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RESEARCH ARTICLE

The Effect of Resveratrol Supplementation on Cardio-Metabolic Risk Factors in Patients with Type 2 Diabetes: A Randomized, Double-Blind Controlled Trial

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The aim of the present randomized controlled trial was to evaluate the effect of a micronized resveratrol supplement on glycemic status, lipid profile, and body composition in patients with type 2 diabetes mellitus (T2DM). A total of 71 overweight patients with T2DM (body mass index ranged 25–30) were randomly assigned to receive 1000 mg/day trans-resveratrol or placebo (methyl cellulose) for 8 weeks. Anthropometric indices and biochemical indices including lipid and glycemic profile were measured before and after the intervention. In adjusted model (age, sex, and baseline body mass index), resveratrol decreased fasting blood sugar (−7.97±13.6 mg/dL, p=0.05) and increased high density lipoprotein (3.62±8.75 mg/dL, p=0.01) levels compared with placebo. Moreover, the mean difference in insulin levels reached significance (−0.97±1.91, μIU/mL, p= 0.02). However, no significant differences were observed for anthropometric measures. It was found that 8-week resveratrol supplementation produced useful effects on some cardio-metabolic parameters in patients with T2DM. More studies are needed to confirm these findings.

KEYWORDS

resveratrol, type 2 diabetes mellitus, blood glucose, body composition

Abbreviation: AIP, atherogenic index of plasma; AMPK, AMP-activated protein kinase; BMI, body mass index; BMR, basal metabolic rate; CVD, cardiovascular disease; ELISA, enzyme-linked immunoassay; FM, fat mass; FBS, fasting blood sugar; GLUT4, glucose transporter 4; HbA1c, glycated hemoglobin; HC, hip circumference; HDL, high-density lipoprotein; HOMA-β, homeostasis model assessment of beta-cell function; HOMA-IR, homeostatic model assessment of insulin resistance; HPLC, high-pressure liquid chromatography; LDL, low-density lipoprotein; PPAR, peroxisome proliferator activated receptor; QUICKI, quantitative insulin sensitivity checks index; SIRT1, silent information regulator 1; T2DM, type 2 diabetes mellitus; WC, waist circumference; WSR, waist-to-stature ratio

1 | INTRODUCTION

Type 2 diabetes mellitus (T2DM), the most common endocrine disorder, is one of the growing worldwide public health challenges (Zheng, Ley, & Hu, 2018). Diabetes is accompanied by a wide range of complications, for instance, cardiovascular disease, retinopathy, nephropathy, and neuropathy (Girach & Vignati, 2006; Tripathi & Srivastava, 2006). Previous studies reported that most patients with diabetes are overweight or obese (Al-Sharafi & Gunaid, 2014; Mugharbel & Al-Mansouri, 2003; Thomas, Zimmet, & Shaw, 2006). Obesity is a key component in the pathophysiology of diabetes and development of complications and exerts its effect through insulin resistance, excessive oxidative stress, and impaired metabolic regulation (Al-Goblan, Al-Alfi, & Khan, 2014; Van Gaal & De Block, 2012; Van Gaal, Mertens, & Christophe, 2006). Furthermore, obesity is identified as a factor associated with poor glycemic control in patients with T2DM (Fonseca, 2004). There are some bodies of evidence suggesting that weight loss in diabetic patients is associated with an improvement in cardio-metabolic risk factors and reduction in the use of medication and mortality (Anderson, Kendall, & Jenkins, 2003; Williamson et al., 2000). Cardio-metabolic risk factors are factors which increase the possibilities of cardiovascular and metabolic diseases like atherosclerosis and diabetes, including insulin resistance, dyslipidemia, obesity, and a cluster of related metabolic risk factors (Ruilope, De La Sierra, Segura, & Garcia-Donaire, 2007). As a result, weight management, as well as glycemic control, is an important therapeutic goal in patients with T2DM (Schwartz & Kohl, 2010).

In this context, polyphenols, a family of phytochemicals, are one of the most popular active biomolecules which may be helpful in body weight management and glycemic condition (Fernández-Quintela et al., 2016; Kim, Keogh, & Clifton, 2016). Resveratrol, which is structurally known as a stilbenoid, is a type of natural polyphenol found mostly in red grapes, peanuts, and berries (Burns, Yokota, Ashihara, Lean, & Crozier, 2002).

It seems that resveratrol induces its metabolic effects through several pathways. Studies showed that SIRT1 (silent information regulator 1) and AMPK (AMP-activated protein kinase) activation by resveratrol is accompanied by an improvement in insulin resistance (Bagul & Banerjee, 2015; Movahed, 2016). Furthermore, resveratrol increases glucose uptake through upregulation of the glucose transporter 4 (GLUT4) gene expression in skeletal muscle and liver (Bagul & Banerjee, 2015; Movahed, 2016; Yonamine et al., 2017). Also, resveratrol has been introduced as a ligand of peroxisome proliferator-activated receptor alpha and gamma (PPARα and PPARγ), and it seems to produce fibrate-like effects on serum lipids (Inoue et al., 2003; Takizawa et al., 2015). In addition, it is suggested that resveratrol improves mitochondrial and consequently metabolic functions (Lagouge et al., 2006).

Antidiabetic effects of resveratrol have been investigated in recent years. A recent meta-analysis including nine trials has shown a significant reduction in serum levels of fasting glucose, insulin, and insulin resistance following resveratrol supplementation in diabetic patients (Zhu, Wu, Qiu, Yuan, & Li, 2017). Although, some studies reached nonsignificant results (Bashmakov et al., 2014; Goh et al., 2014; Timmers et al., 2016). A randomized controlled trial showed no significant effect of 30-day resveratrol treatment on hepatic and peripheral insulin sensitivity (Timmers et al., 2016), while two other studies reported significant beneficial effect on insulin resistance following resveratrol supplementation (Movahed et al., 2013; Zare Javid et al., 2017). Contradictory results prompted us to perform a randomized controlled trial to investigate if resveratrol supplementation affects glycemic control, lipid profile, and body composition in overweight patients with T2DM.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

The present double-blind randomized controlled trial was performed on patients who were diagnosed with T2DM by a specialist in Yazd, Iran. Patients were recruited according to the inclusion and exclusion criteria and were allocated to the resveratrol and placebo groups using stratified randomization based on sex and age (30–45 and 45–60 years) by computer-generated random numbers. Inclusion criteria included patients with type 2 diabetes aged 30–60 years old, with a body mass index ranging 25–30 kg/m^2 and glycated hemoglobin (HbA1c) lower than 8%. Patients were excluded if the following criteria were met: existence of any other complications (cancer, renal or liver failure, gastrointestinal ulcers, Alzheimer's disease, psychological disorders, and cardiovascular diseases). Insulin therapy, pregnant or lactating women, and patients who consumed antioxidant supplements, fibrate lipid-lowering agents, platelet aggregation inhibitor, and antiinflammatory drugs or who drank red wine (for at least 6 months before the enrollment) were also excluded. Patients were asked about medications they took by an endocrinologist collaborator. If any of the exclusion criteria was accrued during the study period, the intervention was terminated in order to keep the participants safe.

Participants in the intervention or placebo groups received either 500 mg/d (twice a day) of resveratrol or placebo capsules (methylcellulose), respectively for 8 weeks. Each capsule of resveratrol provided 500 mg of 99.71% micronized trans-resveratrol with particle size lower than 1.9 μm and without any inactive ingredients, fillers, flavoring agents, and additives (Mega-Resveratrol, Danbury, USA), and the placebo was identical in shape, color, and taste (Barij Essence, Kashan, Iran). A person who was not a member of the research team carried out the packaging and labeling of the containers as A or B, and the researchers or participants were unaware of the content of the bottles until intervention completion. Allocation was performed by a collaborator who was not involved in enrollment using a sealed envelope. All participants were asked to maintain their dietary habits or physical activity during the follow-up period. In order to evaluate compliance, participants were asked to bring back the remaining capsules at the end of the intervention. More detailed information about the study have been provided previously (Abdollahi et al., 2019).

2.2 | Ethical aspects

The study was conducted in complete agreement with the Helsinki declaration. The study protocol was approved by the Medical Ethics Committee of Yazd University of Medical Sciences. A consent form was signed by all participants after they were provided with information about the procedure of the study. The study was also registered in the Iranian Registry of Clinical Trials (www.irct.ir) as IRCT20171118037528N1.

2.3 | Anthropometric measures

Anthropometric parameters, including weight, height, waist circumference, hip circumference, and body composition, were measured at the beginning and end of the intervention by the same person. Bioelectrical impedance technique was used to estimate body composition by a stand-on body analyzer machine (Tanita BC-418, Tokyo, Japan). Body weight, fat mass, fat-free mass, trunk fat mass, and basal metabolic rate (BMR) were measured according to the manufacturer's instruction. Participants were asked to stand on the weighing platform with light clothing and bare feet, so they could touch the electrodes and grab the grips with two hands, then body composition values provided. Height was measured using a stadiometer (Seca, Hamburg, Germany) with an accuracy level of 0.5 cm. Waist and hip circumferences (WC and HC) were measured to the nearest 0.5 cm according to the standard methods, using a flexible tape. Body mass index {BMI= [weight (kg)/height $(m)^2$]}, waist-to-hip ratio {WHR= [waist (cm)/hip (cm)]}, and waist-to-stature ratio {WSR= [waist (cm)/height (cm)]} were calculated using a formula in a previous study (Peterson, Thomas, Blackburn, & Heymsfield, 2016).

2.4 | Biochemical measures

An overnight fasting venous blood sample (10 mL) was obtained from all participants at the beginning and end of the study. Blood samples were centrifuged (3000 × **g**, 10 min at room temperature; Eppendorf AG, Hamburg) and serum aliquots in −70°C until analyses. Fasting blood sugar (FBS), HbA1c, and serum levels of insulin were measured as biochemical metabolic factors. Fasting blood sugar was measured applying automated enzymatic methods using commercial kits [Pars Azmoon, Tehran, Iran; inter- and intra-assay coefficient of variations (CVs) were 1.19 and 1.74%, respectively]. HbA1c was determined in whole blood by high-pressure liquid chromatography (HPLC) method and laboratory kit (Pars Azmoon, Tehran, Iran; inter- and intra-assay CVs were less than 2.6%). Commercially available ELISA (enzyme-linked immunosorbent assay) kit was used to assess serum levels of insulin (Monobind, USA; inter- and intra-assay CVs were 2.9% and 5.8%, respectively). Homeostatic model assessment of insulin resistance {HOMA-IR= [fasting insulin (μIU/mL)×fasting glucose (mg/dL)/405]}, quantitative insulin sensitivity check index {QUICKI= 1/[Log (fasting insulin) (μIU/mL)] + [Log (fasting glucose) (mg/dL)]}, and homeostasis model assessment of beta-cell function {HOMA- β= [360×fasting insulin (μIU/mL)]/[fasting glucose (mg/dL) − 63]} were measured by specific equation (Hong, Chung, & Cho, 2014; Motamed et al., 2016).

Cardiovascular factors, including total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), were measured using automated enzymatic methods by an auto-analyzer machine and commercial kits (Pars Azmoon, Tehran, Iran). Inter- and intra-assay CVs were 1.6% and 1.47% for triglyceride, 0.93% and 0.62% for total cholesterol, 1.8% and 0.81% for HDL-C, and 1.29% and 0.63% for LDL-C, respectively. Atherogenic index of plasma (AIP) was also calculated as an indicator of dyslipidemia according to the formula log (TG/HDL-C) (Dobiasova & Frohlich, 2001).

2.5 | Food record and physical activity

Participants were asked to record all foods and beverages consumed over 3 d (two weekdays and one weekend day) at the first and last weeks of the study. Collected data were analyzed using Nutritionist IV software (The Hearst Corporation, San Bruno, CA).

In order to assess physical activity level, metabolic equivalents (METs) were calculated using a MET physical activity questionnaire at the beginning and end of the intervention (Aadahl & Jorgensen, 2003; Toupchian et al., 2016). This questionnaire contains nine categories, including types of physical activity and intensity of the activities. To obtain MET/h, the time spent on each activity multiplied by the MET value depends on the intensity. Eventually, MET/h per day was calculated by adding the MET/h of each activity together.

2.6 | Sample size and statistical analyses

The sample size of the present research was calculated based on a previous human study regarding the PPARα gene expression in peripheral blood mononuclear cells as our primary outcome (D'Amore et al., 2013). Since gene expression results are not reported here, a power analysis was conducted to assess the quantity of sample size for outcomes reported in the current manuscript. The results of the power analysis showed ideal power for insulin levels (observed power = 0.84).

Statistical analyses were performed using SPSS for Windows (SPSS, Chicago, IL, USA), version 23.0. Data are provided as proportions or mean ± standard deviation for categorical and continuous data, respectively. One-sample Kolmogorov–Smirnov test was used to test normal distribution of the quantitative data. Differences in the mean were tested using independent-samples *t* test and Mann–Whitney *U* test for parametric and nonparametric data between the study groups. Within-group differences were assessed using paired *t* test and Wilcoxon *t* test for parametric and nonparametric variables, respectively. Age, gender, and baseline BMI were used as covariates in analysis of covariance (ANCOVA). P-values ≤ 0.05 were considered statistically significance.

3 | RESULTS

A total of 76 patients (38 participants in each group) were recruited in the study. Five of the participants (three patients in the resveratrol group and two patients in the placebo group) left the study because of pregnancy (n=1), traveling (n=1), and withdrawal of consent (n=3). At the endpoint, 71 participants (35 patients in the resveratrol group and 36 patients in the placebo group) completed the study (Fig. 1). Participants had high adherence, and more than 90% of capsules were taken in both groups based on residual capsules (compliance rate was 92.6% and 93.1% in placebo and resveratrol groups, respectively). No serious adverse events were reported.

Table 1 demonstrates the general characteristics of participants at the beginning of the study. As shown, there were no significant differences for baseline measures between the resveratrol and placebo groups. Dietary intakes and physical activity also remained unchanged during the study period (Table 2).

The analyses revealed that WC (p=0.03), fat mass (FM) (p=0.003), and trunk FM percentages (p=0.02) were significantly reduced compared with baseline levels in the resveratrol group (Table 3). Moreover, serum levels of FBS (p=0.001) and insulin (p=0.005) were reduced, and HDL-C was increased (p=0.05) significantly compared with baseline following resveratrol supplementation. In addition, HOMA-IR (p=0.01), QUICKI (p=0.008), and AIP (p=0.02) also improved after the 8 weeks of resveratrol supplementation (Table 3).

Comparisons of mean differences showed significant decrease in waist circumference (−0.78± 2.13 cm, p=0.02), fat mass percentage (−3.97± 7.26, p=0.05), and trunk fat percentage (−1.14±2.97%, p=0.03) by resveratrol supplementation. In addition, resveratrol reduced FBS (−7.97±13.6 mg/dL, p=0.03) and elevated HDL-C (3.62±8.75 mg/dL, p=0.03) levels compared with control. After adjusting for age, gender, and BMI, no significant changes were observed in anthropometric indices. However, results remained significant for the levels of FBS and HDL-C (p= 0.05 and p= 0.01, respectively). Moreover, significant difference appeared for fasting insulin levels after adjusting for age, gender, and baseline values of BMI (−0.97±1.91, μIU/mL, p= 0.02) (Table 3).

4 | DISCUSSION

In this study, we evaluated the effect of 8-week resveratrol supplementation on anthropometric and biochemical parameters among patients with T2DM. It was found that FBS, HDL, and insulin levels were improved by resveratrol supplementation, without significant change in other cardio-metabolic factors and anthropometric parameters.

Several trials have aimed to investigate the antiobesity effects of resveratrol in human. Contrary to our findings, some trials revealed significant effects of resveratrol supplementation on anthropometric measures in patients with T2DM (Imamura et al., 2017; Kumar & Joghee, 2013; Seyyedebrahimi, Khodabandehloo, Esfahani, & Meshkani, 2018). However, one study reached null results (Bo et al., 2016). In a recent meta-analysis study including 28 trials, resveratrol supplementation showed a beneficial significant effect on weight, BMI, and WC without any significant effect on FM (Mousavi et al., 2019). Contrary to these findings, another meta-analysis with fewer included studies found no significant effect of resveratrol administration on body weight and BMI (Christenson et al., 2016). Since our findings revealed a favorable effect of resveratrol on WC, FM, and trunk

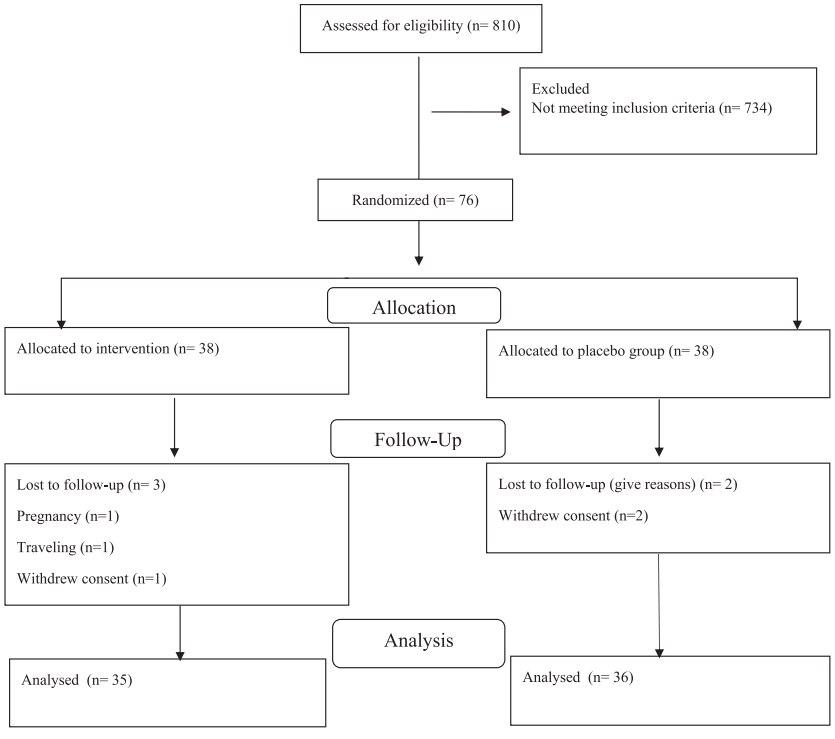

FIGURE 1 Summary of the study flow diagram

TABLE 1 Baseline characteristics of the study participants

Variable[a]	Resveratrol (*n*=35)	Placebo (*n*= 36)	*p* value[b]
Age (years)	50.14 ± 7.38	50.06± 7.69	0.96
Diabetes duration (years)	9.40 ± 7.07	8.11 ± 6.90	0.44
Gender (female), *n* (%)	15 (42.9)	16 (44.4)	0.89
Menopause status, *n* (%)	4 (26.6)	3 (18.8)	0.68
Smoker, *n* (%)	5 (14.3)	2 (5.6)	0.21
Complications			
Hypertension, *n* (%)	11 (31.4)	7 (19.4)	0.24
Kidney stone, *n* (%)	2 (5.7)	3 (8.3)	0.66
Nonalcoholic fatty liver, *n* (%)	3 (8.6)	2 (5.6)	0.62
Neuropathy, *n* (%)	2 (5.7)	2 (5.6)	0.97
Retinopathy, *n* (%)	5 (14.3)	5 (13.9)	0.96
Family history of T2DM, *n* (%)	25 (71.4)	30 (83.3)	0.23
Medications			
Metformin, *n* (%)	30 (85.7)	31 (86.1)	0.96
Glibenclamide, *n* (%)	11 (31.4)	16 (44.4)	0.25
Statins, *n* (%)	3 (8.6)	4 (11.1)	0.70
Blood pressure lowering drugs, *n* (%)	6 (17.1)	5 (13.9)	0.72
Anthropometric measures			
Weight (kg)	73.69± 8.24	72.71± 10.52	0.66
Height (cm)	164.94 ± 7.22	162.08 ± 11.29	0.20
BMI (kg/m^2)	27.10± 2.69	27.66± 2.71	0.39
HC (cm)	101.97± 6.05	103.47± 8.04	0.37
WC (cm)	91.75± 7.4	92.58± 8.53	0.66
WHR	0.9± 0.06	0.89± 0.05	0.53
WSR	0.55± 0.05	0.57± 0.07	0.25
FM (%)	26.57± 11.98	23.69± 10.06	0.27
Trunk FM (%)	29.63± 6.07	29.01± 7.17	0.69
FFM (kg)	53.33± 8.04	52.67± 11.14	0.77
BMR (kcal/d)	1696.17± 235.7	1673.01± 291.02	0.71
Cardio-metabolic factors			
TG (mg/dL)	188.34± 81.86	159.89± 63.19	0.1
LDL-C (mg/dL)	95.86± 34.23	105.13± 48.76	0.36
HDL-C (mg/dL)	42.49± 7.97	45.83± 9.08	0.1
TC (mg/dL)	167.74± 33.82	184.03± 43.34	0.08
AIP	0.58± 0.11	0.58± 0.12	0.83
FBS (mg/dL)	146.8± 28.11	143.97± 29.16	0.67
Insulin (μIU/mL)	9.88±2.07	9.48± 2.98	0.52
HbA1c (%)	7.33± 0.65	7.34± 0.55	0.92
HOMA-IR	3.63± 1.27	3.35± 1.26	0.35
HOMA-β	46.33± 15.82	49.3± 30.44	0.6
QUICKI	0.31± 0.01	0.32± 0.01	0.2

AIP, atherogenic index of plasma; BMI, body mass index; BMR, basal metabolic rate; CVD, cardiovascular disease; FBS, fasting blood sugar; FFM, fat free mass; FM, fat mass; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function; LDL-C, low-density lipoprotein cholesterol; QUICKIE, quantitative insulin sensitivity check index; TG, triacylglycerol; T2DM, type 2 diabetes mellitus; WC, waist circumference; WHR, waist-to-hip ratio; WSR, waist-to-stature ratio.

[a]Data are expressed as mean ± SD for continuous variables or as frequency and percentage for categorical variables.

[b]Differences between the control and intervention groups were evaluated using the independent-samples *t* test for continuous variables and chi-square test for categorical variables.

TABLE 2 Dietary intake and physical activity of participants during study in resveratrol and placebo groups

	Resveratrol (*n*=35)			Placebo (*n*= 36)			
Variable[a]	Before	After	*p* value[b]	Before	After	*p* value[b]	*p* value[c]
Energy (kcal)	1612.87 ± 587.87	1544.71± 597.37	0.45	1708.79 ± 515.39	1674.16± 597.07	0.55	0.47
Carbohydrate (%)	59.76 ± 12.71	61.36± 11.2	0.43	60.82 ± 9.96	60.61± 8.76	0.88	0.7
Protein (%)	15.5 ± 4.65	16.28± 5.17	0.47	15.48 ± 3.48	15.84± 4.02	0.56	0.97
Fat (%)	25.34 ± 14.55	24.14± 11.02	0.58	24.61 ± 10.42	24.26± 9.63	0.77	0.81
Fiber (g/d)	9.43± 4.11	9.69± 4.32	0.81	10.44± 5.23	10.86±5.27	0.64	0.2
Cholesterol (mg/d)	219± 29	208± 47	0.77	189± 71	191± 63	0.61	0.75
PUFA (%)	8.22± 4.13	8.28± 4.24	0.81	9.13± 4.35	9.71± 5.12	0.43	0.76
MUFA (%)	6.32± 4.21	6.12± 5.1	0.53	5.67± 3.72	5.82± 3.22	0.62	0.41
PA (MET-h/d)	35.61 ± 5.22	36.33± 5.7	0.14	37.54 ± 7.82	36.99± 5.87	0.31	0.24

MUFA, mono-unsaturated fatty acid; PA, physical activity; PUFA, poly-unsaturated fatty acid.

[a]Data are expressed as mean ± SD. [b]The presented *p* values are associated with within-group comparisons obtained from paired *t* test. [c]The presented *p* values are associated with baseline comparisons of the resveratrol and control groups obtained from independent-samples *t* test.

FM in unadjusted model, it seems that long-term supplementation could affect these parameters in adjusted model. Furthermore, some studies which reported significant effect of resveratrol supplementation on anthropometric parameters did not consider confounding factors in the analyses (Kumar & Joghee, 2013; Turner et al., 2015).

It seems that resveratrol acts as an antiobesity agent through several pathways. Although the exact mechanisms are not clear, some animal studies showed that resveratrol modulated the expression levels of genes associated with lipid mobilization, like PPARγ and lipogenic enzymes like lipoprotein lipase and fatty acid synthase (Jeon, Lee, & Choi, 2014; Kim, Jin, Choi, & Park, 2011). Moreover, it has been proposed that resting metabolic rate (RMR) increased following resveratrol supplementation through AMPK activation (Goh et al., 2014). Also, this phenolic compound induces an increase in SIRT1 levels; which are decreased in obese individuals (Pedersen, Ølholm, Paulsen, Bennetzen, & Richelsen, 2008; Timmers, Hesselink, & Schrauwen, 2013). Decreased SIRT1 expression levels in obesity contribute to reduction in mitochondrial metabolism and energy expenditure imbalance (Rutanen et al., 2010). Another possible mechanism may relate to the increased gene expression of hormone-sensitive lipase, which is in accordance with lipolysis pathway induced by epinephrine (Szkudelska, Nogowski, & Szkudelski, 2009).

Resveratrol also has the potential to improve insulin resistance indirectly by its antiobesity properties or directly by various pathways. In line with the findings of the present study, several trials reported significant improvement in glycemic control with resveratrol administration (Brasnyó et al., 2011; Timmers et al., 2011). However, we did not find significant changes in HbA1c and HOMA indices. One possible explanation is that patients who participated in our study had controlled diabetes and resveratrol may not affect HOMA indices in these patients. Moreover, the length of the intervention was shorter, which led to changes in HbA1c. Evidence from animal studies demonstrated that resveratrol enhances GLUT4 translocation to plasma membrane and also GLUT4 gene expression in insulin-resistant animals (Chen, Zhang, et al., 2011; Deng, Hsieh, Huang, Lu, & Hung, 2008; Tan et al., 2012). Another resveratrol-dependent mechanism is related to the changes in expression or activation of intracellular SIRT1 and AMPK. These molecules are involved in many cellular processes such as cellular metabolism, inflammation, and mitochondrial biogenesis (Price et al., 2012). Studies showed that insulin resistance is associated with reduced activity of these molecules and that antidiabetic drugs activate them in different tissue (Kitada & Koya, 2013; Ruderman, Carling, Prentki, & Cacicedo, 2013). It is established that resveratrol can activate these molecules in insulin-resistant models (Chen et al., 2012; Chen, Zhang, et al., 2011). The antioxidant property of resveratrol also contributes to betterment in insulin function (Um et al., 2010). This compound may also increase insulin receptor phosphorylation and thereby improve its signaling in skeletal muscle cells (Deng et al., 2008). However, some studies reached contradictory results. In a study conducted by Elliott et al., fasting insulin and HbA1c were unchanged following 5 g/d resveratrol supplementation (Elliott et al., 2009). There is also another study showing a significant effect of resveratrol on HOMA-IR improvement without significant change on FBS (Zare Javid et al., 2017).

Our study also provides evidence that resveratrol plays a role in improving lipid profile. Despite a slight nonsignificant decrease in levels of LDL-C, there was a significant increase in HDL-C levels after resveratrol supplementation, although no significant change was observed for total cholesterol, triglyceride, and AIP. These effects may be related to the role of resveratrol in increasing of carnitine palmitoyl transferase-1 and reducing of fatty acid synthase and acetyl-CoA carboxylase gene expression (Chen, Cheng, et al., 2011; Jeon et al., 2012). Moreover, in a study, this polyphenol resulted in upregulation of LDL receptor (Yashiro, Nanmoku, Shimizu, Inoue, & Sato, 2012). It is also suggested that this compound induces lipid-lowering effects through SIRT1-AMPK axis by stimulation of AMPK phosphorylation and SIRT1 activation, resulting in inhibition of fatty acid synthesis (Alberdi et al., 2013; Hou et al., 2008; Kang et al., 2012). Furthermore, it is established that resveratrol induces expression of cholesterol reverse transporters through PPARγ and adenosine receptor A2a pathways (Voloshyna, Hai, Littlefield, Carsons, & Reiss,

TABLE 3 Effects of resveratrol supplementation on anthropometric, body composition, and metabolic measures in patients with T2DM

	Resveratrol (*n*=35)			Placebo (*n*= 36)				
Variables[a]	After intervention	Mean change	*p* value[b]	After intervention	Mean change	*p* value[b]	Unadjusted *p* value[c]	ANCOVA *p* value[d]
Weight (kg)	73.56± 8.22	−0.13±0.92	0.96	72.7±10.41	−0.002± 0.77	0.3	0.51	0.79
BMI (kg/m^2)	27.08± 2.8	−0.02± 0.36	0.71	27.68± 2.8	0.02± 0.32	0.69	0.59	0.82
WC (cm)	90.97± 7.12	−0.78± 2.13	**0.03**	92.83± 8.37	0.25± 1.6	0.35	**0.02**	0.06
WHR	0.9± 0.06	−0.002±0.02	0.52	0.89± 0.05	0.002±0.02	0.57	0.39	0.72
WSR	0.55± 0.04	0.002±0.01	0.19	0.57± 0.07	−0.003±0.009	0.34	0.38	0.12
FM (%)	22.59± 10.77	−3.97± 7.26	**0.003**	22.98± 9.06	−0.71± 6.62	0.52	**0.05**	0.81
Trunk FM (%)	28.48± 6.3	−1.14± 2.97	**0.02**	29.1± 7.54	0.08± 1.7	0.76	**0.03**	0.86
FFM (kg)	53.34± 8.01	0.007±0.45	0.92	52.84± 11.2	0.16± 1.18	0.41	0.46	0.9
BMR (kcal/d)	1696.74± 234.27	0.45± 21.8	0.87	1673.28± 288.63	0.41± 21.9	0.94	0.99	0.6
TG (mg/dL)	187.8± 85.88	−0.54± 55.99	0.95	161.94± 70.89	2.05± 34.98	0.72	0.81	0.62
LDL-C (mg/dL)	92.6± 38.38	−3.26± 23.12	0.42	105.29± 46.81	0.15± 27.96	0.97	0.58	0.88
HDL-C (mg/dL)	45.4± 9.11	3.62± 8.75	**0.05**	46.89± 8.44	−0.16± 5.75	0.23	**0.03**	**0.01**
TC (mg/dL)	169.31± 35.5	1.57± 25.34	0.71	185.97± 46.33	1.94± 18.21	0.52	0.94	0.75
AIP	0.62± 0.13	0.04± 0.1	**0.02**	0.61± 0.21	0.03± 0.18	0.31	0.79	0.23
FBS (mg/dL)	138.3± 24.88	−7.97 ± 13.6	**0.001**	143.44± 32.19	−0.52 ±15.11	0.83	**0.03**	**0.05**
Insulin (μIU/mL)	8.9± 2.5	−0.97±1.91	**0.005**	9.44± 4.24	−0.04 ±2.49	0.92	0.07	**0.02**
HbA1c (%)	7.38± 0.73	0.04± 0.25	0.27	7.32± 0.63	−0.02± 0.3	0.66	0.29	0.35
HOMA-IR	3.26± 1.39	−0.36± 0.83	**0.01**	3.24± 2.04	−0.10± 1.18	0.59	0.29	0.06
HOMA-β	43.1± 18.36	−3.22± 17.12	0.27	51.64± 40.01	2.34± 22.39	0.53	0.24	0.49
QUICKI	0.32± 0.01	0.006±0.01	**0.008**	0.33± 0.03	0.009±0.02	0.01	0.51	0.59

AIP, atherogenic index of plasma; BMI, body mass index; BMR, basal metabolic rate; FBS, fasting blood sugar; FFM, fat free mass; FM, fat mass; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function; LDL-C, low-density lipoprotein cholesterol; QUICKIE, quantitative insulin sensitivity check index; TG, triacylglycerol; T2DM, type 2 diabetes mellitus; WC, waist circumference; WHR, waist-to-hip ratio; WSR, waist-to-stature ratio.

[a]All variables are expressed as mean ± SD. [b]The presented *p* values are associated with before and after intervention comparisons obtained from paired *t* test. The significance of the entries in bold [c]The presented *p* values are associated with mean changes comparisons obtained from independent-samples *t* test. The significance of the entries in bold. [d]The presented *p* values are associated with mean changes comparisons adjusted for age, gender, and BMI obtained from analysis of covariance (ANCOVA). The significance of the entries in bold.

2013). Also, previous studies reported that resveratrol mediates cholesterol clearance by raising hydroxycholesterol production through regulation of the expression of cytochrome P450 27-hydroxylase enzyme (Bingham et al., 2012). HDL-C formation was also stimulated by resveratrol through adjusting the expression of main cholesterol transporters (Zhao et al., 2019). In addition, studies reported that resveratrol contributes to preventing the conversion of LDL-C to oxidized LDL (Liu, Chen, & Li, 2017). However, some human studies failed to show a beneficial effect of resveratrol supplementation (Bashmakov et al., 2014; Imamura et al., 2017). In a study conducted by Crandall et al., no significant change in lipid profile was observed following resveratrol supplementation in older adults (Crandall et al., 2012). Also, in another study investigating the effect of resveratrol in healthy men who were obese, no significant change was reported for lipid markers (Poulsen et al., 2013). It seems that some factors like type of resveratrol supplement (pure resveratrol or resveratrol-enriched extract), supplementation dosage, intervention duration, and health status of population contributed to the contradictory findings. Furthermore, it seems that resveratrol had a positive effect in studies with an overweight or obese population (Mousavi et al., 2019).

The present study has several strengths. First, resveratrol has poor bioavailability when taken orally (less than 5%) due to its rapid metabolism and elimination (Planas, Alfaras, Colom, & Juan, 2012). For this reason, we used micronized trans-resveratrol, which improves its absorption significantly, across the gastrointestinal tract (Howells et al., 2011). Second, the sample size of the previous studies regarding resveratrol supplementation in patients with diabetes was so small (ranged from 10 to 64), and to the best of our knowledge, the present study has the highest participants. Finally, in order to homogenize the studied patients for oxidative stress status, only overweight patients with controlled diabetes were included in the study.

There are some limitations in this study that should be considered while interpreting results, including short-term intervention, failure to measure resveratrol in the blood or its metabolites in the urine, failure to examine related cellular pathways, and failure to evaluate oxidative stress as well as antioxidant intake from diet.

In conclusion, the findings of the present study showed useful effects of resveratrol supplementation on FBS, HDL-C, and insulin, without any significant effect on anthropometric and body composition parameters in patients with T2DM. Due to the limitations of this study, more trials are needed to confirm these results.

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CONFLICT OF INTEREST

The funding bodies had no role in the design of the study, writing, or decision to submit the manuscript for publication. They also had no role in any aspect of the described data management, analysis, or the reporting of study results. The authors declare that they have no competing interests.

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