Original Article
CLINICAL TRIALS AND INVESTIGATIONS

Obesity

Efficacy of an Orlistat-Resveratrol Combination for Weight Loss in Subjects with Obesity: A Randomized Controlled Trial

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Objective: To evaluate the efficacy of an orlistat-resveratrol (O-R) combination in subjects with obesity over a 6-month period.

Methods: This study was a double-blind, parallel, randomized controlled clinical trial. Patients fulfilling the selection criteria (age from 20 to 60 years and body mass index (BMI) $\geq$30 and $\leq$39.9 kg/m^2) consumed an energy-reduced diet with 500 fewer calories than their usual diet for 2 weeks. Then the participants were randomly assigned to four groups, placebo, resveratrol, orlistat, or O-R, and they consumed the energy-reduced diet for 6 months. The study consisted of seven visits. During each visit, a 24-h recall was performed, along with measurements of anthropometric and serum biochemical parameters.

Results: A total of 161 participants were selected. Of these, 84 participants completed the study. A significant weight loss of −6.82 kg (95% CI −8.37 to −5.26) was observed in the O-R group compared with −3.50 kg (−5.05 to −1.95, $P = 0.021$) in the placebo group. In contrast, the −6.02 kg (−7.68 to −4.36) orlistat and −4.68 kg (−6.64 to −2.71) resveratrol monotherapy losses did not significantly differ from the placebo. Significant decreases in BMI, waist circumference, fat mass, triglycerides, leptin, and leptin/adiponectin ratio were observed with the O-R combination.

Conclusions: The O-R combination was the most effective weight loss treatment.

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Introduction

Obesity is associated with an inflammatory state linked to several pathophysiological mechanisms related to cardiovascular disease, type 2 diabetes, and metabolic syndrome (1). Despite efforts to develop new pharmacological therapeutic compounds, few are approved by the Food and Drug Administration for long-term use, with orlistat, an intestinal lipase inhibitor, being one of them (2). This compound has been found to produce a significant change in body weight loss and to improve fasting glucose and glycosylated hemoglobin (3).

To optimize the prevention and treatment of obesity, several investigators have studied the possible therapeutic effects of natural phytochemicals (4). Resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) is a polyphenol belonging to the stilbenoid group (5) that has gained attention for its beneficial effects on health through its antioxidant, anti-inflammatory, cardioprotective, and neuroprotective activities. Resveratrol also acts against obesity-related diseases by improving mitochondrial function, improving insulin sensitivity and decreasing lipid accumulation (1,6,7).

While the effects of resveratrol have been widely studied in animal models (8-13), few clinical studies concerning obesity have been performed, and the results are inconclusive. The differing results could be due to the variable doses selected in the assays and to the different clinical backgrounds of the study subjects (14-17). It has been observed that resveratrol presents a dose–response hormesis in the biological models in which it has been tested, affecting several outcomes with medical and therapeutic significance (18).

In vitro and *in vivo* studies have demonstrated that resveratrol acts directly on adipose tissue, decreasing adiposity during obesity

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through a mechanism similar to that activated by calorie restriction (19). Moreover, the anti-obesity action of resveratrol also involves modulation of lipid metabolism in the liver and skeletal muscle, preventing lipid accumulation and enhancing fatty acid oxidation (11).

Although debate exists regarding the direct molecular target of resveratrol, the consensus is that its metabolic action converges on pathways involving adenosine monophosphate-activated kinase, Sirt1 (sirtuin 1) (through the inhibition of phosphodiesterases leading to its activation), and peroxisome proliferator-activated receptor-γ coactivator (PGC-1α) (20). In addition, among the mechanisms of action proposed are reductions of proinflammatory cytokines (interleukin-6, interleukin-8) and tumor necrosis factor-α (21) and increased production of anti-inflammatory cytokines. All these effects decrease the adhesion of proteins (for example, intercellular adhesion molecule-1) and chemoattractants (such as monocyte chemoattractant protein-1), preventing adipose tissue inflammation and uncontrolled lipolysis.

For these reasons, resveratrol is a novel therapeutic option for patients with obesity considering its capacity to simultaneously act in several pathophysiological mechanisms involved in obesity-associated complications, coupled with the proven effectiveness of orlistat. The objective of this study was to evaluate the efficacy of an orlistat-resveratrol (O-R) combination in patients with obesity over a 6-month period.

Methods

Participants

This study was conducted at the Department of Nutrition Design and Planning in Medical Research, Guadalajara, Jalisco, Mexico, from September 2013 to July 2015. The participants were Mexican, aged between 20 and 60 years, and with body mass index (BMI) $\geq$30 and $\leq$39.9 kg/m^2. The exclusion criteria were fasting serum glucose $\geq$126 mg/dL, a history of cardiovascular events, weight loss $>$3 kg in the last 3 months, cancer, AIDS, renal or liver disease, pregnancy, smoking, substance abuse, alcohol consumption, or taking any medication. Additionally, the participants were excluded if they consumed hypolipidemics, antihypertensives, hypoglycemics, steroids, chemotherapeutics, immunosuppressants, radiotherapeutics, or anorectics 6 months before the dietary treatment and during the follow-up.

Study design

This was a randomized, controlled, double-blind, parallel study. During the first 2 weeks of standardization, the participants with obesity who met the inclusion criteria followed a low-saturated-fat and hypocaloric diet, which is considered to be 500 calories fewer than the usual diet (22,23). After these 2 weeks, the participants were randomly assigned to one of the four treatments: placebo, resveratrol, orlistat, or O-R, which they followed along with an energy-reduced diet for 6 months. The study consisted of seven visits during the follow-up period. On the first selection visit, the clinical history was taken. During each subsequent visit, a 24-h recall was performed along with a physical activity survey, and anthropometric and serum biochemical parameters were also measured (glucose and triglycerides). The serum concentrations of insulin, adiponectin, and leptin were determined only on the first, 12th, and 24th weeks of treatment. This study was approved by the Ethics Committee of the Center for Medical and Biological Research and Advanced Therapy (Centro de Investigación Medico Biológica y Terapia Avanzada—CimByTA). The informed consent of the participants was also obtained. This study was registered as a controlled clinical trial in the National Clinical Trial Registry (Registro Nacional de Ensayos Clinicos—RNEC) of Mexico under number 133300410A0152 (EC-ORL/RES-052013).

Diet

At each diet visit, the participants received 15 different daily eating plans (50–60% carbohydrates, 15% proteins, 25–35% fats, $<$7% saturated fat based on total energy, $<$200 mg cholesterol, and 20–30 g fiber).

Intervention

During the second stage, the participants consumed the same diet from the first stage and the different treatments were assigned. The study was a randomized block-design controlled trial. Treatment sequence assignment was determined by blocked randomization (block size = 4) using a random number table. This random allocation was performed by an assistant not associated with any other aspect of the research. The treatments were provided as single capsules containing (a) orlistat 120 mg, (b) resveratrol 100 mg, (c) orlistat 120 mg plus resveratrol 100 mg, and (d) placebo. The doses for each medication were based on the amount required to achieve weight loss and beneficial effects (3,14). Each medication was placed inside capsules with identical pellets to ensure a double-blind study. The participants in all groups were instructed to take one capsule before each meal (three times a day).

Treatment evaluation

Compliance with the medication under study was evaluated by counting the number of bottles distributed and recording the number of capsules returned on each visit. Additionally, compliance was supervised by weekly phone calls.

Dietary assessment

Compliance with the diet was evaluated using the 24-h recall and the 3-day food record (food log). The data were processed and converted to gram equivalents using Nutrimind software (version 2013, Nutrimind Mexico).

Anthropometric measurements

Weight, height, and waist circumference (WC) were recorded in duplicate according to the Lohman method (24). The percentages of fat mass (FM) and lean mass were obtained using a total body composition analyzer (TANITA, model BX-568 InnerScan Segmental Body Composition Monitor) in the morning after 12 h of fasting.

Blood sampling and biochemical analysis

Each blood sample was obtained after 12 h of fasting, and serum samples were stored at -80°C until analysis. The concentrations of serum glucose and triglycerides were determined by colorimetric-enzymatic methods using a Thermo Scientific Konelab Prime 30 spectrophotometer. The concentrations of total serum adiponectin

(RD195023100, BioVendor), leptin (RE53151, IBL Hamburg GmbH), and insulin were determined using ELISA kits.

Sample size

Sample size was estimated according to the primary objective (weight loss) and secondary endpoints (biochemical parameters) based on previous studies (14,25), with a power of 80% and $\alpha = 0.05$. We estimated a weight difference of 4.8 kg at 6 months of treatment in the combination group, and there was a 10% difference in biochemical variables for patients consuming O-R compared with placebo. We calculated 13 and 30 patients for the weight and biochemical variables, respectively. Taking into account a 20% loss during follow-up resulted in 36 participants per group.

Statistical analysis

The continuous variables were expressed as means ± standard deviation (SD), standard error, and 95% confidence interval (CI). The dichotomous variables were expressed as frequencies and percentages. All variables were evaluated using the Kolmogorov-Smirnov test and were log-transformed before analysis. The response of each group (placebo, orlistat, resveratrol, and O-R) and of each anthropometric (weight, BMI, WC, lean mass, FM) or biochemical (glucose, triglycerides, leptin, or adiponectin) parameter was compared using two-way analysis of variance adjusted for age, gender, and baseline weight. The baseline and final anthropometric and biochemical parameters were compared among groups using one-way analysis of variance adjusted for baseline weight, age, and gender, followed by a *post hoc* Bonferroni test. The P value was set at <0.05. The data were analyzed using SPSS for Windows (version 15.00, SPSS Inc.).

Results

Participants

A total of 161 participants met the inclusion criteria and were selected for the four treatments (Figure 1). Of these, 84 participants completed the study. The participants who did not complete the study included 4 due to adverse events, 2 due to elimination criteria, 56 due to low adherence, and 15 who withdrew voluntarily (Table 1). The baseline characteristics of the participants were similar among the groups (Table 2).

Energy and nutrient intake

The baseline calorie consumption was similar among all four groups. The intake of macronutrients did not change during the trial in any of the four interventions. Compliance with the pharmacological treatment (means ± SD) was 91.8 ± 8.80% in the O-R group, 90.4 ± 9.63% in the resveratrol group, 88.0 ± 10.6% in the orlistat group, and 90.9 ± 7.30% in the placebo group, as determined by the number of capsules returned on each visit.

Effect of the intervention

The body weight decreased in all four groups when the low-calorie diet was consumed for 2 weeks with no differences observed among the groups: O-R, −1.17 (95% CI −1.54 to −0.79); resveratrol, −0.85 (95% CI −1.31 to −0.37); orlistat, −1.16 (95% CI −1.56 to −0.76); and placebo, −1.04 (95% CI −1.42 to −0.67). Regarding the intervention, the analysis was performed per protocol, and a significant difference was observed for the O-R combination versus the other groups.

A significant reduction in weight was observed in the O-R group: −6.82 kg (95% CI −8.37 to −5.26), equivalent to −6.34% (95% CI −7.96 to −4.72), compared with the placebo −3.50 kg (−5.05 to −1.95), equivalent to −2.74% (95% CI −4.36 to −1.11). In contrast, the orlistat monotherapy results were −6.02 kg (95% CI −7.68 to −4.36), equivalent to −5.41% (95% CI −7.14 to −3.68), and for resveratrol, −4.68 kg (95% CI −6.64 to −2.71), equivalent to −4.18% (95% CI −6.23 to −2.13), which was not different from the placebo (Figure 2A). When the analysis per intention to treat was performed, the significant difference was maintained, with a larger −5.30 kg (95% CI −6.41 to −4.19) decrease in the O-R group, followed by orlistat, −4.26 kg (95% CI −5.38 to −3.13); resveratrol, −2.64 kg (95% CI 3.76 to −1.51); and placebo, −2.59 kg (95% CI −3.71 to −1.47) (Figure 3B).

The anthropometric parameters related to weight loss such as BMI and FM followed the same pattern as the weight, with a larger decrease in the O-R combination, followed by orlistat, resveratrol, and the placebo (Figure 3A, C). Regarding the WC, a larger decrease was also observed in the O-R group, followed by resveratrol, orlistat, and finally by the placebo. In contrast, the percentage of lean mass increased more in the O-R group, followed by resveratrol, orlistat, and the placebo (Figure 3B, D) (Table 2).

No significant differences among the groups were observed for the biochemical parameters glucose and adiponectin. However, the serum leptin and triglyceride concentrations in the O-R group decreased significantly compared with the placebo (Table 3). The analysis of the leptin/adiponectin ratio, which is currently considered an index related to adiposity and susceptibility to atherosclerosis, revealed that the O-R treatment significantly decreased ($P < 0.05$) the leptin/adiponectin ratio compared with the other groups (Figure 4). There were no significant differences in fasting insulin concentrations or homeostatic model assessment indices between groups (Table 3).

Adverse effects

Related and nonrelated adverse effects were observed in the intervention groups, with no differences among the groups (Table 4). No severe adverse effects were reported during the study.

Discussion

This study demonstrates that administration of an O-R combination is more effective for weight loss and BMI reduction in patients with obesity. This reduction in body weight and BMI was accompanied by preservation of lean mass. Orlistat inactivates gastric and pancreatic lipases, reducing fat absorption and, thus, total calorie intake (2), and resveratrol activates cellular pathways involved in lipid utilization and energy expenditure in metabolically active tissues (5-7,19,26,27). Both compounds have been used to manage body weight in subjects who have obesity (2,19); however, we observed that the synergic activity of the O-R combination enhanced their beneficial effects, resulting in a higher percentage of body weight loss.

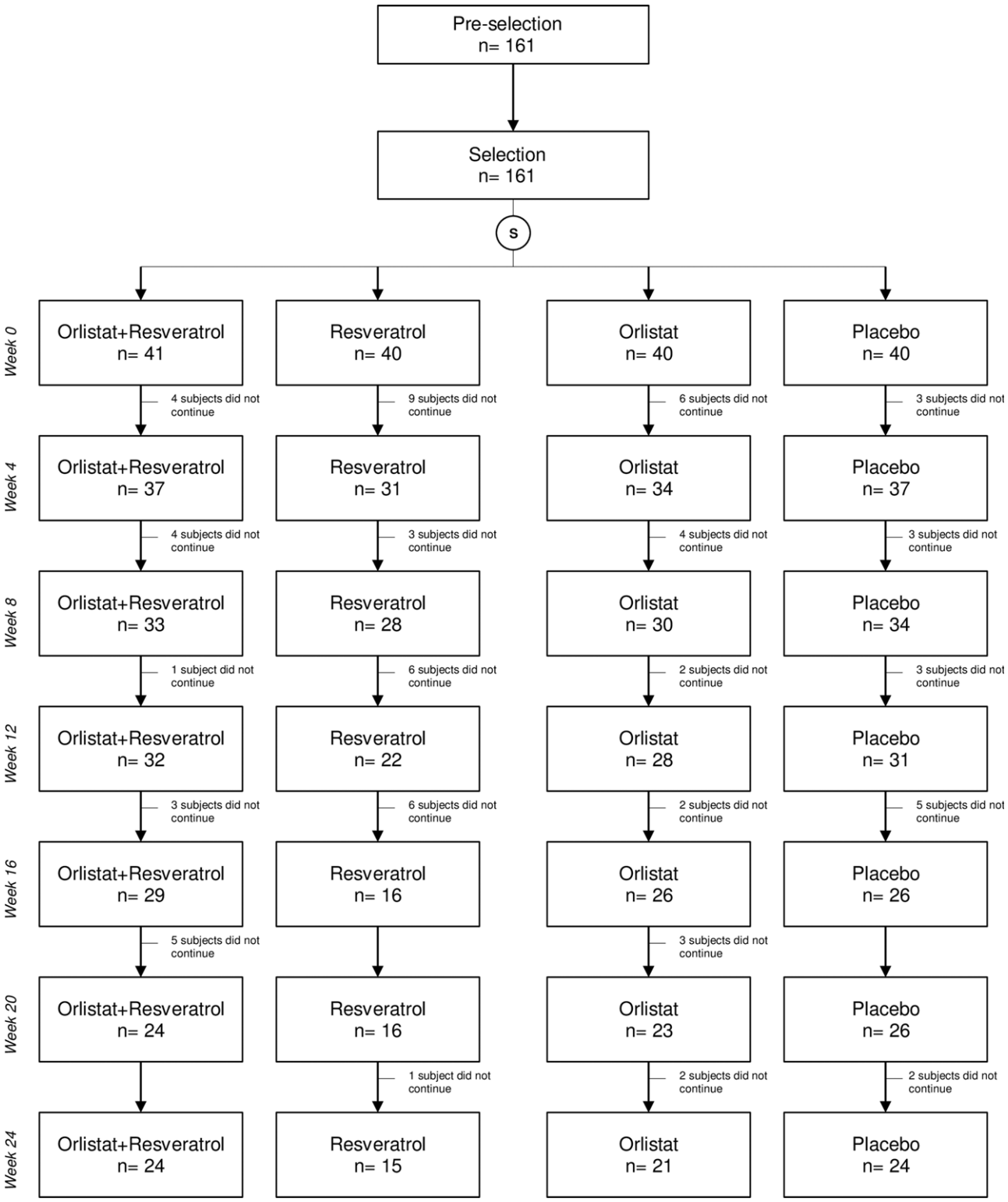

Figure 1 Flow diagram: random allocation and follow-up.

TABLE 1 Patients who did not complete the study and the reasons for their premature termination

	Orlistat + resveratrol	Resveratrol	Orlistat	Placebo	Total
No. patients who did not complete the study	17 (41.4%)	25 (62.5%)	19 (47.5%)	16 (40.0%)	77 (47.8%)
Voluntary withdrawal	3 (7.31%)	6 (15.0%)	2 (5.0%)	4 (10.0%)	15 (9.93%)
Intolerable adverse events	0 (0%)	2 (5.0%)	2 (5.0%)	0 (0%)	4 (2.48%)
Elimination criteria[a] arising during the study	0 (0%)	2 (5.0%)	0 (0%)	0 (0%)	2 (1.24%)
Low adherence	14 (31.7%)	15 (40.0%)	15 (40.0%)	12 (30.0%)	56 (36.0%)

Low adherence indicates patients who did not comply with any or several study visits.
[a]The elimination criteria manifested in two patients, i.e., hypertriglyceridemia in one subject and depression in another.

Importantly, the amount of weight loss observed in patients administered the O-R combination was greater than 5%, which leads to significantly reduced cardiovascular risk in subjects with impaired glucose tolerance, hypertension, and nonalcoholic liver disease (28,29) Furthermore, we also found significant reductions in others parameters related to cardiovascular risk, such as BMI, CC, and the percentage of body fat (30).

Several studies have demonstrated that weight loss and the loss of body fat decrease leptin concentrations in the serum (31). As expected, circulating leptin concentrations were lower in the group administered O-R at the end of the study. Administration of an O-R combination also decreased the leptin/adiponectin ratio. Evaluation of the leptin/adiponectin ratio is of clinical relevance because it has been observed that changes in circulating leptin and adiponectin are inversely related to BMI and inflammatory markers in adipose tissue. Thus, the leptin/adiponectin ratio is currently considered an index related to adiposity, susceptibility to atherosclerosis and cardiovascular risk (30,32-34). The results of this work suggest that the O-R combination may provide cardiovascular protection in subjects with obesity.

It is recognized that during intentional weight loss, a considerable loss of muscle mass occurs. The importance of maintaining lean mass during weight loss involves the need to maintain resting energy expenditure and muscle strength and function. An interesting finding in this study was the increase in the % of lean mass in patients who consumed O-R, followed by patients who consumed resveratrol. Several basic studies have demonstrated that resveratrol enhances the activity of several transcription factors and coactivators governing skeletal muscle growth and repair (35). Thus, the increase in lean mass observed in patients administered resveratrol was likely the result of enhanced preservation of muscle mass integrity during weight loss. However, this hypothesis requires further experimental confirmation.

Although lifestyle improvement is the cornerstone for the treatment of obesity, its long-term efficacy is unfortunately limited (36) Therefore, pharmacotherapy can be an important adjuvant to diet and

TABLE 2 Baseline anthropometric, clinical, and biochemical characteristics of the patients before the diet and treatment periods

	Orlistat + resveratrol ($n = 24$)	Resveratrol ($n = 15$)	Orlistat ($n = 21$)	Placebo ($n = 24$)	*P*
Gender (%)					
Male	12.5	20	23.8	12.5	0.90
Female	87.5	80	76.2	87.5	
Age (years)	40.9 ± 10.0	33.7 ± 11.9	39.7 ± 8.91	38.8 ± 9.59	0.17
Weight (kg)	89.9 ± 8.12	94.6 ± 15.5	90.6 ± 11.8	89.3 ± 13.6	0.58
BMI (kg/m^2)	35.3 ± 2.83	35.6 ± 2.71	34.8 ± 2.89	34.7 ± 2.89	0.74
Waist (cm)	101 ± 6.50	98.8 ± 7.95	97.4 ± 9.09	96.4 ± 8.13	0.32
Leptin (ng/mL)	32.6 ± 20.4	25.2 ± 16.9	25.3 ± 15.2	24.7 ± 9.65	0.29
Adiponectin (μg/mL)	7.75 ± 4.52	7.76 ± 3.52	6.97 ± 4.97	7.15 ± 3.53	0.90
Insulin (μIU/L)	13.3 ± 6.1	12.8 ± 4.82	10.8 ± 4.71	13.2 ± 6.41	0.43
Glucose (mg/dL)	91.7 ± 8.96	90.2 ± 6.94	90.6 ± 7.16	92.1 ± 1.72	0.87
Triglycerides (mg/dL)	141 ± 68.2	131 ± 13.0	134 ± 10.9	146 ± 11.3	0.83
Systolic arterial pressure (mm Hg)	113 ± 12.5	115 ± 13.4	110 ± 10.4	111 ± 2.51	0.23
Diastolic arterial pressure (mm Hg)	71.7 ± 7.18	68.9 ± 7.98	69.6 ± 8.06	71.1 ± 7.85	0.66
Lean mass (%)	54.1 ± 5.81	56.3 ± 6.57	55.6 ± 4.84	55.3 ± 4.83	0.64
Fat mass (%)	42.6 ± 5.69	40.9 ± 7.11	41.2 ± 4.81	41.7 ± 5.03	0.80

Data are presented as the means ± SD. Differences are based on one-way ANOVA; significant $P \leq 0.05$.

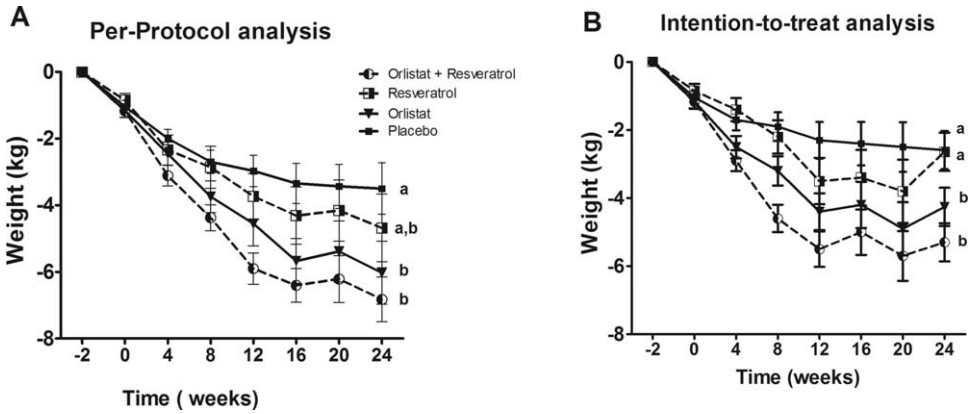

Figure 2 Weight difference in kilograms according to intervention group during two stages: in the first stage, the participants were instructed to consume an energy-reduced diet 500 calories fewer than their usual diet for 2 weeks (week −2 and 0). In the second stage, participants were randomly assigned to consume placebo, resveratrol, orlistat, or orlistat + resveratrol, along with the energy-reduced diet for 24 weeks. (**A**) Analysis per protocol ($n = 84$); (**B**) analysis per intention to treat ($n = 161$). The data are presented as the means ± SEM; among-group differences were assessed using one-way ANOVA followed by a multiple comparison by the Bonferroni test, and the differences are shown as different letters for each group (a > b > c).

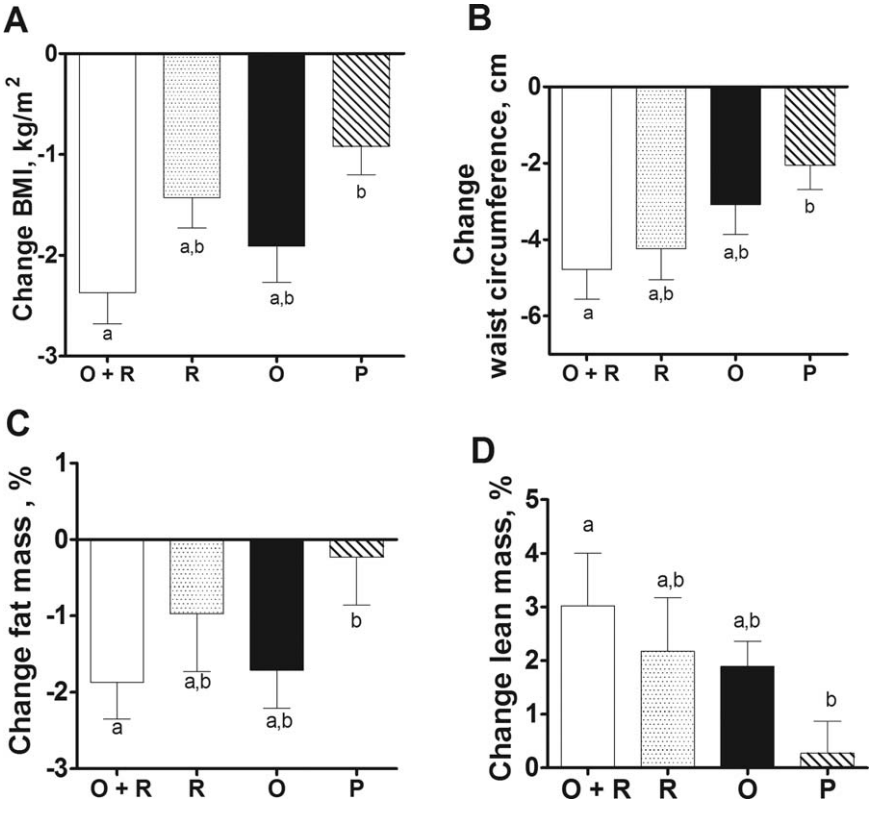

Figure 3 Change in the different anthropometric and clinical parameters after treatment with orlistat + resveratrol (O-R); resveratrol (R); orlistat (O); or placebo (P). (**A**) Change in waist circumference with different treatments; (**B**) change in BMI; (**C**) change in fat mass percentage; (**D**) change in lean mass percentage. Data are presented as the means ± SEM; among-group differences were assessed using one-way ANOVA, followed by a multiple comparison by the Bonferroni test, and the differences are shown as different letters in each bar (a > b > c).

TABLE 3 Anthropometric, clinical, and biochemical characteristics of the patients at each visit according to treatment

	Day 0	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Change*	*P*, treatment	*P*, time	*P*, treatment × time
Weight (kg)											
Orlistat + resveratrol	88.6 ± 8.23	86.7 ± 7.98	85.4 ± 7.97	83.9 ± 8.02	83.4 ± 8.02	83.6 ± 7.9	83.0 ± 7.98	−5.65 ± 3.29[a]	0.001	0.001	0.001
Resveratrol	93.7 ± 15.1	92.2 ± 14.6	91.7 ± 14.6	90.9 ± 14.5	90.3 ± 15.3	90.4 ± 15.4	89.9 ± 15.4	−3.83 ± 3.41[a,b]			
Orlistat	89.4 ± 11.3	88.1 ± 11.7	86.9 ± 11.6	86.0 ± 11.2	84.9 ± 11.0	85.2 ± 11.1	84.6 ± 11.1	−4.86 ± 4.00[a,b]			
Placebo	88.2 ± 13.7	87.3 ± 13.7	86.6 ± 13.2	86.3 ± 13.9	85.9 ± 13.8	85.8 ± 13.9	85.8 ± 13.6	−2.46 ± 3.66[b]			
BMI (kg/m^2)											
Orlistat + resveratrol	35.0 ± 2.73	34.1 ± 2.74	33.5 ± 2.67	33.0 ± 2.67	32.8 ± 2.61	32.8 ± 2.66	32.6 ± 2.63	−2.37 ± 1.56[a]	0.001	0.001	0.001
Resveratrol	35.1 ± 2.70	34.8 ± 2.61	34.4 ± 2.63	34.1 ± 2.70	33.9 ± 3.01	33.9 ± 3.07	33.7 ± 3.38	−1.43 ± 1.17[a,b]			
Orlistat	34.3 ± 2.77	33.8 ± 2.84	33.2 ± 3.00	33.0 ± 3.03	32.6 ± 3.15	32.6 ± 3.31	32.4 ± 3.59	−1.91 ± 1.63[a,b]			
Placebo	34.4 ± 2.95	33.9 ± 3.07	33.7 ± 2.93	33.5 ± 23.13	33.4 ± 3.27	33.4 ± 3.37	33.4 ± 3.20	−0.92 ± 1.40[b]			
Lean mass (%)											
Orlistat + resveratrol	54.2 ± 6.17	54.9 ± 6.58	55.8 ± 5.66	56.8 ± 6.32	57.5 ± 6.44	57.1 ± 6.12	57.2 ± 6.07	−1.87 ± 0.48	0.001	0.001	0.001
Resveratrol	55.1 ± 7.90	56.2 ± 6.58	56.1 ± 6.40	56.8 ± 6.44	56.9 ± 7.08	57.0 ± 6.98	57.3 ± 6.71	−0.98 ± 0.48			
Orlistat	55.8 ± 4.26	56.5 ± 4.63	56.7 ± 4.62	57.5 ± 4.58	57.6 ± 5.11	56.8 ± 6.68	57.7 ± 5.45	−1.71 ± 2.30			
Placebo	56.1 ± 5.64	55.7 ± 4.79	55.9 ± 5.11	56.0 ± 4.47	55.5 ± 5.17	55.3 ± 6.58	56.4 ± 4.96	−0.24 ± 3.09			
Fat mass (%)											
Orlistat + resveratrol	41.8 ± 6.22	41.7 ± 6.53	41.1 ± 6.55	40.6 ± 6.86	39.2 ± 6.83	39.7 ± 6.38	39.9 ± 6.07	−1.87 ± 2.36	0.001	0.001	0.001
Resveratrol	40.8 ± 7.19	40.8 ± 6.67	40.7 ± 6.63	40.2 ± 6.90	40.1 ± 7.34	40.1 ± 6.93	39.9 ± 6.89	−0.96 ± 2.94			
Orlistat	41.1 ± 4.53	40.6 ± 5.00	40.2 ± 4.85	39.4 ± 5.14	39.3 ± 5.37	38.9 ± 5.33	39.4 ± 5.76	−1.71 ± 2.29			
Placebo	40.8 ± 5.89	41.3 ± 4.85	41.4 ± 5.08	41.0 ± 4.69	41.2 ± 5.48	40.4 ± 5.30	40.6 ± 5.25	−0.24 ± 3.09			
WC (cm)											
Orlistat + resveratrol	100.5 ± 6.49	99.1 ± 6.49	97.4 ± 6.07	96.2 ± 5.67	95.8 ± 5.54	95.8 ± 5.33	95.7 ± 6.06	−4.78 ± 3.84[a]	0.001	0.001	0.001
Resveratrol	98.8 ± 8.36	96.5 ± 7.73	96.2 ± 8.66	96.2 ± 7.62	96.1 ± 8.92	95.0 ± 9.18	94.6 ± 9.45	−4.24 ± 3.15[a,b]			
Orlistat	97.4 ± 9.08	95.9 ± 9.74	94.8 ± 9.27	95.2 ± 8.98	94.4 ± 9.12	94.0 ± 9.35	94.3 ± 9.59	−3.10 ± 3.57[a,b]			
Placebo	96.4 ± 8.13	95.7 ± 7.77	95.1 ± 7.64	94.8 ± 8.31	94.6 ± 8.62	94.4 ± 8.84	94.3 ± 8.47	−2.07 ± 3.10[b]			
Leptin (ng/mL)											
Orlistat + resveratrol	32.6 ± 20.4			25.9 ± 11.1			27.1 ± 10.2	−5.50 ± 21.3	0.007	0.001	0.024
Resveratrol	25.1 ± 16.9			21.9 ± 13.2			26.3 ± 10.4	1.12 ± 13.8			
Orlistat	25.3 ± 15.2			21.2 ± 11.7			23.5 ± 12.7	−1.78 ± 16.3			
Placebo	24.7 ± 9.65			24.8 ± 10.9			25.5 ± 10.1	0.76 ± 11.4			
Adiponectin (μg/mL)											
Orlistat + resveratrol	7.75 ± 4.52			8.07 ± 3.91			8.41 ± 2 77	0.66 ± 4.14	0.437	0.951	0.781
Resveratrol	7.76 ± 3.51			9.23 ± 4.53			8.30 ± 2.74	0.54 ± 3.92			
Orlistat	6.97 ± 4.97			9.33 ± 3.82			8.89 ± 3.38	1.92 ± 4.91			
Placebo	7.15 ± 3.52			7.93 ± 3.40			8.15 ± 3.09	1.00 ± 3.79			

TABLE 3. (continued).

	Day 0	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Change*	*P*, treatment	*P*, time	*P*, treatment × time
Insulin (μIU/L)											
Orlistat + resveratrol	12.0 ± 3.83			11.4 ± 4.82			11.9 ± 6.88	−0.04 ± 5.99	0.001	0.461	0.011
Resveratrol	11.5 ± 4.20			11.0 ± 4.52			11.9 ± 4.03	0.40 ± 4.00			
Orlistat	10.7 ± 3.69			9.91 ± 3.98			9.88 ± 5.01	−0.87 ± 3.29			
Placebo	11.6 ± 6.61			13.1 ± 7.63			13.5 ± 10.3	1.97 ± 7.22			
Glucose (mg/dL)											
Orlistat + resveratrol	88.7 ± 9.43	89.1 ± 10.7	91.0 ± 8.04	91.7 ± 8.04		89.1 ± 7.17	90.2 ± 8.09	1.48 ± 10.3	0.007	0.023	0.263
Resveratrol	88.5 ± 8.98	88.1 ± 8.05	91.6 ± 9.13	91.0 ± 8.92		93.2 ± 7.66	91.3 ± 6.25	2.81 ± 6.73			
Orlistat	89.7 ± 10.0	88.4 ± 9.16	90.3 ± 6.20	91.4 ± 7.18		89.4 ± 7.84	89.1 ± 8.24	−0.60 ± 7.45			
Placebo	88.1 ± 7.60	91.3 ± 9.42	90.1 ± 7.44	93.5 ± 8.07		93.7 ± 9.71	92.4 ± 9.27	4.28 ± 6.52			
TG (mg/dL)											
Orlistat + resveratrol	138 ± 103	128 ± 51.4	141 ± 73.8	140 ± 58.6	134 ± 52.0	133 ± 67.6	129 ± 63.6	−8.85 ± 115	0.001	0.001	0.001
Resveratrol	111 ± 36.4	114 ± 32.6	113 ± 32.3	109 ± 40.8	116 ± 54.0	108 ± 46.2	122 ± 49.4	11.6 ± 46.5			
Orlistat	125 ± 55.6	129 ± 45.0	130 ± 46.6	126 ± 39.5	121 ± 48.3	126 ± 49.4	125 ± 60.3	0.06 ± 59.7			
Placebo	137 ± 45.6	129 ± 43.9	120 ± 43.6	144 ± 89.6	126 ± 57.3	124 ± 55.7	136 ± 61.6	−1.13 ± 53.2			

The data are presented as the means ± SD; statistical value of the treatment; *P* value per time and statistical value of the treatment × time interaction using two-way ANOVA adjusted for age, gender, and baseline weight.
*Differences are based on one-way ANOVA. The Bonferroni correction was used as *post hoc* analysis and the differences are shown as different letters for each group (a > b > c); number of patients = 84.
WC, waist circumference; TG: triglycerides.

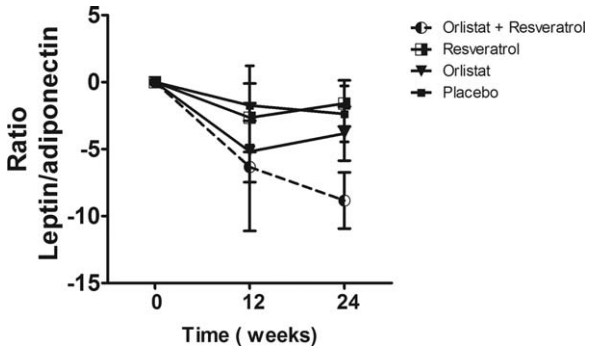

Figure 4 Difference in the leptin/adiponectin ratio decrease whereby participants were randomly assigned to consume placebo, resveratrol, orlistat, or orlistat + resveratrol, as well as an energy-reduced diet, for 24 weeks. Data are presented as the means ± SEM; the statistical analysis was performed using two-way ANOVA to assess the time × treatment interaction ($P < 0.05$).

TABLE 4 Adverse effects of the interventions

Related adverse effect	Orlistat + resveratrol	Resveratrol	Orlistat	Placebo
Patients with adverse effects[a]	1	3	1	3
Abdominal pain		1		
Constipation				1
Diarrhea	1	1		2
Nausea		1		
Steatorrhea			1	

[a]Number of patients with total adverse effects related to the intervention.

exercise as a therapeutic option for achieving the 5 to 10% weight loss goal reported to reduce cardiovascular risk and subsequently for maintaining this achievement over time (28,37).

This study had two main limitations: (a) the 48% loss of participants during the intervention, which led to a calculation of power with the sample used of 83%, calculated *post hoc*, and b) the follow-up period because, although weight loss was maintained with the O-R combination during all 6 months, longer studies are required.

In conclusion, the combination of orlistat-resveratrol constitutes a novel therapeutic option for obesity because it is able to simultaneously act in several of the pathophysiological mechanisms involved in obesity-associated complications. The results obtained from this study allow us to conclude that the combined use of O-R during 6 months is effective and safe for weight and BMI loss and for increasing lean mass in patients with obesity.O

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