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Metabotropic Potential of Hesperidin in Female Rats with Metabolic Syndrome

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ABSTRACT

Background & Objective: Metabolic syndrome (MS) is a major health challenge among post-menopausal women and lacks effective treatment. Hesperidin (Hsp), a bioflavonoid, has demonstrated therapeutic effects in cancer, neurodegenerative disorders, and cardiovascular diseases. Therefore, this study aimed to investigate the effects of combined Hsp treatment and eight-week MICT on MS indices in a rat model.

Materials & Methods: Forty female Wistar rats were assigned to five groups: sham-operated control group, ovariectomized (OVX+Saline), moderate intensity exercise training (OVX + Exe), hesperidin (OVX + Hsp), MICT, and Hsp (OVX + Exe + Hsp). After intraperitoneal (i.p.) administration of Hsp, saline, and completion of the MICT for eight weeks, anthropometric and biochemical indices were assessed.

Results: We found a significant reduction in body mass, abdominal fat, blood glucose, insulin resistance, and lipid profiles (p=0.001) in the OVX+Exe+Hsp group compared with the OVX control group. Comparison of the Hsp-treated group alone with that of sedentary ovariectomized rats showed significant differences in the MS indices (P<0.05).

Conclusion: The present study indicates that administration of Hsp alone or in combination with MICT significantly reduces visceral fat, body weight, and blood LDL, glucose, and insulin resistance.

Keywords: *Menopause, Metabolic Syndrome, Ovariectomy, MICT, Hesperidin, Insulin resistance*

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1. Introduction

One of the main public health concerns is the increase in obesity and metabolic syndrome (MS) among menopausal women (1). Metabolic syndrome affects 25–33% of the population and is predicted to increase substantially due to a sedentary lifestyle (2). Similarly, ovariectomy surgery causes MS due to increases in weight, visceral fat, metabolic disturbance, and dyslipidemia (3).

Exercise training has been reported to exert beneficial effects on MS (4). For example, moderate-intensity continuous training (MICT) has been reported to alleviate dyslipidemia and hyperglycemia and to reduce oxidative DNA damage, which is a causative factor for cancer, neurodegenerative, and metabolic disorders (5, 6). Meanwhile, MICT is capable of improving heart function and insulin sensitivity (7), reducing waist circumference (8), and decreasing visceral fat (9) through AMPK (6).

We hypothesized that one strategy to combat MS, could be rebalancing the oxidant–antioxidant status by administration of particular antioxidant components (10). It is known that native bioflavonoids exhibit free radical scavenging activity and are potent agents for reducing oxidative stress, mitochondrial dysfunction (11), and inflammation (12).

Hesperidin (C16H14O6; 3', 5, 7-trihydroxy-4' -methoxy flavanone), is a citrus bioflavonoid that exerts beneficial effects against type 2 diabetes mellitus, cancer, and cardiovascular disorders due to its anti-inflammatory and antioxidant properties (13). Thus, it is considered a promising flavonoid for the prevention or treatment of

MS. The novelty of our study lies in evaluating the co-treatment of MS with the MICT protocol in a rat model of MS.

2. Materials and Methods

2.1 Design of study and animal groups

A total of forty female Wistar rats (3 months old, weighing 200–220 g) were housed under standard laboratory conditions with *ad libitum* access to food and water (14).

To induce an MS model, the animals underwent ovariectomy and were maintained in their cages for four weeks. Subsequently, animals exhibiting weight gain, increased adiposity, and central obesity were included in the study (15).

2.2 Ovariectomy surgery

All animals, except the sham-operated control group, underwent bilateral ovariectomy under deep anesthesia induced by intraperitoneal (i.p.) injection of 65 mg/kg ketamine and 5 mg/kg xylazine (14). Both ovaries were subsequently removed according to our previous studies (16).

2.3 Assessment of Methodological Quality

Before inclusion in the review, two independent reviewers assessed the methodological quality of each selected study. This evaluation was conducted using the Joanna Briggs Institute Qualitative Assessment and Review Instrument (JBI-QARI) (13). Discrepancies between reviewers were resolved through discussion or by consulting a third reviewer. The JBI-QARI tool includes ten criteria focused on the philosophy, design, and credibility of qualitative research.

2.4 Animal groups

Animals were randomly allocated into 5 groups (n = 8/group): sham-operated control, control untreated ovariectomized (OVX+Saline), OVX+ Exe, OVX + Hsp, and OVX + Exe + Hsp. Animals assigned to the exercise groups ran on a five-lane rodent treadmill (DSI-580; Danesh Salar Iranian) for 8 weeks (3 sessions per week). The experimental timeline is presented in Figure 1.

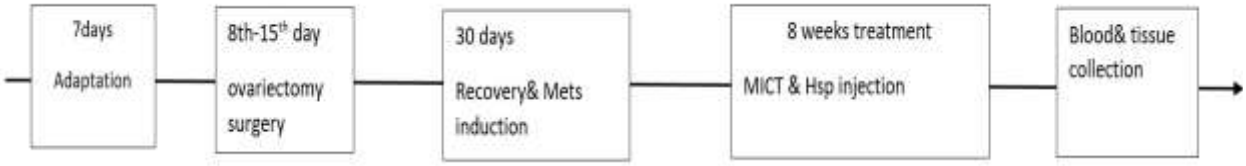

Figure 1. Experimental design and timeline of drug administration exercise intervention, and biochemical analyses. (**Prepared by Authors, 2026**).

2.5 Hesperidin preparation

Hesperidin was purchased from Sigma (USA). The pure powder was dissolved in phosphate-buffered saline (PBS), 5% dimethyl sulfoxide, and Tween 80. The mixture was gently vortexed until a homogeneous suspension was obtained. Rats received either an i.p. injection of 50 mg/kg Hsp or an equivalent volume of saline three times per week for 8 weeks. (17)

2.6 MICT protocol

Initially, rats were acclimatized to the five-lane rodent treadmill for 10 min/day for one week, to alleviate new arena stress.

MICT consisted of treadmill running three days per week at a speed of 16 m/min for 50 min/day over eight weeks (18).

2.7 Morphometric parameters

Animals were weighed in the morning using a digital scale (Jadever Scale Co). After completion of the interventions and after 24 h fasting, rats were anesthetized, and body mass, height, and WC were measured; then blood samples were drawn from the inferior vena cava, and serum was separated by centrifugation (3,000 rpm /15 minutes), and transferred to –80°C.

Then, following blood collection, all abdominal visceral fats were immediately collected and weighed (19).

2.8 Biochemical measurements

Serum insulin levels were measured using an enzyme-linked immunosorbent assay (ELISA) method, with a Rat Insulin ELISA Kit (Zellbio GmbH· code ZB-10062C-M9648). Glucose, total cholesterol (TC), and high- and low-density lipoproteins (HDL-C; LDL-C) were quantified using a colorimetric method (GOD-PAP; Pars Azmoun), respectively. Triglyceride (TG) concentration was determined using a specific kit (Cat NO: MAK266; Pars Azmoun company, Iran) (3). Finally, insulin resistance (HOMA-IR) was calculated using the formula: insulin (µU/mL) × glucose (mmol/L) / 22.5.

2.9 Statistical analysis

Data distribution was assessed using Shapiro-Wilk in SPSS software (version 22). One-way analysis of variance (ANOVA) followed by Tukey's test was used for group comparisons. $P < 0.05$ was considered statistically significant.

3. Result

One-way ANOVA revealed significant differences among groups in body weight ($F(4,35) = 41.042$), WC ($F(4,35) = 11.268$), visceral fat mass ($F(4,35) = 8.969$), and BMI ($F(4,35) = 11.209$, $P = 0.001$). Further analysis using the LSD post hoc test showed increased body weight in the OVX+Saline or control group ($P = 0.001$) in comparison with the Sham group, which was

subsequently reduced in all three groups of OVX+Exe+Hsp, OVX +Exe, and OVX + Hsp (P = 0.001, Figure 2). In addition, OVX + Exe + Hsp group showed a significant reduction in body weight compared with OVX + Hsp (P = 0.03) and OVX +Exe (P = 0.007, Figure 2). In addition, a significant increase in BMI was observed in the ovariectomized group (P = 0.001) compared with the Sham group, and this was further diminished in OVX +Exe + Hsp (P= 0.001), OVX + Exe (P = 0.01) and OVX + Hsp (P= 0.001, Figure 2). In addition, significant differences between OVX + Exe + Hsp and OVX + Exe (P = 0.03) and between OVX + Exe and OVX + Hsp (P = 0.02) were found. Using the LSD post hoc test, a significant increase in WC of OVX + Saline (P = 0.001), in contrast to the Sham group, which was significantly reduced only in OVX+Exe+Hsp (P =0.001), OVX + Hsp (P =0.03) (Figure 2). Further comparison found a significant difference between OVX + Exe + Hsp and OVX + Hsp (P = 0.05) and OVX + Exe (P = 0.02) as well. Also, a noticeable difference was found in WC between OVX + Hsp and OVX +Saline (P = 0.03). Moreover, visceral fat increased in OVX+ Saline compared with Sham (P = 0.001), and then decreased after treatment with Exe, Hsp, and co-treatment with Exe +Hsp (P = 0.001, Figure 2). Comparing visceral fat between OVX + Hsp and OVX +Saline was significant (P = 0.001).

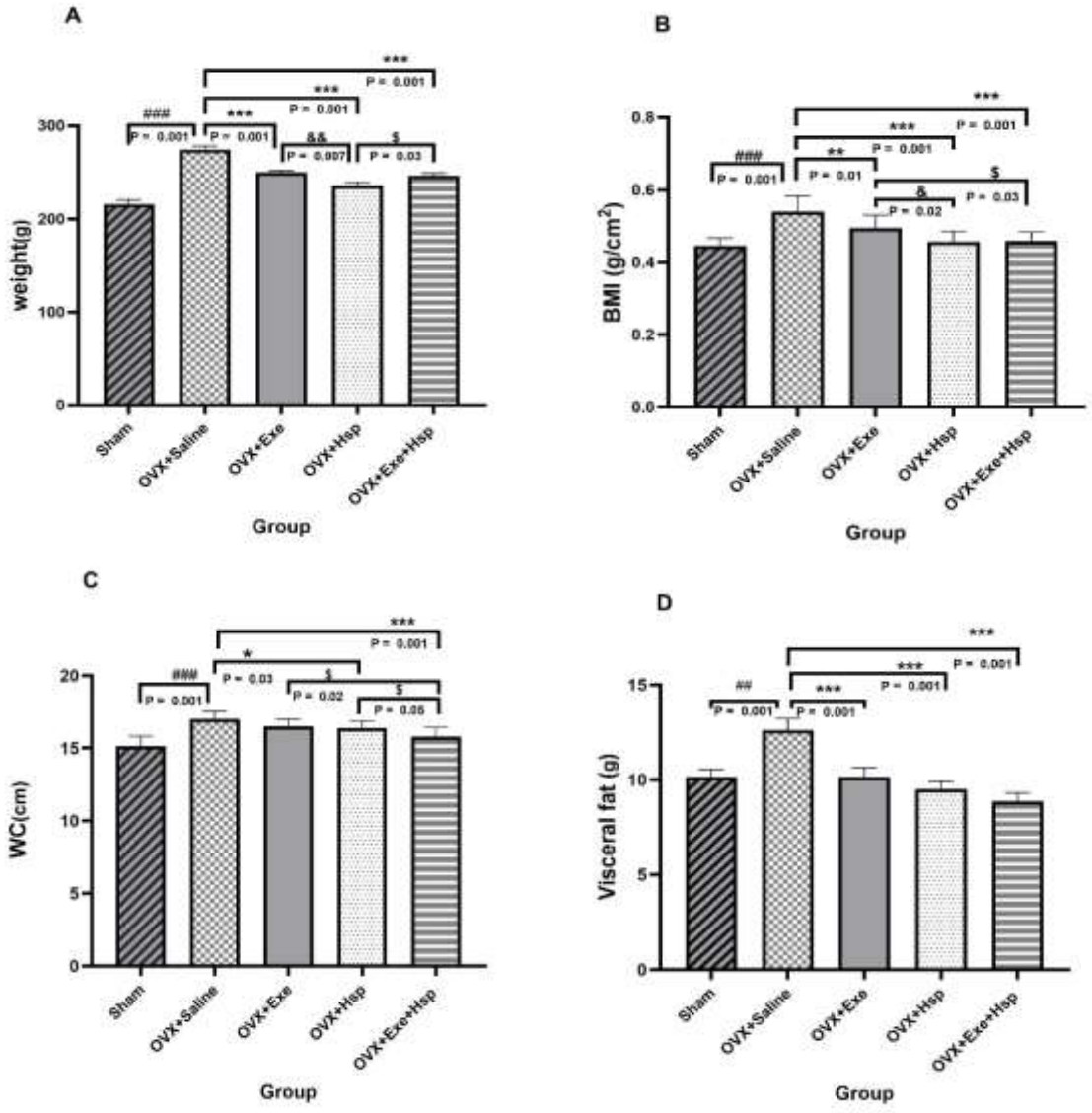

Figure 2. Effects of Hsp, exercise, and the combination of both on body weight (A), body mass index (BMI) (B), waist circumference (WC) (C), and visceral fat (D) in ovariectomized rats. OVX + Saline: control; OVX + Exe: MICT; OVX + Hsp: hesperidin-receiving group; OVX + Exe + Hsp: hesperidin with MICT. Data are reported as the mean ± SE, n = 8 rats per group. *P ≤ 0.05, **P ≤ 0.01, ***P ≤ 0.001 versus OVX + Saline group. ##P ≤ 0.01, ###P ≤ 0.001 against sham. $P ≤ 0.05 versus OVX + Exe + Hsp group and & P ≤ 0.05, && P ≤ 0.01 versus Exe group. (**Prepared by Authors, 2026**).

Statistical analysis of biochemical measurements revealed significant differences in glucose (F(4, 35) = 43), insulin (F(4, 35) = 7.637), and HOMA-IR (F(4, 35) = 25; P = 0.001; Figure 3). Glucose levels decreased significantly in OVX + Exe + Hsp, OVX + Exe, and OVX + Hsp (P = 0.001), compared with ovariectomized sedentary rats. The differences between OVX + Exe + Hsp and OVX + Exe and between OVX + Exe and OVX + Hsp were also significant (P < 0.01). Similarly, insulin decreased markedly in OVX + Exe + Hsp (P = 0.001), OVX + Exe (P = 0.01), and OVX + Hsp (P = 0.002), and the reduction was significantly greater in OVX + Exe + Hsp than in OVX + Exe (P = 0.01) and OVX + Hsp (P = 0.04, Figure 3). These findings suggest a synergistic effect.

Finally, HOMA–IR levels, which were elevated in OVX + Saline (P = 0.004) compared with Sham, were reduced in OVX + Exe + Hsp, OVX + Exe, and OVX + Hsp (P = 0.001), which were significantly greater compared with OVX + Exe (P = 0.007), but not with OVX + Hsp (Figure 3).

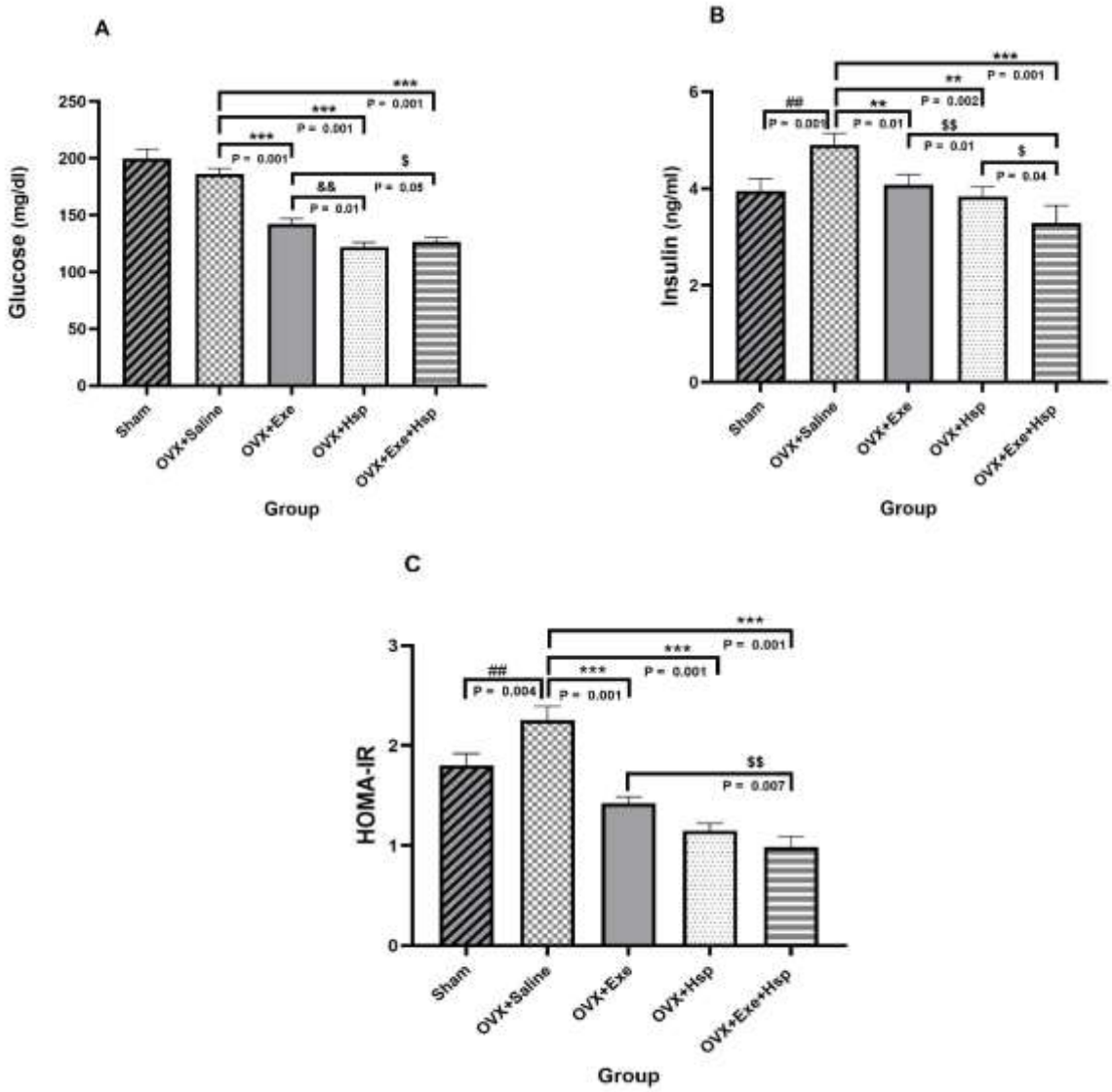

Figure 3. Effects of Hsp, Exercise and combination of both on glucose (A), Insulin (B), HOMA-IR (C) in ovariectomized rats. OVX + Saline: control group; OVX + Exe: MICT group; OVX + Hsp: hesperidin; OVX + Exe + Hsp: hesperidin with MICT group. **P ≤ 0.01, ***P ≤ 0.001 against OVX + Saline. ##P ≤ 0.01. $P ≤ 0.05, $$P ≤ 0.01 versus OVX + Exe + Hsp group and && P ≤ 0.01 compared with the Exe group. (**Prepared by Authors, 2026**).

Likewise, significant differences were found by one-way ANOVA for TG (F(4, 35) = 6.868, P = 0.001), TC (F(4, 35) = 29.09, P = 0.001), HDL (F(4, 35) = 27.419, P = 0.001), and LDL (F(4, 35) = 3.223, P = 0.02). TC levels increased in the OVX + Saline group (P = 0.001) compared with the Sham group and decreased in the OVX + Exe + Hsp and OVX + Exe groups (P = 0.001) compared with the OVX + Saline group. A noticeable difference was found between OVX + Exe + Hsp and OVX + Exe (P = 0.03), and OVX + Hsp (P = 0.001). The groups of OVX + Exe also showed a significant difference with OVX + Hsp (P = 0.001, Fig 4). LDL levels were significantly elevated in the OVX + Saline group (P = 0.01), in contrast to the control, and were remarkably reduced in OVX + Exe + Hsp (P = 0.004), OVX

+ Exe (P = 0.009), and OVX + Hsp (P = 0.02, Figure 4). Finally, HDL was significantly elevated in OVX + Exe + Hsp, OVX + Exe, and OVX + Hsp (P = 0.001), compared with the control ovariectomized group. In addition, OVX + Exe + Hsp differed from OVX + Exe (p = 0.05) and OVX + Hsp (P = 0.004), and similarly OVX + Exe compared with OVX + Hsp (p= 0.001, Figure 4). Also, LDL (p=0.02) and HDL (p=0.001) differed significantly in OVX + Hsp compared with OVX +Saline.

Finally, our findings showed a crucial reduction in TG for the co-treatment receiving group and OVX + Exe (P = 0.001) compared with OVX + Saline. OVX + Hsp alone was significantly different from OVX + Exe (P = 0.007, Figure 4).

No significant difference was found in cholesterol and TG between OVX + Hsp and OVX +Saline (p > 0.05).

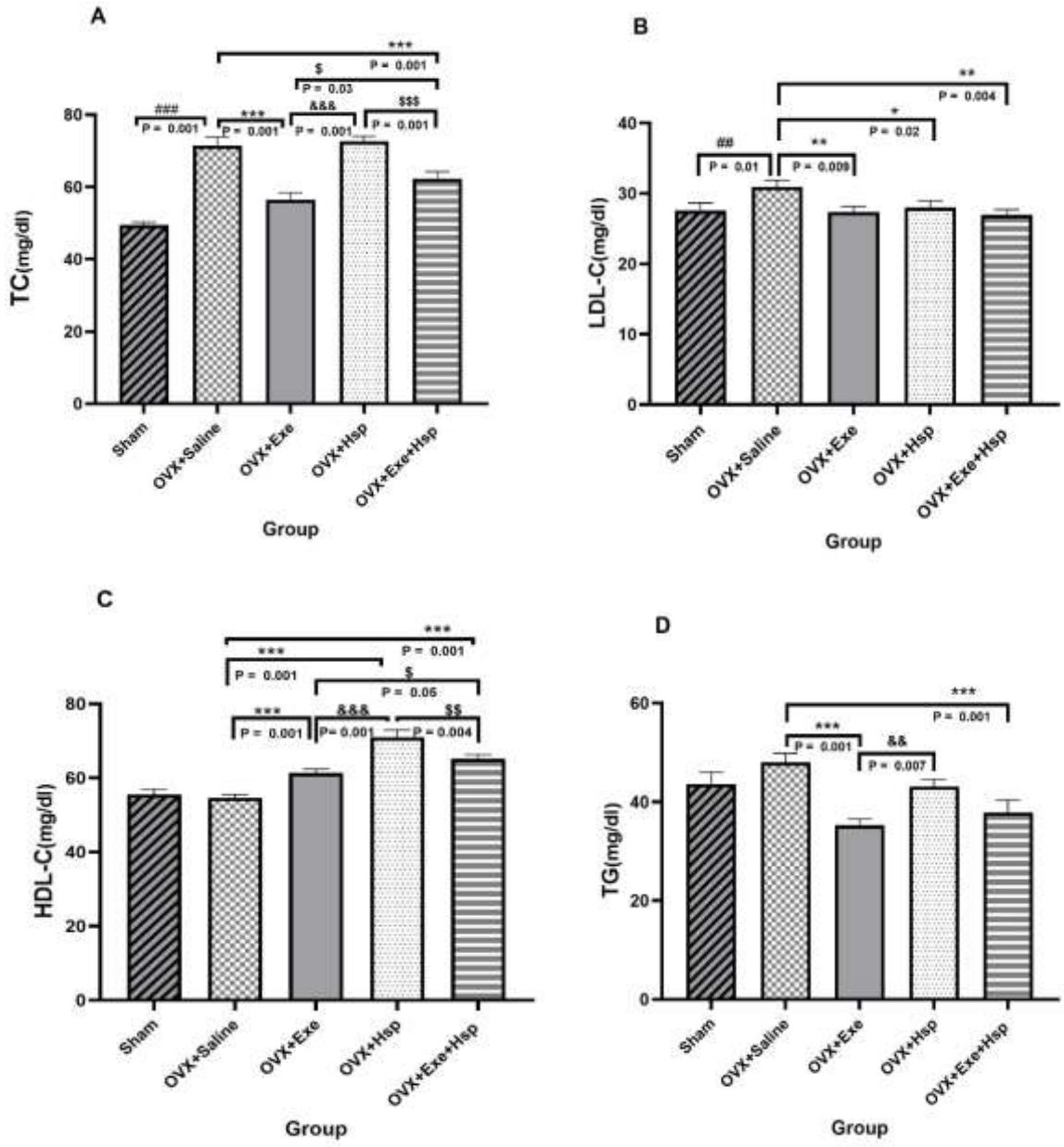

Figure 4. Effects of Hsp, Exercise and combination of both on TC (A), LDL (B), HDL (C), and TG (D) in ovariectomized rats. OVX + Saline: control group; OVX + Exe: MICT; OVX + Hsp: hesperidin; OVX + Exe + Hsp: hesperidin with MICT. *P ≤ 0.05, **P ≤ 0.01, ***P ≤ 0.001 compared with the OVX + Saline group. ##P ≤ 0.01, ###P ≤ 0.001 compared with sham. $P ≤ 0.05, $$P ≤ 0.01, $$$P ≤ 0.001 compared with the OVX + Exe + Hsp group and && P ≤ 0.01, &&& P ≤ 0.001 versus Exe group. (**Prepared by Authors, 2026**).

4. Discussion

In the present study, Hesperidin (Hsp) significantly improved most of the metabolic syndrome (MS) indices, with particularly pronounced effects on blood glucose levels and insulin resistance (IR) in an ovariectomy-induced MS rat model. Our findings demonstrated that ovariectomy led to a significant increase in body mass, visceral adipose tissue, BMI, and waist circumference (WC), aligning with previous reports (20). This escalation in body weight and central obesity in ovariectomized animals is consistent with the established effects of estrogen withdrawal on metabolic disturbances, insulin resistance, and diminished lipase activity (14)(21).

Furthermore, our results indicate that moderate-intensity continuous training effectively alleviates several MS indices, including central obesity and insulin resistance (7). While MICT alone attenuated dyslipidemia, its combination with Hsp exerted a superior, synergistic effect in significantly reducing dyslipidemia, IR, and BMI. This improvement may be attributed to the capacity of MICT to stimulate lipolysis and fat oxidation (22). Regarding the mechanistic role of Hesperidin, our findings suggest that Hsp remarkably mitigates insulin resistance, potentially through its antioxidant and anti-inflammatory properties. This may be mediated via the suppression of pro-inflammatory mediators, such as nuclear factor kappa B (NF-κB), TNF-α, and IL-6 (23, 24). Notably, since no significant differences were observed in food intake among the groups, the reduction in body weight is unlikely to be attributed to alterations in central feeding mechanisms. Instead, the weight-reducing effects of Hsp may stem from its ability to enhance the activity of key antioxidant enzymes, specifically catalase and superoxide dismutase (25), and improve insulin sensitivity through the AMPK and PPARγ signaling pathways (26, 27).

While our results align with the findings of Prasatthong et al., who reported beneficial effects of daily Hsp administration (30 mg/kg) on MS indices in a high-fat diet model (28), they contrast with the findings of Shams-Rad et al., who observed no significant impact of Hsp on fasting glucose, insulin, HbA1c, or HOMA-IR (29). These discrepancies may arise from variations in biochemical assessment timing, dosage, bioflavonoid formulation, or the duration of exposure.

Finally, our data suggest that the combination of MICT and Hsp exerts a synergistic effect on improving both IR and dyslipidemia. Although the specific signaling pathways underlying this synergy were not directly evaluated in the current study, it is plausible that the mechanism involves the activation of the phosphorylated AMP-activated protein kinase (P-AMPK) pathway. Given that both Hsp (27) and MICT (35) are known to increase P-AMPK activity—thereby enhancing mitochondrial function and metabolic homeostasis (30). AMPK likely plays a pivotal role in restoring energy balance and modulating lipid metabolism (31). Consequently, Hsp may enhance glucose and lipid metabolism via downstream AMPK signaling, potentially exerting a therapeutic effect on the chronic inflammatory state associated with obesity (32).

From a clinical perspective, the combined application of Hesperidin supplementation and a structured eight-week moderate-intensity exercise protocol represents a promising therapeutic strategy for managing insulin resistance and dyslipidemia in menopause-induced metabolic syndrome.

5. Conclusion

The present study suggests that chronic administration of Hsp alone or in combination with moderate-intensity continuous training successfully alleviated most components of metabolic syndrome in female rats.

6. Declarations

6.1 Acknowledgments

The authors would like to thank Mahan Abassi for technical support.

6.2 Ethical Considerations

All interventions were conducted in accordance with the EU ethics guidelines (2010/63/EU) for laboratory animal investigations. The study received Ethical approval code from Guilan University of Medical Sciences (IR.GUMS.AEC.1403.004).

6.3 Authors' Contributions

PB designed this study, wrote, and revised the paper for important intellectual content. AM performed the experiments and prepared the first draft of the manuscript; ZB performed all statistical analyses and prepared the graphs, and also contributed to the experiments and manuscript preparation. AE performed ELISA analysis for insulin measurement. All authors approved the final version of the paper.

6.4 Conflict of Interest

The authors declare no competing interests.

6.5 Fund or Financial Support

This study was supported by a grant awarded to Dr. Parvin Babaei from the Research and Technology Chancellor of Guilan University of Medical Sciences, Iran (No: IR.GUMS.AEC.1403.001). The funder did not participate in data collection and analysis, manuscript preparation, or submission.

6.6 Using Artificial Intelligence Tools (AI Tools)

The authors declare that no generative AI or AI-assisted technologies were used in the preparation, analysis, or writing of this manuscript.

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