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The Effect of Saffron Extract Consumption Along with Aerobic Training on Glycemic Indices in Streptozotocin (STZ)-Induced Diabetic Male Wistar Rats

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ABSTRACT

Introduction: Diabetes is one of the most common chronic diseases and one of the main causes of death all over the world. This study aimed to investigate the effect of consumption of saffron extract combined with aerobic exercise on glycemic indices in streptozotocin induced diabetic male rats with.

Method: This experimental study was conducted on 40 adult male rats aged 10-12 weeks weighing 220-250g. Rats were randomly allocated to diabetic control, diabetic exercise, diabetic saffron, and diabetic exercise + saffron groups after the induction of diabetes. Moderate intensity exercise was administered five days a week for eight weeks. Before and after eight weeks glycemic indices were measured, and the data were analyzed with Kolmogorov-Smirnov, one-way analysis of variance, and Tukey's post hoc tests.

Results: The results showed that fasting glucose in the saffron extract + aerobic exercise was significantly lower than the control and the aerobic training groups (p=0.014). Glycosylated hemoglobin in the saffron extract + aerobic exercise group was lower than the control group (p=0.001), and insulin resistance in the saffron group was lower than the control group with aerobic exercise (p=0.001).

Conclusion: Both an aerobic exercise and a consumption of saffron extract can probably prevent diabetes by reducing hyperglycemic indicators. Aerobic exercise and consumption of saffron extract co-administration can exert more beneficial effects.

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Introduction

Diabetes mellitus (DM) is a very severe metabolic endocrine disorder worldwide (1) and includes a heterogeneous group of disorders usually characterized by varying degrees of insulin resistance, impaired insulin secretion (3,2), and increased glucose production. The increase in blood sugar is called hyperglycemia (4).

Diabetes is known as one of the most common chronic diseases and one of the main causes of death worldwide. The prevalence of this disease is increasing, and it is estimated that the number of individuals involved will reach from 171 million people in 2000 to more than 336 million people in 2030 (5). In addition, more than 220 million people worldwide have diabetes, which is estimated to double by 2030 (6). Currently, 11% of Iranians have diabetes. Every 10 seconds, a person in the world dies due to a lack of awareness of diabetes and its control methods. Every 39 seconds, a person in the world loses their leg due to the lack of knowledge about diabetes and its control method. The inappropriate lifestyle of people has caused the spread of this disease (6).

The criteria for diagnosing diabetes mellitus are established based on the agreement between the National Diabetes Information Group and the World Health Organization (3). Normal methods for diagnosing diabetes are based on different urine and blood chemical tests (7).

The main diabetes treatment methods are insulin therapy, diet, and exercise. There is a need to adjust the diet, drug treatment, and exercise to properly treat this complex disease, along with the patient's cooperation.

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Exercise is one of the critical interventions in managing diabetes treatment. Interestingly, abnormalities that cause insulin resistance can be reversed by weight loss, diet, and physical activity (8). However, when exercise is performed simultaneously with nutritional interventions, it can create more effects. Special attention has recently been paid to medicinal plants, including saffron (9).

In addition to being a widely used food seasoning, saffron has many pharmacological effects. It has been reported that a small oral consumption (daily 100mg of saffron or 30mg of saffron hydroalcoholic extract powder) can cause many pharmacological effects in humans (10).

In folk medicine in different parts of the world, saffron is used as a sedative, antispasmodic, fatigue-resistant, glucose and blood-decreasing agent (11). On the other hand, various methods of treatment are recommended for the treatment or control of diabetes, including the use of natural plants, exercise activities, or lifestyle modification (12).

Some plants, such as saffron extract (13), almond (14), and dill (15), have been studied as interventions to reduce blood sugar and fat in people with diabetes; in this regard, one of the effective medicinal plants is saffron (13).

Skourtis et al. (2020) investigated the effect of using saffron supplements on oxidative stress, which plays a critical role in the pathogenesis of diabetes, and showed that saffron extract has an antioxidant effect in diabetic rats (16). In a review study, Sunny (2022) examined the effects of saffron supplementation in diabetic patients and concluded that the use of saffron supplementation in diabetic patients improves metabolic factors, blood sugar control, lipid profile, oxidative stress, and inflammation (17).

Another review study evaluated the effect of aerobic exercise and the consumption of saffron supplementation and showed that consumption of saffron and short-term aerobic physical activity increases antioxidant capacity and cardio-respiratory function and reduces muscle pain. Consumption of saffron and long-term aerobic exercise activity causes increased antioxidant capacity, improved blood sugar, strengthened respiratory diseases, and improved glycemic indices (18).

This study aimed to determine the effect of saffron extract consumption on glycemic indices in male Wistar rats treated with streptozotocin (STZ).

Some limitations the researcher could not control include the impossibility of precise control of the food consumed by rats and the Impossibility of precise control of rats' sleep.

Material and Methods

This study was conducted at the student's expense and with the support of the university's vice chancellor for research and approved by Islamic Azad University, South Tehran Branch.

This experimental study was conducted on male Wistar rats, and the animals were selected randomly and controlled accurately, this research is an experimental type with a post-test design and a control group.

The statistical population of this research included male Wistar rats purchased from the Laboratory Animal Center of Shiraz University of Medical Sciences. The sampling method was random, and 50 rats weighing 200-250g were randomly selected from among the animals.

Then, the selected rats were divided into five groups (n = 10 in each group), including healthy control, diabetic control, diabetic training, diabetic saffron, and training + diabetic saffron. The independent variables of the present study included aerobic training and consumption of saffron extract, and the dependent variable included blood sugar.

All standard conditions were considered, including temperature, relative humidity, free access to water and standard food, and dark/light cycle (12 hours). In addition, the ethical principles of maintaining and working with laboratory animals were observed based on the instructions of the National Institute of Health for the care and use of laboratory animals during the whole period of the study.

All animals were allowed to adapt to the laboratory environment for two weeks. At the beginning of the experiment, there was no statistical difference in the animals' weight and blood glucose levels. The intervention was five days a week and eight weeks with moderate intensity.

The aerobic training protocol consisted of 10 minutes of warm-up (soft running, combined movements of arms and legs, and stretching), 40 minutes of the main training (running with an intensity of 60 to 75% of the maximum heart rate), and finally, 5 minutes of cooling down and returning to the initial state (19).

The target heart rate of the training was obtained from the Karvonen formula:

$$Target\ Heart\ Rate = [(max\ HR - resting\ HR) \times Intensity\%] + resting\ HR$$

The maximum heart rate was obtained from the formula (220-age) (20). A hand-held heart rate monitor (Polar watch) was used, and the subjects' heart rate was controlled. Besides, the Rockport walking test was used to obtain the subjects' VO2 max. Before starting the training protocol, two preparatory training sessions were considered to familiarize the subjects with the training protocol and heart rate counting.

Aerobic training consisted of fast walking in the first two weeks (the intensity in these two weeks was about 60% of the heart rate, and the duration was between 15 and 20 minutes) due to the lack of regular exercise and low physical fitness. The intensity and duration of training increased gradually and continuously every week. The placebo group and saffron supplement group were asked not to do any exercise during this period.

Oral administration of saffron extract was performed by gavage. The rats were taken by the researcher every day to consume aqueous saffron extract and received 25 mg/kg body weight of aqueous saffron extract at 11:00 a.m. using needle gavage (21).

Serum glucose levels were measured using a biochemical kit and enzymatic (glucose oxidase) method (22). In addition, fasting insulin was measured by the competitive enzyme immunoassay method.

The index based on HOMA-IR was used to investigate insulin resistance. High-performance liquid chromatography (HPLC) was also used to measure glycosylated hemoglobin (HbAIC) using the Nycorard (Norway) system.

The rats were sacrificed to measure the studied parameters 24 hours after the last training session, at the end of the 8th week, and the biochemical changes caused by the effect of aerobic training and saffron extract could be investigated.

The rats were sacrificed, and their tissue samples were paraffin-embedded and frozen at -60℃. Laboratory analysis was conducted to obtain the data, and gene expression was determined using the RT-Real Time PCR method.

The measurement tool for this study comprised various equipment and instruments, which included a laboratory digital scale sensitive enough to weigh subjects with a precision of 0.001 grams. In addition, a treadmill specifically designed for the physical activity of laboratory rats was made in Iran as a part of the measurement tool. Various surgical instruments such as carpal blades, scissors, forceps, and others were also included. A timer also adjusted the laboratory environment's darkness and brightness, and a thermometer regulated the temperature. Other necessary equipment included laboratory tubes, Erlen, Sten, alcohol, surgical gloves made of latex, two and a half and five cc syringes, a dissection tray, and cotton.

Descriptive and inferential statistics were used to analyze the data. The Kolmogorov-Smirnov statistical test, one-way analysis of variance, and Tukey's *post hoc* test were used for inferential statistics. The significance level was considered $P \leq 0.05$, and SPSS statistical software (version 26) was used for statistical analysis.

Results

The results showed that fasting glucose in the saffron extract group with exercise Aerobics was significantly lower than in the control group and lower than in the aerobic training group. Glycosylated hemoglobin in the saffron extract group with aerobic exercise was lower than the control group. Insulin resistance was lower in the saffron consumption group, which was lower than the control group with aerobic exercise.

The results indicated a significant difference in fasting glucose levels in different groups (P=0.001). Fasting blood sugar in the aerobic training group, the saffron extract consumption group, and the saffron extract consumption along with the aerobic training group were lower than the control group (P=0.001). Moreover, blood sugar was lower in the saffron extract and aerobic training group than in the aerobic training group (P=0.01).

According to the results, there was no significant difference in fasting insulin levels in different groups (p>0.05), while there was a significant difference in the ranks of glycosylated hemoglobin in the studied groups (p=0.001). Levels of glycosylated hemoglobin in the aerobic training group, the saffron extract consumption group, and the saffron extract in the aerobic training group were lower than those of the control group (p=0.001). In addition, there was a significant difference in the levels of insulin resistance in different groups (p=0.001). Levels of insulin resistance in the aerobic training group, the saffron extract consumption group, and the saffron extract consumption along with the aerobic training group were lower than in the control group (P=0.001) (Table 1).

Table 1. Comparison of the mean and standard deviation of fasting glucose, insulin, glycosylated hemoglobin and insulin resistance levels in the studied groups.

Group	Glucose (milligrams per deciliter)	Insulin (microunits per milliliter)	Glycosylated hemoglobin (percentage)	Insulin resistance (HOMA-IR)
Control	395.2±19.06	6.61±0.93	9.58±0.78	6.45±0.92
Aerobic training	315.33±20.91*	6.15±0.9	7.39±0.44*	4.78±0.78*
Consumption of saffron extract	305.44±4.21*	6.20±0.36	6.97±0.22*	4.67±0.31*
Consumption of saffron extract + aerobic training	291.88±10.69*	6.84±0.70	6.93±0.26*	4.92±0.49*

* Significant difference compared to the control group (p<0.05).

Discussion

Most studies have shown that the consumption of saffron extract and aerobic physical activity significantly affect the glycemic indices of people with diabetes (23-26).

This study aimed to investigate the effect of aerobic training, consumption of saffron extract, and simultaneous consumption of saffron extract and aerobic training on fasting glucose, insulin, insulin resistance, and HbAIC.

Aerobic training led to a significant decrease in blood sugar, insulin resistance, and glycosylated hemoglobin. These results are consistent with those of (20-27).

Exercise activity has been less addressed as a primary factor in the treatment of type 1 diabetes to improve glycemic control. Several studies have failed to show the independent effect of exercise activity in improving glycemic control by measuring HbAIC in type 1 diabetic patients. In contrast, most studies have reported the improvement of glycemic indices in this regard (19, 20, and 27).

Many studies have shown that aerobic training effectively improves glycemic indices, which is in line with the results of the present study. For example, Haji-Hasani et al. (2012) showed that eccentric and concentric exercises cause a significant decrease in blood sugar, HbAIC, and blood lipids in diabetic patients (28). David et al. (2006) reported that following aerobic training, HbAIC significantly decreases in diabetic patients (29).

Researchers in Fenicchia et al. examined diabetic women's glucose and insulin responses to glucose loading using short-term aerobic training. According to (2004), short-term aerobic training improved total glucose concentration but did not significantly change insulin concentration (30).

The present findings showed that resistance to insulin in the aerobic training group rats was significantly lower than in the control group, meaning that eight weeks of aerobic training improved insulin resistance.

Exercise training reduces the amount of insulin resistance in cells. Moreover, exercise training increases insulin sensitivity, resulting in less insulin needed to regulate blood glucose after exercise.

The results of the present study showed that the consumption of saffron leads to a significant decrease in fasting glucose levels and resistance to insulin. This finding is consistent with previous research of Hazman and Ovalı (2015) and Tajaddini et al. (2015). Hazman and Ovalı reported that saffron injection significantly improved FBS and insulin in diabetic rats (31,32). The antidiabetic effects of saffron on diabetic patients are probably exerted through different mechanisms, such as stimulating glucose uptake and increasing insulin sensitivity in skeletal muscle cells by activating AMP-activated protein kinase (AMPK) and mitogen-activated protein kinases (MAPKs) pathways (33). However, further research is still needed to establish this statement for clinical recommendations.

Further, consuming saffron extract and aerobic training has a more significant effect on reducing fasting glucose than consuming saffron extract alone.

The results of this study were consistent with those of Rajabi et al. (2022) and Shavandi et al. (2010). Rajabi et al. (2022) showed that saffron at a concentration of 400mg has a significant effect on homeostatic model assessment for insulin resistance (HOMA-IR) and serum levels of insulin and adiponectin (34), which were consistent with the results of other studies in this regard (23).

Conclusion

Based on the results, both a period of aerobic training and a period of saffron extract consumption could probably control diabetes by reducing hyperglycemic indices. Aerobic exercise and consumption of saffron extract simultaneously can lead to more beneficial effects. However, this was the first time that the impact of aerobic training on the consumption of saffron extract was examined in diabetic rats, and further research is needed to draw more accurate conclusions in this regard.

Declarations

Acknowledgments

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Conflict of Interest

The authors declare the existence of any conflict of interest in this study.

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