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Original Article

The Effect of Combined Exercise Training with Zataria Multiflora on RBP-4 and Resistin Levels in Sedentary Women: a Randomized Double-blind Clinical Trial

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Abstract

Background: Exercise training and zataria multiflora exert anti-inflammatory effects alone and together; these anti-inflammatory effects are partly related to modulating adipokines secretion from adipose tissue. This research aimed to investigate the effect of combined training (aerobic-resistance) and zataria multiflora supplementation on serum resistin and retinol binding protein 4 (RBP-4) in sedentary women.
Methods: The present randomized clinical trial, under the registration number IRCT20200812048388N1, was conducted in the winter and spring of 2021. The participants included 40 overweight and obese women who were assigned in four groups (10 women in each group), namely combined training with zataria multiflora (TZ), combined training (T), zataria multiflora (Z), and placebo (C) groups. Each combined training session consisted of 30 min of aerobic exercise, followed by 30 min of resistance exercise. Zataria multiflora supplement was also consumed at 500 mg daily. We carried out blood sampling before and after (48 hours after the last training session) the intervention period and measured the serum levels of RBP-4 and resistin via ELISA method. For data analysis, the SPSS software version 24, and analysis of covariance (ANCOVA) with Bonferroni post-hoc tests were used.
Results: We observed a significant decrease in RBP-4 levels of T compared to that of C group ($P=0.045$), and in TZ compared to C and Z groups ($P<0.001$). In addition, the obtained findings indicated a significant decrease in resistin of T compared to that of C group ($P=0.046$), and in TZ group compared to C and Z groups ($P<0.001$). In addition, there was a significant decrease in HOMA-IR of T and TZ groups compared to that of C and Z groups ($P<0.05$).
Conclusion: According to the results, Zataria multiflora supplementation amplified the anti-inflammatory properties of combined training and combined training effect in insulin resistance improvement. Furthermore, it was found to have a synergistic effect along with combined training.

Keywords: Exercise training, Adipokines, Inflammation, Resistin

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1. Introduction

The prevalence of obesity is increasing remarkably worldwide and has become a major health concern over the last decades (1). Obesity has adverse effects on health and leads to an increased risk of different complications, including cardiovascular disease, diabetes, and hypertension (2). A number of researchers have introduced adipokines (adipose tissue secretory factors) as a main link between obesity and its associated diseases (3). In support of this hypothesis, it was reported that adipose tissue is a large secretory and endocrine body organ, which can secrete different types of adipokines into the blood circulation 4)). Therefore, obesity was recognized as a chronic inflammatory state, resulting from macrophage infiltration into adipose tissue (5) and was associated with an increased level of inflammatory adipokines, such as IL-6, TNF-α, and IL-1β (6).

Researchers have suggested RBP4 as a new adipokine whose concentration increases in obesity. Additionally, in obesity-related disorders, including metabolic syndrome, type 2 diabetes, and cardiovascular disorders, its concentration rises (7). RBP4 was found to be highly expressed by human adipose tissue, and circulation levels of RBP-4 were observed to have a positive correlation with adipose tissue (8). Moreover, serum levels of RBP4 and its expression level in adipose tissue were associated with inflammation (9); therefore, an increase in RBP4 levels can also be considered as an inflammatory condition. Resistin is another adipokine with potent proinflammatory properties (10). The expression of resistin have been observed in adipose tissue and other peripheral tissues, including adrenal glands, skeletal muscle, kidney, and brown adipose tissue (11). In obese and diabetic patients, strong positive correlations were reported between resistin and certain inflammatory cytokines (TNF-α, CRP, and IL-6) (12). Resistin affect obesity and promote the insulin resistance through its interaction with other tissues and this adipokine may lead to the AMP-dependent protein kinase (MAPK) activation in the skeletal muscle and liver (13). On the other hand, resistin affects the lipid and glucose metabolism (14). Therefore, inhibition of resistin as a therapeutic target has attracted a great deal of attention and reducing the secretion of resistin can result in modulation of metabolic abnormalities caused by obesity, like inflammation, endothelial disorders, hypertension, and atherogenesis (15).

Sedentary lifestyle is the main risk factor for developing obesity (16). In contrast, exercise training plays an important role in body weight control and counteracting pathological effects of obesity (17). In addition to exercise training, zataria multiflora, as an herbal supplement, exert several pharmacological effects and is identified as anti-inflammatory, antioxidant, and immunomodulatory supplement (18). In addition, it was reported that zataria multiflora decreases insulin resistance through different mechanisms, such as up-regulation of the PPARγ and adiponectin expression, and exerting insulin-like effects (19). Tayebi and colleagues reported that exercise training (circuit resistance training) along with zataria multiflora have a synergic effect on decreasing inflammatory adipokines, including TNF-α and RBP-4 levels, in postmenopausal women (20). Despite the positive effects of different training modalities (resistance and endurance), it is suggested that combined training in obese people is superior to resistance or endurance training alone for the improvement of the cardiovascular risk factors and the body composition (21). This training type (combined) increases protein synthesis and muscle growth while simultaneously decreasing adipose tissue and raising lipid metabolism. Thus, it is effective in improving insulin resistance (22). Since the effect of different exercises training, especially combined training with zataria multiflora, on inflammatory adipokines levels (such as RBP-4) and resistin needs further investigation, we conducted the present study to investigate the effect of combined exercise training with zataria multiflora on these two factors in overweight and obese sedentary women.

2. Methods

2.1. Subjects

The participants consisted of 40 Iranian (Tehran) overweight and obese healthy women, in the age range of 20–35 years. They all took part in the present intervention voluntarily and signed informed consent.

2.2. Study Design

The current study was a randomized double-blind placebo- zataria multiflora-controlled trial, conducted in the winter and spring of 2021 in Tehran, Iran, under the following registration number: IRCT20200812048388N1. After the baseline blood sampling and testing, the 40 sedentary women were matched based on their height, weight, and BMI (the obese participants “with a BMI of 30<kg.m^2” were equally distributed in different groups). Finally, they were randomly assigned to four equal groups (10 subjects in each group), including the placebo (C) (not receiving supplements and not participating in training program), zataria multiflora (Z) (receiving zataria multiflora for 12 weeks and not participating in training program), training (T) (participating in combined training for 12 weeks without taking zataria multiflora), and training+zataria multiflora (TZ) (receiving zataria multiflora supplement and simultaneously participating in combined training for 12 weeks) groups. For the random allocation, the subjects randomly chose a number ranging from 1-40 (1-10 for the placebo, 11-20 for the zataria multiflora, 21-30 for the training, and 31-40 for the training+zataria multiflora groups) from a bag containing the numbers (1-40). This way, the groups were determined. The randomly allocation was conducted as reported previously (23). Due to COVID-19 pandemic, we were unable to conduct a training program with further participants and the number of subjects were 10 in each group, as previously reported that eight to 12 participants could be suitable for similar protocols (24). For estimating the sample size, the means and standard deviation of serum levels of RBP4 (before exercise: 55.4±3.4 μg.ml, after exercise: 49.9±2.8 μg.ml) and resistin (before exercise: 7.9±1.6 ng.ml, after exercise: 8.1±1.2 ng.ml) were used in the similar subjects (25). For the calculation of the sample size, the following formula was used (26):

$$n_A = \kappa n_B \text{ and } n_B = \left(1 + \frac{1}{\kappa}\right)\left(\sigma \frac{z_{1-\alpha/2} + z_{1-\beta}}{\mu_A - \mu_B}\right)^2$$

The subject’s allocation for consuming the placebo or zataria multiflora supplement was performed as a double-blind procedure. For this purpose, the participants were provided with placebo or zataria multiflora capsules by a third person (not a part of the research team). The contributors (researcher and subjects) were unaware of the consumed capsules (placebo or zataria multiflora) until the end of the eight weeks of intervention.

2.3. Inclusion and Exclusion Criteria

The inclusion criteria herein were: BMI <35 and >25 kg.m^2, being sedentary (defined as less than one-hour of physical activity per week) in the past years, not having obesity-related diseases (like cardiovascular diseases, hypertension, and type 2 diabetes), no alcohol consumption, not taking any dietary supplements or medication within 12 weeks of intervention, having no physical limitation for completing combined training sessions, and signing the informed consent. On the other hand, the exclusion criteria included not regularly participating in exercise training sessions, allergy to zataria multiflora supplement, having to take medication within the intervention period, as well as any injury and inability impairing the combined training program.

2.4. Zataria Multiflora Supplementation

The leaves of zataria multiflora (Shirazi thyme) were dried for 10 days in the shade. The leaves were then dried in an oven at 48 °C for 48 hours and then powdered with Chinese pounder. 500 mg of the dried and powdered leaves was poured into a capsule and prepared for consumption. The subjects in the TZ and Z groups consumed 500 mg of zataria multiflora on a daily basis after breakfast (as a 500-mg capsule) with 100 ml of water. The placebo group also consumed placebo capsule (500 mg of wheat flour) daily after breakfast (20).

2.5. Combined Exercise Training

The T and TZ groups participated in the combined training program (aerobic-resistance) within 12 weeks/ three sessions per week. Each combined training session lasted for about 1 hour. Primarily, the subjects walked or run on a treadmill for 30 minutes with 60 to 70% of their maximum heart rate (220 minus age). The intensity of the aerobic exercise was controlled with a Polar heart rate monitor. Following the aerobic section, 30 minutes of resistance training was performed. The resistance part of the combined training consisted of chest press, push-ups, shoulder presses, leg presses, leg extension, and sit-ups. Each exercise was performed in three sets with an intensity of 10 repetitions maximum (10-RM) (10-RM would be approximately 75% of 1-RM) (27). The rest intervals between the sets were 2 minutes and the rest intervals between different exercises was considered as 1 minute. Warm-up and cool-down were performed before and after all the combined exercise sessions for 10 and 7 minutes, respectively. The warm-up included stretching, walking, and light-weight exercise. In order to cool-down, walking on a treadmill with a low intensity and different types of stretching movements were performed.

2.6. Blood Samples Analysis

We collected the blood samples prior to and following 12 weeks of intervention after 10-12 hours of night fasting under similar conditions. Before the blood sampling, all the subjects rested and adapted to the atmosphere for 30 minutes. The participants were asked to avoid high intensity physical activity for 24 hours before collection of the blood samples. At the end of the 12 weeks of combined training period and 48 hours after the last session of the exercise training or taking zataria multiflora supplement (for eliminate the last combined training session or taking zataria multiflora supplement effects), we conducted the post-test blood sampling. The blood samples were centrifuged, and the obtained serum was stored in a freezer for subsequent laboratory analysis. Blood glucose levels were measured using Pars Azmoun company kit. The level of insulin was also measured with ELISA method (demeditec company, catalog number: DE2935, sensitivity 1.76/IU/ml). In addition, measurement of the serum levels of RBP-4 (Adipogen, catalog number: AG-45A-0010YEK-KI01, sensitivity 1ng/ml) and resistin (from biovendor, catalog number: RD191016100, sensitivity 0.012 ng/ml) was performed via ELISA assay. All the measurements stages were performed based on instructions of the manufacturer of ELISA kits.

2.7. Body Fat Measurement and Calculation of Insulin Resistance

In order to measure the percentage of body fat, we utilized a body composition analyzer made in South Korea (BOCA-X1), which determines the body fat percentage by bioelectrical impedance analysis. It should be noted that in order to perform the body composition analysis test, the subjects were asked to fully comply with the conditions considered for performing the body composition test (no metal objects, minimum coverage, at least 6 hours of fasting). Insulin resistance was calculated with the aforementioned formula (28):

Insulin (μU/ml) × Glucose (mg. dl) / 405

2.8. Statistical Analysis

Statistical analysis of the obtained data was performed via SPSS software version 24. We checked data distribution using Shapiro-Vilk test, which represented a normal data distribution (P>0.05). Subsequently, the inter-group differences were investigated through the analysis of covariance (ANCOVA) test with Bonferroni post-hoc test. The level of significance was considered at P<0.05 for all the analysis tests.

3. Results

The participants, consisting of 40 healthy overweight and obese women (with an age range of 20-35 years), completed the considered intervention and were included in the final outcomes analysis. Figure 1 schematically illustrates the stages of this study protocol, and Table 1 exhibits the participants demographic characteristics (age, height, body weight, and BMI).

Analysis of covariance test for HOMA-IR indicated a significant difference between the groups (P<0.001). HOMA-IR decreased significantly in T compared to that in C (P=0.006); the same trend was also observed in TZ compared to C (P<0.001) and Z (P=0.004) groups. Moreover, the percentage of body fat and BMI significantly decreased in the T and TZ groups compared to that in the C and Z groups (Table 2). The result regarding glucose showed a significant decrease in glucose in the T (P=0.035) and TZ (P=0.004) groups compared to that in the C group. Insulin levels significantly decreased only in the TZ group compared to the C group (P=0.016) (Table 2).

The analysis of covariance test for RBP-4 levels showed a significant difference between the groups (P<0.001). Comparing the RBP-4 changes with Bonferroni post-hoc test between the groups, RBP-4 levels significantly decreased in T compared to C (P=0.046), which was also observed in TZ compared to C (P<0.001) and Z (P<0.001) (Figure 2).

In addition, a statistically significant difference was observed concerning the serum levels of resistin between the groups (P<0.001). According to Bonferroni post-hoc test, the resistin levels in the T group was significantly reduced compared to those in the C group (P=0.045); the same trend existed in TZ compared to C (P<0.001), Z (P<0.001), and T (P=0.041) (Figure 3).

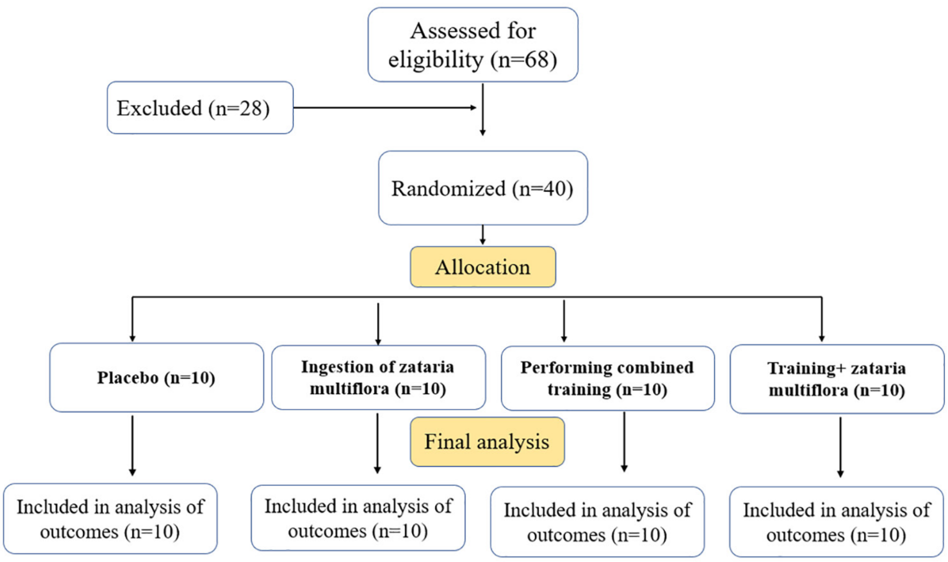

Figure 1: The figure shows the CONSORT flowchart.

Table 1: The subjects' characteristics (Mean±SD)

	C	Z	T	TZ	P value
Age (years)	27.37±4.80	25.90±3.66	26.77±3.31	28.30±4.13	0.599
Height (cm)	159.45±4.78	158.70±4.19	160.90±5.07	159.65±3.85	0.746
Weight (kg)	72.87±5.89	74.36±5.61	76.29±8.36	72.33±4.53	0.501
BMI (kg.m^2)	28.68±2.01	29.56±2.48	29.42±2.40	28.40±1.66	0.572

C: Placebo; Z: Zataria Multiflora; T: Training; TZ: Training+Zataria Multiflora

Table 2: The levels of the desired variables (Mean±SD)

Groups / Variables	Stage	C	Z	T	TZ	Inter-group P value
Glucose	Pre test	93.0±10.42	97.5±11.26	94.1±10.24	95.6±7.63	0.002
	Post test	94.9±9.26	95.7±9.26	89.4±8.08	88.7±6.25	
Insulin	Pre test	8.5±1.28	8.8±1.37	9.3±1.42	8.9±1.08	<0.001
	Post test	8.4±1.39	8.5±1.46	8.2±1.20	7.7±1.22	
HOMA-IR	Pre test	1.95±0.33	2.14±0.52	2.17±0.45	2.10±0.29	<0.001
	Post test	1.96±0.28	2.02±0.47	1.81±0.31	1.68±0.28	
Percentage of body fat (%)	Pre test	30.6±2.63	31.9±2.49	32.6±4.03	30.5±2.70	0.014
	Post test	30.9±2.76	32.3±2.48	30.8±3.68	28.8±2.43	
BMI (kg.m^2)	Pre test	28.68±2.01	29.56±2.48	29.42±2.40	28.40±1.66	0.821
	Post test	28.74±2.02	29.59±2.43	28.93±2.38	27.83±1.66	

C: Placebo; Z: Zataria Multiflora; T: Training; TZ: Training+Zataria Multiflora

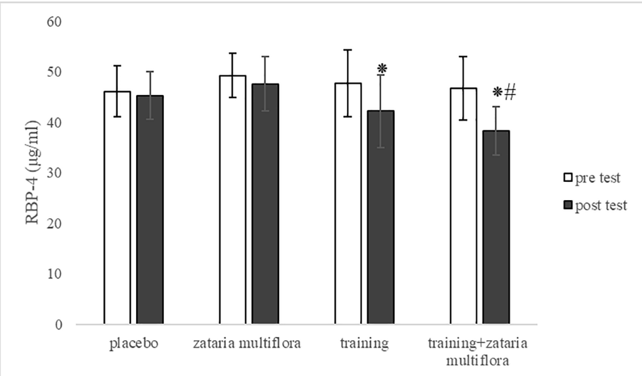

Figure 2: The figure shows the serum levels of RBP-4. ⁎Significant reduction compared to the C group, # Significant reduction compared to the Z group

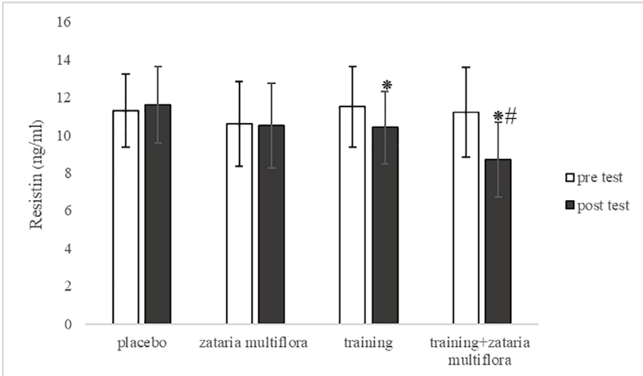

Figure 3: The figure shows the serum levels of Resistin. ⁎Significant reduction compared to the C group, # Significant reduction compared to the Z and T group

4. Discussion

The most remarkable finding in this research was that 12 weeks of combined training alone or in combination with zataria multiflora consumption results in a significant decrease in the circulation levels of RBP-4 compared to that in the placebo (wheat flour) group. Moreover, the reduction in RBP-4 in the training+zataria multiflora group was significant compared to that in the zataria multiflora group. Based on the present findings, further decline in RBP-4 levels was observed in the training+zataria multiflora (17.98% reduction), training (11.71% reduction), and zataria multiflora (3.44% reduction) groups.

Until 2005, the only identified role for RBP4 was to transmit vitamin A, but today, RBP4 is believed to be an adipocyte-derived hormone that plays an important role in the pathogenesis of insulin resistance. Christou and co-workers identified RBP4 as a cardiometabolic risk factor (29). In line with our results, Babaei and colleagues confirmed that 12 weeks of water training in type 2 diabetic women contributes to a significant down-regulation in RBP-4 levels, which was associated with a significant reduction in insulin resistance. The researchers attributed the decrease in insulin resistance to attenuation of the inhibitory effect of RBP-4 on the PI3K pathway and the increase in PI3K activity as a result (30). Although there is scarce information about the effects of combined training on RBP-4 levels, Hosseini and colleagues reported that combined training in female with type 2 diabetes can significantly decrease the RBP-4 levels following eight weeks. They indicated GLUT-4 increase in adipocytes (as a result of adaptation to combined training) as one of the major mechanisms to reduce RBP-4 with combined training (31).

In addition, given the fact that RBP-4 has been identified as an adipokine (8), it seems as if losing body fat mass can also be one of the major mechanisms in reducing RBP-4 levels. In support of this hypothesis, it has been reported that adipose tissue is the main secretory organ for RBP-4, and among different types of adipose tissue, visceral adipose tissue results in a greater secretion of RBP-4 than subcutaneous adipose tissue (32). Similarly, in the present study, in addition to a decrease in RBP-4 levels in the training and training+zataria multiflora groups, we observed a significant reduction in the percentage of body fat in both of these groups. Although the effect of zataria multiflora on the RBP-4 levels is unknown, it was founded that 12 weeks of circuit resistance training alone or with zataria multiflora ingestion resulted in a significant decrease in RBP-4 levels; the decrease in RBP-4 in the training+zataria multiflora group was higher (20). In addition, the above-mentioned study indicated that RBP-4 has a significant positive correlation with other inflammatory mediators, including TNF-α, and according to the available evidence, the decrease in RBP-4 levels is closely related to body fat mass (20). In another study, Tayebi and co-workers suggested that 12 weeks of circuit resistance training with 35% and 55% 1RM in postmenopausal women results in a decrease in the level of RBP-4 and a significant decrease in RBP-4 levels following circuit training (different intensities) along with zataria multiflora supplementation (33); this finding is in accordance with our results. Moreover, the above-mentioned results, confirming the present research results, indicated that RBP-4 was further downregulated in the trained groups with zataria multiflora supplementation in comparison with the trained groups without zataria multiflora. The comparison of low and high intensities of circuit resistance training also indicated that 55% 1RM results in further decrease in RBP-4 levels compared to 35% 1RM (33).

In contrast to our findings, Moghadasi and colleagues reported no change in RBP-4 levels with eight weeks of high-intensity aerobic training in female athletes (34). This finding can be attributed to the high level of the initial preparation of the subjects and no significant changes in the percentage of body fat with exercise training. These results confirm the fact that the decrease in body fat mass is required for RBP4 levels reduction. On the other hand, RBP4 levels are associated with weight and glucose sensitivity, body fat mass, and waist to hip ratio (WHR), all of which are the markers of metabolic disorders and obesity (35). It was also reported that RBP4 gene expression is remarkably correlated with adipose tissue inflammatory indicators (CD68, MCP-1) (36). Based on the available evidence, RBP4 is correlated with chronic inflammation markers and may directly stimulate the secretion of the proinflammatory cytokines involved in leukocyte recruitment and adhesion, consisting of MCP-1, interleukin-6 (IL-6), ICAM-1, and VCAM-1 (37). Confirming the link between RBP-4 and inflammatory factors, we observed that 12 weeks of combined training and combined training+zataria multiflora in overweight and obese women, in addition decreasing RBP-4 levels, resulted in a significant reduction in resistin levels. The resistin levels declined in the training+zataria multiflora group more significantly compared to those in the zataria multiflora and training groups. Moreover, we found a decrease by 9.56% and 22.32% in resistin in the training and training+zataria multiflora groups, respectively.

Consistent with the present findings, it has been shown that 16 weeks of endurance training with 50-85% of maximum oxygen consumption contributes to a significant reduction in resistin along with lower levels of other inflammatory mediators, including IL-6 and IL-18, in addition to a reduction in insulin resistance. Researchers have attributed the decline in resistin levels and other inflammatory factors to the anti-inflammatory effects of endurance training by reducing fat mass (38), in which macrophages and adipocytes have been identified as major sources of resistin secretion (39). Considering the significant decrease in the percentage of body fat in the trained groups herein, it seems as though the decrease in body fat mass (as a major site of resistin secretion) can be the main mechanism of resistin reduction. In another study, researchers showed that eight weeks of combined training in men with type2 diabetes significantly reduced resistin levels, which simultaneously decreased insulin resistance significantly of in the combined training group (40). However, in contrast to our findings, Lopes and co-workers reported that 12 weeks of combined training in overweight girls had no significant effects on resistin levels, which was associated with the unchanged percentage of body fat (41). These findings seem reasonable considering the fact that adipose tissue is known as the main site of resistin secretion (8). Despite these results, Lopes and colleagues indicated higher levels of resistin in overweight individuals compared to those in normal weight individuals, confirming the adipose tissue importance function for resistin levels up-regulation (41). In addition, a decrease in resistin levels in the present study leads to a significant reduction in insulin resistance. In support of these findings, the up-regulation of resistin expression in the obese individuals' adipose tissue was recognized as one of the effective mechanisms for glucose tolerance impairment and insulin resistance development (42).

There is no information about the effect of zataria multiflora with or without exercise training on resistin levels; meanwhile, studies have shown that resistance training alone or in combination with zataria multiflora supplementation reduces inflammatory adipokines, including vaspin and visfatin. In another paper, the reduction rate of these inflammatory adipokines was higher in the resistance training+zataria multiflora group compared to that in the training group (43). According to the findings obtained herein, the decreased insulin resistance in the training+zataria multiflora, training, and zataria multiflora groups was 5.6%, 16.5%, and 20%, respectively, which represented a non-significant decrease in insulin resistance in zataria multiflora group, and an increase in the combined training role in insulin resistance improvement after zataria multiflora ingestion. Zataria multiflora insulin-sensitizing effect is partly attributed to the rise in adiponectin and PPARγ protein expression (19). In addition, exercise training anti-inflammatory effects are exerted by different mechanisms, including the followings: up-regulation of anti-inflammatory mediators (IL-10) (44); adipose tissue macrophages phenotypic switching from M1 to M2 and inhibition of M1 macrophage infiltration into adipose tissue (45). However, there is scarce information in this field, particularly on the simultaneous effect of exercise training with zataria multiflora supplementation on the levels of inflammatory and anti-inflammatory adipokines. Hence, it is not possible to draw any exact conclusion based on our finding. There were certain limitations in the present study, including the small number of participants in each group, as well as no measurement of the levels of other inflammatory and anti-inflammatory adipokines, such as adiponectin. Thus, further investigation should be conducted in order to answer the existing questions.

5. Conclusion

According to our results, 12 weeks of zataria multiflora supplementation amplified the anti-inflammatory effect of combined training and its role in insulin resistance improvement. Furthermore, it had a synergistic effect in combination with training. Consumption of zataria multiflora could be recommended as a supplement, especially in combination with exercise training, for prevention and management of obesity and its related diseases, including type-2 diabetes and inflammation in women.

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Ethical Approval

Ethics committee of Islamic Azad University-Science and Research Branch approved the present study conducted intervention with the code of IR.IAU.SRB.REC.1399.087. Also, written informed consent was obtained from the participants.

Conflicts of interest: None declared.

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