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The Effect of Geraniol on Biochemical Parameters and Brain Markers in Male Wistar Alzheimer's Rats

B. Seifi-Nahavandi[a], M. Ghobeh[a], S. Ahmadian[b], A. Ebrahim-Habibi[c,d] and P. Yaghmaei[a,*]

[a]*Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran*

[b]*Department of Biochemistry, Institute of Biochemistry and Biophysics, University of Tehran, Tehran, Iran*

[c]*Biosensor Research Center, Endocrinology and Metabolism Molecular-Cellular Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran*

[d]*Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran*

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ABSTRACT

Alzheimer's disease (AD) is characterized by amyloid plaques and neuronal death ultimately leading to dementia. Using natural therapies has always been a great concern for AD. Herein, Geraniol, as a natural monoterpene, was applied to examine its protective and therapeutic effects on a rat model of AD. In order to create Alzheimer's rat model, bilateral injection of Amyloid β1-42 (Aβ1-42) was performed into rats' hippocampus. Both therapeutic (post-AD induction) and protective effects of Geraniol consumption (100 mg kg^{-1}) were investigated on the antioxidant and brain histological parameters. In addition, Aβ1-42 peptide was driven toward fibril formation *in vitro* and effect of Geraniol (100 µM) was observed on Aβ1-42 fibrils. Alzheimer's-induced group showed impairment in the antioxidant parameters along with loss of neuronal cells and amyloid plaque formation. Administration of Geraniol, in both treatment and protective modes, increased neurogenesis, reduced amyloid plaques, and improved antioxidant parameters. Therefore, Geraniol showed capability of improving AD signs as well as direct anti-fibril effect and it could be considered as neuroprotective.

Keywords: Geraniol, Aβ1-42, Alzheimer's disease, Neurogenesis, Amyloid plaques

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder associated with central nervous system and characterized by dementia among the elderly [1]. One of the main indications of AD include extracellular senile plaques in the various regions of the cerebral cortex [2]. Several studies have specified that Amyloid β [Aβ], derived from the proteolytic cleavage of amyloid precursor protein (APP), plays a crucial role in the pathogenesis of AD [3]. It has been stated that the imbalance between Aβ generation and its clearance causes to start the amyloid cascade and lead to induce neuron cell death [4]. Moreover, extra Aβ remained in the brain polymerizes and leads to the toxic plaques in AD [5].

Essential oils have exhibited to include neuroprotective compounds by improving both cognitive performance and reduction in amyloid deposition [6,7]. Monoterpenes are the main chemical compounds of essential oils extracted from a large variety of aromatic plants, including edible and medicinal plants with therapeutic properties [8-10]. Geraniol, a common components of essential oils, is an acyclic monoterpene isolated from *Palmarosa* oil [11]. This compound has shown outstanding biological properties [12,13], including antioxidant and anti-inflammatory effects as well as activities against prostate, liver, kidney and skin cancers [14,15]. It seems that Geraniol can induce apoptosis pathway and enhance the pro-apoptotic proteins expression [16]. Furthermore, antibacterial activity of Geraniol has been confirmed on respiratory and skin infections [17]. It has also been stated that Geraniol displays antidepressant effects through modulation of oxidative stress [18]. Significant reduction in lipid peroxidation activity or inhibition of ROS generation are other suggested ways for

*Corresponding author. E-mail: yaghmaei_p@srbiau.ac.ir

treated cells with Geraniol [19]. As many evidence suggests that inflammatory pathways and oxidative stress play key roles in the pathogenesis of AD [20], in the present study, the effects of Geraniol have been investigated on Alzheimer's rat models.

In the present study, both therapeutic and preventive effects of Geraniol, as a natural compound, were investigated on antioxidant parameters and AD brain markers using Alzheimer's rat brain as an *in vivo* model system. Moreover, in an *in vitro* experiment, Aβ preformed fibrils were observed in the presence of Geraniol to further determine the possible destabilizing mechanism of this compound.

MATERIALS AND METHODS

Compounds

Aβ42 and Geraniol were purchased from Sigma (St. Louis,MO, USA). Aβ1-42 (5 μg μl^{-1}) was prepared in double-distilled water and 200 μl of prepared Aβ1-42 solution was incubated at 37 °C for 1 week before use in the *in vivo* experiment [23]. Geraniol (100 mg Kg^{-1}) was prepared in double-distilled water.

Animals

36 male Wistar rats weighing 200 ± 50 g were purchased from Pasteur Institute of Iran. Rats were kept in in standard cages at 20 °C and light and darkness cycle was maintained at 12:12 h while they had free access to water and food. To induce Alzheimer's disease (AD), animals were anesthetized by ketamine and xylasin injection and placed within stereotactic device. Using stereotaxy and brain atlas [24] to localize hippocampus, 2 μl of Aβ1-42 (5 μg μl^{-1}) solution was injected slowly with a Hamilton syringe in the CA region on both sides of the hippocampus. After one week, amyloid plaques were formed in the animal's brain which were visible by the use of histological method. Experimental procedures were carried out strictly in accordance with the Guide for the Care and Use of Laboratory Animals (Institute of laboratory Animal Resources, 1996), and approval was received from the Islamic Azad University, Science and Research Branch Animal Ethics Committee (No 63688/29/8). Treatment with Geraniol was done for a total of three weeks. In the protective mode, Geraniol was administered one week prior to Aβ1-42 injection.

Experimental groups (n = 6 in each group) were defined as follows:

1. Control group (Ctrl): Rats received regular water and food and did not undergo surgery.
2. Second control group (S + W): Rats underwent surgery, and distilled water was injected into their brains' ventricles.
3. Alzheimer's group (Aβ): Rats underwent surgery, and Aβ1-42 solution was injected into their brains' ventricles.
4. Sham group (Aβ + W): Prepared similar to group #3 and then received distilled water (as Geraniol solvent) through intraperitoneal injection.
5. Experimental group 1 (Aβ + T): Prepared similar to group #4 and received Geraniol 100 mg kg^{-1} therapeutically.
6. Experimental group 2 (Aβ + P): Received Geraniol 100 mg kg^{-1} in a protective mode for 7 days and then underwent Aβ injection (induction of AD).

At the end of the experiment period, animals were anesthetized and blood samples were taken from the heart. Serum was separated using a centrifuge and stored at -20 °C. Brain was removed, rinsed with physiological serum and then placed in glass containers containing 10% formalin and later processed for paraffin embedding.

Measurement of Biochemical Parameters

Serum level of malonedialdehyde (MDA) and superoxide dismutase (SOD) activity level were measured using ELISA kit from the ZellBio GmbH (Germany) according to the manufacturer's instructions. SOD activity measurement is made based on the enzyme ability to inhibit the auto-oxidation of pyrogallol, which is checked at 420 nm [25], while MDA reacts with thiobarbituric acid (TBA) in serum to produce a state of MDA-TBA, which is then measured by colorimetric (OD = 532) method [26].

Assessment of Neurogenesis and Amyloid Plaque Formation

At the end of the experiment, the rats were decapitated under anesthesia and their brains were removed. Three brains were fixed in 10% formalin and consequently embedded with paraffin. Serial sections of 6 μm-thickness were then prepared and stained with hematoxylin and eosin. The slides were examined by light microscopy to assess

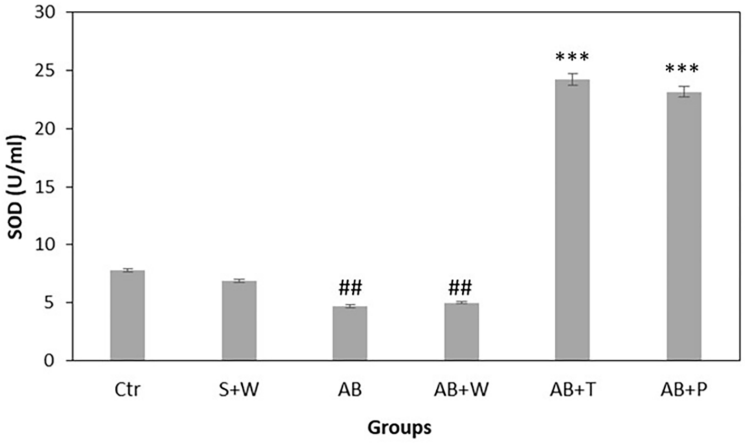

Fig. 1. Overall activity level of SOD in different groups. Ctr: control group; S+W: rats underwent surgery with water being injected into brain; AB: Aβ1-42 was injected into brain to induce Alzheimer's disease; AB + W: Alzheimer's-induced group receiving water as Geraniol solvent; AB+T: Alzheimer's-induced group treated with 100 mg kg^{-1} Geraniol; AB + P: Alzheimer's-induced group receiving protective dose of Geraniol (100 mg kg^{-1}). *** $p < 0.001$ compared with the Alzheimer's disease group. ## $p < 0.01$ compared with the control group.

neurogenesis. Thioflavin S staining method was employed to detect amyloid plaques, and the images were observed by a fluorescence microscope [27]. The number of both the plaques and neurons were counted using Image J software.

In vitro Experiment

Aβ42 peptide was first dissolved in deionized water (DW) to a final concentration of 1 mg ml^{-1}. In order to make mature fibrils, tubes containing monomers were incubated at 37 °C for 2 and 4 days while the water bath containing the tubes was being gently stirred by a Teflon magnetic bar. In order to check the destabilization potential of Geraniol, stock solutions of Geraniol was prepared in DW as solvent. For destabilization experiments, aliquots of 1 mg ml^{-1} of four-day-old preformed Aβ42 fibrils were further incubated with Geraniol 100 µM at 37 °C for 3 weeks [28]. In all experiments, the water bath containing the tubes of samples was being gently stirred by a Teflon magnetic bar.

Transmission Electron Microscopy

About 5 µl of 1 mg ml^{-1} samples, including Aβ42 solution incubated with or without Geraniol, were adsorbed onto copper 400 mesh F-C grids and let dry for 2 min. Excess fluid was then removed and 5 µl of 1% uranyl acetate was added onto the grid. Excess dye was removed after 2 min and samples were observed after being completely dried out with the use of Hitachi HU-12A electron microscope (Hitachi, Japan).

Statistical Analysis

SPSS software V.21 was used with ANOVA and TUKEY analysis of variance in order to investigate the significant differences between the groups. Data is reported as MEAN ± SEM with significance level of $p < 0.05$ and $p < 0.001$ for groups at all stages.

RESULTS

Treatment Effects of Geraniol on Biochemical Factors, Amyloid Plaques and Neurogenesis

The activity level of SOD was lowered in the disease-induced groups compared with the control group, while the SOD activity level of the group treated with Geraniol (100 mg kg^{-1}) was significantly increased ($p < 0.001$) compared to the Alzheimer's-induced group (Fig. 1). On the other hand, serum level of MDA was increased in the disease-induced group compared with the control group ($p < 0.001$), while the MDA level of the Geraniol-treated group was significantly decreased ($p < 0.001$) compared to the Alzheimer's-induced group (Fig. 2).

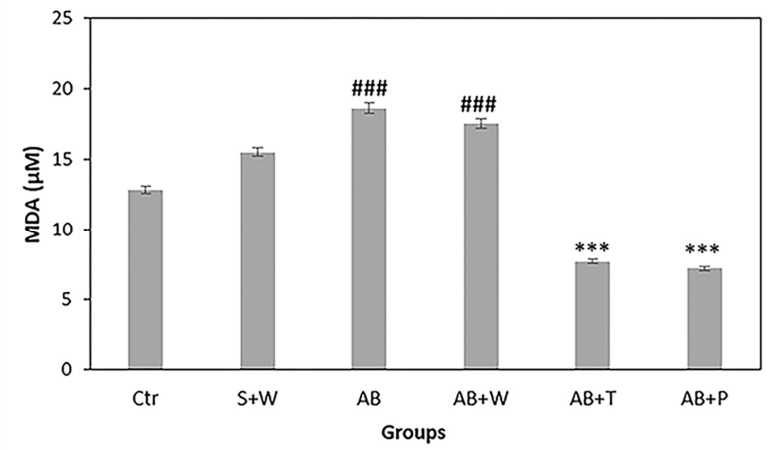

Fig. 2. Overall serum level of MDA in different groups. Ctr: control group; S + W: rats underwent surgery with water being injected into brain; AB: Aβ1-42 was injected into brain to induce Alzheimer's disease; AB + W: Alzheimer's-induced group receiving water as Geraniol solvent; AB + T: Alzheimer's-induced group treated with 100 mg kg^{-1} Geraniol; AB + P: Alzheimer's-induced group receiving protective dose of Geraniol (100 mg kg^{-1}). *** $p < 0.001$ compared with the Alzheimer's disease group. ### $p < 0.01$ compared with the control group.

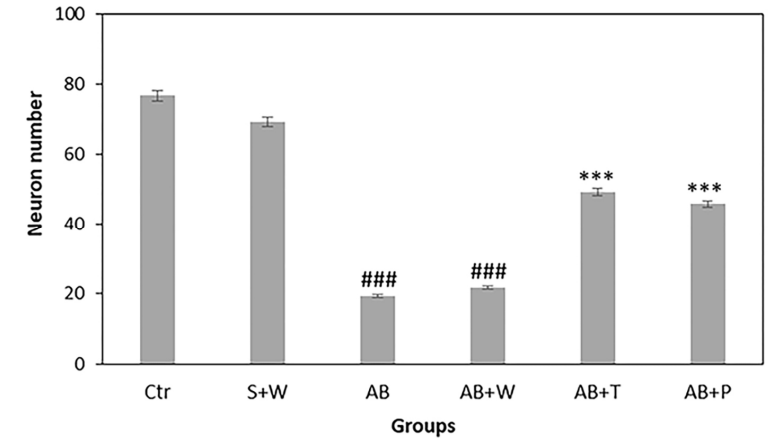

Fig. 3. Number of neurons in different groups. Ctr: control group; S + W: rats underwent surgery with water being injected into brain; AB: Aβ1-42 was injected into brain to induce Alzheimer's disease; AB + W: Alzheimer's-induced group receiving water as Geraniol solvent; AB + T: Alzheimer's-induced group treated with 100 mg kg^{-1} Geraniol; AB + P: Alzheimer's-induced group receiving protective dose of Geraniol (100 mg kg^{-1}). ***$p < 0.001$ compared with the Alzheimer's disease group. ###$p < 0.01$ compared with the control group.

Amyloid plaques formation (Figs. 4C, D and G) along with reduced neurogenesis (Fig. 3) occurred as a consequence of inducing Alzheimer's disease. Treatment with Geraniol notably resulted in a higher number of neurons (Fig. 3) and decreased amount of plaques compared with the Alzheimer's-induced group ($p < 0.001$) (Figs. 4E).

Protective Effects of Geraniol on Biochemical Factors, Amyloid Plaques and Neurogenesis

Activity level of SOD in the group which received

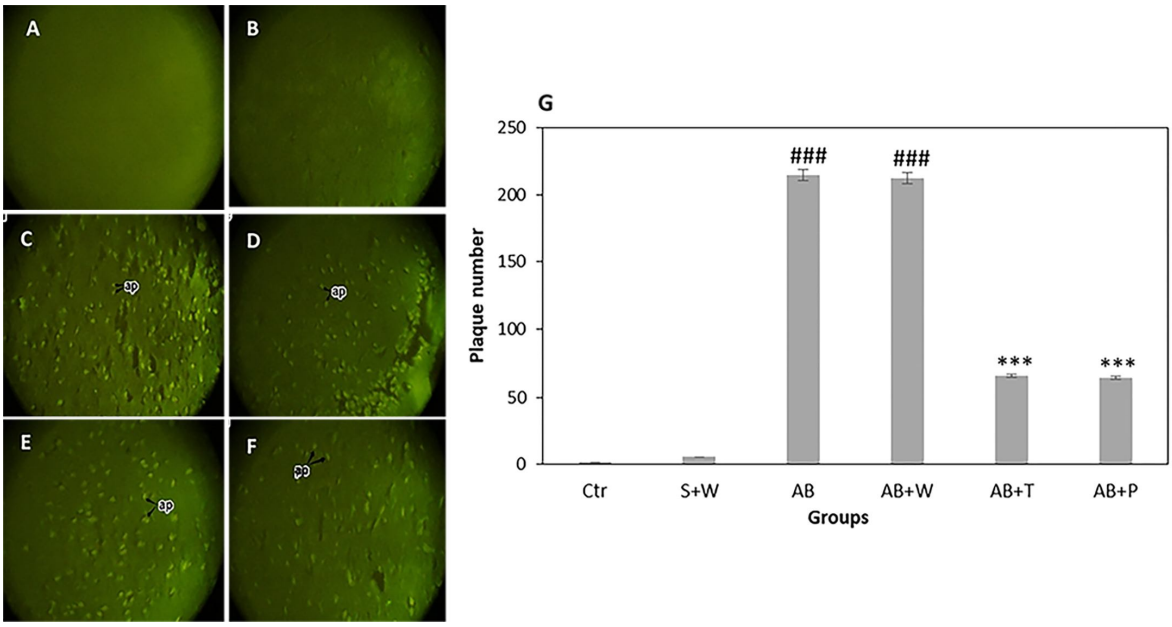

Fig. 4. Thioflavin S staining of amyloid plaques in the hippocampus CA1 region. A: Control group (Ctr); B: group underwent surgery with water being injected into brain (S + W); C: Aβ group in which Alzheimer's disease was induced (Aβ); D: Alzheimer's-induced group receiving water as Geraniol solvent (Aβ + W), E: Alzheimer's-induced group treated with 100 mg kg^{-1} Geraniol (Aβ + T); F: Alzheimer's-induced group receiving protective dose of 100 mg kg^{-1} of Geraniol (Aβ + P). Black arrows represent amyloid plaques (ap) in the tissue. Images are magnified at X100. H: number of amyloid plaques in different groups as described above.

100 mg kg^{-1} Geraniol in the protective mode was significantly higher than the Alzheimer's-induced group ($p < 0.001$) (Fig. 1). On the other hand, serum level of MDA in Aβ + P group (receiving 100 mg kg^{-1} Geraniol) was significantly lower than the disease-induced group (Fig. 2) ($p < 0.001$).

In the histological investigations, the number of neurons increased significantly ($p < 0.001$) in the group receiving Geraniol (100 mg kg^{-1}) in the protective mode compared with the Alzheimer's-induced group (Fig. 3). Moreover, the plaque numbers were notably reduced ($p < 0.001$) in the Aβ + P group compared with the Alzheimer's-induced group (Figs. 4F and G).

Destabilizing Effects of Geraniol on Preformed Aβ42 Fibrils *In Vitro*

The second part of this study involved monitoring destabilizing effect of Geraniol 100 µM on four-day-old preformed Aβ42 fibrils for 3 weeks of incubation *in vitro*. It was first demonstrated that Aβ42 fibrillation proceeded from monomeric species to long and well-matured fibrils after 4 days (Figs. 5A and B). During the first week of incubation of matured fibrils with Geraniol 100 µM, TEM images revealed that Geraniol had changed the structure of long fibrils to condensed aggregates (Figs. 5C). However, images taken from samples incubated with Geraniol for three weeks showed disappearance of aggregates and only fewer and less condensed aggregates were observed (Fig. 5D). It was confirmed that significant removal of fibrils occurred after more than one week of incubation in the presence of Geraniol 100 µM which was in accordance with the removal of plaques over *in vivo* treatment.

DISCUSSION

Several studies have proved that Aβ42 plays an

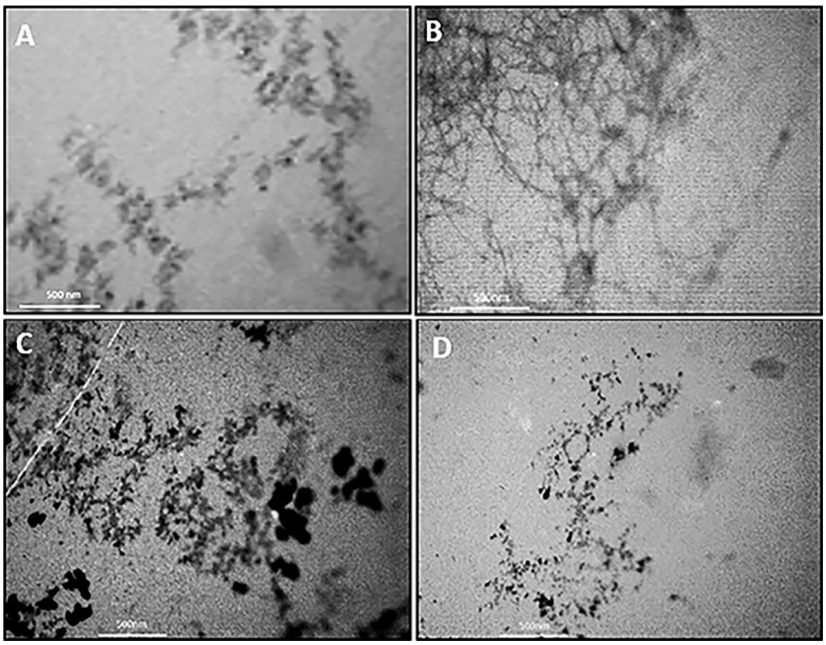

Fig. 5. Transmission electron microscope images of Aβ42 fibrillation process with and without Geraniol. (A) Aβ42 monomers after immediate incubation in the absence of Geraniol; (B) Aβ42 fibrils formed after 4 days of incubation in the absence of Geraniol. The second row indicates the four-day-old Aβ42 fibrils incubated with Geraniol 100 μM for 1 week (C) and 3 weeks (D).

important role in the pathophysiology and the neurodegeneration process of Alzheimer's disease (AD) [29,30]. It has been proved that Aβ toxicity on neuronal cells occurs after fibril formation [31]. Injection of Aβ fibrils into animals' brains is now an established method of generating AD model. By forming amyloid plaques in the brain, these animals show impairments in the memory and the level of biochemical factors [32].

Anti-amyloid compounds, including aromatic or polycyclic components [28,33] along with monoterpenes have shown great potential to prevent AD neurotoxicity [23,32,34]. Monoterpenes are present in the essential oils from plants and possess various therapeutic antioxidant and anti-inflammatory properties [35], where oxidation of biomolecules by free radicals has shown to be part of aging and AD pathology [20,36]. Geraniol is an acyclic monoterpene alcohol occurring in the essential oils of several aromatic plants. It possesses several biological activities such as antimicrobial, anti-oxidant, and anti-inflammatory while exhibiting low toxicity [37]. In agreement with the present study, Rasoolijazil *et al.* reported that Aβ41 injection in rat's hippocampus could lead to neuronal degeneration [38]. In the present study, injection of Aβ42 into the rats' hippocampus also resulted in neuronal degradation and reduction of antioxidant strength leading to the formation of amyloid plaques. Applying Geraniol to AD-induced rats exhibited a significant reduction in the number of amyloid plaques, in both treated and protective modes.

In the present study, the activity level of SOD was decreased in the AD-induced rats. SOD is considered to be one of the most active enzymes whose activity is sufficient for inactivation of free radicals produced during oxidative stress in cells [38]. It has been reported that beta amyloid produces oxygen free radicals after entering the nerve cells [39] causing the development and progression of Alzheimer's disease [40]. It has been demonstrated that in both humans and rodents, accumulation of oxidative damage to lipids, proteins, and nucleic acids ultimately leads to cognitive impairment [41]. With respect to this fact, it has been shown that injection of intra-hippocampal Aβ leads to reduced antioxidant activity [42]. Herein, Geraniol

demonstrated the ability of increasing SOD activity level and therefore could offer protection against Aβ-induced oxidative stress. Linalool and Nerol, two monoterpenes with similar structure to Geraniol, have also shown to reverse cognitive deficits and has altered the level of the antioxidant (SOD) activity in mice injected with Aβ [32,43]. Accordingly, Myrtenol, a phenolic monoterpene, and phenolic monoterpenes such as thymol have shown antioxidant potential by increasing the activity of SOD [44,45].

The direct measurement of free radicals *in vivo* is hard, and one way is to quantify the cellular components reacting with the free radicals, such as lipids [46]. One of the final products of polyunsaturated fatty acids peroxidation in the cells is malondialdehyde (MDA) [47]. An increase in free radicals causes overproduction of MDA whose level is commonly known as a marker of both oxidative stress [47] cell membrane injury [46]. In the present study, decreased activity level of SOD was consistent with an increase in the level of MDA along with destruction of neuronal cells of the brain in the Alzheimer's-induced rats. Applying Geraniol to AD-induced rats, in both treated and protective modes, exhibited a considerable increase in SOD level leading to a notable decrease of MDA level. By improving the levels of SOD and MDA, neurogenesis was resumed. In accordance with our study, Tiwari *et al.* also demonstrated a great potential for Geraniol to increase the SOD activity, inhibit NO release, decrease lipid peroxidation, and protect against ROS in stressed cells. They also indicated pharmacological potentials of Geraniol in lung inflammatory diseases where oxidative stress is a critical control point [48]. Abe *et al.* also assessed the anti-inflammatory activity of some essential oils on neutrophil activation and they found that Geraniol, as major constituent terpenoid, could clearly suppress TNF-α-induced neutrophil adherence [49]. Furthermore, several biological properties of Geraniol, including antimicrobial, anti-oxidant and anti-inflammatory activities along with negligible toxicity have been reported [37].

Further than antioxidant and anti-inflammatory properties, the results of this experiment show that Geraniol could also act on the AD model *via* its anti-fibril effect that has been demonstrated in the *in vitro* experiment. Anti-fibrillation effect of natural compounds has been reported for a variety of compounds and on various types of fibrils [28,50].

Monoterpenes represent a large group of naturally occurring organic compounds whose derivatives exhibit various activities, including analgesic, anti-inflammatory, anticonvulsant, antidepressant, anti-Alzheimer, anti-Parkinson, antiviral and antibacterial effects [51]. Therefore, they can play an important role in the creation of new biologically active compounds, including drugs.

CONCLUSIONS

It has been demonstrated that the intra-hippocampal injection of Aβ42 induced significant amyloid plaque formation and neurodegeneration, and Geraniol administration offered a great potential in counteracting AD by demonstrating antioxidant, anti-plaque, and neurogenesis activities in both therapeutic and protective modes. Finally, Geraniol has been shown to have a disaggregating effect on pre-formed amyloid fibrils. Therefore, this compound seems interesting enough to be further investigated.

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