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# Cinnamon extract combined with high-intensity endurance training alleviates metabolic syndrome via non-canonical WNT signaling

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ABSTRACT

*Objectives:* The incidence of metabolic syndrome (MetS) in menopausal women is one of the main health care concerns. MetS clusters are related to an imbalance in pro- and anti-inflammatory adipokines such as secreted frizzled–related protein 5 (SFRP5) and wingless-type mammary tumor virus integration site family, member 5A (WNT5A). WNT5A induces an inflammatory state to induce insulin resistance and further pathologic consequences. Recent strategies to prevent progression of MetS to diabetes have focused on conservative treatments such as exercise and herbal medicine. The aim of this study was to investigate the mechanistic effects of cotreatment with cinnamon extract and 12-wk high-intensity endurance training on MetS components considering the non-canonical WNT5A signaling.

*Method:* Thirty-two female ovariectomized Wistar rats were divided into the following four groups (n = 8/group): exercise (Ova+Exe), cinnamon extract (Ova+Cin), exercise with cinnamon extract (Ova+Exe+Cin) and saline (Ova+Sal). One group of rats undergoing surgery without removal of the ovaries was considered as a sham. After 3 mo of experimental intervention, waist circumference, serum concentrations of glucose, insulin, lipid profile, tumor necrosis factor-α, WNT5A, and SFRP5 were measured.

*Results:* Data showed a significant reduction in serum glucose, low-density lipoprotein, homeostasis model assessment estimate of insulin resistance, and tumor necrosis factor-α, but an increase in SFRP5 level in Ova +Exe, Ova+Cin and Ova +Exe+Cin groups compared with Ova+Sal group ($P < 0.05$). Serum WNT5A significantly was reduced only in Ova+Exe+Cin group ($P = 0.02$).

*Conclusion:* The present study indicated that high-endurance training combined with aqueous cinnamon extract supplementation for 12 wk more efficiently alleviated insulin resistance and metabolic dysfunctions via reduction in noncanonical WNT signaling in ovariectomized rats.



## Introduction

Metabolic syndrome (MetS) is a prediabetes stage with multiple risk factors consisting of abdominal obesity, hypertension, hyperglycemia, and dyslipidemia [1,2]. The prevalence of MetS is increasing worldwide, especially in postmenopausal women, owing to estrogen withdrawal and its further consequences such as visceral fat accumulation and dyslipidemia [3]. Therefore, menopause may predispose women to MetS, even independently of their age [4].

Visceral fat accumulation has been associated with changes in macrophage infiltration and proinflammatory signaling via both classical and non-classical cytokines including wingless-type mammary tumor virus integration site family, member 5A (WNT5A) [5]. WNT5A is a growth factor typically secreted by different cells and exerts its effects through canonical and noncanonical pathways to control cell proliferation, survival, and behavior [6,7]. The noncanonical pathway has been shown to be mainly associated with inflammatory responses and adipogenesis [8], whereas the canonical cascade stands as anti-adipogenic signaling [9].

Healthy adipocytes have been known to release the WNT5A inhibitor secreted frizzled–related protein 5 (SFRP5) as an anti-inflammatory adipokine [10] that modulates metabolic dysfunction and prevents insulin resistance) IR) [11]. SFRP5 as a decoy receptor

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sequesters WNT5A and antagonizes noncanonical WNT signaling. Reduction in SFRP5 in obesity [10] and metabolic disorders [12] allows the progress of more inflammation and IR. Therefore, imbalance in canonical and noncanonical WNT signaling appears to be an important homeostatic mechanism to regulate both accumulation of lipids in adipocytes and progress of IR in diabetes [13].

Considering the fact that women spend at least one-third of their life in a menopausal period [14], finding conservative treatments to prevent the progressions of MetS to diabetes and cardiovascular diseases (CVDs) is important.

It is well known that one of the non-pharmacologic treatments to combat some of the components of MetS is endurance exercise training [15,16]. Previous studies revealed that high-intensity endurance training has higher energy expenditure [17,18] and is capable of inducing the secretion of lipolytic hormones to facilitate postexercise energy expenditure [17,19]. However despite the existing literatures showing different beneficial effects of endurance training on MetS [16,20], there are some contradictory results [17,21]. For example, Irving et al. reported that high-intensity endurance training reduces visceral fat, with no significant change in blood triacylglyceride (TG), high-density lipoprotein (HDL), and fasting blood glucose (FBG) in middle-aged women with MetS [17]. Another study carried out by Johnson et al. also showed that high-intensity endurance training does not change some of the MetS indices in middle-aged postmenopausal women diagnosed with MetS [22]. Here we hypothesized that signaling pathways determining the rate of metabolism in the estrogen-deficiency state might antagonize the beneficial effects of exercise. Therefore, we assumed that treatment with a plant source that contains metabolism-enhancer specificity combined with a protocol of chronic endurance exercise training might prevent the progress of MetS.

Recently, cinnamon has received attention for its ability to raise metabolism [23,24], improve inflammation [24], and alleviate IR [24]. Cinnamon is a species belonging to *Lauraceae* family [25], with wide distribution in India, Iran, and Turkey [26]. It has been used since ancient times for treatment of inflammation and gastrointestinal tract infection. Both water and alcoholic cinnamon extract are rich sources of bioactive compounds such as cinnamaldehyde, cinnamate, cinnamic acid, and eugenol [27].

Anderson et al, [28] reported that taking 500 mg of aqueous cinnamon extract for 2 mo reduces insulin, glucose, low-density lipoprotein (LDL), and total cholesterol (TC) in individuals with elevated serum glucose. However, there are some studies that show no significant improvement in metabolism after cinnamon extract treatment simultaneously [29,30]. Therefore, this study was designed to evaluate the effects of cotreatment with physical activity and cinnamon extract on MetS, considering the role of non-canonical WNT5A signaling.

To approach this, ovariectomized rats were used as an acceptable model of menopause-induced MetS [16,31,32].

## Materials and methods

### *Animals*

Forty adult female Wistar rats (3 mo of age and weighing 160–195 g) were used in this study. Animals were housed four per cage in a room with a temperature of 22° C ± 2°C, and 12/12-h light/dark cycle (light on 07:00) and fed standard-pellet rat chow and tap water ad libitum. All experiments were performed in accordance with National Institutes of Health guide for the care and use of laboratory animals and the Ethics Committee of the Guilan University of Medical Sciences.

### *Ovariectomy surgery*

All animals were ovariectomized under general anesthesia with an intraperitoneal injection of ketamine (Alfasan, Holland) and xylazine (Alfasan, Holland) in a ratio of 4:1 [33]. After complete anesthesia, ovaries were accurately removed through midline incision. The sham group had the surgical procedure but no removal of ovaries.

### *Groups and intervention protocol*

One month after ovariectomy, animals showing three criteria of MetS (significant high serum cholesterol LDL, TG, large waist circumference [WC], and FBG) were randomly divided into the following four groups (n = 8/group): receiving saline (Ova+Sal), exercise (Ova+Exe), cinnamon extract (Ova+Cin, 100 mg · kg · $d^{-1}$), and combination of exercise with cinnamon extract (Ova+Exe+Cin, 100 mg · kg · $d^{-1}$). Exercised groups ran with 80% of maximum running speed approximately equal to 80% maximal oxygen uptake ($VO_2$ max), 1 h/d, 5 d/wk for 12 wk with a 5% slope on rodent treadmill.

### *Measurement of visceral fat and biochemical and morphometric parameters*

All animals were weighed weekly, between 0900 h and 1130 h using a precise digital scale (Jadever Scale Co, Taiwan) with accuracy of 0.01 g.

Measurement of food intake was carried out according to the previous work [33]; briefly an equal amount of food (20 g/d per rat) was given to each cage (four rats in each cage) in the morning, and then consumed food was measured by subtracting the weight of the uneaten food from the total given on the following day.

At the end of the intervention, 48 h after the last exercise session and 16 h of fasting overnight, rats were anesthetized and morphometric characteristics were measured. WC was measured on the largest region of the rat's abdomen using a flexible plastic meter with accuracy of 0.1 cm according to the previous studies [34]. Blood was collected directly from the right atrium of the heart and centrifuged at 3000*g* for 15min and serum was kept at −80°C. Visceral fats were isolated from surrounding tissues of mesenteric, urogenital,and retroperitoneal regions [35] and weighed using lab weighing scale (AND Scale, Japan, with an accuracy of 1 mg).

Serum glucose, LDL, TG, and TC were measured by automated analyzer (Alfa-Classic, Tajhizat-Sanjesh Company, Isfahan, Iran) using Pars Azmoun Kit (Tehran, Iran). Serum insulin was assayed using Rat Insulin Enzyme-Linked Immunosorbent Assay (ELISA) Kit (Hangzhou Eastbiopharm, Hangzhou, China) according to the manufacturer's instructions. Insulin resistance index (IRI) was assessed by homeostasis model assessment estimate of insulin resistance (HOMA-IR) by the following formula [16]:

$$\text{Fasting insulin } (\mu\text{IU/mL}) \times \text{fasting glucose}(\text{mmol/L})/22.5.$$

SFRP5 concentration was assayed using Rat SFRP5 ELISA Kit (Hangzhou Eastbiopharm), and WNT5A by Rat WNT5A ELISA kit (ZellBio GmbH., Veltlinerweg, Germany). The sensitivity for all kits purchased from Hangzhou Eastbiopharm were 0.04 ng/mL, and intra- and interassay coefficients of variation were <10% and <12%.

Tumor necrosis factor (TNF)-α concentration was measured using Rat TNF-α ELISA Kit (Diaclone, Besancon, France). The sensitivity was <15 pg/mL and intra- and interassay coefficients of variation were <7.9% and <6.1%, respectively.

### *Calculation of the MetS severity Z-score*

MetS severity *Z*-score was calculated by the following formula according to the previous studies [36–38]:

$$[(\text{HDL}-37)/8.3] + [(\text{LDL}-22)/3.9] + [(\text{TG}-42)/7.1] + [(\text{fasting glucose}-130)/15.5] + [(\text{insulin}-7)/2.6] + [(\text{WC}-17)/1.14,$$

### *Cinnamon extract*

Cinnamon (*Cinnamomum zeylanicum*) with the herbarium code of GUMS-C17, approved by Pharmacognosy Department of Guilan University of Medical Sciences, was used for providing aqueous extract according to Shen's study [39]. Briefly 40 g of cinnamon powder was dissolved in 400 mL of double-distilled water and placed on shaker incubator (110 r/min, 24 h at a temperature of 25°). Supernatant was filtered and placed on a rotary machine made by OPC BUCHI, model RE120, Germany (40°C) to obtain concentrated solution. Concentrated solutions were placed in a freeze dryer (Martin Christ, model: alpha 1–2 ld plus, Germany) for 24 h for lyophilizing. Finally, dried extract was kept in a refrigerator at 4°C for further administrations. Cinnamon extract was injected intraperitoneally (100 mg/kg for 12 wk) [58]. The normal saline was injected as vehicle in the same volume of cinnamon extract to the Ova+Sal group.

### *Endurance training program*

Four weeks after surgery, rats were initially acclimatized with running on a treadmill for 1 wk with speed of 10 m/min, 10 min, 5 d/wk. Training program included warm up (10 min), workout (1 h), and cool-down (5 min). The training started at speeds of 15 m/min for 15 min/d. Speed, duration, and slope gradually increased, so that from week 4 to week 12, slope and duration remained unchanged (1 h/d, 5% slope with 80% of the maximum running speed). Maximum running speed test was performed at the start of intervention weeks 1, 4, and 8. The aerobic exercise protocol is shown in Table 1.

**Table 1**
Aerobic exercise protocol

| Week of training | Speed (M/min) | Duration (min) | Slope (grade) |
|---|---|---|---|
| Week 1 | 15 | 15 | Zero |
| Week 2 | 17 | 30 | 2 |
| Week 3 | 19 | 45 | 4 |
| Week 4 | 20 | 60 | 5 |
| Week 5 | 20 | 60 | 5 |
| Week 6 | 20 | 60 | 5 |
| Week 7 | 20 | 60 | 5 |
| Week 8 | 24 | 60 | 5 |
| Week 9 | 24 | 60 | 5 |
| Week 10 | 24 | 60 | 5 |
| Week 11 | 24 | 60 | 5 |
| Week 12 | 24 | 60 | 5 |

**Table 2**
Comparison of mean ± SE components of MetS between Ova and sham group one month after ovariectomy

| Variable | Groups | |
|---|---|---|
| | Sham | Ova |
| Glucose (mg/dL) | 130.33 ± 2.28 | 148.00 ± 5.06* |
| TG (mg/dL) | 36.31 ± 1.906 | 45.75 ± 3.106* |
| LDL-C (mg/dL) | 21.16 ± 0.955 | 26.75 ± 2.447* |
| HDL-C (mg/dL) | 29.62 ± 0.350 | 30.62 ± 1.263 |
| WC (cm) | 15.62 ± 0.26 | 17.87 ± 0.20* |
| Insulin (μU/mL) | 7.22 ± 0.37 | 9.66 ± 1.06* |
| Body weight (g) | 178.91 ± 3.95 | 239.5 ± 8.08* |

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ova, ovariectomy; TG, triacylglyceride.
Values are reported as the mean ± SE for eight animals per group.
*$P < 0.05$ vs (sham) sham-operated group.

*Statistical analysis*

Normality of variables and variance homogeneity were estimated by Kolmogorov–Smirnov test and the Levene test, respectively.

Variables were analyzed using one-way analysis of variance (ANOVA) followed by post hoc Tukey's test. Independent *t* test was used for comparing parameters between ovariectomy and sham group means. Correlation was analyzed using Pearson's correlation coefficient. Results are expressed as mean ± SE and $P < 0.05$ was considered statistically significant (SPSS 19 software, Chicago, IL, USA).

## Results

One month after ovariectomy, body weight (P = 0.001), LDL (P = 0.049), TG (P = 0.02), FBG (P = 0.007), and WC (P = 0.001) were significantly increased in ovariectomized rats compared with the sham group. There was no significant difference in HDL cholesterol (HDL-C) concentration between these two groups (Table 2).

At the end of the interventions, insulin (P = 0.011), glucose (P = 0.001), and HOMA-IR (P = 0.001) were significantly elevated in ovariectomized group compared with the sham group (Table 3).

The results showed no significant change in body weight in either of the treated groups (Table 3).

LDL was significantly reduced by 26% in the Ova+Exe group, 23% in Ova+Cin rats, and 29% in Ova+Cin+Exe arm compared with the Ova+Sal group (P = 0.001), although it was increased in Ova+Sal ≤35% (P = 0.001) compared with the sham group.

As Table 3 shows, HDL was significantly increased by 56% in Ova +Exe rats, and 39% in Ova+Cin+Exe rats compared with the Ova+Sal group (P = 0.001). Ova+Cin rats showed an elevation of ~9%, which was insignificant.

At the end of week 12, insulin, glucose, and HOMA-IR were significantly decreased in Ova+Exe, Ova+Cin and Ova+Cin+Exe groups compared with Ova+Sal rats (P = 0.001) and returned almost to normal value (Table 3).

One-way ANOVA test showed significant between-group differences in serum SFRP5, WNT5A, TNF-α, and visceral fat ($P = 0.001$). The Ova+Sal group displayed strongly significantly lower SFRP5 (−60%; $P = 0.001$) and higher WNT5A (300%; $P = 0.001$), TNF-α (213%; $P = 0.001$; Fig. 1A–C), and visceral fat (79%; $P = 0.001$, Table 3) compared with the sham group.

According to data illustrated in Figure 1A to C and also Table 3, SFRP5, TNF-α, and visceral fat were remarkably changed in all three intervention groups; WNT5A was only reduced in the Ova+Cin+Exe group compared with the Ova+Sal group (−55%; $P = 0.026$).

Finally, one-way ANOVA test showed a significant difference in MetS *Z*-score between groups (Fig. 2). MetS severity *Z*-score was significantly decreased in the treated groups compared with the Ova+Sal group ($P = 0.001$). Figure 2 shows the MetS *Z*-score, which was successfully decreased in the Ova+Cin+Exe rats compared with the sham group. Moreover, MetS *Z*-score was positively related to

**Table 3**
Clinical outcomes after 12 wk of intervention between groups

| Variables | Groups | | | | |
|---|---|---|---|---|---|
| | Sham | Ova+ Cin | Ova+Exe | Ova+Cin+Exe | Ova+Sal |
| Body weight (g) | 178.9 ± 3.95 | 248.94 ± 6.81* | 251.08 ± 9.20* | 234.84 ± 9.86* | 257.48 ± 6.63* |
| BMI (kg/m$^2$) | 0.41 ± 0.006 | 0.49 ± 0.008* | 0.48 ± 0.014* | 0.49 ± 0.010* | 0.50 ± 0.015* |
| WC (cm) | 15.62 ± 0.26 | 17.44 ± 0.13* | 17.12 ± 0.29* | 17.00 ± 0.43*,† | 18.25 ± 0.30*,‡ |
| Visceral fat (g) | 7.11 ± 1.07 | 8.60 ± 0.70† | 8.82 ± 0.47† | 7.63 ± 0.48† | 12.75 ± 0.74*,‡,§,‖ |
| Glucose (mg/dL) | 130.33 ± 2.28 | 117.22 ± 3.39*,‡,‖ | 131.46 ± 1.84‡,§ | 121.14 ± 1.71† | 157.00 ± 3.70*,‡,§,‖ |
| Insulin (μU/mL) | 7.22 ± 0.37 | 5.74 ± 0.81† | 7.83 ± 0.52† | 5.45 ± 1.12† | 10.80 ± 0.56*,‡,§,‖ |
| HOMA-IR | 2.33 ± 0.15 | 1.6 ± 0.19†,‖ | 2.55 ± 1.53†,‡,§ | 1.6 ± 0.33†,‖ | 4.05 ± 0.26*,‡,§,‖ |
| TC (mg/dL) | 61.56 ± 3.57 | 84.22 ± 3.46* | 91.68 ± 6.06* | 77.07 ± 3.20 | 83.00 ± 4.10* |
| LDL (mg/dL) | 21.16 ± 0.95 | 21.91 ± 0.95† | 21.20 ± 1.20† | 20.15 ± 0.82† | 28.46 ± 0.98*,‡,§,‖ |
| HDL (mg/dL) | 29.62 ± 0.35 | 33.52 ± 0.38‡,‖ | 48.12 ± 3.01*,‡,§ | 42.92 ± 1.20*,‡,§ | 30.81 ± 0.26‡,‖ |
| TG (mg/dL) | 36.31 ± 1.90 | 43.55 ± 1.51 | 43.78 ± 2.59 | 43.80 ± 2.40 | 45.78 ± 3.55 |
| Food intake (g) | 12.75 ± 0.09 | 15.13 ± 0.26*,† | 14.96 ± 0.03 | 14.74 ± 0.20*,† | 17.33 ± 0.47*,‡,§,‖ |

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Ova+Cin, cinnamon extract group; Ova+Cin+Exe, cinnamon extract with high-intensity endurance training group; Ova+Exe, high-intensity endurance training group; Ova+Sal, saline group; sham, sham-operated group; TC, total cholesterol; TG, triacylglyceride
One-way analysis of variance test followed by Tukey's post hoc test. Values are shown as the mean ± SE for eight animals per group.
*$P < 0.05$ vs sham group.
†$P < 0.05$ vs Ova+Sal group.
‡$P < 0.05$ vs OVa+Cin+Exe group.
§0.05 vs Ova+Cin group.
‖$P < 0.05$ vs Ova+ Exe group.

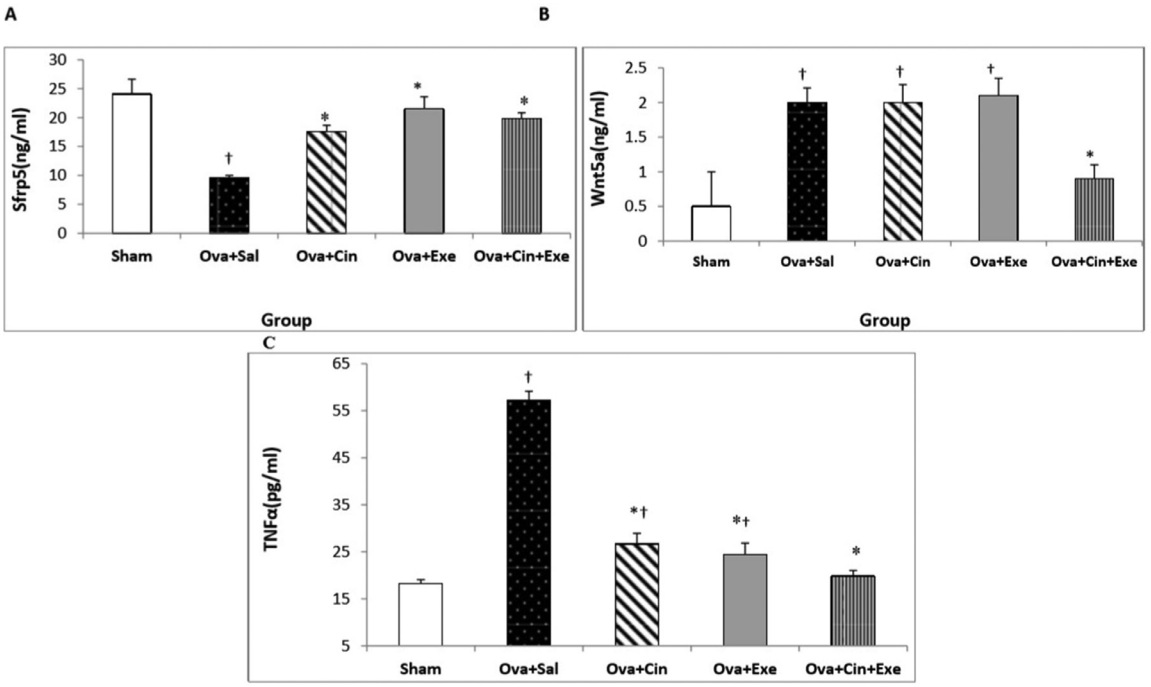


**Fig. 1.** The effect of exercise, cinnamon extract, and combination of both on (A) SFRP5, (B) WNT5A, and (C) TNF-α. Values are reported as the mean ± SE for eight animals per group. ova, ovariectomy; Ova+Cin, cinnamon extract group; Ova+Cin+Exe, cinnamon extract with high-intensity endurance training group; Ova+Exe, high-intensity endurance training group; Ova+Sal, saline group; sham, sham-operated; TNF-α, tumor necrosis factor. $^{*}P < 0.05$ versus Ova+Sal group. $^{\dagger}P < 0.05$ versus sham group.

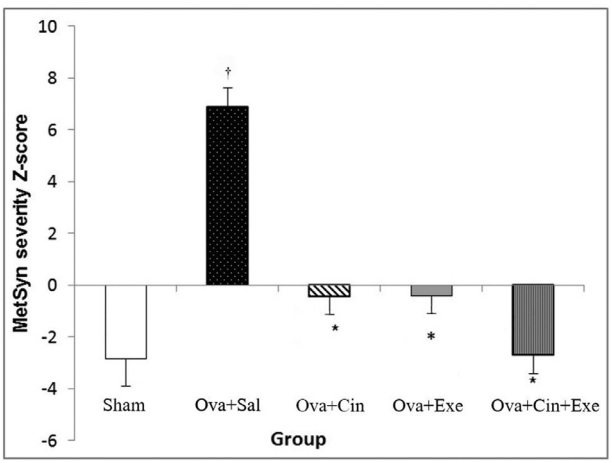


**Fig. 2.** Change in MetS *Z*-score after interventions. One-way analysis of variance test followed by Tukey's post hoc test revealed significance difference. $^{*}P < 0.0001$ versus saline group. $^{\dagger}P < 0.0001$ versus sham group. ova, ovariectomy; Ova+Cin, cinnamon extract receiving group; Ova+Cin+Exe, cinnamon extract with high-intensity endurance training group; Ova+Exe, high-intensity endurance training group; Ova +Sal, saline receiving group; sham, sham-operated.

serum WNT5A ($r = 0.471$, $P = 0.002$) and negatively to serum SFRP5 ($r = -0.487$, $P = 0.002$).

In addition, WNT5A was positively correlated with HOMA-IR ($r = 0.34$, $P = 0.006$), LDL ($r = 0.312$, $P = 0.014$), WC ($r = 0.397$, $P = 0.002$), TG ($r = 0.559$, $P = 0.000$), TC ($r = 0.54$, $P = 0.000$), and TNF-α ($r = 0.382$, $P = 0.016$). SFRP5 was negatively correlated with HOMA-IR ($r = -0.48$, $P = 0.000$), LDL ($r = -0.505$, $P = 0.000$), WC ($r = -0.513$, $P = 0.000$), TC ($r = -0.35$, $P = 0.049$), and TNF-α ($r = 0.632$, $P = 0.000$). HDL showed a positive relationship only with SFRP5 ($r = 0.257$, $P = 0.046$). A reverse correlation was observed between SFRP5 and WNT5A ($r = 0.55$, $P < 0.001$).

## Discussion

The results of the present study are in line with previous findings [16,32] and confirmed that ovariectomy in MetS leads to increases in body weight, body mass index, visceral fat, WC, FBG, insulin, TG, TC, and LDL-C. Our results, for the first time, revealed that serum TNF-α and WNT5A increases 1 mo after ovariectomy; whereas SFRP5 decreases. In line with our findings, Ouchi et al. showed that SFRP5 expression is downregulated in both obese mice and diabetic rats fed high-fat diets [11]. An increase in IR and noncanonical WNT signaling in menopausal model of MetS in the present study is in agreement with previous reports on obese children [40], adult patients [41], individuals with type 2 diabetes [42], and patients with atherosclerosis [43]. In the present study, IR was positively associated with WNT5A but negatively with SFRP5. Why menopause and estrogen withdrawal leads to elevation in serum WNT5A and reduction in SFRP5 has not yet been elucidated. It is known that ovariectomy and estrogen withdrawal leads to an increase in TNF-α, which is a marker of systemic inflammation and the development of visceral fat. TNF-α, is known to activate mitogen-activated protein kinase [44], upregulates inflammatory genes to impair insulin sensitivity [44], and increases plasma cholesterol levels [45]. Additionally, TNF-α induces WNT5A secretion from adipocytes and causes imbalance in WNT5A/SFRP5 signaling [41,46]. Mechanistically, non-canonical WNT signaling shifts the storage of lipids from adipose tissue to liver and muscle, promotes metabolic complications of obesity such as IR [47,48] via activating c-Jun N-terminal kinase (JNK) cascade, and is increased serine phosphorylation of insulin receptor substrate-1 [11]. Therefore, cross-talk of these signaling pathways promotes the proinflammatory state and progression of MetS [41,49].

Previously, WNT5A was reported as a prognostic biomarker in estrogen receptor–positive premenopausal breast cancer [50]. We assume here that WNT5A will possibly stand as a biomarker of metabolic disturbances in menopausal women, too. However, to prove it, more investigation is needed that will consider the up- and downstream of WNT5A in relation to estrogen.

On the other hand, SFRP5 appears to be a reversible consequence of visceral fat accumulation; however, the molecular mechanism of decreased SFRP5 levels remains unknown. Significant inverse correlations between serum SFRP5 and TNF-α, LDL, WC, HOMA-IR, and TC in the present study suggest that SFRP5 as an anti-inflammatory adipokine may suppress TNF-α and IR to protect against CVD in menopausal women.

In the second part of our experiment, we found that ovariectomized rats displaying MetS and receiving daily intake of aqueous cinnamon extract (100 mg/kg for 3 mo) in combination with high-intensity endurance training showed remarkable reduction in serum glucose, IR, LDL, visceral fat, TNF-α, WNT5a, and increased levels of HDL and SFRP5, as well as significant improvement in insulin sensitivity. MetS *Z*-score also was significantly decreased in the Ova+Cin, Ova+Exe, and Ova+Cin+Exe groups; however, the Ova +Cin+Exe rats displayed a remarkable reduction.

Although in line with previous findings, IR was significantly decreased in both exercised [16,51], and cinnamon-treated groups [28,39]. Cinnamon extract supplementation simultaneously failed to alleviate dyslipidemia compared with exercise. Considering LDL as an atherogenic lipoprotein [52], which is associated with CVDs in menopause [53], endurance training still remains a golden standard for cardiovascular protection [54].

Reduction in visceral adipose tissue parallel with decreased TNF-α in the groups receiving cinnamon extract, exercise, or combination of both, suggest that both cinnamon and exercise reduce inflammation probably via inhibition of TNF-α secretion from visceral fat [30,55].

Improvements in HOMA-IR in groups treated with cinnamon extract confirm the previous finding displaying increase in Glut4, glucose uptake [39], and glycogen synthesis [24,56]. Moreover, the finding of inverse correlation between IR and SFRP5 in all the exercise, cinnamon, and combined groups, indicates that SFRP5 probably inhibits non-canonical WNT5A pathway in order to improve insulin sensitivity [57]. In agreement with this assumption, the study carried out by Ouchi et al. [11] showed that acute administration of SFRP5 to models of obese and diabetic mice improved metabolic functions.

One question raised here is why, despite increases in SFRP5 in three experimental groups, was WNT5A only reduced in the group receiving the combination of exercise and cinnamon. It is assumed that other signaling pathways together with non-canonical WNT might be involved synergistically in the group receiving both treatments to amplify the influence of each one. Thus, the signaling cross-talk and synergy between endurance training and cinnamon extract should be further investigated as a potential therapeutic approach to combating MetS in menopause.

## Conclusion

A protocol of 12 wk of high-endurance training combined with supplementation of an aqueous cinnamon extract might be an effective strategy to prevent the progression of MetS to diabetes and CVD, partially via noncanonical WNT signaling in a MetS model of ovariectomized rats. Considering the importance of the balance between WNT5A and SFRP5 in controlling inflammation, blocking non-canonical signaling might be a useful target to restore insulin sensitivity.

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