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Hypolipidemic and Hepatoprotective Effects of Myricitrin and Solid Lipid Nanoparticle-containing Myricitrin on the Male Mouse Model with Type 2 Diabetes Induced by Streptozotocin-Nicotinamide

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Abstract

Background: Type 2 diabetes mellitus (T2DM) has several complications such as hyperlipidemia and hepatotoxicity. Myricitrin has an antidiabetic action along with low bioavailability. So, the aim of the present study was to investigate hypolipidemic and hepatoprotective effects of myricitrin and solid lipid nanoparticle (SLN) containing myricitrin on the T2DM mouse model induced by Streptozotocin-nicotinamide (STZ-NA).

Methods: In this experimental study, 90 Naval Medical Research Institute (NMRI) adult male mice were divided into 9 groups (n=10 per group): control, vehicle, diabetic, diabetic + myricitrin, or SLN containing myricitrin 1, 3, and 10 mg/kg groups. The cold homogenization method was used to prepare SLN containing myricitrin. The diabetic model was induced by one injection of STZ-NA (65-120 mg/kg) with a 15-min interval. Animals' treatment was done for 4 weeks. At the end of the experiment, plasma samples were taken for experimental assessments.

Results: Plasma level of triglyceride (TG), low-density lipoprotein (LDL-C), very-low-density lipoprotein (VLDL), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) increased and high-density lipoprotein cholesterol (HDL-C) decreased in diabetic mice compared to the control group ($P<0.05$). Administration of myricitrin or SLN containing myricitrin decreased plasma levels of TG, LDL-C, VLDL, AST, and ALT and increased HDL-C in the treated diabetic groups compared to the untreated groups ($P<0.05$).

Conclusion: According to the results, myricitrin and SLN containing myricitrin showed hypolipidemic and hepatoprotective effects in T2DM mice. Also, SLN containing myricitrin was more potent than myricitrin especially in a low dose of administration.

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Introduction

Type 2 diabetes mellitus (T2DM) is a lifelong progressive chronic disease characterized by hyperglycemia along with hyperinsulinemia. This disease showed an increase over the past 20 years and it is estimated that there are 451 million people with diabetes between 18-99 years old worldwide in 2017 (1,2). Diabetes has several complications such as hyperlipidemia and hepatotoxicity. Dyslipidemia occurs in two-thirds of patients with T2DM and its prevalence is about 72-85%. This disorder is associated with hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C), and increased plasma levels of low-density lipoprotein cholesterol (LDL-C), as well as the dramatic rise of atherosclerosis (3). Liver enzymes are the variables that demonstrate the incidence, development, and prognosis of hepatic disease, health, and liver metabolic status. However, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increase during T2DM but, alkaline phosphatase (ALP) is not specific of T2DM and it is a factor for liver disease, exclusively nonalcoholic fatty liver disease (4).

Flavonoids belongs to the polyphenols that act as protective agents against cardiovascular and neurodegenerative diseases, diabetes, and cancer (5). Myricitrin, a flavonoid glycoside compound of Myrica cerifera, Myrica esculenta, and Ampelopsis grossedentata, has revealed many pharmacological actions, such as anti-diabetic, anti-nociceptive, anti-inflammatory, and anti-oxidative actions. It was demonstrated that this compound decreased cyclooxygenase-2 (COX-2) and tumor necrosis factor (TNF-α) in the liver of carbon tetrachloride-induced hepatotoxicity mice, the vascular wall thickness of the aortic arch, oxidized low-density lipoprotein (OxLDL) in endothelial cell, H9c2 cell apoptosis induced by high levels of glucose, and exhibits anti-atherogenic effects (6,7). The aqueous extract of *Chrysobalanus icaco* L. can prevent fat storage or increase fat utilization along with maintaining glucose homeostasis and insulin sensitivity. It was shown that these effects could be related to the polyphenol content of *Chrysobalanus icaco* L. such as myricitrin which can scavenge free radicals and mediate antioxidant activity (8). Moreover, *Polygonum aviculare* L. extract contains myricitrin which can inhibit hepatic enzymes increasing in the high-fat diet-fed mice (5). The bioavailability and biotransformation of flavonoids are the main limiting variables for biological activities in humans. So, it is essential to focus on the absorption and pharmacokinetics of these components (5). Solid lipid nanoparticles (SLN) is an alternative carrier system which has several advantages such as long-term stability, low danger of acute and chronic toxicity, more control on the release kinetics, more bioavailability of entrapped bioactive, and high dosage of functional compound (9). Streptozotocin-nicotinamide (STZ-NA)-induced diabetes is an acceptable model of non-obese T2DM in many types of research and used for testing the beneficial effects of various chemical and natural compounds during the treatment of diabetes. This model of diabetes is suitable for studies on diabetic complications including hyperlipidemia and hepatic injury (10,11).

So, according to the previous study about negative effects of T2DM on lipid variables and hepatic enzymes as liver health status, and the probable ameliorating effect of myricitrin as an antioxidant on these factors, and there is no study on the effects of this compound on the liver and hyperlipidemia during non-obese T2DM condition, and according to the low bioavailability of flavonoid glycoside, the present study was conducted to investigate the hypolipidemic and

hepatoprotective effects of myricitrin and SLN containing myricitrin on the mouse model with STZ-NA-induced T2DM.

Materials and Methods

Preparation of SLN

Solid lipid nanoparticle (SLN) containing myricitrin (purity 98%) (AvaChem Scientific, USA) was prepared by the cold homogenization method. Briefly, oleic acid was added to compritol up to 65°C. Then, a mixture of Tween 80 and Span 20 (1:1) and myricitrin was added to the above combination. Afterwards, this mixture was sonicated at 37°C for two minutes. Finally, a mixture of water-propylene glycol (4:1) at 4°C was added to the above-mentioned combination until the volume of 50 mL was achieved while it was homogenized by a high-speed homogenizer (IKA® T25 digital ULTRA-TURRAX®, Germany) for 20 minutes (12).

Experimental design

In this experimental study, 90 Naval Medical Research Institute (NMRI) adult male mice (3-month-old) weighing 25-30 g were obtained from the animal facility of Ahvaz Jundishapur University of Medical Sciences (AJUMS). The animals were treated according to the principles and guidelines on the animal care of AJUMS as reviewed by the Ethics Committee of AJUMS (Ethical code: IR.AJUMS.REC.1395.136). They were kept at a 23 ± 4°C temperature with a 12-hour light/12-hour dark cycle. They had access to tap water and commercial chow ad libitum.

After one week of animal's acclimatization, in order to induce T2DM, a single dose of NA (120 mg/kg) dissolved in normal saline (Sigma-Aldrich, USA) was injected through intraperitoneal injection. Then, after a 15-minute interval, STZ (65 mg/kg) (Solar Bio, South Korea) dissolved in citrate buffer (pH 4.5) was injected through intraperitoneal injection. Diabetes induction was confirmed by assaying blood glucose levels more than 200 mg/dL at 3 days after the STZ-NA injection (13). Myricitrin, SLNs containing myricitrin, and vehicle were orally gavaged for 4 weeks in the treatment groups. So, animals were divided into 9 groups (n=10 per group): control, vehicle (injected one dose of STZ and NA solvent and gavaged Tween 80 (3%) + normal saline (97%) as myricitrin and its SLN solvent) (14), diabetes, diabetes + myricitrin 1, 3, and 10 mg/kg, diabetes + SLN containing myricitrin 1, 3, and 10 mg/kg groups (15).

Six hours after the last treatment, the mice fasted for 12 hours were anesthetized by ketamine/xylazine (70 mg/kg/10 mg/kg) (Alfasan, Netherlands), the blood samples were collected by cardiac puncture, and plasma samples were obtained after centrifuging at 3500 ×g for 20 minutes. All plasma samples were kept at -80°C until experimental assessments.

Lipid profile and hepatic enzyme measurement

Plasma levels of total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were measured by commercial kits (Pars Azmoon, Iran) and auto-analyzer device. The concentration of very low-density lipoprotein (VLDL) was calculated by TG/5 (16).

Statistical analysis

The results were statistically analyzed by SPSS software (version 16) using one-way analysis of variance (ANOVA), followed by the post hoc the least significant difference (LSD) tests. Data are represented as mean ± standard error (SE) and differences were considered statistically significant at $P<0.05$.

Results

Effects of myricitrin and SLN containing myricitrin on lipid profile

The results of the lipid profile measurement showed that the plasma level of TG increased in diabetes (P<0.001) and diabetes + myricitrin 1 mg/kg (P<0.05) groups compared to the control group. This variable decreased in the vehicle and all treated groups compared to diabetes group (P<0.001, Figure 1). Plasma cholesterol levels increased in diabetes + myricitrin 1, 3, and 10 mg/kg groups compared to the control group (P<0.05). Also, this parameter showed a significant increase in diabetes + myricitrin 1 (P<0.01), 3, and 10 mg/kg (P<0.05) groups compared to diabetes group (Figure 2). The level of HDL-C decreased in the diabetes group compared to the control group (P<0.05). This variable increased in diabetes + myricitrin 1, 3 (P<0.01), and 10 mg/kg (P<0.05), and diabetes + SLN containing myricitrin 1, 3, and 10 mg/kg (P<0.05) groups compared to the control group. Also, the plasma level of HDL-C increased in all treated groups compared to diabetes group (P<0.001, Figure 3). Plasma levels of LDL-C increased in diabetes group compared to the control group (P<0.001). This factor decreased in the vehicle and other treated groups compared to diabetes group (P<0.001, Figure 4). The measurements of VLDL showed a significant increase in diabetes (P<0.001) and diabetes + myricitrin 1 mg/kg (P<0.05) groups compared to the control group. This variable decreased in the vehicle and all treated groups compared to diabetes group (P<0.001, Figure 5).

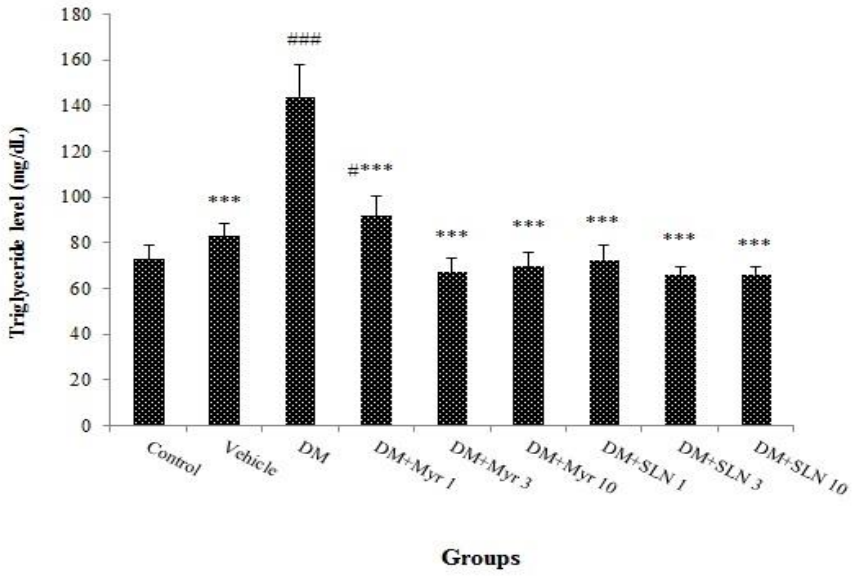

Figure 1. Effects of myricitrin and SLN containing myricitrin on the triglyceride level. Data are presented as mean ± SEM; n=10; #P<0.05 and ###P<0.001 compared to the control group, ***P<0.001 compared to the diabetic group. DM: Diabetes mellitus, Myr: Myricitrin, SLN: Solid lipid nanoparticle (One-way analysis of variance (ANOVA), followed by the post hoc least significant difference (LSD) tests).

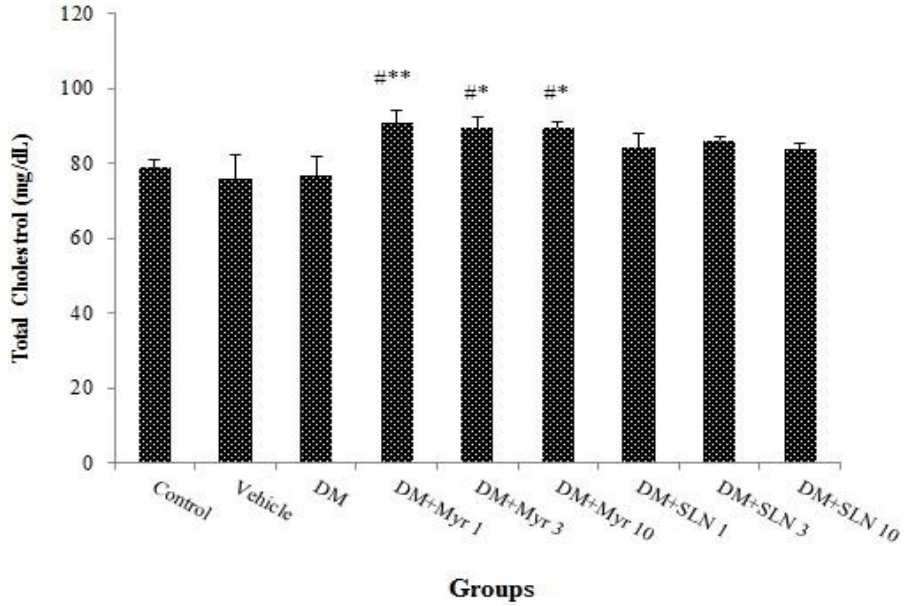

Figure 2. Effects of myricitirn and SLN containing myricitrin on the total cholesterol level. Data are presented as mean ± SEM; n=10; #P<0.05 compared to the control group, *P<0.05 and **P<0.01 compared to the diabetic group. DM: Diabetes mellitus, Myr: Myricitrin, SLN: Solid lipid nanoparticle (One-way analysis of variance (ANOVA), followed by the post hoc least significant difference (LSD) tests).

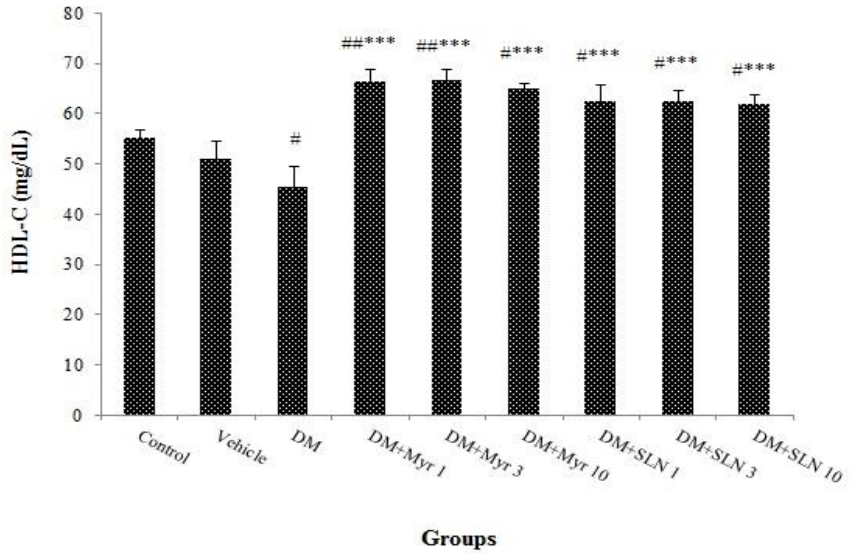

Figure 3. Effects of myricitirn and SLN containing myricitrin on the HDL-C level. Data are presented as mean ± SEM; n=10; #P<0.05 and ##P<0.01 compared to the control group, ***P<0.001 compared to the diabetic group. DM: Diabetes mellitus, Myr: Myricitrin, SLN: Solid lipid nanoparticle (One-way analysis of variance (ANOVA), followed by the post hoc least significant difference (LSD) tests).

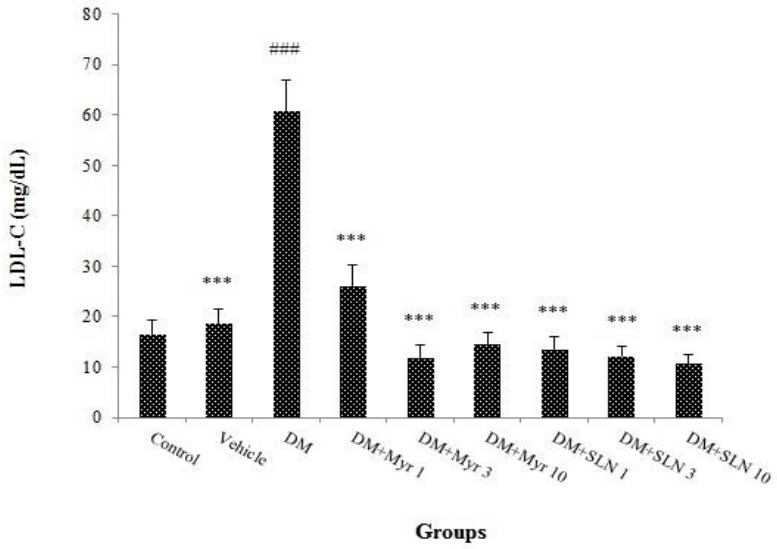

Figure 4. Effects of myricitirn and SLN containing myricitrin on the LDL-C level. Data are presented as mean ± SEM; n=10; ###P<0.001 compared to the control group, ***P<0.001 compared to the diabetic group. DM: Diabetes mellitus, Myr: Myricitrin, SLN: Solid lipid nanoparticle (One-way analysis of variance (ANOVA), followed by the post hoc least significant difference (LSD) tests).

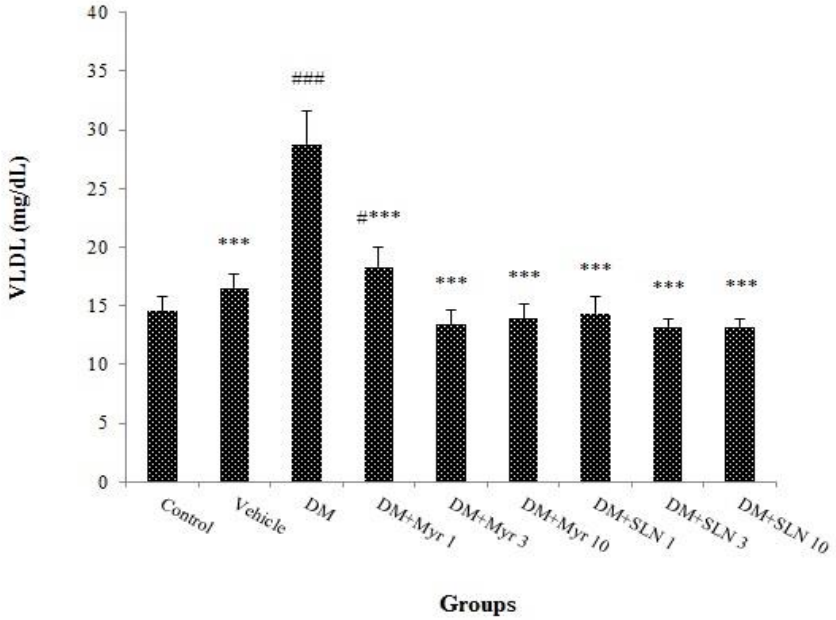

Figure 5. Effects of myricitirn and SLN containing myricitrin on the VLDL level. Data are presented as mean ± SEM; n=10; #P<0.05 and ###P<0.001 compared to the control group, ***P<0.001 compared to the diabetic group. DM: Diabetes mellitus, Myr: Myricitrin, SLN: Solid lipid nanoparticle (One-way analysis of variance (ANOVA), followed by the post hoc least significant difference (LSD) tests).

Effects of myricitrin and SLN containing myricitrin on the liver enzymes

The results of AST assessment revealed a significant increase in diabetes, diabetes + myricitrin 10 mg/kg (P<0.01), and diabetes + SLN containing myricitrin 10 mg/kg (P<0.05) groups compared to the control group. This hepatic enzyme decreased in the vehicle, diabetes + myricitrin 1 and 3 mg/kg (P<0.01), diabetes + SLN containing myricitrin 1 (P<0.05), and 3 mg/kg (P<0.01) groups compared to diabetes group (Figure 6). ALT measurement indicated an increase in the plasma level in diabetes group compared to the control group (P<0.001). This variable decreased in the vehicle (P<0.001), diabetes + myricitrin 1 (P<0.01), 3 and 10 mg/kg (P<0.001), diabetes + SLN containing myricitrin 1 (P<0.01), 3, and 10 mg/kg (P<0.001) groups compared to diabetes group (Figure 7).

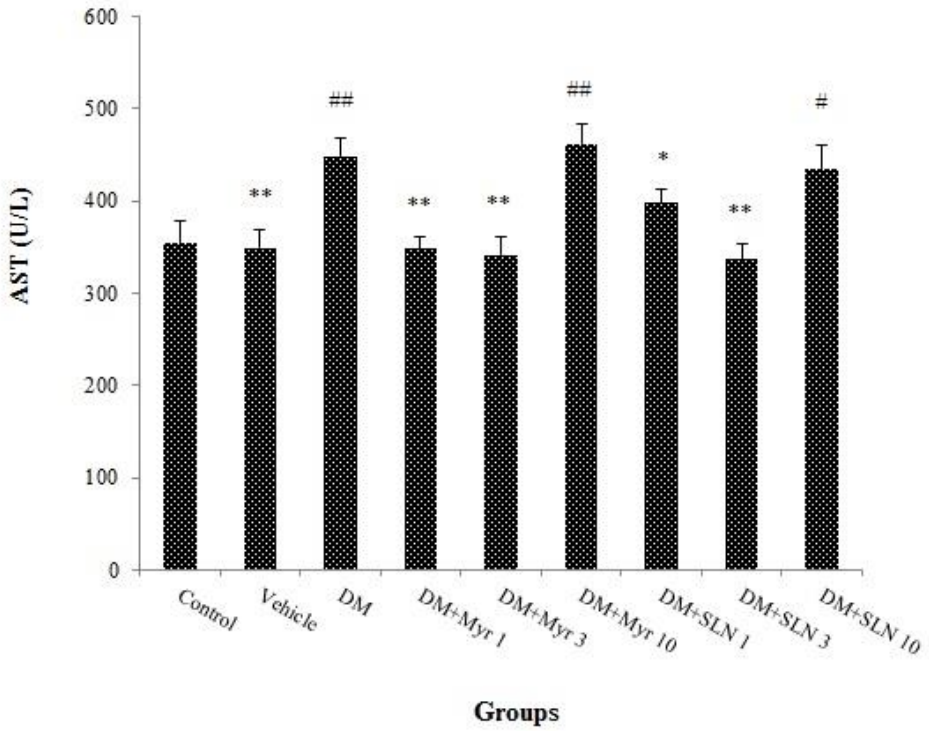

Figure 6. Effects of myricitirn and SLN containing myricitrin on the AST level. Data are presented as mean ± SEM; n=10; #P<0.05 and ##P<0.01 compared to the control group, *P<0.05 and **P<0.01 compared to the diabetic group. DM: Diabetes mellitus, Myr: Myricitrin, SLN: Solid lipid nanoparticle (One-way analysis of variance (ANOVA), followed by the post hoc least significant difference (LSD) tests).

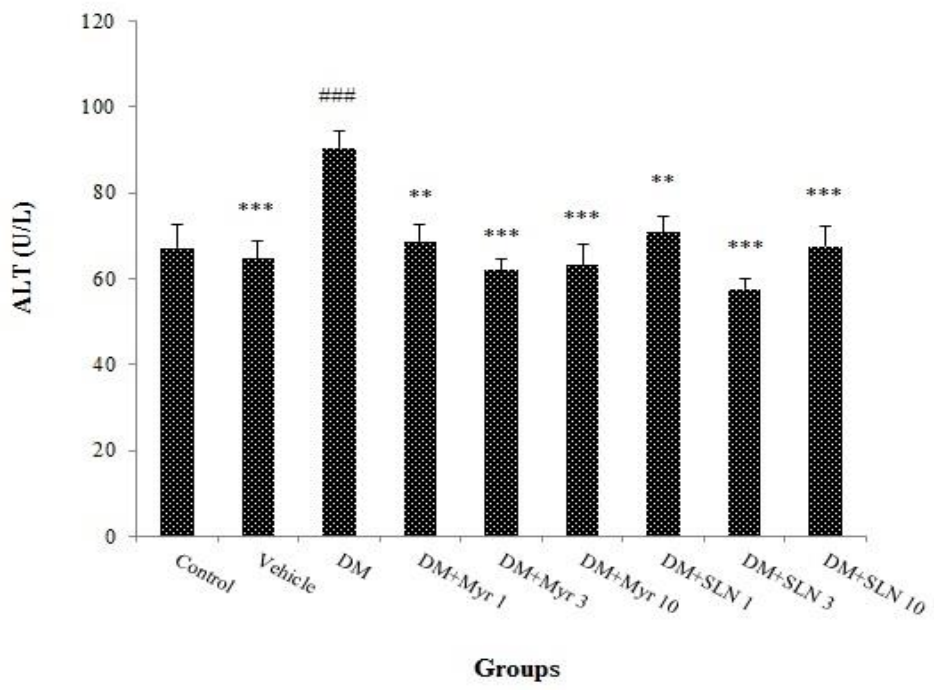

Figure 7. Effects of myricitirn and SLN containing myricitrin on the ALT level. Data are presented as mean ± SEM; n=10; ###P<0.001 compared to the control group, **P<0.01 and ***P<0.001 compared to the diabetic group. DM: Diabetes mellitus, Myr: Myricitrin, SLN: Solid lipid nanoparticle (One-way analysis of variance (ANOVA), followed by the post hoc least significant difference (LSD) tests).

Discussion

The results of the lipid profile assessment showed that the levels of TG and LDL-C increased and the level of HDL-C decreased in the untreated diabetic mice, but the cholesterol level did not change in this group. Dyslipidemia in T2DM is characterized by increased levels of TG and LDL-C, and decreased level of HDL-C (17). These conditions are the main quantitative lipid abnormalities of diabetic dyslipidemia (3). Insulin dysfunction is associated with lipid abnormality. In this condition, the function of insulin on the liver apoprotein production, regulation of lipoprotein lipase (LPL), and activity of cholesterol ester transfer protein (CETP) has been destroyed. So, lipolysis of adipocytes, release of fatty acid from fat cells, and transport of released fatty acid to the liver were increased, and as a result, the secretion of VLDL increased (18). The results of the present study indicated that myricitrin and SLN containing myricitrin decreased the levels of TG, LDL-C, and VLDL, and increased the level of HDL-C. TC is consisted of HDL-C and LDL-C. Hence, HDL-C increased and LDL-C decreased in the SLN-treated mice, it could be suggested that the interaction between LDL-C and HDL-C causes no change in the level of TC in those groups, while it seems that the levels of LDL-C and HDL-C in the myricitrin-treated groups were a little higher than those in the SLN-treated groups, which lead to an increase in the TC level compared to the untreated

diabetic group. Polyphenols play a main role in modulating lipid metabolism, reducing dyslipidemia, and improving adipose tissue metabolism. Hesperidin, as a flavanone glycoside, could reverse neuropathic pain by control over hyperlipidemia and decrease the production of free radical (19). Also, Naringin, as a flavanone-7-O-glycoside, could reduce white and brown adipose tissue weights and normalize visceral adipose tissue (20). Concomitant with the hypolipidemic effect of myricitrin and its SLN in the present study, it was revealed that myricitrin ameliorated ethanol-induced steatosis and lipid accumulation in cells by reducing reactive oxygen species and lipoperoxides (21).

The results of liver enzymes measurement in the present study showed an increase in the plasma level of AST and ALT in T2DM mice, indicating diabetes-induced hepatotoxicity in these animals.

In previous research, a positive correlation between serum ALT and increased risk of T2DM was observed. Also, it has been reported that AST independently predicted T2DM. However, AST is a variable for liver cell health but, it is a less specific factor of liver pathology related to the development of T2DM than ALT. There are several mechanisms between liver enzymes enhancement and T2DM. One of them is that increased serum levels of AST and ALT reflect an excessive visceral fat deposition in the liver (22). Quercetin (as a flavonoid) treatment could decrease the level of AST and ALT in diabetic rats by preventing intracellular enzyme leakage and increasing cell membrane stability (23). Furthermore, lithospermic acid B, jasmonic acid, ursolic acid, and other phenolic compounds could reduce the levels of ALT and AST enzyme by improving the antioxidant defense system in the liver cells (24). According to the results of the present study, myricitrin can be a novel compound for improving the hepatic disorder by reducing aminotransferases. Also, similar to myricitrin, silymarin as a flavonoid glycoside recovered the AST and ALT serum level elevation induced by carbon tetrachloride (25). Moreover, it was revealed that flavonoids can act as pro-oxidant agents in high doses of administration and worsen the altered conditions resulting from the disease (26, 27). So, the results of increased AST in myricitrin and SLN containing myricitrin 10 mg/kg groups may be related to the dose-dependent function of flavonoids.

Conclusion

According to the results, myricitrin and SLN containing myricitrin showed hypolipidemic and hepatoprotective activities in type 2 diabetic mice by decreasing the levels of TG, LDL-C, VLDL, ALT, and AST, and increasing the level of HDL-C. Also, myricitrin and SLN containing myricitrin 3 mg/kg showed potent hypolipidemic and hepatoprotective effects compared to the other doses of administration.

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Conflict of interests

The authors declare that they have no conflict of interests.

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