

Studying the Effect of Garlic Consumption and Endurance Training on Serum Levels of Some Pro-and Anti-inflammatory Cytokines in Female Mice with Breast Cancer - A Randomized Trial

Abstract

Background: This study aimed to determine the effect of garlic consumption and endurance training on the serum levels of some pro-inflammatory and anti-inflammatory cytokines in female mice with breast cancer. **Methods:** This study is an experimental research randomly conducted on 32 female BALB/c mice divided into 4 equal groups ($N = 8$), including: Cancer Control (CC), Garlic Supplementation (GS), Endurance Training (ET), Endurance Training + Garlic Supplementation (ET + GS). One million cancerous cells were injected to all mice's upper right thigh using the subcutaneous injection method. Exercise groups performed endurance training for 8 weeks (5 days a week). (Garlic supplement groups received 1 ml of the garlic extract orally per kilogram of body weight. The control groups -were not given any task, activity or exercise during the research. At the end of the research, all the mice were anesthetized, and their blood samples were collected. **Results:** The period of 8-week simultaneous endurance exercise and consumption of garlic supplement significantly decreased the serum level of interleukin-6 ($F = 75 P = 0.00$), interleukin-8 ($F = 97.9 P = 0.00$), and interleukin-17 ($F = 95.7 P = 0.00$), and increased the serum level of interleukin-10 ($F = 50.4 P = 0.00$). **Conclusions:** Along with other existing methods, reduction of inflammatory factors, endurance exercises and consumption of garlic supplement have been proved to be an extremely effective treatment for breast cancer patients.

Keywords: Breast cancer, cytokine, endurance training, garlic extract, inflammation, interleukin

Introduction

Breast cancer is the most common cancer among women in both developed and developing countries.^[1] Tumor proliferation and its malignancy can weaken the immune system of the body.^[2] In this regard, around 25% of cancers are associated with chronic inflammation derived from infection or inflammatory states of various sources.^[3] Inflammatory, anti-inflammatory cytokines and their receptors are key factors in cancer-induced inflammation. In fact, cytokines, including IL-6, IL-8, IL-10, and IL-17 affect leukocyte employment and function, cell proliferation, survival, tumor invasion and metastasis.^[4]

IL-6 is a pro-inflammatory cytokine playing a role in the growth of cancer and immune cells. The major sources of IL-6 production are leukocytes, monocytes and macrophages^[5] Large amounts of IL-6 have been reported in the breast, prostate and

serum tumors of cancer patients.^[6] IL-6 is the strong growth factor and promotes epithelial-mesenchymal phenotype (EMT) in breast cancer cells, implying that IL-6 is found in the tumor micro environment.^[7] IL-6 increases the expression of the vascular endothelial growth factor (VEGF), thereby contributing to the increased intravascular angiogenesis, which is a fundamental process in tumor growth.^[8]

IL-8 is classified as a cxc chemokine and contributes to white blood cell chemotaxis, especially neutrophils and lymphocytes, which stimulate and enhance angiogenesis.^[9] Interleukin-8 has various pro-inflammatory effects and is secreted by natural cells such as fibroblasts and monocytes. However, cytokines are secreted by diverse tumor cells such as the prostate, lung, breast, stomach, and uterus. Interleukin-8 is involved in angiogenesis, tumor progression, as well as cell invasion and is associated with metastatic

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phenotype.^[10] IL-17 is a pro-inflammatory cytokine produced by Th17 cells. Th17 cells play an essential role in autoimmune diseases and inflammation.^[11] The ability of IL-17 to recruit neutrophils accounts for the central role of neutrophilic of TH17 cells inflammation in adaptive immune reactions in which neutrophil inflammation is prominent. The production of interleukin 17 rapidly releases them from innate immune cells against pathogen or tissue damage.^[12] IL-17-producing cells are found mainly in uterine cancer, lung cancer, breast cancer, and prostate cancer.^[13] IL-17 enhances the VEGF production in cancer cells, and it is likely to be the possible mechanism of IL-17 in angiogenesis and tumor growth.^[14] IL-10 is an anti-inflammatory cytokine and primarily regulates the immune system limiting inflammatory reactions to tissue damage.^[15] The cytokine is produced by various immune cells such as TH2 cells, macrophages and CD8 cells, and is capable of inhibiting different immune and inflammatory responses.^[16] IL-10 inhibits macrophage activation and inhibits the expression of inflammatory mediators such as silico oxygenase-2 (COX-2), pro-inflammatory cytokines like interleukin-6 and 8 (IL-6 and IL-8), and tissue necrosis factor alpha. (α -TNF). Decreased IL-10 has antiangiogenic effects on many cancers.^[17] It inhibits the growth of breast tumors angiogenesis by preventing the growth of metalloproteases. IL-10 can be used as a diagnostic indicator for recurrence, metastasis and survival of breast cancer patients.^[18]

Researchers seek the best ways to cure and prevent cancer. Post-treatment is an integral part of medical achievement in this respect. One of the most effective ways to treat and prevent cancer is exercise. Exercise at high levels of intensity can play a crucial role in preventing cancers, chiefly breast cancer. In addition, as a powerful preventive agent, it reduces cancer by up to 40%.^[19] Exercise can make various changes in the immune system. Numerous studies have explored changes of cytokines during exercise under different conditions.^[20,21] Expression of cytokines during exercise is highly dependent on the type, intensity, duration, volume of exercise, and training period.^[22-24] During intense exercise, pro/anti-inflammatory cytokines (such as interleukin 6 and interleukin 10) increase and suppress or repress the immune function of the body.^[25] Regular exercise training has anti-inflammatory effects and restrains the system inflammatory with low degree.^[26] However, regular moderate-intensity training positively affects the efficiency of the body as well as maintenance of health and prevention of disease.^[27] Regular moderate-intensity exercise plays a key role in the prevention and more likely treatment of diseases such as hypertension, osteoporosis, diabetes and cardiovascular disease.^[28] Currently, researchers focus on other diseases that are associated with significant risk factors such as cancer and lifestyle-related diseases. Moreover, there is

also evidence indicating that physical activity helps to reduce the risk of cancer.^[29,30]

One of the influential factors on the immune system is the food used. Cancer is also one of the diseases closely associated with diet. Low-fat vegetable foods and high fibers are anti-cancer nutrients that help to strengthen the immune system in order to fight against cancer. Consumption of plants including *Sativum Allium* plays an integral role in improving the immune system as well as preventing a number of diseases. Its main crucial properties include antimicrobial, antithrombotic, anticancer, immune system modifier, and liver protector.^[31-33] This medical plant can stimulate the production of anti-inflammatory cytokines and inhibit pro-inflammatory cytokines. Therefore, it appears that physical activity, along with the consumption of plant foods such as garlic can lead to enhancement of the immune system and reduction of many diseases. Garlic is one of the most widely used medical plants. Its many beneficial effects, such as immunosuppressive and antimicrobial, anti-inflammatory and anti-tumor enhancing effects in laboratory and non-laboratory conditions, have led to formation of several compounds. This plant naturally cures all kinds of viral, bacterial and fungal infections, so that many researchers refer to garlic as an antibiotic component (34). Studies have indicated that garlic has antiviral effects against coxsackie viruses, HIV-1, human rhinovirus and vaccinia. Garlic extract can be effective in reducing the severity of influenza by improving the activity of immune cells. Additionally, the function of the immune system in these conditions will be less inflammatory.^[34] By inhibiting NF- κ B, garlic can impede the transcription of TNF- α , IL-12, IL-8, IL-6, and IL-1B cytokine genes, which are the most important factors in pre-inflammatory reactions. Moreover, stimulation of IL-10 production as an anti-inflammatory cytokine is another important effect. Other anti-inflammatory functions of garlic include inhibition of PGE2 and NO production in macrophages.^[35] According to the above-mentioned materials, the purpose of the present research was to determine the effect of the garlic extract and endurance training on serum levels of some anti/pro-inflammatory cytokines in female mice with breast cancer.

Methods

Animals

The present research was an experimental study. For this purpose, 32 female Balb/c mice (4-5 weeks old, average weight (15-20 g) were selected as a sample and examined in the Animal Laboratory of Isfahan University (Department of Biology). The mice were randomly divided into 4 equal groups (N = 8) including Cancer Control (CC), Garlic Supplementation (GS), Endurance Training (ET), Endurance Training + Garlic Supplementation (ET + GS). In the present study, policies regarding the protection of laboratory animals were observed.^[36] During the research,

Table 1: Endurance training schedule

Category	Training period	Speed (m/min)	Duration (min)	Duration (day per week)
1	Familiarization	10	20	5
2	First week	14	20	5
3	Second week	14	25	5
4	Third week	16	30	5
5	Fourth week	16	35	5
6	Fifth week	18	40	5
7	Sixth week	18	45	5
8	Seventh week	20	50	5
9	Eighth week	20	55	5

the test specimens were kept in the groups of 8 mice/c in polyethylene cages at an ambient temperature of 20 to 24 ° C, humidity of 45 to 55%, while maintaining a 12:12 h dark-light cycle. They were fed with both water and pellets. All procedures were approved by the Research Ethics Committee of the University of Isfahan (Ethics Identity: IR.UI.REC.1398.038).

Injection cancer cells

Initially, one million 4 T1 cancer cells were subcutaneously injected into the mice's upper right thigh. The mice rested for two weeks after the injection, so that the cancer cells were palpable and measurable at the injection site.

Training protocol

The experimental rats performed a week of familiarization with the laboratory environment and the endurance training (continuous treadmill running) at 10 m/min for 20 minutes. Afterward, the exercise protocol was performed for 8 weeks (5 days per week), and the training intensity was progressively increased. The first week of speed training was started from 25 minutes with the intensity of 12 m/min. It finally reached 55 minutes with 20 m/min intensity in the final week. In the present research, intensity of exercise was (70-55% VO₂ max) [Table 1].^[37]

Supplementation

Supplementation was orally-given garlic extract 5 times a week for 8 weeks (1 ml of garlic extract per kg of body weight).^[38] Both control and experimental groups received the same amount of saline. The control group was also kept in special cages during the study and did not participate in any exercise.

Sample preparation

To investigate the biochemical variables, the required amount of the blood sampling from the subjects' eyes was taken 24 h prior to the start of the training protocol and frozen at -70 ° C. Furthermore, 48 hours after the last training session and after 12 to 14 hours of fasting, rats became unconscious with the ratio of 5 to 2 by the intraperitoneal injection of ketamine and xylazine, and then

they were killed. Blood was exited from the rats' eyes and was immediately centrifuged for 5 minutes with 2000 rpm to separate them. Concentrations of cytokines (IL-6, IL-8, IL-10, IL-17) were quantitatively determined by the ELISA method using ELISA commercial kits (USA, Rat Eliza Kit, Assaypro co.) according to the manufacturer's instructions, and they were computed and measured in immunology laboratories.

Statistical analysis

Data were initially described using the Excel software as mean and standard deviation. Then, the statistical test assumptions were examined. Analysis of variance with repeated measures (RM-ANOVA) was used to examine changes in each of the research variables as well as the variation between different groups. The Bonferroni test was used to determine the significant difference between the groups. The significance level for all calculations was ($P < 0.05$), and all calculations were performed using the SPSS21 software.

Results

The results of the present study demonstrated that eight weeks of endurance training with garlic supplementation significantly ($P < 0.05$) decreased the serum levels of interleukin 6, interleukin 8, and interleukin 17, and it significantly increased ($P < 0.05$) the serum levels of interleukin 10. Table 2 presents the mean and standard deviation (IL-6, IL-8, IL-10, IL-17). The table shows the results of RMANOV. RMANOVA makes three comparisons, namely interaction, within, and between. The interaction comparison is the most important one, and when it is significant, it would be sufficient to focus on it. Table 2 demonstrates that interactions are significant for interleukin-6 ($F = 75 P = 0.00 \eta^2 = 0.93$), interleukin-8 ($F = 97.9 P = 0.00 \eta^2 = 0.94$), and interleukin-17 ($F = 95.7 P = 0.00 \eta^2 = 0.94$), and they increase the serum level of interleukin-10 ($F = 50.4 P = 0.00 \eta^2 = 0.90$). Figures 1-4 illustrate the detailed comparisons. They demonstrate that, during the study, control group had no progress, while the experimental groups made significant improvement.

The results of the post hoc test illustrated a significant decrease at IL-6, IL-8, and IL-17 serum levels in garlic supplementation and endurance training groups compared to other groups, but these changes were not significant in other three groups ($P > 0.05$). Furthermore, IL-10 was significantly increased in garlic supplementation and endurance training groups compared to the other groups, but the change was not significant in the other groups ($P > 0.05$).

Discussion

The results of the present study revealed that eight weeks of endurance training and garlic supplementation

Table 2: Patients' descriptive statistics and the result of repeated measure analysis of variance

Group	Variable	GS + ET	ET	GS	CC	Intraction	Within-subjects	Between-subjects
IL-6 (pg/ml)	Pre test	105.51±17.61	124.57±12.09	120.17±32.44	104.16±55.39	$F=75$ $P=0.00^*$	$F=221.8$, $P=0.00$	$F=0.85$, $P=0.50$
	Post test	70.64±14.26	90.12±12.72	106.25±27.37	111.27±57.95	$\eta^2=0.93$		
IL-8 (pg/ml)	Pre test	24.53±2.00	26.25±5.66	23.62±4.06	17.39±5.68	$F=97.9$ $P=0.00^*$	$F=170.4$, $P=0.00$	$F=0.70$, $P=0.59$
	Post test	12.32±2.27	16.12±4.31	20.09±3.19	22±7.08	$\eta^2=0.94$		
IL-17 (pg/ml)	Pre test	58.63±22.13	72.65±16.77	70.76±24.93	63.97±13.38	$F=95.7$, $P=0.00^*$	$F=253.8$, $P=0.00$	$F=0.92$, $P=0.46$
	Post test	39.31±18.81	57.76±16.66	62.42±23.5	68.34±13.13	$\eta^2=0.94$		
IL-10 (pg/ml)	Pre test	142.2±29.08	136.24±40.19	129.33±31.64	137.35±29.30	$F=50.4$ $P=0.00^*$	$F=151.8$, $P=0.00$	$F=1.80$, $P=0.16$
	Post test	175.5±33.57	159.49±42.19	143.29±34.47	129.56±27.15	$\eta^2=0.90$		

IL-6=interleukin-6, IL-8=interleukin-8, IL-17=interleukin-17, IL-10=interleukin-10, pg/ml=Picograms per millilitre. F = F value, P = P value, GS + ET=Endurance Training + Garlic Supplementation, ET=Endurance Training, GS=Garlic Supplementation, CC=Cancer Control

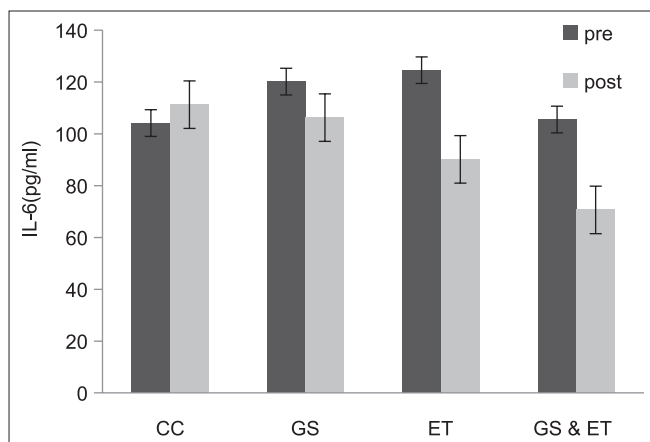


Figure 1: Changes in IL-6 in different groups. Cancer Control (CC), Garlic Supplementation (GS), Endurance Training (ET), Endurance Training + Garlic Supplementation (ET + GS)

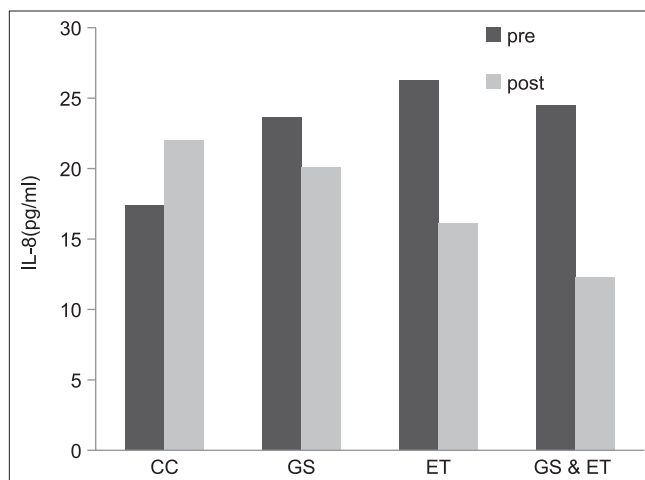


Figure 2: Changes in IL-8 in different groups. Cancer Control (CC), Garlic Supplementation (GS), Endurance Training (ET), Endurance Training + Garlic Supplementation (ET + GS)

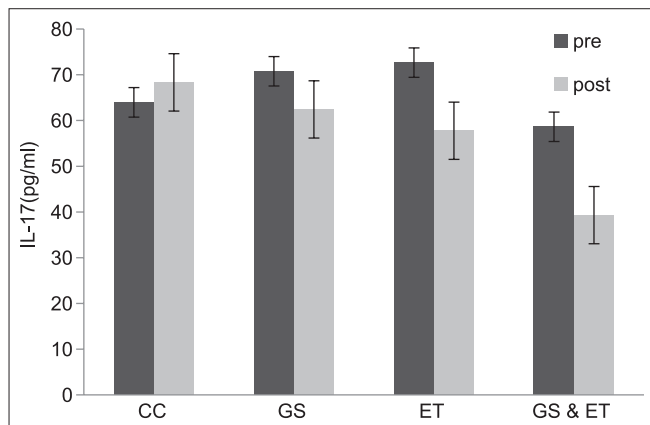


Figure 3: Changes in IL-17 in different groups. Cancer Control (CC), Garlic Supplementation (GS), Endurance Training (ET), Endurance Training + Garlic Supplementation (ET + GS)

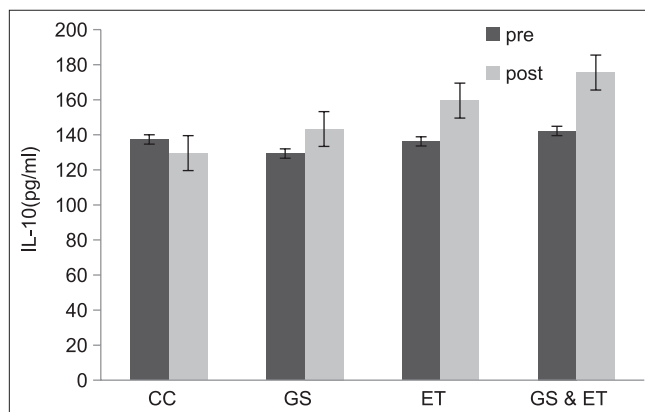


Figure 4: Changes in IL-10 in different groups. Cancer Control (CC), Garlic Supplementation (GS), Endurance Training (ET), Endurance Training + Garlic Supplementation (ET + GS)

significantly decreased the serum levels of (IL-6, IL-8, IL-17), ($P < 0.05$), and also significantly increased the serum level of IL-10 ($P > 0.05$).

In the present study, we explored the effects of endurance exercise as well as garlic supplementation on pro- and anti-inflammatory cytokines. Comparing the four groups of cancer control, garlic supplementation, endurance training,

and endurance training with garlic supplementation, it was found that after eight weeks, the level of pro-inflammatory cytokines was increased in the cancer control group (IL-6: 6/82%, IL-8: 26/5%, IL-17:6/83%), whereas the level of pro-inflammatory cytokines was decreased in the three following groups of garlic supplementation that consumed garlic supplement (IL-6: -11/58%, IL-8: -14/94%,

IL-17: -11/78%), endurance training (IL-6: -27/65%, IL-8: -38/59%, IL-17: -20/49%) and endurance training with garlic supplementation (IL-6: -33/04%, IL-8: -49/77%, IL-17: -32/95%). On the contrary, the level of anti-inflammatory cytokines was decreased in the cancer control group (IL-10: 67.5%), whereas it was increased in the three groups of the garlic supplementation, endurance training and endurance training with the garlic supplementation group, (IL-10: 79.10%), (IL-10: 17/06%) and (IL-10: 23/41%), respectively. Based on the above-mentioned results, it can be claimed that injection of cancer cells increased the inflammation, growth and tumor progression. Moreover, taking garlic supplements and endurance training can be effective factors in preventing inflammatory diseases like cancer. Combination of these two factors will have a far greater impact on preventing the disease. The IL-6 concentration was significantly decreased after eight weeks of exercise and garlic intake. Since IL-6 activates various signaling pathways such as NF-kB, JNK, ERK, and MAPK P38, which promotes angiogenesis and enhances tumor growth, thus endurance training can be a leading factor in reducing this factor and plays a central role in preventing tumor development and cancer. In this regard, Murphy *et al.* (2009), in their studies conducted on 26 Balb/C mice bearing breast cancer, concluded that exercise could decrease tumor progression in the mice. In addition, these effects may be at least partially associated with reduced inflammation (MCP-1 and IL-6).^[39] Similarly, in their research, Amani *et al.* (2014) stated that endurance exercise reduced IL-6 levels in tumor tissue. This decrease can lead to reduced angiogenesis within the tumor. They also concluded that lowering IL-6 levels due to exercise in addition to its preventive role was an adjunctive treatment for breast cancer.^[40]

The findings of the present research indicated that the IL-8 concentration was decreased after eight weeks of endurance exercise and garlic intake. In patients with cancers, over-expression of interleukin-8 is associated with increased tumor development and disease growth. In addition, there is a direct relationship between interleukin-8 levels and angiogenesis, tumor growth and metastasis.^[9] Overexpression of interleukin-8 and its receptors in cancer cells, endothelial cells, and macrophages is associated with tumors. Cytokine is a regulatory factor in the tumor microenvironment and is involved in angiogenesis, tumor progression, and cell invasion, associated with metastatic phenotype.^[41] Long-term activity with proper intensity can reduce the level of the pro-inflammatory cytokine and inhibit tumor growth and development. It can even prevent the detrimental effects of cancer. In this regard, other studies have confirmed the results of the present research. In their research, Kazemi *et al.* (2016) showed that the exercises did not significantly increase the serum IL-10 concentration. On the contrary, it decreased the serum IL-8 concentration and increased the number of

white blood cells.^[42] A'qaalinejad *et al.* (2014), in their study, demonstrated that endurance training with 55-75% VO₂ max intensity on 40 Balb/C mice significantly reduced the serum levels of pro-inflammatory IL-8 cytokines and decreased angiogenesis and tumor development.^[43]

The findings of the present study also signified that the serum IL-10 concentration increased after eight weeks of endurance exercise and garlic supplement intake. IL-10 is an immunosuppressive cytokine with anti-angiogenic effects. When breast cancer is concerned, it can act as a double-edged sword. Furthermore, its increased levels can promote tumor growth by protecting tumor cells before immune responses. Owing to its anti-angiogenic effects, it can suppress tumor growth and development. Indeed, it plays a protective role against the spread of tumor development. In general, the role of IL-10 in breast cancer appears to be mostly more supportive, and this cytokine prevents cancer cell proliferation and metastasis in the tumor environment.^[38] Moderate-intensity aerobic activity can enhance the anti-inflammatory cytokine, resulting in prevention and reduction of the effect of metastasis and cancer cells. In line with the present study, some studies have confirmed that the intensity and type of exercise can prevent angiogenesis and tumor growth. Denato *et al.* (2013), in their study, demonstrated that the levels of some cytokines after training increased the cytokines of TNF- α , IL-6 and IL-10, which led to tumor diminution.^[44] Similarly, Farrinha *et al.* (2015) reported that in obese women with metabolic syndrome, the IL-10 serum level was significantly increased after 12 weeks of endurance exercise.^[45] In another study, Farazandeh Nia *et al.* (2018) conducted a research on 28 obese male Wistar rats, and concluded that eight weeks of swimming training with garlic supplement intake could have a positive effect on inflammatory factors by increasing IL-10 and decreasing TNF- α .^[46]

Furthermore, the findings of the present study indicated that the serum concentration of IL-17 was significantly decreased after eight weeks of endurance exercise and garlic supplementation. Interleukin 17 affect tumor growth and development through various mechanisms such as the spread of angiogenesis in the tumor microenvironment via the STAT-3 signaling pathway and other mechanisms; it plays a role in boosting the blood flow to the tumor tissue. Moreover, IL-17 enhances the growth and angiogenesis of cancer tumors by increasing inflammatory and antigenic cytokines such as IL-8 and IL-6.^[11] Given that cytokine also has a mechanism similar to that of other pro-inflammatory cytokines, endurance activities can decrease the serum levels of interleukin-17, which ultimately reduces angiogenesis and tumor growth. Other studies have been conducted in this respect that their findings are consistent with those of the present study. For instance, in their research, Ahmadlu *et al.* (2019) found that these trainings could have a significant effect on the IL-17

depletion and the IL-18 expression in cadmium-poisoned mice.^[47] In another study, Gelzari *et al.* (2010) examined the impact of combined training on plasma IFN- γ , IL-4 and IL-17 levels in peripheral blood plasma and lymphocytes. They demonstrated that moderate-intensity endurance training reduced the production of plasma peripheral blood mononuclear cells (PBMC) IL-17 and IFN- γ in women with multiple sclerosis.^[48] Similarly, Heidarianpour *et al.* (2016) in their research explored the effect of 8-weeks moderate intensity exercise on the immune system. They suggested that moderate exercise could increase IFN- γ and decrease serum IL-17 levels in morphine-dependent mice. Thus, this type of exercise can improve the immune system function.^[49]

The findings of the present study also indicated that garlic supplementation without any exercise component after eight weeks could improve the immune system (but the decrease in the serum levels of IL-6, IL-8, and IL-17 and the increase in serum IL-10 levels were not significant). Consumption of food made of plants and vegetables such as garlic plays an important role in improving the immune system as well as preventing a number of diseases. Owing to the many beneficial effects of garlic, some researchers maintain that it is like an antibiotic and is highly effective in curing various diseases and cancers. Various beneficial effects of garlic, such as the antimicrobial, anti-inflammatory and anti-tumor enhancing effects, produce numerous compounds of this nutritional supplement under *in vitro* and *in vivo* conditions. The plant naturally cures various viral, bacterial, and fungal infections, where many researchers have introduced garlic as an antibiotic.^[34] Through the inhibition of NF- κ B, garlic can inhibit the transcription factors of the genes of TNF- α , IL-12, IL-8, IL-6, IL-1B, IL-17 cytokines, which are the most vital factors of pro-inflammatory reactions. Stimulation of IL-10 production as an anti-inflammatory cytokine is also another chief impact of garlic. Other anti-inflammatory functions of garlic include inhibition of PGE2 and NO production in macrophages.^[35] In this respect, other studies have been conducted that are in line with the present study. For example, Alizadeh Navaei *et al.* (2018) investigated the effect of garlic extract on cancer patients. They illustrated that garlic consumption could reduce gastric cancer mortality.^[50] Damirchi *et al.* (2010) demonstrated that 14 days of garlic extract consumption could counteract antioxidant capacity by reducing free radical production after exhaustive aerobic activity. It also decreases undesirable changes in the oxidative processes induced by aerobic exercise in athletes.^[51]

Conclusions

The findings demonstrated that eight weeks of endurance training and garlic consumption significantly decreased the serum levels of IL-6, IL-8, and IL-17, and significantly increased the serum levels of IL-10. Therefore, regular moderate intensity exercise is a leading factor playing

a crucial role in improving the health and performance of athletes as well as preventing inflammatory diseases. Additionally, plant foods containing antioxidant fibers and compounds can boost the immune system and reduce many diseases. In other words, they can lead us to a healthier life. Hence, they can be considered, along with other treatments as an adjunct remedy to treat many inflammatory diseases like breast cancer.

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Conflicts of interest

There are no conflicts of interest.

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