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Research article

# Enhanced behavioral response by decreasing brain oxidative stress to 6-hydroxy-L-nicotine in Alzheimer's disease rat model

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## HIGHLIGHTS

- 6HLN ameliorated scopolamine-induced spatial memory impairment.
- 6HLN decreased oxidative stress in scopolamine-treated rats.
- 6HLN may be a viable therapeutic alternative to improve memory.

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## ABSTRACT

6-Hydroxy-L-nicotine (6HLN) is a nicotine metabolite resulted from nicotine degradation within *Arthrobacter nicotinovorans* with positive effects on spatial memory and oxidative stress damage. In the present study, the effects of 6HLN on spatial memory performance were assessed in scopolamine-treated rats. Scopolamine-induced memory impairments were observed, as measured by the Y-maze and radial arm-maze tasks. Decreased activities of superoxide dismutase, glutathione peroxidase and catalase along with decrease of total content of reduced glutathione were observed in the rat hippocampal homogenates of scopolamine-treated animals as compared with control. Production of malondialdehyde (lipid peroxidation) significantly increased in the rat hippocampal homogenates of scopolamine-treated animals as compared with control, as a consequence of impaired antioxidant enzymes activities. Additionally, in scopolamine-treated rats 6HLN significantly improved memory formation and decreased oxidative stress, suggesting memory-enhancing and antioxidant effects. Therefore, our results suggest that administration of 6HLN ameliorates scopolamine-induced spatial memory impairment by attenuation of the oxidative stress in the rat hippocampus.



## 1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia [7]. It has been shown that the progressive nature of neurodegeneration in AD leads to synaptic failure and neuronal damage in brain cortical areas [21]. In particular, many findings support the hypothesis that the memory failure in AD results from synaptic dysfunction and loss of synapses is a key event in early cognitive decline [10].

Numerous studies have focused primarily on the effects of nicotine metabolites derived from nicotine metabolism in mammalian cells, because of their potential contribution to the neuropharmacological effects resulting from nicotine exposure [13]. Also, it has been reported that cotinine, a nicotine metabolite in humans, induced a pronounced increase of synaptic density in entorhinal cortex, dentate gyrus, and hippocampus (CA1 and CA3 regions) [9]. Growing interest into the therapeutic potential of cotinine is continually providing support for the hypothesis that cotinine likely underlies many of the benefits associated with nicotine use [33], including improved attention, learning, and executive functions [3].

It is known that oxidative stress plays an important role in the ethiopathogenesis of AD. One of the most accepted hypotheses for AD onset implicates that mitochondrial dysfunction and oxidative stress are one of the primary events in the insurgence of the pathology [28]. There is accumulating evidence suggesting that oxidative stress is an early event in the development of the disease and such oxidative changes are pervasive throughout the body [24]. Several

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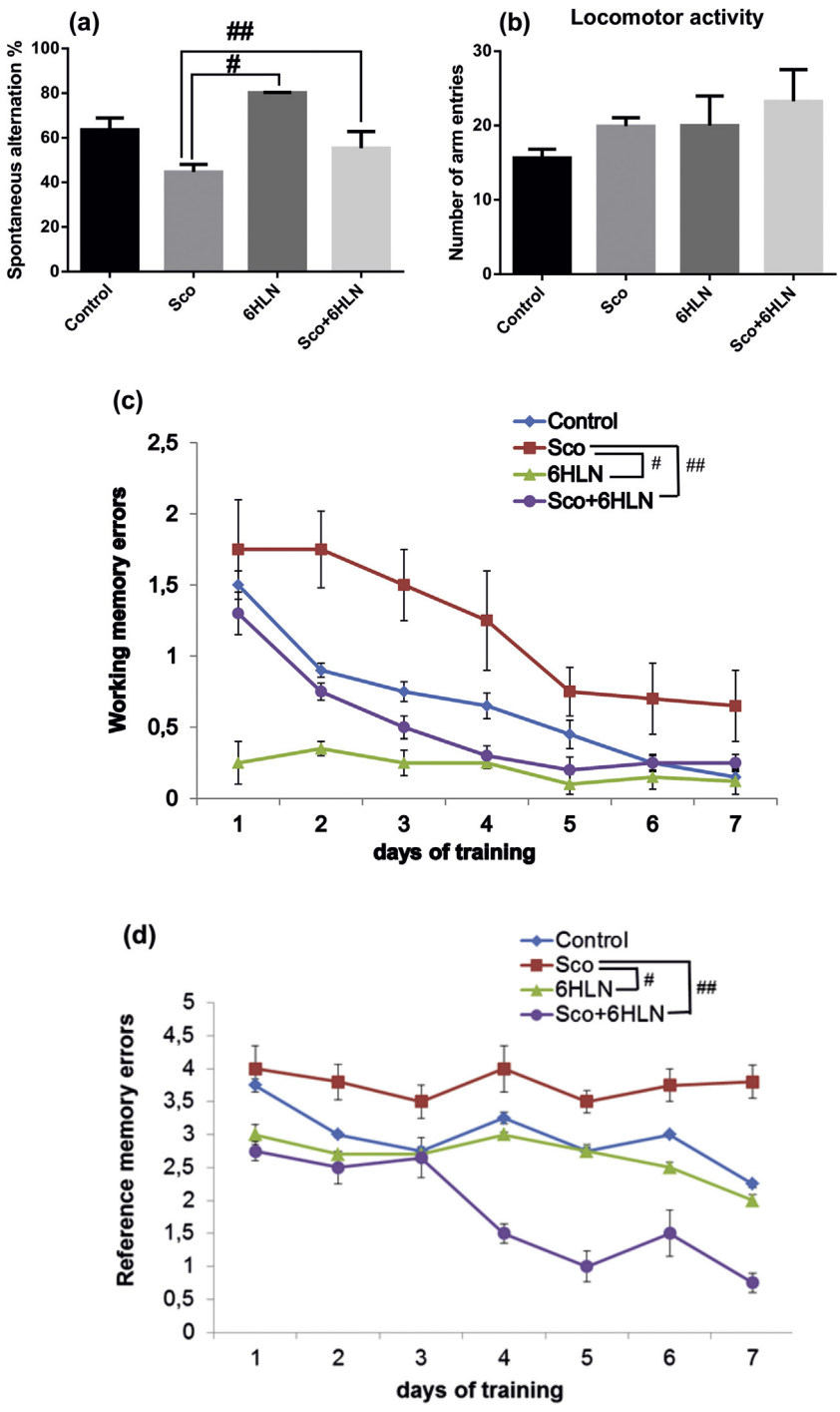


**Fig. 1.** Effects of the 6HLN (0.3 mg/kg b.w., i.p.) administration in the Y-maze task on the spontaneous alternation % (a) and the number of arm entries (b), on the working memory errors (c) and the reference memory errors (d) during 7 days training in radial arm-maze task in the scopolamine (Sco)-treated rats. Values are mean ± SEM ($n = 10$ animals per group). For Turkey's post-hoc analyzes – $^{\#}$Sco vs. 6HLN: $p < 0.0001$ and $^{\#\#}$Sco vs. Sco + 6HLN: $p < 0.001$ (a), $^{\#}$Sco vs. 6HLN: $p < 0.0001$ and $^{\#\#}$Sco vs. Sco + 6HLN: $p < 0.0001$ (c) and $^{\#}$Sco vs. 6HLN: $p < 0.001$ and $^{\#\#}$Sco vs. Sco + 6HLN: $p < 0.0001$ (d).

studies are reported the presence of elevated DNA, RNA, protein and lipid oxidation in brains of patients with AD and mild cognitive impairment (MCI) [5,6,20].

We have previously shown that 6HLN, a natural product obtained from nicotine degradation within *Arthrobacter nicotinovorans*, prevented memory loss and diminished oxidative stress in the rat hippocampus when is administered for 7 consecutive days in normal rats [13]. Furthermore, we have shown by in silico-docking method that theoretically, 6HLN has a higher affinity for the acetylcholine binding protein (AChBP) when compared to nicotine and thus could mediate actions considerate positive such as memory formation by stimulation of the nicotinic acetylcholine receptors (nAChRs) [23]. Moreover, QSAR calculation have shown that 6HLN has improved antioxidant proprieties as compared to nicotine that could explain its neuroprotective effects [23].

Despite extensive knowledge about the nicotine degradation within *A. nicotinovorans*, there is no study clarifying the possible cognitive-enhancing and antioxidant potentials of 6HLN in the animal models of AD.