Nutr Res Pract. 2025 Feb;19(1):30-40
https://doi.org/10.4162/nrp.2025.19.1.30
pISSN 1976-1457·eISSN 2005-6168

Nutrition Research and Practice

Original Research

Check for updates

Combination of ferulic acid and exercise alleviates menopause symptoms and skin remodeling in ovariectomized rats

Wonyoung Lee [1*], **Jinkyung Cho** [2*], **Seung-Yeon Yoo** [3], **and Eunmi Park** [1§]

[1]Department of Food and Nutrition, School of Life Science and Nano-Technology, Hannam University, Daejeon 34054, Korea
[2]College of Sport Science, Sungkyunkwan University, Suwon 16419, Korea
[3]Department of Nursing, School of Life Science and Nano-Technology, Hannam University, Daejeon 34054, Korea

OPEN ACCESS

Received: Aug 8, 2024
Revised: Sep 15, 2024
Accepted: Sep 24, 2024
Published online: Oct 11, 2024

[§]Corresponding Author:
Eunmi Park
Department of Food and Nutrition, School of Life Science and Nano-Technology, Hannam University, 1646 Yuseong-daero, Yuseong-gu, Daejeon 34054, Korea.
Tel. +82-42-672-8793
Fax. +82-42-629-8789
Email. eunmi_park@hnu.kr

*Wonyoung Lee and Jinkyung Cho have equally contributed to this study.

ORCID iDs
Wonyoung Lee
https://orcid.org/0000-0002-9433-7362
Jinkyung Cho
https://orcid.org/0000-0002-4500-3622
Seung-Yeon Yoo
https://orcid.org/0000-0003-2620-1073
Eunmi Park
https://orcid.org/0000-0002-1911-4652

ABSTRACT

BACKGROUND/OBJECTIVES: Estrogen regulates certain biological functions, including bone health, maintenance of skin components, and cardiovascular and brain protection. Estrogen deficiency manifests as hot flashes, wrinkles, skin dryness, reduced bone mineral density (BMD), sleep disorders, and cardiovascular diseases. This study aimed to investigate the effects of aerobic exercise combined with ferulic acid (FA) in ovariectomized rats.
MATERIALS/METHODS: Female Sprague–Dawley rats were classified into control (N), ovariectomy (OV), ovariectomy and exercise (OV+EX), and ovariectomy and exercise with ferulic acid (OV+EX+F) groups. Following ovariectomy at 22 weeks of age, the rats were tower climbing exercise at gradually increase the load (3 days/week for 12 weeks) with or without FA (5 g/kg diet) administration.
RESULTS: Estrogen deficiency in female rats (OV group) resulted in increased body weight, increased blood triglyceride (TG) levels, and decreased BMD following ovariectomy. Interestingly, compared with the rats in the OV group, the rats in the OV+EX+F group exhibited reduced body weight and blood TG levels and maintained BMD following ovariectomy, similar to those in the N group. Histological analysis of the skin of estrogen-deficient rats (OV group) revealed significantly decreased skin thickness with fewer dermal cells and distorted subcutaneous fat layers, similar to the aging phenotype. Interestingly, the rats in the OV+EX+F group exhibited rescued skin phenotypes compared with those in the OV and OV+EX groups. The skin of rats from all groups was analyzed for the expression of DNA damage and repair proteins. The OV+EX+F and OV+EX groups exhibited enhanced protein levels of pCHK1 (S345), an initiator of DNA repair signaling, and p53, indicating increased cellular DNA damage because of ovariectomy and ultimately an underlying DNA repair process.
CONCLUSION: Exercise with FA had beneficial effects on lipid profiles, BMD, and skin remodeling during menopause.

Keywords: Ferulic acid; exercise; ovariectomy; p53; skin

Nutrition Research and Practice

Funding

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (RS-2021-NR060250).

Conflict of Interest

The authors declare no potential conflicts of interest.

Author Contributions

Conceptualization: Park E; Formal analysis: Cho J; Funding acquisition: Lee W; Investigation: Lee W; Methodology: Lee W, Yoo SY; Supervision: Park E; Writing - original draft: Cho J, Lee W, Park E; Writing - review & editing: Cho J, Lee W.

INTRODUCTION

The skin, the largest organ of the body, is composed of the epidermis, dermis, subcutaneous fat layer, and muscle layers, all of which are affected by aging [1]. Notably, various estrogen receptors (ERs) are located on the skin. Of these, ERα and ERβ are expressed in a tissue-specific manner in humans, with ERβ showing higher expression than ERα. ERβ exerts an anti-inflammatory effect and promotes wound healing and DNA repair signaling in human skin tissues via dermal and biomechanical mechanisms [2,3]. Menopause-induced estrogen deficiency affects skin component remodeling at cellular levels. Moreover, this hypoestrogenic state affects dermal cellular metabolism, leading to changes in collagen content, alterations in glycosaminoglycan concentration, and alterations in water content [4].

The positive effects of aerobic exercise are well documented in menopausal women [5]. In addition, exercise may help improve muscle mass, muscle strength, bone mineral density (BMD), and quality of life after menopause [6]. Moreover, moderate aerobic exercise can improve estrogen deficiency-induced morphological changes in skeletal muscle, total cholesterol and triglyceride (TG) levels, and vascular health [7]. Although the importance of exercise in treating estrogen deficiency has been established, its combined effect with natural products on the skin has not been well reported.

Ferulic acid (FA) is a natural product commonly found in fruits and vegetables, including rice bran, sweet corn, and tomatoes [8]. FA is a non-steroidal agent with anti-inflammatory and platelet-inhibitory properties. In our previous study, we found that FA treatment resulted in weight loss and improved glucose homeostasis, lipid profiles and hepatic steatosis in a high-fat diet induced mice model [9,10]. In particular, FA enhanced the levels of NANOG mRNA and its related genes in adipose-derived mesenchymal stem cells [9].

Therefore, the present study aimed to investigate the role of exercise with FA in skin remodeling during estrogen deficiency in ovariectomized rats.

MATERIALS AND METHODS

Animal model and experimental design

Forty female Sprague-Dawley rats aged 7 weeks old were obtained from Nara Biotech (Seoul, Korea). The rats were housed at pathogen-free animal care facility under standard conditions (temperature 24 ± 1°C, 12-h light-dark cycle) with ad libitum access to chow and tap water. The rats were fed either a standard chow diet (D12450J; Research Diet, New Brunswick, NJ, USA) or a standard chow diet with FA (5 g/kg diet) [9,10]. Following previous studies, ovariectomy surgery was performed at 6 mon of age [11]. Thus, the rats underwent a 1-week acclimation period, followed by ovariectomy surgery at 22 weeks of age. After a 2-week recovery period, exercise and dietary interventions were conducted for 12 weeks. The rats were randomly assigned to 4 groups: control (N, n = 10), ovariectomy (OV, n = 10), ovariectomy with exercise (OV+EX, n = 10), ovariectomy with exercise plus FA treatment (OV+EX+F, n = 10) (**Fig. 1**). All rats were checked body weight once a week. At the end of the experiment, the rats were anesthetized using a combination of ketamine and 2% xylazine and then sacrificed. The skin tissues, femurs, and serum samples were collected and stored at −80°C until analysis.

https://doi.org/10.4162/nrp.2025.19.1.30

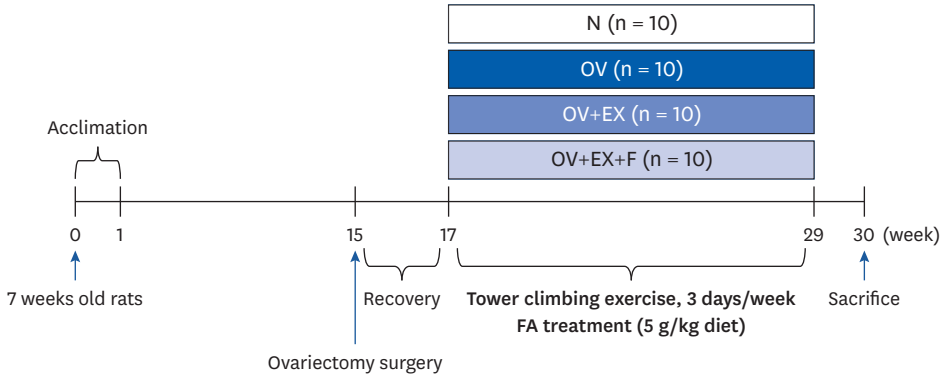

Fig. 1. Schematic overview of study design. Rats underwent ovariectomy at week 15, followed by a 2-week recovery period. Exercise and dietary interventions were performed for 12-week, and the rats were sacrificed at week 30. N, control (normal); OV, ovariectomized rats that were fed a control diet; OV+EX, a control diet with exercise training; OV+EX+F, a diet including ferulic acid with exercise training; FA, ferulic acid.

This study was approved by the Institutional Animal Care and Use Committee of the Hannam University (approval No. HNU 2018-1), and all protocols and animal care followed the animal ethics guidelines.

Ovariectomy

For ovariectomies and placebo surgery, the rats were anesthetized using a combination of ketamine and 2% xylazine, and the designated skin areas were shaved and cleaned using 70% alcohol. Subsequently, a surgical incision of approximately 1 cm was carefully made in the center of the abdomen, and the ovaries were securely ligated with a surgical suture thread. Both ovaries were then removed, and the surgical wound was closed using a synthetic thread. The rats were intramuscularly administered antibiotics (cefazolin, 50 mg/kg) to prevent potential infections. All rats were then reared for a recovery period of 2 weeks.

Exercise program

Fig. 2 shows the results of the tower-climbing exercise program. The rats in the exercise group performed tower-climbing exercises 3 times per week for 12 weeks [12]. The rat climbed a 1.35-m ladder, with steps spaced 2.5 cm apart and inclined at 60°. The training sessions were conducted on alternate days. The first week of the exercise program focused on adapting the rats to the training environment by climbing ladders and adjusting the load attached to their tails. In the second week, the one-repetition maximum (1RM) for each rat was measured. The rats were considered to have adapted to the intensity if they successfully completed 8 climbs at an intensity of 50% of their 1RM during 8 weeks of training. Subsequently, the load was progressively increased to 75%, 90%, and 100% of the 1RM levels, with an additional 30 g of weight added over a follow-up trial period of 9–12 weeks. A rest period of 2 min was provided before the next trial, following one successful climb from the bottom to the top of the ladder.

Hematoxylin and eosin (H&E) staining

Rat skin and femur tissues were fixed in a 4% formaldehyde solution, embedded in paraffin blocks, sliced into 3-μm-thick sections, and stained with H&E. The stained slides were observed under a Leica DMLS microscope at 4× and 10× magnification for skin and bone head/shaft samples, respectively. Images were captured using a Leica Qwin image analyzer system (LEICA Imaging Systems Ltd., Cambridge, UK). Skin size and dermis length

https://doi.org/10.4162/nrp.2025.19.1.30

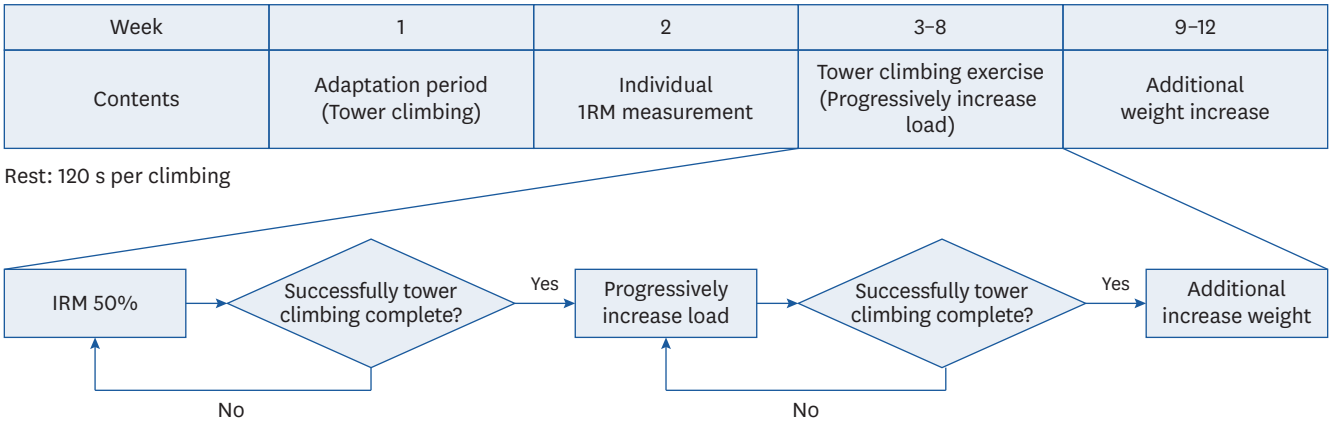

Fig. 2. Tower climbing exercise program.
1RM, one-repetition maximum.

were measured using the ruler function of the LAS 4.8 program (LEICA Imaging Systems Ltd.). Subcutaneous fat volume was analyzed using the region analysis function of Adobe Photoshop (Adobe Photoshop 2021; Adobe Systems Inc., San Jose, CA, USA).

Blood biochemistry

Serum insulin levels were assessed using ELISA kits (ALPCO, Salem, NH, USA), following the manufacturer's instructions. Serum total cholesterol and TG levels were evaluated using enzymatic kits (Wako Chemicals Inc., Richmond, VA, USA).

Western blotting

Skin tissues were homogenized in lysis buffer (protease inhibitor half unit, 1M NaVO4, 1M PMSF, 1M NaF, 1M DTT) with RIPA buffer (Thermo Scientific Inc., Waltham, MA, USA) to extract proteins. The protein concentration was measured and determined using a spectrophotometer (Bio-Rad Laboratories, Hercules, CA, USA) and the body surface area method, respectively. Total 60 μg of protein samples were electrophoresed on 8–12% sodium dodecyl sulfate-polyacrylamide gel electrophoresis gels and transferred onto a polyvinylidene fluoride membrane. The membranes were blocked with 5% non-fat milk powder in TBS-T buffer and incubated overnight at 4°C with the following primary antibodies: pCHK1 (1:500, Cat# 2348S; Cell Signaling Technology, Danvers, MA, USA), p53 (1:500, Cat# 9282S; Cell Signaling Technology), and β-actin (1:1,000, Cat# sc-47778; Santa Cruz Biotechnology, Santa Cruz, CA, USA). Subsequently, the blots were incubated with secondary antibodies. Finally, the band intensities were visualized using a chemiluminescence imaging system (Vilber Lourmat, Collégien, France).

Statistical analysis

Statistical analyses were performed using SPSS for Windows (version 25.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism 9 (Graph Pad Software Inc., San Diego, CA, USA). Data were expressed as the mean ± SD. Data were analyzed using one-way analysis of variance, followed by Tukey's *post hoc* test, as required. Statistical significance was set at $P < 0.05$.

https://doi.org/10.4162/nrp.2025.19.1.30

Nutrition Research and Practice

RESULTS

Body weight and blood markers

At the end of the intervention, the final body weight of the rats in the OV and OV+EX groups were significantly higher than the rats in the N group ($P < 0.001$). No difference was observed in the body weights of the rats in the OV and OV+EX groups; however, the rats in the OV+EX+F group ($P < 0.05$) had lower body weights than the rats in the OV group (**Fig. 3A**). Blood TG levels were higher in the rats in the OV group ($P < 0.05$) than the rats in the N group; however, the decrease in the blood TG of the rats in the OV+EX ($P < 0.05$) and OV+EX+F groups ($P < 0.01$) was similar to that in the N group (**Fig. 3B**). Blood total cholesterol levels were higher in the rats in the OV group ($P < 0.01$) than in the rats in the N group; however, no significant differences were observed in any of the OV groups (**Fig. 3C**). Moreover, no statistically significant differences were observed in blood insulin levels among the groups (**Fig. 3D**).

Femur head and shaft

Histopathological analysis of the femur head and shaft tissue was performed using H&E staining (**Fig. 4A**). Notably, increased adipocyte accumulation was observed in the OV group compared with that in the N group in places where the BMD was decreased (**Fig. 4A**). However, this increase in adipocytes in the bone marrow was suppressed in the OV+EX and OV+EX+F groups (**Fig. 4B and C**).

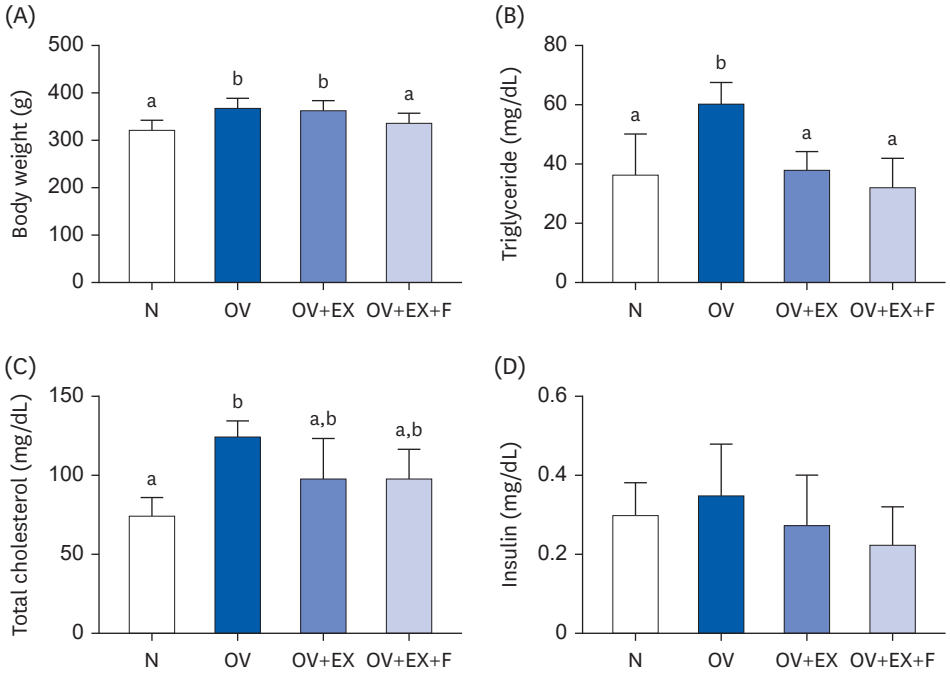

Fig. 3. Final body weight (A), total cholesterol (B), TG (C), and insulin (D) levels. All values are presented as the mean ± SD. Data were statistically analyzed using one-way analysis of variance, followed by a Tukey's multiple range test.
N, control (normal); OV, ovariectomized rats that were fed a control diet; OV+EX, a control diet with exercise training; OV+EX+F, a diet including ferulic acid with exercise training.
[a,b]Different letters indicate statistically significant differences.

https://doi.org/10.4162/nrp.2025.19.1.30

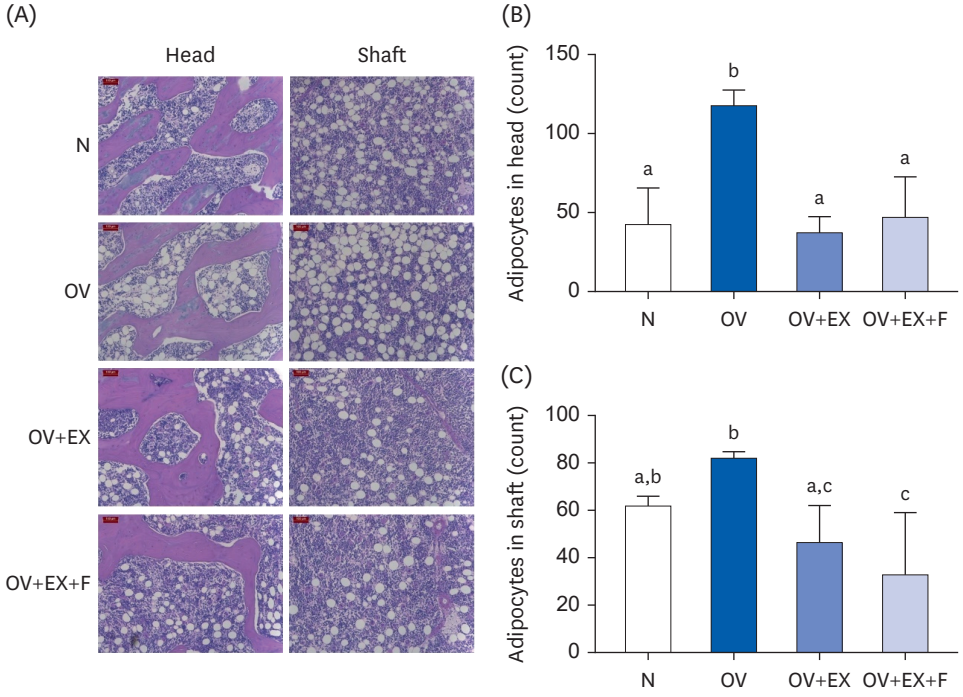

Fig. 4. (A) The representative femur bone head and shaft tissues stained by hematoxylin and eosin (magnification 10×, scale bar 100 μm). Graph presenting adipocytes count in (B) bone head and (C) shaft. All values are presented as the mean ± SD. Data were statistically analyzed using one-way analysis of variance, followed by a Tukey's multiple range test.
N, control (normal); OV, ovariectomized rats that were fed a control diet; OV+EX, a control diet with exercise training; OV+EX+F, a diet including ferulic acid with exercise training.
[a,b,c]Different letters indicate statistically significant differences.

Changes in dermis length and area of subcutaneous fat

Fig. 5A shows the histological sections of H&E-stained skin tissue sections. The skin area was larger in the OV group than in the N group ($P < 0.001$). Among all OV groups, the OV+EX+F group had a smaller area than the OV ($P < 0.01$) and OV+EX ($P < 0.001$) groups. The dermal length was smaller in the OV group than that in the N group ($P < 0.001$), whereas the dermal length was mostly recovered in the OV+EX ($P < 0.001$) and OV+EX+F ($P < 0.001$) groups (**Fig. 5C and D**). The areas of the subcutaneous fat layer in the N and OV groups were significantly different ($P < 0.001$). Only the OV+EX+F group ($P < 0.001$) exhibited reduced subcutaneous fat compared with the OV group ($P < 0.001$).

Changes in DNA repair-related protein levels

Fig. 6 shows the levels of DNA repair-related proteins analyzed using western blotting. Notably, pCHK levels did not differ between the N and OV groups. However, pCHK levels were significantly higher in the OV+EX ($P < 0.05$) and OV+EX+F ($P < 0.05$) groups than in the OV group (**Fig. 6B**). No difference in p53 levels was observed between the N and OV groups. However, p53 levels were significantly higher in the OV+EX ($P < 0.01$) and OV+EX+F ($P < 0.05$) groups than in the OV group (**Fig. 6C**).

https://doi.org/10.4162/nrp.2025.19.1.30

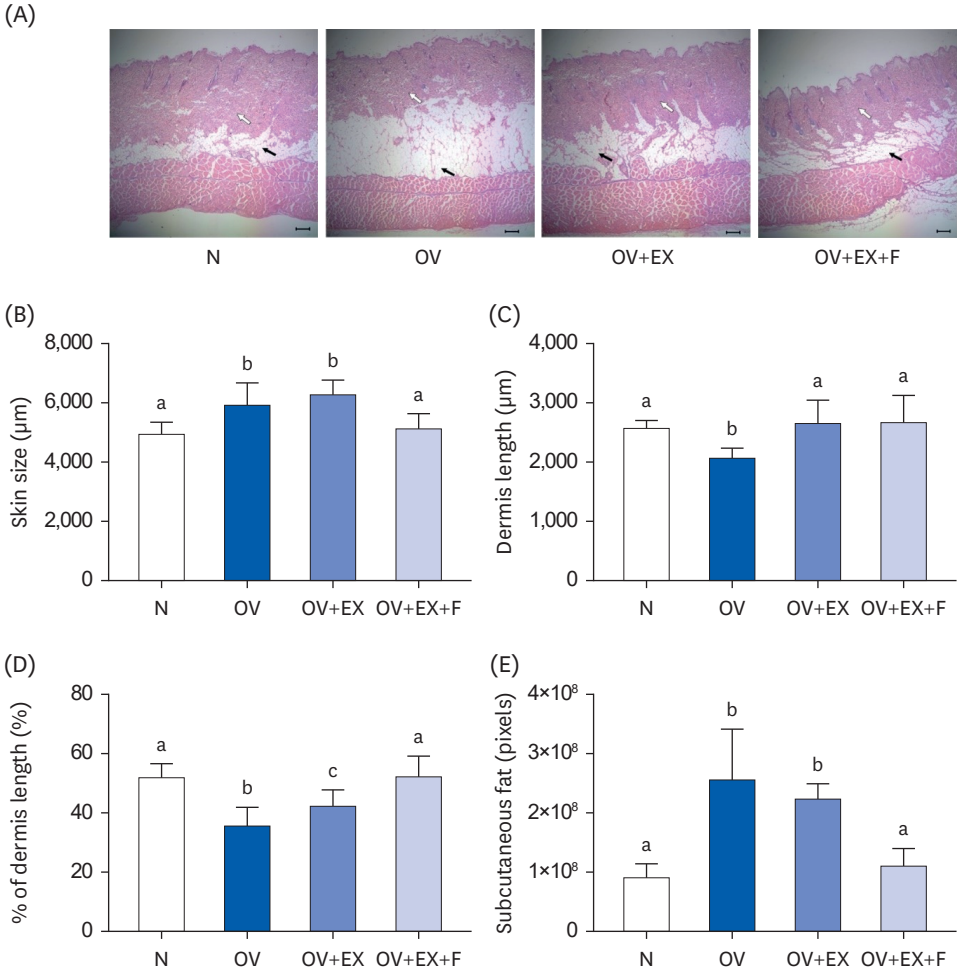

Fig. 5. (A) The representative skin tissue stained by hematoxylin and eosin (magnification 4×, scale bar 50 μm). Graphs presenting changes in (B) skin size, (C), dermis length, (D) percent of dermis length, and (E) area of subcutaneous fat. All values are presented as the mean ± SD. Data were statistically analyzed using one-way analysis of variance, followed by a Tukey's multiple range test.
N, control (normal); OV, ovariectomized rats that were fed a control diet; OV+EX, a control diet with exercise training; OV+EX+F, a diet including ferulic acid with exercise training.
[a,b,c]Different letters indicate statistically significant differences.

DISCUSSION

Although exercise and FA are known for their antioxidant and health benefits, their combined effects on skin health during menopause are not well understood. In this study, we examined the effects of exercise alone and in combination with FA on body weight, lipid profiles, BMD, and skin health in ovariectomized rats. In addition, we investigated the mechanisms underlying the observed positive changes in the skin. Notably, both exercise alone and exercise combined with FA improved estrogen deficiency-induced deterioration in serum TG levels, BMD, and skin remodeling. The combined exercise and FA treatment exhibited further beneficial effects on body weight and skin remodeling parameters, such as dermal length and subcutaneous fat of the skin tissue. Moreover, the beneficial effects of this combined treatment on skin tissue are likely associated with the DNA repair mechanism by increasing pCHK1 and p53 protein levels.

https://doi.org/10.4162/nrp.2025.19.1.30

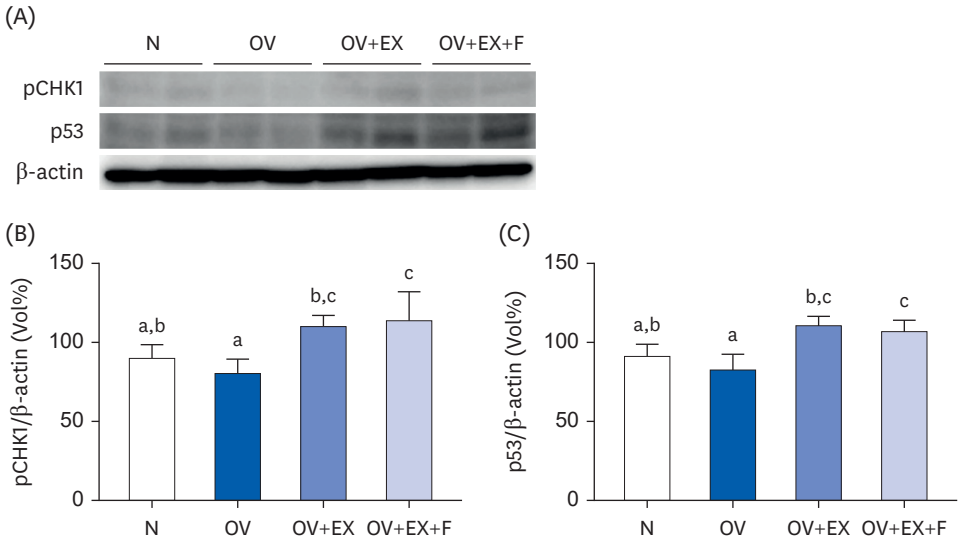

Fig. 6. (A) The protein levels of pCHK1 and p53 analyzed by western blotting. (B, C) The relative band intensities were normalized by β-actin. All values are presented as the mean ± SD. Data were statistically analyzed using one-way analysis of variance, followed by a Tukey's multiple range test.
N, control (normal); OV, ovariectomized rats that were fed a control diet; OV+EX, a control diet with exercise training; OV+EX+F, a diet including ferulic acid with exercise training.
[a,b,c]Different letters indicate statistically significant differences.

Ovariectomy-induced estrogen deficiency is associated with decreased and increased expression of energy expenditure- and lipid synthesis-related genes, respectively, resulting in menopausal symptoms, including weight gain and a dysregulated lipid profile [13]. Consistent with previous studies, the rats in the OV group exhibited higher body weight and increased serum TG and total cholesterol levels than the rats in the N group. Although exercise alone could improve serum TG levels, it had no effect on weight loss. Notably, previous studies have reported a significant weight loss in ovariectomized rats subjected to aerobic exercise or a combination of aerobic and resistance exercise [14,15]. However, in this study, the 12-week resistance exercise program did not result in significant weight loss. Despite the positive effect of resistance exercise on menopausal symptoms [16], the resistance exercise applied in this study may not have expended sufficient energy to induce weight loss. In addition, our previous study revealed that FA treatment to high-fat diet-induced obese mice resulted in weight loss and improved glucose tolerance through the self-renewal of embryonic stem cells [9]. Wang *et al.* [17] reported weight loss in obese mice, along with enhanced antioxidant effects in the muscles and liver and improved exercise capacity, following a combined treatment with exercise and FA, thus demonstrating a synergistic effect. A combination of FA, a natural antioxidant, and exercise is believed to exert a synergistic effect [17]. Similarly, in this study, exercise with FA treatment exhibited more positive effects on weight loss and blood lipid profile than exercise alone in ovariectomized rats.

Ovariectomy may result in reduced BMD, accompanied by an increase in adipocytes in the bone marrow [18]. Reduced BMD may likely be associated with ovariectomy-induced unbalanced bone remodeling [19], increased osteoclast generation [20], and increased secretion of cytokines such as IL-6, TNF-α, and TGF-β in the bone marrow [21]. In the present study, BMD decreased with increased adipocyte accumulation in the OV group compared with that in the N group. Additionally, both the 12-week exercise and exercise with FA groups showed a significant increase in the femur head and shaft BMD, with decreased adipocyte accumulation in ovariectomized rats. Weight-bearing training improves bone

https://doi.org/10.4162/nrp.2025.19.1.30

health-related parameters, including BMD, microstructure, and mechanical properties, in ovariectomized rats [22]. Moreover, Hou *et al.* [23] showed that 20- or 30-mg/kg body weight of FA treatment improved BMD loss by maintaining bone formation and mineralization in osteoporotic animals. Sagar *et al.* [24] reported that FA suppressed osteoclast fusion and induced apoptosis in mature osteoclasts, suggesting the attenuation of BMD loss. Although previous studies have reported the beneficial effects of FA on BMD, we did not observe synergistic effects of exercise and FA treatment on BMD in ovariectomized rats. Notably, we only assessed histological changes in BMD and did not evaluate other bone-related variables. Consequently, further studies are warranted to comprehensively evaluate changes in BMD.

Skin structure, including a decrease in dermal thickness, indicates skin aging and is related to the decline in skin functions such as immune response, elasticity, and wound healing [25]. Estrogen deficiency results in thinner and weaker skin [26]. Our results revealed thinner dermis and thicker subcutaneous fat in the OV group than in the control group. However, both exercise and exercise with FA treatments suppressed the estrogen deficiency-induced reduction in dermal thickness and increase in subcutaneous fat. Nishikori *et al.* [27] showed that exercise training, especially resistance training, inhibits skin aging by reducing inflammation and increasing the dermal extracellular matrix. Similarly, low-intensity tower-climbing resistance exercise improves overall skin health by regulating serum Ig levels and mRNA expression of pro-inflammatory cytokines in individuals with atopic dermatitis [28]. Furthermore, Hahn *et al.* [29] reported the protective role of FA on the dermis layer through regulating the extracellular matrix reconstruction in ultraviolet A-induced cell damage in human dermal fibroblasts [30]. In our study, combined exercise and FA treatment were more effective in maintaining dermal thickness in ovariectomized rats, suggesting the protective effect against estrogen deficiency-induced skin aging.

Estrogen deficiency accelerates dermal aging associated with DNA damage [4]. These changes are accompanied by a reduced efficacy of skin remodeling [4]. In this study, exercise training and the combination of exercise training and FA increased p53 and pCHK1 protein levels. Notably, p53 is recruited in response to DNA damage, as it regulates DNA damage [31]. Similarly, pCHK1 has been identified as a mediator of DNA damage checkpoints, cell cycle arrest, and DNA repair [32]. Therefore, exercise with FA might suppress estrogen deficiency-induced DNA damage by modulating p53 and pCHK1, subsequently restoring skin remodeling, such as maintaining dermal thickness.

First, in the limitations of the current study, we presented combined effect of exercise and FA on an estrogen-deficient rat model. Furthermore, additional studies including FA alone treatment groups may be needed to clarify the distinct contributions of exercise and FA in the model.

In second, an estrogen deficiency *in vivo* model was used to analyze the combined effects of exercise and FA on rat skin tissue. Although our study found that DNA repair mechanisms are associated with mitigating skin aging on the estrogen deficiency model, the exact cellular level mechanism is not fully illustrated. Therefore, an *in vitro* experiment analyzing DNA damage and repair mechanisms may need to show our hypothesis.

Despite these limitations, we have clarified that exercise with FA exerts beneficial effects on estrogen deficiency-induced skin damage by restoring the DNA repair system. Therefore, a combination of exercise and FA may be a promising strategy for developing therapies to inhibit skin aging in postmenopausal women.

https://doi.org/10.4162/nrp.2025.19.1.30

ACKNOWLEDGMENTS

We wish to thank Dr. Yoon-Jin Hwan who passed away for helping with valuable support and animal experiments.

REFERENCES

1. Peate I. The skin: largest organ of the body. Br J Healthc Assist 2021;15:446-51. CROSSREF
2. Campbell L, Emmerson E, Davies F, Gilliver SC, Krust A, Chambon P, Ashcroft GS, Hardman MJ. Estrogen promotes cutaneous wound healing via estrogen receptor beta independent of its antiinflammatory activities. J Exp Med 2010;207:1825-33. PUBMED | CROSSREF
3. Thornton MJ. Estrogens and aging skin. Dermatoendocrinol 2013;5:264-70. PUBMED | CROSSREF
4. Calleja-Agius J, Brincat M. The effect of menopause on the skin and other connective tissues. Gynecol Endocrinol 2012;28:273-7. PUBMED | CROSSREF
5. Khalafi M, Habibi Maleki A, Sakhaei MH, Rosenkranz SK, Pourvaghar MJ, Ehsanifar M, Bayat H, Korivi M, Liu Y. The effects of exercise training on body composition in postmenopausal women: a systematic review and meta-analysis. Front Endocrinol (Lausanne) 2023;14:1183765. PUBMED | CROSSREF
6. Mendoza N, De Teresa C, Cano A, Godoy D, Hita-Contreras F, Lapotka M, Llaneza P, Manonelles P, Martínez-Amat A, Ocón O, et al. Benefits of physical exercise in postmenopausal women. Maturitas 2016;93:83-8. PUBMED | CROSSREF
7. Cho EJ, Choi Y, Kim J, Bae JH, Cho J, Park DH, Kang JH, Yoon JH, Park E, Seo DY, et al. Exercise training attenuates ovariectomy-induced alterations in skeletal muscle remodeling, apoptotic signaling, and atrophy signaling in rat skeletal muscle. Int Neurourol J 2021;25:S47-54. PUBMED | CROSSREF
8. Kumar N, Pruthi V. Potential applications of ferulic acid from natural sources. Biotechnol Rep (Amst) 2014;4:86-93. PUBMED | CROSSREF
9. Cho J, Park E. Ferulic acid maintains the self-renewal capacity of embryo stem cells and adipose-derived mesenchymal stem cells in high fat diet-induced obese mice. J Nutr Biochem 2020;77:108327. PUBMED | CROSSREF
10. Fang W, Peng W, Qi W, Zhang J, Song G, Pang S, Wang Y. Ferulic acid combined with different dietary fibers improve glucose metabolism and intestinal barrier function by regulating gut microbiota in high-fat diet-fed mice. J Funct Foods 2024;112:105919. CROSSREF
11. Yousefzadeh N, Kashfi K, Jeddi S, Ghasemi A. Ovariectomized rat model of osteoporosis: a practical guide. EXCLI J 2020;19:89-107. PUBMED | CROSSREF
12. An JH, Yoon JH, Suk MH, Shin YA. Up-regulation of lipolysis genes and increased production of AMP-activated protein kinase protein in the skeletal muscle of rats after resistance training. J Exerc Rehabil 2016;12:163-70. PUBMED | CROSSREF
13. Pellegrini M, Pallottini V, Marin R, Marino M. Role of the sex hormone estrogen in the prevention of lipid disorder. Curr Med Chem 2014;21:2734-42. PUBMED | CROSSREF
14. Gao L, Li Y, Yang YJ, Zhang DY. The effect of moderate-intensity treadmill exercise on bone mass and the transcription of peripheral blood mononuclear cells in ovariectomized rats. Front Physiol 2021;12:729910. PUBMED | CROSSREF
15. Zheng W, Rogoschin J, Niehoff A, Oden K, Kulling SE, Xie M, Diel P. Combinatory effects of phytoestrogens and exercise on body fat mass and lipid metabolism in ovariectomized female rats. J Steroid Biochem Mol Biol 2018;178:73-81. PUBMED | CROSSREF
16. Capel-Alcaraz AM, García-López H, Castro-Sánchez AM, Fernández-Sánchez M, Lara-Palomo IC. The efficacy of strength exercises for reducing the symptoms of menopause: a systematic review. J Clin Med 2023;12:548. PUBMED | CROSSREF
17. Wang O, Zhang N, Han C, Huang J. Regular exercise combined with ferulic acid exhibits antiobesity effect and regulates metabolic profiles in high-fat diet-induced mice. Front Nutr 2022;9:957321. PUBMED | CROSSREF
18. Li J, Chen X, Lu L, Yu X. The relationship between bone marrow adipose tissue and bone metabolism in postmenopausal osteoporosis. Cytokine Growth Factor Rev 2020;52:88-98. PUBMED | CROSSREF
19. Guo X, Yu X, Yao Q, Qin J. Early effects of ovariectomy on bone microstructure, bone turnover markers and mechanical properties in rats. BMC Musculoskelet Disord 2022;23:316. PUBMED | CROSSREF

20. Kim TH, Jung JW, Ha BG, Hong JM, Park EK, Kim HJ, Kim SY. The effects of luteolin on osteoclast differentiation, function *in vitro* and ovariectomy-induced bone loss. J Nutr Biochem 2011;22:8-15. PUBMED | CROSSREF
21. Wang T, He C. TNF-α and IL-6: the link between immune and bone system. Curr Drug Targets 2020;21:213-27. PUBMED | CROSSREF
22. Tang L, Cao W, Zhao T, Yu K, Sun L, Guo J, Fan X, Ta D. Weight-bearing exercise prevents skeletal muscle atrophy in ovariectomized rats. J Physiol Biochem 2021;77:273-81. PUBMED | CROSSREF
23. Hou T, Zhang L, Yang X. Ferulic acid, a natural polyphenol, protects against osteoporosis by activating SIRT1 and NF-κB in neonatal rats with glucocorticoid-induced osteoporosis. Biomed Pharmacother 2019;120:109205. PUBMED | CROSSREF
24. Sagar T, Rantlha M, Kruger MC, Coetzee M, Deepak V. Ferulic acid impairs osteoclast fusion and exacerbates survival of mature osteoclasts. Cytotechnology 2016;68:1963-72. PUBMED | CROSSREF
25. Farage MA, Miller KW, Elsner P, Maibach HI. Intrinsic and extrinsic factors in skin ageing: a review. Int J Cosmet Sci 2008;30:87-95. PUBMED | CROSSREF
26. Zomer HD, Cooke PS. Targeting estrogen signaling and biosynthesis for aged skin repair. Front Physiol 2023;14:1281071. PUBMED | CROSSREF
27. Nishikori S, Yasuda J, Murata K, Takegaki J, Harada Y, Shirai Y, Fujita S. Resistance training rejuvenates aging skin by reducing circulating inflammatory factors and enhancing dermal extracellular matrices. Sci Rep 2023;13:10214. PUBMED | CROSSREF
28. Kim J. Low-intensity tower climbing resistance exercise reduces experimentally induced atopic dermatitis in mice. J Exerc Rehabil 2019;15:518-25. PUBMED | CROSSREF
29. Hahn HJ, Kim KB, Bae S, Choi BG, An S, Ahn KJ, Kim SY. Pretreatment of ferulic acid protects human dermal fibroblasts against ultraviolet A irradiation. Ann Dermatol 2016;28:740-8. PUBMED | CROSSREF
30. Zduńska K, Dana A, Kolodziejczak A, Rotsztejn H. Antioxidant properties of ferulic acid and its possible application. Skin Pharmacol Physiol 2018;31:332-6. PUBMED | CROSSREF
31. Wang YH, Ho TLF, Hariharan A, Goh HC, Wong YL, Verkaik NS, Lee MY, Tam WL, van Gent DC, Venkitaraman AR, et al. Rapid recruitment of p53 to DNA damage sites directs DNA repair choice and integrity. Proc Natl Acad Sci U S A 2022;119:e2113233119. PUBMED | CROSSREF
32. Patil M, Pabla N, Dong Z. Checkpoint kinase 1 in DNA damage response and cell cycle regulation. Cell Mol Life Sci 2013;70:4009-21. PUBMED | CROSSREF