

The effect of eight weeks of resveratrol supplementation on serum levels of Resistin, Interleukin 1 beta, Sestrin 2 and TNF- α in inactive obese women

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Abstract

Introduction: Obesity is recognized as one of the most serious public health threats worldwide and is associated with inflammation in adipose tissue and changes in the secretion of adipokines and oxidative stress. Resveratrol, with its anti-inflammatory effects, can be effective in improving obesity-related problems. The aim of the present study was to investigate the effect of eight weeks of resveratrol supplementation on serum levels of resistin, interleukin 1 beta, sestrin 2 and TNF- α in inactive obese women.

Methods: In this study, 20 obese women with a mean $\pm$ SD of weight of 87.8 ± 4.25 kg, body mass index of 34.2 ± 57 kg/m², age of 29.85 ± 3.04 years, height of 1.61 ± 0.035 m, and fat percentage of 39.9 ± 2.78 were selected through voluntary sampling and randomly divided into two supplement and control groups. Subjects in the supplement group took one 250 mg Quetrol Resveratrol capsule daily for eight weeks as a supplement. Before and after 8 weeks, a 5 cc blood sample was taken from the left brachial vein. Data were analyzed using analysis of covariance and paired t-test.

Results: To eliminate the pre-test effect in the post-test comparison of the two groups, the analysis of covariance statistical test was used. The results showed that there was a significant difference ($p=0.001$) between the groups for all variables in the post-test. Also, the results of the paired t-test showed that in the supplementation group, the post-test values of resistin ($p=0.006$), interleukin 1 beta ($p=0.004$) and TNF- α ($p=0.002$) decreased compared to the pre-test, and the values of sestrin 2 ($p=0.01$) increased compared to the pre-test.

Conclusions: Based on the findings of this study, it can be concluded that eight weeks of resveratrol supplementation improves the serum levels of resistin, interleukin 1 beta, sestrin 2 and TNF- α in inactive obese women.

Key Words: Obesity, Interleukin 1 beta, Sestrin2, Resveratrol

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1. Introduction

Obesity is a chronic, non-communicable disease characterized by excessive accumulation of body fat, which can pose a threat to health. Its development is influenced by various behavioral, environmental, and biological factors. This condition affects approximately 650 million people worldwide (1, 2). In addition to affecting various metabolic tissues in the body, obesity contributes to the expansion of adipose tissue. White adipose tissue consists of dendritic cells, macrophages, neutrophils, and T and B lymphocytes. Elevated levels of pro-inflammatory cytokines, such as tumor necrosis factor- α (TNF- α) and interleukin-1 beta (IL-1 β), have been observed in the adipose tissue of individuals with obesity. Resistin is another adipokine secreted by white adipose tissue (3, 4). It is a protein composed of 108 amino acids, with a molecular weight of approximately 12.5 kDa, and is encoded by the RETN gene (5). Resistin acts directly on adipocytes and may also inhibit insulin-mediated glucose uptake (5). Evidence suggests that Resistin secretion increases with obesity. In humans, Resistin is expressed predominantly in bone marrow and macrophages (5). Regarding its pro-inflammatory effects, Resistin may bind to Toll-like receptor 4 (TLR4) and subsequently activate nuclear factor kappa B (NF- κ B) in macrophages through signaling pathways involving p38 mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinase (JNK) (5). TNF- α , a pro-inflammatory cytokine belonging to the TNF family, was initially recognized for its ability to induce apoptosis and cell death (6, 7). Subsequent research has demonstrated that TNF- α influences a broad range of cellular functions and plays an important role in maintaining cell survival (7). TNF- α signaling is mediated through two receptors, TNFR1 and TNFR2 (7).

By disrupting insulin receptor signaling, this pro-inflammatory cytokine can reduce insulin sensitivity (8). IL-1 β is a cytokine belonging to the interleukin-1 (IL-1) family. It is a multifunctional pro-inflammatory cytokine that exerts pleiotropic effects on various cell types (9). Findings from several studies indicate that plasma IL-1 β levels are elevated in individuals with obesity (10). Sestrin-2 is one of the three members of the sestrin protein family. It is associated with several environmental stressors, including oxidative stress, which is itself considered an important

contributor to obesity-related metabolic disorders (11, 12). As a metabolic regulator and protective antioxidant, sestrin-2 is induced not only by oxidative stress but also by various forms of cellular damage, including inflammation, hypoxia, DNA damage, and endoplasmic reticulum stress (13). Sestrin-2 appears to suppress mTORC1 activity through the activation of AMP-activated protein kinase (AMPK). Through this mechanism, it plays an important role in regulating lipid and glucose metabolism and may consequently contribute to the control of obesity (14). Resveratrol is a naturally occurring polyphenolic compound with anti-inflammatory properties, partly mediated through the inhibition of NF- κ B, as well as antioxidant effects (15, 16). Resveratrol exists in two geometric isomeric forms, and the trans form exhibits more pronounced antiproliferative effects than the cis form (16). Certain plants, including members of the Vitaceae family, produce resveratrol biosynthetically as part of a non-specific response to infection and physical injury. Natural sources of resveratrol include red wine, berries, peanuts, and grape skin (16).

A study conducted by Tahmina Yasmin and colleagues (2025) found that eight weeks of resveratrol supplementation significantly improved obesity-related outcomes and reduced body weight. The intervention also restored antioxidant enzyme activity and reduced markers of oxidative stress in plasma and the liver (17). Another study investigated the effects of Pilates training combined with resveratrol supplementation on serum sestrin-2, lipocalin-2, and oxidative stress in obese middle-aged women. In this clinical trial, 40 obese adult women from Tehran were randomly assigned to four groups: control, Pilates training, resveratrol supplementation, and combined Pilates training and resveratrol supplementation. The exercise groups followed a moderate-intensity training program three times per week for eight weeks. Participants in the supplementation groups received 500-mg resveratrol capsules in the morning. The findings showed that resveratrol supplementation increased serum sestrin-2 levels and decreased serum lipocalin-2 levels in obese middle-aged women (18). Resveratrol has attracted considerable attention because of its availability, relatively low cost, widespread distribution, and effects on multiple signaling pathways. Nevertheless, factors such as poor

intestinal absorption, metabolism, and substantial excretion limit its systemic bioavailability and may affect the extent of its beneficial effects on health (19). Therefore, the aim of the present study was to investigate the effects of eight weeks of resveratrol supplementation on serum levels of resistin, IL-1 β , sestrin-2, and TNF- α in inactive obese women.

2. Methods

The present study was a semi-experimental, applied research study, using a pre-test, post-test design with a control group. The study was approved by the Ethics Committee of the University of Mohaghegh Ardabili (ethics code: IR.UMA.REC.1403.056). The study population consisted of obese women living in Ardabil. Twenty volunteers aged 25–35 years, with a body mass index (BMI) greater than 30 kg/m², were recruited and randomly assigned to two groups: a supplementation group (10 participants) and a control group (10 participants). Before participating in the study, the volunteers completed informed-consent forms and medical history questionnaires to assess their health status and eligibility to receive the supplement. Initially, physical and anthropometric measurements were obtained using standardized equipment and procedures (Figure 1). body weight was measured in kilograms using a Seca 803 digital scale manufactured in Germany, with an accuracy of 100 g. Participants wore light clothing and no shoes. Each participant was weighed three times, and the mean value was recorded as body weight. Height was measured in centimeters, without shoes or socks, using a stadiometer with an accuracy of 0.1 cm. Three measurements were taken, and the mean was recorded as the participant's height. Body fat percentage was assessed using an Omron BF-306 digital body-fat analyzer manufactured in Japan. BMI was calculated by dividing body weight by the square of height. Waist-to-hip ratio (WHR) was also determined. Measurements were taken while participants wore light clothing, using a non-elastic measuring tape with an accuracy of 0.1 cm. Waist circumference was measured at the narrowest point below the ribs and above the iliac crest, while hip circumference was measured around the widest part of the buttocks. Care was taken to ensure that the tape did not compress the body. WHR was calculated by dividing waist circumference by hip circumference. An electronic heart-rate monitor (Polar, model FT31, manufactured in Finland) was used to monitor exercise intensity. For eight weeks, participants in the supplementation group consumed one 250-mg capsule of Quetrol resveratrol, manufactured by Raha Pharmaceutical

Company, each morning on an empty stomach. Participants' dietary intake was monitored by a nutrition specialist using food-record forms, beginning one week before the supplementation program and continuing until the end of the study. Information regarding dietary intake, energy consumption, and macronutrient intake was collected using 24-hour dietary recall questionnaires. Participants were also provided with dietary guidance and instructed not to make any changes to their usual diet without informing the researcher (20).



Figure 1. Equipment and Supplement Used in the Study

2.1. Biochemical assessment

Following an overnight fast at the pre-test stage and 48 hours after the final training session at the post-test stage, approximately 5 mL of venous blood was collected from the antecubital vein of the participants while they were in a seated position. Blood sampling was performed at 8:00 a.m. to minimize the effects of circadian variations on the measured variables. The blood samples were centrifuged at 3,000 rpm for 15 minutes to separate the plasma, and the resulting serum samples were then frozen and stored at -80°C . Serum resistin levels were measured using the enzyme-linked immunosorbent assay (ELISA) method and a human resistin ELISA kit manufactured by Cusabio Biotech (China), with a sensitivity of 0.08 ng/mL and an intra-assay coefficient of variation (CV) of 6.5%. Interleukin-1 beta (IL-1 β) was measured by ELISA using a human IL-1 β ELISA kit manufactured by ELISA (Austria), with a measurement range of 0.1–0.8 pg/mL and a sensitivity of 0.36 pg/mL. Sestrin-2 was measured by ELISA using a human Sestrin-2 ELISA kit manufactured by Fine Biotech (China), with a

sensitivity of 0.094 ng/mL and a measurement range of 0.156–10 ng/mL. Serum tumor necrosis factor- α (TNF- α) was measured by ELISA using a human TNF- α ELISA kit manufactured by IBL International GmbH, with a sensitivity of 6.4 pg/mL.

2.3. Statistical analysis

To examine the differences in post-test mean values between the groups, and to control for the effect of the pre-test measurements analysis of covariance ANCOVA was used. To examine within-group changes, the paired-samples t-test was used. All

statistical analyses were performed using SPSS statistical software, version 24, at a significance level of $P < 0.05$.

3. Results

The study sample consisted of inactive obese women aged 25–35 years, with a body mass index (BMI) greater than 30 kg/m². The characteristics of the participants are presented in Table 1.

Table 1. Mean and Standard Deviation of Anthropometric and Demographic Variables in the Study Groups

Variable	No.	Group	Mean $\pm$ Standard Deviation (SD)	Significance Level
			Pre-test	
Age (years)	10	Supplement	30.40 $\pm$ 2.98	0.77
	10	Control	29.30 $\pm$ 3.09	
Height (cm)	10	Supplement	1.60 $\pm$ 0.04	0.44
	10	Control	1.61 $\pm$ 0.03	
Weight (kg)	10	Supplement	86.60 $\pm$ 4.50	0.6
	10	Control	89 $\pm$ 4	
BMI (Kg/m ²)	10	Supplement	33.85 $\pm$ 3.12	0.20
	10	Control	34.15 $\pm$ 2.02	
Body Fat Percentage	10	Supplement	40.20 $\pm$ 2.44	0.44
	10	Control	39.60 $\pm$ 3.13	
Waist-to-Hip Ratio (WHR)	10	Supplement	0.88 $\pm$ 0.015	0.62
	10	Control	0.89 $\pm$ 0.019	

Table 2 presents the results of the analysis of covariance (ANCOVA) used to compare serum levels of resistin, interleukin-1 beta (IL-1 β), Sestrin-2, and tumor necrosis

factor- α (TNF- α) between the two groups at the post-test. The significance level was 0.001, indicating a statistically significant difference between the groups.

Table 2. Results of the Between-Group Analysis of Covariance (ANCOVA) for Post-Test Comparisons Between the Study Groups

Variable	Degrees of Freedom (df)	Mean Square (MS)	F	Significance Level
Resistin (ng/mL)	3	3.79	12.74	0.001
Interleukin-1 beta (pg/mL)	3	2.30	10.21	0.001
Sestrin-2 (ng/mL)	3	0.02	10.40	0.001
TNF- α (pg/ml)	3	5.04	27.58	0.001

The results of the paired t-test reported in Table 3 indicated that in the supplement group, post-test values of resistin ($p=0.006$), interleukin-1 beta

($p=0.004$), and TNF- α ($p=0.002$) showed a significant decrease compared to the pre-test, while Sestrin 2 values ($p=0.01$) showed a significant increase

compared to the pre-test. Therefore, based on the results, it can be stated that eight weeks of resveratrol supplementation had a significant effect on serum

levels of resistin, interleukin-1 beta, Sestrin 2, and TNF- α in inactive obese women. Furthermore, these changes are illustrated in Figures 1 to 4.

Table 3. Results of the Paired-Samples t-Test for Assessing With in- Group Effects

Variable	Group	No.	T-value	Significance Level
Resistin (ng/mL)	Supplement	10	3.58	*0.006
	Control	10	-1.50	0.16
Interleukin-1 beta (pg/mL)	Supplement	10	3.87	*0.004
	Control	10	0.56	0.58
Sestrin-2 (ng/mL)	Supplement	10	-3.25	* 0.01
	Control	10	1.000	0.34
TNF- α (pg/ml)	Supplement	10	4.31	*0.002
	Control	10	-1.40	0.19

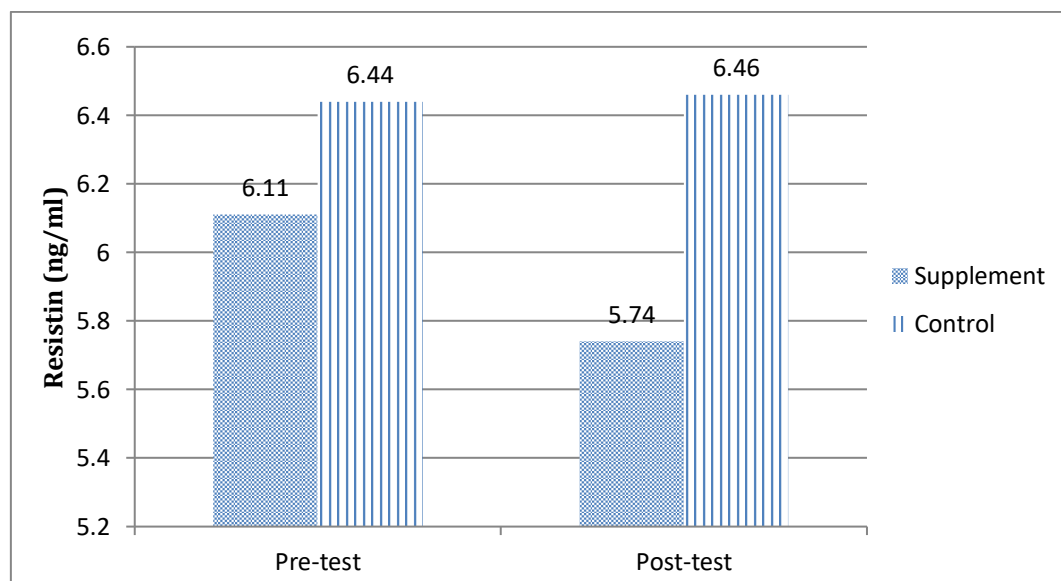


Figure 2. Changes in Resistin Levels from Pre-Test to Post-Test in the Supplement and Control Groups

* indicates a statistically significant difference from the pre-test in the supplement group, and # indicates a statistically significant difference from the post-test in the control group.

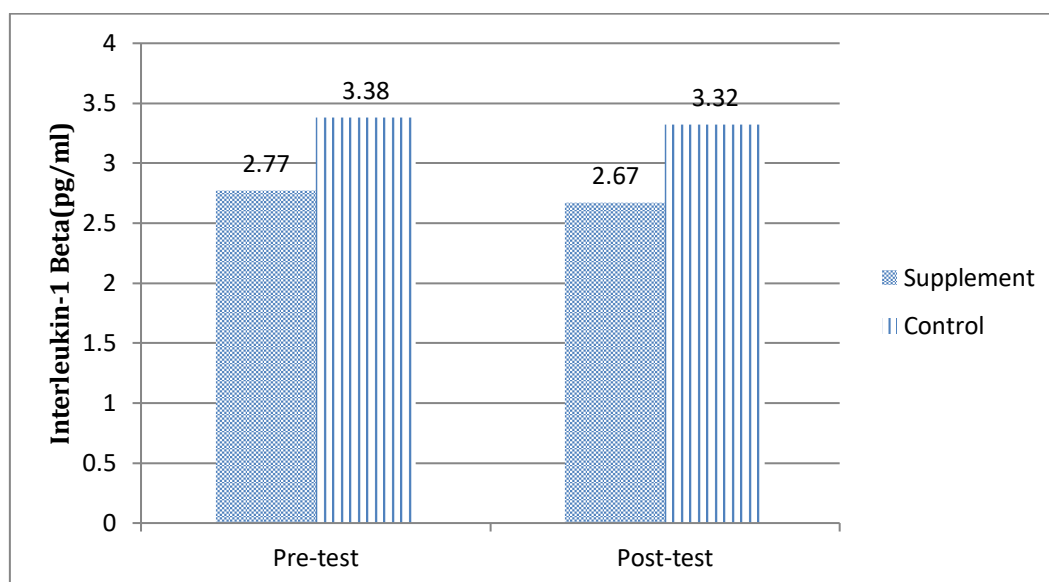


Figure 3. Changes in Interleukin-1 Beta Levels from Pre-Test to Post-Test in the Supplement and Control Groups
 * indicates a statistically significant difference from the pre-test in the supplement group, and # indicates a statistically significant difference from the post-test in the control group.

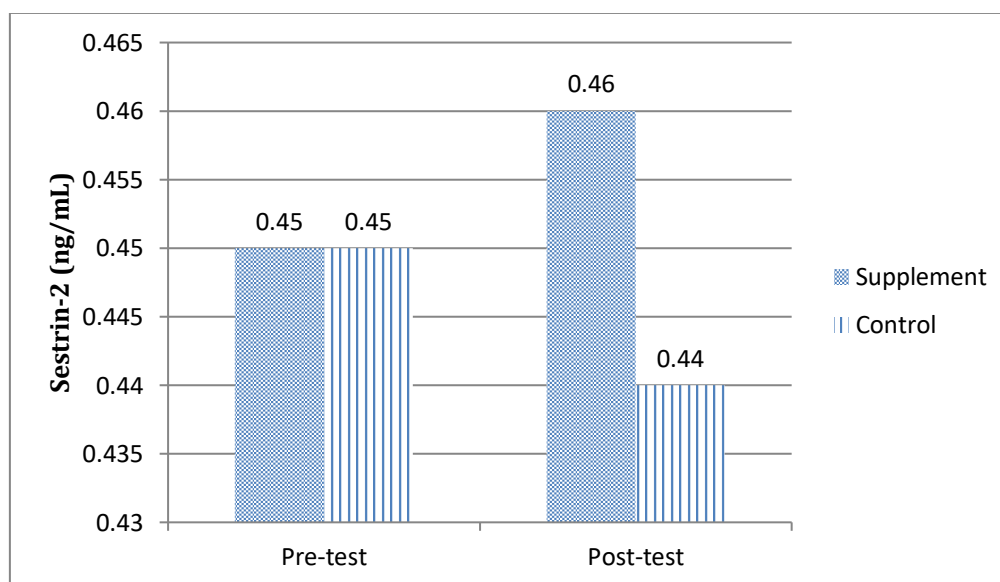


Figure 4. Changes in Sestrin-2 Levels from Pre-Test to Post-Test in the Supplement and Control Groups
 * indicates a statistically significant difference from the pre-test in the supplement group, and # indicates a statistically significant difference from the post-test in the control group.

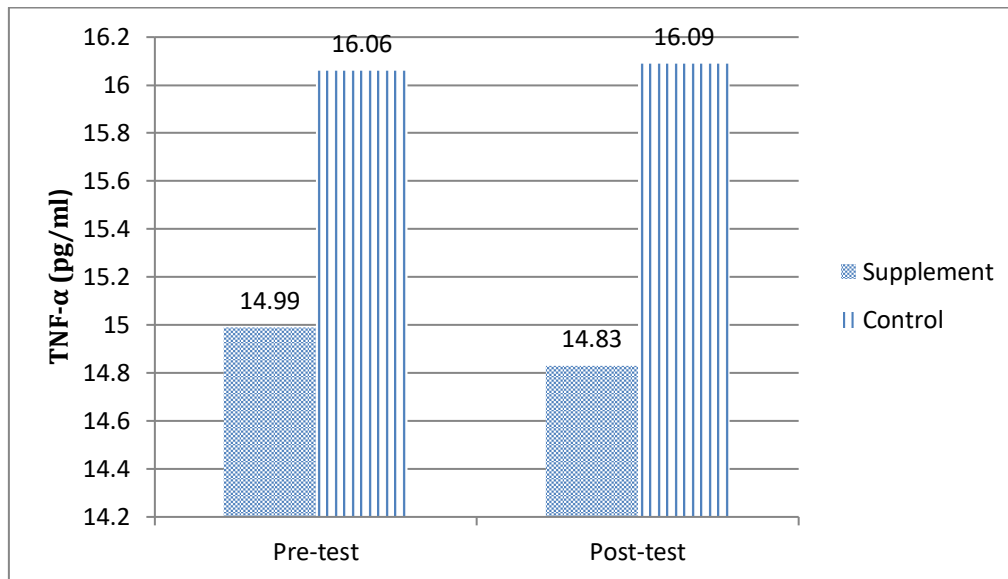


Figure 5. Changes in TNF- Levels from Pre-Test to Post-Test in the Supplement and Control Groups

* indicates a statistically significant difference from the pre-test in the supplement group, and # indicates a statistically significant difference from the post-test in the control group.

4. Discussion

The findings of the present study demonstrated that resveratrol supplementation significantly increased serum sestrin-2 levels while significantly decreasing serum resistin, IL-1 β , and TNF- α levels in the supplementation group. The observed increase in serum sestrin-2 following resveratrol supplementation is consistent with the findings of Alipour Ghazichaki and colleagues (2023) (21). Their results indicated that resveratrol supplementation, through its effects on sestrin-2, oxidative stress, and insulin resistance homeostasis, may help counteract obesity-related metabolic disturbances. Similarly, Seo and colleagues (2014) reported that resveratrol supplementation increased sestrin-2 levels. Their study suggested that resveratrol may inhibit oxidative stress and mitochondrial dysfunction through sestrin-2, making this protein one of the potential targets of resveratrol's biological effects (22). Jin and colleagues (2013) also found that resveratrol induced sestrin-2 expression and suppressed hepatic lipogenesis (23).

According to various studies, resveratrol may help inhibit oxidative stress by activating SIRT1, suppressing inflammatory mediators, inhibiting NADPH-related pathways, modulating eicosanoid

(synthesis, and activating antioxidant enzymes (21). The reduction in serum resistin levels observed following resveratrol supplementation in the present study is consistent with the findings of Riyahi Malayeri and colleagues (2018) (24). Their study showed that eight weeks of resveratrol supplementation significantly reduced serum resistin levels. It also

resulted in reductions in mean fasting glucose, insulin, and insulin resistance in the supplementation group (24). Zarei and colleagues (2016) likewise reported that resveratrol supplementation significantly decreased resistin levels and blood glucose concentrations (25). Mercader and colleagues (2011) reported that resveratrol reduced resistin gene expression in cultured 3T3-L1 cells by affecting oxidative and lipogenic pathways (26). Blander and colleagues (2004) also suggested that resveratrol may inhibit certain genes associated with adiposity, including resistin (27). However, the findings of Picard and colleagues (2004) were inconsistent with those of the present study. They reported that resveratrol could increase resistin gene expression in cultured cells derived from adipose tissue (28). These discrepancies may be attributable to differences in experimental models, resveratrol dosage and duration of supplementation, as well as variations in the pathways activated in cellular and whole-body environments. The reduction in serum IL-1 β and TNF- α levels following resveratrol supplementation in the present study is consistent with the findings of Bastin and colleagues (2025) and Elmorsy Ekramy and colleagues (2025) (29, 30). Bastin and colleagues (2025) investigated the effects of resveratrol supplementation on biochemical markers, blood parameters, and selected pro-inflammatory cytokines including IL-1 β and TNF- α , in patients with COVID-19. Their findings revealed statistically significant reductions in the levels of both pro-inflammatory cytokines. These results suggest that resveratrol, as a

plant-derived supplement, may be beneficial in reducing blood glucose levels and inflammatory markers, neutrophil counts, and platelet counts in patients with COVID-19 (29). IL-1 β and TNF- α , in patients with COVID-19. Their findings revealed statistically significant reductions in the levels of both pro-inflammatory cytokines. These results suggest that resveratrol, as a plant-derived supplement, may be beneficial in reducing blood glucose levels and inflammatory markers, neutrophil counts, and platelet counts in patients with COVID-19 (29). Elmorsy Ekramy and colleagues (2025) investigated the anti-inflammatory effects of resveratrol against palmitate-induced lipotoxicity in RAW 264.7 macrophages. Their findings indicated that resveratrol substantially improved the viability of macrophages exposed to palmitate, significantly reduced the release of pro-inflammatory cytokines such as TNF- α and IL-1 β , and downregulated the expression of genes associated with these inflammatory mediators. Resveratrol also improved the phagocytic capacity of the cells. Thus, resveratrol, as a bioactive phytochemical with potential therapeutic benefits, may reduce the effects of palmitic acid on macrophage viability and oxidative damage, while also counteracting the effects of oxidative-stress-related genes, including p65, NF- κ B, and Nrf2 (30). Riyahi Malayeri and colleagues (2007) and Wu and colleagues (2017) also reported that resveratrol supplementation led to significant reductions in TNF- α levels (31, 32). In a study conducted by Shakibaei and colleagues (2008), resveratrol was found to reduce the harmful effects of IL-1 β by suppressing inflammatory and matrix-degrading gene expression and inhibiting the NF- κ B pathway (33). Likewise, Liu and colleagues (2014) demonstrated that resveratrol could prevent IL-1 β -induced inflammation by inhibiting TLR4 (34).

5. Conclusion

The findings of the present study indicate that eight weeks of resveratrol supplementation may improve serum levels of resistin, IL-1 β , sestrin-2, and TNF- α in inactive obese women. Given the apparent role of resveratrol supplementation in improving the body's inflammatory status, it is suggested that individuals with obesity or excess body weight, those with metabolic disorders, and those with cardiovascular diseases consider incorporating resveratrol supplementation into their rehabilitation programs only under medical supervision and with the approval of a qualified physician. The limitations of this study included the lack of assessment of other inflammatory and anti-inflammatory factors, the absence of control over participants' psychological and mental states, and the lack of control over the secretion levels of the participants' hormones.

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Conflicts of Interest

The authors declare that there is no conflict of interest.

Authors' Contributions

All authors participated in the design, implementation, and writing of all parts of this study.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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