Huperzine-A, a versatile herb, for the treatment of Alzheimer's disease

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Dementia, characterized by the impairment of cognition and behavior, is one of the most important health problems in the aging populations. Alzheimer's disease (AD) is the most common form of dementia seen in the people over 65 years.[1] The AD brain is characterized microscopically by the combined presence of the intracellular neurofibrillary tangles (NFT) and the extracellular amyloid plaques.[2] The NFTs are mainly formed by the hyperphosphorylated microtubule-binding protein, tau, while the amyloid plaques are clumps of β-amyloid protein cleaved from the amyloid precursor protein by the β and γ-secretases.[2] To date, the main pharmacotherapy for mild to moderate AD are cholinesterase inhibitors (ChEIs). They slow down hydrolysis rate of acetylcholine by inhibition of acetylcholine esterase (AChE).[2] Meantime, a partial N-methyl-D-aspartate (NMDA) antagonist is approved for the treatment of moderate and severe AD. Despite the proven effectiveness of these medications, their efficacy remains unsatisfactory especially in patients with more advanced AD. In addition, the international pharmacovigilance study demonstrated the common adverse drug reactions induced by ChEIs include neuropsychiatric (31.4%), gastrointestinal (15.9%), general (11.9%), and cardiovascular (11.7%) disorders.[3] These adverse effects may affect treatment adherence. In view of the prevalence and expected increase in the incidence of AD,[1] there is a need for new, targeted, effective, and safe treatments for AD.

In recent years, natural products have gained much popularity as supplements or alternative medicine because of the cost effectiveness and fewer side effects. In this sense, many alkaloids isolated from natural sources, which possess anticholinesterase activity, could have therapeutic potential for AD. Among them, huperzine-A, a sesquiterpene alkaloid extracted from Huperzia serrata (club moss), was identified by Wang et al in the 1980s as a potent, reversible, selective AChE inhibitor.[4] Huperzine-A has been used in China for centuries for the treatment of swelling, fever, and blood disorders. Later study demonstrated that huperzine-A, as an AChE inhibitor, is more potent than donepezil, rivastigmine, and galantamine in vivo.[5] Data from preclinical studies also showed that huperzine-A can reverse or attenuate cognitive deficits, and has multiple neuroprotective effects in animal AD models.[5,6] In addition to AChE inhibition, huperzine-A has some beneficial effects for AD treatment, including NMDA antagonism, increasing nerve growth factor levels, antiapoptotic effects, antioxidant, and antiamyloidogenic effects.[7] These properties make huperzine-A a promising agent for AD treatment.

The study by Gul et al tested the huperzine-A therapeutic effect in cognitive impairment and task switching deficits in 50 Pakistan patients with AD.[8] They found significant improvement in cognition (by Addenbrooke's Cognitive Examination) and task switching abilities (by Trail Making Test) after 8-week huperzine-A (0.4 mg/day) treatment, compared with baseline performance.[8] There is no adverse effect reported by any patient and no drop out of patients from the study. The findings are very impressive regarding the fast cognitive improvement effect of huperzine-A and its favorable side-effect profile. These findings are similar to previous clinical trials that presented beneficial effect of huperzine-A for patients with AD without severe adverse effects.[9] However, most of the trials were generally small and of limited quality. The study by Gul et al is not a randomized placebo-controlled trial; therefore, we cannot judge whether there is a real drug effect.[8] The ability to detect differential treatment effects across randomized trial patients is enhanced by meta-analyses of individual participant data.[10] In a meta-analysis with eight placebo-controlled trials including 733 AD subjects, the study showed that huperzine-A is a well-tolerated agent that could significantly improve cognitive performance in AD patients.[9] It should be noted that, among the eight studies of the meta-analysis, seven were done in China. The remaining one was a 16-week multicenter trial with 210 AD subjects in the United States.[11] In contrast to most studies in China and the study by Gul et al, this study found no evidence that huperzine-A (0.4 mg/day) has cognitive improvement effect in patients with mild to moderate AD.[11] However, some secondary analyses in the study found that a higher dose (0.8 mg/day) may modestly improve cognition.[11] The varying therapeutic responses to huperzine-A could be due to different ethnic groups. In addition, the methodological quality of most included trials had a high risk of bias.[9] We recommend that further well-designed studies should pay attention to the dose-effect of huperzine-A as well as therapeutic effects in different ethnic AD subjects.

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The study by Gul et al only investigated cognitive function in AD patients after huperzine-A treatment. The fact that psychological and behavioral symptoms in AD patients are important predictors of caregiver burden, as well as institutionalization, should be noted.[12] Therefore, these parts should be the focus of AD treatment. In addition to cognitive improvement effect, improved mood, behavioral problems, and activities of daily living in AD patients had been reported after longer use of huperzine-A.[13] Further randomized double-blind placebo-controlled huperzine-A trials are needed to draw conclusions about these important outcomes.

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