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Mini Review

Alzheimer's Disease: Wrestles for Newtrack Counteragents

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Background

Neurodegeneration is a unified term defining the hereditary and sporadic conditions characterized by dysfunction of nervous system encompassing gradual structural and functional aspects of neurons often leading to death [1]. Alzheimer's disease (AD) is renowned as the most prevalent multifactorial neurodegenerative disorder (after Parkinson's disease) marked primarily with progressive decline in cognition and impairment in memory [2]. AD is the main cause of dementia in more than 80% of geriatric population and it is expected that the present number of 46.8 million persons in the world suffering from dementia will reach a height of 74.7 million in 2030 and 131.5 million in 2050 [3]. Owing to the dramatic increase in the population as the year and age progresses, AD is often hired as life threatening as well as economic and social burden to the health-care system.

AD is characterized by two major pathological remarks. Neuritic plaques of amyloid- β (Aβ) peptide [4] and neurofibrillary tangles of hyperphosphorylated tau proteins (Fig.1) [5].

Uncanny accumulation of β-amyloid (Aβ) peptide, a key component of extracellular neuritic plaques, is one among the major responsible factors for neuronal death in AD. Oligomeric Aβ (1-42) is considered as highly toxic among the Aβ species and Aβ (1-42)-induced oxidative stress tightly floors the pathogenesis of AD [6]. Aβ peptide, is synthesized from amyloid precursor protein (APP) catalyzed by enzymes- β and γ – secretase, of which β- secretase is considered as the rate limiting enzyme and is also attributed to BACE1 protein in the brain [4,7]. Aging, diet and metabolism, genetic and pathogenic alterations exist as contributors to increase the amount of Aβ peptide and may occur through higher APP expression, increased APP metabolism, decreased Aβ catabolism, failure in clearing of Aβ from the brain etc. [8]. Rather than insoluble deposits of Aβ peptide soluble oligomeric Aβ peptide depositions are more toxic and contribute to plaque formation responsible for enhanced neuronal loss and cholinergic dysfunctions resulting impairments in learning and memory (amnesia) [9,10].

The second lesion in AD brain is by Tau, a microtubule associated protein, whose hyperphosphorylated form make polymers to assemble in neurofibrillary tangles (NFT) [5]. Phosphorylation of Tau alters microtubule assembly of brain by inhibiting polymerization of tubulin into microtubules. Hyperphosphorylated Tau results in oligomerization and aggregation leading to the formation of tangles in AD patients [11]. Hyperphosphorylated Tau also gets misfolded in both synaptic nerve terminals causing synaptic dysfunctions [12] contribute to neurodegeneration and dementia. Besides AD, Tau exists as a prominent factor in many additional neurodegenerative diseases as Taupathies [13]. Apart from these main causatives, AD is also contributed by mitochondrial dysfunctions, oxidative stress, inflammatory responses, etc., ending upto difficulties in social and personal living owing to minimal communication (aphasia) and frailty to perform day-to-day activities (apraxia) and defective sensory output (agnosias) [14,15] (Figure 2).

Dietary and lifestyle factors posit its own role in adding to the risk of AD even though more research findings are yet to be unveiled to tighten the floor. Studies report that consuming high calorie and high fat diets, low education level and a sedentary lifestyle may increase the risk of AD [16,17]. Studies on mouse models have also come up with the fact that low dietary folate and homocysteine levels increase the risk of AD [17]. On the other hand, regular physical exercise is found to be neuroprotective

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by promoting neurogenesis and hippocampal synaptic plasticity [18]. Smoking may also increase the risk of dementia, AD and impairment in cognition by increasing oxidative stress and inflammatory responses [19]. Studies exploring dietary interlinks between high cholesterol levels, Type 2 diabetes mellitus, Mid-life obesity with risk progression of AD and cognitive decline is highly vocal and makes platforms for future research [8,20,21].

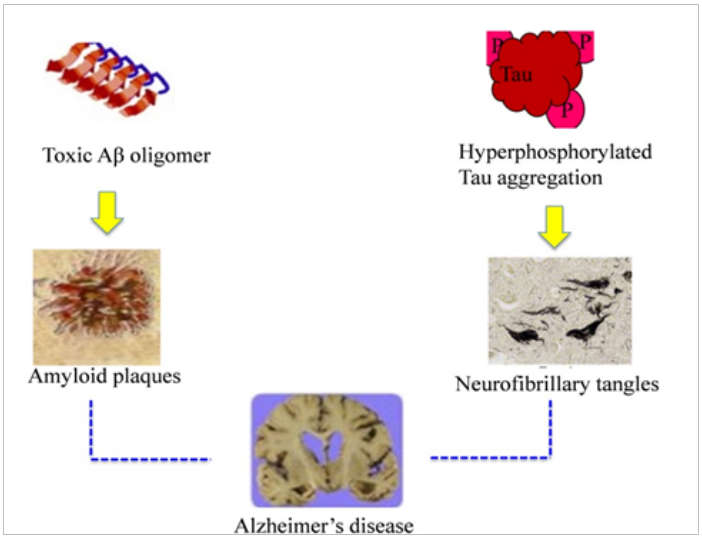

Figure 1. Major pathological remarks of Alzheimer's disease. Neuritic plaques of amyloid- β (Aβ) peptide and neurofibrillary tangles of hyperphosphorylated tau proteins forms the major pathological remarks of AD. (Adapted from Dana MN *et al*., 2011)

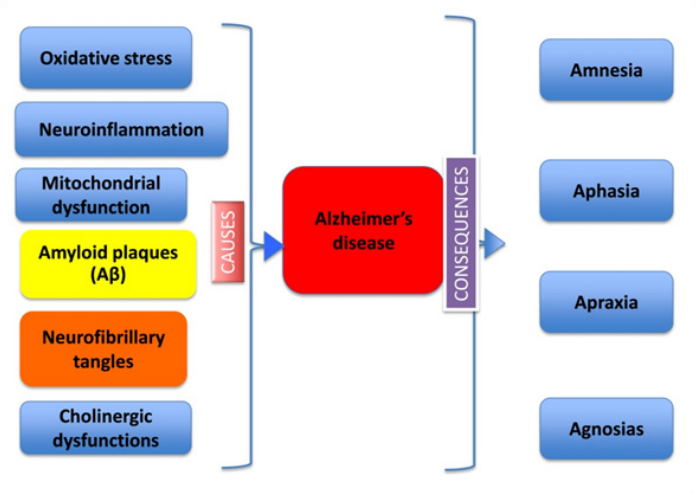

Figure 2: Causes and consequences of Alzheimer's disease. (adapted from R. N Kalaria *et al*., 2008 and Russo P *et al*., 2015).

Counteragents of Alzheimer's Disease: from Drugs to Natural Resources

Ever since the discovery of first case of AD by Alois Alzheimer in 1906, enormous researches and development efforts were taken for the upsurge of effective treatment practices for this globalized disease. Cholinesterase inhibitors - Tacrine, rivastigmine, donepezil, and galantamine and N-methyl-D-aspartate (NMDA) receptor antagonist- memantine, were the firstline drugs approved by the Food and Drug Administration (FDA) recommended for the treatment of AD [22]. Apart from many reports came up with disadvantages and side-effects while treating the old aged, the drugs have no significant role in preventing disease progression but in only ameliorating symptoms in limited number of people for limited time [23]. Also, none of these drugs have proved to be effective in the treatment of Mild Cognitive Impairment (MCI). MCI, defined as 'symptomatic pre-dementia stage' is often a fear in old people for progressing to dementia, mainly AD dementia. Hence the studies targets this phase is more important to disclose suitable interventions [24]. These ramparts created a paucity in treating the disease for a while. Subsequently, current science inclined to natural remedies as treatment strategies for AD which were found beneficial without side-effects. Herbal compounds from medicinal plants pioneered the series: extending from *Murraya koenigii* (curry leaves) to Ginkgo biloba in inhibiting amyloid-beta aggregation [10], curry leaves improving spatial memory and reducing brain Aβ level [25,26], isoflavones from soyabean and temph improving cholinergic activities and reducing neuroinflammation in brain (27), reversal of memory deficits by coriander leaves [28], managing cognitive functions by *Daucus carota* [29], alleviation of cholinergic pathways, reduction of oxidative stress thereby betterment of spatial memory by resveratrol found in red grape skin [30] and improving memory and neuronal metabolism in AβPP-PS1 mouse model of Alzheimer's disease by Amlakirasayana (a preparation derived from Indian goose- berry *(Emblica officinalis)* fruit) [31]- to highlight the list.

In parallel, bioactive compounds from marine resources in treating AD were also unveiled. Bryostatin-1 (Bry-1) from the extract of *Bugulaneritina* or brown bryozoans, Homotaurine from red marine algae, Anhydroexfoliamycin from *Streptomyces exfoliates*, Gracilins from *Spongionella sp.* and Rifampicin, previously known to be produced only by soil actinobacteria *Amycolatopsis* is also synthesized in marine bacteria Salinispora isolated from the marine sponge *Pseudoceratinaclavata* [15]. According to preclinical studies, Bryostatin-1enhance learning and memory in rats, mice, rabbits and nudibranch, reduce Aβ levels in monomeric Aβ -treated cells "in vitro" enhance synaptogenesis, leading to recovery of cognitive deficits, regaining neurotrophic activity and synapses loss and prevent neuronal apoptosis Bryostatin proves to be a potential candidate for AD therapy and other forms of dementia [15]. A

study report conducted in 10 MCI patients, it was observed that based on its effects related to cortical GABA transmission, Homotaurine may ameliorate the cholinergic transmission [32]. Anhydroexfoliamycin came up with reducing tau phosphorylation in mice models [33]. Alzheimer's mice models treated with Gracilins shown improvement in learning and memory in behavioral studies. Observations also clarified reduction in Aβ 42 and hyperphosphorylation of tau protein [34]. Dictyostatin from Spongia sp was found to exert Microtubule stabilization in mice intraperitoneally administered with 5mg/kg [35]. Owing to the free radical scavenging property and inhibition of Aβ fibrillar formation, Rifampicine was expected for neuroprotection. But preclinical evidences in AD patients gave discouraging results [34,35].

Awareness of exploiting marine compounds in hitting therapeutics were rolled into the pipeline through the successful crowning of FDA/EMA-approved drugs Cytarabine (from *Cryptotethyacrypta*),Trabectedin (from *Ecteinascidia turbinate)* and Eribulinmesylate (from *Halichodriaokadai*) as anticancer agents, and Ziconotide (from *Conus magus*)for treatment of neuropathic pain [15,32]. Chemical complexity and natural scarcity stay as barricades in synthesizing bioactive compounds from marine environment. This could be overcome by proper maintenance of marine environment and development of novel technologies for extraction, purification and synthesis of bioactive compounds from marine resources.

Conclusion

Alzheimer's disease is considered as social and economic burden to the health care system devoid of any specific diagnostic step and treatment strategies. Upcoming therapeutic interventions should really focus on the key factors behind AD for reversing or preventing the same. Apart from targeting the symptoms, treatments heading towards preventing accumulation of Aβ peptide and clearance of neurofibrillary tangles will be of utmost importance. Scientific research paving toward the credibility and efficacy of dose and long-term drug supplementation is highly demanding and challenging. People should be properly made aware to encourage lifestyle factors and future research exploiting the possibility of reducing dementia with physical activity oriented interventions will be an arable field.

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