influence cognitive functions because of the fact that they are involved in some features of synaptic plasticity. Similarly, synaptic plasticity declines whenever there is excess calorie due to increase in ROS formation beyond the buffering capacity of the cell. Thus, reasonable reduction of caloric intake can reduce the risk of oxidative damage in the brain (Gómez-Pinilla 2008).

3.3 Role of Nutrition in Healthy Aging

The estimates of the year 2100 shows that nearly one third of the world population will be 60 years and older (Hardman et al. 2015). However, as the size of population reaching advanced age expands, the public health problems rise due to age-related diseases like coronary heart disease (CHD), stroke, AD, and PD. Majority of these diseases resulted from sustained OS and low-grade inflammation (López-Miranda et al. 2010). According to the WHO, avoiding the main risk factors for the chronic disorders (smoking, lack of exercise, and poor diet) can reduce the risk of stroke, cardiovascular diseases (CVD), and type II diabetes by 80% (Shlisky et al. 2017). Although the effect of caloric restriction is not well defined in human, it has been found robust and reproducible in mitigating age-related conditions as well as extending life span in animal models. The impact of caloric restriction on human aging is the most important area to be studied but it is still a gap in modern biogerontology. Yet, various epidemiological studies and short-term human studies underlined the vital role of caloric restriction in human health (Willcox et al. 2007). Moreover, newer study findings demonstrate that caloric restrictions have an impact on life span that differs based on genotype, sex, and the type of diet. Despite all the controversies, caloric restriction is generally deemed to have beneficial influence on age-related health and health span, and it positively acts across a range of taxa from yeast to humans (Simpson et al. 2017).

Observational studies have related the risk of age-related diseases with increased level of oxidants, and conversely they showed that the association of increase in consumption of antioxidant-containing diet was with reduced chronic disease incidence. Hence, consuming dietary monounsaturated fatty acids (MUFA) and n-3 polyunsaturated fatty acids (n-3 PUFA), in addition to fish, fruits, vegetables, and adequate coffee, can benefit the body (Solfrizzi et al. 2017). Increase in consumption of fruits and vegetables or antioxidant-rich diet comprising vitamins, fiber, carotenoids, and magnesium has been associated with raised serum level of nutrients, decline in OS,

and lower C-reactive protein (CRP) levels, which is a cognition-related inflammatory marker. Besides, the vegetable- and fruit-derived flavonoids have a good neuroprotective, cardioprotective, and anti-inflammatory activities (Hardman et al. 2015). Thus, individuals with a risk of CVD shall consume diet low in saturated and trans-fats and high in fruits, vegetables, and whole grains. Functional foods and supplements such as red yeast rice, soy protein, marine-derived omega-3 fatty acids, plant sterols, green tea, and probiotic yogurt are helpful in statin-intolerant patients who failed to attain target Low density lipoprotien (LDL) level (Hunter and Hegele 2017; Bule et al. 2018). Pertaining to the type of diet, people who comply with the Mediterranean diet style benefit in the long term through reducing the chance of cognitive decline from normal to mild cognitive impairment (MCI) and then to dementia. The Mediterranean diet mainly consists of fruits, vegetables, nuts, cereals, legumes, fish, and olive oil, with a moderate intake of alcohol and lower consumption of red meat and poultry (Hardman et al. 2015). Furthermore, some animal studies have also recommended that membranes with higher MUFA content are less affected by ROS and protect aged cells. In this regard, olive oil has beneficial effect against OS due to its high oleic acid, which is enriched in lipoproteins and cellular membranes (López-Miranda et al. 2010). A reduced incidence of MCI, lesser incidence of vascular events, as well as lower risk of mortality have been associated to adherence to Mediterranean diet style (Hardman et al. 2015; Prinelli et al. 2015).

3.4 Role of Vitamins and Minerals in Health

In order to sustain life, all organisms need organic and inorganic nutrients such as proteins, carbohydrates, lipids, vitamins, minerals, and water. These nutrients have significant role in regular biological activities like metabolism, growth, and repair. Unlike other nutrients vitamins and minerals can't serve direct energy production but they act as cofactors in a variety of biological functions including hormonal signaling and mitochondrial energy metabolism. We obtain the minerals and vitamins via diet since human body can't synthesize them. In case of deficiency of vitamins and minerals, a range of cellular activities will be halted resulting in a number of deficiency diseases (Lee et al. 2015). For instance, the deficiency of vitamin B6, B12, and folate causes rise in homocysteine, which is a precursor of methionine and cysteine, concentration via various pathways. Homocysteine is in charge of AD pathways through vascular mechanisms because it is active in brain tissue. Therefore, through reducing homocysteine level in the brain, increased intake of folate is believed to be associated with minimal risk of stroke (Luchsinger and Mayeux 2004). On the other hand, strong antioxidants like carotenoids, vitamin C, and vitamin E are potent electron donors that quench radical reactions in blood and plasma. Vitamin C is a strong inhibitor of lipid peroxidation; likewise, vitamin E is also reported to decrease isoprostanes (biomarkers for lipid peroxidation) levels in animal models. Vitamin C has been shown to speed up the synthesis of vitamin E in membranes and lipoproteins. Moreover, vitamin C regenerates vitamin E (α-tocopherol) and reduces α-tocopherolxyl free radical reactions in membranes. In

addition, vitamin C and vitamin E act in conjunction to prevent lipid peroxidation (Thapa and Carroll 2017). Other antioxidant molecules like β-carotene, dietary polyphenols (flavonoids), and Se also reduce OS in neurons. The antioxidant, anti-inflammatory, and neuroprotective effect of vitamin D has also been widely reported (Alles et al. 2012).

The other most important nutrients are the mineral elements such as Fe, Ca, Mg, Mn, Cu, Zn, Se, P, K, Na, S, Cl, I, Mb, Cr, and F. These trace mineral elements serve as enzyme cofactors and they are named "antioxidant micronutrients" because of their antioxidant functions. For instance, Se is an integral part of selenoproteins in humans, which plays a key role as body's own antioxidant defense (e.g., glutathione peroxidase) and protects the body against CVD or cancer (Kozarski et al. 2015; Gil and Gil 2015). Zn is a central cofactor to over 300 enzymes that have various roles including DNA and RNA metabolism and serves a major function in the stabilization protein structures. Cu is also a catalytic cofactor involved in various important enzymatic reactions due to its tendency to change its oxidation state (Gil and Gil 2015). Furthermore, the antioxidant action of various other micronutrients in mitochondria is significant. For example, the coenzyme α-lipoic acid has essential function in maintaining energy homeostasis in mitochondria. It is mainly available in animal meat including in the liver, heart, kidney, and vegetables like potato, broccoli, and spinach (Gómez-Pinilla 2008).

3.5 Dietary Supplements, Herbs, and Functional Foods in Health

A broader range of items are included under the term "nutraceutical." Nutraceuticals are dietary products such as functional foods, dietary supplements, and medicinal foods (formulated foods that can be consumed upon recommendation by physician or dietician in relation to certain disease condition) (LaRocca et al. 2017). According to the US Department of Agriculture, functional foods are defined as "natural or processed foods that contain known or unknown biologically active compounds, which, in defined, effective nontoxic amounts, provide a clinically proven and documented health benefit for the prevention, management or treatment of chronic disease." The functional food comprises items like probiotic yogurt and fortified grain products. On the other hand, dietary supplements as defined by the FDA are "a product intended for ingestion that contains a 'dietary ingredient' intended to add further nutritional value to (supplement) the diet." For instance, vitamins, minerals, herbs, extracts, metabolites, and amino acids are dietary supplements (Hunter and Hegele 2017). Generally, the underlying concepts behind nutraceutical are as follows: i. some dietary patterns have beneficial effects because of the abundant particular nutrient composition they have and ii. the strong activity of these molecules against OS and inflammation is important to prevent physiological/arterial dysfunction (LaRocca et al. 2017).

Plants produce enormous amount of health-promoting compounds including polyphenols, dietary fibers, antioxidant molecules, vitamins, and minerals (Filannino

et al. 2018). Basically, food items of plant origin provides a higher nutritive value, low caloric density, and low-energy constituents (e.g., minerals, vitamins, dietary fibers) as well as being rich sources of bioactive phytochemicals such as carotenoids, sterols, polyphenols, and glucosinolates (Table 3.1) (Manach et al. 2017). Dietary polyphenols like flavonoids are strong antioxidant that acts through interacting with ROS-producing reactive metals. For example, curcumin is a dietary polyphenol with strong antioxidant activity that have been used against a number of age-related diseases like AD for more than a century. Curcumin acts via chelating reactive metal ions like Fe^{2+}, thus diminishing their oxidative power and the resulting OS due to free radicals. Ginkgo biloba extract has also been on use to treat age-related disease. Ginkgo biloba extracts various polyphenols such as flavonoids, and terpenes interact with superoxide anion, hydroxyl, and peroxyl free radicals to quench the radical chain reactions in mitochondrial respiratory chain function. Besides, it has been reported that ginkgo biloba extract prevents neuronal apoptosis due to OS via increasing the rate of neurotransmitter uptake. In AD, the improvement in cognitive function along with neuroprotective activity in animal model of Ginkgo biloba extract is related to downregulation of toxic Aβ aggregates (Thapa and Carroll 2017; Tiwari et al. 2018). The important effect of tea polyphenols on cognitive function of aged people is attributed to its flavonoid (catechin) content. There is a profound inverse association between tea drinking and the risk of dementia, AD, and PD. Green tea catechins administered for seven months to old Wister rats protected the rats from memory and spatial learning decline, probably as a consequence of its strong antioxidant potential (Mandel et al. 2012). In general, bioactive chemicals from plants are important though not essential, and they have been referred to as "life span essential," since they have beneficial effect in healthy aging. Most plant secondary metabolites are commonly available in vegetables and fruits; however, their concentration varies widely with the type of the plant, for example, isoflavones are abundant in soya, lycopene in tomatoes, glucosinolates in cruciferous vegetables, and anthocyanins in berries (Manach et al. 2017).

3.6 Protein and Energy in Healthy Aging

Protein is possibly the most essential macronutrient responsible for aging among the three essential macronutrients (i.e., carbohydrates, protein, and fat). A further breakdown studies revealed that particular amino acids like tryptophan and methionine, which are common in dietary protein, fed to laboratory animals improved the animal's health and delayed aging (Simpson et al. 2017). In order to avoid age-related loss of lean body mass, the daily-recommended dietary allowance (RDA) of protein for adults is 0.8g/kg of body weight. Studies have demonstrated that in aged people, taking protein above the RDA helps to increase muscle strength, muscle mass, and muscle function, boosts immune status, and improves wound healing (Ahmed and Haboubi 2010). Despite the

Table 3.1 Natural Products, nutrients, and foods with direct and indirect action on AD

Foods	Biological activity	Natural products	Biological activity	Nutrients	Biological activity
Fish and seafood Solfrizzi et al. (2017), Gómez-Pinilla (2008), Hennebelle et al. (2013), and Cederholm et al. (2013)	↑AD pathology	Rice bran extract (Hagl et al. (2015)	Improves mitochondrial function	B12 (Eastley et al. (2000)	Improves cognitive function
Salad dressing Gu et al. (2010)	↓Risk of AD	Curcumin Thapa and Carroll (2017)	↓OS	Lower SFA Gu et al. (2010)	↓Risk of AD
Olive oil Abbatecola et al. (2018)	↓Risk of MCI	Ginkgo Thapa and Carroll (2017)	Neuroprotective	Niacin Morris et al. (2004)	↓Incidence of AD and cognitive decline
Eggs Solfrizzi et al. (2017)	↓Risk of MCI	*Red yeast rice extract* Hunter and Hegele (2017)	↓LDL	Ascorbic acid Monacelli et al. (2017)	Delay in AD onset
Meat Xu et al. (2015)	↑Memory function	Catechin Mandel et al. (2012)	↓Risk of AD and dementia	Docosahexaenoic acid (DHA) Solfrizzi et al. (2017), Gómez-Pinilla (2008), Hennebelle et al. (2013), and Cederholm et al. (2013)	Improves cognitive function and AD
Nuts Dong et al. (2016) and Rajaram et al. (2016)	↓Risk of MCI, better overall cognition	Caffeine Beydoun et al. (2014) and Travassos et al. (2015)	↓Risk of MCI	Vitamin E and tocopherol forms Gu et al. (2010), Luchsinger and Mayeux (2004), and Morris et al. (2005)	↓Risk of AD and cognitive decline
Tomatoes Gu et al. (2010)	↓Risk of AD	*Policosanol* Hunter and Hegele (2017)	↓LDL	Folate Alles et al. (2012) and Gu et al. (2010)	↓Risk of AD
Cruciferous vegetables Gu et al. (2010)	↓Risk of AD, ↓ROS	*Galanthus nivalis* extract (galantamine) Brown et al. (2016)	Treating AD	β-Carotene Gu et al. (2010), Dai et al. (2006), and Kesse-Guyot et al. (2014)	↓Risk of AD, ↓ROS
Poultry Shakersain et al. (2016)	↓Risk of AD	Flavonoids Alles et al. (2012)	↓OS	PUFA Gu et al. (2010) and Dai et al. (2006)	↓Risk of AD

Low fat dairy Shakersain et al. (2016) and Wengreen et al. (2013)	↓Risk of MCI	Jujube extract Chen et al. (2017)	Improves memory and learning	MUFA Gu et al. (2010) and Dai et al. (2006)	↓Risk of AD
Whole grain Abbatecola et al. (2018)	↓Hypertension, ↓Risk of MCI	Phytoestrogens (genistin, daidzein) Zhao et al. (2002)	Neuroprotective	Vitamin D Alles et al. (2012)	Anti-inflammatory and neuroprotective
Fruits Dong et al. (2016)	↓Risk of MCI	Anthocyanins Shih et al. (2010)	Improves cognitive function	Vitamin C Gu et al. (2010) and Dai et al. (2006)	↓Risk of AD, ↓ROS
Red fruits Abbatecola et al. (2018)	↓Hypertension, ↓Risk of MCI	Choline Jones et al. (2017)	Improves cognition	Vitamin B1 Rodríguez et al. (2001)	↓AD progression
Dark and green leafyvegetables Gu et al. (2010)	↓Risk of AD, ↓ROS	Ferulic acid Jones et al. (2017)	Prevents AD	Low Zn level Jones et al. (2017)	OS
Tea Mandel et al. (2012) and Dai et al. (2006)	Neuroprotection			Al Barnard et al. (2014)	↑ Risk of AD
Coffee Solfrizzi et al. (2017) and Araújo et al. (2015)	↓Risk of MCI			Excess Fe and Cu Barnard et al. (2014)	Causes cognitive problems

evidences of 0.8 g protein/kg/day, others have recommended that slightly higher level of protein intake (i.e., 1.0–1.3g/kg/day) is helpful in old age. This increase in protein consumption among elderly offers ability to maintain nitrogen balance, improve insulin action, offset a potentially lower energy intake, and improve protein synthesis. However, these recommendations could pose a potential risk of nephrotoxicity or renal malfunction. In this regard, sulfur-containing proteins have been associated with adverse events when taken at higher amount (45% energy), yet moderate amount of protein-containing diet (20–35% energy) appears to be safe (Paddon-Jones et al. 2008). The common manifestation of early aging is a change in body composition, such as decrease in lean mass and increase in fat mass. The most significant age-related risk that could lead to functional impairment and mortality is a fast reduction in skeletal muscle mass (sarcopenia). A number of age-related factors can contribute to a fast drop in skeletal muscle mass; however, insufficient protein in the daily diet is the most significant factor that accelerates this process. On top of this, most elderly people do not consume enough amount of protein in their diet as per the RDA (Houston et al. 2008). Thus, energy dense supplements can be used as meal replacement therapy in elderly people so as to maintain the daily protein balance along with controlled energy and essential nutrient intake. In cases where there is accelerated protein catabolism (e.g., cachexia, trauma, and sarcopenia), the required amino acid should be given as a supplement; however, for most of the elderly individuals, the problem of skeletal muscle protein anabolism can be alleviated by serving high protein meal in their daily diet (Paddon-Jones et al. 2008).

The current sedentary life trends in the world have resulted in increased risk of metabolic disorders like type II diabetes and obesity. The situation is even worse because of the wide use of ready-made foods of high caloric content in addition to the sedentary life style; consequently an imbalance between the energy intake and expenditure will contribute to health risks such as CVD, diabetes, and other age-related disorders (vel Szic et al. 2015). Caloric restriction (CR) sometimes referred to as "energy restriction in the absence of malnutrition" has beneficial impact on various physiological parameters during aging. CR decreases arterial oxidative stress and inflammation, and increases nitric oxide bioavailability. As a result, the arterial functions will be improved leading to a modulation in the body's key energy sensing networks, which is mostly affected with aging. In addition, CR boosts the endogenous antioxidant and anti-inflammatory defense system. Therefore, CR represents a novel approach toward modulating age-related disorders along with consuming nutritional supplements and nutraceuticals (LaRocca et al. 2017).

3.7 Nutrition in the Prognosis of Alzheimer Disease (AD)

3.7.1 Glucose and Oxidizing Agents

The complex nature of diet make it difficult to whether CR can be achieved through decreased caloric intake or reducing a particular macronutrient or both (Simpson et al. 2017). Current research findings showed that controlling the caloric

composition of the diet has a potential to affect the cognitive functions due to the fact that the cellular metabolic activities in the mitochondria can regulate certain aspects of synaptic plasticity (Gómez-Pinilla 2008). In this regard, studies have observed a severe decline in glucose metabolism in AD-affected brain regions. In vivo imaging studies of patients with dementia also depicted a progressive decline of glucose metabolism and lowering of blood flow in the affected brain regions. However, the cerebral energy pool is slightly affected in the process of normal aging. Impaired glucose metabolism in the brain leads to limited synthesis of aspartate, glutamate, gamma-aminobutyric acid (GABA), glycine, acetylcholine, and ATP production (Münch et al. 1998). Furthermore, a diet containing low fats and highly processed carbohydrate causes a swift increase in blood glucose level upon consumption. Thus, the resulting glycation will impair serum proteins by forming modified proteins called advanced glycation end products (AGEs). For instance, glycated hemoglobin (HbA1c) is an AGE protein, the level of which in serum serves as a standard in diabetes test (Suzuki et al. 2010). Furthermore, other mechanisms of glucose in the pathogenesis of AD have been suggested such as the process that induces OS via nonenzymatic reaction of glucose to form AGEs on long-lived protein deposits and consequently disrupting glucose metabolism. Accordingly, more than any other protein in the body, apolipoproteins are susceptible to glycation. Although high level of glucose is mostly suggested as the main cause of AGEs, fructose is by far the worst reducing agent as compared to glucose (Seneff et al. 2011). Naturally, glucose is the least reactive sugar among those usable by the body, and probably that is why it remained an evolutionary biological energy carrier. One of the major challenges of AGE formation is that once it is formed, it is irreversible, and it leads to protein deposition and amyloidosis since it is a protease-resistant cross-linking of proteins and peptides (Münch et al. 1998). The major factor contributing to Aβ plaque deposition in AD is the high level of AGEs in the patients' brain. Since apolipoproteins are susceptible to glycation, glycated ApoE is excessively available in the cerebrospinal fluid (CSF) of AD patients (Shuvaev et al. 2001). This indicates that ApoE could be the initial stage in Alzheimer's cascade. Moreover, various proteins in neurons and astrocytes are vulnerable to glycation upon exposure to excess glucose (Li and Dickson 1997). The consequent loss of function, vulnerability to oxidative stress, and lesser degradation and disposal of AGEs and their presence in microscopic slices where Aβ is absent show that glycation is an early hallmark of AD (Seneff et al. 2011).

3.7.2 Impaired Glutamate and AD

Glutamate-induced excitotoxic cascade is one of the pathologic mechanisms associated with AD. Several studies have also suggested that impaired glutamatergic transmission is the hallmark of Alzheimer's disease. Initially, Aβ and tau activate the N-methyl-D-aspartate (NMDA) receptors. Then the activated NMDA receptors boost the making of Aβ and tau (Lesné et al. 2005; Amadoro et al. 2006). Increase in excitatory amino acids in the synapse that results in activation of glutamatergic

receptors and increased ROS level are cascades of inter-related pathways that lead to AD, PD, multiple sclerosis, and ischemia. The ionotropic and metabotropic glutamatergic receptors are both shown to play a role in etiology of Alzheimer's disease. Moreover, abnormal glutamate transport function has been identified in mutant amyloid-β protein precursor (AβPP) transgenic (tg) mice models of AD (Jacob et al. 2007). The impairment of synapses in AD encompasses Aβ-induced OS in the synapse that damages the glutamate receptors and the function of membrane ion along with a decline in mitochondrial efficiency because of the OS (Mattson 2004). In postmortem brain of APP tg mouse models of AD, the expression of glutamate transporters has been found low. Recent studies have also stipulated that Aβ-mediated synaptic suppression is partially due to inhibition of the GABAA receptor. These findings indicated that Aβ inhibits glutamate uptake, increases extracellular glutamate, and thus activates extrasynaptic GluN2B receptors and it also diminishes GABAA receptor-mediated inhibition, finally resulting in neuronal hyperexcitability (Lei et al. 2016). Moreover, a number of studies have reported diminished glutamate uptake in the frontal and temporal cortices of AD brains. These changes were suggested as the main reason for the rise in extracellular glutamate level (Cassano et al. 2012). Results of in vivo imaging studies demonstrated that AD patients brain show a significant shrinkage in the temporal, parietal, and frontal lobes of the cortex in addition to sulcal widening and ventricular enlargement. Such atrophies results from loss of pyramidal neurons and their synapses as well as the surrounding neuropil. Biochemical evidence identified glutamate as the neurotransmitter of these pathways, and hence it is obviously understandable that the glutamatergic neurons degenerate in AD (Francis 2003).

Medicinal plants and alternative medicines have been used to treat AD since the pharmacological interventions does not have satisfactory option for AD. *Hericium erinaceus* is an edible and medicinal mushroom which has been used to treat a number of diseases because of its potential antitumor, antimutagenic, antioxidant, hypolipidemic, immunomodulatory, and neuroprotective activities. According to Zhang J. et.al. (2016), *Hericium erinaceus* prevents neurodegenerative diseases. *Hericium erinaceus* prevented DPC12 cells against neurotoxicity induced by L-Glu. Additional observations on AlCl3- and D-gal-induced AD mice have proved that *Hericium erinaceus* has neuroprotective activity that involves neurotransmitter modulation (Zhang et al. 2016). Furthermore, it has been reported that ascorbic acid release mediated by neurons is related to glutamate metabolism and kinetics in the brain. Especially, the extracellular release of ascorbic acid is directly linked to astrocyte swelling mediated by glutamate receptors' increased sodium uptake. Henceforth, ascorbic acid in the brain and the CSF acts against glutamate excitotoxicity via antioxidant and neuroprotective mechanism (Nualart et al. 2014).

3.7.3 Role of Dietary Fats in AD

The brain is rich in lipids, although the content of fat differs among tissues. The content and composition of fatty acids (FAs) play a key role in brain functions like

cognition. Thus, knowing the lipid composition of the brain is an important step toward understanding the role of consuming altered fatty acid (FA) on its function. The dry weight of the gray matter, white matter, and myelin contains about 40%, 66%, and 81% lipid, respectively (Cederholm et al. 2013). Of all the nutrients essential to brain, some of the ω-3 FAs such as docosahexaenoic acid (DHA) have a special importance. Seafood and fatty fish are rich sources of both DHA and eicosapentaenoic acid (EPA) (Hennebelle et al. 2013). The DHA content in the brain has inverse relation with age, although it normally increases over the first two decades (Cederholm et al. 2013). Regularly consuming vegetables and fish fats of high PUFA, moderate unsaturated fats, and low saturated fat can lower the incidence of CVD and AD. Conversely, increased hydrogenated and saturated fats consumption is associated with insulin resistance, which is indirectly related to higher incidence of AD (Luchsinger and Mayeux 2004). Additionally, a high fat and low carbohydrate diet (Ketogenic diet) has been suggested to be effective against a range of neurologic diseases. In clinical settings, ketogenic diet has been utilized to treat AD, PD, epilepsy, and autism (Ma et al. 2018). Moreover, there are a number of evidences from preclinical studies showing the therapeutic activities of ketogenic diet for various disease conditions including AD, ischemia, and traumatic brain injury (Van der Auwera et al. 2005; Prins et al. 2005; Puchowicz et al. 2008).

3.7.4 Role of Omega-3 Fatty Acids in AD

The impact of dietary factors on various brain processes is through modulating neurotransmitter pathways, membrane fluidity, synaptic transmission, and signal transduction pathways. On the other hand, the direct effect of lipids on the brain function is attracting attention in addition to their indirect action through their impact on the CVS physiology. ω-3- PUFAs are cell membrane constituents, and they are essential nutrients of the brain. The dietary deficiency of ω-3 FAs has been linked with various severe cognitive disorders such as dementia, schizophrenia, depression, bipolar disorder, dyslexia, and attention-deficit disorder. Among the ω-3 FAs, DHA is an integral part of neuronal membranes, but the human body cannot synthesize DHA, and it has to obtain from dietary sources (Gómez-Pinilla 2008). ω-3 PUFA have various therapeutic benefits including anti-inflammatory, antioxidant at lower doses, and anti-amyloidogenesis (Alles et al. 2012). On the contrary, low consumption of ω-3- FAs has been widely associated to increased risk of suboptimal brain development and cardiovascular diseases (Hennebelle et al. 2014). As a major component in neuronal membranes, DHA has a number of physiological activities including sustaining the normal cell membrane fluidity and structure and also plays a role in cellular functions and response (Calder 2012). Furthermore, ω-3 FAs activate transcription factors like PPAR-g so as to modulate gene expressions that in turn controls the inflammatory mechanisms (Alles et al. 2012). In addition, animal studies have reported that the level of hippocampal brain-derived neurotrophic factor (BDNF) is increased and cognitive function is enhanced in brain trauma rodent models treated with dietary DHA supplements. Mechanistically, DHA might

enhance cognitive functions via aiding synaptic plasticity and/or enhancing synaptic membrane fluidity; its actions on metabolism might also contribute through enhancing glucose utilization and decreasing OS. However, the exact mechanisms of action through which the ω-3- FAs (particularly that of DHA) act on brain plasticity and cognition are not fully understood (Gómez-Pinilla 2008).

3.7.5 Role of Dietary Antioxidants in AD

The brain is prone to OS due to its high metabolic burden and its rich content of oxidizable materials including PUFA of the neuronal membranes. ROS are related to neuronal impairment in AD. Rise in oxidative stress and excess production and deposition of Aβ are early events in AD. Aβ deposition mainly results in reduced iron and copper level in the brain tissues, which in turn causes cascade of processes like production of hydrogen peroxide, increased OS, and neuronal damage (Luchsinger and Mayeux 2004). Quite a number of antioxidant foods have been known for their beneficial effects on neuronal functions (Fig. 3.1). For instance, barriers have been used for their strong antioxidant potential, yet the individual compounds evaluated so far are few, namely, the tannins procyanidin, and prodelphinidin, some anthocyanins and phenolic compounds. Moreover, curcumin is another dietary antioxidant well known as preservative and herbal medicine mainly in Indian subcontinent. Curcumin has a strong antioxidant property and reduces nitric-oxide-based radicals as well as preventing lipid peroxidation in the brain. In addition, animal model studies have been demonstrated to reduce memory deficit in AD and brain trauma. Curcumin is safe even at doses higher than the dose used in animal

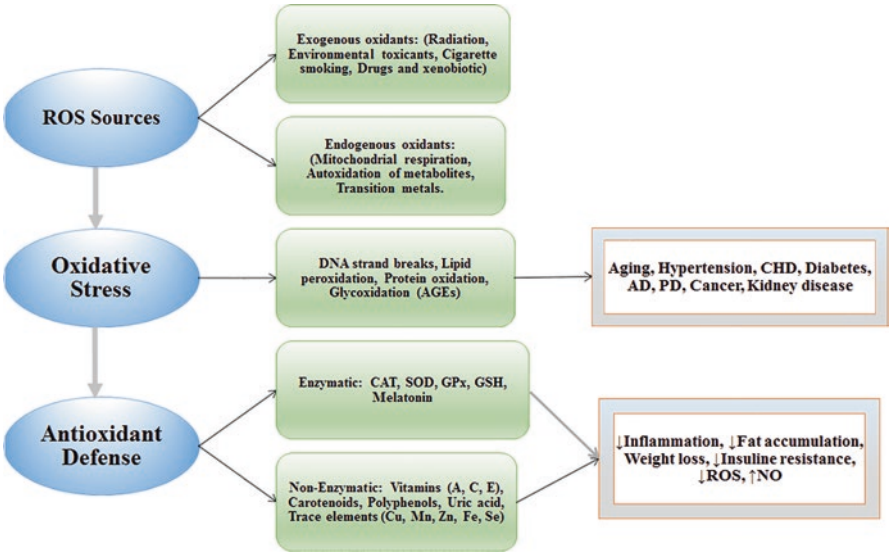

Fig. 3.1 The possible effects of oxidative stress and antioxidant nutrients. CAT: catalase, SOD: superoxide dismutase, GPx: Glutathione peroxidase, GSH: glutathione

models (Gómez-Pinilla 2008). Various studies have confirmed that vegetable and fruit juices available commercially also have high level of antioxidant polyphenolic compounds. This might be due to the high-pressure mechanical extraction during processing of vegetable and fruit juices that drives out all the antioxidant compounds from the peels and pulp in addition to the main fruit and vegetable fluids. According to various in vitro, in vivo, and clinical studies, a stronger neuroprotective activity than antioxidant vitamins has been reported in polyphenols from grape, apple, and citrus fruit juices (Dai et al. 2006). Dietary antioxidants have been related to reduce risk of stroke and thus AD, since stroke is mostly associated to higher incidence of AD through cerebrovascular events that links antioxidants, vitamins, and AD (Luchsinger and Mayeux 2004).

3.8 Conclusion

In today's world, the population size of aged people is growing faster. In the coming few decades, their numbers will double leaving the age-related disease to become a public health burden. Cognitive dysfunctions, in particular AD, are one of the most prominent the public health threat related to aging. Various pharmacological therapies have been used to counter the risk of AD and to prevent its progression. However, none is efficient in mitigating the problem of AD in relation to aging. Yet, nutritional interventions have attracted researcher's attention since most of the antioxidant-containing vegetables and fruits are important in reducing the incidence of AD. The basic pathology studies on AD have claimed that the major contributing factor in the onset and progression of AD is oxidative stress. Henceforth, controlling the environmental risk factors responsible for OS and consuming dietary antioxidants including dietary supplements and nutraceuticals has been proved effective in treating AD. Especially, the importance of caloric restriction and consuming PUFAs, proteins, vegetables, and fruits are reported in many observational studies. Therefore, dietary interventions along with avoiding risk factors will reduce the risk of age-related degenerative diseases and increase healthy life span among elderly.

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