

## Research Article

# The effect of aerobic exercise combined with mealworm protein consumption on oxidant, antioxidant indices and FGF21 and mTOR gene expression in soleus muscle of rats with fatty liver

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## Abstract

Non-alcoholic fatty liver disease (NAFLD) is a prevalent chronic liver disorder associated with fat accumulation, sedentary lifestyle, and poor diet. This study examined the effects of aerobic exercise and mealworm protein supplementation on oxidative balance and the expression of FGF21 and mTOR genes in the soleus muscle of rats with NAFLD. Fifteen male Wistar rats (250 ± 50 g, aged 10–12 weeks) were randomly assigned to five groups: healthy control, fatty liver, fatty liver + supplement, fatty liver + exercise, and fatty liver + supplement + exercise. A high-fat diet was used to induce NAFLD. The exercise group performed moderate-intensity treadmill running (12–16 m/min) for eight weeks, five days per week. Mealworm protein (20 mg/kg) was administered via oral gavage. Liver and muscle tissues were analyzed using Real-Time PCR (FGF21, mTOR) and ELISA (TOS, TAC). Combined treatment significantly increased FGF21 expression (~130%;  $p = 0.022$ ), reduced total oxidant status (~40%;  $p = 0.001$ ), increased total antioxidant capacity (~45%;  $p = 0.009$ ), and lowered SGPT and ALP levels (~32% and ~38%, respectively;  $p < 0.05$ ). mTOR expression showed no significant change ( $p = 0.113$ ), and the 18% SGOT reduction was not significant ( $p = 0.169$ ). The combination had greater effects than either treatment alone. Aerobic exercise combined with mealworm protein supplementation improves oxidative balance and FGF21 expression in NAFLD. This integrative strategy may offer a novel therapeutic approach targeting liver-muscle metabolic interactions. Further human studies are recommended.

**Key Words:** Aerobic exercise, Protein supplement, Nonalcoholic fatty liver disease, FGF21, Oxidative stress


## Introduction

Non-alcoholic fatty liver disease (NAFLD) is one of the most common global health problems that has attracted the attention of many researchers due to its increasing prevalence, especially in developed countries (Stefan et al., 2022). This disease is defined by the abnormal accumulation of fat in liver cells that occurs without alcohol consumption (Eslamparast et al., 2017). Predictions indicate that by 2030, NAFLD will be one of the leading causes of death from liver diseases (Allen et al., 2022; Sayanthan et al., 2023).

This disease is also associated with a sedentary lifestyle, high-fat and high-calorie diet, and other unhealthy habits. However, many studies have shown that a sedentary lifestyle and high-fat diet are associated with an increased prevalence of NAFLD (Byrne & Targher, 2022). The prevalence of NAFLD is influenced by various factors, including age, gender, ethnicity, obesity, insulin resistance, type 2 diabetes, and problems such as sleep apnea (Hayashi et al., 2023). On the other hand, exercise training, especially aerobic training, has been shown to have positive effects on reducing liver fat accumulation, reducing oxidative stress, and improving chronic inflammation (Nam et al., 2023). It activates multiple signaling pathways, including PPAR $\alpha$ , AMPK, and SIRT1, and improves glucose and lipid metabolism (Saxton & Sabatini, 2017; Xing et al., 2022). The communication between the liver and muscle through the exchange of metabolic signals (hepatomuscular cross-talk) plays an important role in the prevention and management of NAFLD (Mounesan et al., 2023). This communication involves hormones such as FGF21, which are involved in regulating energy and fat metabolism as well as reducing inflammation (Tillman & Rolph, 2020). Exercise training can increase the expression of genes related to fat metabolism, such as FGF21, and improve liver function (Yan et al., 2023). The proteins in millet, due to their essential amino acids, can activate key signaling pathways such as mTOR, leading to increased protein synthesis and muscle growth. Also, consumption of these proteins can lead to a decrease in fat accumulation in the liver and an improvement in the health of

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this tissue (Gimeno et al., 2014). In this regard, aerobic exercise and nutritional interventions such as protein supplementation can have positive effects on the disease status by affecting these pathways (Morton et al., 2018). Previous studies have examined the independent effects of exercise training or protein supplementation on NAFLD, but limited research has examined the combined effects of these two interventions on liver-muscle cross-talk and metabolic changes (Chen, 2020; Townsend et al., 2020). The aim of this study was to investigate the combined effects of aerobic exercise and mealworm protein supplementation on the oxidant-antioxidant status and expression of FGF21 and mTOR genes in the soleus muscle of rats with fatty liver.

Therefore, beyond examining the individual effects of exercise or dietary protein, this study is among the first to investigate the combined impact of aerobic training and mealworm protein supplementation on the hepatic-muscular axis in a fatty liver model. This integrated approach aims to elucidate novel therapeutic interactions between skeletal muscle and liver tissue through shared metabolic and signaling pathways.

## Materials and Methods

### Animals

This was an experimental study conducted on 15 male Wistar rats, with an average weight of  $250 \pm 50$  g and an age of 10 to 12 weeks. The animals were housed under standard conditions including a 12-hour light/12-hour dark cycle, a temperature of 20 to 23°C, and a relative humidity of 50%. The animals were randomly divided into five groups: healthy control group (n=3), fatty liver group (n=3), fatty liver + supplement group (n=3), fatty liver + exercise group (n=3), and fatty liver + supplement + exercise group (n=3) (Lee et al., 2021).

The number of animals used in each group (n = 3) was selected based on previous peer-reviewed studies that demonstrated detectable changes in gene expression and oxidative stress markers using similar sample sizes (Erel, 2004; Nam et al., 2023). Moreover, ethical considerations regarding the reduction in animal use, in line with the 3Rs (Replacement, Reduction, and Refinement) principle, were also taken into account to minimize animal suffering while still achieving the scientific objectives of the study. While this design allowed the detection of statistically significant differences in several key outcomes, it is acknowledged that a small sample size may increase the risk of Type II errors and limit the generalizability of the findings. Future studies with larger groups are therefore recommended to validate and extend these observations (Charan et al., 2013; Festing & Altman, 2002). To induce fatty liver, animals in the fatty liver groups were fed a high-fat diet containing 15% animal fat, 4% cholesterol, and 1% cholic acid for 8 weeks (Eslam et al., 2020).

This diet was obtained from Sigma and was freely available to the animals. After the end of the feeding period and before the start of the interventions, blood samples were taken from the animals. Then, the levels of liver enzymes SGPT (alanine aminotransferase) and SGOT (aspartate aminotransferase) were measured using commercial kits (Pars Azmun, Iran) and a spectrophotometer (Biochrom WPA Lightwave II model) (Eslam et al., 2020; Habibullah et al., 2024).

### Exercise program

The aerobic exercise protocol was performed on a treadmill for 8 weeks, 5 days a week. Each session consisted of three phases: warm-up (5 min at an intensity of 5 m/min), main activity (20 min at a moderate intensity of 12-16 m/min and a zero-degree incline), and cool-down (5 min at an intensity of 5 m/min). This protocol was based on previous studies demonstrating its efficacy in improving metabolic and oxidative parameters in rodent models of NAFLD. This level of intensity has been shown to activate key signaling pathways such as AMPK and PGC-1 $\alpha$  without inducing excessive physiological stress, making it appropriate for evaluating adaptive responses in liver-muscle interactions (Nam et al., 2023).

### Supplement

Animals in the supplement group and the exercise + supplement group received the protein supplement Mylorm by gavage at a dose of 20 mg/kg body weight for 8 weeks, 5 days a week. Mylorm supplement was obtained from a reputable source (Entomo Farms, Canada) (Siddiqui et al., 2023). The dose of mealworm protein supplementation (20 mg/kg body weight) was selected based on prior experimental research that demonstrated its bioactive and antioxidant properties in rodent models (Moruzzo et al., 2021). This dose falls within the effective range for evaluating nutritional interventions in metabolic diseases. Furthermore, using the standard allometric scaling method recommended by the FDA, this dose in rats is approximately equivalent to 3.2 mg/kg in humans, which corresponds to ~224 mg/day for a 70 kg adult—a physiologically attainable and safe intake level for dietary protein supplementation (Reagan-Shaw et al., 2008).

### Laboratory measurements

After the end of the interventions, the animals were anesthetized using CO<sub>2</sub> and blood samples were taken from their hearts. Liver and soleus muscle tissues were isolated and fixed in 10% formalin. FGF21 and mTOR gene expression was measured using Real-Time PCR (Takara kit, Japan) and ABI StepOne Plus device. TOS and TAC indices were examined with commercial kits (Rel Assay Diagnostics, Turkey) and spectrophotometer (Erel, 2004, 2005).

### Statistical analysis

Data analysis was performed using SPSS 21. One-way analysis of valiance (ANOVA) were used for comparisons between groups. A significance level of 0.05 was applied.

### Results

The levels of liver enzymes SGPT and SGOT were significantly increased in the fatty liver group compared to the healthy control group ( $p < 0.001$ ). These data confirm that the fatty liver induction model was implemented correctly. Aerobic exercise and Mealworm supplementation interventions significantly decreased these enzymes compared to the fatty liver group ( $p = 0.003$  and  $p = 0.005$ ). The combination of these two interventions showed a greater decrease in SGPT and SGOT levels and was significantly better than either intervention alone ( $p < 0.01$ ). The ALP level also increased significantly in the fatty liver group compared to the healthy control group ( $p = 0.001$ ) and decreased with both interventions. The results of the SGPT, SGOT, and ALP data are

shown in Figures 1, 2, and 3.

The expression of the FGF21 gene in the fatty liver group was significantly reduced compared to the healthy control group ( $p=0.002$ ). The intervention of aerobic exercise and the consumption of the mealworm protein supplement each independently significantly increased the expression of this gene compared to the fatty liver group ( $p = 0.001$  and  $p = 0.001$ ). The combination of aerobic exercise and mealworm supplementation also significantly increased the expression of FGF21 compared to both the exercise alone ( $p = 0.020$ ) and supplement alone ( $p = 0.015$ ). No significant effect was observed in the expression of the mTOR gene between the different groups ( $p > 0.05$ ). The results of the FGF21 and mTOR data are shown in Figure 5, 4.

Total TOS oxidative index was significantly increased in the fatty liver group compared to the healthy control group ( $p=0.001$ ). Aerobic exercise intervention and mealworm supplementation each independently significantly decreased TOS compared to the fatty liver group ( $p = 0.003$  and  $p = 0.005$ ). The combination of

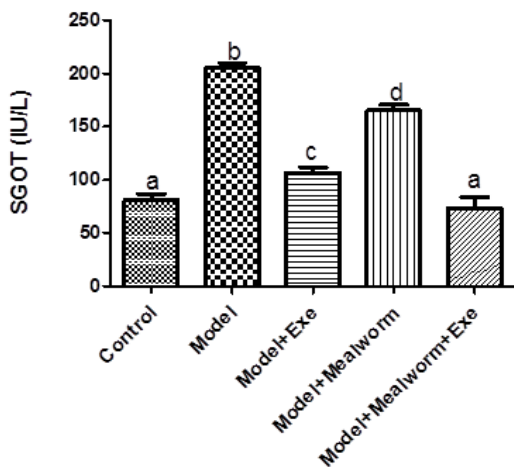


Figure 1. Comparison of SGPT in different groups. Means±SD.

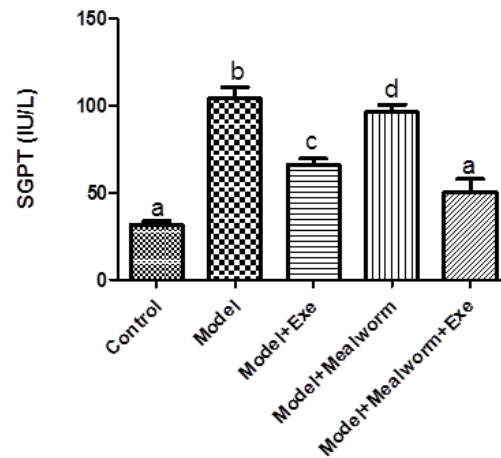


Figure 2. Comparison of SGOT in different groups. Means±SD

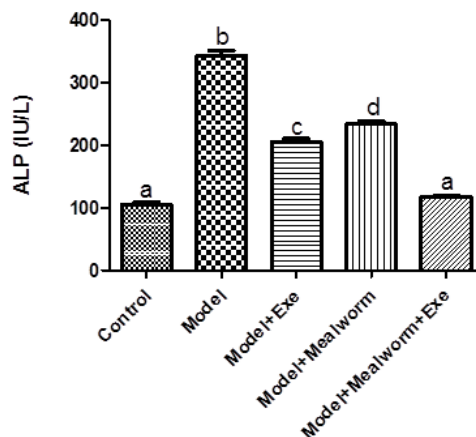


Figure 3. Comparison of ALP in different groups. Means±SD

these two interventions showed a greater decrease in TOS and was significantly lower than both the exercise alone ( $p = 0.012$ ) and supplement alone ( $p = 0.018$ ) groups. Total TAC antioxidant capacity was significantly decreased in the fatty liver group compared to the healthy control group ( $p = 0.002$ ). Aerobic exercise and mealworm supplementation independently significantly increased TAC compared to the fatty liver group ( $p = 0.004$  and  $p = 0.006$ ). The interaction effect of exercise and supplementation also caused a further increase in TAC and was significantly higher than the exercise alone ( $p = 0.014$ ) and supplement alone ( $p = 0.011$ ) groups. The results of the TOS and TAC data are shown in Figure 6, 7.

In addition to statistical significance, the effect sizes of key findings were calculated to assess their clinical relevance. The increase in FGF21 expression ( $p = 0.022$ ) corresponded to a large effect size (Cohen's  $d = 1.89$ ), indicating a meaningful biological response. Similarly, the reduction in TOS ( $p = 0.001$ )

and the increase in TAC ( $p = 0.009$ ) were associated with large effect sizes ( $d = 1.73$  and  $d = 1.62$ , respectively). These values suggest that the observed changes are not only statistically significant but also physiologically relevant.

### Discussion

This study investigated the combined effect of aerobic exercise and Mealworm protein supplementation on the oxidant-antioxidant status and expression of FGF21 and mTOR genes in the soleus muscle of rats with fatty liver. The significant increase in FGF21 gene expression in the intervention groups indicates the key role of this gene as a regulator of energy and fat metabolism. The improvements observed in FGF21 expression and oxidative stress markers in this study are consistent with previous findings demonstrating the regulatory role of aerobic exercise and nutritional supplementation in metabolic diseases. For instance, (Yan et al., 2023) reported that endurance exercise

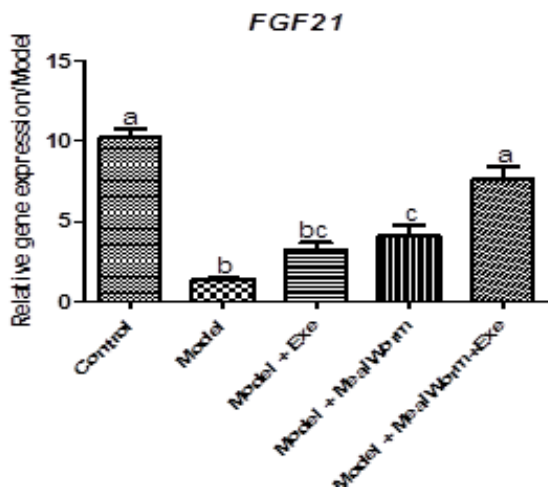


Figure 4. Comparison of FGF21 in different groups. Means±SD

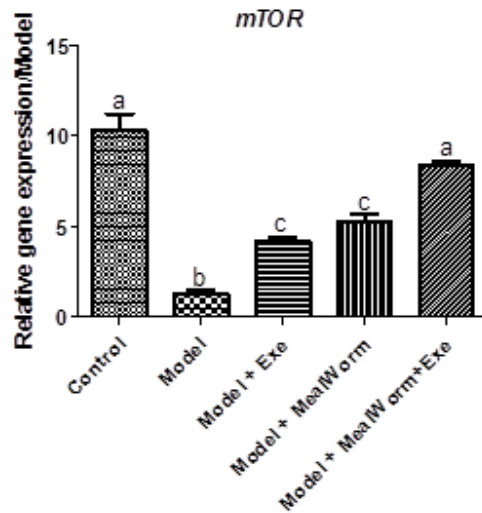


Figure 5. Comparison of mTOR in different groups. Means±SD

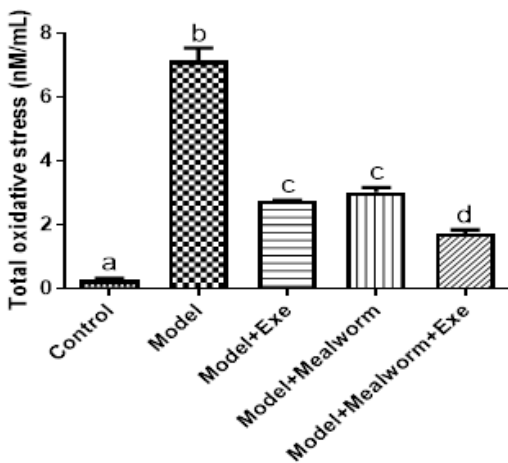


Figure 6. Comparison of TOS in different groups. Means±SD

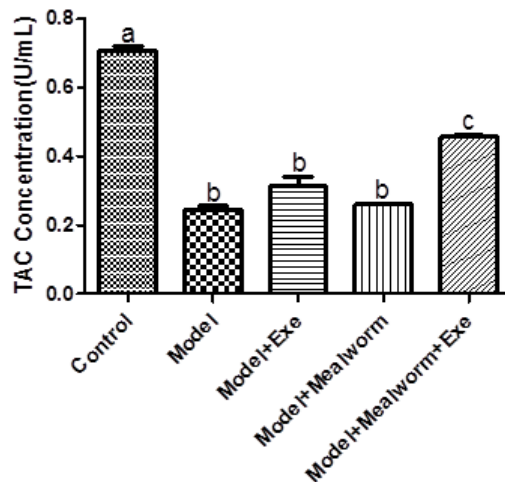


Figure 7. Comparison of TAC in different groups. Means±SD

significantly upregulated FGF21 mRNA in skeletal muscle of obese mice, contributing to enhanced lipid oxidation and reduced hepatic steatosis. Similarly, (Javadikia et al., 2023) found that high-intensity interval training combined with antioxidant-rich supplementation (e.g., purslane) reduced malondialdehyde (MDA) and increased TAC levels in rats with NAFLD. These results support the notion that both exercise and bioactive dietary components act synergistically to modulate redox balance and metabolic gene expression. The current findings expand this understanding by highlighting the potential role of mealworm-derived protein, a novel functional food, in activating these beneficial pathways. Aerobic exercise stimulates FGF21 expression by activating the PPAR $\alpha$  and AMPK pathways and helps to improve insulin sensitivity and reduce inflammation. A study has shown that high-intensity interval training (HIIT) can reduce hepatic FGF21 levels and improve insulin resistance in rats with NAFLD (Ranaei et al., 2023). In addition, Mealworm protein supplementation, due to its richness in essential amino acids, can enhance protein synthesis and intensify the effects of exercise training.

On the other hand, no significant effect on mTOR gene expression was observed in this study (Chen, 2020). mTOR is a key protein kinase in the expression of cell growth and protein synthesis. The lack of change in the expression of this gene may be due to the complexity of the signaling pathways and the interaction of metabolic factors. This issue requires further research to clarify the effects of the combination of exercise and nutritional supplementation on mTOR (Fernandes et al., 2021; Laplante & Sabatini, 2012; Pahlavani, 2022). Despite the inclusion of protein supplementation and aerobic exercise—both of which are individually known to influence muscle growth and anabolic signaling—the present study did not observe significant changes in mTOR gene expression. This finding may be attributed to several factors. First, the duration of the intervention (8 weeks) may not have been sufficient to elicit sustained transcriptional activation of the mTOR pathway, which is known to respond rapidly but transiently to acute stimuli (Baar & Esser, 1999). Second, mTOR activation is often more sensitive to resistance training or higher-protein dosing regimens, whereas moderate aerobic exercise may not provide the necessary mechanical or metabolic stimulus to fully engage this pathway (Damas et al., 2016). Third, the timing and co-ingestion of protein relative to exercise bouts can significantly modulate mTOR-related signaling cascades. Future research should consider these variables and incorporate measurements of upstream (e.g., AKT, PI3K) and downstream (e.g., S6K1, 4E-BP1) effectors of mTOR to provide a more complete understanding of its activation status in response to combined interventions.

The reduction in malondialdehyde (MDA) levels and the increase in total antioxidant capacity (TAC) in the exercise and Mealworm

supplementation groups indicate a reduction in oxidative stress and an improvement in antioxidant capacity. These effects may be due to the increase in the activity of antioxidant enzymes such as superoxide dismutase (SOD) and catalase, which are stimulated by aerobic exercise. A study has shown that high-intensity interval training combined with purslane supplementation can reduce MDA levels and increase TAC (Javadikia et al., 2023).

The significant reduction in liver enzymes in the intervention groups indicates improved liver function and reduced cellular damage caused by fatty liver. These findings are consistent with studies that have confirmed the anti-inflammatory effects of aerobic exercise. For example, one study showed that physical activity, especially aerobic exercise, has a protective role against oxidative liver damage, reducing inflammation, injury, and liver fibrosis (Jalalian, 2020).

Previous studies have shown that aerobic exercise can have positive effects on metabolic and oxidative markers in patients with fatty liver. In addition, rich protein sources such as millet, due to their content of branched-chain amino acids (BCAA), play an important role in regulating mTOR pathways and improving muscle function. In this study, the combination of exercise and millet supplementation had better results than either alone, indicating the importance of combined approaches.

Although the current study demonstrated significant improvements in oxidative stress status and FGF21 gene expression following aerobic exercise and mealworm protein supplementation, the underlying molecular mechanisms mediating these effects remain insufficiently characterized. It is well-established that exercise and dietary interventions influence systemic inflammation and metabolic regulation through various signaling molecules. Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- $\alpha$ ) and interleukin-6 (IL-6), adipokines such as adiponectin and leptin, and myokines including irisin and IL-15, play crucial roles in modulating energy balance, insulin sensitivity, and hepatic lipid metabolism (Hotamisligil, 2006; Ouchi et al., 2011; Pedersen & Febbraio, 2012). These mediators also act as key communicators in liver-muscle cross-talk. Hence, part of the observed physiological adaptations in this study may have been mediated by alterations in these regulatory molecules. The absence of such mechanistic biomarkers limits the depth of interpretation. Future studies should incorporate inflammatory, adipokine, and myokine profiles to better clarify the signaling pathways involved in the beneficial effects of exercise and protein supplementation in NAFLD models.

In the present study, a healthy control group receiving a standard diet was included to serve as a baseline reference for physiological norms. While some designs incorporate a high-fat

diet group without intervention, our objective was to highlight the contrast between normal physiological status and pathological NAFLD conditions, and then evaluate the impact of interventions from both ends of the spectrum. This design choice allowed for a clearer distinction between the preventive and restorative effects of aerobic exercise and mealworm protein supplementation. Moreover, using a standard healthy control group is a well-accepted approach in metabolic research, particularly when the focus is on comparing normalized physiological responses rather than solely attenuated pathology (Farzanegi et al., 2019; Keating et al., 2012).

Overall, the results of this study suggest that the combination of aerobic exercise and millet protein supplementation can be used as an effective strategy to improve metabolic status and reduce oxidative stress in patients with fatty liver. However, to better understand the mechanisms of action and more accurately evaluate the effects of this combination, further studies are needed, especially in the human population. The limitations of this study include the use of an animal model, which limits the generalization of the results to humans. Therefore, it is recommended that further clinical studies be conducted to confirm these findings and optimize the methods.

## Conclusion

Overall, the results of this study show that aerobic exercise combined with Mealworm protein supplementation can produce significant improvements in oxidant and antioxidant status as well as increased FGF21 gene expression in soleus muscle tissue of rats with fatty liver. These findings suggest that the use of the combination of aerobic exercise and Mealworm protein supplementation can be considered as an effective strategy in improving the health status of patients with fatty liver. While the current study provides novel insights into the potential metabolic benefits of aerobic exercise and mealworm protein supplementation in a rat model of NAFLD, it must be acknowledged that extrapolating these findings to human physiology requires caution. Rodent models, although widely used in preclinical research, differ from humans in terms of metabolism, hormonal regulation, and liver architecture. Therefore, while the observed improvements in oxidative status and FGF21 expression are promising, validation through well-controlled clinical trials in human populations is essential to confirm the translatability and therapeutic relevance of these findings (Periman & health, 2016).

## What is already known on this subject?

- NAFLD is a major global health concern associated with metabolic disorders.
- Aerobic exercise improves oxidative stress and metabolic health.

- Mealworm protein supplementation contains essential amino acids that may influence metabolic pathways.
- The liver and muscle interact metabolically through organ cross-talk, particularly via signaling molecules like FGF21.

## What this study adds?

- This study highlights the synergistic effects of aerobic exercise and mealworm protein supplementation in improving antioxidant capacity and reducing oxidative stress.
- It provides evidence that the liver-muscle cross-talk, mediated by FGF21, plays a crucial role in metabolic adaptations to exercise and protein intake.
- Unlike FGF21, the mTOR gene did not show significant changes, suggesting that this pathway might require different stimuli or prolonged intervention.

### Organ Cross-Talk Tips:

- **Liver-Muscle Interaction:** The liver and skeletal muscle engage in metabolic signaling, where exercise-induced FGF21 upregulation enhances lipid metabolism and reduces oxidative damage.
- **Exercise and FGF21:** Aerobic training can stimulate FGF21 secretion, contributing to improved insulin sensitivity and lipid oxidation in both the liver and muscle.
- **Protein Supplementation and mTOR:** While mealworm protein supplementation supports muscle health, its effects on mTOR activation in this study were limited, indicating that additional nutritional or exercise-based stimuli might be required.

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## Compliance with ethical standards

**Conflict of interest** The authors of this research article have no financial and personal conflict of interest statement.

**Ethical approval** The ethical code of this research was IR.IAU.K.REC.1403.066 taken from Islamic Azad University,

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**Informed consent** Animal study

## Author contributions

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

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