Effects of Nobiletin, a Citrus Flavonoid Rescuing Memory Impairment, on the CNS Neurodegeneration

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive and memory deterioration, with a devastating impact on the whole society. Large numbers of compounds from natural resources have provided not only useful pharmacological tools but also novel leading compounds for drug development. In the course of our survey of substances having anti-dementia activity from natural resources, we successfully found nobiletin, a polymethoxylated flavone from *Citrus depressa*. An 11-day oral administration of nobiletin rescued impaired memory in olfactory bulbectomized mice documented to be accompanied by a cholinergic neurodegeneration, as assayed by passive avoidance task. This natural compound also inhibited decreases in both acetylcholinesterase-staining intensity and choline acetyltransferase expression observed in the hippocampus of the olfactory bulbectomized mice. Furthermore nobiletin showed the protective effects on $A\beta_{1-40}$-induced impairment of learning ability in the AD model rats. Thus nobiletin with the activity to improve impaired memory may become a lead compound for development of a novel type of anti-AD drugs.