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Original article

Pistachio Extract Improves Neurocognitive Behaviors in Ovariectomized Mice

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Abstract

Background and objectives: Menopause is associated with depression as well as emotional and memory disorders. Based on the anti-inflammatory and antioxidant effects of pistachio, its effect on depression, cognitive function, anxiety and physical power in ovariectomized mice was investigated. **Methods:** In the current study, fifty female mice were used. They were aliquoted into five groups: control, ovariectomy (OVX), ovariectomy + DMSO, ovariectomy +10 mg/kg pistachioextract and Ovariectomy +100 mg/kg pistachio extract. In order to prepare the required extract, pistachio nuts were powdered (100 g) and macerated in 1 L of ethanol (80%) for 72 h. Pistachio extract was used orally once a day in ovariectomized mice for sixty days. Anxiety, depression, working memory and physical power were evaluated by the Elevated plus-maze (EPM) test, Forced swimming test (FST), Y maze and swimming exhaustion test, respectively. **Results:** The results showed that extract of pistachio (more potentially at the dose of 100 mg/kg) decreased anxiety-like behaviors and depression; besides, increase in working memory and physical power was observed in the ovariectomized mice. **Conclusion:** The findings of the current investigation suggest that pistachio extract could be used as a potential strategy for the attenuation of ovariectomy-related manifestation.

Keywords: mice; Ovariectomy; *Pistacia vera*

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Introduction

Menopause is defined by the loss of ovarian activity and reduction in sexual hormones in the females [1,2]. It is accompanied by depression [3], emotional disorders, mood and cognitive processes [4,5]. Menopausal women suffer from symptoms such as low bone density, muscle mass reduction, tender breasts, flushing, cognitive impairment and anxiety [6,7]. Several experimental studies in rodent and human showed that ovarian hormones affect learning and memory function, including working memory [8-10]. Another study showed that by inducing OVX, learning and memory decline due to gonadal hormones deficiency [11]. Estrogen is necessary for the preservation of learning and memory because of neuroprotective, antioxidant and neurotrophic properties [12,13]. Moreover, there is a powerful relationship between reduced

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estrogen levels and incidence of Schizophrenia and Alzheimer's disease (AD) [14,15]. On the other hand, estrogen replacement therapy is effective for attenuating menopausal symtoms [16]. Nevertheless, the benefits of estrogen replacement therapy in postmenopausal women are usually overshadowed by serious side effects of estrogen such as breast and endometrial cancers [17,18].

Pistacia vera, belonging to the family Anacardiaceae, has been known for its medicinal properties since ancient times [19,20]. *Pistacia vera* seed (pistachio) is a nut with different compounds such as β-carotene, α-tocopherol, and lutein [21]. Also, previous studies reported that *P. vera* contains phenolic compounds and triterpenoids [22]. In addition, it has also been shown that *P. vera* has many pharmacological effects such as antimicrobial [23], anti-hyperlipidemia [24], anti-nociceptive and anti-inflammatory [25] activities. Pistachio flavonoids have demonstrated anxiolytic, sedative and anticonvulsant properties [26].

Due to behavioral manifestations associated with OVX and the effects of pistachio on behavioral disorders, we hypothesized that pistachio may have beneficial effects on behavioral parameters in ovariectomized mice; therefore, we designed the current study to investigate the effects of pistachio extract on ovariectomized mice.

Material and Methods

Ethical considerations

The experiment was approved by the local ethical committee of Rafsanjan University of Medical Sciences (ethical code: IR.RUMS.REC.1397.154) and conducted in accordance with the standard ethical guidelines (NIH, publication no. 85-23, revised 1985; European Communities Directive 2010/63/EU).

Extraction

Dried Akbari pistachio (genetic code: M30), was collected in 2017 from Rafsanjan, Iran. In order to prepare the required extract, pistachio nuts were powdered (100 g) and macerated in 1 L of ethanol (80%) for 72 h. The extract vehicle was then concentrated in a rotary under low pressure. It was stored at -20º C [27]. For administration, the frozen extract was freshly dissolved in dimethyl sulfoxide 10% (DMSO, Sigma-Aldrich, Germany).

Animals

Fifty female mice (20-25 g) were obtained from the animal house of Rafsanjan University of Medical Sciences. Animals were housed under temperature (20-23 ºC) with a 12h light/dark cycle and free access to food and water.

Experimental design

The animals were divided into five groups as follows: control (healthy group without any intervention), OVX group (OVX mice without any intervention), OVX + DMSO group (after induction of OVX the mice received DMSO 10% orally once a day by gavage for two months), OVX +10 mg/kg extract group (after induction of OVX the mice received 10 mg/kg pistachio extract orally once a day by gavage for two months) and OVX +100 mg/kg extract group (after induction of OVX the mice received100 mg/kg pistachio extract orally once a day by gavage for sixty days). After anesthesia with an intraperitoneal injection of ketamine sulfate solution (60 mg/kg) and xylazine (4 mg/kg), a dorsal incision was made. Then, ovaries were removed by a cautery device, the wound was closed, and 22,000 i.u/kg penicillin was injected for two days after surgery. Vaginal smears were taken from mice to confirm the absence of ovarian cycles for at least five days [28]. The doses of extract were selected based on previous investigations [27].

Behavioral tests

Elevated plus-maze (EPM) test

EPM test was used to determine the anxiety-like behavior in mice [29]. The method was mainly similar to our previous studies [30]. The EPM consists of two open arms without walls (50×10 cm) and two enclosed arms with high walls (50×10×40 cm), extending from a common central platform (10×10 cm). Each mouse was individually placed in the center of the maze, its head facing an open arm and was allowed for five min of free exploration. All sessions were videotaped. After each test, the floor was cleaned with ethanol (10%) and dried. Measurements were made from the frequencies of total open and closed arm entries (arm entry = all four paws into an arm) and the time spent in open, closed and central parts of the maze. The percentage of open arm entries (%OAE): [(the number of open arm entries/the number of entries of open and closed arms) ×100]) and open arm time (%OAT): [(time

spent in open arms/time spent in open and closed arms) ×100] as the standard indices of anxiety-like behaviors were calculated. A significant decrease in the percentage of time in open arms and/or open arm entries indicates an increased level of anxiety. Total arm entries were measured as an index of locomotor activity [31].

Forced swimming test (FST)

The forced-swim test was performed according to standard published procedures with minor modifications [32,33]. The mice were placed in a glass cylinder (12 cm diameter) filled to a depth of 10 cm with water (23 °C). A 6 min test session was conducted and videotaped. The immobility time during the last 5 min of a 6-min swim test was defined as the absence of active/escape directed movements. After the test, animals were removed from the water, dried with a towel then carried back to their home cages.

Y maze test

The Y maze test can be used to assess short term memory in rodents using the spontaneous alternation task [34,35]. The mice were placed in the center of the maze and were allowed to freely explore the three arms of the maze for 8 min. The sequence of arm entries was visually counted by an investigator. An alternation was defined as consecutive full entries (excluding the tail) into each of the three arms; and alternation percentage was calculated as the number of alternations vs. the total number of arm visits [36].

$$\% \text{ Correct Alternation} = [\text{number of alternations}/(\text{total number of arm entries} - 2)] \times 100$$

Swimming exhaustion test

Swimming is a well-established experimental model for assessing the animals' physical power [37]. Briefly, the mice were dropped separately into a columnar swimming pool (45 cm height and 20 cm radius) filled with fresh water to a depth of 35 cm so that the mice could not support themselves by touching the bottom with their tails. The temperature of the water was maintained at 34±1 °C. A weight (made of steel ring) equivalent to 5% of body weight was attached to the tail root of each mouse. The animal exhaustion time was recorded when they failed to rise to the surface of the water for breathing within 7s.

Statistical analysis

Statistical analysis was performed via GraphPad Prism program (version 6.01, GraphPad Software, USA). The results were expressed as mean ± SEM. The normality of value was tested by Shapiro-Wilk test. The differences between the groups were tested with one-way ANOVA followed by the Tukey post-hoc analysis and Kruskal-Wallis test followed by Dunn's post-hoc analysis. Statistical significance was defined as $p<0.05$.

Results and Discussion

The results of the EPM indicated that OVX decreases %OAT ($p<0.05$) in comparison with the control group and pistachio extract at the doses 10 and 100 mg/kg increased %OAT ($p<0.01$). Although OVX decreased %OAE, it was not statistically significant and pistachio extract at both doses increased %OAE in ovariectomized mice ($p<0.05$ and $p<0.01$, respectively) in comparison with the OVX group (figures 1 A and B). The results of the FST showed that immobility duration increased in OVX group in comparison with the control group ($p<0.001$). Pistachio extract at the doses of 10 ($p<0.001$) and 100 mg/kg ($p<0.001$) decreased immobility duration in comparison with the OVX group (figure 2).

In the Y maze test, the percentage of correct alternations in the OVX group significantly reduced compared with control group ($p<0.05$). But, pistachio extract at the doses of 10 ($p<0.05$) and 100 mg/kg ($p<0.001$) significantly increased this index in ovariectomized animals (figure 3).

In the exhaustion swimming time test, ovariectomized group showed a nonsignificant decrease compared to the control group. The mice treated with pistachio extract at the doses of 10 and 100 mg/kg exhibited an increased exhaustion swimming time compared to the OVX group ($p<0.01$) (figure 4).

The results of the current study clearly implied that treatment with pistachio extract significantly decreased anxiety-like behaviors and depression besides increasing the working memory and physical power in ovariectomized mice.

In menopausal women, anxiety is one of the most common disorders which is related to reduced life satisfaction and functional impairment [38]. Previous reports have demonstrated that ovariectomized animals reflect mood disturbances similar to menopausal women [39].

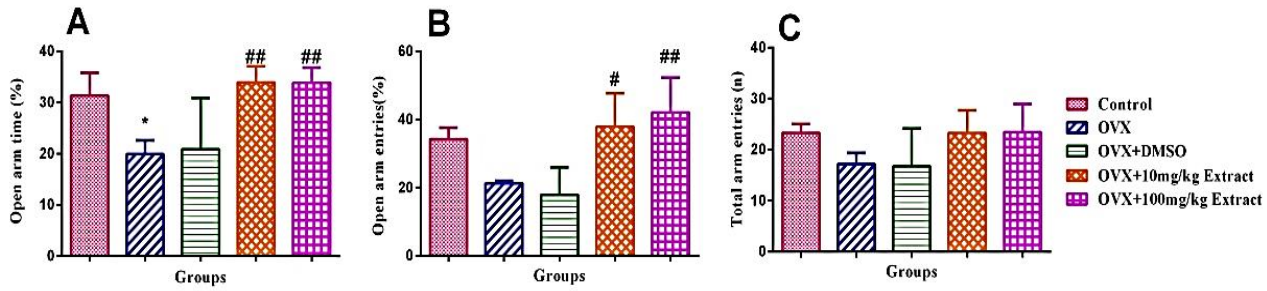

Figure 1. The effect of pistachio extract (10 and 100 mg/kg) on the **A;** open arm time, **B**; open arm entries and **C**; total arm entries in ovariectomized mice. Values are expressed as mean ± SEM. In each group n=10. *p<0.05 compared to the control group; #p<0.05 and ##p<0.01 compared to the OVX group; Kruskal-Wallis test followed by Dunn's test; OVX: Ovariectomy

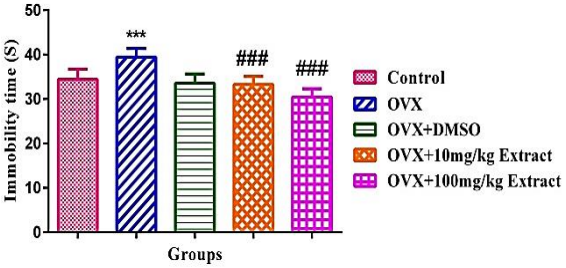

Figure 2. The effect of pistachio extract (10 and 100 mg/kg) on the forced swimming test in ovariectomized mice. Values are expressed as mean ± SEM. In each group n=10; ***p<0.001 compared to the control group; ###p<0.001 compared to the OVX group; One-way ANOVA followed by Tukey test; OVX: Ovariectomy

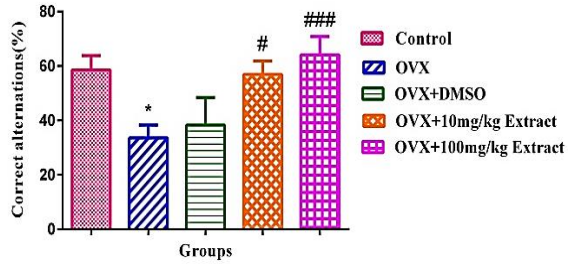

Figure 3. The effect of pistachio extract (10 and 100 mg/kg) on the Y maze in ovariectomized mice. Values are expressed as mean ± SEM. In each group n=10. *p<0.05 compared to the control group. #p<0.05 and ###p<0.001 compared to the OVX group; Kruskal-Wallis test followed by Dunn's test; OVX: Ovariectomy

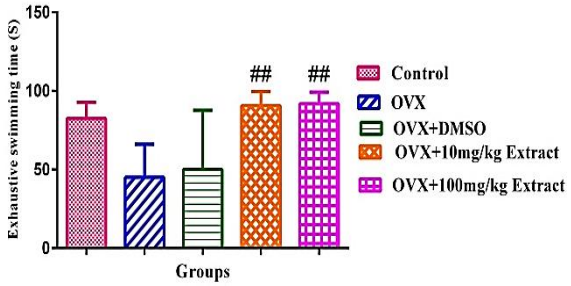

Figure 4. The effect of pistachio extract (10 and 100 mg/kg) on the swimming exhaustion in ovariectomized mice. Values are expressed as mean ± SEM. In each group n=10. ##p<0.01 compared to the OVX group; Kruskal-Wallis test followed by Dunn's test; OVX= Ovariectomy

In agreement with these reports, our results indicated that anxiety-like behavior increased in ovariectomized animal. We also showed that pistachio extract (10 and 100 mg/kg) decreased anxiety-like behavior in ovariectomized animals. Pilsakova et al., showed that pistachio extract had anxiolytic function based on the physiological actions of phytoestrogens [40]. Rostampour et al., reported that the hydroalcoholic extract of pistachio extract showed a preventive effect in experimental model of anxiety. They demonstrated anxiolytic effect of pistachio extract was antagonized by tamoxifen through blockade of estrogen receptor [41].

Our results showed that depression-like behavior increased in ovariectomized mice. On the other hand, pistachio extract decreased the depression-like behavior in ovariectomized mice. Accoeding toTavakkoli-Kakhki et al., pistachio had more effect on depressed patients compared to other fruits and nuts. They also demonstrated that omega-3 content of pistachio was an effective foodstuff for depressed patients [42].

It is established that during menopause, decline of sexual hormones influences cognitive functions [43]. In addition, previous reports indicated that OVX induced learning and memory impairment in rodents [44]. In agreement with these reports, our results indicated that OVX impaired working memory in mice and that pistachio extract improved this index in ovariectomized mice. Hence, pistachio might possibly improve cognition via the antioxidative properties.

Menopause reduces the muscle mass and power [7,45]. Animal studies have demonstrated that ovariectomy reduces the contractile power of muscles [46]. Our results showed that pistachio extract increased the physical power in

ovariectomized mice. Some of the active constituents of pistachio such as naringenin, epicatechin, quercetin and apigenin have significant effects on physical power [47]. For example, it has been demonstrated that quercetin improves cycling time trial performance in humans via antioxidative properties [48]. In another study, it has been reported that epicatechin inhibits adaptations in relative peak aerobic power and skeletal muscle compared with the placebo in human [49].. Moreover, naringenin also has potential anti-fatigue effects on female rats through reducing the oxidative stress and matrix metalloproteinases-9 level [50]. So, it is inferred that these compound in pistachio, to some extent, could be responsible for the anti-fatigue properties exhibited by this plant.

The result of this study demonstrated that pistachio has protective effects on anxiety-like behaviors, depression, working memory and physical power in ovariectomized mice; therefore, pistachio could be a potential medical supplement for improving the cognition in menopause.

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Author contributions

Mohammad Allahtavakoli and Ali Shamsizadeh conceived the study idea. Elham Hakimizadeh, Faezeh Jandaghi and Mojdeh Hajmohammadi conducted the data collection. Iman Fatemi and Ayat Kaeidi analyzed the data. Mohammad Allahtavakoli and Iman Fatemi wrote the manuscript. All authors read, critically revised, and approved the final manuscript.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

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Abbreviations

OVX: Ovariectomy; DMSO: dimethyl sulfoxide; OAE: Open arm entries; OAT: open arm time; EPM: elevated plus-maze; FST: forced swimming test; AD: Alzheimer’s disease