ORIGINAL ARTICLE

Anti-inflammatory properties of combined aquatic extract of *Ferulago angulata* boiss with aerobic exercise on pro-inflammatory indices in obese males

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Background: The application of supplements, herbal extracts, and exercise training for treatment of diseases and reducing chronic inflammation has been increased progressively among people. Thus, the aim of this investigation was to study the combined aquatic extract of *Ferulago angulata* boiss with aerobic exercise on pro-inflammatory indices in obese males. **Materials and Methods:** In this semi-experimental study, forty young obese men (mean and standard deviation of age 34.59 ± 2.24 years, body mass index (BMI) 33.14 ± 2.75 kg/m^2) were selected by purposed sampling and were randomly divided into four equal groups (n = 10), training, training-supplementation, supplementation, and control. Participants in the supplementary groups received 50 mg/ml *F. angulata* extracts daily for 12 weeks. Aerobic training program included 12 weeks of training, 3 sessions/week, and each session was 20 min at 60%–%–70% of maximal oxygen consumption. Blood samples were taken from the participants 48 h before and after the intervention in fasting state. Data were analyzed using dependent t-test, one-way analysis of variance, and *post hoc* Tukey test at a significant level of $P < 0.05$. **Results:** After 12 weeks of exercise and supplementation, levels of interleukin (IL)-6 ($P = 0.001$), IL-18 ($P = 0.03$), IL-1 β ($P = 0.001$), tumor necrosis factor alpha ($P = 0.001$), weight ($P = 0.001$), BMI ($P = 0.001$), body fat percent ($P = 0.001$), and waist-hip ratio (P = 0.001) decreased significantly and the mean changes of these indicators in training + supplementation group were significantly augmented as compared to the other three groups. **Conclusion:** It appears that aerobic training plus *F. angulata* extract consumption have better effect on improvement of serum inflammatory factors in obese young men.

Key words: *Ferulago angulata* extract, interleukins, obesity, tumor necrosis factor alpha, training

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INTRODUCTION

Obesity is a multifactorial disease, and medical condition occurs by gene, lifestyle, and environmental factors interactions.[1] It is now evident that adipose tissue not only stores excess triglycerols, but also functions as an endocrine organ by releasing adipokines, which play important roles in the regulation of appetite, glucose and lipid metabolism, inflammation, and insulin resistance.[2] Research has shown that overproduction of pro-inflammatory cytokines such as interleukin (IL)-6, IL-8, IL-1 β, and tumor necrosis factor alpha (TNF-α) released from adipose tissue plays an important role in the progression of obesity and serum concentrations of these inflammatory markers elevated in overweight and obese individuals, therefore, obesity especially visceral adipocity is now viewed as a low-grade inflammatory disease.[3] Research introduces adipose tissue as one of the main producers of inflammatory cytokines such as IL-6, IL-8, and IL-1 β.[3,4] IL-6 is produced in a variety of tissues such as adipose tissue and skeletal muscle, and may have either pro- or anti-inflammatory

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effects.[5] On the other hand, IL-18, TNF-α, and IL-1β are pro-inflammatory cytokines.[6-8] Physical activity and appropriate diet are among the curative and/or preventive measures for obesity-related complications.[9-12] According to previous studies, aerobic exercise is capable of promoting a transient anti-inflammatory state in healthy and overweight individuals, and it can aid in the control of chronic low-grade inflammation.[13,14]

However, no reduction was reported in the levels of inflammatory cytokines following regular exercise, in some studies.[15,16]

In addition, studies regarding the role of herb consumption in weight control and inflammation inhibition have attracted many researchers. *Ferulago angulata* is a plant from *Apiaceae* family, with thick stem, standing, tall, and stripped. It has 35 species, while *F. angulata* has phenol and antioxidative properties.[17] It is proven that this plant prevents lipid peroxidation and act as anti-inflammatory.[17,18] In an animal study, Amirghofran *et al*. found that *F. angulata* extract consumption downregulates the production of pro-inflammatory cytokines, such as IL-1β, significantly.[19] Consequently, due to contrasting results about the effect of regular exercise on inflammatory profile in obese people, and the lack of evidence about the effect of *F. angulata* supplementation, the aim of this study was to investigate the effects of aerobic exercise along with water extract of *F. angulata* consumption on serum levels of IL-6, IL-18, IL-1β, and TNF-α in obese men.

MATERIALS AND METHODS

Study population

This is randomized placebo-controlled study including four groups containing a pretest, posttest design. The study was approved by the Ethic committee of the medical university of Abadan under the 93U-044 code and the Iranian Registry of Clinical Trials code is www.irct.ir; IRCT20160129026251N4. It is worth noting that the participants were fully informed of any risks and discomforts associated with the experiments before they provided informed written consent for participation. We included forty young, obese men according to MedCalc Statistical Software version 14.8.1 (MedCalc, Ostend, Belgium). This software was used to determine the standard sample size in each group. The sample size was determined based on the main and important variable of the study, "IL-6," based on 80% power, type 1 error is equal to 5%, and number of samples in each group of 10 people and a total of forty people were calculated. All the participants were randomly divided into four groups (training, training + supplementation, supplementation, and control) based on simple randomization procedures.

The inclusion criteria were body mass index (BMI) >30, age range (30–40 years), and gender (men). Exclusion criteria were not taking the researchers' advice, not attending the training sessions regularly, or having a history of special diseases, taking medicine and supplementations, and having a background of physical activity [Figure 1]. Diet monitored by a 24 h questionnaire in the first and last 3 days of the research period. Then, macro and micronutrients and calories in all groups calculated then, macro, micronutrients and calories calculated according to guide to calculate the Nutritional Value Regimes in Iran, book. Then, data were analyzed using analysis of variance (ANOVA) test. There was no significant difference between calories ($P = 0.07$), micronutrients ($P = 0.12$), and macronutrients ($P = 0.23$) in the four studied groups, in pre- and post-test stages.

Intervention

Before the beginning of the exercise program, the participants' weight was measured using a scale (Seca, Germany), following some seconds of staying motionless and their heights were assessed by meter with an accuracy of <0.5 cm. While participants were standing bare feet, their height and BMI were calculated by dividing body weight (kg) to the height^2 (m). Body fat percent was measured using a Caliper (SAEHAN-SH 5020, England), applying the Jackson and Pollockformula 3-site (chest, abdomen, and thigh) and after the 8–10 h of fasting.[20] Waist circumference was measured using a tape at halfway between lowest rib and the top of hipbone, roughly in line with belly button while breathe out normally. At the end of exercise program, all measurements were repeated under identical situations. Serum levels of IL-6, IL-18, IL-1β, and TNF-α were measured using highly sensitive Bender Medsystem kit (USA) and ELIZA method. Inter- and intra-coefficients of variation of the variable measurements were 5%–10%. Blood samples were collected before the first exercise session and 48 h after the last exercise session in fasting state between 8 and 10 am. Participants were asked not to have any strenuous physical activity 48-h before blood sampling. Five milliliters of blood was taken after 12 h fasting from brachial vein, and blood samples were collected in sterilized tubes and then incubated for 10 min at the room temperature. The samples were then centrifuged (at 2000 rpm for 10 min). Serum was separated and stored at −70°C for further analysis.

Study protocol

Maximal oxygen uptake was measured using Bruce Test,[21] and the participants started to exercise after 72 h. Heart rates (HRs) of participants in 1 min were measured using a treadmill,[21] and the following formula was applied in order to calculate the maximal oxygen consumption ($VO_{2\ max}$):[21]

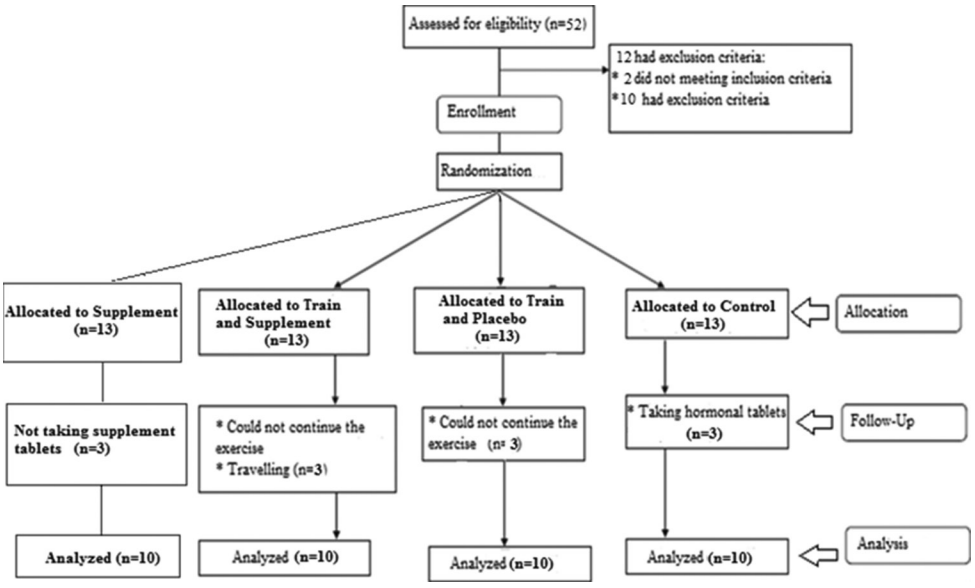

Figure 1: Consort flow diagram of the study

$VO_{2\,max}$: 14.76 − 1.379 (time) +0.451 (time)^2 − 0.12 (time)^3

The target HR of participants were calculated using Karvonen formula:[21]

Target HR: (maximum HR − resting HR) × (intensity) + resting HR

Maximal HR was calculated using the following formula: 220-age (years)

The aerobic training consisted of running on a treadmill at 60%–70% of $VO_{2\,max}$. Each training session included a 5–10 min of warm-up and cool down. After 4 weeks, maximal HR was measured once more, and the training intensity (60%–70% $VO_{2\,max}$) was adjusted accordingly.[21]

Supplement consumption

Leaves form *F. angulata* were grounded using an electric mill, and the powder was then bolted to separate the big particles. To make the *F. angulata* extract, 8 g of the powder was wrapped in a piece of two-layer tiffany cloth and then was put in a flask containing 100 mm of distilled, sterilized water. The container was then put in a shaker for 24 h at room temperature. The extract was then passed through a filter under the laboratory's hood. The produced extract was then stored at 4°C before consumption.[22] According to the literature, the daily supplementation dose for each participant in the supplementation and the combination groups was 50 mg/kg bogy weight.[19] The researchers did not get any side effects of this supplement on human, up to now.[23]

Participants in the supplementation and the control groups did not take part in any exercise activities during this period and were only involved in their daily routine activities. At the end of intervention, the adherence to the supplementation was assessed 85% according to the self-reported information, while it was about 90% for adherence to exercise according to the sessions participants took part.

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences version 19 software (SPSS Inc., Chicago, IL, USA). Data were expressed as mean ± standard deviation percentiles. After assessing the normality and nonnormality of data by Shapiro-Wilk test, differences between the baseline means of three groups in all variables were analyzed using oneway ANOVA. Within-group analysis assessed by paired *t*-test and between-group differences were examined using ANOVA; for pair-wise comparisons, Tukey *post hoc* test was used. A two-sided $P \leq 0.05$ was considered statistically significant.

RESULTS

Results from one-way ANOVA showed no significant statistical differences in pretest values of variables ($P > 0.05$).

Effects of 12 weeks of aerobic training and supplementation on inflammatory cytokines levels

Results from *t*-test shows that following 12 weeks of aerobic exercises and supplementation mean values for IL-6 ($P = 0.003$, $P = 0.01$, $P = 0.001$), IL-18 ($P = 0.03$, $P = 0.02$,

P = 0.001), TNF-α (*P* = 0.03, *P* = 0.02, *P* = 0.001), and IL-1β (P = 0.03, *P* = 0.02, *P* = 0.001) decreased significantly in the three groups of aerobic training, supplementation, and training-supplementation, as compared to the pretest levels [Table 1].

Results of one-way ANOVA also revealed significant differences in IL-6 (*P* = 0.0001), IL-18 (0.03), IL-1 β (*P* = 0.001), and TNF-α (*P* = 0.001) mean changes [Table 1]. *Post hoc* Tukey test showed that in training + supplementation group, mean changes of IL-6 (*P* = 0.01, *P* = 0.01, *P* = 0.02 respectively), IL-18 (*P* = 0.01, 0.001, *P* = 0.001), TNF-α (*P* = 0.001, *P* = 0.001, *P* = 0.01 respectively), and IL-1β (*P* = 0.03, *P* = 0.01, *P* = 0.001) were significantly higher as compared to other three groups of aerobic training, supplementation, and control [Figures 2-4].

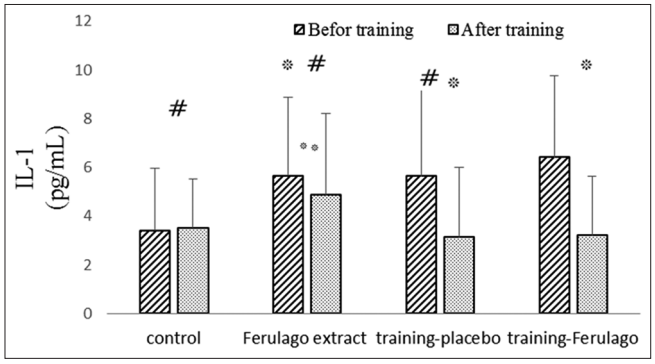

Figure 2: Between-group differences for interleukin-1. *Significant difference with control group (*P* < 0.05). **Significant difference with training-placebo (*P* < 0.05). #Significant difference with training-Ferulago group (*P* < 0.05)

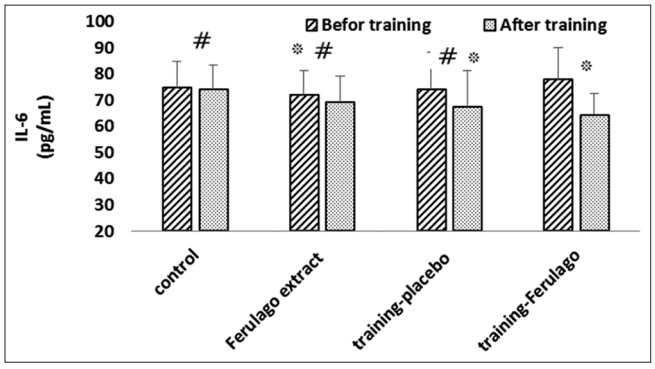

Figure 3: Between-group differences for interleukin-6. *Significant difference with control group (*P* < 0.05). #Significant difference with training-Ferulago group (*P* < 0.05)

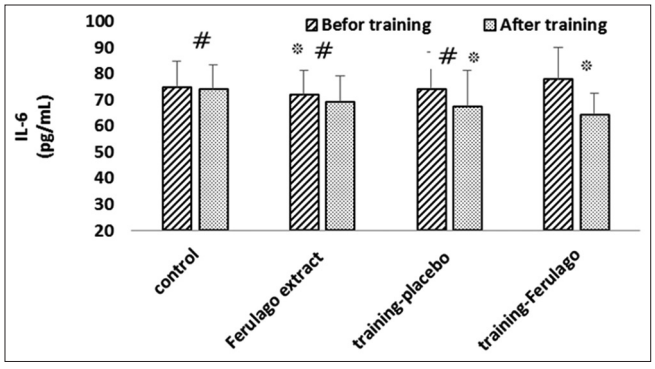

Figure 4: Between-group differences for interleukin-18. *Significant difference with control group (*P* < 0.05). #Significant difference with training-Ferulago group (*P* < 0.05)

Effects of 12 weeks of aerobic training and supplementation on body composition indices

T-test results revealed that in exercise + supplementation, exercise, and supplementation groups; body fat percent (P = 0.01, *P* = 0.008, *P* = 0.01, respectively) and waist-hip ratio (WHR) (P = 0.001, *P* = 0.003, *P* = 0.004, respectively) decreased significantly following 12 weeks of intervention. Kg decreased significantly (*P* = 0.04, *P* = 0.04) as well as their BMI (*P* = 0.01, *P* = 0.02) in exercise + supplementation and exercise groups, respectively [Table 2].

According to Table 1 and one-way ANVOA results, between-group differences were significant in the mean changes of kg, body fat percent, and WHR (*P* = 0.001) [Table 2]. Results from Tukey's test revealed a pronounced impact of exercise-supplementation group rather than the three groups of aerobic training, supplementation and control in weight (*P* = 0.01, *P* = 0.01, and *P* = 0.001, respectively), BMI (*P* = 0.02, *P* = 0.01, and *P* = 0.03, respectively), body fat percentage (*P* = 0.04, *P* = 0.04, and *P* = 0.01, respectively), and WHR (*P* = 0.01, *P* = 0.01, and *P* = 0.001, respectively) mean changes.

Comparison of calorie and macronutrients intake between groups

The mean and standard deviation of participants' calorie and macronutrients intakes are shown in Table 3. Between-group comparison is also summarized in Table 3.

DISCUSSION

In relation to our first hypothesis, the main finding of the present investigation was a significant improvement in IL-6, IL-18, IL-1β, TNF-α, body fat percent, body weight, WHR, and BMI levels after 12 weeks of aerobic training and *F. angulata* supplementation consumption. In accordance to the present study, Mohamadzadeh Salamat *et al*. reported significant reductions in IL-6, IL-18, and IL-1β levels following 8 weeks of endurance training at 75%–80% of reserved HR in forty overweighed men.[24] In Ordonez *et al.'s* study, significant reduction in IL-6 and TNF-α concentration has been shown after 10 weeks of aerobic training, three times a week, for 40 min, at 55%–65% of HR in obese women.[25] There are also some contradictory investigations as well. For instance, Stensvold *et al*. reported no significant differences were observed in the serum levels of IL-6, IL-1β, TNF-α and body composition in 31 syndrome metabolic

Table 1: Pre- and post-test changes in levels of interleukin-6, interleukin-18, interleukin-1β,and tumor necrosis factor-alpha

Variables	Groups	Mean±SD		Significant level of *t*-test	Significant level of ANOVA
		Pretest	Post-test		
IL-6 (pg/mL)	Control	74.74±9.89	74.09±9.43	0.31	0.001*
	Ferulago extract	71.89±9.48	69.26±8.04	0.03*	
	Training-placebo	74.23±6.65	67.41±7.12	0.01*	
	Training-ferulago	77.76±8.81	64.33±7.12	0.001*	
IL-18 (pg/mL)	Control	97.37±5.82	97.14±7.21	0.35	0.03*
	Ferulago extract	107.92±11.89	104.84±9.17	0.03*	
	Training-placebo	107.27±11.46	101.02±9.23	0.02*	
	Training-ferulago	106.12±12.12	96.90±9.15	0.001*	
TNF-α (pg/mL)	Control	189.96±23.40	190.70±19.95	0.18	0.001*
	Ferulago extract	187.98±23.58	185.66±18.28	0.03*	
	Training-placebo	196.54±25.07	189.61±24.12	0.02*	
	Training-Ferulago	202.01±19.12	188.73±18.65	0.001*	
IL-1 (pg/mL)	Control	3.41±0.40	3.52±1.95	0.18	0.001*
	Ferulago extract	5.66±2.58	4.88±2.28	0.03*	
	Training-placebo	5.64±2.07	3.14±2.12	0.02*	
	Training-ferulago	6.41±2.12	3.22±1.65	0.001*	

*Significant difference in $P<0.05$. SD=Standard deviation; IL=Interleukin; TNF-α=Tumor necrosis factor alpha; ANOVA=Analysis of variance

Table 2: Pre-posttest changes in weight, body mass index, fat percentage, and waist-to-hip ratio

Variables	Groups	Mean±SD		Significant Level of *t*-test	Significant Level of ANOVA
		Pretest	Posttest		
Weight (kg)	Control	82.61±4.33	83.15±4.92	0.31	0.001*
	Ferulago extract	83.90±6.85	83.51±6.85	0.35	
	Training-placebo	80.90±5.61	79.58±5.06	0.04*	
	Training-ferulago	84.88±13.86	82.06±13.14	0.04*	
BMI (kg/m^2)	Control	32.37±2.37	32.7±2.01	0.29	0.001*
	Ferulago extract	32.82±2.47	32.65±2.27	0.34	
	Training-placebo	32.91±2.55	32.77±2.23	0.02*	
	Training-ferulago	34.56±4.94	33.38±4.39	0.01*	
Fat percentage (%)	Control	41.74±3.11	42.77±2.30	0.444	0.001*
	Ferulago extract	41.22±3.52	39.91±3.64	0.01*	
	Training-placebo	41.9±4.48	40.47±4.78	0.008*	
	Training-ferulago	34.56±4.94	33.38±4.39	0.01*	
WHR	Control	0.98±0.03	0.98±0.02	0.22	0.001*
	Ferulago extract	0.99±0.04	0.96±0.02	0.004*	
	Training-placebo	0.99±0.04	0.96±0.04	0.003*	
	Training-ferulago	1.01±0.07	0.98±0.06	0.001*	

*Significant difference in $P<0.05$. SD=Standard deviation; ANOVA=Analysis of variance, BMI=Body mass index; WHR=Waist-to-hip ratio

sedentary participants, following 3 months performing endurance training (80%–90% $VO_{2\ max}$).[26] This discrepancy could be due to high-intensity nature of exercise although their body composition did not change after 12-week intervention. Results from a study by Lee *et al.* also revealed no significant changes in IL-6, IL-18, IL-1β, and TNF-content after 12 weeks of aerobic training (50%–60% $VO_{2\ max}$) in obese, diabetic teenagers.[27] The observed differences might be due to varieties in factors such as participants' basal healthy status, resting levels of inflammatory factors, kind of training protocol, and the participants' ages. It seems that the type of activity affects the amount of observed changes. In addition, different training durations and intensities bring about different changes in cytokines' levels.[25,26] There are contradictory findings about the optimal training intensity for attenuating inflammatory factors.[25-27] As compared to lower intensities, high training intensities with long or medium duration exert more effects on inflammatory factors, reducing their levels to a greater extent. Fischer *et al.* showed that exercise duration was the most stimulator factor in increasing postexercise serum levels of cytokines.[28] In fact, it was claimed that 50% of cytokines' changes during exercise could be explained solely through exercise duration.

As mentioned earlier, obesity is one of the factors which augment basic levels of IL-6, IL-18, IL-1β, and TNF-α

Table 3: Pre- and post-test changes in calorie and macronutrients' intake between groups

	Groups	Mean±SD		*F*	*P* ANOVA
		Pretest	Posttest		
Energy (Kcal)	Train+ supplement	1925.5±100.32	1920.5±99.32		
	Train	1933.5±12.34	1910.5±34.34	0.32	0.76
	Supplement	1890.5±19.05	1897.5±10.54		
	Control	1854.5±14.76	1900.5±10.01		
Carbohydrate (g)	Train+ supplement	12.45±156.5	11.03±136.31		
	Train	12.32±144.3	9.54±140.55	0.06	0.55
	Supplement	15.17±165.65	11.43±150.6		
	Control	11.43±155.03	7.05±165.00		
Protein (g)	Train+ supplement	3.05±76.05	1.14±70.54		
	Train	2.02±64.66	4.76±63.06	0.12	0.21
	Supplement	2.23±77.76	2.09±69.06		
	Control	1.87±66.88	1.11±69.08		
Total fat (g)	Train+ supplement	1.05±67.87	1.32±67.09		
	Train	2.43±63.5	2.76±60.06		
	Supplement	3.22±67.07	2.86±59.99	0.20	0.43
	Control	2.21±67.66	2.92±69.09		

SD=Standard deviation

in human through stimulating oxidative stress and inflammation. Weight loss improves serum levels of these factors through reduction in oxidative stress and inflammation status. Previous studies revealed a strong, negative correlation between IL-6, IL-18, IL-1β, and TNF-α concentration with body fat percent and body composition indices.[13,26] The exact reason for this negative correlation has not been fully clarified, but the effect of physical activity on adipose tissue probably is an effective factor.[28] The amount of adipose tissue has the highest correlation with circulating inflammatory indices. Lower levels of inflammation in active people relate to their less amount of net visceral fat.[13,28] Indeed, as adipose tissue is one of the main producers of IL-6, IL-18, IL-1β, and TNF-α, its reduction reduces serum levels of mentioned cytokines. In the present study, weight, BMI, WHR, and body fat percent decreased significantly following 12 weeks of exercise training. Our findings also suggested that body composition indices (body fat percent, BMI, and WHR) are highly correlated with IL-6, IL-18, IL-1β, and TNF-α, respectively. This improvement in participants' body composition could probably correlate with reduction in mentioned cytokines' levels, free radicals, and oxidative stress in obese men.

Here, we showed daily consumption of 50 mg/kg *F. angulata* for 12 weeks leads to significantly reduction in IL-6, IL-18, IL-1 β, TNF-α, body fat percent, and WHR levels. The antioxidant and antilipoid effects of *F. angulata* plant have been investigated in previous studies.[17] It was also reported that *F. angulata* extract has a positive effect on immune indices and activity.[18] Rafieian-Kopaei *et al*. reported low detected serum levels of total cholesterol and triglyceride after taking *F. angulata* extract caused inhibition of per oxidation of lipids.[29] Amirghofran *et al*. did an investigation on 8-week-old male mice and described that *F. angulata* extract (50 mg/ml) significantly decreased production of nitrite oxide after 24 h. In follow-up, 48 h after consumption of this extract level of inflammatory blood laboratory cytokines such as (IL-1β) decreased significantly.[19]

Niu *et al*. believed that flavonoids existing in herbs (gene activator transcription factors such as PGC 1α) may decline differentiation and multiplication of adipocytes and reduces the expression of genes responsible for lipogenesis. In this way, not only IL-6, IL-8, and TNF-α levels diminish but also adiponectin levels raise and blocks catechol– o– methyltransferase enzyme which eventually linked to decreases fat and body weight.[30] After 12 weeks of aerobic training with *F. angulata* supplementation, the present researcher showed body fat percent, BMI, WHR, body weight and as a result levels of IL-6, IL18, IL-1β, and TNF-α decreased significantly. As the observed improvement was greater in exercise-supplementation group compared to other intervention groups, *F. angulata* can be considered as a strong, anti-inflammatory and anti-oxidative supplement, which could be considered effective in obesity severity along with aerobic training. It seems physical activity might affect cytokines' production through different mechanisms such as changes in circulating blood factors (e.g. lactate, catecholamine, and growth factors) stimulation of lymphatic system nodes, making NK cells move faster than T-cells.[26]

In addition, as lymphatic system gets more stimulated, more cytokines are released from the adipose tissue and it has been proven that exercise reduces sympathetic stimulation. It seems that an increase in expression of

muscles' pro-inflammatory IL receptors in people with high $VO_{2\ max}$, which is a consequence of exercising, could justify the decrease in serum levels of these indices.[27,29] In addition, flavonoids in *F. angulata* improve body's anti-oxidation system through increasing inter-cellular anti-oxidative levels such as glutathione, uric acid, and bilirubin, improved intercellular anti-oxidative enzymes capacity such as glutathione peroxides, and catalase. They also prevent lipogenesis and improve fat oxidation through blocking phospholipase A2, and inhibition of transcription factors of free fatty acid synthesis and blocking acetyl-CoA carboxylase.[30] The effects of this supplementation would be more vigorous potentially if they are combined with moderate-to-intense physical activity.[6,28]

CONCLUSION

Although consumption of *F. angulata* leads to an improvement in pro-inflammatory indices in obese young men, it seems that *F. angulata* consumption along with a 12-week aerobic exercise has profound effect on these indices, and we can recommend it as a secondary outcome that nonathlete obese people can take *F. angulata* and perform aerobic exercise to improve body composition and inflammatory system. We suggest further studies with more sample size and precise assessment to conclude whether the positive effect of training with *F. angulata* is permanent or not. In addition, while double blinding condition was not performed in present study, it should be considered in future probes.

Acknowledgments

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Nil.

Conflicts of interest

There are no conflicts of interest.

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