Advanced Herbal Medicine, 2015; 1 (2): 23-33.

herbmed.skums.ac.ir

The effects of *Urtica dioica* extract on lipid profile, insulin resistance index and liver histology in polycystic ovary syndrome-induced Wistar rats

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Original article

Received: 8/Feb/2015 Accepted: 16/Mar/2015

ABSTRACT

Background and aims: *Urtica dioica* as a medicinal herb due to its anti-inflammatory, antioxidant and hypoglycemic effects, improves type 2 diabetes and decreases inflammation, fibrosis and necrosis as the signs of Nonalcoholic steatohepatitis. Polycystic Ovary Syndrome (PCOS) as the most important factor of infertility has an overlap of 30 % to 60% with liver disorders. Hence, the *Urtica dioica* moderator effect on liver function in PCOS rats was examined.

Methods: In this experimental study, 144 adult Wistar rats were divided into control, PCOS and nettle-treated groups. The group PCOS was injected subcutaneously with 2 mg estradiol valerate, after 60 days and confirmed polycystic, the experimental group was injected intraperitoneally the *Urtica dioica* extract doses (150, 250, 450 mg/kg BW). After 21 days, rats were anesthetized by chloroform; blood samples and livers were collected for histological and serological evaluation. Data were analyzed using in stat 3 via one-way ANOVA and $P<0.05$ was considered statistically significant.

Results: Liver sections and serological analysis showed reduced number of necrotic cells, insulin resistance index and lipid profile in PCOS rats that were treated with various concentrations of *Urtica dioica* extract.

Conclusion: Whereas PCOS is described as a low-grade inflammatory state, the results show that *Urtica dioica* by increasing insulin sensitivity and reducing hepatic necrosis may reduce inflammation and improve metabolic symptoms in PCOS and has significant protective effect on liver.

Keywords: *Urtica dioica*, Polycystic ovary syndrome, Liver, Necrosis, Insulin resistance.

INTRODUCTION

Urtica dioica (UD), stinging nettle, is the most valuable member of Urticacease family and has been known for a long time as a medicinal plant. Nettle is an herbaceous perennial flowering herb. The leaves have a strongly serrated margin, a cordate base and an acuminate tip with a terminal leaf tooth longer than adjacent laterals. The length of this species during summer reduces up to 1 to 2 meters and the leaves are 3 to 15 cm in length. Among 50 species of Urtica genus, the stinging

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nettle plant was used by Avicenna as a medical plant. Nettle for having the components with solubility capacity in water and alcohol such as: lectins, phenols, sterols, and especially lignans has anti-androgenic, antioxidant and anti-inflammatory properties which leads to vasodilation, reduction of fat and blood sugar, treatment of disorders of the kidneys and urinary tract and bladder, gastrointestinal tract, locomotor system, skin, cardio-vascular system, hemorrhage, flu, rheumatism and gout.[1, 2]

Liver tissue injuries can be verified at several levels as a 0.5 ml intraperitoneal injection of carbon tetrachloride 8% /kg BW cause the induction of fatty liver or simple steatosis (Nonalcoholic Fatty Liver Disease; NAFLD) within 30 days, secondary steatosis or fatty liver syndrome (Non Alcoholic Steato Hepatitis: NASH) in 60 days, fibrosis in 90 days and finally cirrhosis in 210 days.[2] NAFLD refers to the situation that the aggregation of fat balloons in a form of Triglyceride (steatosis) is visible and its histology feature affects more than 5% of hepatocytes.[3] Inflammation can be seen in addition to fat aggregation in NASH, a subgroup of NAHD. Due to this reason, it is called secondary steatosis that is the starting point for overlapping with metabolic syndrome for having symptoms such as insulin resistance, type II diabetes and central obesity and hyperlipidemia (i.e. reduction of high-density lipoprotein (HDL), total cholesterol and enhanced triglyceride).[4] Hepatic dysfunction in above mentioned cases can be characterized in two forms of anatomical and functional status such as increase in inflammation index, loss of liver parenchyma and in the end, formation of fibrous tissues in liver, change in the number of liver cells and loss of natural liver function in producing enzyme and elimination the waste substances from blood.[5]

Polycystic Ovary Syndrome (PCOS) is the most common cause of infertility. 6-8% of women in reproductive ages have affected by this endocrine disorder which was found for the first time by Leventhal and Stein in 1935.[6] Polycystic Ovarian Disease (PCOD) also refers to this disorder but PCOS is preferred because it emerges with the range of heterogeneous clinical symptoms such as: hirsutism and acne, menstrual disease (Oligomenorrhea and Amenorrhea), hyperandrogenism, LH/FSH>2, increase in body mass index, metabolically disorders such as Hyperinsulinemia, insulin resistance, type II diabetes, increased risk of cardiovascular diseases, hypertension, histologic disorders such as bilateral ovarian enlargement to more than 10 ml, the presence of 12 or more small cysts measuring 2-9 mm in diameter around central dense stroma, increase in thickness of follicular sheath and ovarian stroma due to increased angiogenesis, vasculogenesis and ovarian blood flow and consequently reduction or chronic anovulation and infertility.[7]

Because of the main role of liver in metabolic pathways, any liver dysfunction is classified as metabolic syndrome. Likewise, the metabolic syndrome shows high correlation with polycystic ovary because of its symptoms such as estrogen and insulin resistance, increased inflammatory cytokines and increasing the number and activity of fat cells. Although the number of animal studies that regarding this correlation is low, the communities studied in Japan and America show PCOS symptoms in women with metabolic disorders and also reduction of metabolic and reproductive symptoms by metformin in women as the most effective and most popular way to treat diabetes

type II.[8] A wide range of liver disorders from NAFLD, steatosis to Fibrosis in various degrees, cirrhosis, liver cancer and hepatic failure can be seen in both syndromes.[9]

According to the effect of metabolic features of PCOS on liver, histologically, and also anti-inflammatory effects of nettle via modulation of cytokines and insulin resistant, this study attempted to investigate the protective effects of nettle on the rat liver tissue which can be partially damaged by metabolic symptoms of PCOS, due to the impact of this syndrome on liver tissue by disruption of liver enzymes release and metabolites production.

METHODS

This experimental study was conducted at Kharazmi University during 1392-1393. Experiments were performed on 144 female Wistar rats (weighing 170±20 g) provided by Kharazmi University, Tehran, Iran. Animals were housed in special cages with a standard space, under a controlled light/dark cycle (Lights on from 08:00 to 20:00). Humidity and temperature were set at 55±15% and 20-24˚C, respectively. A free access to water and commercial food (Behparvar Co, Iran) was provided. The rats under study were maintained for at least 20 days in the above-mentioned conditions before PCOS induction, so that they can completely get accustomed to the environment. All procedures were carried out according to the Guide for the Care and Use of Laboratory Animals (National Research Council 1996).

The rats were randomly divided into 6 groups: control, sham, PCOS and nettle extract-treated PCOS groups at concentrations of 150, 250 and 450 mg per kg of animal's body weight. Each group consisted of eight rats and all steps of the research were repeated three times. In order to induce polycystic ovary syndrome correctly, the rats were examined under vaginal smears, and those were chosen that had two or three regular estrous periods during the twelve to fourteen days of observing vaginal smears and also were in the estrous phase of their reproductive cycle. In this study, among the various methods of induction of PCOS, the single subcutaneous injection of 2 mg/rat estradiol valerate (Aburaihan Co.) (n=32) were used. The control group (n=8) that received no injection was used in order to compare and prove the induction of PCOS. This method of induction was chosen due to the maximum occurrence of symptoms of this syndrome (Hormonal abnormalities in the hypothalamic-pituitary-ovarian, anovulation and histological changes in the ovary, systemic inflammation and liver involvement in occurrence of symptoms of the syndrome) in studied animals.[10] Induction of PCOS was established during eight weeks due to irregular estrous cycle and occurrence of Persistent Vaginal Cornification phase in the vaginal smears during this period. Then, nettle dissolved in Dimethyl sulfoxide (DMSO) were intraperitoneally injected to three groups of PCOS rats with 150, 250 and 450 mg per kg of body weight concentrations. To examine the solvent effect of nettle same volume of DMSO was injected to sham group. After 21 days of treatment with nettle, rats were killed by chloroform inhalation and a part of the right lobe of the liver was removed and fixed in alcoholic Bouin's solution. Then tissue samples were dehydrated by ascending ethanol solution and sectioned in thickness of 6-7 mm and placed on slides covered with gelatin. Then in order to evaluate histomorphometric, after removing paraffin and discharging the slices by decreasing degrees of alcohol solutions, they were stained with hematoxylin and eosin. The cord hepatocytes rupture and the number of kupffer and hepatocytes cells in each section was counted using a light microscope with a

magnification of 250X in a total of 20 sections of liver tissue. In addition to study the liver, rats' blood was also examined serologically. To accomplish this, two ml of blood was taken from the animal's heart and incubated at 37°C. After the closure of fibrin strands, Blood samples' serum was separated using 1500 rpm centrifuge for 10 minutes, and until carrying out the Serologic tests to determine the changes in serum lipid profile (CHOD-PAP/endopoint method using reagents supplied by the biochemistry company), insulin (Ultrasensitive ELISA ALPCO Diagnostics, USA) and glucose (oxidase reaction Glucose Oxidase Analyzer, Beckman, Fullerton, CA) were kept at-20°C. Insulin resistance index HOMA-IR was used to evaluate insulin resistance. This index was calculated by multiplying the fasting blood glucose density (mmol/L) in fasting insulin density (mU/L) divided by the constant 22.5. The INSTAT3 Software and one way ANOVA were used for data analysis, P value less than 0.05 was considered significant, related graphs were plotted using EXCEL program. All values in this study were reported as Mean ± SD.

RESULTS

After statistical analysis, because of the lack of significant differences between sham and the control group, the data of sham group was omitted. The results of this study indicated changes in lipid profile in PCOS compared with control group. These changes include an increase in the average levels of LDL-cholesterol, triglycerides, total cholesterol, whereas HDL-cholesterol levels were reduced on average. In nettle extract-treated groups, improvement in this ratio was observed related to PCOS group. This means that the levels were close to the control group (Figure 1-3).

Serum cholesterol and triglyceride levels in control, PCOS and UD extract-treated PCOS groups (n= 8). Significant increases were observed in cholesterol and triglycerides in PCOS group in comparison with control group, While PCOS group treated with nettle extract showed a significant decrease in serum cholesterol and triglycerides versus PCOS group. (Figure 1)

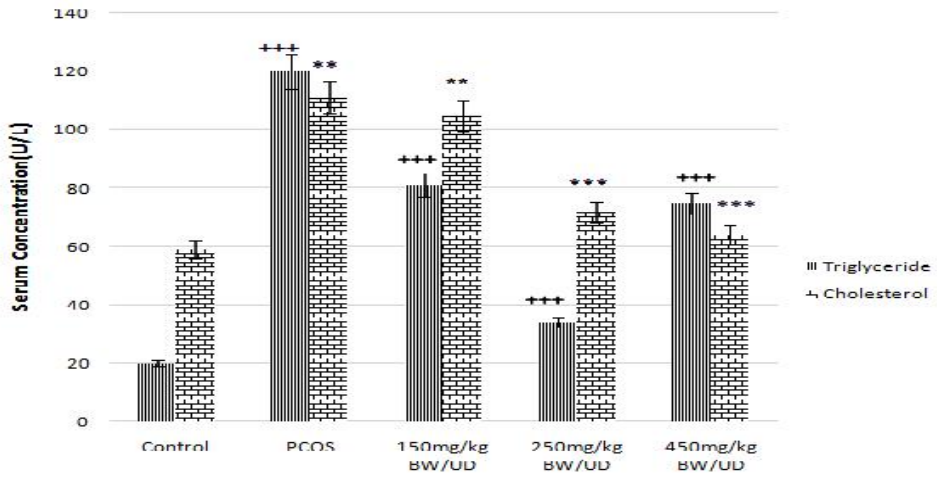

Fig 1: Serum triglyceride and cholesterol concentration

*[+]Differences PCOS group versus control group; *Differences PCOS group versus UD extract-treated PCOS groups; (Mean ± SD), [+++] P<0.001, *** P<0.001; **P<0.01, PCOS: Polycystic Ovary Syndrome, UD: Urtica dioica.*

Serum LDL-cholesterol levels in control, PCOS and UD extract-treated PCOS groups (n= 8). Significant increases were observed in LDL-cholesterol in PCOS group compared with control group; While PCOS group treated with nettle extract at a concentration of 250 mg per kg of body weight for 21 consecutive days, compared with PCOS, showed a significant decrease (Figure 2).

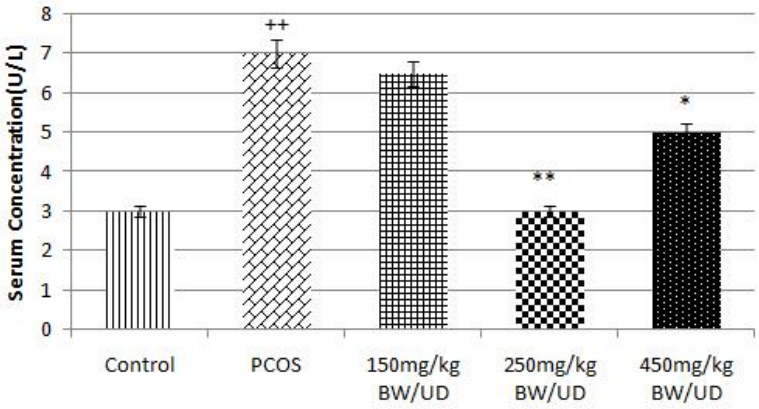

Fig 2: Serum LDL concentration

*[+]Differences PCOS group versus control group; *Differences PCOS group versus UD extract-treated PCOS groups; (Mean ± SD), [++]P<0.01, *P<0.05;**P<0.01; PCOS: Polycystic Ovary Syndrome; UD: Urtica dioica.*

Serum HDL-cholesterol levels in control, PCOS and UD extract-treated PCOS groups (n= 8). HDL-cholesterol levels in PCOS group versus control group showed a significant decrease, while the treatments concentration of 250 mg per kg of body weight showed a significant increase compared to PCOS (Figure 3).

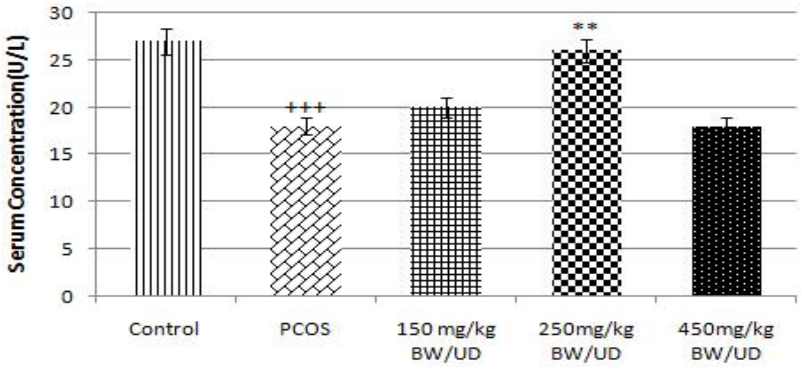

Fig 3: Serum HDL concentration

*[+]Differences PCOS group versus control group; *Differences PCOS group versus UD extract-treated PCOS groups; (Mean ±SD); [+++]P<0.001; **P<0.01; PCOS: Polycystic Ovary Syndrome; UD: Urtica dioica.*

Another part of the results indicated a significant increase in the level of insulin and blood glucose in PCOS group compared to control group and possibly inability of insulin on blood glucose muster, while in PCOS group treated with

nettle extract, this cases did dependently and significantly reduced.

Serum glucose and insulin levels and insulin resistance index (HOMA-IR) in control, PCOS and UD extract-treated PCOS groups (n= 8). Index of insulin Impassibility was calculated. Obtained results indicated that the amount of glucose and insulin in the PCOS group versus control group significantly increased, whereas the group treated with nettle extracts for 21 days Impassibility index decreased significantly compared to PCOS (Figure 4).

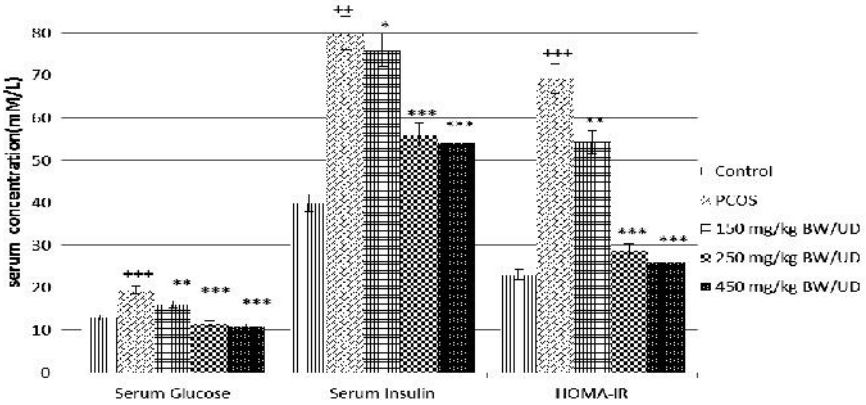

Fig 4: Serum glucose, insulin and HOMA-IR

*[+]Differences PCOS group versus control group; *Differences PCOS group versus UD extract-treated PCOS groups; (Mean ±SD); [+++]P<0.001; [++]P<0.01; ***P<0.001; **P<0.01;*P<0.05; Polycystic Ovary Syndrome; UD: Urtica dioica.*

After sectioning the liver and staining with hematoxylin and eosin, it revealed that the cytoplasm of hepatocytes of PCOS groups changed as inflation and in the shape and location of their nuclei and disturbance of sinusoids and cords of hepatocytes was observed in samples treated with nettle extract reduced the severity of tissue (Figure 5).

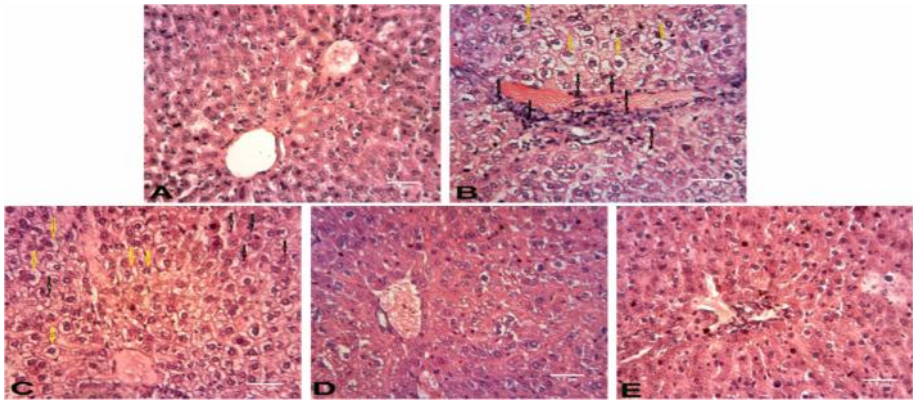

Fig 5: Photomicrograph of healthy liver tissue slices in control, PCOS and UD extract-treated PCOS groups (n= 8)

A) Control liver. Hepatocytes are normally and border between them is clear and sinusoids are distinguishable. B) PCOS liver. Yellow arrows indicate degenerated hepatocytes with swollen cytoplasm and black arrows indicate increased kupffer cells compared to control groups. C, D, E) Liver treated with various concentrations of the extract of nettle. Hepatocytes in images C, D, E not swollen state, sinusoids can be detected and the number of damaged hepatocytes decreased compared to PCOS group. Hematoxylin and eosin staining (X250), PCOS: polycystic ovary syndrome, UD: Urtica dioica.

Highly significant increase in the number of kupffer cells in PCOS group that represents the increase in liver inflammation was observed in this group compared to the control group, while significant decrease in the number of kupffer cells in samples treated with nettle extract compared to the PCOS group was observed (Table 1).

Table 1: Number of kupffer cells and hepatocyte cells in control, PCOS and UD extract-treated PCOS groups (n=8)

Groups / Cells	Control	PCOS	150 mg/kg BW UD	250 mg/kg BW UD	450 mg/kg BW UD
Normal hepatocytes	156	72^{+++}	68	126***	121***
Kupffer cell	9	82^{+++}	44***	35***	30***

*$^{+}$Differences PCOS group versus control group; *Differences PCOS group versus UD extract-treated PCOS groups; $^{+++}$P<0.001;***P<0.001; PCOS; PCOS: Polycystic Ovary Syndrome; UD: Urtica dioica.*

DISCUSSION

In this experimental study, the effects of UD on metabolic parameters such as insulin resistance, lipid profile and changes of the liver tissue as the main tissue in metabolite production were examined in PCOS-induced rats. The first and most important known common factor between PCOS and Metabolic Syndrome is Insulin Resistance. Studies showed that at least 50% of women with PCOS; unrelated to their obesity, have insulin resistance. However, at least 50% of the women who have PCOS are obese and approximately 20 percent of these women suffer from glucose intolerance or diabetes mellitus type II at the age of 40.[4]

In the insulin resistance situation, the cells are not able to response to the insulin, and the excess insulin causes the ovarian dysfunction that can result in hormonal Disorders of the hypothalamic–pituitary–ovary axis. Since Hepatocytes and adipocytes are metabolic superachievers in the body and the primary goals of insulin, insulin resistance is one of the supporter mechanisms of the fatty liver formation. In the insulin resistance, triglyceride are exported and stored in hepatocytes. This triglyceride storage leads to the abdominal fats and muscles. Since insulin resistance is a risk factor for cardiovascular diseases, it seems that people with PCOS will face with increased risk of developing diabetes, metabolic syndrome and heart diseases in the future. So that the metabolic syndrome is seen in the 33-47% and the insulin resistance is seen in 50-80% of people with PCOS.[11]

In the study of Bnouhan and Kazemyan, it was found that after using the extract of Nettle, there was a significant increased need to insulin injection.[12] Alisi and colleagues during their research on rats concluded that the needed insulin decreased in the group of receiving the decoction of Nettle and they reported its possible relation with insulin resistance.[13] Qujeq and colleagues showed 20-30% reduction of blood glucose of healthy animal, about 6 hours after using of these extracts.[14] Petlevski and colleagues showed 20% reduction of blood sugar, during 120 minutes after using Nettle extract.[15] Findings of this study were in accordance with their results, so that the index of insulin resistance increased significantly in comparison with the control group.

There isn't any unique mechanism to increase the sensitivity to insulin and

decrease the blood glucose. So, it is possible that in this study Koersitin – one of the family of poly phenols and one of the favonoid compounds of the nettle leaf results in supportive effects on the liver tissue of PCOS rats, via its anti-oxidant properties. It is proved that this substance also changes the function of the beta cells of pancreas and so it can be effective in development of indexes of blood glucose. Daher *et al,* (2006) concluded that the hydro-alcoholic extract of Nettle resulted in reforming of beta cells of pancreas with its antioxidant and clear of free radicals. So, it causes the reduction of blood glucose of rats.[16] In the study of Kamalkhan and colleagues, polyphenols resulted in reduction of glucose and Glycosylated hemoglobin of diabetic rats after 45 days, while it doesn't have any effect on the indexes of glucose of healthy rats. The lectin of Nettle also resulted in insulin secretion from beta cells of islets of Langerhans and it causes the reduction of blood glucose with the release of insulin.[17]

So, the possible mechanisms of reduction of blood glucose by Nettle are: increased secretion of insulin from the beta cells and release of insulin from its storages, reduction of glycosylated albumin and fructosamine, inhibition of intestinal alpha-glucosidase and reduction of glucose uptake.[18] It can be attributed to the findings of this study that proved the effects of this herb and its metabolites on the liver of PCOS rats and the effectiveness of its extract in the insulin and glucose level of blood.

The liver has the functional and structural role in the metabolism of glucose and lipid. Low density Lipoprotein (LDL) transfers the cholesterol from the liver to the tissues, while High density lipoprotein (HDL) facilitates the transfer of cholesterol from the peripheral tissues to the liver. So HDL has the positive effect on the decrease of histological cholesterol. Increase of total cholesterol, LDL- cholesterol and triglyceride and decrease of HDL- cholesterol is one of the most important lipid disorders in the people with metabolic syndrome and PCOS.[19] In this study, the induction of polycystic ovarian syndrome with Estradiol had the same results in changing of fat profile. Ultrasound studies of liver and analysis of liver enzymes in blood are indicative of 55% overlapping of symptoms of fatty liver with PCOS, because of similar abnormal lipid profile.[20] In 2011, the Lerchbaum group in Australia during the study on 611 rats showed that the index of fatty liver that is the algorithm, based on body mass index, triglycerides, gamma glutamyl transferase and also serologic disorders of liver, was more higher in the rats with PCOS.[21] In 2010, Golalipour and colleagues observed the increased serum HDL and decreased serum LDL due to injection of 100mg/kg BW of nettle in the diabetic rats.[22] Also in this study it was observed that nettle extract, especially at a concentration of 250 g/kg resulted in meaningful changes in the levels of each compound of lipid profile.

The observation of degenerated hepatocytes with inflated and eosinophilic cytoplasm, massive nucleus, mild fibrosis in perivenular areas, irregular hepatocytes lobules and the presence of collagen lamellas around nodules, presence the cells with fibroblastic schema in the fibrosis areas are of histological; liver dysfunctions like nonalcoholic fatty liver. In 2008, Wang proved that increased oxidative stress in the liver and imbalance between factors of pro apoptotic and anti-apoptotic can result in increased liver apoptosis that it has an important role in pathogenesis of this animal model. In his idea, increased oxidative stress and subsequent increase in expression of TNF-α result in inflammation in the liver of Sprague-Dawley rats.[23] Studies of liver

tissue sections are also indicative of increased damage of liver cells among increased kupffer cells, degenerated hepatocytes, irregular hepatocyte cords and massive cytoplasm that is based on Wang study in 2008, possibly because of increased tissue inflammation and also oxidative stress. In 2000 Kullak Ublik and colleagues found that hepatocyte damage like involvement of inflammatory cells and platelets, increased number and activity of kupffer cells and subsequently the release of cytokines are related to inflammatory process and free radical that are certainly as contributing factors of tissue fibrosis possibly.[24] The antioxidant effect of Kotersitin causes adjustment of inflammatory factors involved in PCOS like Tumor Necrosis Factor (TNF-α) and interlukin (IL-6) and C Reactive protein (CRP), based on the studies of Teucher and colleagues.[25] In addition to Koersitin, Caffeic malic that is the most important compound of Nettle, inhibits the Dose dependent synthesis of cyclooxygenase and so inhibits the synthesis of cytokines.[26]

In this study in tissue sections of PCOS rats and under treatment, the reduction of mentioned elements was observed that it was indicative of anti-inflammatory and anti-oxidant effects of Nettle on this tissue and these results are in accordance with the study of Basarn *et al*, in 1997. These researchers, who analyzed the biochemical hypoglycemic and antioxidant effects of nettle, showed that nettles prevent the liver damages in rats.[27]

CONCLUSION

In this survey, the total effect of Nettle on metabolic factors in PCOS-induced rats was analyzed for the first time. Our results indicated that the extract of Nettle, regarding to its ability in adjusting of lipid profile and increase the sensitivity to insulin, because of its flavonoid compounds, can be an effective method to decrease some of common symptoms between the metabolic syndrome and diabetes 2 and PCOS. Further investigation such as evaluation the effect of compounds of Nettle on the other symptoms of this complicated syndrome like increase angiogenesis and cardiovascular problems and the changes in the level of oxidative stress of involved tissues is suggested.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests.

ACKNOWLEDGMENT

This study that has been derived of the Master's thesis, has been performed in the laboratory of animal's reproduction and breeding, has enjoyed the support of the faculty of science, hereby thank President of the Kharazmi University.

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How to cite the article: Zare S, Nabiuni M, Tayanloo A, Hoseini S, Karimzadeh Bardei L. The effects of Urtica dioica extract on lipid profile, insulin resistance index and liver histology in polycystic ovary syndrome-induced Wistar rats. Adv Herb Med. 2015; 1(2): 23-33.