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The Effect of 12 Weeks of Combined Training with Nettle Supplementation on IL-18 and IL-10 Levels in Women with Type 2 Diabetes

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ABSTRACT

Introduction: Inflammatory factors are recognized as playing a significant role in the development of cardiovascular diseases and type 2 diabetes. Regular exercise with anti-inflammatory effects has been shown to reduce mild systemic inflammation in type 2 diabetes. Therefore, the purpose of this study was to investigate the effects of combined exercise and nettle supplementation on IL-18 and IL-10 levels, as well as glucose and insulin resistance, in women with type 2 diabetes.

Methods: Sixty women with type 2 diabetes voluntarily participated in the study and were divided into four groups: 1) Combined training (Com), 2) Nettle supplementation (NS), 3) Combined training + Nettle supplementation (Com+NS), and 4) Control group. The participants in the training group performed resistance training (40-70% 1 repetition maximum) and aerobic interval training (60-75% maximum heart rate) three sessions per week for 12 weeks. Serum levels of fasting blood glucose, insulin, HbA1c, IL-18, IL-10, and the insulin resistance index were measured. Data were analyzed using analysis of variance (ANOVA).

Results: There was a significant reduction in insulin, fasting blood glucose, insulin resistance, and IL-18 levels in the Com, NS, and Com+NS groups compared to the control group ($p < 0.05$). Additionally, IL-10 levels were significantly increased in the Com, NS, and Com+NS groups compared to the control group ($p < 0.05$).

Conclusion: These findings suggest that both combined training and nettle supplementation are effective for blood glucose control and reducing inflammation. Furthermore, the combination of both methods is more effective for glycemic control in patients with diabetes.

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Introduction

Type 2 diabetes is a complex metabolic and endocrine disorder influenced by various environmental and genetic factors, leading to varying degrees of insulin resistance and pancreatic beta-cell dysfunction, which eventually results in diabetes (1). Diabetes can arise from genetic disorders affecting insulin receptor proteins, hyperglycemia, mitochondrial dysfunction, increased free radicals, inflammation, or obesity (2, 3). Additionally, evidence suggests that hyperglycemia itself contributes to the production of pro-inflammatory agents (4). Interleukin-18 (IL-18) is a pro-inflammatory cytokine secreted in response to inflammation, playing a limiting and reversing role in the inflammatory process. Research has reported that IL-18 is elevated in individuals with diabetes and interferes with insulin signaling (5). In contrast, inflammation associated with metabolic disorders is linked to a reduction in anti-inflammatory cytokines, such as IL-10 (6, 7). IL-10 is a member of the interleukin-1 cytokine family, secreted following cell injury, and functions as a suppressor of NF-κB gene transcription. It not only promotes cytokine production from helper T cells but also regulates the function of immune cells. Moreover, it inhibits natural killer (NK) cells and regenerates oxidative reaction products; thus, IL-10 functions as a safeguard against obesity, insulin resistance, and diabetes mellitus (8). Increased IL-10 expression has been shown to improve glucose tolerance and fasting blood glucose levels (9). In contrast, its absence or removal may enhance the toxicity induced by NK

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cells and promote the release of inflammatory factors, including TNF-α, leading to increased insulin resistance (7).

Therapeutic aims in diabetes primarily focus on stimulating insulin secretion and reducing insulin resistance through lifestyle changes, dietary modifications, physical training, and the use of herbal medicines containing antidiabetic agents (10, 11). In traditional medicine, nettle has been used as a natural treatment for diabetes (12-14). Nettle (Urtica dioica) is a plant belonging to the Urticaceae family, found in various parts of the world, including Iran. It contains biologically active ingredients such as tannins, fatty acids, flavonoids, steroids, isolectins, proteins, and terpenes. Nettle consumption has been shown to improve hyperglycemia in patients with type 2 diabetes (15). Some studies have also reported that the active compounds in nettle can be effective in modulating inflammation, although research in this area remains limited (12, 16).

Additionally, the impact of habitual training on the improvement of type 2 diabetes has been reported, with a positive regulation of plasma anti-inflammatory cytokines and a negative regulation of pro-inflammatory cytokines (8). Combined training programs, due to the dual effects of the compensatory mechanisms of both types of training methods, further improve insulin sensitivity. The various effects of training on regulatory proteins involved in controlling glucose metabolism and mitochondrial biogenesis may enhance prevention and treatment strategies for individuals with diabetes. Given the relationship between systemic inflammation and insulin resistance in diabetes, the use of intervention methods that reduce systemic inflammation in patients with diabetes could be beneficial.

Considering the complementary role of nettle and exercise in the mechanisms associated with the management of type 2 diabetes, no study has specifically examined the simultaneous effect of combined training (aerobic interval training and resistance training) and nettle consumption on inflammatory markers in individuals with type 2 diabetes. Therefore, this study aimed to evaluate the effect of 12 weeks of combined training (aerobic interval training and resistance) with nettle consumption on the expression of IL-10, serum IL-18, and blood glucose levels in women with type 2 diabetes.

Materials and Methods

Participant

The current study employed a quasi-experimental design with a pretest-posttest format and a control group. Among women with type 2 diabetes referred to the Diabetes Association based on the initial call, 60 women (aged 50 to 60 years, BMI ≥ 28 kg/m^2) were selected after completing consent and health assessment forms (17). These participants were randomly assigned to four groups: Control (Com), Nettle Supplement (NS), Combined (Com+NS), and Control (Figure 1). Participants in the training group underwent 12 weeks of selected training, consisting of three sessions per week. The nettle supplement groups used nettle for 12 weeks, while the control group did not engage in any training activities and did not use the nettle supplement. Inclusion criteria included: being diagnosed with diabetes for at least 6 months, no prior regular training, at least 6 months of metformin use, and a fasting glucose level of 126 mg/dL or higher. Exclusion criteria included unwillingness to continue participation, use of other dietary supplements or weight loss treatments, irregular attendance at training sessions, and injury during the study period.

Training Protocol

The training methodology employed in this study involved a combined training approach, consisting of resistance training (1RM 40-70%) and aerobic interval training (60-75% of maximum heart rate). The intensity and volume of the training were designed according to the recommendations for exercise in diabetic patients (6). Resistance training and aerobic training were performed for 12 weeks, three sessions per week, with a progressive increase in both intensity and duration. The training protocol was structured so that resistance exercises were always performed before aerobic exercise to prevent premature fatigue caused by aerobic training. Aerobic interval training began with 20 minutes in the first session and gradually increased to 35 minutes in the final sessions. Each session of aerobic interval training included cycling on a treadmill. In the first week, participants cycled during the activity phase at 60% of maximum heart rate (MHR) for 60 seconds, followed by a rest phase at 50% of MHR. The intensity of training gradually increased to 75% of the maximum heart rate (MHR).

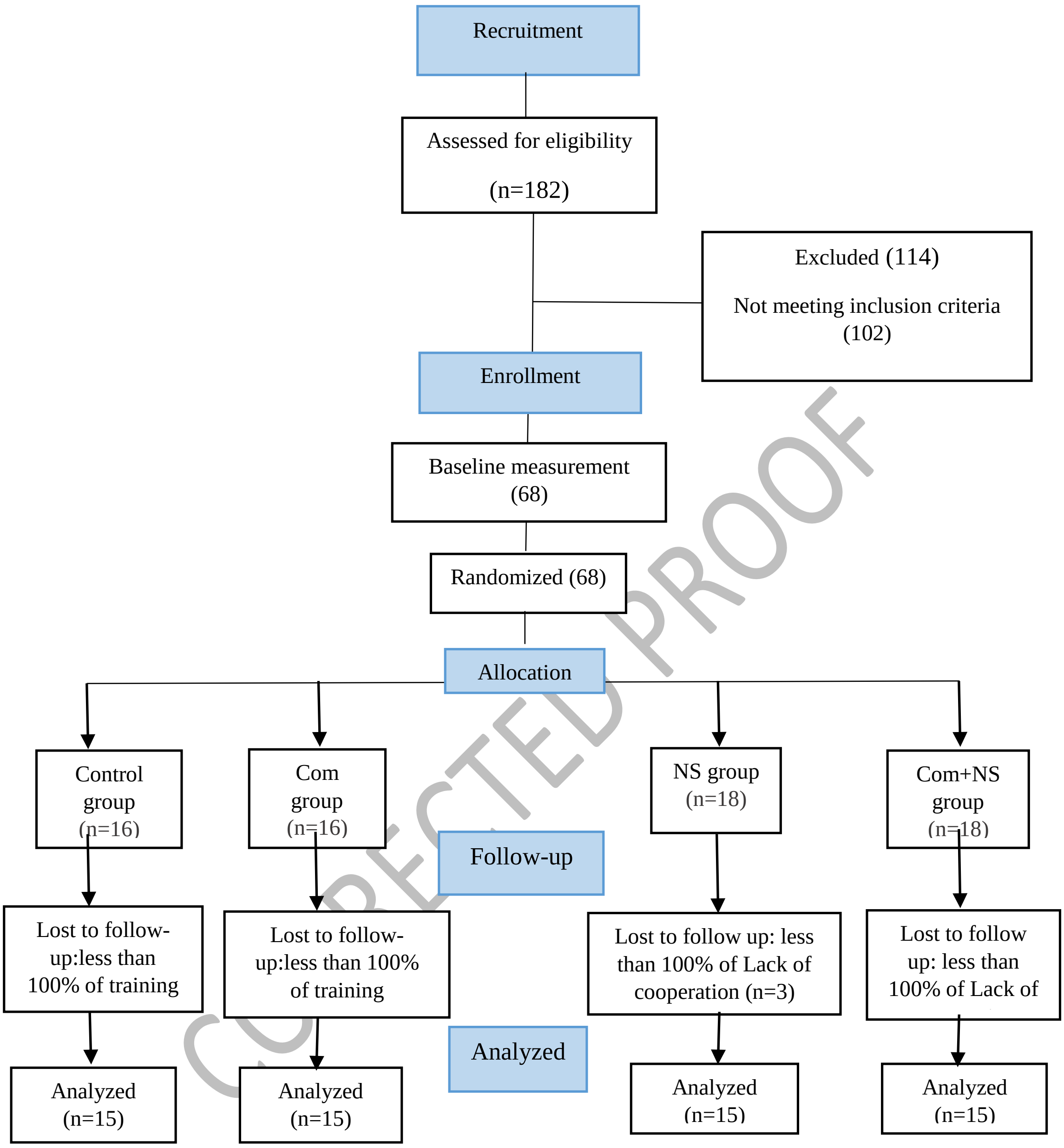

Figure 1. Participants' flow chart

The intensity of training was controlled using a Polar chest strap monitor (18). The resistance training program lasted approximately 20 minutes per session and included movements designed to target the core muscles of different parts of the body. There was a one-minute rest between each set and a three-minute rest between each movement. In the first and second weeks of training, two sets were performed, and from the third week until the end of the training period, three sets were performed (19). Rest between each set in the resistance training program was one minute, and rest between movements was three minutes. Each session began with a 10-minute warm-up program, and a 5-minute cool-down program was performed at the end of each training session (Table 1).

Table 1. Resistance and aerobic interval training protocol of the subjects

week	1-2	3-4	5-6	7-8	9-10	11-12
aerobic training (MHR)	20 minutes Training: 60 seconds with 60% MHR Rest: 60 seconds with MHR 50%	25 minutes Training: 60 seconds with 65% MHR Rest: 60 seconds with MHR 50%	25 minutes Training: 60 seconds with 65% MHR Rest: 60 seconds with MHR 55%	30 minutes Training: 60 seconds with 70% MHR Rest: 60 seconds with MHR 55%	30 minutes Training: 60 seconds with 70% MHR Rest: 60 seconds with MHR 55%	35 minutes Training: 60 seconds with 75% MHR Rest: 60 seconds with MHR 60%
Resistance training (1RM)	1RM 40% up to 10 repetitions	1RM 50% up to 10 repetitions	1RM 55% up to 10 repetitions	1RM 60% up to 10 repetitions	1RM 65% up to 8 repetitions	1RM 70% up to 8 repetitions

How to Use Nettle

The intervention involving nettle herbal supplement consumption in the nettle supplement groups was administered 15 minutes before the three main meals (breakfast, lunch, and dinner) daily for 12 weeks. Based on previous research, the daily dosage of nettle was set at 10 grams, which was divided into three doses and consumed as an infusion (14, 20). Patients were excluded from the study if they made any changes to their diet, physical activity, or medication status, or if they did not consume the extract regularly.

Measurement of Biochemical Variables

Blood samples of 5 cc were obtained from the brachial vein after 12 hours of fasting in two phases (pre- and post-). In the first phase, according to the instructions provided for blood sampling conditions, participants were instructed to avoid vigorous physical activity, stressful conditions, and the use of supplements or medications for one week before the blood sampling. Serum samples from the blood were frozen at -70°C until the second stage of testing was performed. The second-stage blood sampling was conducted 48 hours following the last training session to minimize the impact of prior sessions on the results for both the intervention and control groups.

Serum IL-18 levels were evaluated using the ELISA method and the Bioassay Technology Laboratory kit (EK0864, Boster Biological) with a sensitivity of 2.6 ng/L. Serum glucose levels were measured using the ELISA method with a Pars kit manufactured in Iran, which has a sensitivity of 5 mg/dL. Serum insulin levels were measured using an ELISA kit produced in the United States, with a sensitivity of 1 µU/L. The insulin resistance index was calculated using the standard formula for insulin resistance.

$$HOMA\text{-}IR = (Glucose\ (mg/dl) \times Insulin) / 405$$

The real-time PCR method was applied to evaluate changes in IL-10 gene expression. For this purpose, RNA was first extracted from blood samples using TRIzol reagent.

Statistical Method

The normality of the data distribution was evaluated using the Shapiro-Wilk test. After confirming the normal distribution of the data, a one-way analysis of variance (ANOVA) was used to compare the mean scores of pre- and post-test indices between the experimental groups and the control group. If significant, Tukey's post hoc test was applied to assess differences between groups. All statistical analyses were conducted using SPSS software version 22, with a significance level set at $p < 0.05$.

Results

The physiological characteristics of the subjects at the pre-test and post-test stages, after 12 weeks of combined training, are presented in Table 2. No significant differences were observed in the levels of glucose, insulin, insulin resistance, IL-10, and IL-18 at the pre-test stage, and the groups were homogeneous. Additionally, this study evaluated the indices of insulin, glucose, insulin resistance, IL-10, and IL-18, as well as their changes between the pre-test and post-test stages after 12 weeks of combined training. In the post-test results, ANOVA showed that glucose levels differed significantly between the study groups after 12 weeks of intervention ($P = 0.001$, $F = 34.39$). Tukey's post hoc test indicated that glucose levels were significantly different in the control group compared with the Com group ($p = 0.001$), the control group compared with the NS group ($p = 0.001$), and the control group compared with the Com + NS group ($p = 0.001$). However, no significant differences were found in the other comparisons ($p > 0.05$) (Tables 3 and 4).

Table 2. Anthropometric and physiological characteristics of women with type 2 diabetes in research groups

variable	group	Mean±SD	F	P
	control	50.64±0.61		
Age (years)	Com	50.52±0.60	0.354	0.786
	NS	50.69±0.61		
	Com+NS	50.74±0.62		
	control	158.74±0.78		
Height (cm)	Com	159.17±0.67	0.988	0.405
	NS	158.99±0.71		
	Com+NS	159.04±0.58		
	control	80.41±2.94		
Weight (kg)	Com	78.85±3.83	2.262	0.091
	NS	80.13±2.21		
	Com+NS	78.03±2.13		
	control	31.54±1.11		
BMI (kg / m2)	Com	31.13±1.73	0.860	0.467
	NS	31.82±1.27		
	Com+NS	31.74±0.90		
	control	165.75±7.89		
Glucose (mg / dl)	Com	166.38±6.72	0.334	0.801
	NS	168.28±8.36		
	Com+NS	167.11±5.83		

Table 3. Results of one-way ANOVA statistical test to determine the differences in changes in research variables

variable	time	groups				F	P
		control	Com	NS	Com+NS		
IL-10	pre	2.07±0.2	1.91±0.27	1.86±0.25	1.93±0.27	2.19	0.99
(AU)	post	2.01±0.21	3.05±0.29	2.55±0.23	3.35±0.30	74.30	0.001*
IL-18	pre	262.46±3.67	261.34±2.94	263.21±2.62	261.33±2.45	1.43	0.242
(ng/l)	post	263±3.00	231.61±2.56	255.04±3.59	221.59±2.27	686.37	0.001*
Glucose	pre	165.75±7.89	166.38±6.72	168.28±8.36	167.11±5.83	0.334	0.801
(mg/dl)	post	169.27±4.46	154.29±5.14	156.64±4.62	153.68±1.30	34.39	0.001*
HbA1C	pre	6.46±0.91	6.11±0.86	6.76±0.76	6.09±0.92	2.072	0.114
(%)	post	6.39±0.68	5.88±0.68	5.71±0.80	5.49±0.63	4.39	0.008*
Insulin	pre	11.04±0.96	11.04±0.96	10.98±0.85	10.96±0.79	0.036	0.991
(µIU/ml)	post	10.80±0.63	10.03±0.47	10.44±0.48	9.92±0.44	9.38	0.001*
HOMA-	pre	4.33±0.53	4.65±0.85	4.63±0.59	4.56±0.55	0.775	0.513
IR	post	4.46±0.63	2.45±0.74	2.51±0.46	2.08±0.43	50.73	0.001*

Before: Pre-test values After: Post-test values ($p<0.05$)

Table 4. Tukey post hoc test results of variables in research groups

Group1	Group2	IL-10	IL-18 (ng/l)	Glucose (mg/dl)	Insulin (µIU/ml)	HOMA-IR
control	**Com**	0.001*	0.001*	0.001*	0.001*	0.001*
control	**NS**	0.001*	0.001*	0.001*	0.233	0.001*
control	**Com+NS**	0.001*	0.001*	0.001*	0.001*	0.001*
Com	**NS**	0.001*	0.001*	0.548	0.136	0.994
Com	**Com+NS**	0.017*	0.001*	0.985	0.924	0.297
NS	**Com+NS**	0.001*	0.001*	0.345	0.032	0.191

*($p<0.05$)

Additionally, the results of the ANOVA indicated a significant difference in IL-10 gene expression between the study groups after 12 weeks of intervention (P = 0.001, F = 74.30). In contrast, the findings from Tukey's post hoc test showed a significant difference in the expression of IL-10 gene in the control group relative to the Com group (p = 0.001), the control group compared with the NS group (p = 0.001), and the control group compared with the Com + NS group (p = 0.001) (Figure 2).

Additionally, the findings of variance analysis indicated a significant difference in IL-18 values between the research groups after 12 weeks of intervention (P = 0.001, F = 686.37). In contrast, the findings from Tukey's post hoc test showed a significant difference in IL-18 values between the control group and the Com group (p = 0.001), the control group and the NS group (p = 0.001), and the control group and the Com + NS group (P = 0.001) (Figure 3).

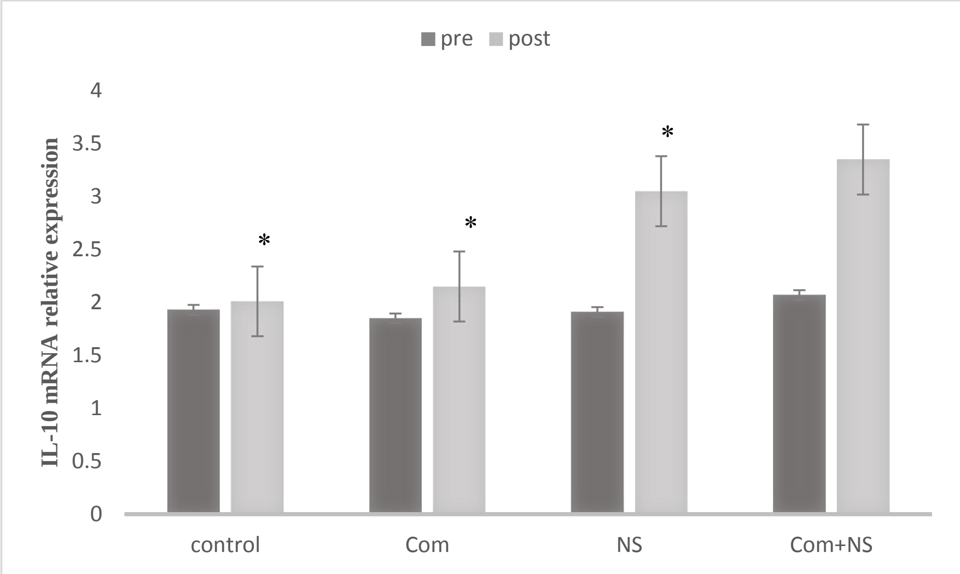

Figure 2. IL-10 changes in groups, Com: combined training (resistance and aerobic interval training), NS: Nettle supplement, Com+NS: combined training + Nettle. The values represent means ± SEM, * Significant differences compared to the control group, p<0.05

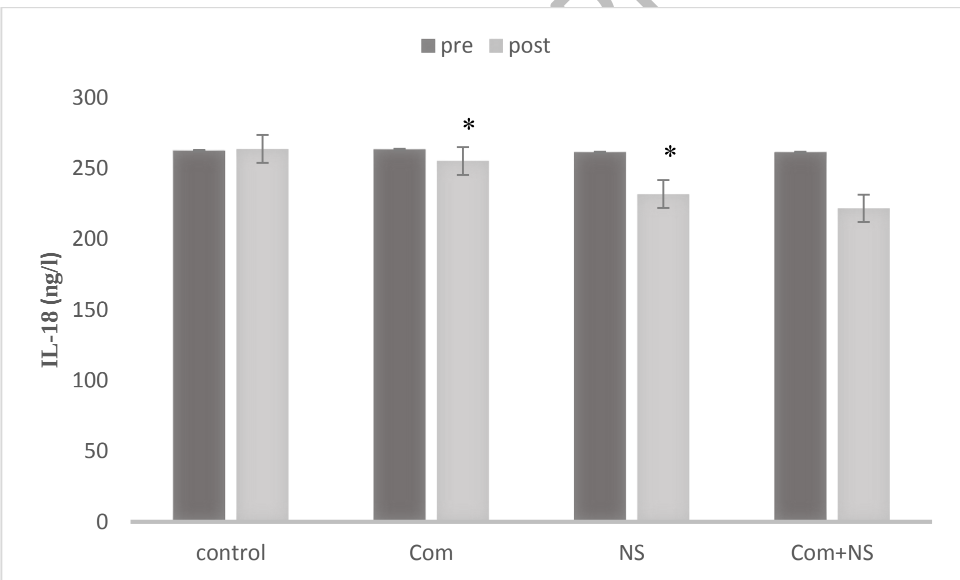

Figure 3. IL-18 (ng/l) changes in groups, Com: combined training (resistance and aerobic interval training), NS: Nettle supplement, Com+NS: combined training + Nettle. The values represent means ± SEM, * Significant differences compared to the control group, p<0.05

Discussion

Exercise inherently increases insulin sensitivity, and when combined with herbal supplements, it has been introduced as one of the most effective options for treating and preventing metabolic disorders and injuries. The purpose of this research was to assess the effect of 12 weeks of combined training with nettle supplementation on IL-10 gene expression and serum levels of IL-18 in women with type 2 diabetes. The findings of this research indicated that 12 weeks of combined training with nettle supplementation had a synergistic effect, resulting in a significant increase in IL-10 expression compared to the pre-test. The findings also indicated a significant decrease in IL-18 and improvement in plasma glucose levels after 12 weeks of combined training with nettle supplementation in women with type 2 diabetes. A significant improvement in these factors was observed in the Com + NS group compared to the other groups.

According to the findings of this research, 12 weeks of combined training significantly decreased pro-inflammatory cytokines in women with type 2 diabetes. The exact mechanism by which training affects IL-18 reduction has not yet been fully elucidated; however, it has been suggested that training programs that improve body mass index (BMI) and reduce body fat may be involved in reducing inflammatory factors. Training inhibits the release of inflammatory mediators, including IL-18, from adipose tissue by reducing sympathetic activity and increasing the production of anti-inflammatory cytokines (5). Hajiforoosh et al. indicated that 8 weeks of combined exercise, combined with the consumption of Mulberry leaf extract, reduced the inflammatory cytokines TNF-α and IL-18 in older adults with type 2 diabetes (21). The researchers stated that exercise, by positively regulating the dual-specificity phosphatase (DUSP) family, reduced inflammatory cytokine expression. This family is responsible for the dephosphorylation of phosphotyrosine and phosphotyrosine residues, which are essential in Mitogen-activated protein kinases (MAPKs). MAPKs play a significant role in stimulating the production of IL-18, a pro-inflammatory cytokine. DUSPs are also involved in inactivating the active stress pathways of protein kinases (22). On the other hand, the active stress pathways of protein kinases play a key role in the cellular response to pro-inflammatory cytokines. Thus, activation of the DUSP gene in blood cells during exercise inhibits the production of pro-inflammatory mediators (23). Accordingly, it appears that the decrease in blood levels of this index after exercise can be attributed to both the anti-inflammatory effects and metabolic adaptation resulting from training. However, based on the results of this research, different periods and training intensities should also be considered for their impact on these pro-inflammatory cytokines.

Another result of the present study is an increase in IL-10 levels following 12 weeks of combined training in women with type 2 diabetes. IL-10 is a protective cytokine that is typically reduced in patients with diabetes. Anti-inflammatory cytokines have also been shown to be expressed in human adipose cells, offering metabolic protection in cases of obesity and diabetes (11, 24). Wigono et al. reported that after combined training, the concentration of IL-10 increased to maximize immunological benefits. It is essential to consider the duration and recovery intervals, as these factors affect the immune response (9). Additionally, a significant increase in serum IL-10 levels was observed in the study by Wang et al., but only in subjects who, in addition to the physical activity intervention, also adhered to dietary restrictions (8). The difference between the subjects in this study and those in other studies lies in the varying exercise protocols and the absence of dietary control.

The lack of information about the interactive effect of training and medicinal plants, especially nettle, on IL-10 and IL-18 makes it challenging to compare the findings of this research with those from other studies. In this research, the expression of IL-10 was enhanced in the NS and Com groups, with the highest increase observed in the Com + NS group. Additionally, the expression of IL-18 and plasma glucose levels in the nettle supplement group and the training plus nettle supplement group showed significant decreases, with the greatest decrease observed in the training plus nettle supplement group. In this regard, Jenk et al. reported that nettle seed oil reduced the plasma levels of pro-inflammatory cytokines, triglycerides, and cholesterol (13). Darabi et al. showed a significant reduction in inflammatory markers in streptozotocin-induced diabetic rats after 21 days of nettle consumption (12). Research indicates that caffeic acid and malic acid, the major phenolic components of nettle, suppress cytokine production by blocking the synthesis of cyclooxygenases in a dose-dependent manner (13). Nettle can also reduce cytokine production by blocking the NF-κB pathway. NF-κB is present in the cytoplasm as an inactive complex when bound to the IkB-α inhibitory subunit. Phosphorylation of this inhibitory subunit causes its spatial deformation, release from the complex, and activation of NF-κB. Nettle promotes the stability of the IkB-α inhibitory subunit by inhibiting phosphorylation and altering the protein structure of IkB-α. As a result, NF-κB remains inactive. Thus, nettle inhibits this crucial pathway in cytokine production (14). The findings of these studies align with the results of this research, which suggest that nettle plays a role in reducing systemic inflammation in diabetic patients. Another result of this research was the improvement in blood glucose levels following combined training (resistance and aerobic interval training) with nettle supplementation, which is consistent with the results of various studies (12, 25) that demonstrate the effectiveness of nettle in blood glucose control. Regarding the mechanisms by which nettle reduces blood glucose levels, it can be stated that nettle increases its effect on muscle cells and enhances glucose transporter activity, leading to increased glucose uptake in muscles and a reduction in hyperglycemia in diabetic patients. Nettle also improves blood sugar levels in type 2 diabetes by acting on pancreatic beta cells and increasing insulin secretion. Another factor in nettle's control of blood sugar is its effect on carbohydrate hydrolysis inhibitors (inhibition of alpha-amylase activity), which ultimately leads to a decrease in hyperglycemia in type 2 diabetes (25, 26).

In this research, the combination of combined training (resistance and aerobic interval training) with nettle supplementation, through synergistic effects, led to improved glycemic control, blood glucose levels, and ultimately, a reduction in inflammation in women with type 2 diabetes. There was also a significant reduction in insulin resistance in all experimental groups. As patients with type 2 diabetes are constantly prone to inflammation, the use of combined training (resistance and aerobic interval training) with nettle supplementation can improve the inflammatory condition. However, the cellular mechanism by which combined training with nettle supplementation affects IL-18 and IL-10 is not well understood and requires further research into the signaling pathways and molecules involved in these processes.

The findings of this study suggest that combined exercise offers a promising solution to reduce chronic inflammation in diabetic patients. The combination of exercises was one of the notable advantages of this research, as this type of exercise, despite its performance limitations, may lead to distinct responses and adaptations compared to other exercise regimens. However, the present study had certain limitations, including the absence of measurements for other inflammatory and anti-inflammatory factors. Evaluating the NF-κB pathway could contribute to a clearer explanation and interpretation of the findings, especially in diabetic subjects. This limitation suggests that future studies should include measurements of these indicators in patients with diabetes.

Study Limitations

Several limitations are inherent in our study. Firstly, the mechanisms underlying the potential enhancement of cytokine levels by the bioactive constituents of nettle supplementation have not been determined. Furthermore, the generalizability of our study is limited due to the exclusion of males from the patient enrollment. Another limitation of our research is the lack of measurement of blood pressure, heart rate, body fat percentage, and lipid profile in the study subjects.

Conclusions

The findings of this research indicate that performing combined training (resistance and aerobic interval training) with nettle supplementation results in a reduction in insulin resistance and fat mass, and has a favorable effect on both anti-inflammatory and pro-inflammatory factors in women with type 2 diabetes. Additionally, as suggested by the findings of this research, combined training (resistance and aerobic interval training) with the use of nettle supplements, and their combination, can be considered, alongside diet and medications, as contributing factors in the process of improving diabetes management. Furthermore, control and positive changes in blood glucose were observed in patients with type 2 diabetes. Therefore, it is recommended that individuals with diabetes utilize the benefits of combined training and nettle supplementation to reduce chronic inflammation associated with diabetes.

Declarations

Funding

None.

Ethical Considerations

This research with the code IR.SSRI.REC-1400-1242 was approved by the ethics committee.

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

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