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Research Article

The effect of herbal supplement and exercise training on plasma lipid profile in diabetic male rats

Reza Sheikh[1*], Mohammad Gallehdari[2]

Abstract

The present study was conducted to investigate the effect of six weeks of intermittent exercise and curcumin consumption on the lipid profile of diabetic male rats. In an experimental trial, 30 male Wistar rats were randomly divided into six groups (5 rats in each group): control, diabetic, healthy intermittent exercise, intermittent exercise +diabetes, curcumin +diabetes and curcumin+ exercise +diabetes. Diabetes was induced by intraperitoneal injection of streptozotocin poison (50 mg/kg). Intermittent training consisted of 5-12 bouts of intense work (75 to 100% of maximum speed) of 60 seconds with active rest intervals of 75 seconds, six days a week for six weeks. Curcumin was fed to animals by gavage at a dose of 50 mg per kilogram of body weight. After six weeks, unconscious animals and blood samples were collected from their hearts. The data were analyzed using ANOVA statistical test and Bonferroni post hoc test. Induction of diabetes caused an increase in cholesterol, TG and LDL levels (P=0.01). Intermittent training and curcumin, each alone, caused them to decrease (P=0.01). In addition, diabetes decreased HDL while intermittent exercise increased it, but curcumin supplementation did not have a significant effect. The effect of combining interval training with curcumin supplement was significant only for TG and did not have a significant effect on other data. Exercise training and curcumin can have an anti-inflammatory effect with reducing lipid profile and increasing HDL in diabetic animal.

Key Words: **Curcumin supplementation, Diabetes, Intense intermittent exercise, Plasma lipid profile**

1. PhD student in sports physiology, Faculty of Sports Sciences, Shahid Chamran University of Ahvaz, Ahvaz, Iran. 2. Ph.D. in Biochemistry and Sports Metabolism, Department of Physical Education, Faculty of Humanities, Islamic Azad University, Ahvaz Branch, Iran.

*Author for correspondence: dreza.sheikh@gmail.com

R SH: 0000-0001-5554-9250; M G: 0000-0002-0414-6520

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Introduction

Diabetes is a metabolic disease characterized by a hyperglycemic state caused by defects in insulin action (insulin resistance), insulin secretion, or both (Kumar & Sandhya, 2018). It is predicted that the number of people with diabetes will increase to 693 million by 2045. Interestingly, it is estimated that almost half of all people with diabetes (49.7%) are undiagnosed, which is not included in these statistics. The increase in the incidence of diabetes indicates that the complications related to diabetes will be more in the future. Complications such as coronary heart disease, peripheral artery disease, stroke and other conditions are caused by endothelial dysfunction in diabetic conditions (Artha et al., 2019). Also, diabetes is usually associated with undiagnosed dyslipidemia. The condition of dyslipidemia is characterized by abnormalities of two or more parameters of the lipid profile. According to the recommendations of the American Diabetes Association, the measurement of serum lipids periodically should be performed in diabetic patients as a screening method to determine the status of dyslipidemia (Association, 2014).

Because many people with diabetes who have poor blood sugar control experience a dyslipidemic state such as increased triglycerides, low-density lipoprotein cholesterol, and decreased high-density lipoprotein cholesterol (Awadalla et al., 2018). The existence of dyslipidemia phenomenon in diabetes can be explained by changes in plasma lipoproteins that are modulated in fasting and post-meal diabetes patients due to insulin deficiency and increased blood sugar. Cardiovascular mortality is a common complication of diabetes and can be associated with dyslipidemia. Therefore, the control of lipid profile and glycemic index are a vital factor in preventing cardiovascular complications in this disease (Artha et al., 2019).

Fat and carbohydrates provide the most important form of fuel for exercise and athletic activities. During exercise, there are four main sources of endogenous energy: plasma glucose from liver glycogenosis's, free fatty acids (FFAs) released from adipose tissue lipolysis, and from the hydrolysis of triglycerides

Journal of Exercise & Organ Cross Talk

(TG) in very low-density lipoproteins (VLDL- TG); and muscle glycogen and intracellular triglycerides (IMTGs) in skeletal muscle fibers. Fats and carbohydrates are oxidized simultaneously, but their relative use as fuel sources during physical activity is influenced by various factors, including the type of exercise, duration, and intensity of exercise (Muscella et al., 2020). Physical activity has been repeatedly reported to be associated with reduced cardiovascular morbidity and mortality and is recommended for the treatment of hyperlipidemia, which is known to be a risk factor for coronary heart disease (Last et al., 2017). Exercise improves lipid and glucose metabolism in patients with obesity and diabetes. The beneficial effect of exercise in obesity and diabetes is based on the fact that the contraction of skeletal muscles during exercise increases fatty acid and glucose absorption (Fujita et al., 2018).

On the other hand, nowadays, due to the lack of complete treatment of diabetes with synthetic drugs, and the complications that these drugs cause in the long term, the tendency to use natural compounds has increased. Medicinal plants have found a significant role in the treatment of diabetic patients due to their low side effects, availability and effectiveness (Shamsi-Goushki et al., 2020). Meanwhile, curcumin, dipropylmethane, is a hydrophobic polyphenol derived from the rhizome of Curcuma longa plant. This natural compound has a wide range of biological and medicinal activities, including lowering blood cholesterol, lowering blood sugar, antioxidant and anti-inflammatory properties (Mantzorou et al., 2018). Reactive oxygen species are known to be the cause of many complications of diabetes. It is stated that curcumin is an effective neutralizer of reactive oxygen species, the protective function of curcumin on oxidative damage of biological membranes, DNA and protein in various diseases is mainly due to the removal of these radicals by curcumin (Mantzorou et al., 2018).

Streptozotocin's mechanism for killing pancreatic beta cells is through GLUT2 receptors, which damage DNA and alkylate it. DNA alkylation contributes to the damage of pancreatic beta cells by excessive production of nitric oxide (Szkudelski, 2001). In this study, the same method was used to model conditions similar to uncontrolled diabetes in humans. Then, by applying six weeks of curcumin supplementation and performing an interval training program (each one alone, and together), lipid profile changes were investigated in male Wistar rats. Curcumin was used due to its anti-diabetic and nitric oxide neutralizing properties, and interval training was used due to its popularity, and the ability to apply higher tolerable training intensity, and in less time (for each training session).

Materials and Methods

Animals

The statistical population of the present study consisted of 30 male Wistar rats aged 10 weeks and weighing 230-250 grams, which were obtained from the laboratory animal breeding and breeding center of Jundishapur University of Ahvaz. Mice were kept in a special room for keeping animals in Shahid Chamran University of Veterinary Medicine, Ahvaz, with a temperature of 22 ± 2 degrees Celsius and a relative humidity of 50 ± 5% in 50 x 25 cm cages (each 5 mice in one cage). The dark and light cycle was 12:12 with light starting at 7 am. During the period, the animals had free access to standard food and water. After a week of familiarization with the new environment, the animals were randomly divided into six groups, each group containing five mice. The groups include: 1) control healthy (H) (n=5), 2) diabetes(D) (n=5), 3) diabetes and curcumin(D+C) (n=5), 4) diabetes and interval training(D+T) (n=5), 5) Diabetes, curcumin and exercise(D+C+T) (n = 5) and 6) were healthy interval training (H+T).

Induction of diabetes

Diabetes was induced by intraperitoneal injection of Streptozotocin. Streptozotocin (Sigma Aldrich, USA) in sodium citrate solvent and citric acid, a solution with a dose of 50 mg per kilogram of body weight, was injected into the animals. All injections were done between 9 and 9:30 am. 48 hours after the injection, after 12 hours of fasting, fasting blood sugar was measured by making a scratch at the end of the mouse's tail and using a glucometer. Animals with blood sugar higher than 250 mg/dL were considered as diabetic. To equalize the stress in the group of non-diabetic rats, sodium citrate solvent was injected only for them. In order to confirm the diabetes status of the rats, fasting blood sugar was measured every week using blood from the tail vein with a glucometer.

Maximum speed test

Rats were trained on the treadmill for three days. On the fourth day, the test for determining the maximum speed was performed at 11 am in the condition of 4 hours without food. Warm up was done at a speed of 5 meters per minute for 5 minutes. Then, for 5 minutes at a speed of 9 meters per minute, the speed was increased by 2 meters per minute every 2 minutes until the animals stopped. The disability criterion was the inability to return to running on the treadmill within 10 seconds (Charrin et al., 2018).

Exercise training protocol

Intermittent training including running on the rodent treadmill at a speed of 24 to 34 meters per minute, equivalent to 75 to 100% of

Table 1. Interval training program.

Weeks	Repetition × (intensity of light work) duration of light work × (intensity of heavy work) duration of intense work
1	5×1min(24m/min) ×75sec (5m/min)
2	8×1min(24m/min) ×75sec (5m/min)
3	10×1min(28m/min) ×75sec (5m/min)
4	10×1min(30m/min) ×75sec (5m/min)
5	12×1min(30m/min) ×75sec (5m/min)
6	12×1min(34m/min) ×75sec (5m/min)

the maximum oxygen consumption, was performed six days a week for six weeks. This protocol was designed based on the study of Little et al. (2010). The reason for choosing this exercise protocol was that it was very small in volume and the exercise started with a lower intensity than the original protocol, because the animals of the current study were obese. The exercise protocol is given in Table 1.

Supplement

All training sessions were accompanied by 5 minutes of warming up and 5 minutes of cooling at a speed of 5 meters per minute. Pure curcumin powder was obtained from Merck, Germany. Then it was prepared in phosphatidylcholine (Kurita & Makino, 2013) and as a suspension. Animals were gavage six days a week early in the morning (between 7 and 8 am) with a dose of 50 mg per kg of body weight (Wang et al., 2016).

Laboratory measurements

48 hours after the last training session and after 12 hours of fasting, the animals were anesthetized by injecting ketamine (0.87 cc per kg of body weight) and xylazine (0.13 cc per kg of body weight). In addition, blood sampling was done from the heart. In order to evaluate triglyceride, cholesterol, LDL and HDL, the diagnostic kits of Pars Azmoun Company, made in Iran, with a sensitivity of 5 mg/dL were used.

Statistical analysis

One-way analysis of variance (ANOVA) was used to compare the studied groups. Then Bonferroni's follow-up test was used to test each hypothesis.

Results

Diabetic rats experienced an increase in blood cholesterol levels compared to the control rats (P=0.01). Intermittent exercises and curcumin supplementation, each alone, caused a significant decrease in blood cholesterol levels in diabetic groups (P=0.01). However, the combination of interval training and curcumin supplementation did not produce more changes (Figure 1).

The amount of triglycerides in diabetic rats increased significantly (P=0.01), which decreased with intermittent exercise, but this decrease was not significant. However, curcumin supplementation was able to significantly reduce the amount of triglycerides in diabetic rats (P=0.01), and the combination of curcumin supplementation and exercise caused another significant reduction compared to curcumin consumption (P=0.01) (Figure 2).

The diabetic group showed an increase in plasma LDL. Intermittent training and curcumin supplementation, each alone, caused a significant decrease (P=0.01), but the combination did not cause more changes (Figure 3).

Plasma HDL decreased in the diabetic group compared to the healthy group. Exercise increased it again (P=0.01), but curcumin supplement could not have a significant effect on HDL level (Figure 4).

Discussion

This study aimed to investigate the effect of intense intermittent exercise and curcumin supplementation on plasma levels of lipid profile in diabetic male rats. The findings show that the induction of diabetes causes adverse changes in all lipid indices. Nevertheless, fortunately, the data shows that performing intense interval training can improve the condition by improving the level of plasma lipid indices. Consistent studies have shown that diabetes increases the amount of TG, cholesterol and LDL in the blood and decreases HDL. These changes can be caused by the destruction of insulin sensitivity in skeletal muscle cells and other tissues of the body and the lack of regulation of glucose levels in diabetic patients, and therefore, defects in the metabolism of glycoproteins. Wang et al. (2017) found that in the training groups, cholesterol and triglycerides showed a significant decrease compared to the control groups. According to the results of the studies conducted, intense intermittent exercise expression of degraded genes involved in beta oxidation (PPARa, CPT1a and HAD) (and lipogenesis (SREBP1, ACC1 and FAS) due to diet restores fat and improves the lipid profile (Wang et al., 2017).

The most common lipid disorder in type 2 diabetes is an increase in triglycerides, blood cholesterol and a decrease in HDL, which are diagnostic factors. Diseases are metabolic syndrome and diabetes. Regarding the effect of sports activity on lipid profile in-

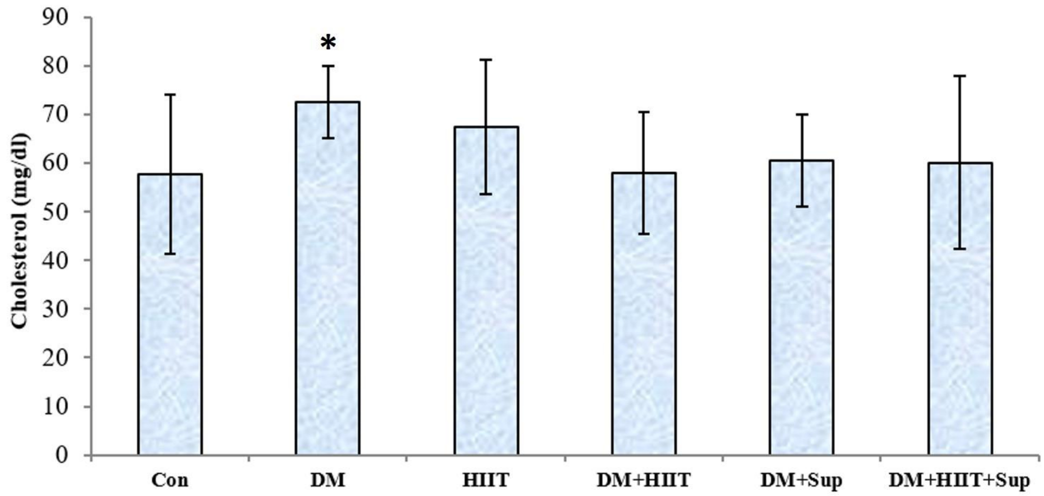

Figure 1. Comparison of mean and standard deviation of plasma cholesterol between six groups. Con: Control, DM: Diabetes Mellitus, HIIT: High Intensity Interval Training, Sup: Curcumin. *: Sign of significant compare to Con group.

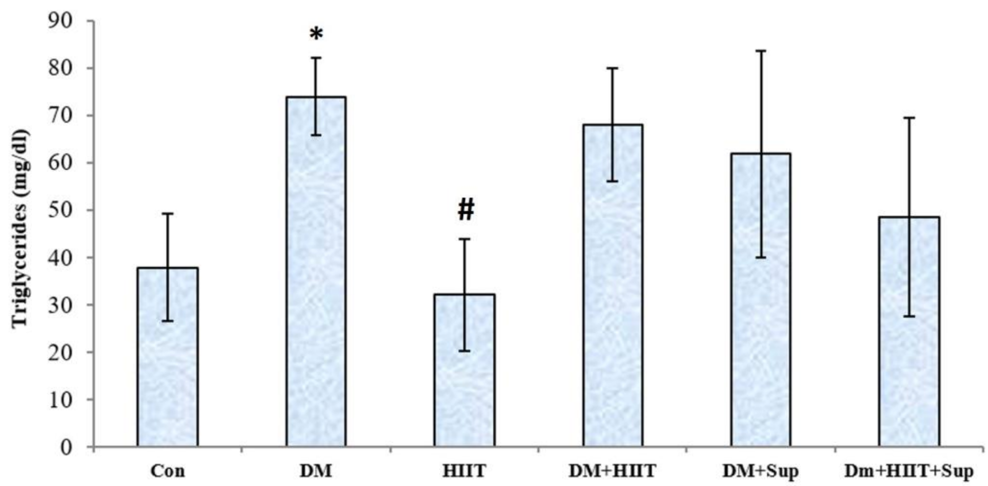

Figure 2. Comparison of mean and standard deviation of plasma triglyceride between six groups. Con: Control, DM: Diabetes Mellitus, HIIT: High Intensity Interval Training, Sup: Curcumin. *: Sign of significant compare to Con group. #: Sign of significant compare to DM group.

-dicators, it can be stated that intermittent exercise, by affecting the activity of the lipoprotein lipase (LPL) enzyme, leads to a decrease in triglycerides and the conversion of VLDL to HDL, and finally, the amount of HDL increases. It also seems that intense intermittent activity has led to an increase in the amount of catecholamine hormones and growth hormone, which can also increase the level of lipolysis (Rashidlamir et al., 2013). The findings of the present study are consistent with those of Magalhães et al. (2020) who found in their research that because the ATP required for sports activity is produced through the process of oxidation and reduction of fats including lipolysis and transfer of fat from the blood to the muscle cytosol and then it would be accessible to the mitochondria of moving muscles, high-intensity interval training can have benefits in improving the lipid profile of people with diabetes and prevent further disruption of total cholesterol and LDL (Alguwaihes et al., 2020).

In addition to the role of intermittent exercise, we found in this study that curcumin supplementation also plays a significant role in improving the lipid status of diabetic groups. Curcumin supplementation was able to reduce LDL, TG and cholesterol in diabetic groups. However, it had no significant effect on HDL levels. Curcumin improves insulin sensitivity by affecting three processes. First, curcumin improves glucose homeostasis by stimulating glucokinase activity in the liver. Second, by increasing the activity of lipoprotein lipase to reduce triglycerides, it promotes lipid metabolism. Thirdly, curcumin independently affects the insulin pathway by expressing the glucose transporter to increase peripheral glucose absorption (Altobelli et al., 2021).

It seems that γ-PPAR, the activator of curcumin, creates a good combination effect that improves insulin secretion, lipid metabolism and the expression of free fatty acid receptors. Therefore, all the mentioned mechanisms probably cause the reduction of glucose and lipids. Several in vitro and in vivo studies have provided strong evidence to investigate the effect of curcumin against diabetes. The data reported in these studies show that curcumin has therapeutic potential to deal with diabetes and its complications. It has been shown that doses of curcumin up to 21 grams per day are safe, tolerable and non-toxic for humans (Naghizadeh & Heydari, 2023).

Based on clinical trials, the therapeutic efficacy of curcumin see-ms promising. Neerati et al. (2014) reported that curcumin supplementation for a 10-day period-reduced hyperglycemia and blood lipids in people with type 2 diabetes treated with glyburide. In addition, LDL, TG and VLDL decreased significantly and HDL increased (Neerati et al., 2014). In a study on overweight and obese type 2 diabetes patients, Na et al. showed that curcumin supplementation (300 mg for 3 months) significantly reduced fasting blood sugar, insulin resistance, and HbA1c. In addition, serum TG and free fatty acids (FFAs) decreased significantly and lipoprotein lipase activity improved. They stated that the effect of curcumin on hypoglycemia is partly due to the reduction of serum FFA, which may be caused by the oxidation and utilization of free fatty acids (Na et al., 2013).

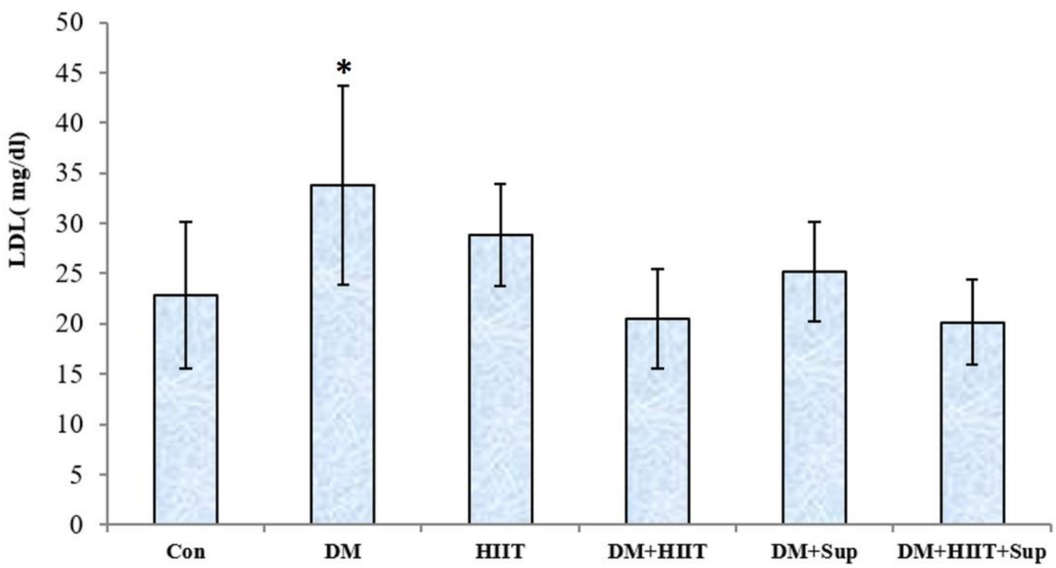

Figure 3. Comparison of mean and standard deviation of plasma LDL between six groups. Di: Diabetes, HIIT: High Intensity Interval Training, Cur: Curcumin. *: Sign of significant compare to Con group.

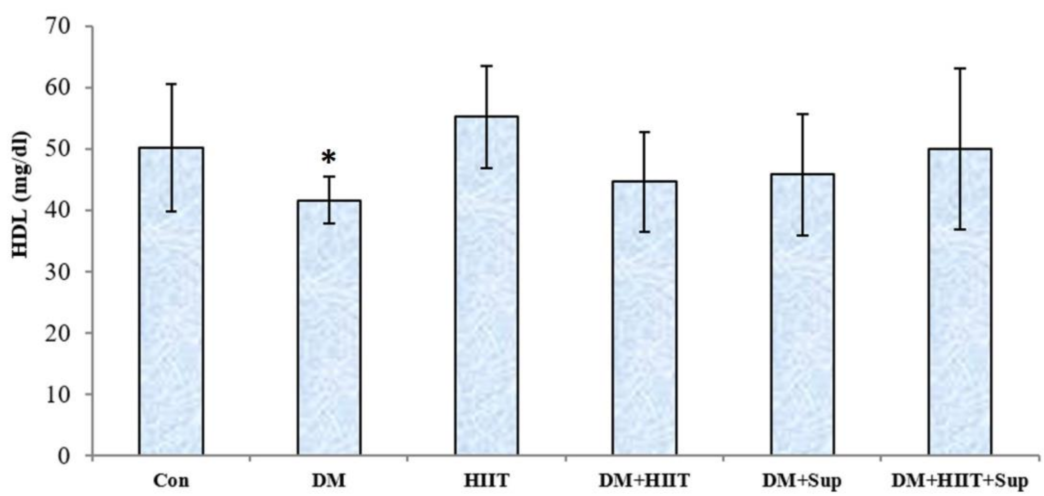

Figure 3. Comparison of mean and standard deviation of plasma HDL between six groups. Di: Diabetes, HIIT: High Intensity Interval Training, Cur: Curcumin. *: Sign of significant compare to Con group.

Journal of Exercise & Organ Cross Talk

In the present study, it was shown that the combination of curcumin supplement and intermittent exercise could improve lipid indices to some extent compared to intermittent exercise or curcumin supplement alone. However, the combination of these two did not create a significant effect and the difference was small. Naghizadeh et al. (2022) their research found that 12 weeks of HIIT and curcumin supplementation alone are associated with significant changes in glycemic indices, adiponectin and lipid profiles of obese men with type 2 diabetes with high blood lipids, which is in line with the present study. On the other hand, they reported that the interactive effect of HIIT with curcumin supplementation had the highest percentage of beneficial and significant changes on glycemic indices, adiponectin and lipid profile (Naghizadeh & Heydari, 2023), which is not in line with the present study. This difference may be due to the difference in the duration of the research (12 weeks - 6 weeks).

Conclusions

The present study showed that both intermittent exercise and curcumin supplementation could improve blood lipid indices, which are disturbed in diabetic conditions, to a certain extent. There are studies that support our findings; therefore, it can be suggested that diabetics perform periodic exercises in order to control and reduce the complications of diabetes, especially complications caused by blood lipid disorders, and use curcumin supplement, which has been proven safe in the stated doses.

What is already known on this subject?

Diabetes is a metabolic disease characterized by a hyperglycemic state caused by defects in insulin action (insulin resistance), insulin secretion, or both.

What this study adds?

both intermittent exercise and curcumin supplementation could improve blood lipid indices, which are disturbed in diabetic conditions, to a certain extent.

Organ Cross-Talk Tips:

- Cross-talk between skeletal muscle and adipose tissue following regular exercise and curcumin supplementation modulates lipid profile in diabetes.
- Understanding the cellular and molecular events of this cross-talk requires future research.

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Compliance with ethical standards

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

Ethical approval Experimental protocols were approved by the Ethics Committee of Islamic Azad University, Ahvaz, Iran (Ethcal code: IR.IAU.AHVAZ.REC.1400.056).

Informed consent Animal study.

Author contributions

Conceptualization: M.G., R.SH.; Methodology: M.G., R.SH.; Software: R.SH.; Validation: M.G.; Formal analysis: M.G.; Investigation: M.G.; Resources: M.G.; Data curation: M.G., R.SH.; Writing - original draft: M.G., R.SH.; Writing – review & editing: M.G.; Visualization: M.G.; Supervision: M.G.; Project administration: M.G., R.SH.; Funding acquisition: R.SH.

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