Orginal Article

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Evaluation of the Effects of Grape Seed Oil on the Anxiety Level and Motor Coordination of Male Wistar Rats

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Abstract

BACKGROUND AND OBJECTIVES: Anxiety is a common psychological disorder in developing societies, in which several neurotransmitters are involved. Use of pharmaceutical drugs in the treatment of anxiety has been associated with numerous side effects. This study aimed to evaluate the anxiolytic effects of grape seed oil on male rats in the elevated plus maze (EPM) model.

METHODS: This experimental study was conducted on rats weighing 250- 300 grams divided into five groups of eight. Animals were administered with grape seed oil via gavage for five consecutive days, and behavioral tests were carried out 30 minutes after the intervention. Anxiolytic properties of grape seed oil were evaluated using the EPM model, and motor coordination of rats was assessed using the Rotarod apparatus. After behavioral evaluations, the animals were deeply anesthetized, and blood samples were obtained from their heart. After the extraction of blood serum, the antioxidant capacity test was performed.

FINDINGS: In animals administered with grape seed oil at doses of 50 (15±2.1), 100 (21.5±1.8), and 200 (27.5±1.8) milligram per kilogram of body weight, the number of open arm entries in EPM increased significantly compared to the control group (p=0.008, p=0.005, p=0.008). Moreover, gavage of grape seed oil at the dose of 200 mg/kg (177.5±95.17) significantly increased the time spent in the open arms of EPM (p=0.023). In addition, serum antioxidant capacity was significantly higher in rats receiving grape seed oil compared to control subjects.

CONCLUSION: According to the results of this study, grape seed oil could be effective in the reduction of anxiety levels through the inhibition of oxidative stress in rats in the EPM model.

KEY WORDS: *Grape seed oil, Elevated plus maze (EPM), Locomotor activity*.

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Introduction

Anxiety is a common experience throughout life, while severe and chronic anxiety is associated with numerous problems and complications. According to the literature, anxiety is more prevalent among women, low-income social classes, and middle-aged and elderly individuals (1). Due to the negative side effects and high costs associated with the use of anti-anxiety medications, researchers have been investigating new pharmaceutical agents to treat anxiety without health risks (2, 3). In recent years, extensive research has proposed herbal compounds as effective alternatives in the treatment of patients with anxiety (4-8).

These compounds have been shown to have various therapeutic and prophylactic properties (9-16). Grape is an agricultural product, which is planted and harvested abundantly across the world. Approximately 46% of fresh grapes are used in the wine industry. In the production of wine, large amounts of grape flesh remain as the by-product. Grape seed contains 20-26% flesh and high amounts of protein, as well as 10-20% oil with considerable levels of vitamin E, which has significant benefits for human health (17).

Similar to other vegetable oils, such as palm and coconut, grape seed oil is a major source of tocotrienols. In general, these compounds are known to have more potent antioxidant activities compared to tocopherols. Therefore, despite the high degree of unsaturation, these compounds are more stable against oxidative stress due to the presence of stabilizing agents (18, 19). Oxidative stress is a major risk factor for high concentrations of serum lipids and oxidized protein in the central nervous system (CNS) and other body organs, which has been shown to cause significant tissue damage (20-22). Production of free radicals has been associated with a variety of natural cellular processes, such as cell metabolism, mitochondrial respiration, and lipoxygenase and cyclooxygenase activities (23-26). Variations in the levels of reactive oxygen species (ROS) produced in different regions of the brain could be attributed to oxygen consumption level in each area. As such, brain regions such as the hippocampus and striatum are considered more vulnerable due to the higher oxygen consumption (27).

Although the exact underlying mechanisms of anxiety remain a matter of debate, the involvement of oxidative stress in the occurrence of the anxiety disorder has been confirmed by several researchers (28). Considering the potent antioxidant properties of grape seed and the relationship between oxidative stress and anxiety, this study aimed to evaluate the anxiolytic effects of grape seed oil on male rats.

Methods

Animal model tests: This experimental study was conducted on adult male Wistar rats weighing 200-250 grams divided into five groups of eight. The animals were kept at an appropriate temperature (21±2 °C) within a light cycle of 12 hours of light and 12 hours of darkness and had access to adequate food and water.

Provision of grape seed oil: In this study, grape seed oil was purchased from a reputable store in Shahrekord city, Iran to be used in the experiments.

Psychomotor coordination test using the Rotarod apparatus: The Rotarod apparatus is composed of a rotating rod with the rotation speed of 0-40 rpm. In this study, the rotation speed was determined at 10 rpm with acceleration of 7 rpm^2, which is equal to 10-11 rotations per minute. Rats administered with grape seed oil and control subjects were placed on the rotating rod of the Rotarod apparatus 30 minutes after the intervention using the grape seed oil.

The rod was set in rotation for 300 seconds (maximum), and the duration in which the rat was able to keep the balance and resist the movement of the rotating rod was recorded as the resistance time. This process was repeated three times for each rat, and the mean duration of resistance was calculated (29).

Method of stress induction: In order to induce hypothermic stress, animals in the experimental groups were placed in restrainers and kept at the temperature of 4°C for 10 minutes in a fridge for five days before receiving the grape seed oil. On day five, the EPM anxiety test was conducted on the experimental animals 30 minutes after the administration of grape seed oil (30, 31). Animals in the experimental groups were administered with grape seed oil daily via gavage. In addition, diazepam was injected intraperitoneally every day in one group. All the medications were administered at 11 a.m.

Method of anxiety measurement: To measure the level of anxiety, we used the EPM device, which has been known as a standard apparatus for the assessment of anxiety in rodents. EPM is composed of two open arms (diameters: 50×5 cm), two closed arms (diameters: 50×5×40 cm), and a central pan (diameters: 5×5 cm). The open and closed arms are set opposite to each other separately at 50 cm above the floor. This model is used to determine the level of

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unconditional anxiety without the need for the training of test animals. After the injection of the required drugs to the animals on the intervention day, each rat was transferred separately to the workshop at five minutes before the intervention and placed in a black plexiglass box (diameters: 40×40×30 cm) in order to enhance the explorative activity. Afterwards, the animals were placed in the EPM (on the central pan and opposite to the open arms) in order to measure the anxiety. Moreover, exploratory activity, number of entries into the open arms, and time spent in the open arms were evaluated and recorded for five minutes. Reduced level of anxiety in rats was defined with the increased number of entries and time spent in the open arms of the maze (32). The aforementioned examinations were performed on the rats divided into five groups of eight, as follows:

1. Group one, which consisted of control subjects administered with normal saline via gavage for five days;
2. Group two, which consisted of the animals administered with grape seed oil at the dose of 50 mg/kg of body weight via gavage for five days;
3. Group three, which included the animals receiving grape seed oil at the dose of 100 mg/kg of body weight via gavage for five days;
4. Group four, in which the animals received grape seed oil at the dose of 200 mg/kg of body weight via gavage;
5) Group five, which consisted of the animals receiving intraperitoneal injection of diazepam at the dose of one mg/kg of body weight for five days.

Evaluation of serum antioxidant capacity: To assess the serum antioxidant capacity, blood samples were obtained from the animals immediately after the intervention. Afterwards, the evaluation of serum antioxidant capacity was carried out using the ferric-reducing antioxidant power (FRAP)method, and the absorption was recorded using a spectrophotometer (33).

Data analysis: Data analysis was performed in SPSS V.16 using one-way analysis of variance (ANOVA) to compare the differences between the groups and Tukey's post-hoc test to compare the mean values. In all statistical analyses, $p<0.05$ was considered significant.

Results

Time spent in the open arms of EPM: In this study, animals receiving grape seed oil at the dose of 200 mg/kg had a significant difference regarding the time spent in the open arms of EPM compared to control subjects (p=0.032). In addition, administration of grape seed oil at doses of 50 and 100 mg/kg increased the time spent in the open arms of the maze, which was not statistically significant (fig 1).

Time spent in the closed arms of EPM: In this study, administration of grape seed oil at the dose of 200 mg/kg significantly decreased the time spent in the closed arms of EPM (p=0.023). As such, no significant difference was observed between the control subjects and other groups in this regard (fig 1).

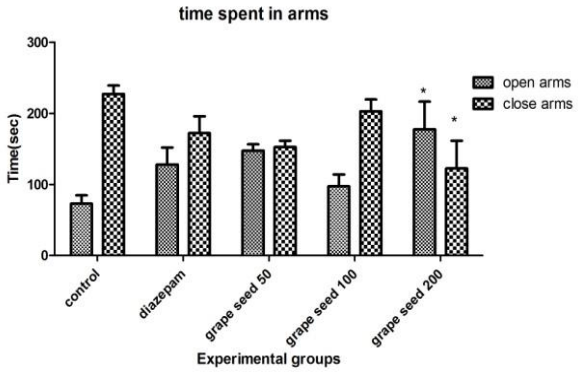

Figure 1. Time spent in open and closed arms of elevated plus maze (EPM) in experimental groups ($p<0.05$)

Number of entries to the closed arms of EPM: In this study, treatment of the animals with grape seed oil at the dose of 200 mg/kg significantly decreased the number of entries to the closed arms of the maze in group four compared to the control subjects (p=0.041). Furthermore, administration of grape seed oil at the dose of 100 mg/kg reduced the number of entries to the closed arms of EPM, which was not statistically significant. According to our findings, number of entries to the closed arms of the maze in the group receiving grape seed oil at the dose of 200 mg/kg had a significant decrease compared to the group administered with 50 mg/kg of grape seed oil ($p<0.05$) (fig 2).

Number of entries to the open arms of EPM: According to the results of this study, number of entries to the open arms of EPM had a significant increase in the animals receiving diazepam compared to control subjects. Furthermore, number of entries to the open arms of the maze significantly increased in the animals receiving grape seed oil at doses of 50, 100, and 200 mg/kg compared to control subjects (p=0.005, p=0.008, p=0.008). On the other hand, a significant difference was observed in the number of entries to the open arms of the maze in groups receiving grape seed oil at doses of 100 and 200 mg/kg

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compared to the rats administered with 50 mg/kg of the herbal oil ($p<0.01$). Moreover, number of entries to the open arms of EPM in animals receiving grape seed oil at the dose of 200 mg/kg increased significantly compared to the group administered with 100 mg/kg of the herbal oil (fig 2).

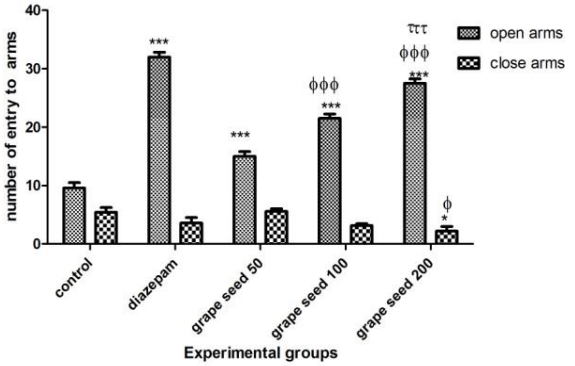

Figure 2. Number of entries to open and closed arms of EPM in experimental groups compared to control group

(*=significant difference in control group with other groups; ϕ=significant difference in rats receiving 50 mg/kg of grape seed oil with other doses (100 and 200 mg/kg);

τ=significant difference between doses of 100 and 200 mg/kg;

*** τττ, ϕϕϕ=p<0.01, ϕ*=P< 0.05)

Effects of grape seed oil on motor coordination: According to our findings, motor coordination in male rats had no significant difference in the groups administered with grape seed oil and animals injected with diazepam with the control subjects (fig 3).

Effects of grape seed oil on serum antioxidant capacity: In this study, use of grape seed oil at three doses of 50, 100, and 200 mg/kg increased the serum antioxidant capacity of the male rats. However, this increase was not statistically significant at doses of 50 and 100 mg/kg, while it was statistically significant at the dose of 200 mg/kg (fig 4).

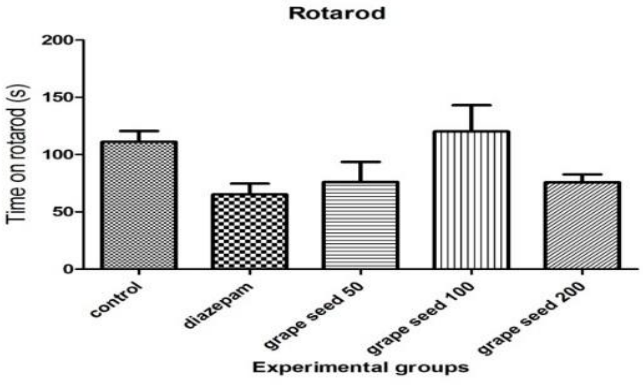

Figure 3. Comparison of motor coordination in experimental groups

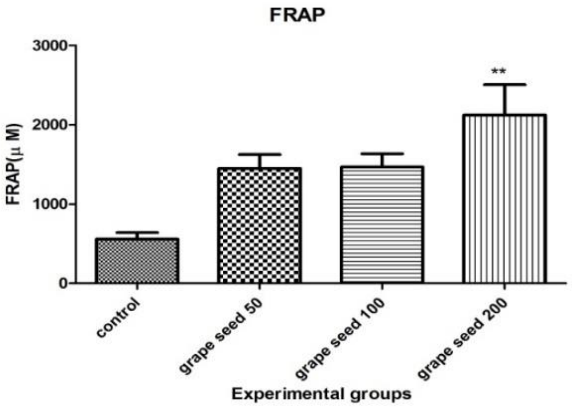

Figure 4. Comparison of serum antioxidant capacity in experimental groups (p=0.01-0.05)**

Discussion

In the present study, injection of diazepam, which is commonly used in the treatment of anxiety disorders, could significantly increase the number of entries to the open arms of the EPM apparatus in adult male rats. Furthermore, our findings indicated that use of grape seed oil at the dose of 200 mg/kg could increase the time spent by the animals in the open arms of the maze compared to the control group, which was considered an indicator for reduced anxiety levels in the studied animals.

In addition, number of entries to the open arms of EPM was significantly higher at the dose of 200 mg/kg of grape seed oil. Therefore, it could be concluded that grape seed oil decreases the indices and symptoms of anxiety in rats modulating anxiety responses through its anxiolytic properties.

Oxidative damage to the brain has been shown to be a major cause of CNS disorders. In living organisms, lack of balance between the production of oxidants and antioxidant protection, which is in favor of the oxidants, could lead to oxidative stress. This may also be associated with the expression of various genes, structural changes of proteins, and cell signaling changes. These changes might impair the performance of neurotransmitters, neuronal functions, and membrane integrity, and even lead to cell death (34). In a recent study, Rammal et al. reported an association between oxidative stress and specific anxiety disorders, which indicates that other systems, such as oxidative metabolism, could influence anxiety (35). In 2005, Hovatta et al. observed a close correlation between antioxidant defense mechanism and the anxiety-related phenotype in six different mixed races of rats.

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According to the findings, the expression of glutathione reductase-1 and glyoxalase-1 genes in the brain, which are involved in antioxidative metabolism, significantly involves the anxiety-related phenotype. Furthermore, they observed that these enzymes were significantly more active in rats with high anxiety levels compared to those without anxiety (34). Although no studies have specifically investigated the anxiolytic properties of grape seed oil, modern medicine has proposed several therapeutic benefits for this plant. Grape seed extract is a rich source of potent antioxidants, such as polyphenols and proanthocyanidins. In human body, proanthocyanidins are 20 times more effective compared to vitamin C and 50 times more effective compared to vitamin E.

These antioxidant compounds could prevent the cell damage caused by free radicals through neutralizing these radicals. Therefore, grape seed oil could be used in the treatment of the disorders associated with the release of free radicals (29). Grape juice is widely available in the market and is an abundant source of numerous flavonoids, polyphenols, and proanthocyanidins with remarkable antioxidant properties. Furthermore, resveratrol, which is a polyphenolic antioxidant found in red wine, has been shown to be effective in the prevention of cardiac diseases and protection of the brain against ischemic injury (36). According to the literature, pretreatment of glial cell cultures with grape seed proanthocyanidin extract increases the number of viable cells following the oxidative stress induced by H2O2. Moreover, grape seed could increase the production of intracellular nitric oxide in astroglial cell cultures in the brain of rats (37).

Previous studies have proposed that resveratrol decreases the induced mitochondrial ROS production and lipid peroxidation in rats. Furthermore, this compound has been shown to exert protective effects against oxidative DNA damage in rats with cerebrovascular accident that were prone to high blood pressure (38). In one research conducted in this regard, the antioxidant activity of grape seed oil was observed to be twice higher compared to that of the rosemary plant. Grape seed contains 6-20% oil, which is rich in fatty acids essential to human nutrition. For instance, linoleic acid, which is considered to be one of the most effective fatty acids in the reduction of blood cholesterol, is the dominant fatty acid found in grape seed oil at different varieties, constituting as much as 53.6-69.6% of the total fatty acid content of this herbal oil (39). In another study, consumption of high doses of proanthocyanidins found in grape seed extract were reported to diminish tissue damage in colitis induced by 3-nitrobenzene sulfonic acid, which is a chronic model of experimental ulcerative colitis. According to the literature, free radicals play a pivotal role in the pathogenesis of ulcerative colitis. As such, the production of free radicals increases in this disease, and some enzymes such as superoxide dismutase, glutathione peroxidase, and catalase protect cells against oxidative agents. However, the activity of these enzymes is likely to reduce in ulcerative colitis. Therefore, enhancement of the cell protection system through free radical elimination is a noteworthy therapeutic goal for ulcerative colitis, and numerous antioxidant compounds have been used in this regard so far. Grape seed extract has been proven to have several antioxidant compounds, such as proanthocyanidins, which neutralize the adverse effects of free radicals, inhibit fatty acid oxidation in cell membranes, and prevent the activation of NF-kappa B transcription factor (40).

Proanthocyanidins, as well as other effective compounds in grape, are able to hinder the cell death induced by glutamate through restraining calcium signals and inhibiting nitric oxide formation in hippocampal cell cultures. Protective effects of grape seed oil against memory disorders and long-term potentiation have been attributed to the presence of antioxidant agents in this plant, as well as the inhibition of antagonistic glutamate activities in the brain (29). According to the findings of Sarkaki et al., grape seed oil could significantly decrease the brain damage caused by focal cerebral ischemia enhancing the cerebral blood flow. Moreover, this herbal extract could significantly reduce malondialdehyde (MDA) levels in the brain, which is considered an indicator of lipid peroxidation level (41).

Results of the present study denoted that grape seed oil could reduce the level of anxiety in male rats owing to its anxiolytic properties. Furthermore, previous studies in this regard have confirmed that grape seed oil could reduce the level of MDA, which is indicative of the inhibitory effects of this extract against oxidative stress.

In conclusion, findings of the current study indicated that grape seed oil has potent antioxidant properties. According to the results of our experiment, serum antioxidant capacity of the rats administered with grape seed oil (200 mg/kg) was higher compared to the control subjects. Therefore, this anxiolytic effect could be attributed to the antioxidant components found in this natural oil. It is recommended that future investigations be performed so as to determine the exact mechanism of such anxiolytic effects of grape seed oil, as well as the protective effects of this herbal oil against oxidative stress.

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