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Editorial

Pro-Oxidants and Antioxidants Imbalance in Alzheimer's Disease

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Alzheimer's disease (AD) is an irreversible progressive neurological disorder that is manifested by gradual deterioration of cognitive reserve and impairment of activities in daily living. There are 50 million AD patients globally and this number will likely be doubled by 2050 [1]. Two dominant hypotheses, the amyloid-β (Aβ) cascade [2] and the tau propagation [3], were considered causally linked to the progression of AD. However, a disease-modifying drug for AD is not available, although significant number of clinical trials based on Aβ cascade and tau phosphorylation are already being conducted [4, 5]. A recent report based on a meta-analysis on the effect of anti-Aβ drugs on brain revealed that β-secretase inhibitors like verubecestat accelerated hippocampal and whole brain atrophy compared to changes observed after placebo administration [6].

Therapeutic development is urgently required based on potential role of oxidative stress (OS) in AD as early causal process [7–9]. OS is identified as an imbalance in the over production of harmful reactive oxygen species (ROS) by prooxidants and neutralization of these ROS by antioxidants [9]. Recently, significant depletion of master antioxidant, glutathione (GSH), as well as elevation of prooxidant (iron, etc.) in the hippocampus region of AD patients were reported [10–12]. A transgenic AD mice model study also showed that GSH depletion precedes amyloid plaque formation [13]. Significant depletion of plasma GSH from mild cognitive impairment (MCI) subjects has also been reported in a longitudinal study [14, 15].

This supplemental issue of the *Journal of Alzheimer's Disease* highlights OS-based AD research from various laboratories around the globe. The salient extracts of these research works are presented below:

Syed and co-workers have indicated the molecular aspects of aging and age-related disorders, especially in AD. They have emphasized the significance of metal ions, protein ligands, and the oligomerization state of amyloid-β protein precursor (AβPP) in the proteolytic processing of AβPP [16].

Bian and coworkers investigated the potential therapeutic effects of long-term administration of Tocovid, a novel vitamin E mixture, in a transgenic AD mice model. Tocovid treatment significantly improved motor and memory deficits in the AD mice

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and has potential neuroprotective role in combating AD. Dietary intake of antioxidant supplements is associated with a reduced risk of AD [17]. The meta-analysis by Zhao et al. investigated association between antioxidants and the risk of dementia from seventeen research studies with a total of 98,264 participants. The striking point in this meta-analysis indicated that high antioxidant intake significantly reduced the incidence of AD [18]. Soto-Mercado and coworkers analyzed the therapeutic potential of a combination of epigallocatechin-3-gallate (EGCG) and melatonin (MT) in a three-dimensional *in vitro* model of familial AD with a mutation in the presenilin-1 gene. The combination of EGCG and MT treatment effectively reduced these pathological markers more efficiently than individual treatments. This study highlights the combined therapy of EGCG and MT which holds a therapeutic promise for familial AD due to inherent antioxidant capability [19].

Majd and coworkers reported the protective effects of coenzyme Q10 (CoQ10) and high-intensity interval training (HIIT), both individually and in combination, on Aβ-induced AD rats. Pretreatment with CoQ10, HIIT, or the combination of both significantly improved cognitive functions and mitigated OS [20].

Yang and coworkers assessed the efficacy of docosapentaenoic acid and/or eicosapentaenoic acid supplements in MCI patients. The meta-analysis revealed that supplementation with n-3 polyunsaturated fatty acids had a positive impact on global cognition compared to a study with placebo. However, no significant differences were observed in language fluency, executive functions, and depression between the intervention and placebo arms [21].

Qaiser and coworkers reported the protective functions of the thioredoxin system [thioredoxin (Trx), thioredoxin reductase (TrxR)], and nicotinamide adenine dinucleotide phosphate in the context of AD-induced damage. Trx shields cells from OS, while TrxR is essential for detoxifying ROS in the brain [22].

Mamelak has presented potential strategies to address early events in AD involving microvasculature deterioration in the hippocampus that precedes Aβ deposition. NADPH oxidase (NOX) activity is elevated with age and contributes to OS and inflammation. Elevated NOX activity in the AD brain correlates inversely with cognitive ability. It is also indicated that apocynin, a NOX inhibitor, and sodium oxybate have potential in mitigating NOX-related damage [23].

Hambali and coworkers investigated the antioxidative and anti-neuroinflammatory effects of *Centella asiatica* and its triterpene fractions on lipopolysaccharide-induced microglial cells for AD management. Potential therapeutic value of *Centella asiatica* is highlighted through reduction of OS and neuroinflammation associated with AD [24].

Zhou and coworkers have proposed a computational system pharmacology workflow to uncover the OS triggering AD as well as the potential therapeutic targets and neuroprotective drugs. They have integrated preliminary screening data of pharmacological experiments with drug-targeted interactions. This research group concluded that glucocorticoid receptor gene, sex hormone binding globulin, estrogen receptor 1, etc., are promising therapeutic targets, and several drugs may be repurposed from the perspective of OS in AD [25].

Lazarova and coworkers reported significant improvement of working memory in rats with induced dementia due to *Marrubium vulgare* extract. This extract also reduce acetylcholinesterase activity in the hippocampus by 20% and alleviate OS in the cortex. These findings suggest that *Marrubium vulgare* water extract may have a working memory-preserving effect [26].

Timothy Daly emphasized the importance of maintaining diversity in drug development for AD research. The article suggested an option to enhance the flow of information from randomized clinical trials. It focuses on factors like adherence to reporting guidelines, and increased precision in the hippocampus involving GSH–iron tandem biomarker [27].

Accumulating evidence from clinical studies lead us to the converging idea that enrichment of brain GSH is the way forward through candidates with superior bioavailability and efficacy. Recently developed innovative platform, GLUTASCAN will be employed to determine GSH enrichment in the brain non-invasively [28]. It is my hope that multicenter studies from various continents could help in inhibiting the progression of the disease through efficient GSH replenishment in the brain of MCI population. The outcome from singular use of iron chelators (e.g. Deferiprone) in randomized clinical trials (RCT) involving Prodromal and mild AD patients for cognitive preservation is awaited. The efficacy of the RCT can be monitored from the analysis of plasma GSH and serum iron levels from the trial participants [14]. These valuable data can be kept in a dedicated database called SWADESH [29].

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