Original Article

Zahedan Journal of Research in Medical Sciences

Journal homepage: www.zjrms.ir

Comparison Between the Effects of the Alcholic Extract of Mellissia Officinalis and Atorvastatin on Serum Levels of Thyroid Hormones in Hypercholesterolemic Male Rats

Ali Zarei,[1] Saeed Changizi Ashtiyani,*[2] Mansour Sokhandani,[3] Azam Rezaei,[4] Saeed Zaheiri,[5] Soheila Taheri[6]

1. Department of Physiology, Science and Research Branch, Azad University of Damghan, Damghan, Iran
2. Department of Physiology, Arak University of Medical Sciences, Arak, Iran
3. Department of Nursing, Shiraz University of Medical Sciences, Shiraz, Iran
4. Department of Physiology, Azad University of Arsanjan, Arsanjan, Iran
5. Department of Biology, Payam-e-Noor University, Tehran, Iran
6. Staff of Education Development Center, Arak University of Medical Sciences, Arak, Iran

Article information

Article history:
Received: 9 May 2012
Accepted: 14 Oct 2012
Available online: 30 Dec 2012
ZJRMS 2013; 15(8): 6-12

Keywords:
Atorvastatin
Hypercholesterolemia
Mellissia officinalis
Thyroid

*Corresponding author at:
Department, of Physiology,
Department of Physiology,
Arak University of Medical Sciences, Arak, Iran
E-mail:
dr.ashtiyani@arakmu.ac.ir

Abstract

***Background*:** Consumption of unsaturated fats reduces the serum level of lipids and leptin. Thyroid hormones and leptin play pivotal roles in metabolism and their amounts are inter-related. This study was done to compare the effects of *Mellissia officinalis* extract and atorvastatin on the serum levels of thyroid hormones in hypercholesterolemia rats.

***Materials and Methods*:** Consumption of unsaturated fats reduces the serum level of lipids and leptin. Thyroid hormones and leptin play pivotal roles in metabolism and their amounts are inter-related. This study was done to compare the effects of *Mellissia officinalis* extract and atorvastatin on the serum levels of thyroid hormones in hypercholesterolemia rats.

***Results*:** The results showed that in experimental groups receiving the plant extract and atorvastatin, the concentration of thyroid hormones increased, whereas the amount of the thyroid-stimulating hormone showed a significant decrease ($p<0.05$).

***Conclusion*:** *Mellissia officinalis* extract decreases TSH but it increases T_3 and T_4. Further studies are required for applying this extract to the treatment of hyperthyroidism.

Introduction

Thyroid hormones play a key role in growth, cell division, and regulation of the basic metabolism of body. To date, the role of these hormones and their relationship with the metabolism of several compounds have remained unknown, e.g. the relationship between thyroid hormones and blood fats so that in hypothyroidism, the concentration of blood fats, especially cholesterol, increases [1, 2].

Since ancient times, medicinal plants have been applied to the treatment of various diseases. The history of using medicinal plants in Iran dates back to several thousands of years ago and it has been particularly emphasized in maintaining health and treating diseases. Indeed, in various eras, natural remedies, especially medicinal plants, were the basis of and, in some instances, the only methods of treatment. Moreover, the majority of the plants and herbs used in traditional medicine were native to Iran [3, 4].

Melissa officinalis or Lemon balmon, belonging to the Lamiaceae family, is a medicinal plant native to East Mediterranean region and West Asia. In Iran, this plant is known as Badranjoobeh and grows largely in Tehran, Golestan, Azarbayjan, Lorestan, and Kermanshah [5, 6]. This herb possesses antispasmodic, sedative, hypnotic, nutritional, anti-flatulent, and perspirational properties [5, 7]. *Melissa officinalis* also enhances memory and relieves stress [8, 10] and it is applied to the treatment of sore throat, herpes, and headache [3, 5]. In Iran, it is used for treating bad-temper, anxiety, and nervousness in young girls and women [5, 6, 11, 12]. *Melissa officinalis* can be effective in the treatment of fever, indigestion, insomnia, and epilepsy as well as epilepsy [13]. One of the main properties of *Melissa officinalis* is its anti-oxidant property [14] which is due to the presence of special compounds in it. *Melissa officinalis* extract has polyphenolic compounds, such as quercetin, gallic acid, and rutin, as well as flavonoid, aldehyde, and tannin compounds [14].

Thyroid glands regulate the metabolism of body through secreting T_3 (triodothyronine) and T_4 (thyroxine) hormones and their function is of particular importance so that changes in their function bring about extensive changes in the body. During the low metabolism state, the level of thyroid hormones decreases and during the high metabolism state, this level increases. TRH (thyrotropin-releasing hormone) which is released from the para-ventricular nuclei of hypothalamus affects the anterior hypophysis gland and results in secretion of TSH

(thyroid-stimulating hormone) [15-18] which, in turn, leads to the secretion of T_3 and T_4 [19-21].

Statin family of drugs is highly effective in lowering plasma cholesterol and preventing heart diseases. Statins inhibit HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) and increase the activity of LDL (low-density lipoprotein) receptors. Statins which are currently used include atorvastatin, simvastatin, fibrates, and nicotinic acid [22, 23]. By stimulating the production of free radicals from neutrophils and monocytes, hyperlipidemia plays an indirect role and it is considered a major risk factor for cardiovascular diseases worldwide [24, 25].

Due to its medicinal properties, *Melissa officinalis* has been used in other studies for examining its effects on Alzheimer's disease, memory, learning, and depression. However, to date no study has been done comparing the effects of *Melissa officinalis* extract and atorvastain on the amount of thyroid hormones in hypercholesterolemic rats. Therefore, the present study was done to compare the effects of *Melissa officinalis* extract and atorvastatin on thyroid hormones in hypercholesterolemic rats.

Figure 1. Melissa officinalis

Materials and Methods

This experimental study was done on male Wistar rats supplied from the animal breeding center of Arak University of Medical Sciences. The rats were kept in special cages in standard conditions of temperature and light ad libitum. Animal care and handling was performed according to the guidelines and ethical codes set by the Iranian Ministry of Health and Medical Education for lab animals. Before launching the project, all of the rats were weighed to make sure that they were within the same range of weight (170±5 g). Overall, 60 rats were randomly assorted into 6 groups of 10 each:

1. Control group: Throughout the experiment, the rats did not receive any vehicle or drugs and had a normal diet.

2. Injection sham group: Hypercholesterolemic rats (cholesterol 2% was added to their food to render them hypercholesterolemic) were daily administered 0.2 ml of normal saline.

3. Treatment group 1: Hypercholesterolemic rats were administered 25mg/kg (minimum dose) of the alcoholic extract of *Mellissia officinalis* oral emulsion through gavage over 21 days.

4. Treatment group 2: Hypercholesterolemic rats were administered 50mg/kg (moderate dose) of the alcoholic extract of *Mellissia officinalis* oral emulsion through gavage over 21 days.

5. Treatment group 3: Hypercholesterolemic rats were administered 75mg/kg (maximum dose) of the alcoholic extract of *Mellissia officinalis* oral emulsion through gavage over 21 days.

6. Atorvastatin group: In this group, 10 mg/kg of atorvastain in the form of oral emulsion was administered to hypercholesterolemic rats through gavage over 21 days. For preparation of the alcoholic extract of *Mellissia officinalis* (Fig. 1), standard methods of extraction were utilized. After providing *Mellissia officinalis* plant, it was cleaned, dried, powdered, and eventually poured into a capped glass container and was mixed with ethanol alcohol 96%. The mixture was allowed to mix well for 72 hours. After that, it was first filtered and then centrifuged. The resulting mixture was placed in a hot bath to allow its alcohol to evaporate completely.

After this stage, due to the presence of water, the extract was still like a fluid and for complete evaporation of water; it was kept at 40ºC and then placed adjacent to sodium chloride. Eventually, the intended doses were obtained from the resulting compound (the plant extract). Since this extract was not soluble in distilled water, its oral emulsion was administered to the rats through gavage.

For preparing high cholesterol 2% food, 20g of Merck pure cholesterol powder (Fluke Chemika) was solved in 5 ml of heated olive oil and was mixed with 1kg of the rats food. All of the treatment groups received a fatty diet during the experiment. The experiment was carried out over a 21-day period and the injections were done through gavage everyday at 9 am. Injections were made in the form of an oral emulsion. After this period, mild anesthesia using ether was done for obtaining blood samples from the rat's heart to examine the concentration of thyroid hormones in the samples. After centrifuging the blood samples at 6000 rounds per minute, serum samples were isolated and transferred to the lab for measuring the intended factors. The obtained mean values for the activity of thyroid hormones and thyroid stimulating hormone (TSH) in different groups was statistically analyzed by one-way ANOVA, Duncan test, and Tukey test using SPSS 11.5. F-test was used to determine the degree of significance (p<0.05) (values are given as mean).

Results

The comparison between the results of statistical analysis indicated that the amount of T_3 in the sham group

Table 1. The comparison between effect of different doses of Melissa officinalis and atorvastatin on parameters of thyroid function.

Groups Parameters	Control	Sham	MO Minimum Dose (25 mg/kg)	MO Moderate Dose (50mg/kg)	MO Maximum Dose (75mg/kg)	Atorvastatin
T_3(ng/dl)	1.79±0.2	1.11±0.1*	2.17±0.05	2.01±0.1†	2±0.1†	1.8±0.1†
T_4(g/dl)	4.18±0.1	4.32±0.3	5.41±0.1†	5.88±0.1†	5.10±0.3	5.54±0.4†
TSH (μ IU/dl)	5.91±0.1	5.65±0.2	4.07±0.1†	4.52±0.1#†	3.91±0.2†	3.46±0.1†

† Comparison with the sham group,* Comparison with the control group, # Comparison with atorvastatin

receiving a fatty diet significantly decreased in comparison with the control group, whereas changes in all of the treatment groups presented significant increases compared with the sham group (p=0.001). However, none of the treatment groups receiving the extract presented significant changes compared with one another and the atorvastain group (Table 1).

Although T_4 level in the sham group did not significantly differ from its corresponding level in the control group. All of the treatment groups except for the sham group presented significant increases (p=0.001). Nevertheless, none of the treatment groups that received the extract revealed significant changes compared with each other and the atorvastatin group.

In terms of TSH, the control group did not present any significant changes compared with the sham group while all of the treatment groups showed significant decreases compared to the sham group. In addition, the treatment group receiving the moderate dose of the extract showed a significant increase in comparison with the atorvastatin group (p=0.001), whereas none of the treatment groups receiving the extract presented significant changes compared to each other.

The amount of cholesterol in the sham group which only received a fatty diet showed a significant increase in comparison with the control group. This indicated that receiving a fatty diet could render the rats hypercholestromic. Moreover, all of the treatment groups presented significant decreases in comparison with the sham group which indicates the effects of the extract on the amount of cholesterol and thyroid hormones (p=0.001).

Discussion

The findings of the present study showed that thyroid hormones increased in treatment groups receiving the extract as well as the group receiving atorvastatin; however, TSH levels decreased in these groups. In addition, the amount of cholesterol in the sham group showed a significant increase compared with the control group but its amount decreased in all of the treatment groups. In fact, there was a significant negative relationship between thyroid hormones and fat level.

In the sham group, with an increase in the level of fat, the amount of thyroid hormones decreased [21]. Furthermore, increase in fat and its residue in liver results in the dysfunction of liver e.g reduction in the synthesis of plasma proteins especially albumin. Since albumin is responsible for transferring thyroid hormones, their lack of transfer and reduction in plasma occurs which confirms what was observed in the hypercholesromic sham group. With increase in the expression of fat into the liver, the incidence of liver dysfunction is likely and increases in cholesterol and bilirubin may ensue. With progression of liver cirrhosis and stimulation of liver tissue, the amount of plasma proteins, especially albumin, increases. Hence, due to the transfer of thyroid hormones by these proteins, increase in their amount in blood may even be observed in the hypercholestromic sham group in the long-run. In Shekarforoush et al's study on *Mellissia officinalis*, this was accompanied by increases in liver enzymes and plasma proteins which, in turn, lead to increases in thyroid hormones [2, 22, 23].

To date, ample scientific evidence indicating the effects of *Mellissia officinalis* extract which grows abundantly in Iran, on the pituitary -thyroid axiom has not been found. The studies done on *Mellissia officinalis* so far have only dealt with the anti-oxidant [14], anti-microbial [14], and genotoxic and anti-genotoxic [13] properties and its effects on memory, learning, and Alzheimer's disease [8, 9]. A study on the effect of hydro-alcoholic extract of *Mellissa officinalis* on mice demonstrated its sedative properties at low doses. At higher doses, it had analgesic effects on writhing test following the administration of acetic acid as well as hypnotic effects at lower doses of phenobarbital [3, 6].

Another study showed that the hydro-alcoholic extract of *Mellissia officinalis* (through percolation and sacculation methods of extraction) at 75, 50, 100, 200, and 300 mg/kg had analgesic effects at minutes 15 and 30 which gradually decreased with the passage of time. The maximum analgesic response was induced in minute 15 of injection and the most effective dose was the 200 mg/kg dose.

In addition, the analgesic effect of the extract obtained through percolation method was more than sacculation method which was hypothesized that probably compounds sensitive to heat in *Mellissia officinalis* which are responsible for the analgesic effect are partly damaged and decomposed due to the heat generated in sacculation method of extraction which eventually decrease the effective part of the plant [7].

Akhoonzade et al. demonstrated that *Mellissia officinalis* in addition to possessing acetylcholine substrate and hence manifestation of agnonistic effects on cholinergic receptors, inhibits acetylcholine esterase enzyme and enhances the function of cholinergic system and eventually improves the memory. Thus, it has a multitude of effects on the central nervous system and is effective in

treatment of Alzheimer's disease [8, 9]. Rostami et al. in their study entitled "The comparison between the anti-oxidant effects of *Mellissia officinalis* leaves and vitamin C on learning disorders induced by lead acetate in rats" showed that the effect of *Mellissia officinalis* is similar to vitamin C and it can be used as a natural anti-oxidant [9].

Solimani et al. stated that the chemical compounds present in *Mellissia officinalis*, including citral, citronellal, geraniol, caffeic acid, atenolol, citronellal, and geraniol, Thymol, Trans- ocimene, Ursolic-acid., Ogenol acetate, rosmarinic acid, mono-carbon phenolic acid, and flavonoids. It should be noted here that the anti-spasmodic and anti-inflammatory effects of the extract on rats have been attributed to Ogenol. This plant contains flavonoids and terpenoids as well and anti-spasmodic and anti-inflammatory effects have been reported for flavonoids and terpenoids and the direct interaction of flavonoids and prostaglandin synthesis have been proven. Therefore, from among different candidates, flavonoids present in this extract can probably influence pain [26, 27]. Compounds present in *Mellissia officinalis*, in addition to being capable of bonding with muscarinic and nicotinic acetylcholine receptors have the inhibitory effect on acetylcholine esterase enzyme; therefore, they can improve cognitive functions such as memorization [9].

In another study it has been mentioned that narcotics may lead to the generation of anxiolytic effects. Researchers also maintain that anxiety is a compelling factor in heroine addicts' tendency for taking medications. Hence, anxiety may affect the increased preference of dependent rats in morphine places on CPP (conditioned place preference). By treating anxiety, tendency toward morphine may decrease in dependent animals; thus, noticing the anti-anxiety effect of *Mellissia officinalis* (probably through its activity in transferring serotonin or bonding with GABA receptors), the effect of increased preference on CPP test decreases and moderates the symptoms of morphine withdrawal syndrome [6, 26]. Moreover, the ethanolic extract of *Mellissia officinalis* has a moderating function in bonding with the location of GABA receptors. One study showed that intracerebral and intraperitoneal administration of GABA A and B agonist receptors results in leaping and ESC due to naloxone in morphine withdrawal syndrome in mice. Hence, it is likely that one part of the effects of *Mellissia officinalis* is manifested through empowering acetylcholine esterase and the remaining part is brought about by bonding with GABA receptors [7, 27]. The secretion of TSH is triggered by hypothalamus para-ventricular nucleus TRH and studies have shown that some neurotransmitters and neuromediators control the neurons that release TRH in hypothalamus. Some of these neuromediatory structures, such as catecholamines (epinephrine, norepinephrine, serotonin, and dopamine) have an intensifying role while some others, such as interleukin-1 and GABA, have a reducing role [28].

Increase in serotonin decreases TRH secretion which is followed by decreased levels of plasma TSH and, eventually, T_3 and T_4 hormones. Other studies have indicated that dopamine both at hypothalamus level, by decreasing TRH release, and at pituitary level, directly, prevents the secretion of TSH and reduces the plasma levels of TRH both in free and linked with plasma proteins forms [28, 29].

Through D_2 receptors, dopamine prevents the secretion of TSH from the anterior hypophysis **(**pituitary gland**)** and by stimulating the secretion of somatostatin, it decreases the secretion of thyroid releasing hormone and T_3 and T_4 levels [30]. Hence, the results of the present study confirm the findings of other researchers. The findings of other studies on the antidepressant effects of *Mellissia officinalis* indicate that during depression, MAO enzyme is inhibited [5]. Dopamine and other catecholamines are decomposed and neutralized by MAO enzyme and extra-neuronal enzyme named catechol-O-methyltransferase (COMT) [31]. In the anti-depressant mode, MAO enzyme is inhibited which results in dopamine increase that eventually prevents the secretion of TSH. Therefore, in the present study, TSH reduction sounds more reasonable. On the other hand, when the level of thyroid hormones surpasses the normal level, its negative feedback on hypophysis and hypothalamus prevents the synthesis and secretion of TSH [3].

Based on the findings of this study, increases in the level of thyroid hormones and lack of a significant increase in TSH level seem normal. Gamma-aminobutyric acid (GABA) is a major inhibiting neurotransmitter in human central nervous system [32]. In fact, GABAergic system is a desirable target in pharmacologic strategy which cures stress [32]. *Mellissia officinalis* extract, on the other hand, affects GABA through two mechanisms: 1) GABAergic property which inhibits GABA) col inergic property by inhibiting acetylcholine esterase and 2) the ability of colinergic cerebral receptors [33]. Various studies have shown that GABA inhibits and reduces TRH; therefore, its inhibition increases TRH and eventually other thyroid hormones. Based on the findings, increases in the level of thyroid hormones in the presents study is natural. Thyrotropin which is a stimulating hormone released from hypothalamus affects the anterior part of hypothalamus and results in the secretion of thyroid-releasing hormone [34, 35].

Thyroxin and triiodothyronine thyroid hormones are affected by TRH secreted from adnohypophys [36, 37] and increase in thyroid hormones through negative feedback mechanism can result in TSH decrease. In the present study, noticing the increase in T_3 and T_4 thyroid hormones, TSH reduction is predictable. Establishment of equilibrium between energy intake and expenditure is done by a variety of complex hormonal and neural mechanisms. These mechanisms affect energy metabolism and appetite based on the nutrient molecules existing in blood and body fat reserves [38].

Studies have shown that blood fat level, including triglycerides and cholesterol, in a group treated with a fatty diet increases and there is a direct relationship between the level of fat and leptin while there is a significant negative relationship between T_3 and leptin. This study indicates the presence of a relationship between fat, leptin, and thyroid hormones [39].

In addition, Saeb et al. in their study on the effect of wild pistachio on thyroid hormones, leptin, and fat showed that during their experiment, with increases in the level of thyroid hormones, leptin and fat levels decreased which indicated the presence of a negative relationship between them [21]. Leptin is a hormone with the molecular weight of 16 KDA which is essentially secreted from fat tissue cells. By bonding its specific receptors in hypothalamus, leptin affects appetite and some other biological functions. Leptin is coded by Ob gene and its main physiological role is decreasing weight via reducing appetite for food and increasing the production of energy from body fat reserves.

The serum leptin concentration has a direct relationship with the amount of fat tissue and its amount increases with obesity and severely decreases during hunger and malnutrition [40, 41]. Leptin is essentially responsible for transmitting information on the amount of energy reserves to the brain and through connecting to its receptor in the central nervous system participates in regulation of the energy level of body. Increase in the plasma concentration of leptin decreases the energy or appetite while during decreased energy intake, it leads to more energy consumption from the body fat storage reserve.

The results of studies on animals have shown that leptin injection increases thyroid hormones, decreases thyrotrpine (TSH), and increases pholicolic cells [15]. Also, Fain et al. reported leptin mRNA increase in hypothyroid rats which was reduced by T_3 administration [21, 39]. As it was observed, in the present study, T_3 level decreased in the sham group receiving the fatty diet which is in agreement with the findings of the aforementioned studies. The fatty diet probably through increasing the level of leptin caused the reduction of thyroid hormones in the sham group. Unsaturated fatty acids reduce serum leptin level and reductions in serum leptin and serum cholesterol level and their relationship with thyroid hormones have a positive effect on the prevention of cardiovascular diseases [21]. In this regard, Reseland stated that that in rats fed with diets rich in unsaturated fatty acids, the amount of leptin decreases [42].

In his study, Kratz compared the effect of a diet rich in MUFA and alpha-linoeic acid and a diet rich in unsaturated fatty acids on decreasing serum leptin level. The diet rich in sunflower and olive oil did not reduce serum leptin level while the Celexa oil diet (rich in α-Linolenic acid) reduced leptin level since Celexa unsaturated fats, especially α-Linolenic acid, are determining factors and their effect as plasma leptin level reducers is critical [43]. Commisoto showed that unsaturated fatty acids with one or several dual bonds present in triglycerides stored in adipocytes, such as oleic, linolenic, eicosapentaenoic, and docosapentaenoic acids, inhibit leptin secretion [44].

In a study by Duque-Guimaraes, the consumption of fatty acids belonging to omega-3 and omega-6 family decreased the expression of leptin gene in fat tissues [45]. Therefore, according to these studies as well as the presence of unsaturated fatty acids, oleanolic acid, and Rosmarinic Acid, reductions in leptin level and the level of liver enzymes following that are expected.Okere demonstrated that unsaturated fats in diet can decrease serum leptin level [46]. Atorvastain is one of the chemical drugs that are used for treating blood fat (hyperlipidemia).

As it was observed in the present study, similar to *Mellissia officinalis* extract, atorvastatin increased thyroid hormones, probably through decreasing leptin and fats. Also, similar to *Mellissia officinalis*, it could reduce TSH level due to the negative feedback of thyroid hormones [21].

Mellissa officinalis increases the level of thyroid hormones probably through increasing albumin synthesis, decreasing fat level, and eventually decreasing leptin hormone levels. This extract also reduces TSH level probably due to the negative feedback of thyroid hormones. In sum, it can be said that *Mellissia officinalis* extract can be applied to the treatment of hypothyroid activity problems.

Authors' Contributions

All authors had equal role in design, work, statistical analysis and manuscript writing.

Conflict of Interest

The authors declare no conflict of interest.

Funding/Support

Arak University of Medical Sciences.

References

1. Nazifi S, Pilevarian AA, Jalaei J. [The relationship between thyroid hormones, some antioxidant enzymes and trace elements in blood serum of Mehraban sheep] Persian. J Veterinary Med Lab 2009; 1(1): 47-59.
2. Zarei A, Ashtiyani SC, Rasekh F, et al. [The effect of physalis alkekengi extracts on lipids concentrations in rats] Persian. J Arak Univ Med Sci 2011; 14(55): 48-55
3. Miladi-Gorji H, Vafaei AA, Rashidy-Pour A, et al. Anxiolytic effects of the aqueous extracts of Melissa officinalis and the role of opioid receptors in mice. Tehran Univ Med Sci 2005; 12(47): 145-153.
4. Dadgar T, Ghaemi E, Asmar M, et al. [Antibacterial activities of six medicinal plants against methicillin-resistant and sensitive Staphylococcus aureus] Persian. J Med Plants 2007; 23(1): 73-84.
5. Emamghorishi M, Talebianpour MS. Antidepressant effect of Melissa officinalis in the forced swimming test. DARU J Pharm Sci 2009; 17(1): 42-47.
6. Soulimani R, Fleurentin J, Mortier F, et al. Neurotropic action of the hydroalcoholic extract of Melissa officinalis in the mouse. Planta Med 1991; 57(2): 105-109.
7. Heidari MR, Darban M. [Evaluation of the analgesic effect of Mellissa officinalis extract by Tail-flick test in mice]. Persian. Physiol Pharmacol 1999; 3(1): 81-87.
8. Akondzach S, Noroozian M, Mohammadi M, et al. Melissa officinalis extract in the treatment of patients with mild to

moderate Alzheimer's disease a double blind, randomized, placebo controlled trial. J Neurol Neurosurg Psychiatry 2003; 74(7): 863-866.
9. Schultz V, Hansel R, Tyler V. Rational phytotherapy: A physician's guide to herbal medicine. 15th ed. New York: Springer-Verlag; 1998:117-120.
10. Rostami S, Momeni Z, Behnam-Rassouli M and Ghayour N. Comparison of antioxidant effect of Melissa officinalis leaf and vitamin C in lead acetate induced learning deficits in Rat. Daneshvar Med 2010; 17(86): 1-9.
11. Shafie-Zadeh F. Lorestan Medicinal Plants. 2nd ed. Tehran: Hayyan Press; 2002: 32
12. Imami A, Shams-Ardekani MR, Mehregan I. The illustrated encyclopedia of herbal medicines. Research center for traditional medicine and pharmacognosy, Tehran: Shahid Beheshti University of Medical Sciences Press; 2003: 192.
13. De Carvalho NC, Correa-Angeloni MJ, Leffa DD, et al. Evaluation of the genotoxic and antigenotoxic potential of Melissa officinalis in mice. Genet Mol Biol 2011; 34(2): 290-7.
14. Pereira RP, Fachinetto R, De Souza Prestes A, et al. Antioxidant effects of different extracts from Melissa officinalis, Matricaria recutita and Cymbopogon citrates. Neurochem Res 2009; 34(5): 973-83.
15. Moshtaghi-Kashanian GhR, Gholamhoseinian A, Sanjari M and Kor M. Evaluation of Ghrelin and Leptin in patients with thyroid malfunction. J Kerman Univ Med Sci 2006; 12(4): 219-227.
16. Shekar-Foroosh S, Changiz-Ashtiyani S, Akbarpour B, et al. The effect of physalis alkekengi alcoholic extract on concentration of thyroidhormones in rats. Zahedan J Res Med Sci (ZJRMS) 2012; 13(9): 1-7.
17. Melmed S, Polonsky KS, Larsen R. Williams Textbook of endocrinology. 12thed. Philadelphia: W.B. Saunders; 2001: 341-346
18. Hall JE, Guyton A. Guyton and Hall Physiology review. 12th ed. Philadelphia: W.B. Saunders; 2006: 235-259.
19. How Your Thyroid Works? A Delicate Feedback Mechanism. www.uptodate.com; 2009-05-21.
20. Cooper DS, Kilbanski A, Chester Ridgway E. Dopamine modulation of TSH and its subunits: in vitro studies. Clin Endocrinol 2008; 18(3): 265-75.
21. Saeb M, Nazifi S, Sabet M, et al. [Effect of dietary wild pistachio oil on serum thyroid hormones, lipids and leptin concentration in experimental hyperthyroidism in male rat] Persian. J Gorgan Univ Med Sci 2010; 11(4): 8-22.
22. Robert Murrey K, Bender D, Botham KM et al. Harper's illustration biochemistry. 28th ed. USA: McGraw-Hill Medical Press; 2009: 212-220.
23. Ashtiyani SC, Zarei A, Taheri S, et al. The effects of Portulaca oleracea alcoholic extract on induced hypercholesteroleomia in rats. Zahedan J Res Med Sci (ZJRMS) 2013; 15(6): 34-39.
24. Ashtiyani SC, Zarei A, Shariati M, et al. [The effects of Physalis alkekengi alcoholic extract on certain plasma biochemical factors in Rats] Persian. J Arak Univ Med Sci 2011; 14(58): 18-25.
25. Prasad K. Hypocholesterolemic and antiatherosclerotic effect of Flax ligana complex isolated from flax seed. athrosclerosis. Atherosclerosis 2005; 179(2): 269-75.
26. Miladi-Gorji H, Vafaie A, Taherian A and Vaezi T. [The effects of aqueous extracts of Melissa officinalis on withdrawal syndrome in rats] Persian. Sci J Kurdistan Univ Med Sci 2008; 13(2): 27-33.
27. Kennedy DO, Scholey AB, Tildesley NT, et al. Modulation of mood and cognitive performance following acute administration of Melissa officinalis (lemon balm). Pharmacol Biochem Behav 2002; 72(4): 953-64.
28. Gharib-Naseri MK., Handali S, Hoseini H. Antispasmodic activity of Physalis alkekengi L. leaf hydroalcoholic extract on rat ileum. J Med Plants 2007; 23(3): 340-349.
29. Monsef HR, Ghobadi A, Iranshahi M and Abdollahi M. Antinociceptive effects of Peganum harmala L. alkaloid extract on mouse formalin test. J Pharm Pharm Sci 2004; 7(1): 65-9.
30. Farouk L, Laroubi A, Aboufatima R, et al. Evalution of the analgesic effect of alkaloid extract of peganum harmala L.: Possible mechanisms involved. J Ethnopharmacol 2008; 115(3): 449- 54.
31. Haeri-Rohani SA. [Neurophysiology and endocrinology.] Persian. 10th ed. Tehran: Samat; 2008: 37-52.
32. Domschke K, Zwanzger P. GABAergic and endocannabinoid dysfunction in anxiety - future therapeutic targets? Curr Pharm Des 2008; 14(33): 3508-3517.
33. Awad R, Levac D, Cybulska P, et al. Effects of traditionally used anxiolytic botanicals on enzymes of the gamma-aminobutyric acid (GABA) system. Can J Physiol Pharmacol 2007; 85(9): 933-42.
34. Hossini E, Sadeghi H, Daneshi A. [Evaluation of hydro-alcoholic extract of peganum harmala on pituitary-thyroid hormonesin adult male rats] Persian. Yasuj Univ Med Sci 2010; 14(4): 23-30.
35. Mitsuma T, Kayama M, Yokoi Y, et al. Effects of serotonin on the release of thyrotropin-releasing hormone from the rat retina in vitro. Horm Metab Res 1996; 28(5): 220-2.
36. Hall JE. Guyton and Hall textbook of medical physiology. 12th ed. Philadelphia: W.B. Saunders; 2010: 866-928.
37. Cooper DS, Kilbanski A, Chester-Ridgway E. Dopamine modulation of TSH and its subunits: In vitro studies. Clin Endocrinol 2008; 18(3): 265-75.
38. Obici S. Minireview: Molecular targets for obesity therapy in the brain. Endocrinology 2009; 150(6): 2512-7.
39. Pourjafar M, Mohebbi A, Nazifi S, Tarakeme S. [In vitro study of effect of high-fat diet on serum leptin and thyroid hormone levels in mice] Persian. J Shaheed Sadoughi Univ Med Sci 2010; 18 (5) :428-435
40. Lee MJ, Fried SK. Integration of hormonal and nutrient signals that regulate leptin synthesis and secretion. Am J Physiol Endocrinol Metab 2009; 296(6): 1230-8.
41. Morris DL, Rui L. Recent advances in understanding leptin signaling and leptin resistance. Am J Physiol Endocrinol Metab 2009; 297(6): 1247-59.
42. Reseland JE, Haugen F, Hollung K, et al. Reduction of leptin gene expression by dietary polyunsaturated fatty acids. J Lipid Res 2001; 42(5): 743-750.
43. Kratz M, von Eckardstein A, Fobker M, et al. The impact of dietary fat composition on serum leptin concentrations in healthy nonobese men and women. J Clin Endocrinol Metab 2002; 87(11): 5008-5014.
44. Cammisotto PG, Gelinas Y, Deshaies Y and Bukowiecki LJ. Regulation of leptin secretion from white adipocytes by free fatty acids. Am J Physiol Endocrinol Metab 2003; 285(3): E521-6.
45. Duque-Guimaraes DE, de Castro J, Martinez-Botas J, et al. Early and prolonged intake of partially hydrogenated fat alters the expression of genes in rat adipose tissue. Nutrition 2009; 25(7-8): 782-9.
46. Okere IC, Chandler MP, McElfresh TA, et al. Differential effects of saturated and unsaturated fatty acid diets on cardiomyocyte apoptosis, adipose distribution, and serum

leptin. Am J Physiol Heart Circ Physiol 2006; 291(1): 38- 44.

Please cite this article as: Zarei A, Ashtiyani SC, Sokhandani M, Rezaei A, Zaheiri S, Taheri S. Comparison between the effects of the alcholic extract of mellissia officinalis and atorvastatin on serum levels of thyroid hormones in hypercholesterolemic male rats. Zahedan J Res Med Sci (ZJRMS) 2013; 15(8): 6-12.