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The Effect of Detraining Followed by Endurance Training and *Salvia Officinalis* supplementation on Psychological Indicators and Physiological Performance in Rats

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A B S T R A C T

Introduction: This study examined the effects of two and four weeks of detraining, followed by four weeks of endurance training (ET) and Salvia *officinalis* (S) supplementation, on anxiety-like behaviors, aerobic capacity (AC), depression, and pain threshold (PT) in rats.

Methods: In this experimental study, 40 adult female rats were randomly assigned to five groups: (1) Control, (2) Sham, (3) S, (4) ET, and (5) ETS. Rats in groups 4 and 5 underwent treadmill training for four weeks (five sessions per week, 60 minutes per session). Groups 3 and 5 received *Salvia officinalis* extract at 100 mg/kg/day. Data were analyzed using analysis of covariance (ANCOVA) and one-way analysis of variance (ANOVA) with repeated measures.

Results: The percentage of time spent in the open arms (OA) of the elevated plus maze in the S, ET, and ETS groups was significantly higher than in the control group during both two and four weeks of detraining. However, after four weeks of detraining, this percentage was significantly lower compared to two weeks of detraining ($P \le 0.05$). No significant differences were observed in AC, depression levels, or PT between the two- and four-week detraining periods following four weeks of ET+S ($P \le 0.05$).

Conclusion: The findings suggest that four weeks of *Salvia officinalis* supplementation and endurance training can reduce anxiety-like behaviors. However, two and four weeks of detraining may lead to an increase in anxiety-like behaviors.

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Introduction

Activity and movement are fundamental characteristics of most living organisms, including humans. However, with increasing urbanization, the type and amount of physical activity have changed, leading to a decreased necessity for movement in daily life. Consequently, to compensate for this reduced physical activity and maintain overall well-being, individuals should engage in structured exercise programs to reap its benefits (1).

The rise in body weight and obesity is closely linked to an increase in blood lipid levels (2). Data indicate that physical inactivity is the fourth leading risk factor for global mortality, accounting for six percent of deaths worldwide. Furthermore, evidence suggests that inactivity has severe adverse effects on both physical and mental health, contributing to the development of cardiovascular diseases, diabetes, cancer, and mental disorders (3).

Evidence suggests that a decline in physical activity is primarily associated with increased body fat and obesity, reduced physical performance, and decreased overall fitness. Additionally, insufficient physical activity can disrupt the body's homeostasis, potentially leading to both physical and psychological disorders (4). Furthermore, research indicates a significant relationship between reduced physical activity and the occurrence of anxiety disorders, psychological distress, and appetite dysregulation (5).

On the other hand, given the critical role of regular physical activity in public health, evidence suggests that structured exercise enhances physical performance, boosts self-confidence, improves overall fitness, and reduces mental disorders. Research indicates that

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exercise improves lipid metabolism and promotes mitochondrial biogenesis (6), as well as increases neurotrophins, serotonin, and dopamine, thereby enhancing both physical and psychological well-being (7). Furthermore, studies have demonstrated that sports activity is associated with improved myokine levels, increased ephedrine production, enhanced pain tolerance, and better physical fitness in animal models with psychological disorders (8). Additionally, previous research has shown that exercise, even under varying temperature conditions, can improve liver enzyme function (9). Moreover, improvements in memory and reductions in depression have been linked to diabetes in animal models (10). Regular physical activity has also been reported to prevent mental disorders such as depression and anxiety, particularly in the elderly population (11). However, evidence suggests that detraining reverses the benefits of exercise, leading to a return to baseline physiological states. In this context, Dabidi Roshan et al. observed a non-significant increase in C-reactive protein levels after four weeks of detraining in the training group, while a significant increase was reported in the control group (12). Similarly, Coyle et al. (1983) reported a 7% decrease in aerobic capacity following two weeks of detraining (13). Costill et al. (1985) extensively studied detraining and reported an 8–10% reduction in anaerobic threshold after one week of detraining (14), a 25% decline in buffering capacity after three weeks (15), and a 39% decrease in muscle glycogen levels following four weeks of detraining (14).

On the other hand, it is widely believed that a diet rich in anti-aging compounds plays a crucial role in reducing the risk of obesity-related and metabolic disorders (7). In addition to pharmaceutical interventions, medicinal plants have been explored—both traditionally and experimentally—for their potential in treating cognitive disorders. Among these, *Salvia officinalis* is particularly noteworthy (16). *Salvia officinalis* is one of the largest genera in the mint family, comprising over 900 species, many of which grow naturally as weeds in parks and gardens (17). Moreover, various studies have examined the effects of exercise and herbal medicines on obesity and its associated psychological and physiological consequences, including anxiety, aerobic capacity, depression, and pain tolerance. For instance, one study reported that swimming training combined with fenugreek supplementation improved lipid profiles and glycemic indices in diabetic rats (6). Similarly, swimming training alongside cinnamon extract enhanced spatial memory in diabetic rats (10). Additionally, endurance training combined with beetroot extract was found to reduce anxiety and depression while increasing serotonin and dopamine expression in diabetic rats (7). Despite existing research, the long-term effects of exercise and medicinal plants on physiological and psychological health remain insufficiently explored in both applied and fundamental studies. Understanding the sustained impact of these interventions could provide valuable insights for optimizing physical and mental health. Given the limited information on the effects of detraining (two and four weeks) on health indicators, the present study aims to investigate the impact of two and four weeks of detraining following four weeks of endurance training and *Salvia officinalis* supplementation on anxiety, body mass index, aerobic capacity, depression, and pain threshold in rats.

Materials and Methods

In this experimental study, 40 female Wistar rats (average weight: 150–200 grams; average age: 8 weeks) were obtained from the Laboratory Animal Reproduction and Breeding Center at Islamic Azad University, Marvdasht Branch. The animals were housed for seven days in the sports physiology laboratory of the same institution to acclimate to the new environment. Throughout the study, the rats were maintained under standard laboratory conditions, including polycarbonate cages with autoclave capability, an optimal temperature of 20–24°C, relative humidity of 55–65%, and a 12-hour light-dark cycle. All procedures complied with ethical guidelines for laboratory animal research under the Helsinki Convention. Following the adaptation phase, the rats were randomly divided into six experimental groups (n = 8 per group): Control (C), Endurance training (ET), Salvia officinalis consumption (S), Sham (Sh), and Endurance training + Salvia officinalis (ETS).

Endurance Training Protocol

Initially, to familiarize the animals with the endurance training protocol, they were placed on a treadmill and ran 8 meters per minute with a zero-degree incline for 10 minutes. This warm-up intensity was chosen as it did not affect the study variables. A mild electric stimulus was installed at the end of the treadmill to encourage continuous movement. To minimize potential stress or injury from the stimulus, the animals were conditioned beforehand using gentle tapping on the treadmill, soft auditory cues, or light tail touches. The endurance training protocol lasted four weeks, consisting of five weekly sessions of progressively increasing treadmill running, without incline (0% incline), at speeds of 18–22 meters per minute for 60 minutes per session. The intensity was adjusted to correspond to 70% of the rats' maximum oxygen consumption (VO_2 max) in the first week, 75% in the second week, and 80% in the third week. Each training session began with a warm-up phase, where the animals ran for 10 minutes at 8 meters per minute before transitioning into the primary training protocol. Upon completing the training session, a cool-down phase was implemented by gradually reducing the treadmill speed until it reached zero, lasting approximately five to seven minutes (18).

Preparation of Salvia officinalis Extract

The Salvia officinalis plant extract was prepared using the soaking method. To achieve this, 50–100 grams of dried Salvia officinalis was first ground and passed through a sieve with a defined mesh size. Depending on the type of extract, distilled water or 80% ethanol was added to moisten the powdered plant material. After approximately one minute, an additional volume of the same solvent was added until the powder was fully submerged, forming an 8–10 cm liquid layer above the plant material. The mixture was then stored in a dark environment for 30 hours before being placed on a shaker for 30 minutes to enhance extraction. Following this step, the solution was filtered using filter paper, separating the extract from the plant residue. The remaining plant material was further extracted by adding fresh solvent, and this process was repeated two to three times. Finally, the filtered extracts from each step were combined and concentrated using a vacuum distillation method with a rotary evaporator. The rats in Groups 3 and 5 received 100 mg/kg of Salvia officinalis extract via intraperitoneal injection.

Evaluation of Anxiety-Like Behaviors

The elevated plus-maze (EPM) was used to assess anxiety-like behaviors in rats. This test is based on the model first introduced by Pellow et al. The apparatus is constructed of wood and consists of four arms arranged in a plus-shaped configuration. Two opposing arms are open, while the other two are enclosed. The dimensions of both the open and closed arms are 10 × 50 cm, with the enclosed arms featuring 40 cm high walls at the sides and ends. These arms extend from a central platform measuring 10 × 10 cm. The maze was elevated 50 cm above the ground using a supporting base. At the beginning of the test, each rat was placed in the central area, facing an open arm. Over five minutes, the animal was allowed to explore freely, and the following parameters were recorded: the number of entries into the open arms, the number of entries into the closed arms, the total time spent in the open arms, and the total time spent in the closed arms. An arm entry was defined as placing all four paws within the respective arm. The duration spent in each arm was calculated based on the same criterion (5).

Assessment of Depression

The forced swimming test (FST) was used to assess depressive-like behavior in rats. For this purpose, a glass container with a height of 25 cm and a diameter of 12 cm was filled with water to a depth of 8 cm, maintained at a temperature of 25°C. Each rat was gently placed in the water from a height of 20 cm. Conventionally, the cessation of limb movements was considered immobility. The total duration of the test was six minutes. The first two minutes were designated an adaptation period, during which immobility time was not recorded. After this initial phase, the rats' movements were observed, and periods during which the animal exhibited no movement or response and remained floating passively were recorded as immobility time using a stopwatch. Following the test, the animals were dried in a chamber maintained at 30 ± 1°C (5).

Assessment of Aerobic Capacity

A progressive treadmill running protocol was implemented to determine maximum oxygen consumption (VO_2 max) or maximum running speed in rats. The rats ran for five minutes at an 8 m/min speed. In the next stage, they ran for eight minutes at speeds ranging from 10 to 15 m/min. In the third stage, they ran for five minutes at 20 m/min, followed by a fourth stage in which they ran for 10 minutes at 25 m/min and then continued for 20 minutes at 30 m/min. In the final stage, the running speed was increased to 35 m/min and maintained until the rats made contact with the end of the treadmill three times within one minute, considered the point of exhaustion (VO_2 max). Based on the obtained results, the training intensity was subsequently determined at 55–60% of the maximum running speed (2).

Assessment of Pain Tolerance Threshold

The Hot-Plate test was used to assess pain tolerance. This test employs a heated plate, which is warmed using an electric current. In this study, each rat was individually placed on the plate, maintained at 55°C, and the start time (time zero) was recorded. The latency to the first nociceptive response, defined as either paw licking or a distinct alteration in gait, was measured as the pain tolerance threshold. The endurance threshold was recorded when the animal exhibited jumping behavior. To prevent tissue damage, the maximum duration of the test was limited to 60 seconds per rat (8).

Data Analysis Method

or statistical analysis, the Kolmogorov-Smirnov test was used to assess the normality of data distribution. A one-way analysis of variance (ANOVA) with repeated measures and analysis of covariance (ANCOVA) was performed, followed by Bonferroni post hoc tests for pairwise comparisons. Data analysis was conducted using SPSS version 21, with a significance level set at $p < 0.05$.

Results

Table 1 presents the mean and standard deviation of the study variables. The results of the analysis of covariance (ANCOVA) indicated a significant difference in the percentage of time spent in the open arms (OA) among the experimental groups (P = 0.001). Furthermore, Bonferroni's post hoc test revealed no significant difference between the control and sham groups (P = 0.27). However, the percentage of time spent in the OA was significantly higher in the Salvia officinalis (P = 0.001), endurance training (P = 0.001), and endurance training combined with Salvia officinalis (P = 0.001) groups compared to the control group after two weeks of detraining.

A significant difference was observed in the percentage of time spent in the open arms (OA) among the experimental groups (P = 0.001). Additionally, the percentage of time spent in the OA was significantly higher in the Salvia officinalis (P = 0.001) and endurance training combined with Salvia officinalis (P = 0.003) groups compared to the control group. The time factor significantly affected changes in the percentage of time spent in the OA (P = 0.005). However, the interaction effect between group and time was insignificant (P = 0.40). In other words, the percentage of time spent in the OA after four weeks of detraining was significantly lower than after two weeks of detraining (P = 0.005) (Figure 1).

There was no significant difference in aerobic power levels of rats after two weeks (P = 0.32) and four weeks (P = 0.51) of detraining, following four weeks of endurance training and Salvia officinalis consumption. Additionally, the results indicated that the time factor (P = 0.051) and the interaction effect between time and group (P = 0.43) had no significant impact on aerobic power during the two- and four-week detraining period (Figure 2).

Similarly, there was no significant difference in depression levels of rats after two weeks (P = 0.42) and four weeks (P = 0.31) of detraining, following four weeks of endurance training and Salvia officinalis extract consumption. Furthermore, the results showed that the time factor (P = 0.99) and the interaction between time and group (P = 0.15) had no significant effect on depression levels during the two- and four-week detraining period.

There was no significant difference in the depression levels of rats after two weeks (P = 0.44) and four weeks (P = 0.07) of detraining, following four weeks of endurance training and Salvia officinalis extract consumption. Additionally, the time factor (P = 0.47) did not significantly affect the pain tolerance threshold during the two- and four-week detraining period. However, the interaction between time and group was significant (P = 0.008), indicating that changes in pain tolerance threshold varied depending on the experimental conditions.

Table 1. Mean and standard deviation of research variables in five groups after two and four weeks of detraining following four weeks of endurance training and consumption Salvia officinalis

Factor	Group	Four weeks of detraining	Four weeks of detraining	After training
Anxiety-like behaviors (percentage of time spent in the open arm)	C	10.43 ± 6.28	10.43 ± 6.53	12.78 ± 9.84
	Sh	17.29 ± 13.30	19.29 ± 13.43	26.67 ± 13.26
	S	48.66 ± 6.92	53.14 ± 3.14	47.46 ± 24.87
	ET	48.66 ± 6.92	55.22 ± 3.00	37.04 ± 12.04
	ETS	47.42 ± 9.94	54.96 ± 3.57	63.10 ± 21.66
Aerobic power (m/min)	C	21.61 ± 6.23	21.42 ± 3.22	20.63 ± 3.01
	Sh	20.82 ± 1.73	20.61 ± 0.68	10.43 ± 6.28
	S	20.03 ± 4.91	22.70 ± 2.44	23.51 ± 2.04
	ET	25.33 ± 2.02	27.16 ± 2.52	30.65 ± 4.38
	ETS	25.13 ± 0.83	24.92 ± 1.70	28.75 ± 1.48
Depression (immobility in seconds)	C	50.54 ± 42.90	43.19 ± 18.41	47.81 ± 25.43
	Sh	37.51 ± 17.21	36.62 ± 24.91	34.00 ± 26.30
	S	7.18 ± 3.81	6.50 ± 3.49	2.62 ± 4.26
	ET	24.21 ± 21.25	8.63 ± 12.56	17.00 ± 13.40
	ETS	10.10 ± 5.54	17.29 ± 15.79	14.75 ± 8.28
Pain tolerance threshold (seconds)	C	11.65 ± 4.61	7.49 ± 4.62	9.58 ± 3.03
	Sh	9.62 ± 4.46	4.75 ± 1.54	5.42 ± 1.60
	S	5.65 ± 2.92	11.30 ± 4.21	18.02 ± 9.23
	ET	9.77 ± 3.72	9.64 ± 5.84	11.40 ± 10.17
	ETS	10.51 ± 5.28	10.97 ± 4.82	20.42 ± 12.17

*** (P≤0.001) Significant increase compared to control group

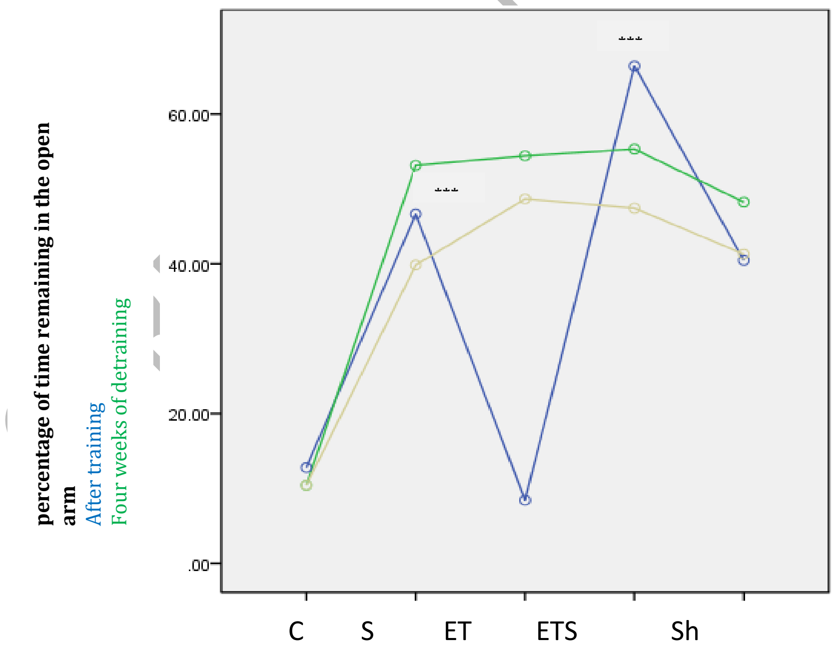

Figure 1. The percentage of time remaining in the open arm in the five research groups after end of training, two and four weeks of detraining followed by four weeks of endurance training and consumption of Salvia officinalis extract

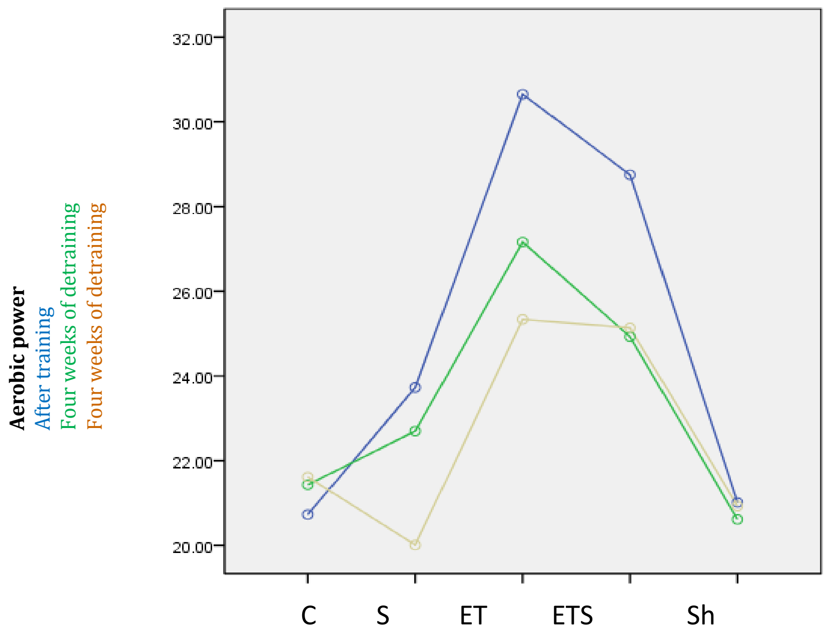

Figure 2. Aerobic power in the five research groups after end of training, two and four weeks of detraining followed by four weeks of endurance training and consumption of Salvia officinalis extract

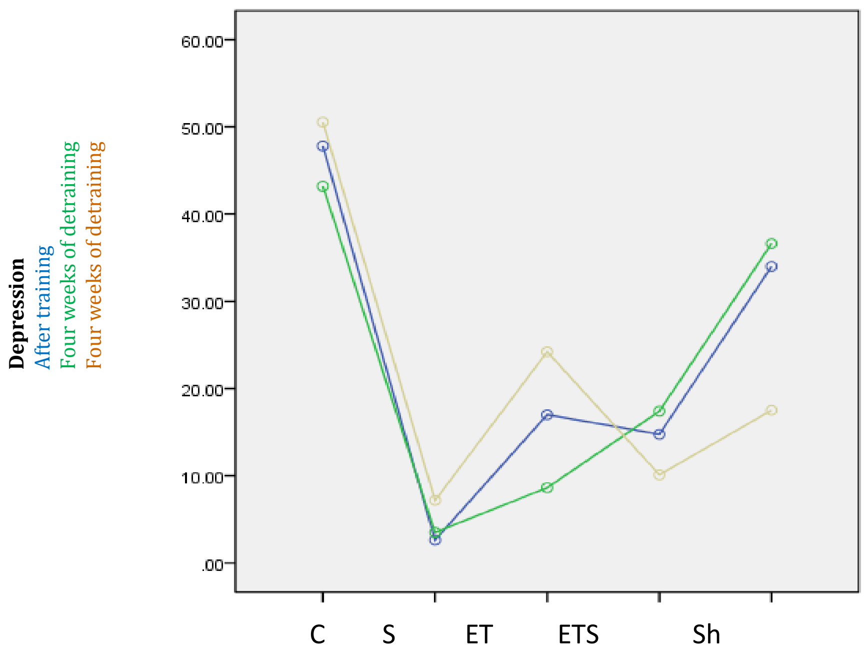

Figure 3. Depression (time of inactivity) in the five research groups after end of training, two and four weeks of detraining followed by four weeks of endurance training and consumption of Salvia officinalis extract

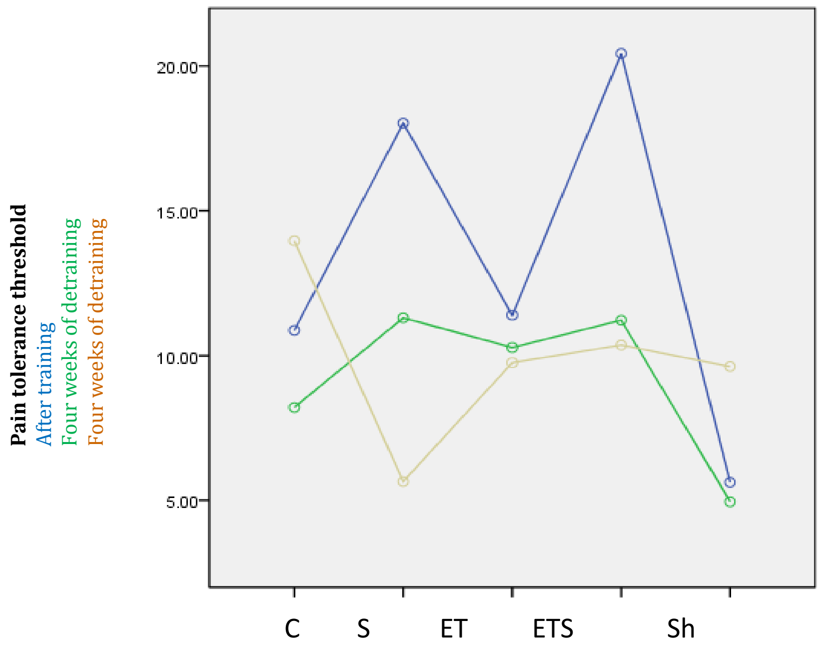

Figure 4. Pain tolerance threshold in the five research groups after end of training, two and four weeks of detraining followed by four weeks of endurance training and consumption of Salvia officinalis extract

Discussion

This study aimed to investigate the effects of two and four weeks of detraining, following four weeks of endurance training and Salvia officinalis consumption, on anxiety-like behaviors, aerobic power, depression, and pain threshold in rats. The results demonstrated that the percentage of time spent in the open arms (OA) was significantly higher in the Salvia officinalis extract, endurance training, and endurance training combined with Salvia officinalis groups after two and four weeks of detraining compared to the control group. Additionally, the percentage of time spent in the OA after four weeks of detraining was significantly lower than after two weeks of detraining.

There were no significant differences in aerobic power, depression levels, and pain tolerance threshold between the two- and four-week detraining periods following four weeks of endurance training and Salvia officinalis consumption. Anxiety is a natural response to psychological stress and encompasses behavioral, physiological, and cognitive components. It is a subjective experience that lacks a tangible external manifestation; however, it plays a crucial role in the interpretation of observable phenomena (19). Prolonged or excessive anxiety is commonly associated with physiological responses, including increased metabolic activity, suppression of immune function, and heightened cardiovascular workload. Moreover, a significant relationship exists between anxiety and mortality (19–22).

Exercise reduces the sympathetic nervous system's activity while enhancing the parasympathetic system's function. As a result of these physiological and neural adaptations, heart rate and blood pressure decrease, leading to improved alertness, enhanced mood, and increased energy levels, collectively contributing to better daily functioning and overall well-being. This physiological regulation plays a crucial role in promoting mental health (7). The observed discrepancies between the present findings and previous studies may be attributed to differences in the study population, exercise duration, and the specific types of physical activity employed. Aerobic exercise, as a non-pharmacological intervention, is efficacious in improving sleep quality and duration (23,24). Therefore, it is

recommended that aerobic exercise be incorporated as an intervention to reduce anxiety and enhance sleep quality in rats.
Consistent with the present study's findings, Motaghi et al. (2016) reported the anxiolytic and sleep-inducing effects of Salvia officinalis. Additionally, Sharifipour et al. demonstrated that Salvia officinalis significantly reduced anxiety levels in women during childbirth (25). In the elevated plus-maze (EPM) test, exploratory behavior drives rats to enter the open arms (OA). In contrast, anxiety-related avoidance of open, brightly lit, and elevated spaces encourages them to spend more time in closed arms (CA). Consequently, higher anxiety levels lead to a greater preference for the CA. Previous studies have further confirmed the anxiolytic effects of Salvia officinalis (4). The bioactive compounds in Salvia officinalis interact with γ-aminobutyric acid (GABA) receptors, functioning as negative, positive, or neutral allosteric modulators, and can influence the effects of other allosteric agonists (26).
A study on the flavones present in the methanolic extract of Salvia officinalis identified apigenin, hispidulin, sircimaritin, and the diterpene 7-methoxyrosmanol as compounds that bind to benzodiazepine receptors in the human brain. In the present study, the alcoholic extract of Salvia officinalis exhibited anxiolytic effects, which may be attributed to the biphasic action of flavonoids. Specifically, at low doses, flavonoids enhance GABAergic function, whereas at higher doses, they exhibit inhibitory effects (27,28). Other phytochemicals soluble in water and alcohol may reduce sleep onset latency by acting on GABAA receptors or through alternative regulatory mechanisms. In this regard, research has identified silyol, a flavonoid in Salvia guaranitica, as one of its key active compounds with sleep-inducing properties (29).
Furthermore, the interactive effect of exercise and Salvia officinalis on anxiety reduction after two and four weeks of detraining suggests that endurance training induces physiological adaptations that contribute to improved mental and physical well-being. These adaptations include increased muscle mass and plasma volume, enhanced pulmonary ventilation and blood circulation, greater cardiac reserve, elevated concentrations of muscle oxidative enzymes, and stimulation of hematopoietic factors. Collectively, these changes help mitigate mental and physical fatigue while promoting a greater sense of control, independence, and self-confidence (7).
The methanolic extract of Salvia officinalis leaves has been found to contain three flavones and two types of diterpenes that function as benzodiazepine receptor activators (30). Flavonoids, plant-derived compounds containing a phenyl-benzopyrone nucleus, can interact with ionotropic GABA receptors through various mechanisms. These compounds are believed to influence different modulatory sites on GABA receptors, thereby contributing to their anxiolytic effects (31). Regarding the lack of a significant effect of exercise and Salvia officinalis supplementation, the absence of differences observed after two and four weeks of detraining may be attributed to the principle of training reversibility. Detraining, a potential increase in caloric intake, and an imbalance between energy expenditure and consumption may lead to weight gain. As body weight increases, more significant energy expenditure is required for movement, imposing additional strain on the cardiopulmonary system (5). One of the limitations of the present study was the inability to precisely monitor the rats' food intake and spontaneous physical activity during non-training periods. Future research should aim to quantify daily food consumption and physical activity levels, alongside investigating the effects of exercise and inactivity to better understand their interactions.

Conclusion

Regarding the effects of Salvia officinalis (S) and endurance training (ETS) on depression, aerobic capacity, and pain tolerance threshold, the findings suggest that these two interventions do not interact. Although four weeks of Salvia officinalis supplementation and endurance training can effectively reduce anxiety-like behaviors, the subsequent two- and four-week detraining periods appear to lead to an increase in anxiety-like behaviors.

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