SL18 Development of Natural Cognitive Enhancer, KD501: From Discovery to Clinical Trial

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Natural products have a long history in the treatment of human diseases. In recent years, the research on natural products has been emerged as a vital science playing a leading role in the new drug development across the globe. From the 19th century, the research on natural products for the new drug development has focused on the isolation and characterization of pharmacologically active compounds from plants. This strategy continues today. In addition to this strategy, developments of the standardized herbal drugs with proved efficacy, safety and quality have drawn great attention. We previously reported that four major constituents isolated from the roots of *Scrophularia buergeriana*, harpagoside (HS), 8-O-(*E*-*p*-methoxycinnamoyl)harpagide (HG), *E*-cinnamic acid (CA) and *E*-*p*-methoxycinnamic acid (MCA), significantly protected primary cultured rat cortical cells against glutamate-induced neurotoxicity. Further mechanism studies revealed that MCA exert its neuroprotective activity through potent inhibition of excess calcium ion influx and antagonizing the NMDA receptor in a non-competitive manner, and HS and HG have antioxidative activity. Moreover, MCA ameliorated the scopolamine-induced memory deficit in the mouse passive avoidance test.

Based on our data, we have attempted to develop a new herbal drug, KD501 with the extract of *S. buergeriana* roots utilizing all these active constituents for the treatment of Alzheimer's disease. To standardize the extract, we studied the chemical profile of these four main bioactive constituents and developed a simultaneous quantitative analytical method using HPLC-DAD-ESI-MS. Subsequently, the extraction method was optimized and the extract was standardized on the basis of the contents of the four main constituents. The efficacy of acute or prolonged administration of the standardized extract, KD501, was evaluated in mouse passive avoidance test or Morris water maze test using scopolamine or amyloid-β as a toxicant. In addition, ex vivo study showed that KD501 treatment preserved activities of glutathione reductase and superoxide dismutase, and the content of glutathione within the cortex and hippocampus of the amnesic mice. Preclinical studies, such as acute or prolonged oral toxicity in rats and acute oral toxicity in beagle dogs, showed KD501 seems to be safe and non-toxic.

With these results, KFDA approved IND application of KD501 in mild to moderate Alzheimer's disease. Currently, randomized, double-blind, placebo-controlled, parallel group studies to evaluate the efficacy, safety and tolerability of oral administration of KD501 are in progress. These whole steps suggest a good example of a development of a new drug from natural products.