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ORIGINAL ARTICLE

Plasma retinol-binding protein-4 and tumor necrosis factor-α are reduced in postmenopausal women after combination of different intensities of circuit resistance training and Zataria supplementation

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Abstract

Purpose *Zataria* is a plant with anti-inflammatory properties, which has been used for the treatment of many diseases. This study investigated the effect of different intensities of circuit resistance training and *Zataria* supplementation on plasma retinol-binding protein-4 (RBP-4) and tumor necrosis factor-α (TNF-α) in postmenopausal women.

Methods Seventy-two postmenopausal women were divided on randomized order into six groups: Control (McGinley and Bishop in J Appl Physiol 121(6):1290–1305, 2016), Training 35% (T35%), Training 55% (T55%), Zataria (Özgünen et al. in Scand J Med Sci Sports 20:140–147, 2010), Zataria/Training 35% (ZT35%), and Zataria/Training 55% (ZT55%). Resistance training program included 12 exercise stations (each: 30 s, intensity: 35% and 55% of 1-RM) for 8 weeks (3 sessions/week). Daily (500 mg) *Zataria* was used after breakfast by participants in *ZG*, ZT35%, and ZT55% groups. Blood samples were taken 48 h before and after the first and last sessions of training.

Results After the training period the percentage of body fat decreased significantly ($P < 0.001$) in all trained groups, whereas muscle mass increased significantly ($P < 0.01$) only in T55% and ZT55% groups. A significant decrease was observed for RBP-4 values ($P < 0.05$) after training in all groups except for ZG and CG. Also, RBP-4 was significantly lower ($P < 0.05$) in all groups as compared to CG at the post-test except for ZG. Moreover, significantly lower values ($P < 0.05$) were found in T55%, ZT35%, and ZT55% as compared to ZG in post-intervention. TNF-α values decreased significantly ($P < 0.05$) at the post-test as compared to pre-intervention in ZT35% and ZT55%. Also, TNF-α was significantly lower ($P < 0.05$) in ZT55% compared to CG and T35% in post-test

Conclusions The results demonstrate clearly that in postmenopausal women, circuit resistance training both at low and moderate intensities cause a greater reduction in RBP-4 and TNF-α when *Zataria* is supplemented in the diet during training.

Keywords Strength training · Herbal supplementation · Retinol-binding protein-4 (RBP-4) · Tumor necrosis factor-α (TNF-α) · Women

Introduction

Menopause in women is a reproductive phenomenon associated with aging. Studies have shown that it significantly increases the likelihood of diseases, such as obesity, metabolic syndrome, type 2 diabetes mellitus, and cardiovascular disease in women [1].

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The development of abdominal obesity and as a result increased incidence of metabolic syndrome and type 2 diabetes mellitus in women after menopause are mainly associated with the loss of the protective role of estrogen and a relative increase in androgen circulation [2]. On the other hand, intra-abdominal fat produces substances that affect inflammatory responses, cause insulin resistance, and increase cardiovascular diseases' risk. Some of the substances that are directly produced by fat cells are known as adipokine [3]. Specific to this study, retinol-binding protein-4 (RBP-4), an adipokine, is derived from adipocyte. Studies have confirmed the relationship between the circulation level of RBP-4 and various aspects of obesity [4, 5] and metabolic syndrome [5]. Furthermore, increased RBP-4 in the serum increases hepatic expression of the gluconeogenic enzyme (phosphoenol-pyruvate carboxykinase) and causes impairing insulin signaling in muscles. Therefore, it would be beneficial to reduce insulin sensitivity (resistance) and risk factors related to cardiovascular diseases in high-risk patients if RBP-4 can be reduced [6].

Tumor necrosis factor-α (TNF-α) can regulate many cellular and biological processes, such as immune function, cell differentiation, proliferation, apoptosis, and cell metabolism. TNF-α released from lipid tissue can lead to dyslipidemia and other metabolic disorders as well as through stimulation of insulin resistance of adipocytes can impair glucose uptake in adipocytes [7]. Studies have reported increased levels of TNF-α in obesity, while weight loss through diet and/or exercise has been associated with a reduction in levels of TNF-α [8].

Healthcare providers recognize the importance of exercise in reducing inflammation and inflammatory factors [9]. Recently, resistance training or weight training has become a prevalent exercise method to improve health and body composition (i.e., increase muscle mass) [10]. Furthermore, it has been suggested that high-intensity resistance training may compensate for the reduction in bone mass and muscle strength in age-related changes found in postmenopausal women [11, 12].

On the other hand, the combination of diet and exercise adjustment can have a positive effect on health-related quality of life more than anyone intervention alone [13]. In particular, nutrient supplementations are extremely popular and are used as adjunctive therapy in the aging population. One such popular supplement in some cultures is *Zataria*. *Zataria* is a plant belonging to the *Labiatae* family with the scientific name *Zataria multiflora* [14]. *Zataria* is used as a tea, spice, and herbal medicine for treatment of asthma and is used as an antiseptic of the stomach and urinary tract as well as diuretic and anti-inflammatory in traditional medicine [15]. Research showed that compounds containing *Zataria* are able to inhibit inflammatory reactions' mediators and serve as an antioxidant, antispasmodic, and anti-pain [16]. Recently, in animal models, thymol and carvacrol, found in *Zataria*, have been demonstrated as bioactive compounds, which reduce pro-inflammatory and increasing anti-inflammatory cytokines [6, 17]. It seems that the combination of high-intensity resistance exercises and *Zataria* supplementation may have beneficial effects on systemic inflammation, antioxidant defense and ultimately induces well-being [18, 19]. However, to the best of our knowledge, the effects of low to moderate intensities of resistance training accompany with *Zataria* supplementation have not been studied yet. Therefore, the purpose of the present study was to investigate the potential additive effects of 8 weeks of low (35% 1-RM) and moderate (55% 1-RM) intensities of circuit resistance training along with *Zataria* supplementation on plasma RBP-4 and TNF-α levels in postmenopausal women.

Measurements

Eighty-eight postmenopausal women volunteered from throughout public centres and offices in Tehran. A gynecologist examined all volunteers prior to entry into the study. Before participating in the study, all procedures were explained to volunteers and written informed consent was obtained. Among the 88 potential participants, 72 within the age range of 48–65 years were selected after being reviewed by a cardiologist. These selected research participants were divided into six equal groups (for each, $n = 12$): Control [20], Training 35% (T35%), Training 55% (T55%), *Zataria* [21], *Zataria*/Training 35% (ZT35%), and *Zataria*/Training 55% (ZT55%). This study was approved by the Education Ethical Research Committee of Babol University of Medical Sciences, Iran and was conducted in accordance with the Declaration of Helsinki.

Anthropometric measurements

The following anthropometric measurements were recorded: height (accuracy of 0.1 cm; Hotain, UK) and body mass (0.1 kg; Tanita BF683W, Munich, Germany). Body mass index was calculated as weight (kg) divided by height^2 (m). An estimation of total body fat and muscle mass was obtained by bio-impedance body composition analyzer (Medigate Company Inc., Dan-dong Gunpo, Korea).

GC–MS

Zataria leaves were collected in March around the gardens of Eghlid, Shiraz, Iran. Then, they were dried in the shade for 10 days. *Zataria* leaves were dried in an oven for 48 h at a temperature of 32 °C and then made into powder in a Chinese pounder. 50 g of the sample powder was extracted for 3 h using water distillation method in Clevenger and at a boiling point. The essential was filtered, then dried on anhydrous sodium sulfate, and finally transferred into a glass container with a lid closed and stored at 4 °C. The essential yield was calculated as dry essential volume divided by the initial dry powder weight multiplied by 100. The yield calculated was 3% [22]. To isolate and identify components of *Zataria* essential oil, GC–MS was used. GC–MS analysis was done using the Agilent 5975 mass spectrometer detector (MSD) coupled with gas chromatography model of Agilent USA GC 7890A MS 5975C. The column used was of welded silica HP-5 (5% phenyl, 1.95% polydimethyl siloxane) with a profile of 30×0.25 mm^2 id and the film thickness of 0.25 μm. Helium was used for carrying gas and flow rate of the gradient was 1 ml/min. The thermal program used was as follows: first column temperature was set at 50 °C for 5 min, then increased at 3 °C per minute to 240 °C, then increased at 5 °C per minute to 300 °C, and finally set for 3 min at this temperature. Essential oil samples stored were diluted by n-hexane at a ratio of 1:10 and 1 µl was injected in gas chromatography. The temperature at the injector and detector was fixed at 290 °C. Compounds in *Zataria* essential oil were identified using fragmentation pattern in the database of wiley7n land NIST08 and also using retention time in chromatography column [18, 19]. For each combination, the ratio of the level below the peak was determined to the total levels below the peak of all compounds and the results are summarized in Table 1.

Supplementation

500 mg of dry *Zataria* [18, 19] leaves and powder was placed in capsules via a Chinese oven and readied for use. In a double-blinded fashion, the ZG, ZT35%, and ZT55% groups received 500 mg of *Zataria* every day after breakfast, one capsule (500 mg) with 100 ml of water. CG, T35%, and T55% also consumed 100 ml of water with placebo capsules (500 mg capsule) after breakfast.

Resistance training

Exercise instructions were given before the circuit resistance training began to insure that participants became familiar with the environment and exercises (1 week). Next, one repetition maximum (1RM) for each of the exercises was determined. Exercises included: (1) squat, (2) chest press, (3) leg press, (4) standing military press, (5) knee extension, (6) seated cable rowing, (7) knee Curl, (8) biceps curl, (9) standing calf raise, (10) triceps press, (11) back extension, and (12) crunch [18, 19]. The 1RM for each exercise was calculated using the Brzycki equation method. Participants in T35% and ZT35% performed the training movements with 35% of 1RM, whereas participants in T55% and ZT55% performed the same training movements with 55% of 1RM, for 8 weeks (three sessions per week). Each resistance training session included 5 min warm-up followed by 12 stations with duration of 30 s for each station. In each session, two sets (turn) of 12 movements were carried out such that between each turn, there was a 3 min active rest [23].

Blood samples were taken from a forearm vein in a sitting position; specifically, 48 h before the beginning of training procedure and 48 h after the last training session and specimens were placed in test tubes containing EDTA and sterile tubes without anticoagulant. Then, specimens were spun at 3000 rpm for 10 min by centrifugation. Obtained plasma was used for the separate analysis of RBP-4 and TNF-α. RBP-4 and TNF-α of plasma were measured using commercial ELISA kits of Abcam Co., (Cat. No. ab108897 and ab46087) with a sensitivity of 6 ng/mL and 10 pg/mL by ELISA method, respectively.

Table 1 Compounds of Zataria multiflora

Compound	Inhibition time (min)	Under peak level (%)
Thymol	35.90	26.8
Carvacrol	36.50	22.9
p-cymene	21.73	7.7
γ-Terpinene	23.55	6.8
α-Pinene	16.53	3.2
β-Caryophyllene	41.36	3
Carvacrol methyl ether	32.86	2.4
α-Terpinene	21.12	2.2
Spathulenol	47.96	2
Linalool	25.59	1.8
β-Myrcene	19.60	1.5
Total	–	80.3

Statistics

Kolmogorov–Smirnov and Leven tests were used to determine the normality of data and homogeneity of variances, respectively. To compare data of the six groups, analysis of covariance (ANCOVA) was used. A paired *t* test was used to assess the differences in measured variables pre- and post study in each group separately. Alpha was considered at the level of 0.05. All data were analyzed using software SPSS.

Results

Demographic parameters

Body mass and BMI decreased significantly at the post-test in ZT35%, T55%, ZT55% compared to the pre-test (Table 2). Similarly, the percentage of body fat decreased significantly after the training period in ZG, T35%, ZT35%, T55%, ZT55% (Table 2). In contrast, muscle mass increased significantly in T55% and ZT55% compared to pre-test (Table 2). After training, the percentage of body fat was significantly lower ($P < 0.05$) in all groups in comparison with CG, except for ZG and T35% (Table 2). Similarly, muscle mass was significantly higher in ZT55% in comparison to ZG (Table 2).

RBP-4

RBP-4 significantly decreased ($P < 0.05$) at post compared to pre in all groups except for ZG ($P = 0.201$) and CG

Table 2 Demographics parameters of participants volunteering in the study at pre- and post-test evaluations

Groups	Age (years)	Height (cm)	Body mass (kg)	BMI (kg/m^2)	Body fat (%)	Muscle mass (kg)
Control						
Pre	56.5 ± 4.2	156.7 ± 2	68.7 ± 5.9	27.9 ± 2.2	20.6 ± 1.7	27.6 ± 2.5
Post	–	–	68.7 ± 4.7	27.9 ± 1.8	20.5 ± 1.6	27.6 ± 2.3
ZG						
Pre	54.4 ± 3.9	160.9 ± 2.9	66.4 ± 6.4	25.6 ± 2.2	19.9 ± 1.9	26.5 ± 2.5
Post	–	–	65.9 ± 5.1	25.4 ± 1.6	18.6 ± 1.4$^{#¥}$	26.8 ± 2.1
T35%						
Pre	57.7 ± 3.6	158.1 ± 2.2	69.3 ± 6.7	27.8 ± 2.9	20.7 ± 2	27.7 ± 2.7
Post	–	–	67.5 ± 3.9	27.0 ± 1.7*	18.7 ± 1.2$^{###¥}$	28.7 ± 1.6
ZT35%						
Pre	55.8 ± 4.5	155.5 ± 2.5	66.8 ± 6.5	27.6 ± 2.7	20 ± 1.9	26.7 ± 2.6
Post	–	–	64.4 ± 5$^{#}$	26.6 ± 1.9$^{#}$	17.5 ± 1.4$^{***###}$	27.8 ± 2
T55%						
Pre	58.0 ± 4.7	158.7 ± 2.4	67.1 ± 7.2	26.7 ± 3.1	20.1 ± 2.1	26.8 ± 2.8
Post	–	–	64.3 ± 5.6$^{#}$	25.6 ± 2.3$^{#}$	17.1 ± 1.9$^{***###}$	28.4 ± 2.2$^{#}$
ZT55%						
Pre	53.8 ± 6	159.2 ± 3.2	69.9 ± 5.7	27.6 ± 2.7	21.0 ± 1.4	28.0 ± 1.9
Post	–	–	67.0 ± 4$^{##}$	26.4 ± 2.1$^{##}$	18 ± 1.1$^{**###}$	29.5 ± 1.9$^{###£}$

T training, *ZG* Zataria multiflora

$^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P \leq 0.001$ versus control at post-test

$^{#}P < 0.05$, $^{##}P < 0.01$, $^{###}P < 0.001$ versus pre-test in same group

$^{£}P < 0.05$ versus ZG at post-test

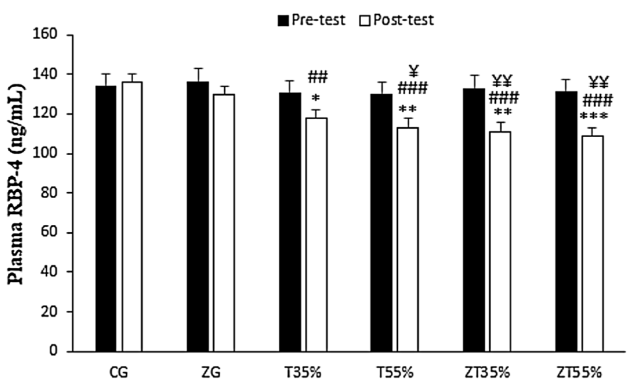

Fig. 1 Plasma RBP-4 in pre- and post-test in all groups. *CG* control group, *ZG* Zataria group, *T35%* training 35% group, *T55%* training 55% group, *ZT35%* Zataria/training 35% group, *ZT55%* Zataria/training 55% group. Data are expressed as means ± SD. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ versus pre-test in same group. $^{##}P < 0.01$, $^{###}P < 0.001$ versus CG in post-test. $^{¥}P < 0.05$, $^{¥¥}P < 0.01$ versus ZG in post-test

($P = 0.596$) (Fig. 1). There was no significant difference in RBP-4 between any of the groups at pre ($P = 0.860$). A significant difference was noted in RBP-4 between groups at post ($P < 0.001$), with RBP-4 which was significantly lower in all groups as compared to CG post, except for ZG ($P = 0.819$) (Fig. 1). Moreover, significantly lower values were noted in T55%, ZT35%, and ZT55% as compared to ZG at post (Fig. 1). However, we found no evidence that performing the circuit resistance training at 55% of 1RM was more effective than performing the movements at 35% of 1RM in decreasing post-RBP-4 levels (T35% and T55%, $P = 0.931$). Similarly, no significant effect was found between the combinations of two training intensities with *Zataria* supplement in decreasing RBP-4 post (ZT35% and ZT55%, $P = 0.996$).

TNF-α

TNF-α values significantly ($P < 0.05$) decreased post as compared to pre in the ZT35% and ZT55% groups (Fig. 2). There was no significant difference in TNF-α between any of the groups at pre ($P = 0.300$). A significant difference was noted in TNF-α between groups at post ($P = 0.002$), with TNF-α which was significantly lower in ZT55% as compared to CG and T35% at post (Fig. 2). However, again we found no evidence that performing the circuit resistance training movements at 55% of 1RM was more effective than performing these movements at 35% of 1RM for TNF-α post (T35% and T55%, $P = 0.901$). Similarly, no significant effect was found between combinations of the two training intensities with *Zataria* supplement in decreasing TNF-α post (ZT35% and ZT55%, $P = 0.187$).

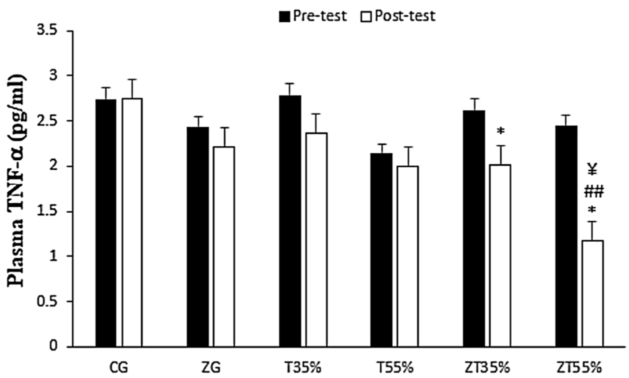

Fig. 2 Plasma TNF-α in pre- and post-test in all groups. *CG* control group, *ZG* Zataria group, *T35%* training 35% group, *T55%* training 55% group, *ZT35%* Zataria/training 35% group, *ZT55%* Zataria/training 55% group. Data are expressed as means ± SD. *$P < 0.05$ versus pre-test in same group. ##$P < 0.01$ versus CG in post-test. ¥$P < 0.05$ versus T30% in post-test

Discussion

In this study, we examined the effects of 8 weeks of circuit resistance training at different intensities along with *Zataria* supplementation on plasma levels of RBP-4 and TNF-α in postmenopausal women. The main findings show that performing circuit resistance training, both at low and moderate intensities, and consuming *Zataria* induce positive effects on RBP-4 and TNF-α levels in postmenopausal women. In addition, a significant decrease was observed in BMI and the percentage of body fat. The reduction in BMI and body fat percent associated with potential anti-inflammatory effects of exercise [24] that makes circuit resistance training and *Zataria* supplementation as an appropriate method for the improvement of health.

In the present study, circuit resistance training, both at low and moderate intensities, induced a significant decrease of BMI and percentage of body fat, and an increase in muscle mass. These results are in accordance with other previous studies [25–27] investigating the effect of high-intensity circuit resistance training.

Our findings showed that the RBP-4 values significantly decreased at the post as compared to pre in all groups except for ZG. Additionally, RBP-4 was significantly lower in all groups as compared to CG in the post except for ZG. Increased plasma RBP-4 is one of the factors associated with the development of glucose intolerance disorder and diabetes in human and animal samples. Research has shown that exercise training in sedentary people and those with impaired glucose tolerance and diabetes caused a reduction in RBP-4 concentration and overall body weight [10]. Although, some conflicting results have been reported on changes in plasma levels of RBP-4 after doing different exercise training programs. For instance, Souri, Hasani Ranjbar and Vahabi [28], in patients with type-2-diabetes showed that 8 weeks of alternative aerobic exercise programs with the intensity of 70–85% of maximum heart rate significantly decreased the RBP-4, cholesterol, triglycerides, and low-density lipoprotein (LDL), as well as a significant relationship, was observed between baseline levels and changes in RBP-4. In addition, low levels of RBP-4 and triglycerides were associated with improved insulin resistance and increased insulin sensitivity [28]. But another study on obese women showed that 12 weeks of combined aerobic and resistance exercise (aerobic exercise with an intensity of 60–75% of maximum heart rate and resistance exercise with an intensity of 50–70% of one repetition maximum) did not lead to significant changes in plasma levels of RBP-4 [29]. It seems changes in plasma levels of RBP-4 (reduction or no change) in adaptation to training is more closely related to changes in body weight and fat percentage [28–30], BMI, waist to hip ratio [29], as well as lipid profile [29, 30]. Along this line, a significant decrease in BMI and percentage of body fat was observed in the training groups that can, at least in part, explain the results of the current study.

Our finding also showed that the RBP-4 was significantly lower in T55%, ZT35%, and ZT55% as compared to ZG post (Fig. 1). *Zataria* has several active compounds; the main ones are thymol and carvacrol. The cumulative beneficial effects of the supplement are attributed to these compounds that can lead to the prevention of fat deposit in vessels [31]. Furthermore, *Zataria* has terpenoids and flavonoids compounds like other plants of Lamiaceae family, which in addition to reducing hyperglycemia effect can cause a reduction in overall levels of blood triglycerides too. In addition, *Zataria* has a very high antioxidant feature, which aids in a reduction in blood lipid as well as plays a role in inhibiting LDL production [17]. Thus, considering the significant relationship between RBP-4 changes and potential changes in levels of blood triglycerides, it seems that *Zataria* may also reduce dyslipidemia, which can cause a reduction in RBP-4 levels.

Our finding showed that the TNF-α values significantly decreased post-intervention as compared to pre in the ZT35% and ZT55% groups (Fig. 2). Additionally, TNF-α was significantly lower in ZT55% as compared to CG and T35% at post (Fig. 2). A main attribute of the cytokine TNF-α is a fast acting agent. Increased serum level of this TNF-α induces increase in resting energy metabolism and as a result whole body weight loss occurs. This cytokine acts according to its target tissue receptor, which can vary, so the physiological action depends entirely on the type of target cells. TNF-α is considered as the main factor in disorders related to glucose and insulin metabolism because it is expressed more in lipid tissue and muscles of obese people and may inhibit insulin action in a multitude of tissues (i.e., resistance) [32]. However, it remains unclear whether the chronic presence of low concentration of TNF-α may inhibit insulin action as changes observed in insulin sensitivity have been detected as the main factor associated with RBP-4 changes. In general, it is well established that the role of exercise in increasing insulin functionality occurs by reducing the accumulation of intracellular triglyceride, increased fatty acid oxidation, and improving mitochondrial biogenesis [32]. It is thought that TNF-α produced through fatty tissue may locally affect insulin act by the autocrine or paracrine method and then be released into the serum where it may have endocrine actions [33]. Exercise can directly reduce cytokines' production in lipid tissue, muscle, and mononuclear cells and thus indirectly increase insulin sensitivity and improve endothelial function. Hence exercise training causes protection against insulin resistance caused by TNF-α. It also leads to reduced levels of TNF-α and IL-6 and increased levels of anti-inflammatory cytokines, such as IL-4 and IL-10 [34]. Reduced TNF-α as a result of exercise training may also be a result of IL-6-dependent and non-dependent paths [35, 36]. Weight loss caused by doing training leads to reduced volume and the number of adipocytes and reduced number of macrophages and endothelial cells. Increased production of anti-inflammatory mediators by adipocytes and production of hepatic fibrinogen and other pre-inflammatory mediators are other results of weight loss caused by training. However, the mechanism of the effect of circuit resistance training on reducing inflammation is not fully known. It seems that intensive resistance training results in a significant reduction in plasma levels of TNF-α, even if no tangible and significant change is observed in body composition and body fat mass. Results showed that doing a combination of aerobic and resistance training with high intensity for 12 months as compared to aerobic training alone reduces the levels of TNF-α more [37]. An important feature of the present study is that the body weight of subjects is the same as before the start of the study. This makes the effect of exercise separate from the effect of changes in body weight-mass alone. Also, there is a relationship between physical activity and physical fitness and lower inflammation independent of adiposity (i.e., obesity) [38]. Thus, according to the present study, which used matched subjects, it seems there are other mechanisms by which physical activities cause a reduction in inflammation.

In addition to the positive role of resistance training on the reduction of inflammatory factors, such as reducing the values of TNF-α and RBP-4 in-group exercise, when *Zataria* intervention was added to the study; the effect of exercise was essentially doubled and caused further reduction in these two indices. *Zataria* is a herb that has a very high antioxidant feature, and its anti-inflammatory and oxidative anti-stress effects have been well reported [39]. In regard to the reduced levels of RBP-4 and TNF-α, in the present study, it seems that consuming *Zataria* essence along with doing resistance exercise can be effective in reducing inflammatory and injury-causing factors and the prevention and treatment of a variety of chronic inflammatory diseases, such as cardiovascular diseases and diabetes. However, we did find no evidence that the performing movements of circuit resistance training at 55% of 1RM were more effective than that of circuit resistance training at 35% of 1RM in decreasing RBP-4 in post-test. Similarly, no significant effect was found between combinations of two training intensities with *Zataria* supplement in decreasing both the RBP-4 and TNF-α in post-test. Taken together, these results suggest that improvements in RBP-4 and TNF-α can apparently be obtained by adding a herbal supplement such as *Zataria* to an exercise program, with no clear discernable effect of exercise intensity.

Conclusion

Our findings showed that there is a positive effect of performing circuit resistance training, both at low and moderate intensities (35 and 55% 1-RM), and consuming *Zataria* on RBP-4 and TNF-α levels in postmenopausal women. In fact, *Zataria* supplementation during a low moderately intense resistance training program is an effective adjunctive therapy to reduce metabolic disorders and abnormalities related to hyper-insulinemia, glucose resistance, and inflammatory factors resulting from menopause and a sedentary lifestyle. However, further research studies are needed to fully investigate the underlying mechanisms of our observations.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved under the procedures of the local Ethics Committee. All procedures were carried out in line with the Declaration of Helsinki.

Informed consent All participants gave written informed consent before participating in the study.

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