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ESP-102, a standardized combined extract of *Angelica gigas*, *Saururus chinensis* and *Schizandra chinensis*, significantly improved scopolamine-induced memory impairment in mice

So Young Kang[a], Ki Yong Lee[a], Kyung Ah Koo[a], Jeong Seon Yoon[a], Song Won Lim[a], Young Choong Kim[a,*], Sang Hyun Sung[b,*]

[a]*College of Pharmacy and Research Institute of Pharmaceutical Sciences, Seoul National University, Seoul 151-742, Republic of Korea*

[b]*Elcom Science Co., Ltd., Seoul 152-050, Republic of Korea*

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Abstract

We assessed the effects of oral treatments of ESP-102, a standardized combined extract of *Angelica gigas, Saururus chinensis* and *Schizandra chinensis*, on learning and memory deficit. The cognition-enhancing effect of ESP-102 was investigated in scopolamine-induced (1 mg/kg body weight, s.c.) amnesic mice with both passive avoidance and Morris water maze performance tests. Acute oral treatment (single administration prior to scopolamine treatment) of mice with ESP-102 (doses in the range of 10 to 100 mg/kg body weight) significantly reduced scopolamine-induced memory deficits in the passive avoidance performance test. Another noteworthy result included the fact that prolonged oral daily treatments of mice with much lower amounts of ESP-102 (1 and 10 mg/kg body weight) for ten days reversed scopolamine-induced memory deficits. In the Morris water maze performance test, both acute and prolonged oral treatments with ESP-102 (single administration of 100 mg/kg body weight or prolonged daily administration of 1 and 10 mg/kg body weight for ten days, respectively, significantly ameliorated scopolamine-induced memory deficits as indicated by the formation of long-term and/or short-term spatial memory. In addition, we investigated the effects of ESP-102 on neurotoxicity induced by amyloid-β peptide ($A\beta_{25-35}$) or glutamate in primary cultured cortical neurons of rats. Pretreatment of cultures

* Corresponding authors. Young Choong Kim is to be contacted at College of Pharmacy, Seoul National University, San 56-1, Shillim-Dong, Kwanak-Gu, Seoul 151-742, Republic of Korea. Tel.: +82 2 880 7842; fax: +82 2 888 2933. Sang Hyun Sung, Institute for Life Science, Elcom Science Co. Ltd., 235 Guro-Dong, Guro-Ku, Seoul 152-848, Republic of Korea. Tel.: +82 2 837 6911; fax: +82 2 837 5744.

E-mail addresses: youngkim@plaza.snu.ac.kr (Y.C. Kim), steve@elcomscience.com (S.H. Sung).

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with ESP-102 (0.001, 0.01 and 0.1 μg/ml) significantly protected neurons from neurotoxicity induced by either glutamate or $A\beta_{25-35}$. These results suggest that ESP-102 may have some protective characteristics against neuronal cell death and cognitive impairments often observed in Alzheimer's disease, stroke, ischemic injury and other neurodegenerative diseases.

Keywords: ESP-102; *Angelica gigas*; *Saururus chinensis*; *Schizandra chinensis*; Learning and memory; Scopolamine; Mice; Passive avoidance performance test; Morris water maze performance test; Glutamate; Amyloid beta peptide; Primary cultured cortical neurons of rats

Introduction

Alzheimer's disease (AD) is a progressive, neurodegenerative disease that primarily affects the elderly population, and is estimated to account for 50–60 percent of dementia cases in persons over 65 years of age (Francis et al., 1999). AD is clinically characterized by a progressive loss of cognitive abilities. The pathophysiology of AD is complex and involves several different biochemical pathways. These include defective beta-amyloid (Aβ) protein metabolism, abnormalities of glutamatergic, adrenergic, serotonergic and dopaminergic neurotransmission, and the potential involvement of inflammatory, oxidative and hormonal pathways. Consequently, these pathways are all potential targets for AD treatment and prevention strategies (Doraiswamy, 2002). Currently, the mainstay treatments for AD are acetylcholinesterase (AChE) inhibitors, which increase the availability of acetylcholine at cholinergic synapses. Until now, four AChE inhibitors have been approved by the FDA for the treatment of AD: tacrine (Cognex®), donepezil (Aricept®), rivastigmine (Exelon®), and galantamine (Reminyl®) (Lahiri et al., 2002). Since the cholinesterase inhibitors confer only modest benefits, additional non-cholinergic AD therapies are urgently needed. One such non-cholinergic AD therapy, memantine (Ebixa®), a non-competitive NMDA receptor antagonist, was recently approved in both Europe and US for the treatment of moderate to severe AD (Doraiswamy, 2003; Ferris, 2003). In Oriental countries, natural products have been used for the treatment of certain neurological illness. Our group has tried searching for neuroprotective and/or cognition-enhancing agents from natural products. Specifically, we have sought to make a preparation with the ability to effect cholinergic as well as non-cholinergic pathways in AD. The designed preparation, named as ESP-102, may be expected to synergistically exert the enhancement of cognition as well as neuroprotection via different mechanisms based on findings from our previous reports (Kang et al., 2001, 2003; Kim et al., 2004a,b). ESP-102, a standardized combined extract, consists of 70% ethanol extract from *Angelica gigas* roots, and a 100% ethanol extract from both *Saururus chinensis* herbs and *Schizandra chinensis* fruits in the ratio of 8:1:1. *Angelica gigas* roots (*Angelica gigas* Nakai, Umbelliferae) have been used traditionally in Korean herbal medicine under the Korean names 'Zam Dang Gui' not only for the treatment of anemia, but also as a sedative, an anodyne, and/or a tonic agent (Han, 1992). Our previous studies revealed that both methanolic extract of *A. gigas* roots and its constituents, coumarin derivatives, inhibited AChE in vitro (Kang et al., 2001). In addition, decursin, a major coumarin derivative, greatly improved scopolamine-induced amnesia in both passive avoidance and Morris water maze performance tests through AChE inhibition in vivo (Kang et al., 2003). It was also recently reported that coumarins and/or extract of *A. gigas* exhibited anti-amnesic (Yan et al., 2004), anti-tumor (Lee et al., 2003a), antinociceptive (Choi et al., 2003), anti-bacterial (Lee et al., 2003b) and anti-