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The Effect of High-Intensity Aerobic-Resistance Training Combined with Cinnamon on the TLR4/MyD88/NF-κB Signaling Pathway in Women with Type 2 Diabetes

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is characterized by chronic low-grade inflammation, which contributes to insulin resistance and disease progression. The TLR4/MyD88/NF-κB signaling pathway plays a central role in mediating inflammatory responses in T2DM.

Objectives: Although physical exercise and cinnamon supplementation have independently demonstrated anti-inflammatory effects, their combined effect on this pathway in women with T2DM remains unclear.

Methods: In this double-blind, randomized clinical trial, 134 women with T2DM aged 35 - 50 years were recruited and randomly allocated to four groups: control, high-intensity aerobic-resistance exercise (RVE), cinnamon supplementation (1000 mg/day; Ci), or combined exercise and cinnamon (RVECi). The exercise intervention comprised supervised sessions at 80% of VO_2max for aerobic training and resistance exercises using TRX bands, conducted over 8 weeks. Pre- and post-intervention levels of TLR4, MyD88, and NF-κB were measured. Statistical analyses included paired t-tests and an analysis of covariance (ANCOVA).

Results: No baseline differences in inflammatory markers were observed between groups. After the intervention, TLR4, MyD88, and NF-κB levels were significantly reduced in the RVE, Ci, and RVECi groups compared with the control group. The combined RVECi group demonstrated greater decreases in TLR4 and MyD88 than the Ci group, whereas the reduction in NF-κB was significantly greater in the RVECi group than in the Ci group. However, RVECi did not significantly outperform the RVE group.

Conclusions: High-intensity aerobic-resistance training effectively attenuates activation of the TLR4/MyD88/NF-κB pathway in women with T2DM. Cinnamon supplementation enhances certain anti-inflammatory effects but does not exceed the benefits of exercise. These findings support exercise as a primary strategy for inflammation management in T2DM, with cinnamon as a potential adjunct.

Keywords: Type 2 Diabetes Mellitus, Inflammation, Exercise Therapy, Cinnamon

1. Background

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycemia and impaired insulin action or secretion. It is a major global health concern, affecting millions of people worldwide and contributing to substantial morbidity and mortality through cardiovascular, renal, hepatic, retinal, and nervous system complications (1). Among the mechanisms implicated in T2DM pathogenesis, chronic low-grade inflammation has emerged as a key factor driving both insulin resistance and the progression of diabetic complications (2). Prolonged inflammation impairs adipocyte function, disrupts insulin sensitivity, and promotes a pro-inflammatory milieu that worsens metabolic control (3).

Toll-like receptors (TLRs), particularly TLR2 and TLR4, are increasingly recognized for their role in mediating inflammatory responses in T2DM. Elevated expression of

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TLR2 and TLR4 in peripheral blood mononuclear cells and subcutaneous abdominal adipose tissue has been documented in individuals with T2DM compared with healthy controls (4). TLR activation can impair pancreatic β-cell function and accelerate disease progression (5). TLR4, which is expressed in multiple tissues, including the liver, adipose tissue, pancreatic islets, and the vasculature, triggers inflammatory cascades primarily through the TLR4/NF-κB pathway, leading to the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). These signals are amplified through both MyD88-dependent and interferon-β-dependent pathways. Diets rich in saturated fats and refined sugars increase circulating lipopolysaccharide (LPS) levels, further activating TLR4 and promoting oxidative stress, inflammation, and insulin resistance (6).

In T2DM, monocytes exhibit significantly elevated levels of TLR4, MyD88, and downstream cytokines, including TNF-α, macrophage chemoattractant protein-1 (MCP-1), IL-6, and IL-8, linking TLR4-driven inflammation to disease severity (7, 8). Overactivation of NF-κB enhances inflammatory gene expression, exacerbating tissue damage and metabolic dysfunction. Preclinical studies indicate that inhibition of the TLR4/NF-κB axis can attenuate islet inflammation, restore β-cell function, and improve glucose homeostasis (9).

Physical activity is a well-established non-pharmacological intervention for the prevention and management of T2DM. Emerging evidence suggests that regular exercise modulates TLR4 expression and its signaling components, including MyD88 and NF-κB, thereby reducing systemic inflammation and improving insulin sensitivity (10, 11). In women with T2DM, both acute and chronic exercise have been shown to reduce TLR4 expression and pro-inflammatory markers, although effects may vary according to exercise type, intensity, and duration (10, 12, 13).

Natural compounds also hold promise for TLR4-targeted interventions. Cinnamon (Cinnamomum spp.), a spice with centuries of traditional use, exhibits anti-inflammatory, antimicrobial, cardioprotective, and antihyperglycemic properties (14, 15). Its bioactive constituents, particularly cinnamaldehyde, can modulate TLR4 signaling, reduce inflammatory cytokine production, and improve metabolic parameters in diabetic models (16-18).

Women with T2DM face distinct clinical challenges, including sex-specific differences in inflammatory responses and treatment outcomes. Understanding the combined effects of physical activity and cinnamon supplementation on TLR4-mediated inflammation in this population could inform targeted lifestyle and nutritional interventions.

Although previous studies have examined the independent effects of exercise or cinnamon on inflammatory pathways, few have investigated their combined impact on the TLR4/MyD88/NF-κB axis in women with T2DM. The synergistic potential of these interventions to modulate inflammation and improve metabolic control remains poorly understood.

2. Objectives

This study aimed to evaluate the effects of a high-intensity aerobic exercise program combined with resistance training and cinnamon supplementation on TLR4/MyD88/NF-κB signaling and related inflammatory markers in women with T2DM. By addressing this gap, the study sought to provide evidence to support integrative, nonpharmacological strategies to improve metabolic health and reduce inflammation in this high-risk group.

3. Methods

3.1. Study Design and Participants

This double-blind, randomized clinical trial was conducted among 134 women diagnosed with T2DM in Nowshahr, Iran, aged 35 - 50 years (mean age, 41.70 ± 4.15 years). Participants were purposively selected in collaboration with the Nowshahr Diabetes Association. Recruitment was based on voluntary participation and accessibility. Before enrollment, the study objectives, procedures, potential benefits, and risks were thoroughly explained to the participants.

3.2. Inclusion and Exclusion Criteria

The inclusion criteria were a diagnosis of T2DM confirmed by a specialist physician, use of oral antidiabetic medications, an HbA1C level greater than 6.5%, absence of foot ulcers, absence of diabetic eye complications, absence of cardiovascular diseases and peripheral neuropathy, and willingness to participate and provide informed consent.

The exclusion criteria were the use of any dietary supplements, regular exercise before the study, allergy to cinnamon, and perceived risk or inability to participate in the exercise program.

Participants were instructed not to alter their dietary habits during the study period. After initial screening via telephone interviews and questionnaires, 36

participants were randomly assigned to 1 of 4 intervention groups:

3.1. Control (C)

2) High-intensity aerobic exercise plus resistance exercise (RVE)

3) Cinnamon supplementation (Ci)

4) High-intensity aerobic exercise plus resistance exercise plus cinnamon (RVECi)

However, the final number of participants in some groups decreased due to attrition. Although participants were blinded to supplementation, blinding was not possible for the exercise intervention because of the nature of exercise training.

3.3. Exercise Protocol

To estimate VO_2max, participants performed a 1-mile (1609 m) walk while wearing a heart rate monitor. VO_2max was calculated using the following formula (19):

$VO_2\text{max}\ (\text{mL/min/kg}) = 132.853 - (0.1692 \times \text{body mass in kg}) - (0.3877 \times \text{age}) + (6.315 \times \text{sex}) - (3.2649 \times \text{time in min}) - (0.1565 \times \text{HR})$

Sex was coded as man = 1 and woman = 0. HR was defined as the heart rate immediately after the end of the walk.

The exercise program is detailed in Table 1 and was performed 5 times per week by each group. Energy expenditure was tracked using smartwatches to ensure a total daily expenditure of 400 kcal, as recommended by the American College of Sports Medicine (ACSM). Each session began with a 10 - 15-minute warm-up under expert supervision. Aerobic exercise was performed on a treadmill. The RVE group exercised at 80% of VO_2max until 200 kcal was expended. After the aerobic phase, participants performed total-body resistance exercises using resistance bands (TRX) to target the upper body, lower body, and abdominal muscles (Table 1). Resistance exercises continued until an additional 200 kcal was expended (20). Each session ended with a 10-minute cool-down period.

The TRX program included push-ups, standing rows, kneeling triceps extensions, biceps curls, jump squats, lunges, leg curls, ab slides, and reverse lying knee pulls. Participants were advised to consume a light meal 1 - 2 hours before each exercise session and to remain hydrated throughout the day and during exercise.

3.4. Cinnamon Consumption

Cinnamon bark was purchased and processed after approval by a certified herbalist. The bark was washed, dried, ground into powder, and encapsulated in 500 mg capsules. To maintain the double-blind design, placebo capsules were prepared and administered in the same manner as the cinnamon capsules, ensuring that the researchers remained unaware of which capsules were administered. Participants in the supplementation groups consumed 2 capsules daily (1000 mg/day), 1 after breakfast and 1 after lunch (21).

3.5. Data Analysis

Data normality was evaluated using the Shapiro-Wilk test. Paired *t*-tests were used to compare within-group differences between pre-test and post-test values. For between-group comparisons, analysis of covariance (ANCOVA) was conducted, followed by Bonferroni post hoc tests. Statistical significance was set at $P < 0.05$. All analyses were performed using SPSS version 26.

4. Results

Descriptive characteristics of the participants, along with statistical results for key variables, are presented in Table 2.

One-way analysis of variance indicated no significant between-group differences in baseline mean values of TLR4 (P = 0.245), MyD88 (P = 0.563), or NF-κB (P = 0.952).

Within-group comparisons demonstrated significant decreases in mean TLR4, MyD88, and NF-κB levels in the RVE group (P = 0.002, P = 0.0001, and P = 0.005, respectively), the Ci group (P = 0.0001, P = 0.009, and P = 0.003, respectively), and the combined RVECi group (P = 0.003, P = 0.0001, and P = 0.0001, respectively) after 8 weeks of the intervention.

Analysis of covariance indicated significant differences in TLR4 gene expression levels among groups (P = 0.0001, F = 15.093). Bonferroni post hoc tests showed significant reductions in TLR4 in the RVE (P = 0.001), Ci (P = 0.043), and RVECi groups (P = 0.0001) compared with the C group. Furthermore, the RVECi group showed a significantly greater decrease than the Ci group (P = 0.002) (Figure 1).

Similarly, ANCOVA demonstrated significant differences in MyD88 levels among groups (P = 0.0001, F = 19.235). Post hoc analysis indicated significant reductions in MyD88 in the RVE (P = 0.0001) and RVECi groups (P = 0.0001) relative to the C group. The RVECi group also exhibited a significantly greater decrease than the Ci group (P = 0.001) (Figure 2).

Finally, ANCOVA revealed significant differences in NF-κB levels among groups (P = 0.0001, F = 13.168). Post

Table 1. Exercise Program Details

Exercise Type	Exercise Program	Energy Expenditure
Warm-up	Stretching (10 - 15 min)	-
Main exercise		
RVE	Treadmill at 80% VO_2max plus TRX resistance exercise	Aerobic exercise: 200 kcal
	TRX program: push-up, standing row, kneeling triceps extension, biceps curl, jump squat, lunge, leg curl, ab slide, and reverse lying knee pull	Resistance exercise: 200 kcal
Cool-down	Stretching (10 min)	-

Table 2. Descriptive Characteristics of the Participants and Key Variables [a]

Variables and Time Point	C	RVE	Ci	RVECi
Age (y)				
Pre-test	41.57 ± 4.39	40.25 ± 2.96	43.13 ± 4.05	41.86 ± 5.39
Height (m)				
Pre-test	1.57 ± 0.03	1.60 ± 0.06	1.56 ± 0.11	1.59 ± 0.05
Weight (kg)				
Pre-test	65.14 ± 4.59	73.00 ± 8.35	70.50 ± 4.20	66.86 ± 3.13
Post-test	65.86 ± 1.40	66.25 ± 6.96 [b]	67.38 ± 4.50 [b,c]	60.71 ± 3.70 [b]
Intragroup P-value	0.220	0.0001 [d]	0.0001 [d]	0.0001 [d]
Body Mass Index				
Pre-test	26.27 ± 2.27	28.52 ± 3.78	29.17 ± 5.45	26.47 ± 2.00
Post-test	26.56 ± 1.20	25.90 ± 3.31 [b]	27.89 ± 5.50 [b,c]	24.05 ± 2.23 [b]
Intragroup P-value	0.230	0.0001 [d]	0.0001 [d]	0.0001 [d]
Body fat (%)				
Pre-test	37.15 ± 4.12	35.50 ± 5.27	38.17 ± 5.43	36.12 ± 4.38
Post-test	37.25 ± 3.69	32.79 ± 5.69 [b]	35.36 ± 6.17 [b]	31.72 ± 3.60 [b]
Intragroup P-value	0.701	0.0001 [d]	0.001 [d]	0.001 [d]
VO_2max (mL/kg/min)				
Pre-test	23.35 ± 3.44	24.44 ± 2.13	23.09 ± 2.86	22.14 ± 2.99
Post-test	22.19 ± 4.81	27.56 ± 3.66 [b]	23.58 ± 2.82	25.53 ± 3.36 [b]
Intragroup P-value	0.218	0.009 [d]	0.056	0.009 [d]

Abbreviations: C, control; Ci, cinnamon supplementation; RVE, high-intensity aerobic exercise plus resistance exercise; RVECi, high-intensity aerobic exercise plus resistance exercise plus cinnamon.

[a] Values are expressed as mean ± SD.

[b] Difference from C.

[c] Difference from RVECi.

[d] Difference from pre-test.

hoc tests indicated significant decreases in NF-κB in the RVE (P = 0.005), Ci (P = 0.014), and RVECi groups (P = 0.0001) compared with the C group. The RVECi group also showed a significantly greater decrease than the Ci group (P = 0.032) (Figure 3).

5. Discussion

The present study demonstrated that high-intensity aerobic exercise combined with resistance training significantly attenuates the activity of the TLR4/MyD88/NF-κB inflammatory signaling pathway in women with T2DM. These findings are consistent with emerging evidence regarding the molecular mechanisms through which exercise modulates inflammation and glucose metabolism in patients with diabetes.

The TLR4/MyD88/NF-κB pathway plays a central role in mediating chronic low-grade inflammation and

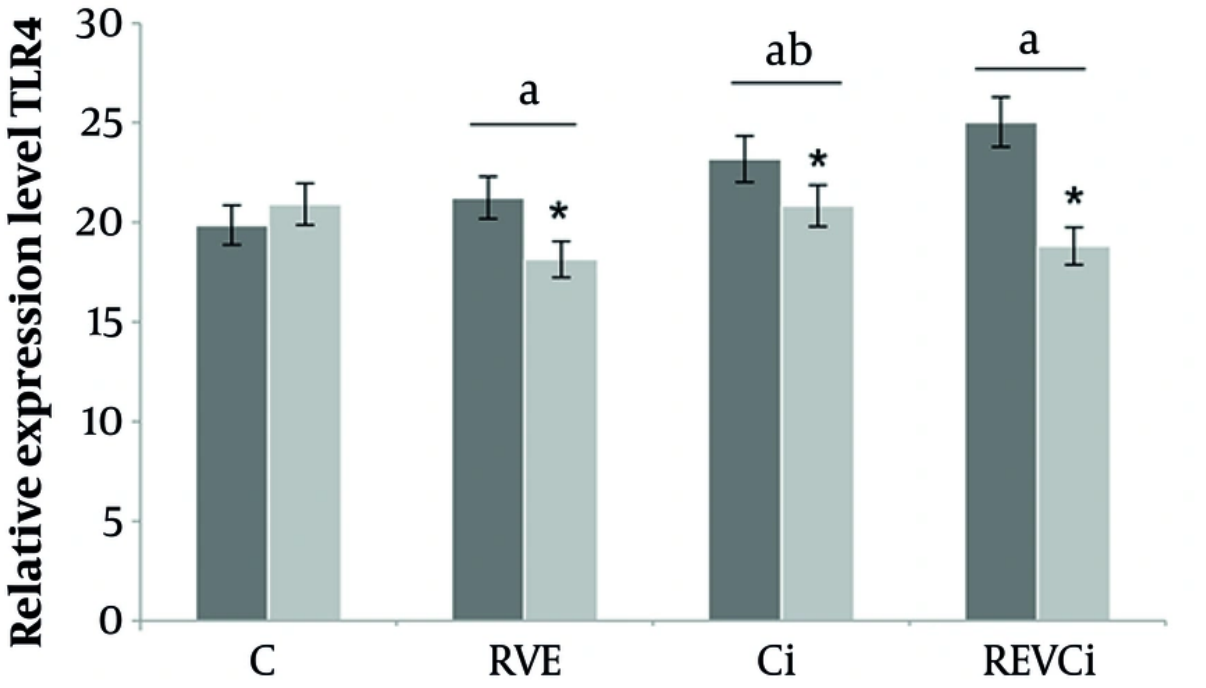

Figure 1. Gene expression levels analyzed in peripheral blood mononuclear cells of TLR4, presented as estimated means with 95% confidence intervals before and after 8 weeks. *Difference from pre-test; a difference from C; b difference from RVECi. Abbreviations: C, control; Ci, cinnamon supplementation; RVE, high-intensity aerobic exercise plus resistance exercise; RVECi, high-intensity aerobic exercise plus resistance exercise plus cinnamon.

insulin resistance in T2DM. Activation of TLR4 by inflammatory stimuli, such as LPS and free fatty acids, initiates MyD88 recruitment, which subsequently activates NF-κB, a transcription factor that upregulates pro-inflammatory gene expression. This cascade contributes to systemic inflammation, β-cell dysfunction, and impaired insulin signaling (22, 23).

Recent studies have consistently shown that combined aerobic and resistance exercise suppresses this pathway. Su et al. (22) reported significant reductions in IL-6, TNF-α, and CRP after such training in women with T2DM, alongside improvements in autonomic cardiac function. Another study demonstrated that combined training reduced both mRNA and protein expression of TLR4 and NF-κB p65 in skeletal muscle, correlating with improved insulin sensitivity and glycemic control (24). More recent research further supports these outcomes: Ma et al. (25) observed that 12 weeks of combined training significantly decreased TLR4 and NF-κB expression in the skeletal muscle of patients with T2DM, with concurrent increases in IL-10 and reductions in HOMA-IR.

Mechanistically, exercise exerts anti-inflammatory effects through multiple pathways. It increases the secretion of cytokines such as IL-10 and adiponectin, which inhibit NF-κB signaling, and enhances GLUT4 translocation to the muscle membrane, facilitating insulin-independent glucose uptake (26). Importantly, Li et al. (27) showed that combined exercise also lowers circulating endotoxin levels, thereby reducing TLR4 activation at its upstream trigger point. Additionally, Lin et al. (28) reported that structured exercise downregulates MyD88-dependent signaling while promoting AMPK activation, further supporting the multifaceted anti-inflammatory potential of exercise.

Systematic reviews and meta-analyses reinforce these findings, showing that long-term combined aerobic-resistance training significantly reduces inflammatory biomarkers and improves metabolic parameters in T2DM (29). Animal studies provide additional support, demonstrating exercise-induced downregulation of

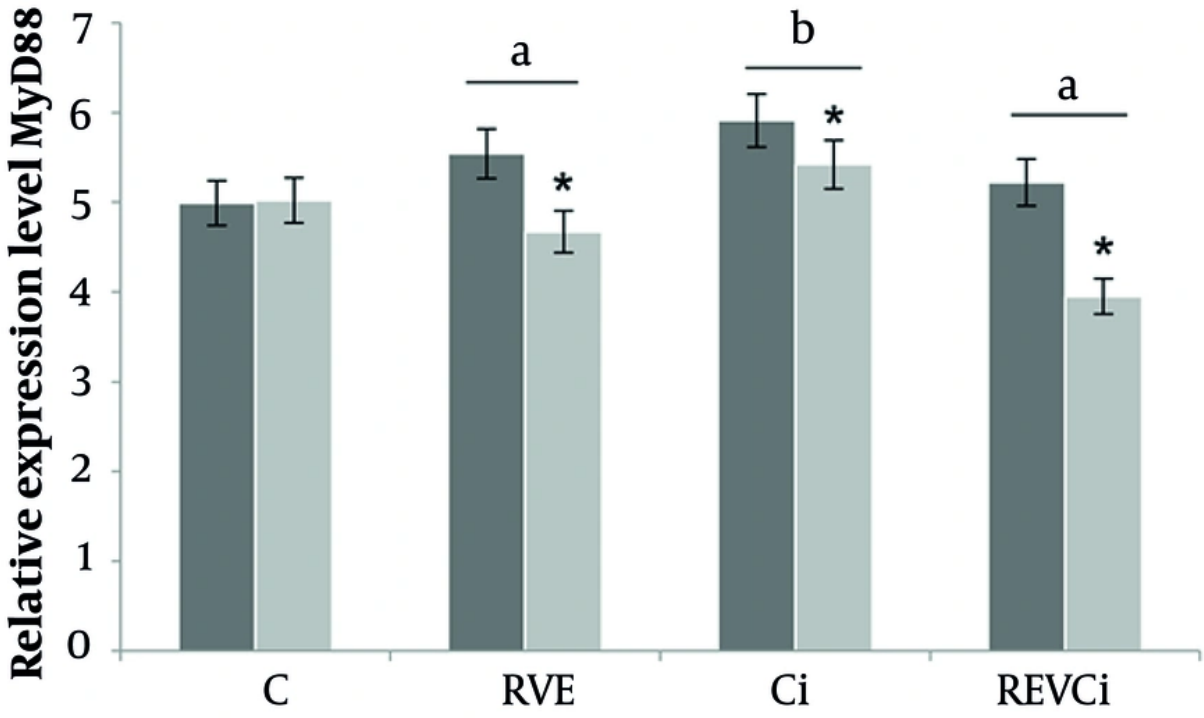

Figure 2. Gene expression levels analyzed in peripheral blood mononuclear cells of MyD88, presented as estimated means with 95% confidence intervals before and after 8 weeks. *Difference from pre-test; a difference from C; b difference from RVECi. Abbreviations: C, control; Ci, cinnamon supplementation; RVE, high-intensity aerobic exercise plus resistance exercise; RVECi, high-intensity aerobic exercise plus resistance exercise plus cinnamon.

TLR4 and NF-κB activity in multiple tissues, resulting in enhanced insulin responsiveness (26).

The current study also found that cinnamon supplementation significantly reduced TLR4 and NF-κB expression, while having no significant effect on MyD88 expression. These results are consistent with evidence that cinnamon and its bioactive polyphenolic compounds can downregulate TLR4 expression and inhibit NF-κB activation by preventing IκBα phosphorylation and degradation, thereby blocking NF-κB nuclear translocation (15, 30). Cinnamon also reduces oxidative stress and free fatty acid-induced TLR4 activation (31, 32). Pang et al. (33) further showed that polyphenol-rich diets, including cinnamon, can synergistically reduce NF-κB activation when combined with resistance training, suggesting potential interaction effects between diet and exercise.

The lack of a significant change in MyD88 expression with cinnamon supplementation may indicate that cinnamon primarily targets downstream elements of the pathway or engages MyD88-independent signaling. The complexity of TLR4 signaling, including MyD88-independent activation routes, warrants further mechanistic studies.

When exercise and cinnamon were combined, the reduction in TLR4/MyD88/NF-κB activity was greater than that observed with cinnamon alone, suggesting that cinnamon may potentiate the anti-inflammatory effects of exercise. However, this combination did not significantly outperform exercise alone, possibly due to overlapping mechanisms, a ceiling effect of the anti-inflammatory action of exercise, or study limitations such as sample size and intervention duration. Similar findings were reported by Gomarasca et al. (34), who found that high-intensity training alone robustly reduced inflammation, leaving limited scope for additive effects from dietary supplementation.

From a clinical perspective, these findings support the integration of structured exercise programs and evidence-based nutritional strategies as complementary interventions for managing chronic inflammation in T2DM. Such approaches may help prevent

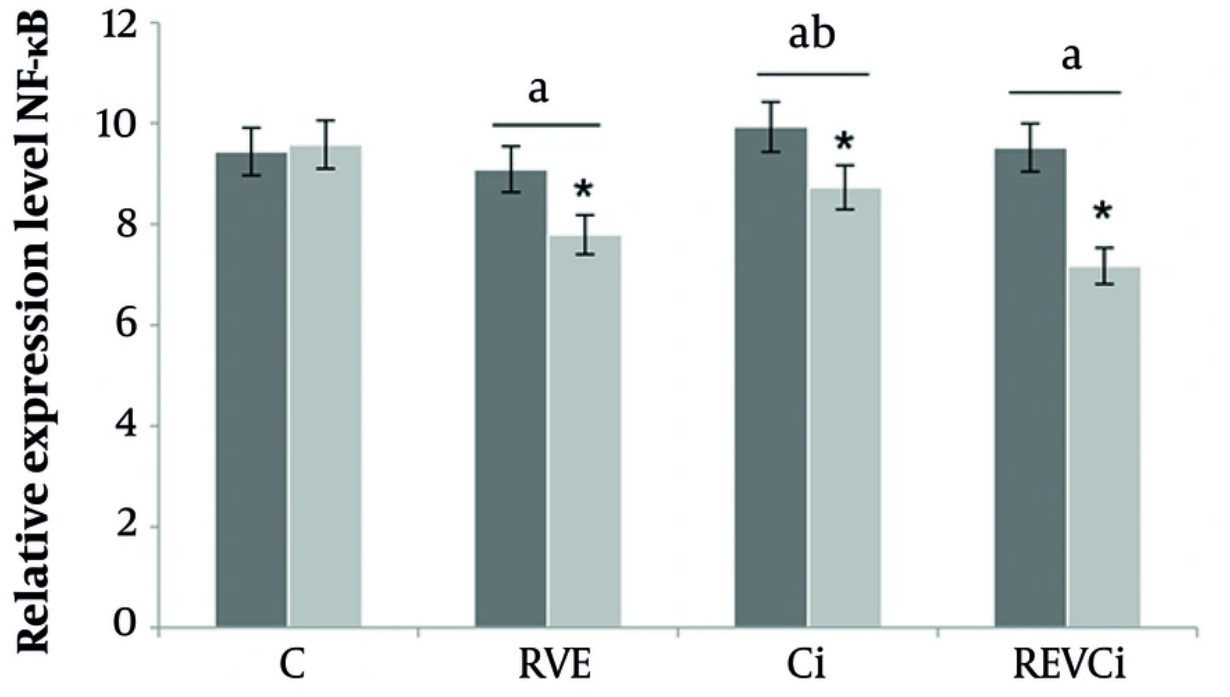

Figure 3. Gene expression levels analyzed in peripheral blood mononuclear cells of NF-κB, presented as estimated means with 95% confidence intervals before and after 8 weeks. *Difference from pre-test; a difference from C; b difference from RVECi. Abbreviations: C, control; Ci, cinnamon supplementation; RVE, high-intensity aerobic exercise plus resistance exercise; RVECi, high-intensity aerobic exercise plus resistance exercise plus cinnamon.

complications, improve metabolic control, and reduce the need for pharmacological interventions.

Limitations of this study include the relatively small sample size, short intervention duration, participant attrition, and lack of blinding for exercise protocols. Additionally, dietary intake outside supplementation was not strictly controlled, which may have influenced inflammatory outcomes. Other limitations include the absence of long-term follow-up to assess the sustainability of the effects, potential variability in exercise adherence and intensity, and the lack of assessment of other relevant inflammatory pathways, such as MAPK or JNK signaling.

Future research should explore longer interventions with larger and more diverse populations, incorporate rigorous dietary monitoring, and investigate combined lifestyle strategies in real-world community settings. Molecular studies should assess broader inflammatory and metabolic signaling networks to better understand synergistic or additive effects between exercise and bioactive dietary compounds such as cinnamon.

This study demonstrated that high-intensity aerobic-resistance training, either alone or in combination with cinnamon supplementation, significantly reduces the activity of the TLR4/MyD88/NF-κB inflammatory pathway in women with T2DM. Cinnamon supplementation enhanced some anti-inflammatory outcomes, although the combined intervention did not significantly surpass the effects of exercise alone.

These findings suggest that structured exercise remains a cornerstone of inflammation management in T2DM, while cinnamon may serve as a safe and potentially synergistic adjunct. The study contributes to the growing evidence base supporting integrated, non-pharmacological strategies for improving metabolic health and reducing inflammation in chronic disease.

Further large-scale, long-term studies are needed to confirm these findings, explore optimal dosing and timing of cinnamon supplementation, and evaluate their combined impact on broader cardiometabolic outcomes. By clarifying these mechanisms, future research could refine personalized lifestyle prescriptions for patients with T2DM, ultimately

advancing the translation of molecular insights into practical, clinically effective interventions.

Footnotes

AI Use Disclosure: The authors declare that no generative AI tools were used in the creation of this article.

Authors' Contribution: Study concept and design: M. A. and A. A. conceived the study. A. A. and A. B. refined the research question and experimental approach. A. A. developed the study protocol, including the high-intensity aerobic-resistance intervention, cinnamon supplementation regimen, primary and secondary outcomes, TLR4/MyD88/NF-κB pathway markers, eligibility criteria, and study timeline. M. A. contributed to protocol drafting and participant assessment procedures. All authors reviewed and approved the final study design.

Clinical Trial Registration Code: This study was registered in the Clinical Trial Center under the number IRCT20250513065713N1.

Conflict of Interests Statement: The authors do not declare any conflicts of interests for this study.

Data Availability: The data presented in this study are uploaded during submission as a supplementary file and are openly available for readers upon request.

Ethical Approval: This study was approved by the Research Ethics Committee of the Islamic Azad University, Ayatollah Amoli Branch, with the code IR.IAU.AMOL.REC.1404.055.

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Informed Consent: Informed consent was obtained from all participants.

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