The Effects of the Extract of *Rosa Canina L.* On Lipid Profile, Liver and Thyroid Functions in Hypercholesterolemic Rats

Saeed Changizi-Ashtiyani, Ph.D.[1], Somayeh Berenji, M.Sc.[2], Ali Zarei, Ph.D.[3], Majid Ramezani, M.D.[4], Nasser Hosseini, M.Sc.[5]

1- Professor, Department of Physiology, Arak University of Medical Sciences, Arak, Iran (Corresponding author; dr.ashtiyani@arakmu.ac.ir)

2- Department of Physiology, Arak University of Medical Sciences, Arak, Iran

3- Assistant professor, Department of Physiology, Shiraz University of Medical Sciences, Shiraz, Iran

4- Associate professor, Health Management Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran

5- Ph.D. Candidate, Department of Medicinal Plants, Faculty of Agriculture and Natural Resources, Arak University, Arak, Iran

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Abstract

Background: *Rosa Canina L.* is a medicinal plant with many therapeutic applications in traditional medicine. This study aimed to evaluate the effectiveness of the extract of *Rosa Canina* on liver function, lipid profiles and thyroid hormones in hypercholesterolemic rats.

Methods: In this experimental study, 60 male Wistar rats were divided into 6 groups (n=10): the control group, hypercholesterolemic vehicle with a diet containing 2% cholesterol, hypercholesterolemia groups receiving either the extract of *Rosa Canina L.* at doses of 50, 500, 1000, or Atorvastatin at a dose of 10 mg/kg as gavage for 48 days.

Results: The extract of *Rosa Canina L* lowered cholesterol and triglycerides from 96±1.3 and 111.8±4.8 in the vehicle group to 79.5±2.4, 98.7±3.5, 73.3±2.5 and 77.5±3.2 in the groups treated with the extract at doses of 500 mg/kg and 1000 mg/kg, respectively. The levels of liver enzymes including alanine transaminase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) were lowered significantly in the group treated with the extract at the dose of 500mg/kg and in the groups treated with the extract at the dose of 1000 mg/kg (P<0.05). The serum levels of thyroid-stimulating hormone and thyroxin in the group treated with the extract at the dose of 1000 and thyroxin at the dose of 500 mg/kg was reduced and the level of triiodothyronine increased compared with the hypercholesterolemic group (P<0.05).

Conclusion: *Rosa Canina L* has healing effects on dyslipidemia and liver protection along with changes in thyroid hormones secretion pattern.

Introduction

Hypercholesterolemia is considered as a common dyslipidemia and a pathological condition characterized by increased levels of cholesterol and lipoproteins in plasma. The increased levels of low-density lipoproteins (LDL) in hypercholesterolemia underlie various diseases such as atherosclerotic plaque formation and hypertension as well as a reduction in the effective function of the vital organs involved

in body metabolism like the liver and kidneys (1). A hypercholesterolemic diet causes the rapid deposition of fat droplets in the liver (2) which results in an imbalance between the entry of fatty acids into the liver and the synthesis and secretion of triglycerides. So, the fat droplets are stored in their basic shapes as triglycerides. A special relationship has been observed between high cholesterol diet and liver damage in animal models (3). Also, thyroid hormones regulate the expression of enzymes involved in lipid metabolism which lead to changes in lipid levels. Thyroid receptors mediate the effects of thyroid hormone in fat metabolism and more specifically mediate the control of lipogenesis in white adipose tissue as well as β adrenoreceptors.

Rosa Canina L. belongs to the family of Rosaceae which is widely spread in Europe, Asia, the Middle East and North America (4-5). Its fruit and leaves have been used in traditional medicine for the treatment and prevention of different diseases such as common cold, cough, bronchitis, eczema, bile duct diseases (6), infectious diseases, fever, gout, rheumatism (7), inflammation of the kidneys (8) and edema (5,7).

Rosa Canina L. includes phenolic compounds, anthocyanins, galactolipids (8), tannins, pectin, unsaturated fatty acids (such as palmitic acid, stearic acid, oleic acid, linoleic acid and arachidonic acid) (9,10), acids (such as ascorbic acid, malic acid and citric acid), flavonoids (6), amino acids, carotenoids (beta-carotene, lycopene, beta-cryptoxanthin, zeoxantin, reboxetine and lutein) (4, 11), minerals, tocopherols and pectin (4,12).

Studies on this herb have shown that many of these compounds have the potential of reducing fat as well as protecting the liver. Anderson and colleagues in their study added the powder of *Rosa Canina* to the diet of obese mice and showed the beneficial metabolic effects of it on the plasma concentration of cholesterol and glucose tolerance (13). The aim of this study was to investigate the potential protective effects of hydroalcoholic extracts of *Rosa Canina L.* on complications of high-cholesterol diet on the lipid profiles, liver and thyroid functions in the rats.

Methods

This experimental study was conducted on Wistar male rats weighing between 140 to 160 g at Arak University of Medical Sciences. This study received the ethics approval code no. 26-166-93 which certifies that all the regulations approved by the National Ethics Committee for using laboratory animals were observed during this study. The animals were given ad libitum access to food and water in a vivarium with a 12:12 hour light/dark cycle in the temperature range of 22-25°C

Study groups

The rats were randomly divided into 6 groups (n=10): the control group which received no carrier or medication over the testing period and were treated with normal diet; the hypercholesterolemic vehicle group receiving high cholesterol diet together with 2 ml normal saline as gavage; the experimental groups including the rats with high-cholesterolemic diet which received the hydroalcoholic extract of the aerial parts of the plant at doses of 50 (14), 500 (14) and 1000 mg/kg (9) as gavage at the same time every day (14). Also, there was an experimental group with hypercholesterolemic diet which received Atorvastatin (Abidi, Iran) as a drug for reducing blood fat level at a dose of

10mg/kg as gavage (6,15). The test lasted for 48 days (16) and the extract and the solvent were daily administrated at 9 a.m (14, 16). Animals were weighed at the beginning and the end of the study. At the end, after anesthesia with ether, blood samples were taken from the hearts of the rats and after centrifuging at 3000 rpm, the serums produced were sent to a laboratory to measure the related factors. The levels of lipid profiles including triglycerides, cholesterol, LDL and HDL (high density lipoprotein) and thyroid hormones such as triiodothyronine (T_3), thyroxin (T_4) and thyroid stimulating hormone (TSH) were determined by using kits from Pars test (Tehran, Iran) with the monobind Elisa kit (Calbiotech, India). Radioimmunoassay was used to measure the levels of liver enzymes using an RIA device (10227 Prague10 Czech, ImmunoTech and kit RIA) and radioimmunoassay kit (Parsazmoon, Iran) (17).

Protocol of high cholesterolemic diet preparation

To prepare hypercholesterolemic diet with 2% cholesterol, 20 grams of pure cholesterol (Merck 3672) were mixed with 5 ml of warm olive oil and then 5 grams of colic acid (Merck, 3671) were added to it (17,18) and the resulting mixture was thoroughly mixed with one kilogram of rat food.

Extraction protocol

The aerial parts of the plant (*Rosa Canina L)* were collected from Arak University Farm for the production and cultivation of medicinal plants. After being approved by an experienced botanist, the aerial parts were washed and dried in shade and then were ground into powder. To make the hydroalcoholic extract, 5 liters of ethanol was added to 2700 g of the powder and then it was put in a mixer for 24 hours.

Then, the resulting mixture was filtered. Again, 3 liters of ethanol was added to the residue and then it was put in the mixer for 48 hours. After filtering the resulting mixture, it was added to the previously obtained mixture. The whole mixture was compressed using spin flash evaporator and then it was transferred to a spray dryer (BUCH B90, Canada) to be changed to dry powder. When testing, the required amount of this powder was solved in normal saline until its volume reached 2 liters. The extraction efficiency was 8% of the dry matter (15,17).

Statistical analysis

All values in the present study were expressed as mean± Standard Error (SE) and data analyses were done using SPSS version 17 statistical software. The mean values were compared using one-way ANOVA analysis followed by Tukey's post-hoc test. The level of significance was set at 0.05 (p<0.05).

Results

The effects of the extract of *Rosa Canina* on lipid profile

Table 1 shows that the levels of cholesterol and triglycerides in hypercholesterolemic vehicle control group significantly increased compared to the controls (P<0.001) and their values in the groups receiving the extract at doses of 500 and 1000mg/kg and atorvastatin significantly decreased compared to the vehicle hypercholesterolemic control group (P<0.05). The mean concentration of HDL and LDL in hypercholesterolemic vehicle control group significantly increased compared to the control group respectively (P<0.001) and their values in the groups receiving the extract at doses of 500, 1000 mg/kg and atorvastatin significantly

increased and decreased respectively compared to the hypercholesterolemic vehicle group (P<0.001, P<0.02, P<0.001) (Table 1).

Table 1. The comparison of the concentration of the lipid profiles and thyroid hormones levels in different groups

Groups / Parameters	Control	Vehicle Hypercholesterolemic	Group receiving Rosa Canina extract at a dose of 50 mg/kg	Group receiving Rosa Canina extract at a dose of 500 mg/kg	Group receiving Rosa Canina extract at a dose of 1000 mg/kg	Group receiving Atorvastatin at a dose of 10 mg/kg
Cholesterol(mg/dl)	65.2 ± 1.7	$96 \pm 1.3*$	$84.2 \pm 3.8 \dagger$	$77.5 \pm 3.2 \dagger$	$73.3 \pm 2.5 \dagger \parallel$	$82.8 \pm 6.6 \dagger$
Triglyceride(mg/dl)	80.2 ± 3.4	$*111.8 \pm 4.8$	$105.7 \pm 3.8 \ddagger$	$98.7 \pm 3.5 \dagger\ddagger$	$79.5 \pm 2.4 \dagger \parallel$	$82.3 \pm 6.6 \dagger$
HDL(mg/dl)	10.4 ± 52.7	$31 \pm 1.2*$	$31.7 \pm 2 \ddagger$	$39.5 \pm 1.6 \dagger\ddagger\S$	$56.4 \pm 1.9 \dagger\P\parallel$	$58.3 \pm 1.7 \dagger$
LDL(mg/dl)	21.22 ± 1.9	$43.08 \pm 2.2*$	$42.39 \pm 2.4 \ddagger$	$35.91 \pm 2.1 \dagger\S$	$29.21 \pm 1.6 \dagger\P\parallel$	$30.1 \pm 2.2 \dagger$
T_3(ng/dl)	25.33 ± 1.8	$42.57 \pm 2.6*$	$41.36 \pm 2.2 \ddagger$	$34.99 \pm 2.1 \dagger\S$	$25.31 \pm 1.5 \dagger\P\ddagger\parallel$	$31.36 \pm 1.6 \dagger$
T_4(µg/dl)	2.12 ± 0.2	1.34 ± 0.2	$1.7 \pm 0.1 \ddagger$	2.3 ± 0.2	$2.13 \pm 0.2 \dagger$	$2.77 \pm 0.6 \dagger$
TSH (mIU/l)	1.37 ± 0.2	$0.54 \pm 0.1*$	$0.55 \pm 0.1\ddagger$	$0.74 \pm 0.1\ddagger$	$1.03 \pm 0.1\dagger\P$	$1.07 \pm 0.1 \dagger$

* Significant changes in the hypercholesterolemia vehicle control group compared to control

†Significant changes in the experimental group compared to the hypercholesterolemia vehicle control group

‡ Significant changes in the experimental groups receiving the extract compared to the atorvastatin group

§ Significant changes in the experimental groups receiving the extract at a dose of 50 mg/kg, compared to the group receiving the extract at a dose of 500 mg/kg

¶ § Significant changes in the experimental groups receiving the extract at a dose of 50 mg/kg compared to the group receiving the extract at a dose of 1000 mg/kg

‖ Significant changes in the experimental groups receiving the extract at a dose of 500 mg/kg compared to the group receiving the extract at a dose of 1000 mg/kgbw.

The effects of the extract of *Rosa Canina* on the liver enzymes

The mean AST and ALT concentrations in the vehicle hypercholesterolemic group increased significantly compared to the control group (P<0.001). Also, these parameters in groups receiving the extract at doses of 500, 1000 mg/kg and atorvastatin were significantly lower than those in the hypercholesterolemic vehicle and control group, respectively (P<0.002, P<0.001, P<0.002) (Figure 1). The me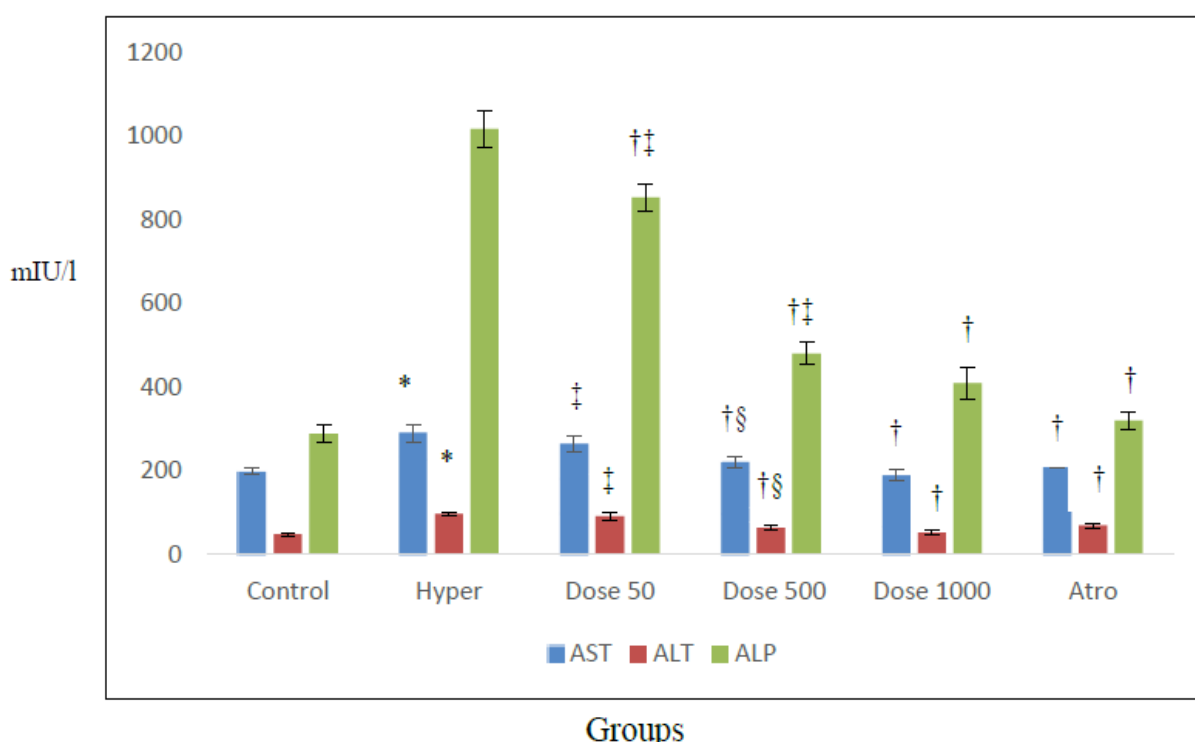an concentration of ALP in hypercholesterolemic vehicle control group significantly increased compared to the controls (P<0.001) and the ALP levels in the groups receiving the extract at all doses and atorvastatin were significantly lower than that in the hypercholesterolemic vehicle control group (P<0.001) (Figure 1).

The effects of *Rosa Canina* extract on thyroid hormones

The mean concentration of T_3 in the hypercholesterolemic vehicle control group significantly increased compared to the control group (P<0.001) and the mean concentration of T_3 in

the groups receiving *Rosa Canina* extract at doses of 500, 1000 mg/kg and atorvastatin was significantly lower than that in the hypercholesterolemic vehicle control group (P<0.001, P<0.001, P<0.01, respectively) (Table 1). The amounts of T_4 in the groups receiving *Rosa Canina* extract at doses of 500, 1000mg/kg and atorvastatin were significantly higher than that in the hypercholesterolemic vehicle control group (P<0.003) (Table 1).

The mean concentration of TSH in the hypercholesterolemic vehicle control group significantly decreased compared to the control group (P<0.001) and TSH levels in the groups receiving the dose of 1000 mg/kg and atorvastatin significantly increased compared to that in the hypercholesterolemic vehicle control group (P<0.002, P<0.004) (Table 1).

Figure 1. The mean of the concentration thyroid hormones levels in different groups

* Significant changes in the hypercholesterolemia vehicle control group compared to control

†Significant changes in the experimental group compared to the hypercholesterolemia vehicle control group

‡ Significant changes in the experimental groups receiving the extract compared to the atorvastatin group

§ Significant changes in the experimental groups receiving the extract at a dose of 50 mg/kg, compared to the group receiving the extract at a dose of 500 mg/kg

¶ § Significant changes in the experimental groups receiving the extract at a dose of 50 mg/kg compared to the group receiving the extract at a dose of 1000 mg/kg

Discussion

The extract of *Rosa Canina* at doses of 500 mg/kg and 1000 mg/kg decreased the concentrations of serum cholesterol, triglycerides, LDL, liver enzymes, TSH, T_4 and increased HDL and T_3 levels. Results of the previous studies on hyperlipidemia showed that hyperlipidemia induced by a high cholesterol diet in rats increased their body weight (19), their levels of plasma cholesterol, triglycerides, LDL and reduced HDL due to the high caloric intake (20). This coincided with the increased levels of liver enzymes (21) and the decreased levels of thyroid hormones (22). The results of the present study confirmed the findings in the study conducted by Khojasteh et al (23). They showed that the administration of the ethanol extract of *Rosa Canina* in streptozotocin-induced diabetic rats at doses of 250 and 500 mg/kg over a period of 28 days reduced cholesterol and triglyceride levels. In their study the lipid profile lowering effects of the extract were attributed to the presence of quercetin in the plant which is an important type of flavonoid (23, 24). Our findings are consistent with the results of that research too.

Several mechanisms can be suggested to explain the reduction of serum cholesterol: It has been reported that the active ingredients of some plants decrease cholesterol synthesis and reduce its plasma levels by indirectly inhibiting HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-coenzyme), which is a mechanism that statins, including atorvastatin, also act through (25, 26).

Also, the alkaloids in the plant are among the substances which can inhibit the synthesis of cholesterol (5, 27). In addition, the fibers in the plant are able to alter the absorption of fat in the intestine (11, 27) and they can increase the intestinal excretion of cholesterol in feces and reduce its absorption by increasing the synthesis of bile acids (21). A diet rich in fiber reduces the amount of triglycerides by inhibiting the lipogenesis in the liver (28, 29).

The study carried out by Ilchizadeh Kavgani showed that the hydroalcoholic extract of *Rosa Canina* at doses of 50, 100, 200 and 300 mg/kg over 14 days could reduce LDL and HDL levels and increase LDL level in the rats diabetized with alloxan which were attributed to the anti-oxidant properties of the plant (30). Our findings are also in line with the results of that study.

Some flavonoids and phenolic acids, by increasing the expression of LDL receptors in the liver hepatocytes, may be involved in this, too (31). Studies on the amount of active ingredients in *Rosa Canina* extract show that this extract is rich in flavonoids and phenolic acids (24). Also, these herbal antioxidant compounds have inhibitory effects on the synthesis of apoprotein 100-B (as the largest component of LDL) in liver cells. As such, polyphenols reduce the production of LDL in the liver and increase their clearance in liver cells (31).

Vitamin C in the extract can lead to beneficial changes in the values of HDL and LDL in two ways: one by applying the antioxidant effect which results in the reduced oxidation of LDL and its increased detection by its receptors, and the other, by applying a competitive effect on the glycation of HDL and LDL for its structural similarity with glucose which leads to increased catabolism of LDL and reduced disposal of HDL (6, 32).

Rosa Canina contains plenty of unsaturated fatty acids such as oleic acid, linoleic acid and linolenic acid with high nutritional values and powerful antioxidant properties (9,10). In our study, these materials so harmoniously regulated the inhibition of the main enzymes involved in glycolysis and

lipogenesis and increased HDL in the groups receiving the extract (27).

Serteser's study showed that the aqueous extract of acetone and the alcoholic extract of *Rosa Canina* could remove the reactive oxygen species and hydrogen peroxide in free radicals (33). In patients with hyperlipidemia, in the absence of these antioxidant systems, lipid peroxidation and oxidative stress may increase and damage the membrane of cells including those of hepatocytes and may increase liver enzymes activities (21).

In this study, it seems that the increased liver enzymes in high-cholesterolemic diet was somehow associated with the increased production of free radicals and the subsequent damage to the hepatocyte membrane. The non-enzymatic antioxidants such as vitamin E, beta-carotene and vitamin C as well as polyphenolic compounds especially the flavonoids present in the extract could neutralize the free radicals in inert atmosphere and exert a protective effect on the liver damages induced by free radicals and toxins (21, 33). Therefore, the decrease in liver enzyme levels in the experimental groups of this study seems to be reasonable.

The results also showed that the level of T_3 increased in the hypercholesterolemic group compared to the control while T_4 and TSH levels decreased. Thyroid hormones have a role in regulating the expression of enzymes involved in all stages of lipid metabolism which lead to qualitative or quantitative changes in lipids. Thyroid receptors mediate the effects of thyroid hormone in fat metabolism and more specifically mediate the α_1 receptors and the control of lipogenesis in white adipose tissue as well as β receptors, which mediate lipogenic and lipolytic enzyme activities in the liver (34).

Basically, there are only limited and contradictory studies on the change of hormone levels in animals with high-fat diet.

Some studies show that in fat diet, the levels of thyroid hormones either increase or remain unchanged (35). In this study, by increasing T_3, the level of TSH decreased. But to explain the reason why T_4 level did not increase as T_3 did (its level even showed a decline), one may say that this was possibly due to the increased activity of monodeiodinase which increased the conversion of T_4 to T_3, eventually leading to decreased T_4 (36).

In this study, the increase in the concentration of T_3 might be due to the changes in iodine supply. It is reasonable to expect that the increased fat in the diet will increase the thyroid activity together with increased iodine intake and increased thyroid hormone synthesis. At the same time, it was right to expect an increase in serum T_4 in the hypercholesterolemic group, could not be seen. Instead, it merely increased T_3 level. This might be due to the diet ingredients which might have somewhat increased the deiodination of T_4. However, more study is necessary to confirm it. Some studies have shown that high-fat diet cannot increase the rate of T_4 uptake by target cells (37).

Furthermore, studies have shown that fatty acids also can differently affect the uptake of T_3 and T_4 in the pituitary gland (36). It is also possible that the increased uptake of T_4 in high-cholesterolemic diet causes a natural concentration of T_4 and an increased level of T_3 which finally improves the performance of thyroid hormone. The increased T_3 can suppress the hypothalamic pituitary-thyroid axis and TSH even when the level of T_4 is normal, because of the fact that about 50% of pituitary receptors are of type T_3 (38). Another possibility is that a T_4 deiodination might have occurred in the pituitary; and finally, it is likely that the high-cholesterolemic diet had a direct effect on the secretion of TSH or T_4 uptake or T_4 deiodination (36).

Conclusion

The results showed that the intake of *Rosa Canina* extract could reduce the complications of dyslipidemia and liver disorders caused by the use of high-cholesterolemic diet in the animal model. The present study reveals significant protective effects of *Rosa canina* extract on hepatocytes too.

References

1. Yelaware Puttaswamy N, Urooj A. In Vivo Antihypercholesterolemic potential of Swietenia Mahagoni leaf extract. Cholesterol 2016; 2016:1-6.

2. Uluisik D, Keskin E. Hepatoprotective effects of ginseng in rats fed cholesterol rich diet. Acta Scientiae Veterinariae 2016; 44(1): 1-5.

3. van der Geest R, Ouweneel AB, van der Sluis RJ, Groen AK, Van Eck M, Hoekstra M. Endogenous glucocorticoids exacerbate cholestasis-associated liver injury and hypercholesterolemia in mice. Toxicol Appl Pharmacol 2016; 306:1-7.

4. Fattahi S, Jamei R, Hosseini Sarghein S. Antioxidant and antiradical activities of Rosa canina and Rosa pimpinellifolia fruits from West Azerbaijan. Iranian Journal of Plant Physiology 2012; 2(4):523-9.

5. Ghazghazi H, Miguel M, Hasnaoui B, Sebei H, Ksontini M, Figueiredo A, et al. Phenols, essential oils and carotenoids of Rosa canina from Tunisia and their antioxidant activities. African Journal of Biotechnology 2010; 9(18):2709-16.

6. Changizi Ashtiyani S, Najafi H, Jalalvandi S, Hosseinei F. Protective effects of Rosa canina L fruit extracts on renal disturbances induced by reperfusion injury in rats. Iran J Kidney Dis 2013; 7(4):290-8.

7. Sadigh-Eteghad S, Tayefi-Nasrabadi H, Aghdam Z, Zarredar H, Shanehbandi D, Khayyat L, et al. Rosa canina L. fruit hydroalcoholic extractseffects on some immunological and biochemical parameters in rats. Bioimpacts 2011; 1(4):219-24.

8. Aptin R, Ghavamaldin A, Ahmad T, Mariamalsadat T. Evaluation of biochemical compounds Rosa cannia L. in North of Iran (Ramsar and Tonekabon Heights). Journal of Medicinal Plants Research 2013; **7**(45):3319-24.

9. Chrubasik C, Roufogalis BD, Muller-Ladner U, Chrubasik S. A systematic review on the Rosa canina effect and efficacy profiles. Phytother Res 2008; 22(6):725-33.

10. Roman I, Stanila A, Stanila S. Bioactive compounds and antioxidant activity of Rosa canina L. biotypes from spontaneous flora of Transylvania. Chem Cent J 2013; 7(1):73.

11. Fan C, Pacier C, Martirosyan DM. Rose hip (Rosa canina L): A functional food perspective. Functional Foods in Health and Disease 2014; 4(11): 493-509.

12. Celik F, Kazankaya A, Ercisli S. Fruit characteristics of some selected promising rose hip (Rosa spp.) genotypes from Van region of Turkey. African Journal of Agricultural Research 2009; 4(3):236-40.

13. Andersson U, Henriksson E, Strom K, Alenfall J, Goransson O, Holm C. Rose hip exerts antidiabetic effects via a mechanism involving downregulation of the hepatic lipogenic program. Am J Physiol Endocrinol Metab 2011; 300(1):E111-21.

14. Farajpour R, Sadigh-Eteghad S, Ahmadian N, Farzipour M, Mahmoudi J, Majdi A. Chronic administration of Rosa canina hydroalcoholic extractsattenuates depressive-like behavior and recognition memory impairment in diabetic mice: a possible role of oxidative stress. Med Princ Pract 2017; 26(3):245-50.

15. Changizi-Ashtiyani S, Alizadeh M, Najafi H, Babaei S, Khazaei M, Jafari M, Hossaini N, Avan A, Bastani B. Physalis alkekengi and Alhagi maurorum ameliorate the side effect of cisplatin-induced nephrotoxicity. Cancer Gene Ther. 2016; 23(7):235-40.

16. Kamesh V, Sumathi T. Antihypercholesterolemic effect of Bacopa monniera linn. on high cholesterol diet induced hypercholesterolemia in rats. Asian Pac J Trop Med 2012; 5(12):949-55.

17. Zarei A, Changizi- Ashtiyani S, Vaezi GH. A Study on the Effects of the Hydroalcholic Extract of the Aerial Parts of *Alhagi Camelorum* on Prolactin and Pituitary–Gonadal Activity in Rats with Hypercholesterolemia. Archivio Italiano di Urologia e Andrologia. 2014; 86(3):188-192.

18. Heidarian E, Rafieian-Kopaei M, Ashrafi K. The Effect of hydroalcoholic extract of allium latifolium on the liver phosphatidate phosphatase and serum lipid profile in hyperlipidemic rats. J Babol Univ Med Sci 2013; 15(4):37-46. In Persian

19. Uthandi A, Ramasamy K. Hepatoprotective activity of sesame meal on high fat fed wistar rats. International Journal of Pharma Sciences and Research 2011; 2(12):205-11.

20. Zarei MA, Eftekhari H, Aqababa H. Effect of hydroalcoholic extract of Zataria multiflora Bioss on serum lipids levels in high cholesterol diet fed Rats. Horizon Med Sci 2014; 19(4):218-2. In Persian

21. Zarei A, Changizi- Ashtiyani S, Rezaei A, Nabi Abdolyousefi. The Experimental Study of the Effect of Hydroalcoholic extracts of *Chelidonium majus* on liver function tests and renal in rats with hypercholesterolemia. Journal of Medicinal Plants. 2013; 12 (4), 117-127.

22. Jimoh A, Tanko Y, Ahmed A, Mohammed A, Ayo JO. Protective effect of resveratrol co-administered with high fat diet on blood glucose homeostasis and thyroid function in rabbits. Cell Biology 2015; 3(1): 19-24.

23. Banan Khojasteh SM, Basirat EL, Sheikhzadeh F, Ozy SA, Dehghan G, Hatami H, et al. Effects of the ethanolic extract of Rosa canina on some serum biochemical factors in diabetic adult male rats. Trakia Journal of Sciences 2015; 13(2):143-8.

24. Ninomiya K, Matsuda H, Kubo M, Morikawa T, Nishida N, Yoshikawa M. Potent anti-obese principle from Rosa canina: structural requirements and mode of action of trans-tiliroside. Bioorg Med Chem Lett 2007; 17(11):3059-64.

25. Zarei A, Changizi-Ashtiyani S, Taheri S, Ramezani M. A quick overview on some aspects of endocrinological and therapeutic effects of Berberis vulgaris L. Avicenna J Phytomed 2015; 5(6):485-97.

26. McFarland AJ, Anoopkumar-Dukie S, Arora DS, Grant GD, McDermott CM, Perkins AV, et al. Molecular mechanisms underlying the effects of statins in the central nervous system. Int J Mol Sci 2014; 15(11): 20607-37.

27. Changizi-Ashtiyani S, Zarei A, Taheri S, Rasekh F, Ramazani M. The effects of portulaca oleracea alcoholic extract on induced hypercholesteroleomia in rats. Zahedan Journal of Research in Medical Sciences 2013; 15(6):34-9. In Persian

28. Talati R, Baker WL, Pabilonia MS, White CM, Coleman CI. The effects of barley-derived soluble fiber on serum lipids. Ann Fam Med 2009; 7(2):157-63.

29. Khogare D. Effect of dietary fiber on blood lipid profile of selected respondent. International Food Research Journal 2012; 19(1):297-302.

30. Ilchizadeh Kavgani A, Eidi M, Ghahramani R, Sasaninejad Z, Ahmarinezhad Z. Antidiabetic effect of Rosa Canina L. fruit in alloxan induced diabetic male rats. Qom Univ Med Sci J 2015; 9 (5):23-34. In Persian

31. Ricardo KF, de Oliveira TT, NagemTJ, Pinto ADS, de Almeida Oliveira MG, Soares JF. Effect of flavonoids morin; quercetin and nicotinic acid on lipid metabolism of rats experimentally fed with triton. *Braz Arch Biol Technol* 2001; 44(3):263-7.

32. Arshadi A, Talebi E, Tahery E, Kargar Jahromy H. Effect of barley and oats on high-density lipoprotein cholesterol and triglycerides in rats. Par J Med Sci 2014; 12(2):29-35.

33. Serteser A, Kargioglu M, Gok V, Bagci Y, Ozcan MM, Arslan D. Determination of antioxidant effects of some plant species wild growing in Turkey. Int J Food Sci Nutr 2008; 59(7-8):643-51.

34. Pourjafar M, Mohebbi A, Nazifi S, Tarakeme S. Invitro study of effect of high-fat diet on serum leptin and thyroid hormone levels in mice. Journal of Shaheed Sadoughi University of Medical Sciences 2010; 18(5):428-35. In Persian

35. Araujo RL, Andrade BM, Padron AS, Gaidhu MP, Perry RL, Carvalho DP, et al. High-fat diet increases thyrotropin and oxygen consumption without altering circulating 3,5,3'-triiodothyronine (T3) and thyroxine in rats: the role of iodothyronine deiodinases, reverse T3 production, and whole-body fat oxidation. Endocrinology 2010; 151(7):3460-9.

36. Brito PD, Ramos CF, Passos MC, Moura EG. Adaptive changes in thyroid function of female rats fed a high-fat and low-protein diet during gestation and lactation. Braz J Med Biol Res 2006; 39(6):809-16.

37. Bianco AC, Salvatore D, Gereben B, Berry MJ, Larsen PR. Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. Endocr Rev 2002; 23(1):38-89.

38. Chatonnet F, Guyot R, Benoit G, Flamant F. Genome-wide analysis of thyroid hormone receptors shared and specific functions in neural cells. Proc Natl Acad Sci U S A 2013; 110(8): 66-75.