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Protective effects of aloe-emodin on scopolamine-induced memory impairment in mice and H_2O_2-induced cytotoxicity in PC12 cells

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ABSTRACT

Aloe-emodin (AE) is one of the most important active components of *Rheum officinale* Baill. The present study aimed to investigate that AE could attenuate scopolamine-induced cognitive deficits via inhibiting acetylcholinesterase (AChE) activity and modulating oxidative stress. Kunming (KM) mice were received intraperitoneal injection of scopolamine (2 mg/kg) to induce cognitive impairment. Learning and memory performance were assessed in the Morris water maze (MWM). After behavioral testing, the mice were sacrificed and their hippocampi were removed for biochemical assays (superoxide dismutase (SOD), glutathione peroxidase (GPx), malondialdehyde (MDA), AChE and acetylcholine (ACh)). In vitro, we also performed the AChE activity assay and H_2O_2-induced PC12 cells toxicity assay. After 2 h exposure to 200 μM H_2O_2 in PC12 cells, the cytotoxicity were evaluated by cell viability (MTT), nitric oxide (NO)/lactate dehydrogenase (LDH) release and intracellular reactive oxygen species (ROS) production. Our results confirmed that AE showed significant improvement in cognitive deficit in scopolamine-induced amnesia animal model. Besides, it increased SOD, GPx activities and ACh content, while decreased the level of MDA and AChE activity in AE treated mice. In addition, AE was found to inhibit AChE activity (IC_{50} = 18.37 μg/ml) in a dose-dependent manner. Furthermore, preincubation of PC12 cells with AE could prevent cytotoxicity induced by H_2O_2 and reduce significantly extracellular release of NO, LDH and intracellular accumulation of ROS. The study indicated that AE could have neuroprotective effects against Alzheimer's disease (AD) via inhibiting the activity of AChE and modulating oxidative stress.

Alzheimer's disease (AD) is a neurodegenerative disease and the most frequent and predominant cause of dementia in the elderly. It is usually concomitant with the presence of senile plaques and neurofibrillary tangles formation, aberrant oxidative and inflammatory processes, a decrease in cholinergic transmission, behavior disturbances and progressive cognitive impairments.[1] The pathogenesis of AD is still unclear at present, but two major hypotheses have been proposed: one is cholinergic hypothesis and the other is amyloid hypothesis. Cholinergic deficits are neuropathological occurrences that consistently associated with memory loss and correlated with the severity of AD.[2] The restoration of cholinergic function is still a reasonable goal for developmental programs targeting the treatment of Alzheimer's symptoms. Prolonging the release of acetylcholine (ACh) into the neuronal synapses clearance has been used as a means of enhancing cholinergic function in AD. This prolongation may be achieved by inhibiting ACh hydrolysis by acetylcholinesterase (AChE). In the AD brains, the major component of senile plaques is β-amyloid (Aβ) peptides. Abundant evidence has demonstrated that Aβ with a series of neurotoxicity exerts direct or indirect injuries on nervous system. Moreover, it also can cause neurological dysfunction, death and further leads to dementia. The excessive deposition and accumulation of Aβ in the brain will initiate the generation of reactive oxygen species (ROS),[3] eventually lead to oxidative damage. Therefore, antioxidant therapy might become the most important strategy for the prevention and treatment of AD. Since AD is highly related to cholinergic deficits, Aβ toxicity and intracellular oxidative stress, simultaneous study of AChE inhibitory, anti-amnesic and antioxidant activities is a worthy approach for the development of promising anti-AD drugs.

Rheum officinale Baill, is one of the most popular traditional medicinal herbs that is officially listed in the Chinese Pharmacopoeia. Aloe-emodin (AE) (molecular structure shown in Fig. 1), is an anthraquinone derivative from the roots of *Rheum officinale* Baill, which has been performed to possess antibacterial, antiviral, anticancer,[4] hepatoprotective,[5] laxative and anti-inflammation

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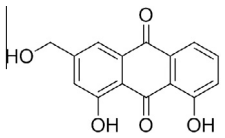

Figure 1. Chemical structure of AE.

effects.[6] In addition, AE, as an antioxidant, to a certain extent, can reduce oxidative damage caused by free radicals. However, little research has addressed the effects of AE on neuroprotection, and the mechanisms underlying it need to be investigated.

The present study aimed to discuss the neuroprotective effects of AE on AD. The mice received intraperitoneal scopolamine injection were employed and treated with AE. The effect of AE on scopolamine-induced learning and memory deficits was evaluated by the Morris water maze (MWM) test. After behavioral testing, the markers of oxidative stress, AChE activity and ACh content in mice hippocampi were determined. Furthermore, we also studied the in vitro AChE-inhibitory activity and the protective effects on H_2O_2-induced PC12 cells injury of AE.

60 Kunming (KM) mice (25 ± 2 g) of both sexes were obtained from the Laboratory Animal Center of Wuhan University (AUP No. S01312028, Wuhan, China) and used in this study. The animals

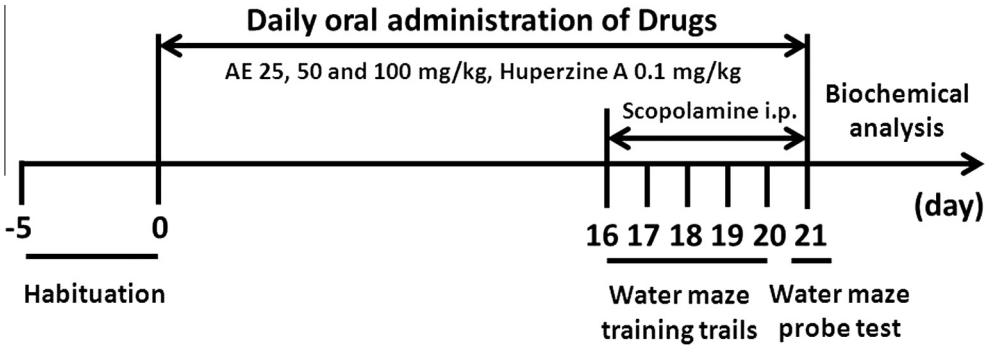

Figure 2. Experimental schedule to study the effects of AE on memory impairment.

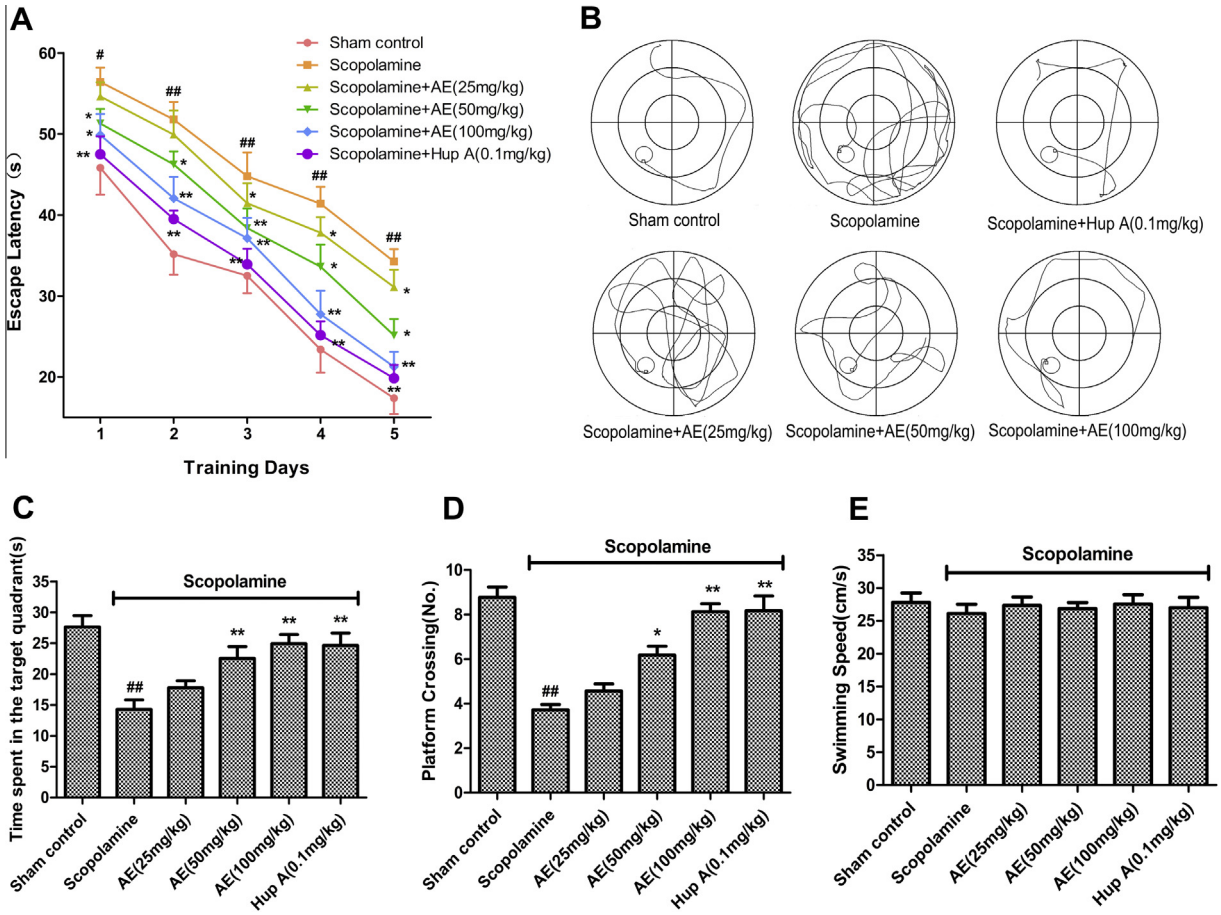

Figure 3. Effects of AE on scopolamine-induced cognitive impairment by the MWM task. Escape latency was the mean value of each trial sessions for five consecutive days (A). Swimming time (C) in the target quadrant, crossing number (D) within previously platform existed zone, and swimming speed (E) were measured during the probe trial session. Representative swimming paths at day 5 of place navigation trial (B) were recorded by a video tracking system. All data were expressed as mean ± SEM, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ versus sham control group, $^{*}P < 0.05$, $^{**}P < 0.01$ versus the scopolamine-treated group.