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Research Article

High intensity interval training and Eryngium billardieri extract consumption on MMP-2 gene expression of visceral fat in rats with metabolic syndrome

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Abstract

Background: Metabolic syndrome includes a set of metabolic disorders that expose the patient to cardiovascular disease and diabetes. The aim of the present study was to evaluate the effect of High intensity interval training and Eryngium billardieri extract consumption on the expression of visceral fat matrix metalloproteinase-2 gene and insulin resistance in rats with metabolic syndrome.

Materials and Methods: In this experimental study, 32 male Sprague-Dawley rats weighing 200-250 g were randomly divided into 4 groups: 1- Healthy group 2- Metabolic syndrome 3- Metabolic syndrome + Eryngium billardieri 4- Metabolic syndrome + Eryngium billardieri + HIIT. The training protocol was performed on a rodent treadmill for 8 weeks and 5 sessions per week and 125 mg of Eryngium billardieri extract per kilogram of body weight was given by gastric gavage 5 days a week for 8 weeks. At the end of the eighth week, sample of visceral adipose tissue was taken to examine the expression of MMP-2 gene. Animal blood was collected from the heart. ANOVA were used for data analysis using SPSS 23 software at a significant level ($p < 0.05$). Tukey significance test was used to compare significant differences.

Results: Eight weeks of intense intermittent exercise with consumption of Eryngium billardieri extract caused a significant decrease in MMP-2 gene levels and glucose and insulin levels in comparison with the metabolic syndrome group ($P < 0.05$).

Conclusion: According to the results of the study, it seems that High intensity interval training with the use of Eryngium billardieri extract helps to improve insulin resistance and reduce MMP2.

Keywords:
High intensity interval training, MMP-2, Eryngium billardieri extract, Glucose, Insulin

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1. Introduction

Components of metabolic syndrome were first identified about 40 years ago (1). In 1998, the World Health Organization was the first body to provide a clear definition of metabolic syndrome (2). In 2001, the Adult Therapy Panel used the term metabolic syndrome for a set of metabolic risk factors, denying the meaning of insulin resistance as the primary or only risk factor. This organ provided practical criteria for determining patients with metabolic syndrome (1). In the definition of metabolic syndrome mentioned by the International Diabetes Federation, the main emphasis is on abdominal obesity, which depends on different races. According to this definition, the waist size set for abdominal obesity in Caucasians is greater than 94 cm for men and greater than 80 cm for women, which is lower than the definition of an adult treatment (3). Metabolic syndrome is defined as a group of physiological, biochemical, and clinical factors associated with insulin resistance and obesity that directly increase the risk of cardiovascular disease and type 2 diabetes (4). Therefore, the clinical concept of diagnosing metabolic syndrome mainly involves identifying patients who need lifestyle changes with an emphasis on weight loss, increased physical activity, and control of blood pressure and blood lipids (5). The first line of treatment is lifestyle changes. Therefore, patients with metabolic syndrome are advised to avoid saturated fatty acid content, trans fatty acids, and foods high in cholesterol and sugar, and to increase their intake of vegetables and grains. Dietary approaches to control high blood pressure and the Mediterranean diet indicate the importance of consuming dairy products, cereals, nuts, legumes, poultry and fish in lowering cholesterol, triglycerides and blood sugar (6).

But if after three to six months of trying to correct the risk factors is not enough, medical treatment is necessary.(7)

Metalloproteinases (MMPs) are endopeptidases that were first introduced in 1962 when their role in the development of a baby frog was recognized. Since the components of the extracellular matrix are involved in various immunobiological processes such as proliferation, differentiation and cell migration, changes in these enzymes are effective on immunological processes (8). Metalloproteinases are made by many cells of the immune system such as macrophages, neutrophils, eosinophils and T lymphocytes and cause the destruction of extracellular matrix and basement membrane and are important in physiological and pathological processes (8). Among the subtypes related to matrix metalloproteinases, the highest release and activity is related to collagen 72 kDa, which is called gelatinase A or matrix metalloproteinase-2 (9). Metalloproteinase-2 is a member of the family of metalloproteinases that is activated by the reaction of its thiol group with reactive oxygen species and plays an important role in the metastasis of cancer cells (10).

The expression of matrix metalloproteinase-2 is primarily in the mesenchyme of cells (mainly fibroblasts) in the development and regeneration of tissues and is regulated by cytokines and growth factors. In physiological and pathological processes, matrix metalloproteinase-2 is a key regulatory molecule; Regeneration is the degradation of the extracellular matrix. The matrix protein metalloproteinase-2 is the most common protein in the basal layer of skeletal muscle(11).

These proteolytic enzymes are involved in the repair of physiological tissue and cellular behaviors such as cell proliferation, migration, differentiation, angiogenesis, and apoptosis. Host defenses also play an important role in pathophysiological conditions such as vulnerability and obesity (12). It is involved in acute myocardial ischemia, so that the activity of matrix metalloproteinases 1, 2, 3, 7 and 9 during the formation and instability of atrial fibrillation (13) .

Eryngium billardieri as the largest and perhaps most complex genus in the Epiaceae family, the genus Eryngium billardieri criticum has about 250 different species of annuals or perennials, mainly found in Eurasia, North Africa, North and South America. And Australia are growing (14). Based on phytochemical studies performed on Eryngium billardieri species, this plant contains various secondary metabolites. Triterpenoid saponins, flavonoids, phenolic acids (mainly rosemary acid), coumarins and polystylenes are the main constituents previously isolated from these taxa (15). Medicinal properties of plant extracts of leaves and roots are different, because they differ in the characteristics of saponins, flavonoids and the level of active compounds. The high content of saponin mainly determines the medicinal properties of the Eryngium billardieri plant. Saponins have antifungal and antibacterial activities (14). Also, the biological activity of the aerial part of the hornbeam plant is mainly produced by polyphenols. This medicinal plant contains alkaloids, , Benedictine, mucilage, lignans, tannins, phytosterols and volatile oils (16).

On the other hand, Eryngium billardieri extract has a direct effect on the enzymatic activities of the liver and is useful for cleansing the liver of toxins and opening the hepatic ducts. It also has a beneficial effect on the adrenal glands and in cooperation with the liver helps to increase insulin and activate the pancreas, which in turn leads to lower blood sugar and treatment of diabetes (17). Polystyrenes in Eryngium billardieri have been shown to have antibacterial, antifungal and antimicrobial activities (14). Eryngium billardieri is widely used as a medicinal plant to treat a variety of inflammatory disorders. Different parts of the plant are used for a wide range of diseases. Such as inflammatory disorders, rheumatism, sinusitis, wound healing, infections and goiter. The anti-inflammatory and anti-diabetic effects of the extracts obtained from the aerial parts and roots of the Eryngium billardieri plant have been reported.(18) A sedentary lifestyle and lack of exercise are the main causes of obesity and its metabolic disorders such as chronic inflammation, type 2 diabetes, cardiovascular disease and non-alcoholic fatty liver. Therefore, the beneficial effects of exercise on metabolism have been studied with great emphasis and attention at both cellular and clinical levels (19). Nowadays, a new method of training has been considered as high intensity interval training, which can be performed by inactive and overweight people and can have a greater effect on improving body composition and weight loss (20). In addition to saving time, low-volume intermittent exercise is in many cases more effective than aerobic exercise in creating or improving fitness and improving health. Also, by consuming more oxygen after activity (21) and also releasing more corticotropin-releasing factor leads to more energy consumption and longer reduction of appetite and obesity.(20)

According to previous studies, in general, there is little information about the effects of high intensity interval training and Eryngium billardieri extract on levels of MMP-2, and the results obtained. Present Research; The combined effect of high-intensity inteval training with Eryngium billardieri extract on visceral fat MMP-2 gene expression and insulin resistance in male rats with metabolic syndrome has been investigated.

2. Materials and Methods

Subjects

This experimental study is of laboratory type and has been done with ethics code IR. IAU. SRB.REC. 1399.110 and the study population was healthy male Sprague Dawley rats from Pastor Research Institute. After transferring the animals to the laboratory in polycarbonate cages, for one week in an environment with a temperature of 22 ± 2 ° C, humidity of 55 % and light cycle to darkness 12:12 with proper ventilation.

In this study, 32 male Wistar rats were divided into 4 groups of 8. 1. Healthy control 2. Metabolic syndrome 3. Metabolic syndrome + Eryngium billardieri extract 4. Metabolic syndrome + high-intensity interval training + Eryngium billardieri extract. How to create the metabolic syndrome model: Mice were fed a high-fat diet (30 to 40% fat) for 4 weeks. The building blocks of a high-calorie diet and a standard diet are listed in Table 1. After 4 weeks, animal obesity was assessed by calculating the Lee index (Lee index more than 310).(22)

Table 1: high-calorie diet and a standard diet

	Standard diet		High calorie diet		Weight percentage
	Percentage of energy	The amount of energy in 100 grams	Percentage of energy	The amount of energy in 100 grams	
Carbohydrate	%58	175	%45	187	%47
Fat	%13	39	%41	171	%19
Protein	%28	84	%14	58	%14/5
Total	%100	302	%100	416	

Exercise protocol

To perform high-intensity interval training, rats first for three to five sessions per week for a week to get acquainted with the treadmill for a week at a speed of 15 meters per minute for 15 to 20 minutes by running on a treadmill They practiced.The training program consisted of 5 sessions of periodic training per week, which was performed on a rodent treadmill for 8 weeks. Each workout session included warming up, main training and cooling down. The HIIT training program protocol includes for 5 minutes with 40% of maximum running intensity, and the main training phase includes 5 to 10 1-minute intense treadmill runs on 80-95% of maximum speed and in alternating speeds.

Slowly run at 55% of maximum speed and zero slope. (Table 2) (23, 24). Groups 3 and 4, in addition to high-intensity interval training program, received 125 mg of Eryngium billardieri billardieri extract per kilogram of body weight 5 days a week for 8 weeks by gastric gavage. The total training time, including warm-up and cooling time, was 20 minutes in the first week and 30 minutes in the last week. The Maximum Running Test (MERT) was used to determine the maximum training capacity and training intensity (23, 24).

Table 2: High intensity interval training

Activity time (weeks)	Number of stages (Interval Intensity)	Maximum running speed (Meters per minute)	Number of stages (Active rest period)	Maximum running speed (Meters per minute)
First	5	80	5	55
Second	6	85	6	55
Third	7	90	7	55
Fourth	8	90	8	55
Fifth	9	95	9	55
six	10	95	10	55
seventh	10	95	10	55
Eighth	10	95	10	55

After the last training session and consumption of Eryngium billardieri billardieri extract and after 12 hours of overnight fasting, the studied rats in each group by intraperitoneal injection of a mixture of 10% ketamine at a dose of 50 mg / kg and xylosin 2% and with Doses of 10 mg / kg were anesthetized. By cutting the abdomen and chest, about 10 ml of blood was taken directly from the hearts of the mice by syringe. Blood samples were centrifuged at 1000 g g for 20 minutes to separate serum and stored at -80 ° C to measure serum glucose and insulin.

Tissue samples were isolated under sterile conditions and stored at -80 ° C for MMP-2 gene expression. To measure the MMP-2 gene in adipose tissue, RT-PCR was performed using the protocol of the manufacturer (Qiagen, Germany). Table 3 shows the pattern of primers.

Table 3: Primers used

Gene	Primer Sequence (5′-3′)	Product Size (bp)	Accession Number
MMP-2	F: GAACACCATCGAGACCATGC	137	BC074013.1
	R: GGTCCAGGTCAGGTGTGTAA		
GAPDH	F:CAAGTTCAAGGGCACAGTCA	102	NM_017008.4
	R: CCCCATTTGATGTTAGCGGG		

Glucose concentration by enzymatic method of colorimetry with glucose oxidase technology and using glucose kit of Pars Azmoun-Tehran company with coefficient of variation of in-test and out-of-test glucose 1.74 and 1.19 percent respectively and measurement sensitivity of 5 mg / d Liters were measured. Serum insulin was measured by ELISA method and in accordance with the instructions of the commercial kit (Demeditec Diagnostic Insulin made in Germany) with in-test and out-of-test coefficients of change of 2.6 and 2.88 percent and measurement sensitivity of 1.76, respectively. Insulin resistance was also calculated by homeostasis evaluation model (HOMA-IR) using the following formula.

Insulin resistance index=Fasting insulin (milt / µIU) × Fasting glucose (lit / mmol) / 22:5

Kolmogorov-Smirnov test was used to ensure normal distribution of data and Levin test was used to ensure homogeneity of variances. The relative expression of the Delta City gene was measured. Descriptive statistics were used to describe the data and draw graphs, and analysis of variance (ANOVA) was used to compare the groups in the studied variables. Significant level was considered P≤0.05. All statistical analysis was performed using 22 SPSS software.

3. Results

According to Table 4, the results of the present study showed that metabolic syndrome significantly increased the expression of MMP-2 gene, blood glucose, serum insulin and insulin resistance in comparison with the healthy control group ($p < 0.05$). Significant reduction ($p < 0.05$) was observed in the patient + Eryngium billardieri extract group and the patient + Eryngium billardieri extract + exercise training group compared to the metabolic syndrome group.

Table 4: Changes in MMP-2, glucose, insulin and insulin resistance levels between different experimental groups

Variables	Metabolic syndrome + Eryngium billardieri extract + exercise training	Metabolic Syndrome + Eryngium billardieri extract	Metabolic syndrome	Healthy control	Sig
MMP-2 (ng / L)	2/07+0/336	2/79+0/903	6/88+0/604	1+0/077	0.000
Glucose (mg/dL)	178/75+2/7	247/25+1/13	332/12+11/16	210/87+2/45	0.000
Insulin (IU)	4/3+0/14	5/96+0/04	7/91+0/41	4/98+0/22	0.000
Insulin resistance	1/64+0/07	3/17+0/14	6/22+0/29	2/7+0/16	0.000

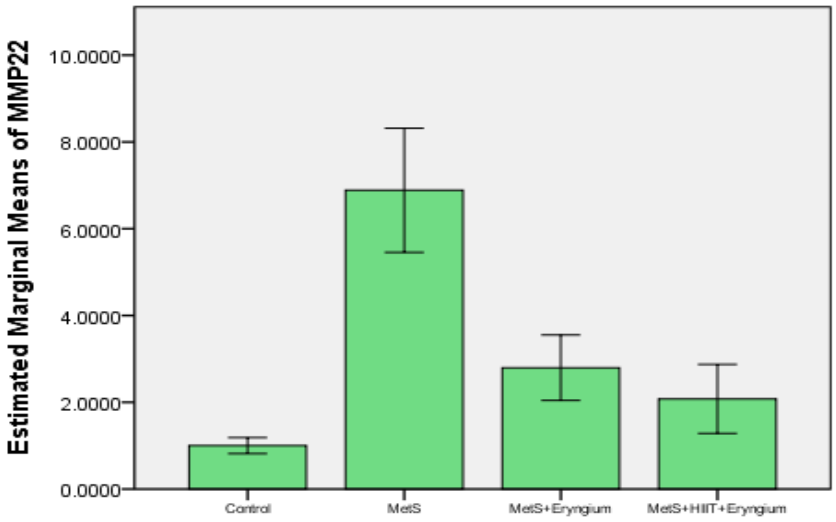

Figure 1: Comparison of MMP-2 expression in four groups of control (healthy), metabolic syndrome (patient), patient + Eryngium billardieri extract consumption, patient + Eryngium billardieri extract consumption + exercise training

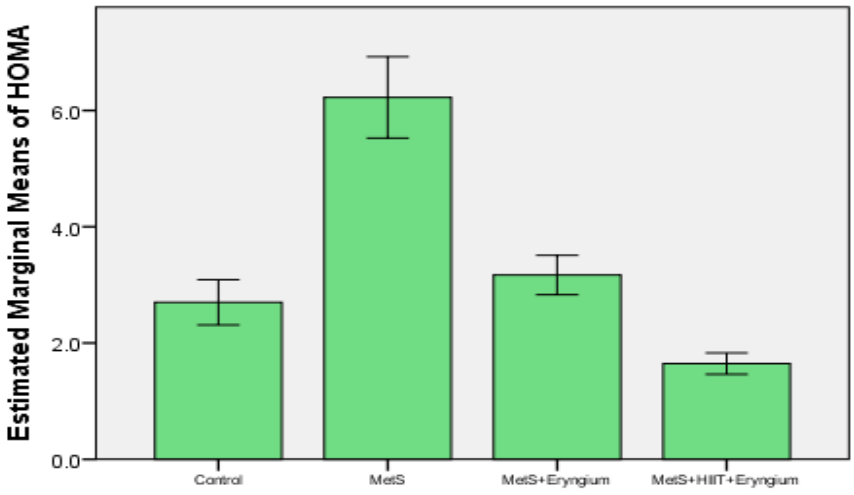

Figure 2: Comparison of insulin resistance in four control groups: metabolic syndrome, patient + Eryngium billardieri consumption, patient + Eryngium billardieri consumption + exercise training.

4. Discussion

In the present study, the effect of eight weeks of high intensity interval training with Eryngium billardieri consumption on visceral fat MMP-2 gene expression in male rats with metabolic syndrome was investigated. The results of this study showed that MMP-2 gene expression was significantly increased in the metabolic syndrome group compared to other groups. The results also showed that the extract of Eryngium billardieri and exercise training is able to significantly reduce the expression of MMP-2 genes in rats with metabolic syndrome.

Consistent with the results of the present study, Arman et al. (2016) by examining MMPs, TIMPs and vascular endothelial growth factor (VEGF) in patients with metabolic syndrome, and comparing these parameters with the control group, observed the level of TIMP-1,2, MMP -2,9, increased significantly in patients with metabolic syndrome compared with healthy individuals. Also, carotid intima thickness and serum VEGF level in metabolic syndrome were significantly higher compared to healthy controls. Their findings suggest that MMP-2 may play a role in increasing cardiovascular risk in patients with metabolic syndrome (25). On the other hand, studies on the extract of Eryngium billardieri have shown that the consumption of the extract of this plant has a direct effect on the enzymatic activities of the liver and are useful for cleansing the liver of toxins and opening the hepatic ducts (17). Different parts of the plant are used for a wide range of diseases, including metabolic disorders (18). Eryngium billardieri plant extracts mainly contain flavonoids. Therefore, the anti-inflammatory properties of the plant extract are due to the synergistic effect of ursolic acid and polyphenols such as rutin, chlorogenic acid, Rosmarinus acid, genistein and daidzein (14).

The study by Pawn et al. (2019) is the first report on the determination of ursolic acid, genistein and isorhamnetin in Eryngium billardieri and also the first study to evaluate the polyphenolic-rich extract of Eryngium billardieri, which is potentially used in the treatment of hyperglycemia. These researchers proved that the extract of the Eryngium billardieri plant has high antioxidant activity. Phenolic compounds in the extract of Eryngium billardieri plant inhibit enzymatic activity related to the management of type 2 diabetes (16).

On the other hand, Farzanegi et al. (2013) showed the effect of portulaca oleracea seed on MMP-2 and MMP-9 levels and tissue matrix inhibitor matrix metalloproteinase 1 in patients with type 2 diabetes. After 8 weeks, MMP-2 and MMP-9 was significantly decreased in the experimental group. However, no significant difference was observed between the two groups. The amount of tissue inhibitor MMP-1 in the experimental group increased significantly, also a significant difference was observed between the experimental and control groups. In general, the findings of these researchers indicate that the consumption of portulaca oleracea seed, which is rich in phenolic compounds and flavonoids, did not improve the levels of atherogenic, anti-atherogenic biomarkers in diabetics (26). And these results are contrary to the results of the present study that the extract of Eryngium billardieri plant containing phenolic compounds and flavonoids could significantly reduce the expression of MMP-2 genes.

The study present, eight-week intensity in terval training with attendant Eryngium billardieri expenditure with way meaning leading to decreases expressions (MMP-2) affected with metabolic syndrome. nowadays propounded increasing physical locomotion and exercise style important component and afew cost the therapy process metabolic syndrome. (27) Heron setting, prove khosravi (1394) expessive study eight-week regular swimming on the cardiac levels (MMP-2) and one beta permutation growth factor on the diabetic rets, reduce levels TGFB1 eight week regular swimming training and normalized activity MMP-2 on the training diabetic rets. Generally, may to bemediated potential benefits swimming sport the decreases cardiac fibrosis caused by diabetic somewhat through cardiac perutiulitiky MMP-2 activity adjust the amount. (28) The study blafiver and et al (2013) considered the effect ten-week endurance activity on the cardiac angiogenesis activity. their results showed, was reduced MMP-2 amount to less than the amount of your control group endurance training after 30 to 40 days.(29) Akbari and et al (2019) compared the effect eight week continuous aerobics training and intensity interval proportional TIMP-2 with MMP-2 on the heart tissue male rats with type2 diabetics. according to the results, was observed proportional gene TIMP-2 with MMP-2 on the interval training group. Increasing proportional with continuous aerobics training. also decreased insulin values and blood glucose in both training groups.

completely the result from the study of these researchers suggests that has it in reducing diabetic cardical fibrosis intensity interval training effects increasing proportional continuous earobics training that probably intensity interval training can with intiation above energy metabolism at improve fibrosis from effective indicators in prevention from progression of heart disorder be caused by diabetes.(30)

Based on research result present, metabolic syndrome become cause increasing meaningfulness at blood glucose values.it was while reduce significantly glucose level to relative to steatosis group with consumption Eryngium billardieri plant extract with intensity interval training. consistent with the result of the present study, dunwan and et al (2019) pointes with investigation of protective effect extracted hexane compounds from Eryngium billardieri plant at diabetic hexane compounds contains such as terpenes and sesqins, farnes,hexanes-N,pinen-B that it is a two ring monoterpene compound and kalaminen,that it significant hypoglycemic and hypolipidemic characteristics at diabetic cardiac mouses.proved ,hypoglycemic producing structural and functional injuries at kidney, brain and liver and antioxidant activity of hexane compounds Eryngium billardieri extract reduces peroxidation lipids in vitro blood glucose and prevention of oxidative damage in diabetic rats (31). Many studies have shown short term and long term effects of exercise on health. In the study of zhang et al (2020) examined the effects of treadmill exercise with youkang green tea diet supplement 10 on the metabolic syndrome caused by high fat diet in C57BL/6J rats. Their results showed, green tea compounds 10 and exercise, regulates the expression of glucose transport genes in skeletal muscle comparison with high fat diet group rats (32).

In another study was checked the effect of hight intensity aerobic interval training on adipose tissue angiogenesis in rats fed with a high fat diet.in this study, hight intensity interval training prevented an increase in the average volume of fat cells and blood glucose due to high fat diet and decreased insulin resistance compared to a high fat diet alone. In addition to, duo to the significant inverse communication between capillary density and blood glucose homeostasis, high intensity interval training with increasing capillary density despite consuming high fat foods, improves blood glucose homeostasis and prevents the increase in the volume of fat cells (33).

In the present study, metabolic syndrome caused a significant increase in serum insulin levels and insulin resistance.it was while reduced significantly Eryngium billardieri plant extract consumption serum insulin levels an insulin resistance to relative to metabolic syndrome group. also, eight weeks intensity interval training by consuming Eryngium billardieri led to a significant reduction serum insulin relative to steatosis group. and insulin resistance also showed a significant decrease many studies have shown that Eryngium billardieri plant extract has benefical and effective effect on the adrenal glands and in cooperation with the liver, it helps to increase insulin and active the pancreas this results in lowering blood sugar and treating diabetes(17) ursolic acid in the extract of Eryngium billardieri plant it is of special importance due to its antioxidant ,antimicrobial, anti-inflammatory and lower blood sugar activities(14).

on the other hand , insulin sensitivity is related to the amount of physical activity and have shown that exercise causes improve insulin function in insulin resistant individuals and the interesting thing is that have showed that plan sport intensity and volume it has several effects on in insulin sensitivity (34). Consistent with the results of the present study, khaleghi et al (1398) .during the assessment, they observed the effect of intensity interval training and Eryngium billardieri extract on protein gene expression monocyte chemotaxis 1 visceral adipose tissue and correlation with insulin resistance index in metabolic syndrome male mice, the interval training group and Eryngium billardieri interval training composition group improved insulin resistunce amount and lipid profile.(35). Studies by yang et al in 2020 showed, yougkang 10 green tea with treadmill sport prevent hight blood suger and weight gain (32). The beneficial effects of exercise on insulin sensitivity and vascular inflammation have been confirmed in various studies and meta-analyzed. specially showed a meta-analysis that in clouded 7487 participant, exercise fasting insulin levels, evolution of homeostatic model –insulin resistance and HbA1C and vascular inflammation intermediates level such as leptin, fibrinogen and angiotensin significantly reduces (34). there with , there is solid evidence that exercise improves the control of the sympathetic system and reduces sympathetic activity, that in this situation insulin resistance is determined as metabolic syndrome and hypertension. On the other hand nazari et al (2019) in the study factors effecting insulin sensitivity and MMPs in women with rheumatoid arthritis, rheumatoid arthritis with increasing MMPs levels and some factors affecting insulin sensitivity which can also have on inflammatory role, Including resistin ,leptin and visfatin in contact and between MMPs and some factors significant positive integration prevails(36).

5. Conclusion

In the present study, it was found that consumption of Eryngium billardieri has positive effects on the expression of MMP-2 gene of visceral fat and blood glucose, blood insulin and insulin resistance in male rats with metabolic syndrome. Also, performing eight weeks of high intensity interval training with Eryngium billardieri reduced the expression of MMP-2 gene in visceral fat and blood glucose, blood insulin and insulin resistance in male rats with metabolic syndrome. Therefore, high intensity interval training can be a good solution to reduce the risk factors for metabolic syndrome and prevent an increase in blood glucose, blood insulin and insulin resistance, and consumption of Eryngium billardieri extract with exercise training can affect better results.

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Compliance with ethical standards

Conflict of interest None declared.

Ethical approval the research was conducted with regard to the ethical principles (Ethic Code: IR.IAU.SRB.REC.1399.110).

Informed consent Informed consent was obtained from all participants.

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