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Basic nutritional investigation

Resveratrol attenuates hepatic steatosis in high-fat fed mice by decreasing lipogenesis and inflammation

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ABSTRACT

Objective: Resveratrol (RSV) is the most studied natural compound that activates sirtuins, which produce beneficial metabolic effects on lipid and glucose metabolism. The aim of the present study was to investigate the role of resveratrol in preventing nonalcoholic fatty liver disease (NAFLD) and expression of liver inflammatory markers in mice treated with a high-fat diet.
Methods and procedures: Eighteen male mice were divided into three groups and fed for 60 d with a standard diet (ST), high-fat diet (HFD), or high-fat diet plus resveratrol (HFD + RSV, 30 mg/kg/d). Body weight, food intake, and serum total cholesterol, triacylglycerol, insulin, alanine transaminase (ALT), and aspartate aminotransferase (AST) were evaluated. Liver histology was analyzed. Expression of ACC, PPAR-γ, ChREBP, SREBP-1 c, CPT-1, tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), NF-κB, interleukin 1 β (IL-1 β), and SIRT1 were evaluated by quantitative real-time reverse transcriptase PCR (qRT-PCR).
Results: The major finding of the present study was that RSV reduced body fat, total cholesterol, triacylglycerol, transaminases, and insulin plasma level. These results were accompanied with a significant reduction in TNF-α, IL-6, and NF-κB mRNA expression in the liver. Analyses of liver adipogenesis related genes indicated that ACC, PPAR-γ, and SREBP-1 mRNA expression were significantly suppressed in HFD + RSV mice. In addition, we observed increased expression of SIRT1 in the HFD + RSV group.
Conclusions: We observed that treatment with resveratrol improved lipid metabolism, and decreased NAFLD and pro-inflammatory profile in liver of mice with obesity-inducible diets. These data suggest an important clinical application of RSV in preventing liver diseases.

Introduction

Obesity is a metabolic state associated with several hepatic abnormalities and increased risk of chronic diseases such as type 2 diabetes, cardiovascular diseases, and cancer [1]. Obesity is described as a major risk factor for nonalcoholic fatty liver disease (NAFLD), a disease spectrum that includes hepatic steatosis, steatohepatitis, fibrosis, and liver cirrhosis [2–4].

Nonalcoholic fatty liver disease is one of the most common manifestations of chronic liver disorders worldwide [4]. NAFLD represents a continuum of hepatic injuries, which progress from simple hepatic steatosis to nonalcoholic steatohepatitis, with some people even ultimately progressing to fibrosis, cirrhosis, and liver failure [5]. The prevalence of NAFLD in the general population is estimated to be between 14% and 24%, and it is so closely associated with obesity, diabetes, and insulin

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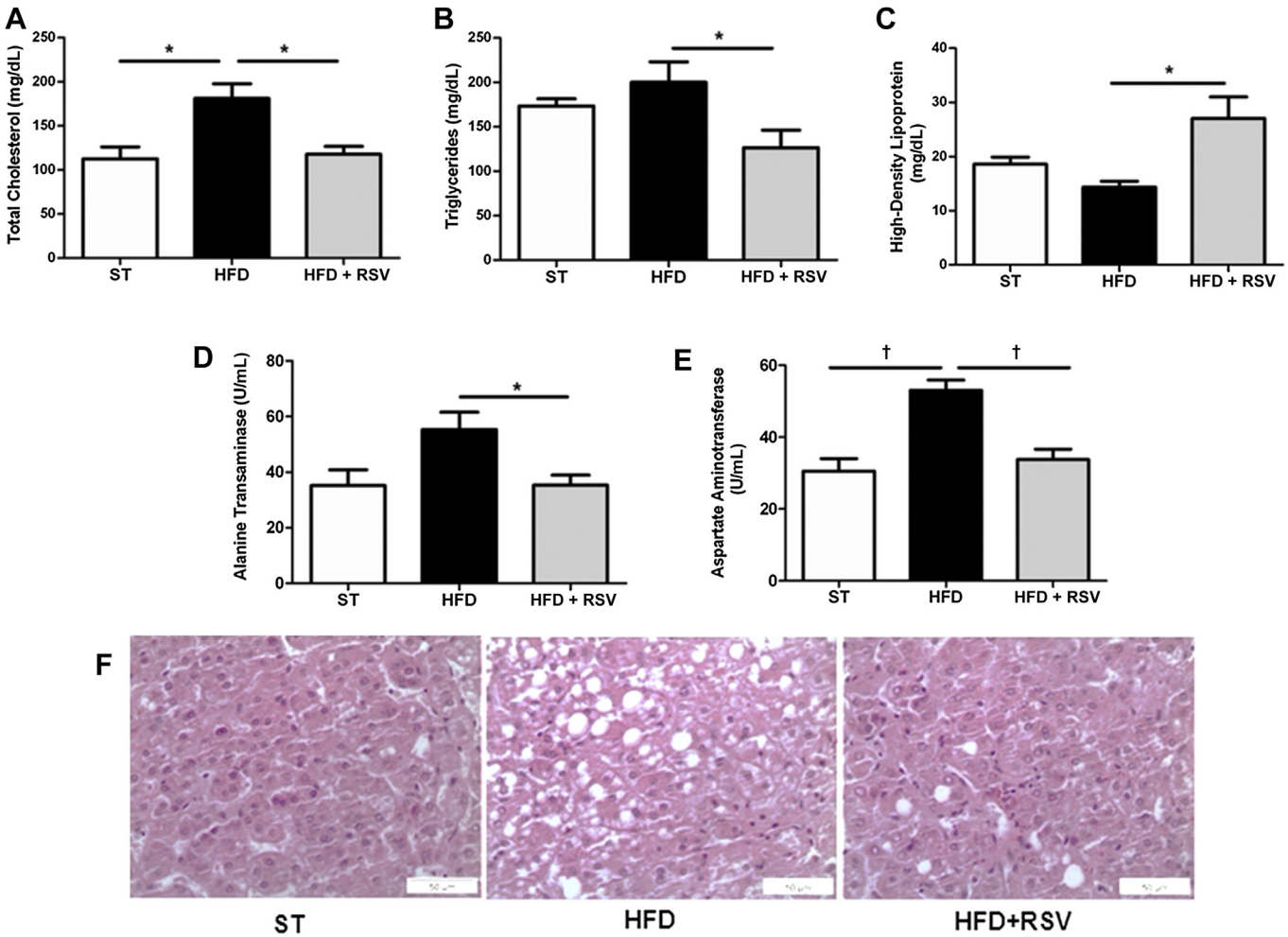

Fig. 1. Plasma parameters, liver histology and analyses of mRNA expression of adipogenesis to related genes by qRT to PCR in liver. (A) Total cholesterol. (B) Triacylglycerols. (C) HDL. (D) ALT. (E) AST. (F) HE staining of liver sample mice. Inlet: HE staining. Scale bar: 20×. *$P < 0.05$, †$P < 0.01$ among HFD versus ST and HFD + RSV.

resistance (IR) that it has been proposed that NAFLD be included as a component of metabolic disorders [6,7].

Resveratrol (3,5,4′-trihydroxystilbene) is a natural polyphenolic compound found in grapes and red wine that has been shown to extend lifespan in many organisms [8,9]. In the last few years, interest in resveratrol has substantially increased, and its broad biological activity at the cellular level has been demonstrated. The cardioprotective [10–12], anticancer [13], antiinflammatory, and antioxidant [14] properties of resveratrol are quite well characterized. In recent animal studies, resveratrol has produced promising protective effects on the liver against lipid accumulation induced by a high-fat diet [8,9,15].

Resveratrol is a natural compound that activates sirtuins (SIRT), the mammalian homolog of yeast silent information regulator 2 (Sir2). SIRT is a highly conserved family of proteins, with one or more sirtuins present in virtually all species from bacteria to mammals [16,17]. Recent studies have indicated that SIRT expression in the liver is significantly decreased in an NAFLD model of rats fed a high-fat diet, and moderate SIRT1 overexpression protects mice from developing NAFLD [18,19].

Thus in this study we aimed to investigate whether RSV treatment could improve NAFLD, and we explored the possible mechanisms associated with lipogenesis and inflammation. A deeper understanding of the role of RSV in modulating the biological markers of NAFLD will substantiate its potential as a therapeutic candidate.

Materials and methods

Animals

The experiment was conducted with 18 male FVB/N mice (4 wk old), which were randomly divided into three groups (n = 6) and fed the following respective experimental diets for 60 d: Standard diet (ST); high-fat diet (HFD); high-fat diet plus resveratrol (HFD + RSV) (30 mg/kg/d) [8,20,21]. According to previous studies, the FVB/N strain is considered a preferable model for evaluation of metabolic disorders [22,23].

Diets

The standard diet (Labina, Purina, St. Louis, MO, USA) used for regular maintenance of the mice is composed of 50.30% carbohydrate, 41.90% protein, and 7.80% fat, with a total of 2.18 kcal per 1 g of diet. The high-fat diet was composed 24.55% of carbohydrate, 14.47% of protein, and 60.98% of fat, presenting a total of 5.28 kcal per 1 g of diet. All the high-fat diet components were purchased from Rhoster LTDA (São Paulo, Brazil).

Measurements of body weight, food intake, and tissue collection

The mice were individually housed and the food intake was measured twice per week during treatment to determine food efficiency (food intake/body weight). Overnight-fasted mice were sacrificed with ketamine (130 mg/kg) and xylazine

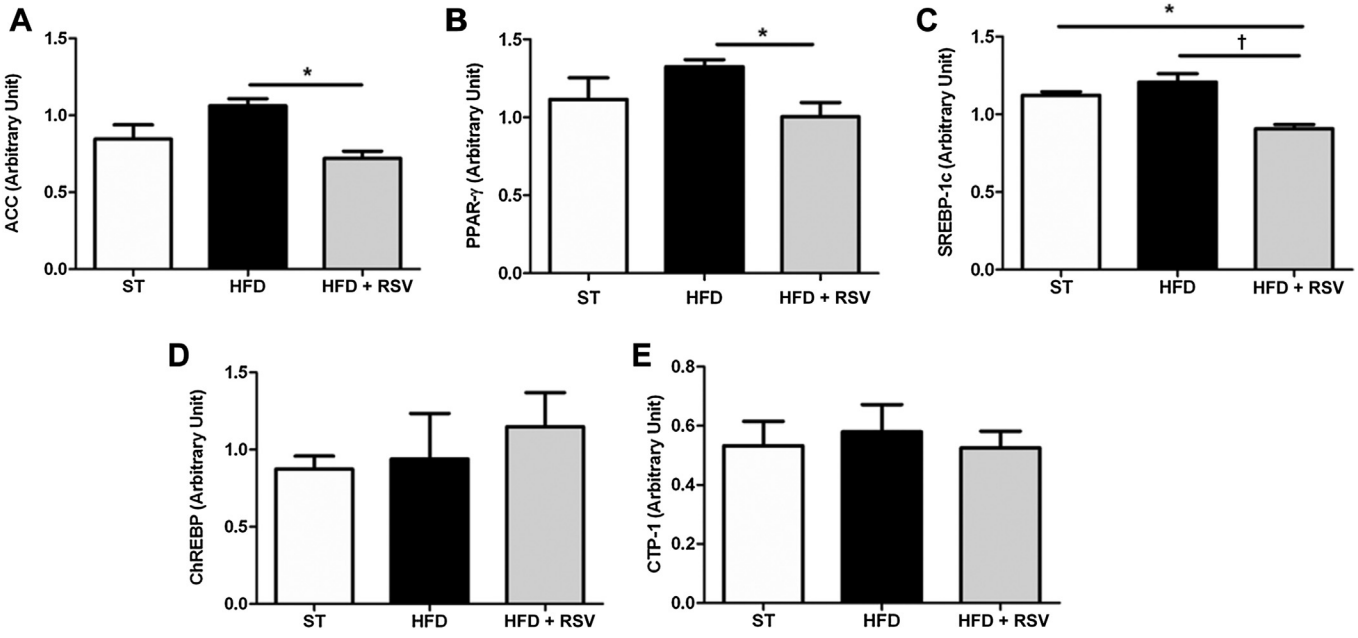

Fig. 2. Analyses of mRNA expression of lipogenesis markers by qRT to PCR in liver. (A) ACC. (B) PPARγ. (C) SREBP-1 c. (D) ChREBP. (E) CPT-1. Control mice (ST; *white bars*), high-fat diet (HFD; *black bars*), and high-fat diet plus resveratrol (HFD + RSV; *gray bars*). *$P < 0.05$, †$P < 0.01$ among HFD versus ST and HFD + RSV.

(0.3 mg/kg) after anesthesia; sample tissues were collected, weighted, and immediately frozen in liquid nitrogen and stored at −80°C for posterior analysis.

Determination of blood measurements

Serum was obtained after centrifugation (3200 rpm for 10 min at 4°C). Total serum cholesterol, high-density lipoprotein (HDL), triacylglycerol, insulin, and aspartate and alanine transaminases (AST and ALT) were assayed using enzymatic kits (Wiener Laboratories, Rosario, Argentina).

Reverse transcription and qRT-PCR

Total RNA from liver tissue was prepared using TRIzol reagent (Invitrogen Corp., San Diego, CA, USA), treated with DNAse and reverse transcribed with M-MLV (Invitrogen Corp.) using random hexamer primers. The endogenous glyceraldehydes-3-phosphate dehydrogenase (GAPDH) (internal control), interleukin 1 β (IL-1 β), tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), NF-κB, ACC, ChREBP, PPAR-γ, carnitine palmitoyltransferase 1 (CPT-1), SREBP-1 c, and SIRT1 mRNA were determined by quantitative real-time reverse transcriptase PCR (qRT-PCR) using SYBR Green reagent (Applied Biosystems®, Grand Island, NY, USA) in a PlusOne platform (Applied Biosystems).

Hematoxylin and eosin staining

Liver samples were fixed in formaldehyde solution (10%) and embedded in paraffin serially sectioned at 5 μm, stained with hematoxylin and eosin (HE), and evaluated under a conventional light microscope using an Olympus BX50 microscope (Tokyo, Japan). Images of fat tissue areas (×10 ocular and ×40 objective lenses) were captured with Evolution LC color light camera (Media Cybernetics, Rockville, MD, USA).

Statistical analysis

All data were transferred to GraphPad Prism software (Version 5.0, GraphPad Software Inc., San Diego, CA, USA) and analyzed with confidence 95% ($P < 0.05$). Data are expressed as the mean ± SD. The statistical significance of differences in mean values among mice groups was assessed by one-way ANOVA followed by Bonferroni post-test.

Results

Mice treated with resveratrol did not reduce their food intake (ST: 0.13 ± 0.024; HFD: 0.13 ± 0.024; HFD + RSV: 0.12 ± 0.016; $P = 0.646$), but significant decrease was observed in final body weight in the ST group (ST: 23.34 ± 1.56; HFD: 25.69 ± 2.17; HFD + RSV: 24.36 ± 2.56; $P = 0.031$) and in fat pad weight in the HFD + RSV group (ST: 0.026 ± 0.013; HFD: 0.037 ± 0.012; HFD + RSV: 0.019 ± 0.008; $P = 0.027$) in relation to the HFD group.

The HFD + RSV group had reduced concentrations of total cholesterol (ST: 112.6 ± 30.14; HFD: 181.2 ± 37.14; HFD + RSV: 117.8 ± 19.92) and triacylglycerols (ST: 173.4 ± 16.47; 200.2 ± 46.12; 126.6 ± 39.47) (Fig. 1A, B). In the HFD group, HDL cholesterol was significantly decreased (ST: 18.59 ± 2.67; HFD: 14.33 ± 2.21; HFD + RSV: 27.04 ± 8.88) (Fig. 1C). Regarding parameters related to liver damage, values of ALT (ST: 35.18 ± 11.24; HFD: 55.36 ± 13.94; HFD + RSV: 35.31 ± 8.05) and AST (ST: 30.5 ± 7.04; HFD: 53.0 ± 5.71; HFD + RSV: 33.7 ± 5.73) were significantly reduced in the HFD + RSV group (Fig. 1D, E).

In addition, analysis indicated that the HFD + RSV group had a substantial decrease in the total liver weight in relation to HFD mice. The liver histologic examinations in mice fed the HFD indicated prominent steatosis (Fig. 1F). Hence, we performed a histologic analysis to examine the effect of resveratrol on the development of fatty liver. Large hepatic lipid droplets were diffusely present in the livers of the HFD group mice compared with the other groups (Fig. 1F).

Analyses of mRNA expression of adipogenesis-related genes indicated that ACC (ST: 0.84 ± 0.18; HFD: 1.06 ± 0.09; HFD + RSV: 0.72 ± 0.09), PPAR-γ (ST: 1.16 ± 0.31; HFD: 1.32 ± 0.10; HFD + RSV: 1.00 ± 0.20), and SREBP-1 c (ST: 1.12 ± 0.03; HFD: 1.20 ± 0.09; HFD + RSV: 0.90 ± 0.05) mRNA expression in the liver was significantly suppressed in HFD + RSV (Fig. 2A, C). However, no difference was noted in the expression of ChREBP ($P = 0.651$) and CPT-1 ($P = 0.866$) among groups (Fig. 2D, E).

The mRNA expression of proinflammatory cytokines by qRT-PCR in liver indicated a significant decrease in IL-6 (ST: 0.79 ± 0.26; HFD: 1.05 ± 0.39; HFD + RSV: 0.40 ± 0.17), TNF-α (ST: 1.06 ± 0.22; HFD: 1.29 ± 0.21; HFD + RSV: 0.80 ± 0.21), and NF-κB (ST: 0.98 ± 0.36; HFD: 1.59 ± 0.34; HFD + RSV: 0.99 ± 0.15) in the HFD + RSV group (Fig. 3A, C). IL-1 β expression did not differ among the groups ($P = 0.273$) (Fig. 3D).

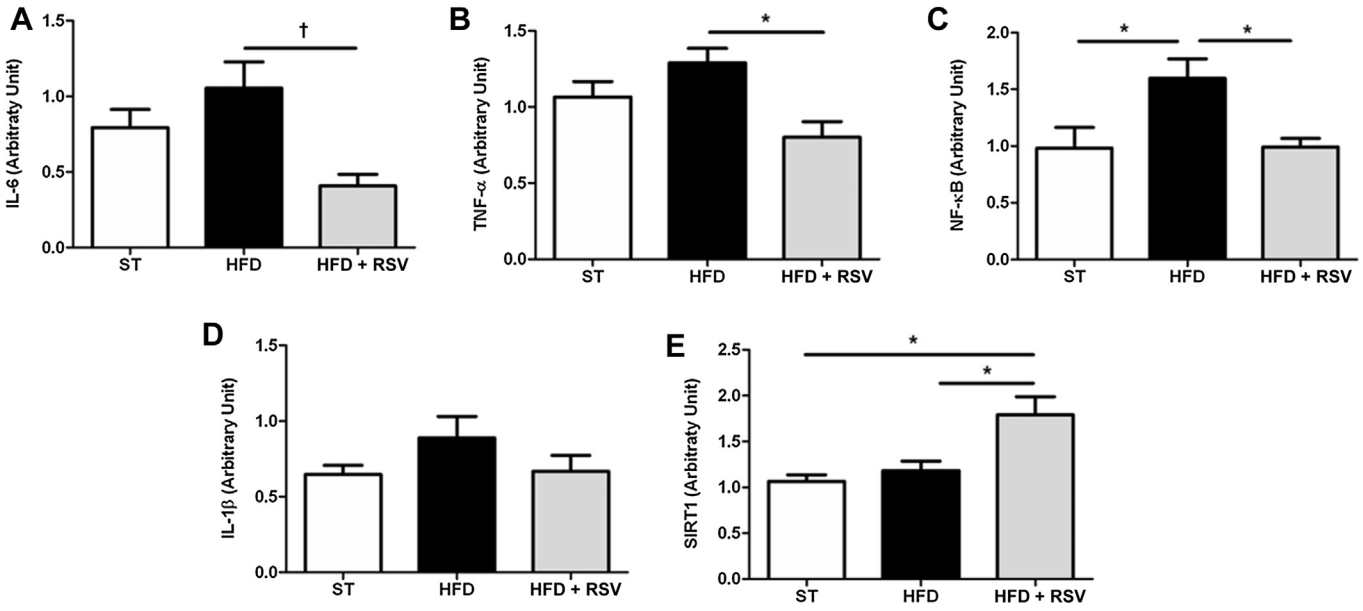

Fig. 3. Analyses of mRNA expression of proinflammatory cytokines and SIRT1 by qRT-PCR in liver. (A) IL-6. (B) TNF-α. (C) NF-κB. (D) IL-1 β. (E) SIRT1. Control mice (ST; *white bars*), high-fat diet (HFD; *black bars*), and high-fat diet plus resveratrol (HFD + RSV; *gray bars*). $^*P < 0.05$, $\dagger P < 0.01$ among HFD versus ST and HFD + RSV.

Additionally, we noted a significant increase in SIRT1 (ST: 1.06 ± 0.14; HFD: 1.18 ± 0.23; HFD + RSV: 1.79 ± 0.44) expression in the HFD + RSV group (Fig. 3E).

Discussion

Resveratrol has been described as having significant effects on lipid metabolism. Several studies have indicated that RSV treatment increases lifespan and improves insulin sensitivity, reduced insulin-like growth factor 1 (IGF-I) levels, increased AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor c coactivator 1 α (PGC-1 α) activity, increased mitochondrial number, and improved motor function at a dosage of 30 mg/kg/d [8,20,21].

In this context, several studies have demonstrated reduced fat accumulation either in isolated adipocytes or in adipose tissue [21] and liver [24], increased fatty acid oxidation in skeletal muscle [21], and reduced serum lipids induced by this polyphenol. All these effects support the hypothesis that resveratrol could be a useful molecule for the prevention of obesity, steatosis, and NAFLD.

Recent studies have demonstrated that resveratrol decreased alcoholic fatty liver in mice by activating SIRT1 [25,26]. Wang et al. suggested that resveratrol might attenuate fat deposition by inhibiting SREBP-1 c expression via SIRT1-FOXO1 pathway [25]. In addition, chemical activators of SIRT1 inhibit the SREBP target gene expression in vitro and in vivo, correlating with decreased hepatic lipid and cholesterol levels and attenuated liver steatosis in diet-induced and genetically obese mice [26].

PPAR-γ is a nuclear receptor central to glucose and lipid homeostasis [27] and is upregulated in the liver of obese patients with NAFLD, representing an additional reinforcing lipogenic mechanism to SREBP-1 c induction in the development of hepatic steatosis [28]. SIRT1 promotes fat mobilization in white adipocytes by repressing PPAR-γ.

Resveratrol has recently been described as a potent antiinflammatory compound in different organs and cell types [29]. Regarding steatohepatitis, it has been reported that resveratrol hampers the inflammatory response, suggesting that this antiinflammatory effect could be responsible for the ameliorating effect in terms of hepatic lipid accumulation [24]. In our study, hepatic steatosis was significantly decreased in mice treated with resveratrol. This effect was associated with a decreased inflammatory markers production.

Several studies have reported that TNF-α, IL-6, and NF-κB are increased in obesity, and this increase is correlated with numerous metabolic disorders [30,31]. In patients with obesity, adipose and liver tissues are characterized by high-intensity inflammation and increased secretion of cytokines [32]. TNF-α, IL-6, and NF-κB may be the most pernicious, because they alter adipose tissue function, influence adipogenesis, and are involved in the metabolic complications of obesity with NAFLD [33].

Recent works have demonstrated that the deletion of SIRT1 in hepatocytes results in increased local inflammation [34]. Other studies have reported that siRNA-mediated knockdown of SIRT1 in 3 T3-L1 adipocytes in vitro increases cytokine mRNA expression when cells are stimulated with TNF-α [35]. In vivo, overexpression of SIRT1 reduces hepatic expression of TNF-α and IL-6 after chronic high-fat feeding [36].

The antioxidant and/or antiinflammatory effects of resveratrol have been demonstrated to play a role in either controlling NF-κB activation or chromatin remodeling through modulation of histone deacetylase (as sirtuins) activity and subsequently inflammatory gene expression in lung epithelial cells [37]. Other studies support the scenario in which immune responses and the aging process can be enforced by the potentiation of NF-κB transactivation efficiency. Longevity factors, such as SIRT1 and its activators, might regulate the efficiency of the NF-κB signaling, the major outcome of which is inflammatory aging via proinflammatory responses [38].

Conclusion

In conclusion, the present study indicates that oral treatment with resveratrol offers a protective effect against the proinflammatory response profile in the liver and improves lipid metabolism in high-fat–fed mice, decreasing liver lipogenesis

markers. These effects were associated with upregulation of SIRT1.

Competing interests

The authors declare no conflict of interest.

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