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ORIGINAL ARTICLE

The Effect of Curcumin Supplementation on Irisin, Nesfatin-1, and Leptin Levels in Rats Subjected to Long-Term Treadmill Exercise

[1]Aysun Delıoglan, [2]Zarife Pancar*, [1]Muhammet Kaan Darendeli, [1]Yesim Kılıcoglu, [3]Hasan Ulusal, [1]Mufit Dal, [4]Ali Muhittin Tasdogan, [5]Xu Yan

[1]Gaziantep University, Department of Physical Education and Sport, Gaziantep, Turkey.
[2]Gaziantep University, Faculty of Sports Science, Department of Physical Education and Sports Gaziantep, Turkey.
[3]Gaziantep University, Department of Medical Biochemistry, Gaziantep, Turkey.
[4]Hasan Kalyoncu University, Faculty of Health Sciences, Gaziantep, Turkey.
[5]Victoria University, Institute for Health and Sport, Melbourne, Australia.
***. Corresponding Author: Zarife Pancar**; **E-mail:** z_pancar@hotmail.com

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ABSTRACT

Background. Curcumin supports metabolism with its antioxidant and anti-inflammatory effects. It is particularly effective in reducing metabolic stress caused by prolonged exercise. **Objectives.** This study aimed to investigate the impact of curcumin supplementation on Irisin, Nesfatin-1, and Leptin hormone levels in rats undergoing prolonged treadmill exercise. **Methods.** A total of 32 male Wistar-Albino rats were divided randomly into four equal groups: The control group (n=8), the curcumin group (n=8), the treadmill group (n=8), and the curcumin+treadmill group. The experiment lasted eight weeks, with one week of treadmill acclimatization. No intervention was applied to the control group. Curcumin was given at 200 mg/kg, and treadmill exercise was performed for 30 min at 45 cm/s, three days weekly. The Curcumin+Treadmill group was fed 200 mg/kg/day and performed three days a week for 30 minutes at an average speed of 45 cm/s. After the study, rats were euthanized, and blood samples were collected for analysis. Irisin, nesfatin-1, and leptin hormone levels were determined using the ELISA method. **Results.** Our study showed a significant increase in irisin levels in both the curcumin and exercise groups compared to the control group. For nesfatin-1, levels were significantly decreased in the curcumin group compared to the control, while they were significantly increased in the curcumin+exercise group. Leptin levels were the highest in the exercise group, showing a significant increase compared to the control group ($p<0.05$). In contrast, the leptin levels in the curcumin group were significantly lower than those in the exercise group. **Conclusion.** This study demonstrates that combining curcumin supplementation and exercise positively affects irisin, nesfatin-1, and leptin hormone levels, contributing to metabolic balance.

INTRODUCTION

Curcumin, a natural compound renowned for its extensive biological activities and cellular mechanisms, is derived from the ginger family. Characterized by its orange-yellow color and crystalline powder form, curcumin is the primary component extracted from the

underground root and stem of the turmeric plant (1). Recognized for its diverse impacts on human health, curcumin is attributed to anticarcinogenic, antiviral, antioxidant, anti-inflammatory, antidiabetic, antibacterial, and anticoagulant properties. Moreover, it aids in the elimination of reactive oxygen species, nitrogen dioxide, hydroxyl radicals, and superoxide ions from the body (2, 3).

The broad spectrum of targets affected by curcumin, encompassing transcription factors, kinases, enzymes, adhesion molecules, proteases, cell surface receptors, transporters, and apoptotic factors, underscores its potential suitability in treating various diseases, including bacterial and viral diseases, inflammation, cancer, neurodegenerative diseases, and diabetes (4). Numerous studies conducted in rodent models have sought to elucidate the multifaceted properties of curcumin, including its antioxidant, anti-inflammatory, hypoglycaemic, and anticancer effects. Notably, curcumin is considered a safe and cost-effective dietary supplement compared to other pharmacological agents used to manage blood sugar and lipid levels (4).

The number of studies exploring the correlation between exercise-induced increases in free radicals and the preventive effect of curcumin on cellular damage caused by these free radicals is relatively limited. Generally, existing research suggests that curcumin enhances post-exercise recovery and positively influences performance outcomes (5-8). Given this background, there is interest in understanding the impact of turmeric (curcumin) supplementation in conjunction with exercise on certain hormones within the body. While curcumin's antioxidant and anti-inflammatory properties are well known, the role of these effects on hormones thought to influence energy balance and metabolic health has been less studied. Hormones such as leptin, irisin, and nesfatin-1 are worthy of research because they influence energy balance, fat metabolism, and oxidative stress management. Investigating the effects of curcumin on these hormones may shed light on developing new therapeutic strategies in both sports and health.

Furthermore, the data obtained from this study may help reveal curcumin's possible benefits on metabolic health in its long-term use. Therefore, studying the effects of curcumin on metabolically important hormones such as leptin, irisin, and nesfatin-1 is a logical and innovative approach. This study aims to investigate the effects of curcumin supplementation on irisin, nesfatin-1, and leptin hormone levels in rats subjected to regular running exercise.

MATERIALS AND METHODS

Study Design. This study randomly divided 32 male Wistar-Albino rats into four equal groups: Control Group, Curcumin Group, Treadmill Group, and Curcumin+Treadmill Group. The experiment continued for eight weeks. Animals in the exercise group underwent adaptation sessions on the treadmill for two weeks before the experiment. The control group did not receive any intervention. The curcumin group received a dose of 200 mg/kg three days a week. Rats in the treadmill group performed treadmill exercise at an average speed of 45 cm/s for 30 minutes three days a week. The Curcumin+Treadmill group received the same treadmill protocol with curcumin supplementation. At the end of the study, rats were decapitated, and blood samples were collected for the measurement of hormone levels. The study procedure was approved by the Gaziantep University Animal Experiments Local Ethics Committee (dated 01.06.2023/Protocol No: 307).

Animals. Wistar-Albino rats weighing 200-250 grams were used in the study. The rats were obtained from the Gaziantep University Experimental Animals Application and Research Centre, where their feeding and care were provided. Rats were housed under standard laboratory conditions (constant ambient temperature of 22-25°C, a 12-hour light/12-hour dark cycle, and 40 ± 5% humidity). Rats were fed a single type of 8 mm standard rat pellet feed ad libitum and were provided with access to water freely. Rats were randomly divided into four groups, with 8 rats in each group (Figure 1).

Control: Rats were fed with standard feed and water throughout the experiment, with no intervention.

Curcumin: Rats were fed standard feed and administered 200 mg/kilogram (kg)/day of curcumin three times a week during the eight-week experiment using a single-dose gavage method.

Treadmill: During the eight-week experiment, rats were fed standard chow and

subjected to treadmill exercise three days a week for 30 minutes at an average speed of 45 cm/s.

Curcumin+Treadmill: Rats were fed standard chow and administered a single dose of curcumin three days a week for eight weeks. In addition, they underwent treadmill exercise three days a week for 30 minutes at an average speed of 45 cm/s.

Curcumin was orally administered via gavage at 200 mg/kg/day for eight weeks. It was dissolved in corn oil and freshly prepared daily. Rats were weighed weekly throughout the study.

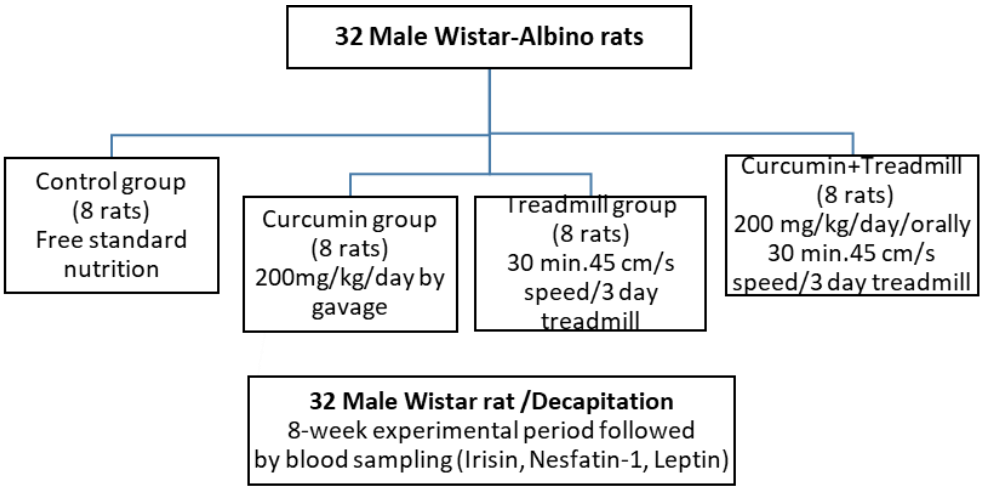

Figure 1. Schematic representation of the experimental design.

Blood Sampling. We measured variables in the blood to accurately assess hormone levels and reliably analyze these hormones' metabolic responses. Blood samples are crucial for tracking changes in biological processes and hormone levels. After the eight-week experimental period, gel tubes with yellow caps (Vacutainer biochemistry tube), blood samples were collected following decapitation using sterile surgical instruments under controlled operating theatre conditions. Subsequently, the collected blood was centrifuged at 4000 rpm for 10 minutes, and the resulting plasma was separated and stored at -80 °C until further analysis. Curcumin utilized in the experiment was obtained from the Cayman Chemical Company in the US. Rat ELISA kits used in the analysis of blood samples included Irisin (catalog no: 201-11-1713), Nesfatin-1 (catalog no: 201-11-1426), and Leptin (catalog no: 201-11-0562) from Shanghai SunRed Biological Technology Co., Ltd. The ELISA kits comprised: Standard solution (96 ng/ml - amount: 0.5 ml), Standard diluent (amount: 3 mL), ELISA microplate strips (96 wells), Washing solution (amount: 20 mL), Biotin-irisin Ab (1 mL), Chromogen A solution (amount: 6 mL), Chromogen B solution (6 mL), Stop solution (amount: 6 mL), along with a manual detailing operating conditions and two gelatins for plate coverage.

Treadmill Exercise Procedure. An eight-week exercise regimen was implemented for the groups designated for physical activity. Groups 3 and 4 underwent a two-week acclimatization phase on the treadmill. During this adaptation period, rats were exercised on a treadmill (Produced by ELİKMAK company, Elazıg) featuring five lanes and distinct sections tailored for rats at a leisurely speed of 10 centimeters per second (cm/s) and an inclination of 0% for 15 min daily. Upon commencement of the experimental period, rats were subjected to running at an average speed of 45 cm/s for 30 minutes per day, three days a week, following the treadmill protocol (9). The rats were given an electrical stimulus of 100 millivolts when necessary to ensure uninterrupted running during the exercise sessions.

Statistical Analysis. Research data was analyzed with the SPSS 22.0 software package. Various methods were employed to assess the normal distribution of the data, including the Shapiro-Wilk test, evaluation of homogeneity of variances, histogram graph, kurtosis, steepness, q-q plot, and branch leaf graph. Based on these analyses, it was determined that the data exhibited

a normal distribution. Subsequently, a One-Way ANOVA, a parametric analysis, was performed, followed by the LSD test to identify significant differences among the groups. The data obtained from the research were presented in tabular form, indicating the mean, standard deviation, standard error, and significance level, with $p<0.05$ considered statistically significant.

RESULTS

The analysis of the data obtained at the end of the application is presented in Tables 1 and 2.

Statistical Table 2 presents outcomes regarding the impact of curcumin supplementation on irisin, nesfatin-1, and leptin hormone levels in rats subjected to prolonged running exercise.

Compared with the control group, irisin levels were significantly higher in the curcumin group ($p=0.000$). The treadmill and curcumin+treadmill groups exhibited higher irisin levels than the control and the curcumin groups ($p=0.000$), without significant differences between the exercise and curcumin+treadmill groups. When compared with the control group, it was found that the nesfatin-1 levels were significantly lower in the curcumin group ($p=0.013$) and significantly lower in the curcumin+treadmill group, with no significant differences in the treadmill group. For Leptin levels, the treadmill group exhibited significantly higher values when compared to the control group ($p<0.017$). The curcumin group had significantly lower values than the exercise and curcumin+treadmill groups.

Table 1. Weights of the animals.

Groups	Pre-test	Post-test		
	Mean+Std.D	Mean+Std.D	t	p
Control Group	167.71 + 24.88	291.0 + 18.52	-13.10	0.000
Curcumin Group	178.5 + 31.6	265.62 + 21.41	-6.01	0.001
Treadmill Group	173.87 + 26.16	229.12 + 27.96	-6.47	0.000
Curcumin+Treadmill	181.00 + 25.04	264.75 + 26.79	-6.07	0.001

Table 2. Effects of curcumin and exercise on Irisin, Nesfatin-1, and Leptin levels.

Parameter	Control	Curcumin	Treadmill	Curcumin+Treadmill
Irisin (ng/mL)	7.02 + 0.48	10.01 + 1.30[a]	11.64 + 0.80[a-b]	11.63 + 1.21[a-b]
Nesfatin-1 (ng/mL)	935.27 + 62.69	724.20 + 89.42[a]	898.46 + 69.18[a]	973.02 + 29.53[a]
Leptin (ng/mL)	182.98 + 34.90	174.78 + 31.83[c]	221.38 + 13.87[a]	198.14 + 35.28

Data represent the mean ± SD; (n=8); $p<0.05$; Differences between the groups were analyzed using one-way ANOVA with LSD post hoc method.

[a]: In comparison with control groups. [b]: In comparison with the curcumin groups. [c]: In comparison with exercise groups. [d]: In comparison with control groups.

DISCUSSION

In this study, we examined the beneficial effects of curcumin supplementation and treadmill exercise on the levels of irisin, nesfatin-1, and leptin. Our findings revealed that exercise significantly increased irisin levels, and curcumin supplementation also led to elevated irisin levels compared to the control group. Notably, in the group receiving curcumin supplementation alongside exercise, irisin reached similar levels as those observed in the exercise-only group. Previous studies have consistently reported increased blood irisin levels in response to exercise (10-14). This increase in irisin is associated with transforming white fat cells, typically involved in energy storage, into metabolically active brown fat cells, thereby enhancing energy expenditure (14, 15). Irisin has a positive effect on conditions like hyperlipidemia and hyperglycemia, prevalent in those with obesity and metabolic syndrome. It facilitates glucose uptake by skeletal muscles and improves hepatic glucose and fat metabolism (16).

Additionally, in a study conducted on rodents, the beneficial effects of energy drinks and treadmill exercises were observed, highlighting the positive influence of exercise on irisin levels (10). Exercise-induced oxidative stress leads to the generation of free radicals within the body. However, curcumin, known for its antioxidant properties, can counteract this oxidative damage. It acts as a chain-breaking antioxidant and a phenolic agent, effectively mitigating the free radical mechanism induced by exercise. Numerous animal

experiments have demonstrated that curcumin enhances antioxidant capacity and protects against oxidative stress (17-19).

In this study, we observed significantly lower nesfatin-1 levels in the curcumin group compared to the control group. In contrast, the curcumin+exercise group exhibited significantly higher nesfatin-1 levels than the control and the curcumin groups. The physiological, histological, and medical aspects nesfatin-1 have been extensively investigated in the literature (20), highlighting its role in appetite and metabolism and as a potential biomarker influencing various body systems (21). Research on nesfatin-1, primarily conducted on humans, has indicated that exercise can modulate its levels, although definitive conclusions are still pending. Nesfatin-1 exhibits prolonged effects on food intake and body temperature, with its impact varying based on the duration of administration. A pioneering study demonstrated that swimming stress, a psychological and physiological model of acute stress, can decrease food intake via nesfatin-1 neurons, possibly mediated through the glutamatergic system. The involvement of the glutamatergic system in stress-induced activation of the neuronal circuits suggests a mechanism whereby synthesis of receptors capable of detecting peripheral stress signals affects peripheral tissues to reduce food intake during acute stress, thereby suppressing appetite (22).

Regarding its direct effect on the cardiovascular system, studies have indicated that nesfatin-1 may influence peripheral cardiovascular responses by affecting peripheral arterial resistance and cardiac contractility (23, 24). Furthermore, in investigations into testosterone secretion, central administration of nesfatin-1 led to a significant increase in plasma FSH, LH, and testosterone levels in rats without significant alterations in plasma GnRH levels compared to controls. These findings suggest that central injection of nesfatin-1 regulates male HPGA (Hypothalamo-pituitary-gonadal) by elevating plasma FSH, LH, and testosterone levels (25).

Leptin levels were observed to be the lowest in the curcumin group and highest in the exercise group, with statistically significant differences noted between the control group and the exercise group, as well as between the exercise group and the curcumin group.

Leptin plays various regulatory roles, particularly in energy intake and metabolism. Besides suppressing the appetite center and inhibiting lipogenesis, leptin regulates T cell activation and actively modulates inflammatory reactions and stress responses through the Hypothalamic-Pituitary-Adrenal (HPA) axis (26, 27). In both humans and rodents, leptin functions as an adipocyte-derived protein crucial for estimating and utilizing energy stores in the body (27, 28). Experimental studies involving leptin administration to animals have shown increased metabolic rate and reduced food intake (29).

In another study, animals that received external leptin intake exhibited an increase in VO2, whereas no such increase was observed in the rats in the control group. Furthermore, considering the rise in oxygen consumption in the experimental group, it was inferred that leptin deficiency in rats led to a decrease in metabolic rate. Consequently, it was noted that leptin-deficient rats could not effectively utilize fat as an energy source (30). Another study aimed to elucidate the relationship between acute exercise and leptin hormone levels. According to the findings, leptin levels remained unchanged even after acute exercise lasting more than 30 minutes (31). However, in studies involving 60 minutes of continuous exercise, significant alterations in leptin hormone levels were observed (32, 33). The Leptin hormone regulates food intake in the digestive system and modulates energy metabolism by influencing the involuntary parasympathetic nervous system. The impact of physical exercise on leptin hormone release remains a topic of debate. A literature review has underscored that the effects of exercise on leptin hormone release vary, depending on the duration and calorie expenditure of the exercise. Consequently, it can be inferred that changes in leptin hormone levels are influenced by factors beyond exercise alone.

CONCLUSION

In conclusion, this study highlights the potential metabolic effects of curcumin supplementation and exercise on key hormones associated with energy balance, specifically leptin, irisin, and nesfatin-1. Our findings demonstrate that curcumin, known for its antioxidant and anti-inflammatory properties, can significantly influence the levels of these hormones in conjunction with exercise, suggesting a synergistic effect. Notably, irisin levels showed a marked increase in both the curcumin and exercise groups, indicating that

curcumin may support fat metabolism and energy expenditure through its effect on irisin. In the curcumin-only group, nesfatin-1 levels decreased compared to the control. In contrast, the curcumin+exercise group increased, implying that combining curcumin and exercise may positively modulate appetite regulation and metabolic processes.

Furthermore, the highest leptin levels were observed in the exercise group, supporting the role of physical activity in regulating energy intake and metabolism. These results suggest that curcumin supplementation, particularly with exercise, may contribute to metabolic health by modulating hormones that play crucial roles in energy homeostasis and oxidative stress management. Future research should further explore these effects in human models to validate curcumin's potential as a metabolic supplement in exercise-based interventions.

APPLICABLE REMARKS

- The study shows that combining curcumin supplementation and exercise supports metabolic balance by positively affecting irisin and nesfatin-1 levels.
- Curcumin may accelerate recovery and maintain hormonal balance by reducing exercise-induced oxidative stress, significantly benefiting exercise performance.
- These findings suggest that curcumin may effectively support metabolic health combined with exercise and contribute to developing new therapeutic strategies.

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AUTHORS'' CONTRIBUTIONS

Study concept and design: Zarife Pancar, Aysun Delioglan. Acquisition of data: Muhammed Kaan Darendeli, Mufit Dal, Hasan Ulusal, Yesim Kılıcoglu. Analysis and interpretation of data: Muhammed Kaan Darendeli, Zarife Pancar, Aysun Delioglan, Hasan Ulusal. Drafting the manuscript: Ali Muhittin Tasdogan, Zarife Pancar, Aysun Delioglan. Critical revision of the manuscript for important intellectual content: Zarife Pancar, Ali Muhittin Tasdogan, Muhammed Kaan Darendeli, Aysun Delioglan, Xu Yan, Hasan Ulusal, Mufit Dal, Yesim Kılıcoglu. Statistical analysis: Aysun Delıoglan, Muhammed Kaan Darendeli. Administrative, technical, and material support: Yesim Kılıcoglu, Aysun Delioglan, Xu Yan. Study supervision: Zarife Pancar, Ali Muhittin Tasdogan, Xu Yan.

CONFLICT OF INTEREST

There is no conflict of interest between the authors.

FINANCIAL DISCLOSURE

The authors declare no financial conflicts of interest.

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ETHICAL CONSIDERATION

Approved by the Gaun Animal Experiments Local Ethics Committee (01.06.2023/307).

ROLE OF THE SPONSOR

There is no sponsor.

ARTIFICIAL INTELLIGENCE (AI) USE

No AI tools were used in this study.

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