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Effect of Ipriflavone &berberine on glucose-6-phosphate dehydrogenase kinetics &behavior in Alzheimer disease induced rats

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By

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VI. SUMMARY

Dementia is a clinical syndrome caused by neurodegeneration (Alzheimer's disease, vascular dementia, Lewy body, and frontotemporal dementia being the most common underlying pathologies) and characterized by progressive deterioration in cognitive ability and capacity for independent living. By 2050, the number of people aged ≥60 years will have increased by 1.25 billion, accounting for 22% of the world's population. Alzheimer's disease (AD) originally described by Alois Alzheimer in 1906 and renamed after several years by Emile Kraybill. Estimations indicate that 35,600,000 people in the world suffer from dementia, predicted that the number will double every 20 years. The total financial burden worldwide is estimated to rant $60,400,000,000 in 2010. Alzheimer's disease is the most common form of dementia. The observation that more women than men have AD and other dementias is primarily explained by the fact that women live longer, on average, than men, and older age is the greatest risk factor for Alzheimer's. The disease can be divided into two main categories, sporadic late-onset AD (LOAD) and early-onset familial AD (FAD).

Symptoms of Alzheimer's disease include decline in memory and in at least one of the following cognitive abilities: recent memory loss, difficulty completing familiar tasks, problems communicating, disorientation, poor judgment, problems with abstract thinking, misplacing, mood changes, personality changes, loss of initiative. But age is the biggest predictor of dementia, and there is nothing we can do to reverse this. When individuals have difficulty moving, they are more vulnerable to infections, including pneumonia (infection of the lungs). Alzheimer's-related pneumonia is often a contributing factor to the death of people with Alzheimer's disease. Pateints with hyperinsulinemia as well as type II diabetes mellitus are among the risk factors for AD and have high levels of blood glucose or insulin, increase disordrs in brain proteins by three to six times higher than all other non-patients of the same age. The rise in the proportion of insulin in the blood lead to disrupt the activity of the enzymes that produce the protein in the brain.

In AD, hyperphosphorylated tau protein is the major component of both neurofibrillary tangles (NFTs) in pyramidal neurons, and neuropil threads in distal dendrites. NFTs are filamentous inclusions of tau which occur both in AD and in other tauopathies. The oxidative stress in the brain has an important role in cognitive impairment in Alzheimer's disease. Oxidative stress increases the beta secretase activity (β-secretase) and the accumulation of amyloid beta (Aβ), which cause DNA damage in mitochondria, and decrease cellular respiration in mitochondria. These events lead to the release of the mitochondrial cytochrome c and induction of

apoptosis mediated by caspase. All glial cells in the central nervous system can produce continuously nitric oxide.

Inducible nitric oxide synthase (iNOS) produces nitric oxide. O_2^{-2} may react with nitric oxide to form peroxynitrite. Both OH˙ and peroxynitrite are strong oxidants and react with nucleic acids, lipids and proteins, finally leading to cell dysfunction and neurodegeneration. The balance between glucose oxidation through glycolysis and pentose phosphate pathway (PPP) may be an important control point of neuronal survival during bioenergetic crises and oxidative stress. NO can upregulate the rate of glucose consumption and lactate production suggesting glycolysis activation which increase the production of glucose 6-phosphate, resulting in activation of glucose 6-phosphate dehydrogenase (G6PD) which catalyzes the rate limiting step in PPP.

Extracellular amyloid beta (Aβ) aggregates, and intracel¬lular (NFT) of tau, constitute the two major pathological hallmarks of AD. The amyloid cascade hypothesis identifies increased Aβ aggregation or decreased Aβ clearance as the primary cause of disease, developing years prior to clinical onset. Under pathogenic circumstances, amyloid precursor protein (APP) is cleaved by β-secretases to produce the more amy¬loidogenic Aβ1-42, the major species detected in the brains of AD patients.

The present study aimed to study the effect of berberine, ipriflavone and nanoberberine on the activity of glucose 6-phosphate dehydrogenase.

Sexually mature 66 albino male rats were categorized into 9 groups; the three negative control groups comprised healthy individuals with normal cognitive abilities, the first control group was intraperitoneally injected with 0.5 ml of saline, the remaining control groups were orally administrated 0.5 ml of poly ethylene glycol or 1 ml of nanochitosan, respectively; while the induced group was intraperitoneally injected with scopolamine at a dose of 2 mg/ Kg body weight for 28 days. Five treatment trail groups were orally administrated with berberine (50 mg/ Kg body weight), ipriflavone (50 mg/ Kg body weight), both of them (25 mg/ Kg body weight from berberine and 25 mg/ Kg body weight from ipriflavone), nanoberberine (1 mg/ Kg body weight) or Aricept (2.25 mg/ Kg body weight) for 28 days, respectively.

Blood plasma as well as liver and brain samples were collected from the whole study groups. Liver and kidney function tests as well as triglycerides, cholesterol, NO,GSH and glucose in plasma were . Prooxidant, enzymatic and non-enzymatic antioxidant profiles in liver and brain were spectrophotometrically determined. Also, brain phospholipids, glucose, NO, and the activities of G6PD, iNOS, IDE as well as Aβ40, Aβ42 levels were spectrophotometrically determined in brain using ELISA. The expression levels of ADAM-17, G6PD and iNOS were determined by PCR.

Scopolamine induced AD, also significantly decreased enzymatic and non-enzymatic antioxidant profiles in brain as well as the level and the activity of G6PD while Aβ42 level was increased significantly.

The present study proved that nanoberberine had given better result than berberine, ipriflavone or both of them as shown in G6PD activity and its level in addition to the inhibition of acetyl cholinesterase and the reduction in the level of both of amyloid beta-42 and tau protein. At the same time, nanoberberine turns back the brain physiological ROS levels and maintains the oxidative homeostasis. Also, nanoberberine improves the brain enzymatic and non-enzymatic antioxidant profiles. Also, it could maintain the physiological brain energetic status. Thus, nanoberberine could easily improve the cognitive abilities. Therefore, nanoberberine could be considered as a novel, potent and effective therapeutic natural antioxidant that alleviates the cognitive impairment and dementia without any mentioned side effects.