Toxic Exposure and Life Style Factors on Ageing Brain Neurodegenerative Disease, Alzheimer’s and Parkinson’s: Role of Natural Antioxidants to Ameliorate the Condition

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Received date: January 18, 2018; Accepted date: April 24, 2018; Published date: April 27, 2018

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Abstract

Toxic exposure is a major risk factor for many neurodegenerative diseases in ageing brain such as, Alzheimer’s (AD) and Parkinson’s (PD), where decline of biological activities in cellular microenvironment render the organism more susceptible to either endogenous or exogenous stressors especially free radical damage, leading to pathological conditions. PCBs, MPTP, organochlorines and organophosphates, paraquat, fipronil, pyrithroid, quinines, and metals like, lead, cadmium, chromium, cobalt, manganese, arsenic etc. are play the crucial role in age-related diseases, AD and PD. Further, the degree of changes in the ageing brain in these cases not only depends on toxic exposures and genetic susceptibility but also on food habit, life style (use of alcohol, smoking, caffeine), environment etc. Certain antioxidants through diet can improve scenario of ageing brain and modulate specific molecular signalling. Therefore, this review briefly discusses the current status of the toxic exposure and life styles on ageing brain neurodegenerative diseases especially, AD and PD, and throws a light on the disease management through natural antioxidant supplements. For this purpose, data were searched through PubMed, MedLine, ResearchGate and Google using several combinations of key words giving stress on different aspect of AD and PD in ageing brain.

Keywords: Toxicants; Alcohol; Smoking; Caffeine; Alzheimer’s disease; Parkinson’s disease; Oxidative impairments; Antioxidant supplements

Introduction

Climate change and urbanization are the biggest threat of our life that affecting several health issues, which broaden the list of environmental chemicals that silently but potentially, change our surrounding day-by-day. Work place exposure of new toxicants, stress, obesity etc. Further decline the biological activities in cellular microenvironment leading to more susceptibility towards diseases [1,2]. Ageing brain is not an exception like other organs in our body as a soft target of degenerative changes i.e., Alzheimer’s (AD) and Parkinson’s (PD) due to exposure of hazardous substances such as, polychlorinated biphenyl (PCB), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), organochlorines and organophosphates, paraquat, fipronil, pyrithroid, quinines, and metals like, lead, cadmium, chromium, cobalt, manganese, arsenic etc. The degree and severity of neurodegenerative changes in ageing brain of AD and PD also deteriorate with life styles i.e. substance abuse (alcohol), smoking, caffeine and so on. All these factors are added burden to our society, where exposure to either endogenous or exogenous stressors causes several pathological conditions. However, certain nutrients derived from diet, including polyunsaturated fatty acids (PUFA) and polyphenolic compounds from fruits and vegetables can improve the scenario of ageing brain, possibly due to their anti-oxidant and anti-inflammatory abilities, as well as specific molecular and cellular signaling [3]. Therefore, this review briefly deals with different theories of ageing, toxic, oxidative and life style impacts on neurodegenerative diseases especially, AD and PD, and the ameliorative role of natural antioxidants from animal and plant origins. For this purpose, research papers and reviews were searched in PubMed, MedLine, ResearchGate, Google etc. using several combinations of key words giving stress on different aspect of AD and PD in ageing brain.

Theories of Ageing

Ageing is defined by Bernard Strehler, an American gerontologist, as (1) Universal i.e., ageing occur in all species but with different degrees of occurrence; (2) Intrinsic i.e., endogenous causes that depend on extrinsic factors; (3) Progressive, means changes occur progressively throughout the life till the end (final form); and (4) Deleterious i.e., ageing, is considered as a part of the ageing process if detrimental for individual [4]. Out of more than three hundred theories of ageing, four theories are discussed here due to close relation with the current topic.

Neuroendocrine Theory of Vladimir Dilman and Ward Dean

Focuses on ‘wear and tear’ mechanism that governs neuroendocrine hormonal release from hypothalamus of the brain, subsequently hypothalamic control to various organs and glands to further release of their respective hormones. However, as age progresses, hypothalams
loses its precision regulatory ability of neuroendocrine hormones, and receptors uptaking these hormones become less sensitive for hormone-receptor binding, which is manifested by decline in many hormone secretions and activity due to receptors down-regulation [5,6].

Membrane Theory of Imre Zs-Nagy

Focused on age-related changes of cell's ability to transfer chemicals, heat and electrical processes that impair its function. With age, older cell membrane contains fewer lipids; hence, become less watery and more solid, resulting in impairments of cell's efficiency to conduct normal function and accumulate toxic substances [7].

Mitochondrial Decline Theory

Mitochondria are the power house of cell organelles that create ATP through energy cycles, involving nutrients such as, acetyl-L-carnitine, Co-enzyme Q10 (Idebenone), NADH and vitamin B. These nutrients and ATP supplements enhance and protect mitochondria, which is an essential aspect of preventing and slowing down the ageing process [8].

Free Radical Theory by Denham Harman

‘Free radical’ means molecule with a free electron, which donates to healthy electron-balanced molecule and creates an extra negative charge, resulting in unbalancing the later in terms of extra negative charge. This unbalanced energy makes free radical to bind with another balanced molecule, and the cycle goes on. Certain diet, life style, drugs like, tobacco and alcohol, radiation, environmental and industrial toxicants such as, manganese, parquat, n-hexane, carbon monoxide, carbon disulphide, ethylene oxide, and pharmaceuticals i.e., chlorpromazine, metoclopramide etc., are the accelerators of free radical-induced ageing within the body [9].

Toxicants and Oxidative Stress in Neurodegenerative Disease

Toxicants like polychlorinated biphenyls (PCBs) can cause oxidative stress and disrupt neuronal function by inhibiting dopamine (DA) uptake into the synaptic vesicles, thus mechanistically linking to PD [10,11]. Environmental toxins also contribute to motor neuron death in amyotrophic lateral sclerosis (ALS) and dementia in AD [12,13]. Pesticides can also cause selective degeneration that resembles PD [14]. Inhalation, ingestion, dermal absorptions are the source of exposure to toxicants in human. However, poor disease registries that could enable population-based case-control studies, and lack of large cohort studies with extensive occupational or environmental exposure information are the limitations in such epidemiological studies [15]. Following segments discuss the impact of oxidative stress on AD and PD separately.

Toxicants and Oxidative Stress in AD

The estimated ageing AD populations in the world will be nearly 106 million by 2050 [16]. AD is the 6th leading cause of death in US alone [17], with 60%-80% of reported cases of dementia [18]. Although being diagnosed as a late-onset (70 years and above) disease [19], early onset (40-50 years) AD has been observed in more than 200,000 people in US only [20]. AD is characterized by a progressive decline of cognitive function, memory and intellectual ability [21] leading to irreversible neurodegenerative impairment, synaptic loss, neuronal cell death due to amyloid-β plaques i.e., dimmers and oligomers of phosphorylated tau protein in the brain, also known as neurofibrillary tangles [22]. Multiple factors are contributed to AD, but not confined to oxidative stress, ageing, genetic [23], head injury [24] and exposure to certain toxicants [25]. Studies have been found that exposure to aluminium, zinc, copper, iron and cadmium chloride salts on neuronal cells causes aggregation of amyloid-β plaques [26]. Aluminium-induced neurofibrillary degeneration, oxidative stress and inflammatory response are found among the AD patients. Although aluminium acts as a cross linker for in vitro amyloid-β oligomerization; but still its role in AD pathogenesis is controversial [26]. Trace amount of copper in diet also induces amyloid-β plaques and learning deficit in animals [27,28]. Copper is physiologically complexed with essential enzymes such as, superoxide dismutase, cytochrome C oxidase and ceruloplasmin, and the brain level of the metal is reduced in severe condition of AD, associated with low level of these enzymes [29,30]. Iron along with aluminium is also play a crucial role in the formation of amyloid-β plaques and amyloid fibrils aggregation [31,32]. Early exposure to lead impact physiological development of nervous system and may be the possible causative factor to increase susceptibility in later life to neurodegeneration and AD pathology, as revealed by increase expression of amyloid precursors upon lead exposure [33]. Elevated levels of cobalt and cadmium are observed in AD brain tissue in comparison with age-matched controls [34,35]. Cadmium causes self-aggregation of tau peptide R3, thereby considers as a potential agent in AD pathogenesis [36] that involving astrocytes and neural cell toxicity [37]. Several studies also showed the association of AD pathogenesis and the role of manganese [38], mercury [39], and arsenic [40]. Further, Se and zinc deficiency are found in the AD patients as compared to the age-matched controls [41,42]. Organochlorines and organophosphates [43], parquat [44], fipronil [45], pyrithroid [46] etc. are critical in degenerative CNS disorders and induce oxidative stress in development of AD pathogenesis. BPA [47], dioxions [48] and phthalates [49] also interfere with synaptic spine formation in the brain, which may have clinical implications resembling AD.

Toxicants and Oxidative Stress in PD

PD is a progressive neurodegenerative movement disorder, the etiology of which remains unknown. The clinical manifestations of PD result from the loss of pigmented dopaminergic (DAergic) neurons in pars compacta of substantia nigra. The symptoms of PD are tremor, bradykinesia, gait disturbances, cogwheel rigidity, postural instability, hypomimia, hypophonia and micrographia, which are increased by Levo-dopa, a DA agonist, and anticholinergics. α-synuclein is crucial in age of onset and etiology of PD, aggregation of which may be involved in Lewy body formation and pathogenesis of autosomal dominant forms of familial PD [50]. Several earlier studies reported the incidence rates of PD upto 190 per 100,000 persons [51,52]; and the mean death age in PD is increased from 60 years in 1950 to 77 years in 1992 irrespective of sexes in Japanese people [53]. In US, nearly 1% of PD population is over 60 years of age [54]. PD is also associated with several industrial chemicals, toxins, pesticides as these agents are linked with up-regulation of oxidative stress-induced neural loss and down-regulation of anti-oxidant enzymes in substantia nigra of the ageing brain. Free radicals and other metabolites that conjugate with glutathione are formed through metabolism of industrial chemicals, and thus exposure may contribute to the progression of nigral degeneration [55,56]. MPTP, a potent meperidine-analog, produces as a by-product of 1-methyl-4-phenyl-4-propionoxypiperidine (MPPP) synthesis, causes cell loss in pars
compacts of substantia nigra in PD patients [57], probably due to inhibition of complex I of the mitochondrial electron transport chain by MPP+ [58]. Oral administration of coenzyme Q10 increases complex-I activity but therapeutic benefit is yet to be discovered [59]. Pesticide paraquat metabolism yields free radicals that induce lipid peroxidation and increase the risk for PD in the ageing brain [60]. However, toxic effects of paraquat are attenuated by the conjugation of free radical metabolites with glutathione-S-transferases [61]. Studies on the patients with PD revealed high iron level in substantia nigra, where iron accumulation is associated with C282Y mutations responsible for hemochromatosis, a hereditary iron overload disorder than the controls, suggesting C282Y mutation increases the risk of PD [62]. Further, redox activity in neuromelanin-aggregates is significantly higher in the PD patients manifested by severe neuronal loss, may be due to severe oxidative stress [63]. Manganese is an essential trace element for normal development and function [64]; however, high dietary manganese with iron may contribute to the risk for PD [65], which is related to neuromelanin content in substantia nigra where divalent manganese oxidizes to form cytotoxic trivalent species [66,67] that potentiates autooxidation of DA, thereby generating toxic free radicals [68] and releasing neuromelanin [69,70]. The adverse effects of trivalent manganese are found when manganese superoxide dismutase, the protective scavenger enzyme is unable to alters oxidative potential of the reactive oxygen species (ROS) [71-73]. Interestingly, levodopa and/or DA agonist therapy is considerably less favorable in those patients with manganese poisoning than in idiopathic PD [74,75]. Moreover, several others factors like, pesticide exposure in home, rural living, well water consumption, diet, printing plants, or quarraies etc. are associated with the higher risk of PD [76-78].

**Radiation Effect on AD and PD**

Several studies also reported AD and PD like symptoms as a result of ionizing radiation to head. Azizova et al. showed remarkable of cerebro-vascular disease in nuclear workers who received cumulative doses of 0.5-0.2 Gy, compared with those of 0.2 Gy, indicating harmful effects of chronic low dose ionization in brain [79]. Further studies provide evidences of cerebro-vascular dysfunctions as a relevant pathogenic factor in AD [80-82] leading to neurodegeneration involving cerebral β-amyloidosis, cerebral amyloid angiopathy and amyloid-β plaque [83]. Further, each cell has numerous copies of mitochondrial DNA, where low-dose radiation alters mitochondrial impairment to causes neuro-degeneration. Malakhova et al. (2005) showed low levels of radiation-induced damage and alterations to mitochondrial DNA in gamma-irradiated (3 Gy) mice brain due to involvement of damaged mitochondrial DNA in the cumulative mitochondrial synthesis cycles as compensation to ATP deficiency, originating from the damaged DNA copies [84]. This is emphasized by general ageing process manifested by accumulation of mutations in mitochondrial DNA [85,86]. Ionizing radiation is also affect learning and memory processes irrespective of dose intensities through p53 and Myc signalling [87]. Interestingly, genes expressed as response to low dose even at the range of 0.1 Gy, are associated with memory, learning, cognition and long-term depression specific to glutamate receptor, integrin and G-protein coupled receptor signalling in the brain tissue of ageing people as well as the AD patients [87]. As the histopathological hallmarks of AD involving extracellular senile plaques of amyloid β-peptide and intracellular neurofibrillary tangles of hyperphosphorylated tau protein [88]; therefore, abnormal protein phosphorylation during AD results from altered activity of several protein kinases and phosphatases [89] though further investigations require to identify ionising radiation in the aetiology of neurodegenerative diseases such as, AD and PD in the ageing brain.

**ROS and Metabolic Changes in AD and PD**

Oxidative stress is involved in PD progression, as increase level of ROS damage the target neuronal cells [90,91]. DAergic neurons are more vulnerable to oxidative stress compared with other brain structures, attributed to their low intracellular levels of antioxidants and higher rate of oxygen consumption and calcium metabolism, leading to higher ROS levels [92]. High calcium turnover also considers as the unique physiology of DAergic neurons with their reliance on L-type calcium channels for their autonomous activity, but not on sodium channels like other neurons [93]. Mitochondria play a central role in the maintenance of high energy in cellular microenvironment, require for pumping out calcium for DAergic firing. Further, DAergic neurons can accumulate and store calcium [94]. Therefore, any mitochondrial dysfunction may result in energy and calcium imbalances, consequently leading to stressful mitochondria and cell death [95,96]. Therefore, it seems that DA metabolism and dysfunctions of mitochondria are the causative factors for the elevated ROS levels as observed in PD [92,97]. Therapeutic administration of levodopa to increase DA level in the brain does not influence the level of intracellular ROS [98], suggesting DA and its metabolites may not directly generate ROS. However, several results are contradictory that explaining relation of DA levels and oxidative stress in DAergic neurons [97,99]. Further, DA can undergo autooxidation in DAergic neurons or enzymatic oxidation to produce ROS, reactive metabolites and toxic quinones [100]. Due to high electron-deficiency of DA quinones, binding with thiol group of proteins enhances and affecting structure and function [100], which leads to protein aggregation, hindering mitochondrial functions by targeting mitochondrial proteins for degradation and increasing oxidative stress [97,100]. Differential expression of tyrosine hydroxylase isoforms, the rate-limiting enzyme for DA biosynthesis, may be the possible mechanism in this kind of brain damage and disease [101]. This indicates shift in metabolism of surviving neurons to compensate DA loss and thereby increase DA level contributing mitochondrial defects and ROS increase during PD progression [101]. All these evidences confirm that the mitochondrial complex dysfunction act as a hallmark of PD in the ageing brain.

Depression of mitochondrial electron transport chain activity has been also observed in the AD patients [102]. High oxidative stress in the AD patients [103] may results from oxidative phosphorylation defects especially, complex I defects during AD [104]. Quantitative proteomics suggesting deregulation of the amount and activity of complex I are associated with formation of tau protein in a triple transgenic AD mouse pR5/APP/PS2, which represents a model for both amyloid β-plaques and neurofibrillary tangles development, deficits in mitochondrial ATP metabolism and progression of AD pathology [104]. Amyloid β-plaque enters mitochondria and inhibits its functions by increasing mitochondrial membrane viscosity with a decrease in ATP/O ratio, increase ROS production, inhibit mitochondrial complexes and enhance cytochrome C release [105]. These observations suggest that the mitochondrial complex I dysfunction is definitely the hallmark of AD in the ageing brain.

**Life Style Factors in AD and PD**

Research has been focused for several decades to identify whether lifestyle exposures such as, smoking, alcoholism, caffeine through...
consumption of coffee and tea are the causative factors in the development of AD and PD, but the conclusion is still conflicting. Substance abuse like, alcohol intake and progression of PD or increase the risk of PD pathogenesis may vary according to the specific associations of beverages. For example, moderate to strong dose-dependent association of Japanese sake is found with PD, but not with the daily intake of different types of alcohol such as, beer, shochu, wine and whiskey [106]. Further an increased risk of PD is linked with daily more than two drinks of liquor [107]. Strong correlation of PD-like ageing brain damage with liquor and wine followed by brandy and bear is also reported by Sipetic et al. [108] though there is a lack of statistically control for finding the role of confounding factors. In contrast, a non-significant relation between beer, wine and liquor drinking, and the risk of PD are also established [109,110]. Overall, these studies collectively provide an inconsistent scenario of the relationship between PD pathogenesis and different alcoholic beverage types. Epidemiological studies further indicating the poor association of alcohol consumption and a risk of AD; however, the potential benefits may vary due to genetics, health history and the type or quantity of alcohol consumed [111,112]. Available data also show that excessive alcohol intake is associated with a higher risk of AD, which is modified by the AD genotype [113,114].

Smoking, another life style confounder depicts controversial results with neurodegenerative ageing brain diseases, AD and PD. Cigarette smoking and these neurodegenerative disorders is negatively associated as cigarette smokers are 50% less likely to have PD or AD than are the age- and gender-matched non-smokers, suggesting the risk of AD or PD in non-smokers has generally been about twice that of the smokers may be due to the undefined neuro-protective impact of cigarette smoke on the development of PD and AD pathogenesis [115]. In contrast, Rotterdam study indicating a positive association between smoking and the incidence of AD though limited to the subjects without any apolipoprotein-E ε4 allele [116]. Another prospective study is also reported a similar positive correlation between smoking and cognitive impairment [117]. Nicotine, one of the components of cigarette smoke binds with nicotine acetylcholine receptor in brain; thereby decreases neurotransmitter acetylcholine in AD; that is why drugs like Aricept increases brain acetylcholine level in AD patients.

A preventative correlation exists between the effects of coffee or tea and PD, where drinking of coffee/tea delays and prevents the onset of PD [118], though the exact mechanism of action is yet to be fully understood. However, DA receptors and neurotrophic factors like G-CSF may play a protective role. Combining coffee with other compounds like L-DOPA and G-CSF may be the more efficient means of treating and preventing PD like ageing brain disease [118]. Further, the available evidence demonstrates the association of coffee with lower risk of developing PD [119] and AD [120,121]. A 65–70% decrease risk of dementia and a 62–64% low risk of AD are found in the population consumed three to five cups of coffee per day during midlife as compared to the group consumed daily two or less cups of coffee [119]. Further, Weinreb et al. reveal that ROS generation and inflammation produce oxidative stress that plays a pivotal role in neurodegenerative diseases such as, AD and PD, where free radical scavengers, transition metal (i.e., iron and copper) chelators and non-vitamin natural antioxidant polyphenols improve the situation [122], suggesting dietary supplementation may improve cognitive deficits in the individuals of advanced age. As a consequence, green tea polyphenols are now being considered as therapeutic agents with an aim to alter the ageing process in the brain and serve as possible neuro-protective agents in progressive neurodegenerative disorders such as, PD and AD [122].

The overall role of ROS on toxic exposure of metals, PCBs, pesticides and ionizing radiation in the development of AD and PD pathogenesis in the ageing brain is summarizes below (Figure 1).

**Natural Antioxidants and Management of AD and PD**

Presence of stress and lack of endogenous enzymatic and nonenzymatic antioxidant substances overload oxidative burden, so supply of antioxidants from different external origins through diet can be of therapeutic impact to manage the age-related neurodegenerative diseases. Synthetic antioxidant can also be used in the food industry but it is not encouraged due to its possible side effects like, carcinogenesis and liver damage. However, natural antioxidants from various plant and animal sources are free from side effects, and less expensive; thus can be included in daily diet to improve the ageing brain scenario.

Plant extracts due to antioxidant and anti-inflammatory properties are interesting therapeutic candidates in recent days. Primarily polyphenols and alkalioids act as free radical scavengers due to multiple phenolic hydroxyl and nitrogen groups, respectively, which are electron donors to the aromatic ring [123]. Many polyphenol compounds are also iron chelators because of multiple hydrophilic groups and become efficient scavengers due to inhibition of the iron-mediated oxidaorylation through phenolic groups like other iron chelators [124]. Cryptotanshinone is an active component of *Salvia miltiorrhiza*. It reduces amyloid β-plaques aggregation in the brain tissue due to its anti-inflammatory, antioxidant, and anti-apoptotic properties [125]. Silimarin exerts anti-amylloid properties *in vitro*, which reduces amyloid β-plaques burden, microglial activation, amyloid β-plaques oligomer formation and hyperactive behavior in the transgenic mice upon chronic administration [126]. Grape seed polyphenolic extract also attenuates cognitive impairment and decreases amyloid β-plaques deposition in the aged AD transgenic mice brain [127]. Flavonoids from citrus plant reduce amyloid β-plaques in hippocampus [128], probably by reducing protein kinase A and inhibiting cAMP response element-binding protein phosphorylation [129]. Piperine, an alkaloid in *Piper longum*, lowers cognitive deficits and neurodegeneration of hippocampus in ethylcholine aziridinium-induced AD model [130]. Mono- and di-acetylated cyanidin and peonidin, the sweet potato anthocyanins attack ROS and act as potent antioxidants in AD and other neurodegenerative diseases [131]. Korean ginseng significantly improves AD assessment scale and clinical dementia rating scale while comparing with the control patients, suggesting a remarkable curative dietary supplement in the AD patients [132].

Plant extracts are also helpful in managing PD like diseases as revealed by green tea polyphenols that control DAergic neuron loss and oxidative damage in substantia nigra of the PD models, and consider as neuroprotective [133]. Echinodides from *Cistanche salsa* also maintain striatal DA levels, increases tyrosine hydroxylase expression and reduces caspase activation, thereby preventing neuronal cell death [134]. Further, anthocyanidin due to neuroprotective property reduces motor neuron loss and histological damage, thus prevents lipid peroxidation in the experimental PD model [135]. S-allyl cysteine and silimarin from plant sources prevent lipid peroxidation and mitochondrial dysfunction, preserve DA level and reduce cell death in substantia nigra of the MPTP-intoxicated...
model of PD [136,137], where Nrf2-mediated nuclear translocation and phase II reactions are involved [138]. Flavonoid luteolin of celery and green pepper shows neuroprotective activity against oxidative stress-induced damage [139]. Plant extract of Uncaria rhynchophylla increases glutathione level and reduces ROS-induced cell death in the experimental PD model [140]. Moreover, root extracts of several plant sources promote neural growth and increase antioxidant enzymes such as, superoxide dismutase, catalase, glutathione etc., and finally down-regulate motor neuron deficit in the MPTP-induced PD [141]. Manyam et al. (2004) reporting a potent activity of Mucuna pruriens as compared to levodopa in controlling motor neuron disease due to restoration of DA and norepinephrine levels, scavenging ROS and increasing mitochondrial complex I activity in substantia nigra during PD [142].

Animal-derived antioxidants are comparatively limited than plant-derived antioxidants, which depends mainly on amino compounds i.e., proteins, peptides and amino acids obtained from skeletal muscle of chicken and pork [143], eggs of hen and duck [144,145] and milk (proteins) of cattle [144]. Proteins and peptides of natural animal antioxidants inhibit lipid peroxidation through inactivation of ROS, scavenging of free radicals, chelation of pro-oxidative transition metals, reduction of hydroperoxides as well as alteration of physical properties of foods. Further, vitamin E and C from animal tissues [146], carotenoids from egg yolks and aquatic animals like, salmon and shrimp [147,148] are also included in the list.

However, clinical trials of some antioxidants derived from animal sources show negative or ambiguous results or insignificant benefits in human due to pro-oxidant properties under specific conditions. Further, life-prolonging effect of antioxidants is limited as it affects endogenous antioxidant system and may be different for various organisms. Recent observations also conclude that β-carotene, vitamin A and E may increase negative health impact as evidenced by increase mortality in well-nourished populations [149,150]. Moreover, antioxidants may have a plethora of other side effects unrelated to its antioxidative properties leading to perturbation of the proper functioning of the system on some traits. Reports also suggesting that
over expression of antioxidative enzymes may not be always relevant for our lifespan [151].

Conclusion and Future Direction of Research

Mediterranean diet is rich in natural antioxidants; thereby consider a most popular food habits in the Western world that mainly consists of fruits, vegetables, whole grains, beans, nuts, seeds, healthy fats and red wine. This diet is also associated with low mortality or higher longevity and reduced the risk of developing chronic diseases like, cancer, metabolic syndrome, depression, and neurodegenerative diseases [152]. Though so-called ‘anti-ageing’ foods are popular among us because of anti-inflammatory and antioxidative nature, but researcher must potentially link the pathophysiological mechanisms of specific age-related neurodegenerative disease and the ‘claimed’ anti-ageing effect. Most importantly, the optimal source of antioxidants come through diet, not from the synthetic supplements in the form of powder, pills or tablets; so we must take care of the fact that the diet limitations of these putative neuro-protective agents appear in the nutritional intake, not from the synthetic supplements [153]. Further, attempts are taken to find out the potential neuro-protector for the management of AD and PD, and other neurodegenerative diseases in the ageing brain, the results of which in animal and cell culture model are encouraging. However, limitations of these putative neuro-protective agents appear in the clinical trials may be due to the difference in species, study design and strains. As none of the animal models used in the experiment replicate all the real features of AD and PD, extrapolation of the possible outcome of these agents in patients is very difficult. Thus, improvisation of refined techniques and their proper coordination is required in next-generation preclinical and clinical trials in order to accelerate the search for natural neuroprotective therapies in the neurodegenerative ageing brain disease such as, AD and PD.

Conflict of Interest

None.

Author’s Contribution

NN conceived, designed and wrote the review. MD and AB partially contribute the natural antioxidant management part of the review. The authors sequence is based on the quantum of work done in the period. All authors have read and approved the manuscript.

Acknowledgement

Thanks to Director, ICMR-NIOH for generous support and encouragement.

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