Medical Laboratory Journal
Online ISSN: 2538-4449
Golestan University of Medical Sciences

Original Article

Effects of Resveratrol Supplementation and Exercise on Apoptosis, Lipid Profile, and Expression of *Farnesoid X Receptor, Liver X Receptor* and *Sirtuin 1* Genes in the Liver of Type 1 Diabetic Rats

Ali Nouri
(PhD Candidate) Department of Exercise Physiology, Faculty of Humanities, Sari Branch, Islamic Azad University, Sari, Iran

Parvin Farzanegi
(PhD) Department of Exercise Physiology, Faculty of Humanities, Sari Branch, Islamic Azad University, Sari, Iran,

Mohammad Ali Azarbayjani
(PhD) Department of Exercise Physiology, Islamic Azad University, Central Tehran

Corresponding author: Ali Nouri

Tel: +98 9111777261

Email: Noori.ali63@gmail.com

Address: Otana Gym, 5th Azar Avenue, Gorgan, Golestan Province, Iran

Received: 2021/12/15
Revised: 2022/02/03
Accepted: 2022/02/12

DOI: 10.29252/mlj.16.4.39

ABSTRACT

Background and objectives: Diabetes mellitus is the most common metabolic disorder in the world. Here, we evaluated effects of resveratrol supplementation alone and combined with exercise on blood glucose, insulin, lipid profile, apoptosis biomarkers, and expression of *farnesoid X receptor (Fxr)*, *liver X receptor (Lxr)*, and *sirtuin 1 (Sirt 1)* genes in the liver of type 1 diabetic rats.

Methods: Streptozotocin was used to induce type 1 diabetes in Wistar rats. The rats were randomly assigned into seven groups. After treatment with resveratrol alone or combined with exercise training, the animals were sacrificed and lipid profile and levels of blood glucose and insulin were measured. Hepatocyte apoptosis was assessed by measuring the level of Bax and Bcl2 proteins using enzyme-linked immunosorbent assay kits. Expression of *Fxr*, *Lxr*, and *Sirt1* was evaluated using real-time polymerase chain reaction. Comparison of the mean levels of all variables between different groups was performed using one-way analysis of variance, at statistical significance level of 0.05.

Results: Resveratrol significantly reduced the level of blood glucose and insulin compared with the control groups (p<0.001). It also significantly affected the lipid profile (p<0.001). Diabetes was significantly associated with decreased expression of *Sirt1*, *Lxr*, and *Fxr* and increased hepatocyte apoptosis. Resveratrol significantly improved the expression of all three genes (p<0.01). Overall, resveratrol supplementation combined with exercise was more effective than other methods.

Conclusion: The results indicate that that combination of resveratrol therapy with exercise could be beneficial for diabetic patients. However, more studies are needed to confirm this finding.

Keywords: Diabetes Mellitus, Resveratrol, Exercise, Apoptosis, Sirtuin 1, Liver X Receptors.

INTRODUCTION

Diabetes mellitus, which is characterized with insulin resistance and chronic hyperglycemia, is a leading cause of mortality worldwide (1). In addition to hyperglycemia, diabetes may be associated with hyperlipidemia, hypertension, ketoacidosis, cardiovascular disease, and nonalcoholic fatty liver disease (NAFLD) (2). In this regard, numerous studies have focused on molecular mechanisms of diabetes pathogenesis and its therapeutic strategies. Several risk factors such as obesity or overweight, impaired glucose tolerance, genetics, age, sedentary lifestyle, and ethnicity are thought to be responsible for development of diabetes (3).

Previous studies have demonstrated that diabetes mellitus can be associated with changes in expression of different genes, especially *farnesoid X receptor* (*Fxr*), *liver X receptor* (*Lxr*), and *sirtuin 1* (*Sirt1*) (4). The *Fxr* gene codes for a ligand-activated transcription factor that is highly expressed in the liver and regulates genes related to lipoprotein and lipid metabolism. Increased serum level of cholesterol and triglyceride was reported in *Fxr*-deficient mice (5). The *Sirt1* gene encodes for a NAD^+-dependent deacetylase that regulates a wide variety of metabolic pathways, such as glucose-lipid metabolism, insulin secretion, oxidative stress, inflammation, and apoptosis (4, 6). Recent studies have demonstrated that *Sirt1* plays an important role in glucose homeostasis and insulin sensitivity (4). The *Lxr* gene is considered as a sensor of cholesterol metabolism and lipid biosynthesis. Similar to *Fxr* and *Sirt1*, *Lxr* is involved in different cell-signaling pathways and regulates hepatic glucose production, inflammation, and lipogenesis (7).

Resveratrol (RES) is a natural antioxidant, which can be extracted from different plants such as grape and peanuts (8). Previous research reported protective effects of RES on the liver and cardiovascular system (9). Some studies reported its anti-apoptotic, anti-inflammatory, and anti-oxidative effects (10-12). More recently, a study has reported that RES improves liver function in rats with NAFLD by increasing the expression of hepatic *Sirt1*, *Fxr*, and *Lxr* (13). Therefore, RES can be considered as a therapeutic candidate for metabolic disorders, such as diabetes (14). Also, a recent study has shown that continuous and interval exercises can improve expression of *Sirt1*, *Fxr*, and *Lxr* genes in the liver of rats with NAFLD (13, 15).

Given the critical role of the *Sirt1*, *Fxr*, and *Lxr* genes in lipid and glucose metabolism, we assumed that RES supplementation alone or combined with interval and continuous exercises may exert beneficial effect on diabetic patients by improving *Sirt1*, *Fxr* and *Lxr* expression. This study was designed to evaluate effects of RES alone and combined with exercise on blood glucose and insulin levels, lipid profile, apoptosis biomarkers, and expression of *Fxr*, *Lxr* and *Sirt1* in the liver of diabetic rats.

MATERIALS AND METHODS

Animals and diabetes induction

Wistar rats (age range: 40-45 weeks) weighting 250-300 g were obtained from laboratory animal research center at Islamic Azad University of Sari (Sari, Iran). The animals were housed in individual cages in a controlled environment, with access to standard laboratory food and water ad libitum. For the induction of diabetes, 50 mg/kg of streptozotocin (ZellBio, Germany) were injected intravenously to 49 rats (16). Streptozotocin treatment induces type 1 diabetes by ablation of beta cells. Two days after the injection, blood samples were taken to determine glucose concentration, and a glucose level of >250 mg/dl along with polyuria confirmed induction of diabetes. Diabetic rats were then randomly divided into seven experimental groups based on treatment regimens (seven animals per group): patient, saline, RES, continuous training (MIT), interval training (HIT), MIT+RES, and HIT+RES. Animals in the RES groups received 25 mg/kg RES daily by intraperitoneal injection (13).

Training program

Before the intervention, animals in the exercise groups were adapted with a rodent treadmill for 5 days (at speed of 10 m/min and 0% inclination for 5 min/day) (17, 18). The interval and continuous exercise programs were done according to a previous study (13).

Samples collection and measurements

Two days after the final exercise training, the animals were anesthetized with ketamine (30-50 mg/kg) and xylazine (3-5 mg/kg). The liver

was removed and homogenized in phosphate buffer saline (pH 7.0) at 4 °C using a homogenizer (Hielscher, Germany). Next, the mixture was centrifuged at 12,000 rpm and 4 °C for 15 minutes (19). Supernatant was collected for Bax and Bcl2 measurement. Blood samples were collected from the abdominal aorta for measurement of blood insulin, glucose, and lipid profile. Blood insulin level was measured using the rat insulin enzyme-linked immunosorbent assay (ELISA) kit (ZellBio, Germany). Blood glucose, triglyceride, cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were measured using an autoanalyzer apparatus (Parspars Azmoon Co., Iran).

Bcl2 and Bax measurements

The amount of Bcl2 and Bax proteins in the liver of all animals were measured using commercial ELISA kits (ZellBio, Germany). The Bax ELISA kit had a sensitivity of 1.95 pg/ml and detection range of 7.8-500 pg/ml, at detection wavelength of 450 nm. The Bcl2 ELISA kit had a sensitivity of 7.8 pg/ml and detection range of 31.2-2000 pg/ml, at detection wavelength of 450 nm.

Real-time polymerase chain reaction (PCR)

For real-time PCR assay, total RNA was extracted from the homogenized liver tissues using the RNX-Plus kit (SinaClon, Iran). Next, cDNA was synthesized using the Revert Aid Reverse Transcriptase kit (Thermo science, Germany).

A Rotor Gene 6000 thermocycler (Corbett Research, Australia) and Real Q-PCR 29 Master Mix kit (Amplicon, Denmark) were utilized for amplifications in 40 cycles. Each reaction solution included 5 µl master mix and 100 nM of each primer. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as the reference gene.

The obtained mRNA levels were normalized relative to the amount of GAPDH mRNA. Relative expression of studied genes was calculated using the $2^{-\Delta Ct}$ method. Table 1 shows the sequences of the primers used in the real-time PCR assay.

Table 1- Sequences of the primers used in the real-time PCR assay.

Gene	Forward primer	Reverse primer
Fxr	5/-AGTTGGAAAGTTGGAGTG-3/	5/-GATTGTTGTATGGGGAGTA-3/
Lxr	5/-CTGATTCTCCGTGTCCTCTGTG-3/	5/-CACCCTACCCTTTGACTCTCT-3/
Sirt1	5/-GAGTTGTGTGTAGGTTAGGTGG-3/	5/-AAATATGAAGAGGTGTTGGTGG-3/
GAPDH	5/AGTTCAACGGCACAGTCAAGG-3/	5/-CATACTCAGCACCAGCATCACC-3/

Statistical analysis

Data were analyzed using SPSS software (version 19). All data are presented as means ± standard deviation (SD). Comparison of the mean of all variables between groups was performed using one-way analysis of variance (ANOVA) with post-hoc Tukey. A *p*-value of less than 0.05 was considered statistically significant.

RESULTS

The mean levels of blood glucose and insulin in each group are presented in figures 1 and 2. The mean concentrations of blood glucose and insulin in the patient and saline groups were significantly higher than in other groups ($p<0.0001$). In addition, RES supplementation alone or in combination with interval or continuous exercises significantly reduced the blood glucose and insulin levels compared with the patient and saline groups ($p<0.001$). Combined therapy with RES and exercise was more effective in reducing blood glucose and insulin levels.

Table 2- The lipid profile of rats in different groups

Groups	Triglyceride (mg/dl)	Cholesterol (mg/dl)	Low-density lipoprotein (mg/dl)	High-density lipoprotein (mg/dl)
Control	92.07±10.16^{c}	81.37±7.76^{d}	23.03±6.54^{d}	42.03±5.13^{a}
Patient	208.67±17.48^{a}	172.14±13.86^{a}	66.30±7.99^{a}	30.96±5.96^{c}
Saline	206.09±20.26^{a}	171.66±16.72^{a}	65.91±14.14^{a}	31.83±6.33^{c}
Resveratrol	135.16±16.41^{b}	128.53±10.11^{b}	42.01±4.75^{b}	36.11±5.27^{b}
Continuous exercise	131.13±15.21^{b}	112.83±14.07^{bc}	34.49±7.18^{bc}	39.01±5.04^{ab}
Interval exercise	128.01±13.61^{b}	121.53±9.01^{bc}	38.34±8.21^{bc}	37.23±4.15^{ab}
Continuous exercise + resveratrol	117.97±18.89^{b}	108.21±10.64^{bc}	31.96±6.36^{bc}	40.81±5.83^{ab}
Interval exercise + resveratrol	124.50±13.82^{b}	119.80±24.97^{c}	35.50±6.86^{c}	38.61±4.43^{ab}
p-value	<0.0001	<0.0001	<0.0001	0.002

There was no significant difference in the mean level of variables between the groups with similar symbols (a-d). The mean level of variables was in this order: a>ab>b>bc>c>d.

The control group had significantly lower blood glucose and insulin levels compared with the other groups (p<0.01).

Table 2 shows the lipid profile of rats in all study groups. The patient and saline groups had significantly higher triglyceride, cholesterol, and LDL levels compared with other groups (p<0.001), while the mean level of HDL in the patients and saline groups was significantly lower than that in other groups (p<0.0001).

Moreover, RES and exercise training significantly increased HDL and significantly reduced triglyceride cholesterol, and LDL levels in diabetic rats. This effect was more significant in rats, which had received combined therapy with RES and exercise training (Table 2).

The mean level of Bax and Bcl2 expression in hepatic tissue, as well as Bax/Bcl2 ratio in each group are presented in table 3. The mean level of Bax protein in the hepatic tissue of rats in the patient and saline groups was significantly higher than that in other groups (p<0.001). However, the mean level of Bcl2 protein in the hepatic tissue of rats in the patient and saline groups was dramatically lower compared with other groups (p<0.0001). Additionally, the Bax/Bcl2 ratio in the patient (17.12±2.67) and saline (18.98±4.23) groups was significantly higher than that in other groups. Also, RES supplementation alone or in combination with interval or continuous training significantly decreased Bax level and Bax/Bcl2 ratio in the liver of diabetic rats (p<0.001). In contrast, Bcl2 level was significantly increased after combined therapy with RES and interval or continuous training (Table 3).

A significant difference was found in the expression pattern of *Fxr*, *Lxr*, and *Sirt1* between the study groups (Figures 3, 4, and 5). The expression of *Fxr* was significantly higher in the control and HIT+RES groups compared with other groups (p<0.0001). However, the expression of this gene in the sham and saline groups was significantly lower than in other groups (p<0.001). The *Fxr* mRNA expression in the HIT and MIT groups was higher than in the saline groups (Figure 3) (p<0.01).

The mRNA expression of *Lxr* was significantly elevated in the control, HIT+RES, and MIT+RES groups compared with other groups (p<0.0001). The mRNA expression of *Lxr* in the RES and exercise training groups was higher than that in the saline groups (p<0.001). The expression of *Sirt1* in the control and HIT+RES groups was significantly higher than that in the saline, MIT, HIT, and RES groups (p<0.001). Both exercises (MIT and HIT) significantly increased the expression of *Sirt1* compared with the saline and RES groups (p<0.001). Remarkably, the increase in mRNA levels of *Fxr*, *Lxr*, and *Sirt1* was more significant in the MIT+RES and HIT+RES groups than in the supplement-only or exercise-only groups (p<0.001) (Figure 4).

Table 3- Comparison of the mean level of Bax and Bcl2 proteins between different groups

Groups	Bax (ng/ml)	Bcl2 (ng/ml)	Bax/Bcl2
Control	8.84±0.74^{d}	2.56±0.43^{a}	3.55±0.7^{d}
Patient	19.33±2.35^{a}	1.14±0.11^{e}	17.12±2.67^{a}
Saline	20.44±3.21^{a}	1.10±0.17^{e}	18.98±4.23^{a}
Resveratrol	12.90±1.95^{b}	1.49±0.19^{cd}	8.72±1.57^{b}
Continuous exercise	10.91±1.68^{bc}	1.95±0.18^{cd}	5.61±0.84^{c}
Interval exercise	12.54±1.93^{b}	1.69±0.26^{cd}	7.60±1.80^{bc}
Continuous exercise + resveratrol	9.81±1.14^{cd}	2.12±0.27^{b}	4.68±0.6^{cd}
Interval exercise + resveratrol	12.30±2.14^{c}	1.88±0.25^{c}	6.58±1.13^{c}
p-value	<0.0001	<0.0001	<0.0001

There was no significant difference in the mean level of Bax and Bcl2 between the groups with similar symbols (a-e). The mean level of Bax and Bcl2 was in this order: a>b>bc>c>cd>d>e.

DISCUSSION

In this study, for the first time, the effect of RES supplementation alone and in combination with exercises was evaluated on *Sirt1*, *Lxr* and *Fxr* expression, blood glucose level, insulin level, lipid profile, and apoptosis markers in hepatic tissue of diabetic rats. Our findings revealed decreased expression of *Fxr*, *Lxr*, and *Sirt1* in the liver of diabetic rats. Many studies demonstrated that diabetes mellitus is associated with decreased expression of *Fxr*, *Lxr*, and *Sirt1* (4, 7, 20, 21). For example, Zhang et al. reported decreased

Expression of *Fxr* either at RNA or protein levels in the liver of diabetic rats (21). Although numerous studies reported downregulation of *Fxr*, *Lxr*, and *Sirt1* genes in diabetes mellitus, the exact role of these genes in this disease remains unclear.

These genes play a key regulatory role in glucose homeostasis as well as in lipid and lipoprotein metabolism (22).

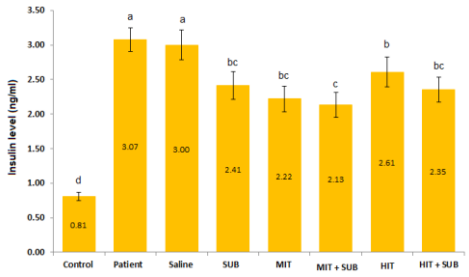

Figure 1- Comparison of the mean level of insulin between the study groups. There was no significant difference in the insulin levels between the groups with similar symbols (a-d). The mean level of insulin was in order a>b>bc>c>d. RES: Resveratrol; MIT: Continuous exercise; HIT: Interval exercise; MIT+RES: Resveratrol+Continuous exercise; HIT+RES: Interval exercise+Resveratrol.

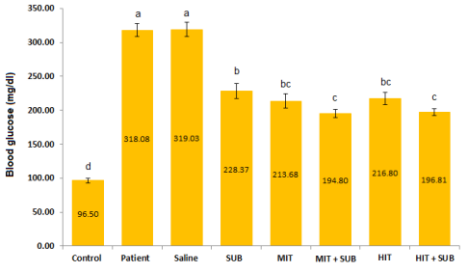

Figure 2- Comparison of the mean level of blood glucose between the study groups. There was no significant difference in the blood glucose level between the groups with similar symbols (a-d). The mean level of blood glucose was in this order: a>b>bc>c>d. RES: Resveratrol; MIT: Continuous exercise; HIT: Interval exercise; MIT+RES: Resveratrol+Continuous exercise; HIT+RES: Interval exercise+resveratrol.

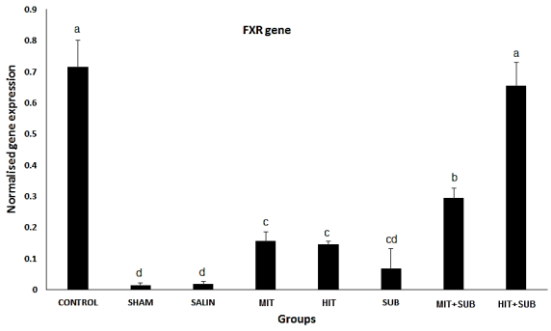

Figure 3- Comparison of the mean Fxr mRNA levels between the study groups. Gene expression was detected by real-time PCR. There was no significant difference in the mean Fxr mRNA levels between the groups with similar symbols (a-d). The mean Fxr mRNA level was in this order: a>b>c>cd>d. RES: Resveratrol; MIT: continuous exercise; HIT: Interval exercise; MIT+RES: Continuous exercise+Resveratrol; HIT+RES: Interval .exercise+Resveratrol

Therefore, dysregulation of these genes may lead to insulin resistance and alterations in the glucose, lipid, and bile acid metabolism in diabetic patients (20).

In this study, we found increased levels of blood glucose, insulin, LDL, triglyceride, and cholesterol in diabetic rats. Furthermore, our results showed that diabetes is associated with increased hepatocyte apoptosis. Nascimento et al. demonstrated that *Sirt1* suppression is associated with inflammation and apoptosis in the liver of rats with NAFLD (23).Therefore, reduced expression of *Fxr*, *Lxr*, and *Sirt1* in the liver of diabetic rats may be the main contributor to these abnormalities. Previous studies also indicate that *Fxr*, *Lxr*, and *Sirt1* genes agonists may serve as useful factors for the treatment of hyperglycemia, hyperlipidemia, and apoptosis in the liver of diabetic patients (21).

We found that the expression of *Sirt1*, *Lxr*, and *Fxr* was significantly increased in diabetic rats after treatment with RES. This effect was associated with a significant decrease in the blood glucose, insulin, LDL, triglyceride, and cholesterol levels. Moreover, we found that RES supplementation significantly decreased Bax/Bcl2 ratio, which suggest the critical role of this natural antioxidant in prevention of hepatic cells apoptosis. Similarly, several studies have shown that RES supplementation can improve the expression of *Fxr*, *Lxr*, and *Sirt1* in different pathologies (24, 25). For example, Sevov et al. reported that RES induces *Lxr* expression in human monocyte-derived macrophages (26). Chen et al. reported that RES induces Sirt1-dependent apoptosis in 3T3-L1 preadipocytes by activating *AMP-activated protein kinase* (AMPK), suppressing AkT strain transforming activity, and inducing *survivin* expression (27). More recently, Hajighasem et al. have reported that RES supplementation increases the expression of *Fxr*, *Lxr*, and *Sirt1* in the liver of rats with NAFLD and decreases hepatocyte apoptosis (13). Resveratrol reduces fat accumulation, induces apoptosis in a dose-dependent manner, and increases lipolysis in bovine muscle adipocytes.

The ability of RES to increase antioxidant defense and inhibit oxidative stress-induced damage may be due to the presence of flavonoids in the extract. In addition, presence of proanthocyanidin compounds in RES might also contribute to the antioxidant properties (28). In this research, we also observed that RES supplementation combined with exercise was more effective. Compared with RES supplementation alone, the combined therapy significantly improved the expression of *Sirt1*, *Lxr*, and *Fxr* genes and decreased blood glucose and insulin levels as well as hyperlipidemia and hepatocyte apoptosis. Several studies reported the positive effects of combined therapy with RES and different exercises on the liver.

For example, Faghihzadeh et al., found that combined use of RES and exercise were associated with a significant improvement in liver disease (29). Similarly, Tung et al. reported that combined therapy with RES and exercise increased the activity of antioxidant defense systems and decreased hepatic cells apoptosis (30). Also, Liao et al. reported that exercise training, RES supplementation, or their combination can significantly increase *p-AMPK* and *Sirt1* expression and decrease p53 acetyl expression and Bax/Bcl-2 ratio in older mice (28).

The small number of rats in the study groups was a limitation of the present study.

Further studies should be carried out to evaluate expression of these genes at the protein level. Since diabetes is significantly associated with oxidative stress and antioxidants depletion, evaluation of expression of antioxidant enzymes such as glutathione peroxidase, catalase, superoxide dismutase, as well as other oxidative stress biomarkers is valuable.

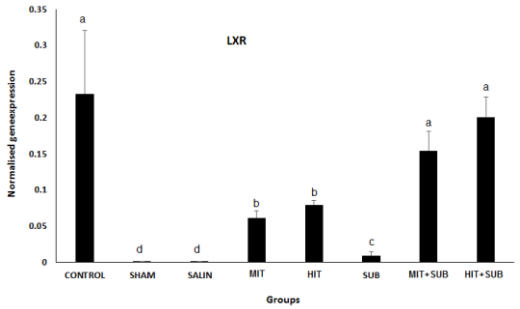

Figure 4- Comparison of the mean Lxr mRNA levels between the study groups. Gene expression was detected by real-time PCR. There was no significant difference in the mean Lxr mRNA levels between the groups with similar symbols (a-d). The mean Lxr mRNA level was in this order: a>b>c>d. RES: Resveratrol; MIT: continuous exercise; HIT: Interval exercise; MIT+RES: Continuous exercise+Resveratrol; HIT+RES: Interval exercise+Resveratrol.

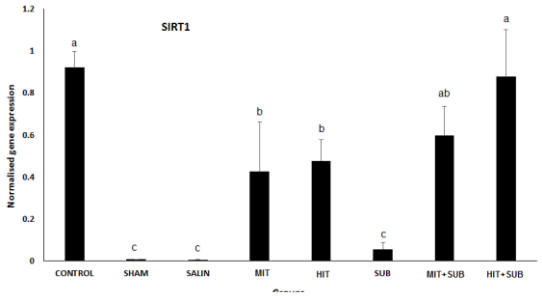

Figure 5- Comparison of the mean Sirt1 mRNA levels between the study groups. Gene expression was detected by real-time PCR. There was no significant difference in the mean Sirt1 mRNA levels between the groups with similar symbols (a-c). The mean Sirt1 mRNA level was in this order: a>ab>b>c. RES: Resveratrol; MIT: continuous exercise; HIT: Interval exercise; MIT+RES: Continuous

CONCLUSION

Our results revealed that diabetes mellitus is associated with decreased expression of *Sirt1*, *Lxr*, and *Fxr*, hyperlipidemia, and hepatocyte apoptosis. Moreover, combination of RES supplementation with exercise could be beneficial for diabetic patients. However, more studies are needed to confirm these findings.

ACKNOWLEDGMENTS

We would like to thank the staffs of the exercise physiology centers of Islamic Azad University, Sari, Iran.

DECLARATIONS

FUNDING

This study was supported by a grant provided by the Exercise Physiology Department of Islamic Azad University, Sari Branch, Sari, Iran.

Ethics approvals and consent to participate

This experiment was approved by the ethics committee of the Islamic Azad University, Sari Branch (IR.IAU.SARI.REC.1397.8).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding publication of this article

REFERENCES

1. Whiting DR, Guariguata L, Weil C, Shaw J. *IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030.* Diabetes Res Clin Pract. 2011; 94(3): 311-21. [DOI:10.1016/j.diabres.2011.10.029] [PubMed]

2. Barbot M, Ceccato F, Scaroni C. *Diabetes Mellitus Secondary to Cushing's Disease. Front Endocrinol (Lausanne).* 2018;9:284. [View at Publisher] [DOI:10.3389/fendo.2018.00284] [PubMed] [Google Scholar]

3. Fletcher B, Gulanick M, Lamendola C. *Risk factors for type 2 diabetes mellitus.* J Cardiovasc Nurs. 2002;16:17-23. [DOI:10.1097/00005082-200201000-00003] [PubMed] [Google Scholar]

4. Kitada M, Koya D. *SIRT1 in Type 2 Diabetes: Mechanisms and Therapeutic Potential*. Diabetes Metab J. 2013;37:315-25. [View at Publisher] [DOI:10.4093/dmj.2013.37.5.315] [PubMed] [Google Scholar]

5. Kong B, Luyendyk P, Tawfik O, Guo GL. *Farnesoid X Receptor Deficiency Induces Nonalcoholic Steatohepatitis in Low-Density Lipoprotein Receptor-Knockout Mice Fed a High-Fat Diet.* The Journal of pharmacology and experimental therapeutics. 2009; 328: 116-22. [View at Publisher] [DOI:10.1124/jpet.108.144600] [PubMed] [Google Scholar]

6. Colak Y, Ozturk O, Senates E, Tuncer I, Yorulmaz E, Adali G, et al. *SIRT1 as a potential therapeutic target for treatment of nonalcoholic fatty liver disease.* Medical science monitor : international medical journal of experimental and clinical research. 2011; 17(5): HY5-9. [DOI:10.12659/MSM.881749] [PubMed] [Google Scholar]

7. Steffensen KR, Gustafsson JA. *Putative Metabolic Effects of the Liver X Receptor (LXR).* Diabetes. 2004;53:S36-S42. [View at Publisher] [DOI:10.2337/diabetes.53.2007.S36] [PubMed] [Google Scholar]

8. Baur JA, Sinclair DA. *Therapeutic potential of resveratrol: the in vivo evidence. Nature reviews Drug discovery.* 2006;5(6):493-506. [View at Publisher] [DOI:10.1038/nrd2060] [PubMed] [Google Scholar]

9. Bujanda L, Hijona E, Larzabal M, Beraza M, Aldazabal P, Garcia-Urkia N, et al. *Resveratrol inhibits nonalcoholic fatty liver disease in rats*. BMC gastroenterology. 2008;8:40. [View at Publisher] [DOI:10.1186/1471-230X-8-40] [PubMed] [Google Scholar

10. Singh CK, George J, Ahmad N. *Resveratrol-based combinatorial strategies for cancer management. Annals of the New York Academy of Sciences*. 2013;1290:113-21. [View at Publisher] [DOI:10.1111/nyas.12160] [PubMed] [Google Scholar]

11. Lanzilli G, Cottarelli A, Nicotera G, Guida S, Ravagnan G, Fuggetta MP. *Anti-inflammatory effect of resveratrol and polydatin by in vitro IL-17 modulation.* Inflammation. 2012;35(1):240-8. [View at Publisher] [DOI:10.1007/s10753-011-9310-z] [PubMed] [Google Scholar]

12. Abba Y, Hassim H, Hamzah H, Noordin MM. *Antiviral Activity of Resveratrol against Human and Animal Viruses.* Advances in virology. 2015;2015:184241. [View at Publisher] [DOI:10.1155/2015/184241] [PubMed] [Google Scholar]

13. Hajighasem A, Farzanegi P, Mazaheri Z. *Effects of combined therapy with resveratrol, continuous and interval exercises on apoptosis, oxidative stress, and inflammatory biomarkers in the liver of old rats with non-alcoholic fatty liver disease.* Arch Physiol Biochem. 2019; 125(2): 142-149. [View at Publisher] [DOI:10.1080/13813455.2018.1441872] [PubMed] [Google Scholar]

14. Chicco AJ, Hydock DS, Schneider CM, Hayward R. *Low-intensity exercise training during doxorubicin treatment protects against cardiotoxicity*. Journal of applied physiology. 2006; 100(2): 519-27. [View at Publisher] [DOI:10.1152/japplphysiol.00148.2005] [PubMed] [Google Scholar]

15. Park SY, Kwak YS. *Impact of aerobic and anaerobic exercise training on oxidative stress and antioxidant defense in athletes.* Journal of exercise rehabilitation. 2016; 12(2): 113-7. [DOI:10.12965/jer.1632598.299] [PubMed] [Google Scholar]

16. Akbarzadeh A, Norouzian D, Mehrabi MR, Jamshidi SH, Farhangi A, Allah Verdi A, et al. *Induction of diabetes by Streptozotocin in rats.* Indian J Clin Biochem. 2007; 22: 60-4. [View at Publisher] [DOI:10.1007/BF02913315] [PubMed] [Google Scholar]

17. Batacan RB, Jr., Duncan MJ, Dalbo VJ, Connolly KJ, Fenning AS. *Light-intensity and high-intensity interval training improve cardiometabolic health in rats*. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme. 2016;41(9):945-52. [DOI:10.1139/apnm-2016-0037] [PubMed] [Google Scholar]

18. Freitas DA, Rocha-Vieira E, Soares BA, Nonato LF, Fonseca SR, Martins JB, et al. *High intensity interval training modulates hippocampal oxidative stress, BDNF and inflammatory mediators in rats.* Physiology & behavior. 2017;184:6-11. [View at Publisher] [DOI:10.1016/j.physbeh.2017.10.027] [PubMed] [Google Scholar]

19. Ma Z, Chu L, Liu H, Wang W, Li J, Yao W, et al. *Beneficial effects of paeoniflorin on non-alcoholic fatty liver disease induced by high-fat diet in rats.* Scientific reports. 2017;7:44819. [View at Publisher] [DOI:10.1038/srep44819] [PubMed] [Google Scholar]

20. Duran-Sandoval D, Mautino G, Martin G, Percevault F, Barbier O, Fruchart JC, et al. *Glucose regulates the expression of the farnesoid X receptor in liver*. Diabetes. 2004; 53: 890-8. [View at Publisher] [DOI:10.2337/diabetes.53.4.890] [PubMed] [Google Scholar]

21. Zhang HM, Wang X, Wu ZH, Liu HL, Chen W, Zhang ZZ, et al. *Beneficial effect of farnesoid X receptor activation on metabolism in a diabetic rat model.* Molecular medicine reports. 2016; 13: 2135-42. [DOI:10.3892/mmr.2016.4761] [PubMed] [Google Scholar]

22. Ma K, Saha PK, Chan L, Moore DD. *Farnesoid X receptor is essential for normal glucose homeostasis*. The Journal of clinical investigation. 2006;116:1102-9. [DOI:10.1172/JCI25604] [PubMed] [Google Scholar]

23. Nascimento AF, Ip BC, Luvizotto RA, Seitz HK, Wang XD. *Aggravation of nonalcoholic steatohepatitis by moderate alcohol consumption is associated with decreased SIRT1 activity in rats*. Hepatobiliary surgery and nutrition. 2013;2(5):252-9. [PubMed] [Google Scholar]

24. Wang XH, Zhu L, Hong X, Wang YT, Wang F, Bao JP, et al. *Resveratrol attenuated TNF-alpha-induced MMP-3 expression in human nucleus pulposus cells by activating autophagy via AMPK/SIRT1 signaling pathway.* Experimental biology and medicine. 2016;241(8):848-53. [View at Publisher] [DOI:10.1177/1535370216637940] [PubMed] [Google Scholar]

25. Goh KP, Lee HY, Lau DP, Supaat W, Chan YH, Koh AF. *Effects of resveratrol in patients with type 2 diabetes mellitus on skeletal muscle SIRT1 expression and energy expenditure.* International journal of sport nutrition and exercise metabolism. 2014;24(1):2-13. [DOI:10.1123/ijsnem.2013-0045] [PubMed] [Google Scholar]

26. Sevov M, Elfineh L, Cavelier LB. *Resveratrol regulates the expression of LXR-alpha in human macrophages.* Biochemical and biophysical research communications. 2006;348(3):1047-54. [View at Publisher] [DOI:10.1016/j.bbrc.2006.07.155] [PubMed] [Google Scholar]

27. Chen S, Xiao X, Feng X, Li W, Zhou N, Zheng L, et al. *Resveratrol induces Sirt1-dependent apoptosis in 3T3-L1 preadipocytes by activating AMPK and suppressing AKT activity and survivin expression.* J Nutr Biochem. 2012; 23(9):1100-1112. [View at Publisher] [DOI:10.1016/j.jnutbio.2011.06.003] [PubMed] [Google Scholar]

28. Liao ZY, Chen JL, Xiao MH, Sun Y, Zhao YX, Pu D, et al. *The effect of exercise, resveratrol or their combination on Sarcopenia in aged rats via regulation of AMPK/Sirt1 pathway.* Experimental Gerontology. Experimental Gerontology. 2017; 98; 177-183. [View at Publisher] [DOI:10.1016/j.exger.2017.08.032] [PubMed] [Google Scholar]

29. Faghihzadeh F, Adibi P, Rafiei R, Hekmatdoost A. *Resveratrol supplementation improves inflammatory biomarkers in patients with nonalcoholic fatty liver disease.* Nutrition research. 2014;34(10):837-43. [View at Publisher] [DOI:10.1016/j.nutres.2014.09.005] [PubMed] [Google Scholar]

30. Tung BT, Rodriguez-Bies E, Thanh HN, Le-Thi-Thu H, Navas P, Sanchez VM, et al. *Organ and tissue-dependent effect of resveratrol and exercise on antioxidant defenses of old mice.* Aging clinical and experimental research. 2015;27(6):775-83. [View at Publisher] [DOI:10.1007/s40520-015-0366-8] [PubMed] [Google Scholar]

How to Cite:
Nouri A, Farzanegi P, Azarbayjani MA [Effects of Resveratrol Supplementation and Exercise on Apoptosis, Lipid Profile, and Expression of *Farnesoid X Receptor*, *Liver X Receptor* and *Sirtuin 1* Genes in the Liver of Type 1 Diabetic Rats]. mljgoums. 2022; 16(4): 39-46 DOI: 10.29252/mlj.16.4.39