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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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 terms pertaining to different aspects of oxidative modification in ageing brain, exposure of several toxicants and life style factors, AD and PD as well as natural antioxidants.

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, hypothalamus

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 Q_{10} (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, paraquat, 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], paraquat [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

compacta 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 Q_{10} 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 quarries 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>0.2 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 autoxidation 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 whisky [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 neurotropic 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).

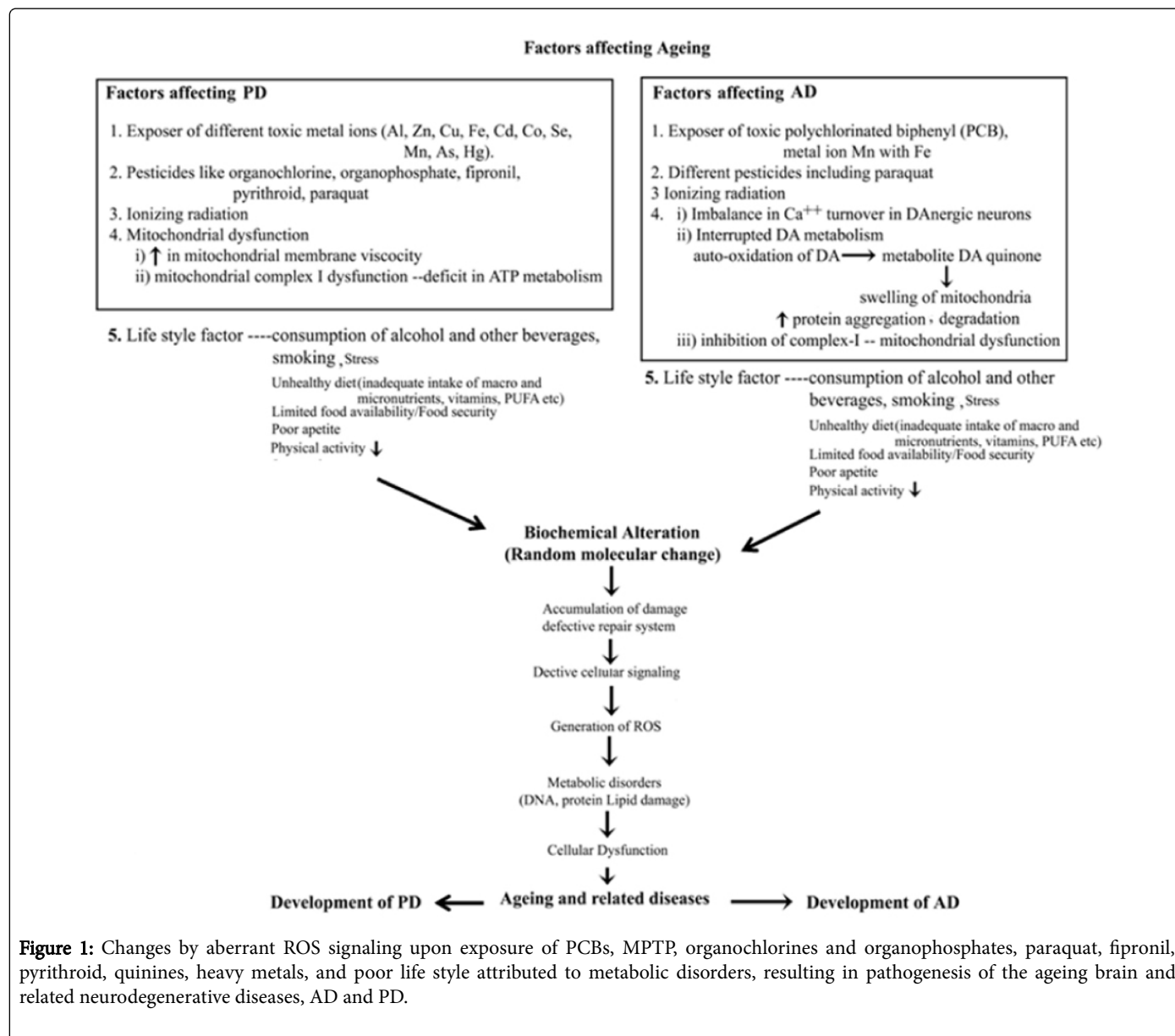## Natural Antioxidants and Management of AD and PD

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 alkaloids 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 oxyradical formation by 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]. Silymarin exerts antiamyloid 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-acetyled 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]. Echinosides 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 silymarin 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 nidgra during PD [142].

Figure 1: Changes by aberrant ROS signaling upon exposure of PCBs, MPTP, organochlorines and organophosphates, paraquat, fipronil, pyrithroid, quinines, heavy metals, and poor life style attributed to metabolic disorders, resulting in pathogenesis of the ageing brain and related neurodegenerative diseases, AD and PD.

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 chart should be in accordance with the need of age to fulfil daily nutritional deficiency. 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.

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References

1. Sebastiani P, Perls TT (2012) The genetics of extreme longevity: Lessons from the New England centenarian study. Front Genet 3: 1-7.

2. Lövdén M, Xu WM, Wang HX (2013) Lifestyle change and the prevention of cognitive decline and dementia: What is the evidence? Curr Opin Psychiat 26: 239-243.

3. Reedy J, Krebs-Smith SM, Miller PE (2014) Higher diet quality is associated with decreased risk of all-cause, cardiovascular disease and cancer mortality among older adults. J Nutri 144: 881-889.

4. Vina J, Borras C, Miquel J (2007) Theories of ageing. IUBMB Life 59: 249-254.

5. Dil'man VM, Dean W (1992) The neuroendocrine theory of aging and degenerative disease. Centr BioGerontol.

6. Nair NPV, Hariharasubramanian N, Pilapil C, Thavundayil JX (1986) Plasma melatonin-an index of brain ageing in humans. Biol Psychiat 21: 141-150.

7. Nagy IZ, Imre A (1978) A membrane hypothesis of ageing. J Theor Biol 75: 189-195.

8. Harman D (1972) The biologic clock: The mitochondria. J Am Geriat Soc 20: 145-147.

9. Harman D (1992) Free radical theory of aging. Mut Res 275: 257-266.

10. Mariussen E, Andersen JM, Fonnum F (1999) The effect of polychlorinated biphenyls on the uptake of dopamine and other neurotransmitters into rat brain synaptic vesicles. Toxicol Appl Pharmacol 161: 274-282.

11. Lee DW, Opanashuk LA (2004) Polychlorinated biphenyl mixture aroclor 1254-induced oxidative stress plays a role in dopaminergic cell injury. Neurotoxicology 25: 925-939.

12. Logroscino G, Beghi E, Zoccolella S (2005) Incidence of amyotrophic lateral sclerosis in southern Italy: A population based study. J Neurol Neurosurg Psychiat 76: 1094-1098.

13. Brown RC, Lockwood AH, Sonawane BR (2005) Neurodegenerative diseases: An overview of environmental risk factors. Environ Health Perspec 113: 1250-1256.

14. Betarbet R, Sherer TB, MacKenzie G, Garcia-Osuna M, Panov AV, et al. (2000) Chronic asystemic pesticide exposure reproduces features of Parkinson's disease. Nat Neurosci 3: 1301-1306.

15. Ritz B (2006) Environmental toxins and neurodegenerative diseases: A challenge for epidemiologists. Epidemiology 17: 2-3.

16. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM (2007) Forecasting the global burden of Alzheimer's disease. Alzheim Demen 3: 186-191.

17. Alzheimer's Association (2016) Alzheimer's disease facts and figures. Alzheimer's and Dementia 12: Washington DC, USA.

18. Alzheimer's-Association (2017) Alzheimer's disease facts and figures. Alzheimer's and Dementia 13: Washington DC, USA.

19. Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA (2003) Alzheimer disease in the US population: Prevalence estimates using the 2000 census. Arch Neurol 60: 1119-1122.

20. Rocca WA, Petersen RC, Knopman DS (2011) Trends in the incidence and prevalence of Alzheimer's disease, dementia and cognitive impairment in the United States. Alzheim Dement 7: 80-93.

21. Hardy J, Selkoe DJ (2002) The amyloid hypothesis of Alzheimer's Disease: Progress and problems on the road to therapeutics. Science 297: 353-356.

22. Perl DP (2010) Neuropathology of Alzheimer's disease. Mount Sinai Journal of Medicine. J Trans Person Med 77: 32-42.

23. Coon KD, Myers AJ, Craig DW (2007) A high-density whole-genome association study reveals that APOE is the major susceptibility gene for sporadic late-onset Alzheimer's disease. J Clin Psychiat 68: 613-618.

24. Guo Z, Cupples LA, Kurz A (2000) Head injury and the risk of AD in the MIRAGE study. Neurology 54: 1316-1323.

25. Calderon-Garciduenas L, Reed W, Maronpot RR (2004) Brain inflammation and Alzheimer's-like pathology in individuals exposed to severe air pollution. Toxicol Pathol 32: 650-658.

26. Kawahara M, Kato-Negishi M (2011) Link between aluminum and the pathogenesis of Alzheimer's disease: The integration of the aluminum and amyloid cascade hypotheses. Int J Alzheim Dis 2011: 1-17.

27. Sparks DL, Schreurs BG (2003) Trace amounts of copper in water induce β-amyloid plaques and learning deficits in a rabbit model of Alzheimer's disease. Proc Natl Acad Sci 100: 11065-11069.

28. Syme CD, Nadal RC, Rigby SE, Viles JH (2004) Copper binding to the amyloid-β (Aβ) peptide associated with Alzheimer's disease: Folding, coordination geometry, pH dependence, stoichiometry, and affinity of Aβ-(1–28): Insights from a range of complementary spectroscopic techniques. J Biol Chem 279: 18169-18177.

29. Deibel MA, Ehmann WD, Markesbery WR (1996) Copper, iron, and zinc imbalances in severely degenerated brain regions in Alzheimer's disease: Possible relation to oxidative stress. J Neurol Sci 143: 137-142.

30. Squitti R, Polimanti R (2013) Copper phenotype in Alzheimer's disease: Dissecting the pathway. Am J Neurodegen Dis 2: 46-56.

31. Ward NI, Mason JA (1987) Neutron activation analysis techniques for identifying elemental status in Alzheimer's disease. J Radioanal Nucl Chem 113: 515-526.

32. House E, Collingwood J, Khan A, Korchazkina O, Berthon G, et al. (2004) Aluminium, iron, zinc and copper influence the in vitro formation of amyloid fibrils of Aß42 in a manner which may have consequences for metal chelation therapy in Alzheimer's disease. J Alzheim Dis 6: 291-301.

33. Basha MR, Wei W, Bakheet SA (2005) The fetal basis of amyloidogenesis: Exposure to lead and latent overexpression of amyloid precursor protein and β-amyloid in the ageing brain. J Neurosci 25: 823-829.

34. Thompson CM, Markesbery WR, Ehmann WD, Mao YX, Vance DE (1988) Regional brain trace-element studies in Alzheimer's disease. Neurotoxicology 9: 1-7.

35. Ward NI, Mason JA (1987) Neutron activation analysis techniques for identifying elemental status in Alzheimer's disease. J Radioanal Nucl Chem 113: 515-526.

36. Jiang LF, Yao TM, Zhu ZL, Wang C, Ji LN (2007) Impacts of Cd(II) on the conformation and self-aggregation of Alzheimer's tau fragment corresponding to the third repeat of microtubule-binding domain. Biochemt Biophys Acta (BBA)-Prot Proteom 1774: 1414-1421.

37. Matés JM, Segura JA, Alonso FJ, Márquezm J (2010) Roles of dioxins and heavy metals in cancer and neurological diseases using ROS-mediated mechanisms. Free Rad Biol Med 49: 1328-1341.

38. Banta RG, Markesbery WR (1977) Elevated manganese levels associated with dementia and extrapyramidal signs. Neurology 27: 213-217.

39. Mutter J, Curth A, Naumann J, Deth R, Walach H (2010) Does inorganic mercury play a role in Alzheimer's disease? A systematic review and an integrated molecular mechanism. J Alzheim Dis 22: 357-374.

40. Dani SU (2010) Arsenic for the fool: An exponential connection. Sci Total Environ 408: 1842-1846.

41. Cardoso BR, Ong TP, Jacob-Filho W, Jaluul O, Freitasa MIDA, et al. (2010) Nutritional status of selenium in Alzheimer's disease patients. Brit J Nutri 103: 803-806.

42. Baum L, Chan HIS, Cheung SK (2010) Serum zinc is decreased in Alzheimer's disease and serum arsenic correlates positively with cognitive ability. Biometals 23: 173-179.

43. Chhillar N, Singh NK, Banerjee BD (2013) β-hexachlorocyclohexane as a risk for Alzheimer's Disease: A pilot study in North Indian population. Am J Alzheim Dis 1: 60-71.

44. Chen L, Yoo SE, Na R, Liu Y, Ran Q (2012) Cognitive impairment and increased Aβ levels induced by paraquat exposure are attenuated by enhanced removal of mitochondrial H_2O_2. Neurobiol Age 33: 432.e15-e26.

45. Limon A, Reyes-Ruiz JM, Miledi R (2012) Loss of functional GABAA receptors in the Alzheimer diseased brain. Proc Natl Acad Sci 109: 10071-10076.

46. Chen N, Luo D, Yao X (2012) Pesticides induce spatial memory deficits with synaptic impairments and an imbalanced tau phosphorylation in rats. J Alzheim Dis 30: 585-594.

47. Hajszan T, Leranth C (2010) Bisphenol A interferes with synaptic remodeling. Frontn Neuroendocrinol 31: 519-530.

48. Sul D, Kim HS, Cho EK (2009) 2,3,7,8-TCDD neurotoxicity in neuroblastoma cells is caused by increased oxidative stress, intracellular calcium levels and tau phosphorylation. Toxicology 255: 65-71.

49. Xu H, Shao X, Zhang Z (2013) Effects of di-n-butyl phthalate and diethyl pthalate on acetylcholinesterase activity and neurotoxicity related gene expression in embryonic zebrafish. Bull Environ Contam Toxicol 91: 635-639.

50. DeStefano AL, Lew MF, Golbe LI (2002) PARK3 influences age at onset in Parkinson disease: A genome scan in the GenePD study. Am J Hum Gen 70: 1089-1095.

51. Zhang ZX, Roman GC (1993) Worldwide occurrence of Parkinson's disease: An updated review. Neuroepidemiology 12: 195-208.

52. Rajput AH, Uitti RJ, Stern W (1987) Geography, drinking water chemistry, pesticides and herbicides and the etiology of Parkinson's disease. Canad J Neurol Sci 14: 414-418.

53. Imaizumi Y, Kaneko R (1995) Rising mortality from Parkinson's disease in Japan 1950-1992. Acta Neurol Scand 91: 169-176.

54. Tysnes OB, Storstein A (2017) Epidemiology of Parkinson's disease. J Neural Transm (Vienna) 124: 901-905.

55. Kim Y, Kim JW, Ito K (1999) Idiopathic parkinsonism with superimposed manganese exposure: Utility of positron emission tomography. Neurotoxicology 20: 249-252.

56. Barbosa ER, Comerlatti LR, Haddad MS, Scaff M (1992) Parkinsonism secondary to ethylene oxide exposure: Case report. Arq Neuro-Psiquiat 50: 531-533.

57. Langston JW, Forno LS, Rebert CS, Irwin I (1984) Selective nigral toxicity after systemic administration of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) in the squirrel monkey. Brain Res 292: 390-394.

58. Schapira AHV, Mann VM, Cooper JM (1990) Anatomic and disease specificity of NADH CoQ1 reductase (complex I) deficiency in Parkinson's disease. J Neurochem 55: 2142-2145.

59. Shults CW, Beal MF, Fontaine D, Nakano K, Haas RH (1998) Absorption, tolerability and effects on mitochondrial activity of oral coenzyme Q_{10} in parkinsonian patients. Neurology 50: 793-795.

60. Liou HH, Tsai MC, Chewn CJ (1997) Environmental risk factors and Parkinson's disease: A case-control study in Taiwan. Neurology 48: 1583-1588.

61. LlioDi C, Sacchetta P, Iannarelli V, Aceto A (1995) Binding of pesticides to α, μ and π class glutathione transferase. Toxicol Lett 76: 173-177.

62. Girotra T, Mahajan A, Sidiropoulos C (2017) Levodopa responsive parkinsonism in patients with hemochromatosis: Case presentation and literature review. Case Rep Neurol Med 2017: 1-3.

63. Faucheux BA, Martin ME, Beaumont C (2003) Neuromelanin associated redox-active iron is increased in the substantia nigra of patients with Parkinson's disease. J Neurochem 86: 1142-1148.

64. Feldman RG, Robert G (1999) Occupational and environmental neurotoxicology. Lippincott-Raven, Philadelphia, USA.

65. Powers KM, Smith-Weller T, Franklin GM (2003) Parkinson's disease risks associated with dietary iron, manganese and other nutrient intakes. Neurology 60: 1761-1766.

66. Swartz HM, Sarna T, Zecca L (1992) Modulation by neuromelanin of the availability and reactivity of metal ions. Ann Neurol 32: S69-S75.

67. Ambani LM, Van Woert MH, Murphy S (1975) Brain peroxidase and catalase in Parkinson's disease. Arch Neurol 32: 114-118.

68. Archibald FS, Tyree C (1987) Manganese poisoning and the attack of trivalent manganese upon catecholamines. Arch Biochem Biophy 256: 638-650.

69. Segura-Aguila J, Lind C (1989) On the mechanism of the Mn3+-induced neurotoxicity of dopamine: Prevention of quinone-derived oxygen toxicity by DT diaphorase and superoxide dismutase. Chem Biol Interac 72: 309-324.

70. Graham DG (1984) Catecholamine toxicity: A proposal for the molecular pathogenesis of manganese neurotoxicity and Parkinson's disease. Neurotoxicology 5: 83-96.

71. Halliwell B (1984) Manganese ions, oxidation reactions and the superoxide radical. Neurotoxicology 5: 113-118.

72. Donaldson J, Barbeau A (1985) Manganese neurotoxicity: Possible clues to the etiology of human brain disorders. Metal ions Neurol Psychiat 8: 259-285.

73. Yoritaka A, Hattori N, Mori H, Kato K, Mizuno Y (1997) An immunohistochemical study on manganese superoxide dismutase in Parkinson's disease. J Neurol Sci 148: 181-186.

74. Lu CS, Huang CC, Chu NS, Calne DB (1994) Levodopa failure in chronic manganism. Neurology 44: 1600-1602.

75. Calne DB, Chu NS, Huang CC, Lu CS, Olanow W (1994) Manganism and idiopathic parkinsonism: Similarities and differences. Neurology 44: 1583-1586.

76. Koller W, Vetere-Overfield B, Gray C (1990) Environmental risk factors in Parkinson's disease. Neurology 40: 1218-1221.

77. Calne S, Schoenberg B, Martin W, Uitti RJ, Spencer P (1987) Familial Parkinson's disease: Possible role of environmental factors. Canad J Neurol Sci 14: 303-305.

78. Kuopio AM, Marttila RJ, Helenius H, Rinne UK (1999) Changing epidemiology of Parkinson's disease in southwestern Finland. Neurology 52: 302-308.

79. Azizova TV, Muirhead CR, Moseeva MB (2011) Cerebrovascular diseases in nuclear workers first employed at the Mayak PA in 1948-1972. Rad Environ Biophys 50: 539-552.

80. Tong XK, Lecrux C, Hamel E (2012) Age-dependent rescue by simvastatin of Alzheimer's disease cerebrovascular and memory deficits. J Neurosci 32: 4705-4715.

81. Kurata T, Miyazaki K, Kozuki M (2011) Progressive neurovascular disturbances in the cerebral cortex of Alzheimer's disease-model mice: Protection by atorvastatin and pitavastatin. Neuroscience 197: 358-368.

82. Viticchi G, Falsetti L, Vernieri F (2012) Vascular predictors of cognitive decline in patients with mild cognitive impairment. Neurobiol Ageing 33: 1127.e1-9.

83. Zlokovic BV (2008) The blood-brain barrier in health and chronic neurodegenerative disorders. Neuron 57: 178-201.

84. Malakhova L, Bezlepkin VG, Antipova V (2005) The increase in mitochondrial DNA copy number in the tissues of gamma-irradiated mice. Cell Mol Biol Lett 10: 721-732.

85. Müller WE, Eckert A, Kurz C, Eckert GP, Leuner K (2010) Mitochondrial dysfunction: Common final pathway in brain aging and Alzheimer's disease-therapeutic aspects. Mol Neurobiol 41: 159-171.

86. Reddy PH, Beal MF (2008) Amyloid beta, mitochondrial dysfunction and synaptic damage: Implications for cognitive decline in aging and Alzheimer's disease. Trends Mol Med 14: 45-53.

87. Lowe XR, Bhattacharya S, Marchetti F, Wyrobek AJ (2009) Early brain response to low-dose radiation exposure involves molecular networks and pathways associated with cognitive functions, advanced aging and Alzheimer's disease. Rad Res 171: 53-65.

88. di Domenico F, Sultana R, Barone E (2011) Quantitative proteomics analysis of phosphorylated proteins in the hippocampus of Alzheimer's disease subjects. J Proteom 74: 1091-1103.

89. Chung SH (2009) Aberrant phosphorylation in the pathogenesis of Alzheimer's disease. BMB Rep 42: 467-474.

90. Hirsch EC (1993) Does oxidative stress participate in nerve cell death in Parkinson's disease. Eur Neurol 33: 52-59.

91. Michel PP, Hirsch EC, Hunot S (2016) Understanding dopaminergic cell death pathways in Parkinson disease. Neuron 90: 675-691.

92. Licker V, Kövari E, Hochstrasser DF, Burkhard PR (2009) Proteomics in human Parkinson's disease research. J Proteom 73: 10-29.

93. Surmeier DJ, Guzman JN, Sanchez-Padilla J (2010) Calcium, cellular aging and selective neuronal vulnerability in Parkinson's disease. Cell Calc 47: 175-182.

94. Starkov AA (2010) The molecular identity of the mitochondrial Ca^{++} sequestration system. FEBS J 277: 3652-3663.

95. Wang X, Michaelis EK (2010) Selective neuronal vulnerability to oxidative stress in the brain. Front Age Neurosci 2: 1-13.

96. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M (2007) Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol 39: 44-84.

97. Greenamyre JT, Hastings TG (2004) Parkinson's: Divergent causes, convergent mechanisms. Science 304: 1120-1122.

98. Fahn S, Parkinson study group (2005) Does levodopa slow or hasten the rate of progression of Parkinson's disease? J Neurol 252: IV37-IV42.

99. Wu YN, Johnson SW (2011) Dopamine oxidation facilitates rotenone-dependent potentiation of N-methyl-D-aspartate currents in rat substantia nigra dopamine neurons. Neuroscience 195: 138-144.

100. Hastings TG (2009) The role of dopamine oxidation in mitochondrial dysfunction: Implications for Parkinson's disease. J Bioen Biomemb 41: 469-472.

101. Elsworth JD, Roth RH (1997) Dopamine synthesis, uptake, metabolism and receptors: Relevance to gene therapy of Parkinson's disease. Expt Neurol 144: 4-9.

102. Parker WD, Parks J, Filley CM, Kleinschmidt-Demasters BK (1994) Electron transport chain defects in Alzheimer's disease brain. Neurology 44: 1090-1096.

103. Butterfield DA, Reed T, Newman SF, Sultana R (2007) Roles of amyloid beta-peptide-associated oxidative stress and brain protein modifications in the pathogenesis of Alzheimer's disease and mild cognitive impairment. Free Rad Biol Med 43: 658-677.

104. Eckert A, Schulz KL, Rhein V, Götz J (2010) Convergence of amyloid-beta and tau pathologies on mitochondria in vivo. Mol Neurobiol 41: 107-114.

105. Aleardi AM, Benard G, Augereau O (2005) Gradual alteration of mitochondrial structure and function by beta-amyloids: Importance of membrane viscosity changes, energy deprivation, reactive oxygen species production and cytochrome c release. J Bioen Biomemb 37: 207-225.

106. Fukushima W, Miyake Y, Tanaka K (2010) Alcohol drinking and risk of Parkinson's disease: A case-control study in Japan. BMC Neurol 10: 1-9.

107. Bettiol SS, Rose TC, Hughes CJ, Smith LA (2015) Alcohol consumption and Parkinson's disease risk: A review of recent findings. J Parkins Dis 5: 425-442.

108. Sipetic SB, Vlajinac HD, Maksimovic JM (2012) Cigarette smoking, coffee intake and alcohol consumption preceding Parkinson's disease: A case-control study. Acta Neuropsychiat 24: 109-114.

109. Palacios N, Gao X, O'Reilly E (2012) Alcohol and risk of Parkinson's disease in a large, prospective cohort of men and women. Mov Disord 27: 980-987.

110. Sääksjärvi K, Knekt P, Männistö S (2014) Reduced risk of Parkinson's disease associated with lowerbody mass index and heavy leisure-time physical activity. Eur J Epidemiol 29: 285-292.

111. Anstey KJ, Mack HA, Cherbuin N (2009) Alcohol consumption as a risk factor for dementia and cognitive decline: Meta-analysis of prospective studies. Am J Geriat Psychiat 17: 542-555.

112. Piazza-Gardner AK, Gaffud TJB, Barry AE (2013) The impact of alcohol on Alzheimer's disease: A systematic review. Age Ment Health 17: 133-146.

113. Kivipelto M, Rovio S, Ngandu T (2008) Apolipoprotein E4 magnifies lifestyle risk for dementia: A population-based study. J Cell Mol Med 12: 2762-2771.

114. Zhou S, Zhou R, Zhong T, Li R, Tan J, et al. (2014) Association of smoking and alcohol drinking with dementia risk among elderly men in China. Curr Alzheim Res 11: 899-907.

115. Fratiglioni L, Wang HX (2000) Smoking and Parkinson's and Alzheimer's diease: Review of the epidemiological studies. Behav Brain Res 113: 117-120.

116. Ott A, Slooter AJC, Hofman A (1998) Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: The Rotterdam study. Lancet 351: 1840-1843.

117. Galanis DJ, Petrovitch H, Launer LJ, Harris TB, Foley DJ, et al. (1997) Smoking history in middle age and subsequent cognitive performance in elderly Japanese-American men. Am J Epidemiol 145: 507-515.

118. Costa J, Lunet N, Santos C, Santos J, Vaz-Carneiro A (2010) Caffeine exposure and the risk of Parkinson's disease: A systematic review and meta-analysis of observational studies. J Alzheim Dis 20: S221-S238.

119. Morelli M, Carta AR, Jenner P (2009) Adenosine A2A receptors and Parkinson's disease. Handb Exp Pharmacol 193: 589-615.

120. Gelber RP, Petrovitch H, Masaki KH, Ross GW, White LR (2011) Coffee intake in midlife and risk of dementia and its neuropathologic correlates. J Alzheim Dis 23: 607-615.

121. Skelinen MH, Ngandu T, Tuomilehto J, Soininen H, Kivipelto M (2009) Midlife coffee and tea drinking and the risk of late-life dementia: A population-based CAIDE study. J Alzheim Dis 16: 85-91.

122. Weinreb O, Mandel S, Amit T, Youdim MB (2004) Neurological mechanisms of green tea polyphenols in Alzheimer's and Parkinson's diseases. J Nutr Biochem 15: 506-516.

123. Skrzydlewska E, Ostrowska J, Farbiszewski, Michalak K (2002) Protective effect of green tea against lipid peroxidation in the rat liver, blood serum and the brain. Phytomedicine 9: 232-238.

124. Bhattacharya M, Ponka P, Hardy P (1997) Prevention of postasphyxia electroretinal dysfunction with a pyridoxal hydrazone. Free Rad Biol Med 22: 11-16.

125. Mei Z, Zhang F, Tao L (2009) Cryptotanshinone, a compound from Salvia miltiorrhiza modulates amyloid precursor protein metabolism and attenuates -amyloid deposition through upregulating -secretase *in vivo* and *in vitro*. Neurosci Lett 452: 90-95.

126. Murata N, Murakami K, Ozawa Y (2010) Silymarin attenuated the amyloid beta plaque burden and improved behavioral abnormalities in an Alzheimer's disease mouse model. Biosci Biotechnol Biochem 74: 2299-2306.

127. Wang J, Ho L, Zhao W (2008) Grape-derived polyphenolics prevent A-oligomerization and attenuate cognitive deterioration in a mouse model of Alzheimer's disease. J Neurosci 28: 6388-6392.

128. Onozuka H, Nakajima A, Matsuzaki K (2008) Nobiletin, a citrus flavonoid, improvesmemory impairment and A-pathology in a transgenic mouse model of Alzheimer's disease. J Pharmacol Expt Therap 326: 739-744.

129. Nagase H, Omae N, Omori A (2005) Nobiletin and its related flavonoids with CRE-dependent transcription-stimulating and neuritegenic activities. Biochem Biophy Res Comm 337: 1330-1336.

130. Chonpathompikunlert P, Wattanathorn J, Muchimapura S (2010) Piperine, the main alkaloid ofthai black pepper, protects against neurodegeneration and cognitive impairment in animal model of cognitive deficit like condition of Alzheimer's disease. Food Chem Toxicol 48: 798-802.

131. Steed LE, Truong VD (2008) Anthocyanin content, antioxidant activity and selected physical properties of flowable purple-fleshed sweetpotato purees. J Food Sci 73: S215-221.

132. Heo JH, Lee ST, Chu K (2008) An open-label trial of Korean red ginseng as an adjuvant treatment for cognitive impairment in patients with Alzheimer's disease. Eur J Neurol 15: 865-868.

133. Levites Y, Weinreb O, Maor G, Youdim MBH, Mandel S (2001) Green tea polyphenol (-)-epigallocatechin-3-gallate prevents N-methyl-4-phenyl-1,2,3,6-tetra-hydropyridineinduced dopaminergic neurodegeneration. J Neurochem 78: 1073-1082.

134. Zhao Q, Gao J, Li W, Cai D (2010) Neurotrophic and neurorescue effects of echinacoside in the subacute MPTP mouse model of Parkinson's disease. Brain Res 1346: 224-236.

135. Vauzour D, Ravaioli G, Vafeiadou K, Rodriguez-Mateos A, Angeloni C, et al. (2008) Peroxynitrite induced formation of the neurotoxins 5-S-cysteinyl-dopamine and DHBT-1: Implications for Parkinson's disease and protection by polyphenols. Arch Biochem Biophy 476: 145-151.

136. Garcia E, Limon D, Perez-De La Cruz V (2008) Lipid peroxidation, mitochondrial dysfunction and neurochemical and behavioral deficits in different neurotoxic models: Protective role of S-allylcysteine. Free Rad Res 42: 892-902.

137. Pérez JH, Carrillo CS, García E, Ruiz-Mar G, Pérez-Tamayo R, et al. (2014) Neuroprotective effect of silymarin in a MPTP mouse model of Parkinson's disease. Toxicology 319: 38-43.

138. Garcia E, Santana-Martínez R, Silva-Islas CA (2014) Sallyl cysteine protects against MPTP-induced striatal and nigral oxidative neurotoxicity in mice: Participation of Nrf2. Free Rad Res 48: 159-167.

139. Kang SS, Lee JY, Choi YK, Kim GS, Han BH (2004) Neuroprotective effects of flavones on hydrogen peroxide-induced apoptosis in SH-SY5Y neurobloÂstoma cells. Bioorg Med Chem Lett 14: 2261-2264.

140. Shim JS, Kim HG, Ju MS, Choi JG, Jeong SY, et al. (2009) Effects of the hook of Uncariarhynchophyllaon neurotoxicity in the 6-hydroxydopamine model of Parkinson's disease. J Ethnopharmacol 126: 361-365.

141. RajaSankar S, Manivasagam T, Surendran S (2009) Ashwagandha leaf extract: A potential agent in treating oxidative damage and physiological abnormalities seen in a mouse model of Parkinson's disease. Neurosci Lett 454: 11-15.

142. Manyam BV, Dhanasekaran M, Hare TA (2004) Neuroprotective effects of the antiparkinson drug Mucunapruriens. Phytother Res 18: 706-712.

143. Elias RJ, Kellerby SS, Decker EA (2008) Antioxidant activity of proteins and peptides. Crit Rev Food Sci Nutr 48: 430-441.

144. Huang WY, Majumder K, Wu J (2010) Oxygen radical absorbance capacity of peptides from egg white protein ovotransferrin and their interaction with phytochemicals. Food Chem 123: 635-641.

145. Nimalaratne C, Wu J (2015) Hen egg as an antioxidant food commodity: A review. Nutrients 7: 8274-8293.

146. Sies H, Stahl W (1995) Vitamins E and C, β-carotene and other carotenoids as antioxidants. Am J Clin Nutr 62: S1315-S1321.

147. Miki W (1991) Biological functions and activities of animal carotenoids. Pure Appl Chem 63: 141-46.

148. Patel R, Sesti F (2016) Oxidation of ion channels in the aging nervous system. Brain Res 1639: 174-185.

149. Farr SA, Price TO, Banks WA, Ercal N, Morley JE (2012) Effect of alpha-lipoic acid on memory, oxidation and lifespan in SAMP8 mice. J Alzheim Dis 32: 447-455.

150. Bjelakovic G, Nikolova D, Gluud C (2014) Antioxidant supplements and mortality. Curr Opin Clin Nutr Metab Care 17: 40-44.

151. Doonan R, McElwee JJ, Matthijssens F (2008) Against the oxidative damage theory of aging: Superoxide dismutases protect against oxidative stress but have little or no effect on life span in Caenorhabditis elegans. Genes Dev 22: 3236-3241.

152. Chedraui P, Pérez-López FR (2013) Nutrition and health during mid-life: Searching for solutions and meeting challenges for the aging population. Climacteric 16: S85-S95.