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Search for the Compounds with Learing and Memory Enhancing Activities from Seaweeds.

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In our laboratory, during the last seven years, we have searched for the biologically active compounds from Korean seaweeds such as antioxidants, various serine protease (e.g. cholinesterase) inhibitors and tyrosinase inhibitors.

Among them, we have isolated several phlorotannins form the methanol extract of *Ecklonia* which showed not only radical scavenging activity but also potent enzyme inhibitory activities against tyrosinase and some of serine proteases such as leukocyte elastase and trypsin. Later, we also found that these phlorotannins have a memory-enhancing ability. The repeated administration of either dieckol or PFF (phlorofurofuko- eckol) dose-dependently reduced the inhibition of latency by administration of ethanol. To investigate the mode of this memory-enhancing actions of these components, the level of major central neurotransmitters (norepinephrine, dopamine, glutamate, GABA, 5-HT, and acetylcholine) in three different regions (striatum, hippocampus, and cortex) of mouse brain was measured. The level of some of major central neurotransmitters was significantly changed by ethanol. The treatment of ethanol significantly decreased the ratio of glutamate / GABA in both striatum and hippocampus. Both dieckol and PFF altered the level of some neurotransmitters modified by ethanol treatment. It is noteworthy that both dieckol and PFF increased the level of acetylcholine, and exerted an anticholinesterase activity. Overall, the memory-enhancing ability of both diekol and PFF may be, at least in part, the increment of brain level of acetylcholine by inhibiting acetylcholinesterase.

A mixture of algal polysaccharides and phlorotannins, named NX42, has been studied *in vitro* and *vivo* in terms of its beneficial effects on cognitive function. It showed mild but dose-dependent acetylcholinesterase inhibition with IC50 = 600~700 ìg/mL. Ethyl acetate fraction of NX42 showed substantial increase of the activity by more than an order of magnitude (IC50 = ~50 ìg/mL). It also showed significant protection of SK-N-SH cells from oxidative stress by H2O2. For an in vivo evaluation of its effect on cognitive function of fear-stressed mice, water-maze test was performed for three groups of mice: Control A (no sample and no stress during learning period),

Control B (no sample and electric shock during learning period), Sample group (4-week oral administration of 100 mg/kg/d NX42 and electric shock during learning period). Learning trial for 5 consecutive days revealed that electric-shock treatment during learning period significantly retarded the learning process in mice. However, NX42-treated mice showed significant resistance to learning deficiency observed in non-treated ones (Control B). Conclusion: The brown alga-derived dietary supplement NX42 showed effective protection from learning deficiency in fear-stressed mice and this beneficial effect is thought to be in part due to its anticholinesterase and neuroprotective activities.

The 100% methanol extract of *Sargassum sagamianum* was also investigated for antioxidants and cholinesterase inhibitors. From this extract, we isolated two potent butyrylcholinesterase inhibitory compounds, sargaquinoic acid and sargachromenol (IC50 values of 0.026, and 7.3 M, respectively), a potent antioxidant, 8-hydroxy-2-phloroeckol, and two moderate butyrylcholinesterase inhibitory farnesylacetone derivatives, (5*E*,10*Z*)-6,10,14-trimethylpentadeca-5,10-dien-2,12-dione and (5*E*,9*E*, 13*E*)-6,10,4-trimethylpentadeca-5,9,13-trien-2,12-dione (IC50 values of 34 and 23 M, respectively). The structures of these compounds were determined by various spectroscopic methods and comparison with the literature data.