

Aqueous extract of lavender (*Lavandula angustifolia*) improves the spatial performance of a rat model of Alzheimer's disease

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Abstract: Objective Alzheimer's disease (AD) is one of the most important neurodegenerative disorders. It is characterized by dementia including deficits in learning and memory. The present study aimed to evaluate the effects of aqueous extract of lavender (*Lavandula angustifolia*) on spatial performance of AD rats. **Methods** Male Wistar rats were first divided into control and AD groups. Rat model of AD was established by intracerebroventricular injection of 10 μg A β 1-42 20 d prior to administration of the lavender extract. Rats in both groups were then introduced to 2 stages of task learning (with an interval of 20 d) in Morris water maze, each followed by one probe test. After the first stage of spatial learning, control and AD animals received different doses (50, 100 and 200 mg/kg) of the lavender extract. **Results** In the first stage of experiment, the latency to locate the hidden platform in AD group was significantly higher than that in control group. However, in the second stage of experiment, control and AD rats that received distilled water (vehicle) showed similar performance, indicating that the maze navigation itself could improve the spatial learning of AD animals. Besides, in the second stage of experiment, control and AD rats that received lavender extract administration at different doses (50, 100, and 200 mg/kg) spent less time locating the platform (except for the AD rats with 50 mg/kg extract treatment), as compared with their counterparts with vehicle treatment, respectively. In addition, lavender extract significantly improved the performance of control and AD rats in the probe test, only at the dose of 200 mg/kg, as compared with their counterparts with vehicle treatment. **Conclusion** The lavender extract can effectively reverse spatial learning deficits in AD rats.

Keywords: Alzheimer's disease; *Lavandula angustifolia*; spatial learning; rat; water maze

1 Introduction

Alzheimer's disease (AD) is known as an irretrievable age-related neurodegenerative disease^[1]. There are 2 forms of AD, including early onset AD that is related with genetic factors, and late onset common form of disease^[2] that is associated with aging^[3]. AD is characterized by intracellular accumulation of neurofibrillary tangles

(NFTs) and extracellular deposition of beta amyloid (A β) plaques^[4]. NFTs are aggregates of hyperphosphorylated tau protein^[5] that form paired helical filaments and related straight filaments^[6]. Extracellular A β is a proteolytic product of amyloid precursor protein (APP) by β and γ secretases^[7]. A β is also a toxic pro-inflammatory agent that causes neuroinflammation in brain^[8]. Inflammatory events are mediated by activation of microglial cells that contribute to neurodegenerative processes such as those occurring in AD^[9].

Inflammatory mediators^[10], defect in cholinergic transmission^[11] and glutamate-induced neurotoxicity^[12]

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have been demonstrated to be involved in AD. The clinical symptoms of AD lie in mainly memory impairment and loss of spatial memory^[12,13].

Memory function is likely to be formed by numerous discrete neural networks that can be disrupted by the pathophysiological processes in AD^[14]. The hippocampus, a well-known brain region involved in memory consolidation, is especially susceptible to AD. Indeed, early degenerative symptoms including significant deficits in the performance of hippocampal-dependent cognitive abilities such as spatial learning and memory have been reported^[15].

Lavandula angustifolia (lavender), commonly known as “Ostokhoddu” in Iran, is a strongly aromatic sub-shrub at the Mediterranean region^[16]. It grows to approximately 0.9 m high. The leaves are evergreen, and the fresh flower tops of this plant are usually used for extract preparation^[17].

Lavender extracts display antioxidant^[18] and acetylcholinesterase (AChE) activities^[19]. Lavender is also reported to be an effective medical plant in treating inflammation, depression, stress and headache^[17,20]. Aromatherapy using lavender for agitation intervention is an aspect of dementia treatment^[21]. Inhibitory effects of lavender on glutamate-induced neurotoxicity have been reported^[19]. Based on these findings, it is assumed that lavender extract may alleviate dementia in some neurodegenerative disorders such as AD. Hence, in the present study, the effect of the lavender extract on spatial performance of AD rats was evaluated in Morris water maze.

2 Materials and methods

2.1 Animals A total number of 80 male Wistar rats, weighing 220–280 g, were employed in the present study. The animals were kept under a 12:12 h light/dark cycle at constant temperature, with free access to food and water. The subjects were first divided into control group and AD group. Each group was further subdivided into 4 subgroups ($n=9$ in each subgroup).

2.2 Establishment of AD model Animal model of AD was established by intracerebroventricular (i.c.v.) injection of 10 μ g A β 1-42 (Sigma Aldrich, St. Louis, MO, USA) dissolved in distilled water, 20 d prior to the administration

of the lavender extract. The injection site (AP=Bregma, LR=1.5 mm, D=4 mm) was determined according to the Stereotaxic Atlas. The animals in control group were introduced to the same procedure except that they were injected with distilled water.

2.3 Preparation of lavender extract *Lavandula angustifolia* was obtained from herbarium of Shaheed Beheshti University of Medical Sciences, Tehran, Iran. For extraction, 250 g dried flowers of lavender was mixed with 1 000 mL boiling water. The mixture was then stirred for 4 h in a fully packed container, filtered, and concentrated by vaporizing. The plant specimen was identified by Pharmaceutics Faculty of the University, where voucher specimens (1092) were kept.

2.4 Extract administration The concentrated aqueous extract of lavender was suspended in distilled water. After the first probe test, the control animals were intraperitoneally injected with either distilled water (COV subgroup), or different doses (50, 100 or 200 mg/kg) of the aqueous extract of lavender (CE50, CE100 and CE200 subgroups, respectively). Similarly, AD animals received distilled water (ALZV subgroup) or different doses (50, 100 or 200 mg/kg) of aqueous extract of lavender (AE50, AE100 and AE200 subgroups, respectively). All the animals were injected at a volume of 0.4 mL/kg body weight. The treatment was conducted once per day for 20 consecutive days.

2.5 Histological observation To confirm the formation of A β plaque in the brain, 20 d after A β injection, 8 rats were decapitated and brains were removed for histological observation. The brain was immersed in fixative formalin for 48–72 h. Then dehydration and paraffin embedding were performed via an automated processor. The brain was sectioned and stained by Congo red according to the previous report^[22]. As shown in Fig. 1, the staining verified the formation of A β plaque in the hippocampal area of brain in A β -treated animals.

2.6 Apparatus A 180-cm diameter, 60-cm deep Morris water maze was positioned in the center of a dimly light testing room enriched with some spatial cues. The water temperature was adjusted to (22 \pm 2) °C and the water surface was 20 cm below the rim. A stable circular plat-

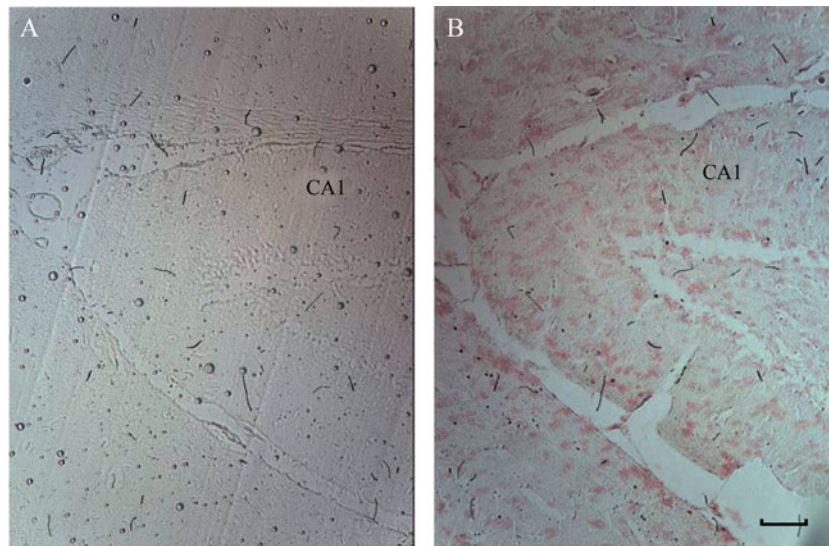


Fig. 1 Congo red staining of sections containing the medial part (including CA1) of hippocampus in control (A) and A β -treated (B) subjects. The staining verified the formation of A β plaque in the hippocampus of A β -treated rats. Red patches indicate plaques formed 20 d after A β injection. Scale bar, 100 μ m.

form measuring 10 cm in diameter was submerged 1.5 cm below the water surface. A video camera connected to an image analysis system was placed above the center of the water maze. Through a running software (Radiab 7, Iran), data of maze navigation were tracked, digitized, and stored for subsequent behavioral analysis.

2.7 Task learning The area of the pool was conceptually divided into 4 quadrants (North, South, East and West) with equal sizes, by 2 imaginary diagonal lines running through the center of the circle pool. Each trial was started by releasing an animal into the water maze, immediately facing the wall of the maze, at one of the 4 start points along the wall of the pool. The rat was allowed 90 s to locate the hidden platform. If it failed to find the platform within 90 s, it was guided to the platform and stayed there for 15 s. After an interval of 10 min, the rat was immediately replaced into the pool. The starting location varied in each trial. Following completion of the trial, the rats were dried and placed back into their home cage. The rats were trained for 5 consecutive days, 4 trials per day (totally 20 trials). The latency to locate the platform was considered as an index of spatial task learning.

2.8 Probe test In both the first and the second stages of the experiments (described below), a probe test was

conducted after completion of 20 trials of spatial task learning, to evaluate the retrieval of spatial memory. In the probe test, the platform was removed from the pool, and the animals were released from the quadrant opposite to the platform place (the target quadrant) and allowed to swim freely for 90 s. The time spent in the target quadrant of the water maze was measured in the spatial memory retrieval trials.

2.9 Two stages of task learning The maze performance protocol was conducted in 2 stages. This protocol excluded the effect of extract on the first stage of maze learning. Additionally, it helped to clarify the difference in spatial performance between pre and post drug treatment. The first stage of task learning consisted of 20 trials (5 d \times 4 trials/d), and was followed by one probe test. Then, the rats in both control and AD groups were treated with either vehicle or lavender extract for 20 d. After that, they were introduced to the second stage of task learning, in the same protocol as that of the first stage. The second stage also consisted of 20 trials (5 d \times 4 trials/d), and was followed by one probe test. Table 1 showed the detailed experimental procedures including A β injection, lavender extract administration and behavioral tests.

2.10 Statistical analysis Data of the latency in task learning and the time elapsed in the target quadrant of the water

Table 1. Experiment schedule in the control and the AD groups

Groups	Intracerebroven-tricular injection	First stage of task learning (20 d after injection)	First probe test	Intraperitoneal injection for 20 d	Second stage of task learning	Second probe test
Control group	distilled water	20 trials (5 d × 4 trials/d)	one trial	distilled water / lavender extract	20 trials (5 d × 4 trials/d)	one trial
AD group	beta amyloid	20 trials (5 d × 4 trials/d)	one trial	distilled water / lavender extract	20 trials (5 d × 4 trials/d)	one trial

maze during the retrieval test were presented as mean±SEM. Two-way repeated measures analysis of variance (ANOVA) was applied to the results pooled from the first stage of task learning and the first probe test. The comparisons in the second stage of the maze learning and the second probe trial were made using two-way repeated measures analysis of covariance (ANCOVA). Generally the LSD *post hoc* was used for post test analysis. $P < 0.05$ was considered as statistically significant.

3 Results

3.1 Difference in the performance between control and AD rats in the first stage of experiment Since the rats introduced to the first stage of maze learning did not receive the herbal extract, data from all animals in the control group were collected for statistical assessment. Also,

data from all AD rats were used for analysis. As shown in Fig. 2, the control animals needed less time to locate the hidden platform than did the AD rats [$F(1, 286)=13.336, P < 0.0001$]. The *post hoc* test indicated a pronounced variation in the behaviors between the control and AD animals ($P < 0.0001$, Fig. 2A). A retrieval test was applied to the animals in both groups after 20 trials of task learning. As shown in Fig. 3, the control and AD animals spent similar time in the target quadrant of the maze ($P=0.477$, Fig. 3).

3.2 Spatial performance of the animals during the second stage of maze learning For the second stage of spatial learning, the 2 groups were further divided into 8 subgroups, including COV, CE50, CE100, CE200, ALZV, AE50, AE100 and AE200 subgroups. General statistical analysis showed a significant variation in the maze steering in the latency time [$F(7, 279)=9.163, P < 0.0001$] among

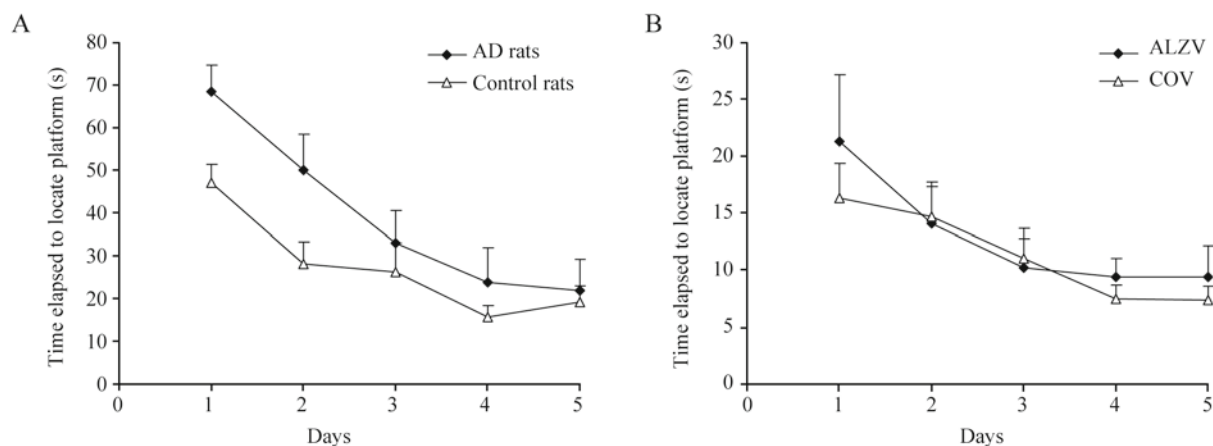


Fig. 2 Spatial performance of the control and the AD animals during the first and the second stages of water maze steering. **A:** In the first stage, the control rats presented better performance in locating the hidden platform than did the AD animals. **B:** In the second stage, ALZV and COV subgroups displayed similar spatial performance. Data on each day were from 4 trials.

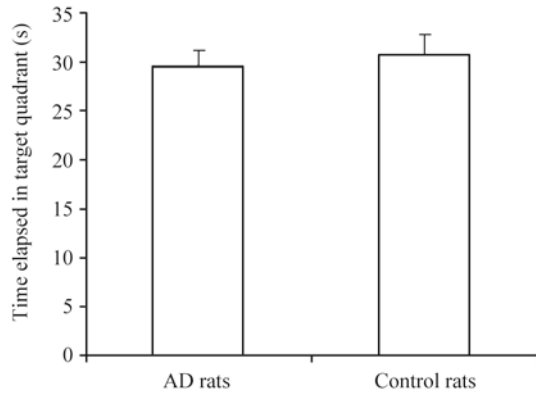


Fig. 3 The time spent in the target quadrant of water maze during the probe trial following the first stage of spatial learning. Control and AD rats spent almost similar time in the target quadrant.

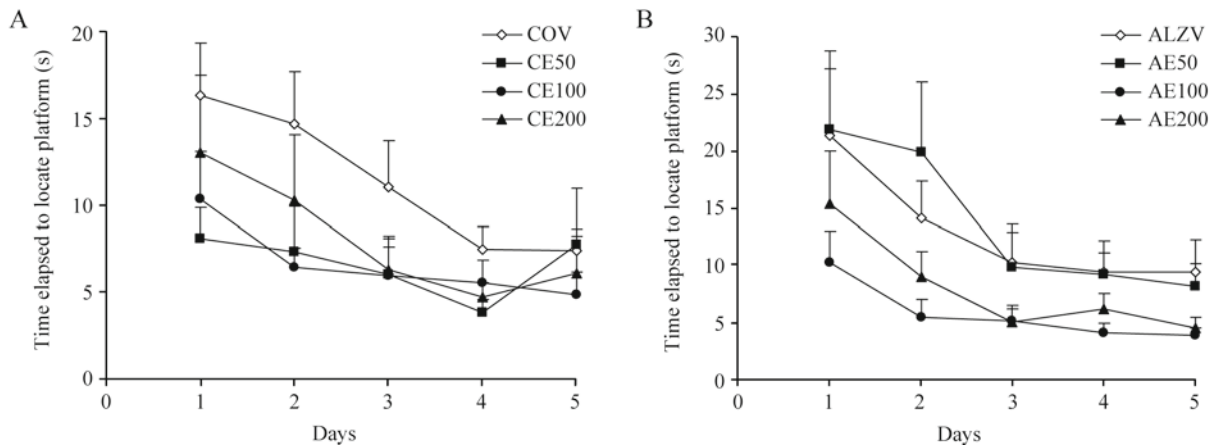


Fig. 4 Performance in the second stage of maze training after 20-d treatment with lavender extract. **A:** The 3 doses of the herbal extract significantly improved learning of the maze task in the control groups. **B:** The AD rats administered with 100 and 200 mg/kg of the herbal extract improved their behavior in the water maze. Each point represents mean \pm SEM summed results of 4 daily trials.

3.4.1 Control groups As shown in Fig. 4A, animals in CE50, CE100 and CE200 subgroups spent less time locating the hidden platform, as compared with the COV rats ($P < 0.0001$ vs CE50 and CE100; $P = 0.002$ vs CE200), indicating that the lavender extract could positively influence the behaviors of the control animals in acquisition of the maze task.

3.4.2 AD groups Analysis of covariance applied to the mean latency to find the platform demonstrated that there was no significant difference in the spatial performance between the AE50 subgroup and the vehicle-treated ALZV

the 8 subgroups.

3.3 Similar performance between COV and ALZV subgroups during the second stage of maze learning The water maze performances of the COV and ALZV rats were compared to clarify whether the first stage of maze learning could underly the task acquisition in the second stage. As illustrated in Fig. 2B, in contrast to the first stage, the COV and ALZV animals showed a similarity in the maze performance especially from the third day of experiment. The *post* test indicated no significant variation between the 2 groups ($P = 0.919$).

3.4 Positive effect of the lavender extract on the spatial performance during the second stage of maze learning

subgroup ($P = 0.192$). However, higher concentrations of lavender (100 and 200 mg/kg) considerably improved the performance of AD rats in the maze learning task (100 mg/kg, $P < 0.0001$; 200 mg/kg, $P = 0.004$). Fig. 4B illustrated the cognitive behaviors of the AD rats treated with vehicle or lavender extract.

3.5 Effect of lavender extract on spatial memory Following the second stage of maze learning, the platform was removed from the water maze and a probe test was performed in the 8 subgroups. The time elapsed in the target quadrant of the maze was recorded to assess the

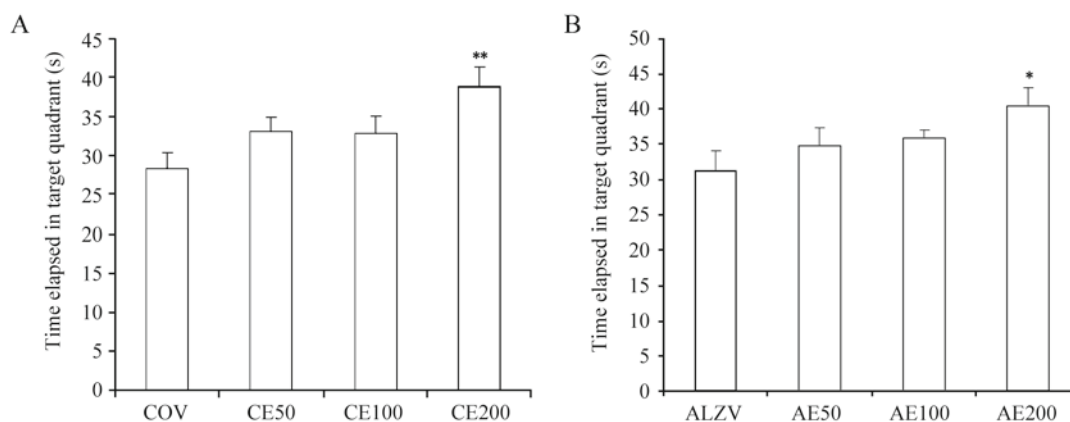


Fig. 5 Histograms showing the time spent in the target quadrant of water maze during probe trials after the second stage of experiment. After finishing the second stage of the experiment, the vehicle- and extract-treated animals were introduced to a probe test. The control (A) and the AD (B) rats receiving 200 mg/kg of the lavender extract spent significantly increased time in the target quadrant, as compared with their counterparts with distilled water treatment. * $P=0.012$ vs ALZV; ** $P=0.002$ vs COV.

retrieval of task learning. Statistics indicated that the different subgroups of the control and AD rats differently remembered the learned task [$F(7, 63)=2.926, P=0.010$]. The *post* test revealed that only the highest dose used in this study (200 mg/kg) improved the performance of control rats ($P=0.002$). In AD animals, administration of the plant extract induced a trend of enhancement in the probe test performance, and the dose of 200 mg/kg had a significant effect ($P=0.012$). The results of the second probe trial in the control and AD groups with administration of the lavender extract were shown in Fig. 5A and B, respectively.

4 Discussion

AD is associated with loss of cognition and mild impairment in memory^[23]. The present study evaluated the effect of extract prepared from *Lavandula angustifolia* on spatial maze performance. In the first stage of task learning, the control and the AD rats displayed different performances in learning the spatial task. The AD animals spent more time in locating the hidden platform in task learning. This variation was maintained over the first stage of experiment. Such a difference was not observed during the second stage when COV and ALZV animals showed a similarity in maze performance. This is consistent with some previous retrospective^[24,25] and prospective longitudinal^[23,26] studies that support the hypothesis that in-

creased use of cognitive skills and higher levels of education can protect against the development of AD. However, epidemiological studies cannot determine which activities or the combination of them are more important^[27].

Here administration of the lavender extract greatly influenced the cognitive performance of the 2 groups during the second stage of water maze searching. However, while the positive effects of the 3 doses of the extract were observed in the control group, performance of the AD rats was improved only at the doses of 100 and 200 mg/kg. In the retrieval test, the lavender-treated animals in both control and AD groups demonstrated a tendency of better function in memory consolidation. However, the improvement was significant only at the highest dose. A broad array of inflammatory mediators have been detected in AD brains^[13]. Lavender is reported to be an effective medical plant in treating inflammation, depression, stress and headache^[18]. Specifically, the anti-inflammatory effect of lavender extract has been revealed in the study of Hajhashemi V *et al.*^[20]. Thus, we propose that the protective effect of lavender extract against AD dementia might be attributed to its anti-inflammatory property.

Based on the cholinergic hypothesis, AD patients may have defects in cholinergic system, which is associated with memory and learning^[14]. Indeed, increasing the level of acetylcholine (ACh) in the brain may be an

effective therapy for AD treatment. Consistently, one of the important treatments for AD is inhibition of AChE, an enzyme responsible for the hydrolysis of Ach and promotes A β formation^[19,28]. Effective inhibitory action of lavender extract on AChE has been demonstrated^[19,29]. Thus, enhancement of cholinergic transmission may serve as another possible mechanism underlying the effect of the extract on cognitive function of AD rats.

It has been shown that A β increases glutamate-induced excitotoxicity^[15]. Indeed, through production of a specific protein, this peptide oxidizes glutamate transporter, resulting in concentration of neurotransmitter glutamate. Vigorous amounts of extracellular glutamate, in turn, over-activates its ionotropic receptors, leading to neural cell death^[30]. This cascade may support a link between functioning of glutamatergic transmission and synaptic damage in AD. It has been reported that aqueous extract of lavender reduces glutamate-induced neurotoxicity^[19]. Hence, suppression of glutamatergic neurotoxicity may be also responsible for the alleviation of the cognitive deficits in AD by the herbal medicine.

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薰衣草水提取物能改善阿尔茨海默大鼠的空间学习和记忆能力

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摘要: 目的 阿尔茨海默病(Alzheimer's disease, AD)是主要的神经退行性疾病之一, 其特征主要表现为痴呆, 包括学习与记忆的衰退。本研究旨在探索薰衣草(唇形科, 薰衣草属)水提取物对AD大鼠空间学习和记忆的影响。**方法** Wistar大鼠分为对照组和AD组, 通过给大鼠脑室注射10 μg A β 1-42 建立AD模型。20天后, 两组大鼠进行为期5天的水迷宫空间记忆采集实验(每天4次), 紧接着进行一次空间探索实验。实验结束后, 分别给予AD组和对照组大鼠不同剂量的薰衣草水提取物(50、100、200 mg/kg) 或 0.4 mL/kg 蒸馏水, 每天一次共20天。随后, 重复上述水迷宫实验。**结果** 在水迷宫实验的第一阶段, AD组大鼠找到平台的潜伏期显著高于对照组大鼠, 而在第二阶段, 接受蒸馏水注射的对照和AD大鼠找到平台的潜伏期没有差异, 说明水迷宫运动本身能提高AD大鼠的空间学习能力。在第二阶段空间记忆采集实验中, 与接受蒸馏水注射的同类大鼠相比, 接受薰衣草水提取物注射的对照和AD大鼠找到平台的潜伏期显著降低。此外, 200 mg/kg 薰衣草水提取物能显著提高对照和AD大鼠的空间探索能力。**结论** 薰衣草水提取物能有效逆转AD大鼠空间学习功能的损伤。

关键词: 阿尔茨海默病; 唇形科薰衣草属; 空间学习; 大鼠; 水迷宫