

# Novel herbal compound offers potential to prevent and treat Alzheimer's disease

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Administration of the active compound tetrahydroxystilbene glucoside (TSG) derived from the Chinese herbal medicine *Polygonum multiflorum* Thunb, reversed both overexpression of  $\alpha$ -synuclein, a small protein found in the brain, and its accumulation using a mouse model of Alzheimer's disease. These results, which may shed light on the neuropathology of AD and open up new avenues of treatment, are available in the current issue of *Restorative Neurology and Neuroscience*.

Aberrant accumulation of  $\alpha$ -synuclein can form insoluble aggregates that have been implicated in several [neurodegenerative diseases](#), including Parkinson's disease, dementia with Lewy bodies, and Alzheimer's disease (AD). Researchers have now found that overexpression of  $\alpha$ -synuclein increases with age and have demonstrated that  $\alpha$ -synuclein aggregates in the hippocampus of older mice compared to normal controls.

"Our results raise the possibility that TSG might be a novel compound for the treatment of AD and dementia with Lewy body," says co-lead investigator Lan Zhang, MD, PhD, Associate Professor, Key Laboratory for Neurodegenerative Diseases of Ministry of Education, Department of Pharmacology of Xuanwu Hospital of Capital Medical University in Beijing.

The study used an animal model of AD: APPV7171 transgenic (Tg) mice with the London mutation. In previous work, the authors showed that these mice show cognitive impairments beginning at 4 months of age and develop amyloid plaques in the brain that are evident by 10 months.

In one series of experiments, 4 month old Tg mice were divided into 3 groups and received daily intragastric administration of distilled water (controls), low dose TSG (120  $\mu$ mol/kg/d), or high dose TSG (240  $\mu$ mol/kg/d). A fourth group consisted of age-matched non-Tg controls. The

mice were treated until 10 months of age. In a second series of experiments, 10-month-old mice were divided into similar control and TSG-treated groups and were treated for 6 months.

The authors used a variety of techniques to hone in on what was happening in the brains of the Tg mice compared to age-matched controls: cDNA microarray analysis, reverse transcription PCR, western blotting, and immunochemistry. They found that  $\alpha$ -synuclein messenger RNA (mRNA) and protein expression levels increase in a time-dependent manner in the hippocampus of Tg mice between ages 4 and 16 months and  $\alpha$ -synuclein aggregation was noticeable at 16 months. Age-related increases in  $\alpha$ -synuclein were also seen in the control mice but to a lesser degree.

"We suggest that, besides increased A $\beta$  (beta-amyloid) and [amyloid plaques](#), overexpression and aggregation of  $\alpha$ -synuclein in the hippocampus might partially account for cognitive impairment in this Tg [mouse model](#) of AD," comments co-lead investigator Lin Li, MD, PhD, Professor and Director, Department of Pharmacology, Xuanwu Hospital of Capital Medical University in Beijing. She adds that " $\alpha$ -synuclein overexpression occurs even in the early phase of AD and may accelerate A $\beta$  production and deposition, which further facilitates  $\alpha$ -synuclein overexpression and accumulation."

Analysis of the TSG-treated groups showed that TSG-treatment from the age of 4 to 10 months significantly downregulated  $\alpha$ -synuclein mRNA and protein overexpression in the [hippocampus](#) of the Tg mice, and the effect was stronger at the higher dose. This suggests that TSG may have a role in preventing the neurotoxic effects of  $\alpha$ -synuclein on synaptic function and cell activity. In addition, the finding that Tg reduced  $\alpha$ -synuclein [overexpression](#) in older animals (>10 months) may indicate that it has therapeutic potential even after neuropathologic changes have occurred.

In previous work, the authors found that TSG acts as a "cognitive enhancer" to improve learning and memory in both APP transgenic [mice](#) and aged rats. The authors emphasize that while it is not completely clear how TSG works, their findings open up a new area of research. "The role of  $\tau$ -synuclein, especially in the early phase of AD, and its interaction with A $\beta$  should be considered when developing new therapeutic strategies to target AD pathogenesis," says Dr. Zhang.

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