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Article

Effects of *Arctium lappa* aqueous extract on lipid profile and hepatic enzyme levels of sucrose-induced metabolic syndrome in female rats

Akram Ahangarpour[1] , Fatemeh Ramazani Ali-Akbari[2,*], Seyyedeh Marjan Mohaghegh[3], Ebtesam Asadinia[3]

[1]Jundishapur University of Medical Sciences, Health Research Institute, Diabetes Research Center, School of Medicine, Department of Physiology, Ahvaz, Iran, [2]Jundishapur University of Medical Sciences, School of Medicine, Departments of Physiology, Physiology Research Center, Student Research Committee, Ahvaz, Iran, [3]Jundishapur University of Medical Sciences, School of Para medicine, Department of Nutrition, Student Research Committee, Ahvaz, Iran

Arctium lappa is known to have antioxidant and antidiabetic effects in traditional medicine. Objectives: The aim of this paper was to study the effects of *A. lappa* root extract (AE) on lipid profile and hepatic enzyme levels in sucrose-induced metabolic syndrome (MS) in female rats. The study used 40 adult female Wistar rats weighing 150 g–250 g randomly divided into five groups: control, metabolic syndrome (MS), metabolic syndrome+AE at 50,100, 200 mg/kg. MS was induced by administering 50% sucrose in drinking water for 6 weeks. AE was intra-peritoneally administered daily at doses of 50,100, and 200 mg/kg for two sequential weeks at the end of the fourth week in metabolic syndrome rats. Twenty-four hours after the last administration of AE, blood was collected and centrifuged, and then the serum was used for the measurement of lipid profile and hepatic enzyme. Serum glucose, insulin, fasting insulin resistance index, body weight, water intake, lipid profile, and hepatic enzymes were significantly increased although food intake was decreased in MS rats compared to the control rats. The lipids and liver enzymes were reduced by AE extracts in the MS group. This study showed that the A. lappa root aqueous extract exhibits a hypolipidemic activity of hyperlipidemic rats. This activity is practically that of a triple-impact antioxidant, hypolipidemic, and hepatoprotective.

Uniterms: *Lappa arctium*/effects. Metabolic syndrome. Sucrose/lipid profile/hepatic enzymes.

INTRODUCTION

Insulin resistance is the main characteristic of the metabolic syndrome (MS), a complex metabolic disorder described by hypertension, obesity, dyslipidemia, hyperinsulinemia, and type 2diabetes (T2DM). MS is a group of risk factors connected to cardiovascular and chronic liver disorders (Poruba *et al.*, 2015; Flores *et al.,* 2016).

This syndrome has a high prevalence all over the world. Also, both environmental and genetic factors are known to relate to its progression. The recent increase in T2DM and MS is believed to be a consequence of a rise in inactive lifestyles combined with access to energy-rich food (Aguilera *et al.*, 2004; Vinagre *et al.*, 2010).

An experimental model that resembles MS can be induced in rats by administering high-fructose or high-sucrose (HS) diets.

Sucrose intake, in particular its fructose part induces the insulin resistance status (Aguilera *et al.*, 2004). Fructose is converted into glycerol-3-phosphate, and acetyl-coenzymeA in the liver is used for very low-density lipoprotein (VLDL) production in the liver (Basciano, Federico, Adeli, 2005).

Insulin resistance increases hydrolysis of stored triglycerides in adipocytes and their presence in the blood stream, causing a decrease in plasma levels of HDL-c (Roselino *et al.*, 2012).

The increases liver size and weight; moreover, the fatty liver observed in MS rats could contribute to

***Correspondence:** F. Ramazani Ali-Akbari. Department of Physiology. Diabetes Research Center, Physiology Research Center Ahvaz. Student Research Committee. Jundishapur University of Medical Sciences. Ahvaz, Iran. E-mail: ramezanizahra66@yahoo.com.

the progression of nonalcoholic steatosis induced by high sugar ingestion, is thought to be connected with obesity, hyperlipidemia, and diabetes (Aguilera *et al.*, 2004).

Previous studies found high plasma concentrations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), approving hepatic tissue pathology in MS rats (Aguilera *et al.*, 2004).

Herbal drugs utilized for the treatment of these conditions are extracts of plants affluent in antioxidants. *Arctium lappa, L.* (burdock) belongs to the Asteraceae family is cultivated in many countries, including Japan, and is greatly utilized in traditional medicine as a diuretic, antipyretic, or detoxifying agent (Predes *et al.*, 2009) and also for the treatment of arthritis, hypertension, gout, arteriosclerosis, hepatitis, and tonsillitis.

The main active components separated from burdock are as follows: tannin, arctigenin, arctiin, beta-eudesmol, caffeic acid, chlorogenic acid, inulin, trachelogenin4, sitosterol-beta-D-glucopyranoside, lappaol, and diarctigenin (Chan *et al.*, 2011).

Clinical trial studies show that burdock roots are hepatoprotective and have free radical scavenging effects in relation to the existence of caffeoylquinic acid derivatives (Feng *et al.*, 2012).

Cao *et al.* assayed the effects of burdock on streptozotocin-induced diabetic rats and realized that burdock's root exhibits hypoglycemic activity (Cao *et al.*, 2012).

Until now, no study has been done on the effects of burdock's root in experimental animals on lipid profiles and hepatic enzymes. Therefore, this study was aimed to assess these parameters in MS rats.

MATERIAL AND METHODS

Plant and extract

Burdock root samples were gathered from different places in Iran and then scientifically confirmed by the Botany Department of AJUMS. Voucher specimens of the plant are deposited in the herbarium of the University of Khorassan, (Khorassan, Iran. No. IT-ES/HE 36942). Fresh roots of burdock were cut into small pieces, washed in water, and dried at a temperature not surpassing 40°C for a week in an oven)Fante, Dieterish, Rodriguez, 2008). Powder weighing 100 g was mixed in 200 ml of distilled water and boiled for 30 min. After the mixture was filtered by Whatman paper (No.1), the filtrate was centrifuged at 3500 RMP for 15 min. The supernatant was evaporated at a temperature 40°C for 24 h and the acquired powder (46.5% and 46.5 g of root powder) was maintained at −20°C until utilized (Roghani *et al.*, 2007; Li *et al.,* 2016).

MS experimental model

A total of 40 adult female Wistar rats, which were normal, healthy, and nearly 150 g–250 g in body weight were purchased from the Physiology Center of Ahvaz. The rats were maintained in plastic cages at 25±2°C with a reverse 12-hour dark-light cycle and 65% ± 10% relative moistness. Food and water ad libitum during the study period. Our study was conducted in accordance with the guidelines for ethical laboratory animals' maintenance of the AJUMS, and the investigation protocol was confirmed by the Research Ethics Committee of AJUMS and certificated under the number 88s113. After a week of adjustment, the rats were divided mainly into two groups, the control group (n = 8) that was fed a standard diet and the metabolic syndrome group (n = 32) that was fed the standard diet plus 50% sucrose in drinking water for 6 weeks (Roghani *et al.*, 2007).

Ten days before inducing the metabolic syndrome, every morning between 8 a.m. and 9 a.m., vaginal smears were taken for all groups, and then pro-estrus was a selective phase of this investigation (Santos *et al.*, 2014).. The blood glucose level was measured by a glucometer (Elegans) at the end of the fourth and sixth weeks. MS rats exhibited blood glucose nearly 145 mg/dl–150 mg/dl and insulin resistance regarded to be MS status, and these are the criteria for inclusion into this study (Ahangarpour *et al.*, 2013). The ingestion of food and water and the body weight were monitored during the experiments.

Experimental diet

After the animals received treatment, during the 6 weeks, their insulin, glucose, lipid profile, and hepatic enzyme levels were measured.

Animals with MS, obtained as depicted above, were divided into four groups (n = 8), the metabolic syndrome group that was fed the standard diet without burdock extract and the metabolic syndrome groups that was fed the standard diet plus burdock extract (50, 100, 200 mg/kg, IP) (Asgari *et al.*, 2010). The burdock extract was administered daily for two sequential weeks from the end of the fourth week (Asgari *et al.*, 2010). At 24 hours after the end of IP injection, the rats were slightly anesthetized through the use of ether, and blood samples were acquired from the heart (Zamami *et al.*, 2008). The blood was centrifuged at 3500 RMP for 20 min, and then the serum was separated. Serum was stored at −70°C

until assessment. The serum was utilized to determine the levels of several biochemical factors, including blood glucose, insulin (IRMA kit, DiaSource Belgium, INS), lipid profile, and hepatic enzymes, using commercial kits and enzyme methods (Pars azmoon, Iran). FIRI was computed via the formula: FIRI = fasting insulin (μIU/ml) × fasting glucose (mg/dl) / 405. VLDL equals one-fifth of the triglycerides quantity (Ahangarpour *et al.*, 2014).

Statistical Analysis

The results are presented as mean ± SD. The data was analyzed via the SPSS program. Comparison between control and MS rats was conducted by t-test, and the difference between the groups was determined by ANOVA and post-hoc LSD tests. The values were regarded as significant when $p<0.05$.

RESULTS AND DISCUSSION

Serum glucose, insulin, fasting insulin resistance index, body weight, food intake, water intake, lipid profile, and hepatic enzymes were analyzed by the MS model.

Serum glucose, AST ($p<0.01$), insulin, FIRI, TG, total cholesterol, ALP levels, body weight ($p<0.001$) and VLDL, water intake ($p<0.05$) were significantly increased although HDL ($p<0.01$), food intake ($p<0.05$) was decreased in MS rats compared to control rats (Table I).

In this study, increased blood glucose, insulin, insulin resistance, body weight, water intake, TG, total cholesterol, VLDL, hepatic enzymes, and low HDL and food intake, are associated with MS, which agrees with previous studies (Ahangarpour, Yahyavi, 2011; Sampath, Karundevi, 2014). Sucrose administration can increase triglyceride levels via various mechanisms, including the liver's extra production of VLDL-c triglycerides and their release in the bloodstream, decrease the lipoprotein lipase effect and the excretion of triglyceride by feces (Khan *et al.*, 2015, Mousavi *et al.*; 2012). The increase of blood cholesterol is related to the reduction of endogenous cholesterol absorption or excretion (Khan *et al.*, 2015).

The elevation of plasma glucose and insulin, as well as FIRI, is related to the insulin resistance condition in the HS group. Abundant studies reported that a HS diet induces insulin resistance in animal models (Mousavi *et al.,* 2012).

It has been regarded that insulin resistance and hyperinsulinemia play an important role in the cause of liver disorder. Hypersediment of fat in muscles and adipocytes characterizes insulin resistance with subsequent gathering of fat in the hepatocyte (Lima *et al.*; 2016), which raises the grade of mitochondrial beta-oxidation of fatty acids and ketogenesis that may increase

TABLE I - Serum glucose, insulin, fasting insulin resistance index, body weight, food intake, water intake, lipid profile and hepatic enzymes in metabolic syndrome (MS) model

Groups	Control n = 8	MS n = 8	p-value
Glucose(mg/dL)	101.43 ± 14.26	140.5 ± 18.73	a**
Insulin (μIU/mL)	0.82 ± 0.44	1.7 ± 0.89	a***
FIRI	3.36 ± 1.87	9.8 ± 4.02	a***
Body weight(g)	250 ± 12.3	280 ± 15.3	a***
Food intake(g/rat/day)	25.46 ± 19.2	19.53 ± 0.44	a*
Water intake(mL/rat/day)	24.0 6 ± 2.4	29.7 ± 2.5	a*
Cholesterol(mg/dL)	57.83 ± 4.6	87 ± 5.63	a***
TG (mg/dL)	67.16 ± 15.2	102.66 ± 13.2	a***
LDL (mg/dL)	45.4 ± 11	43.8 ± 11	
HDL (mg/dL)	45.83 ± 4.6	32.33 ± 5.37	a**
VLDL (mg/dL)	13.6 ± 3	20.53 ± 2.46	a*
AST(u/l)	112.42 ± 8.28	159.85 ± 21.5	a**
ALT(u/l)	62.42 ± 3.16	74 ± 2.63	
ALP(u/l)	125 ± 15.14	590.5 ± 62.52	a***

a = comparison between control group with MS group. T-test was performed for the differences among two groups. FIRI: Fasting Insulin Resistance Index. n = 8; mean ± SD, *= $p < 0.05$**= $p < 0.01$, ***= $p < 0.001$.

lipid peroxidation and the gathering of reactive oxygen species (ROS) in the liver (Albano, Mottaran, Vidalli, 2005). ROS produce a sort of cellular arousal with a subsequent inflammatory effect that has been known as the pathological agent of liver disorder (Marra *et al.,* 2008).

Reduced insulin sensitivity also participates in lipid metabolism and hyperglycemia. Hypertriglyceridemia was demonstrated to be connected to liver disorder and increased FFA levels, which are responsible for increased insulin levels (Marchesini *et al.,* 2001).

Hyperglycemia in MS is associated with a large ROS generation and critical oxidative damage in various tissues, such as those of the liver. Lipid peroxidation and raised ROS have been identified as factors of decreasing antioxidant defense (Silva *et al.,* 2016). It was demonstrated that the extreme plasma-free fatty acids and glucose levels can be related to insulin resistance (Arner, 2002, Tomas *et al.,* 2002).

Effect of AE on lipid profile

Intake of Arctium lappa L. root extract was significantly decreased serum total cholesterol, TG (50,100, 200 mg/kg), serum LDL, HDL (200 mg/kg), VLDL (100, 200 mg/kg) levels ($p<0.001$), HDL, LDL at 50, 100 mg/kg ($p < 0.01$) and VLDL at 50 mg/kg ($p<0.05$) compared to MS rats (Table II).

The levels of serum total cholesterol, LDL, HDL, VLDL, and TG returned to the normal range due to AE administration in MS rats.

Surplus adipose tissue secretes various compounds, such as FFAs, adiponectin, and cytokines. Increased FFA levels indicate that increased muscle with fat in the liver is responsible for increased insulin level and insulin resistance. It seems that weight gain leads to insulin resistance.

Hyperinsulinemia can enhance the production of very-low-density lipoprotein and triglycerides. Insulin resistance in muscles leads to glucose intolerance and hyperglycemia, which may be aggravated via enhanced liver gluconeogenesis (Scott *et al.,* 2004).

The hypolipidemic effect of the burdock in the present investigation is in agreement with results on diabetic rats. Previous studies indicated that burdock root extract administration was associated with the improvement of glycogen content in the liver and muscles, lipid metabolism, and blood glucose in diabetic rats (Cao *et al.,* 2012). The hypolipidemic effect of burdock might be related, in part, to its antioxidative activity, which decreases the oxidative stress of hepatocytes, or to other unknown protective mechanism(s), such as the declination in the TG liver and muscle content, fat accumulation, serum insulin, insulin resistance, and glucose.

Burdock includes a wide range of effective pharmacological compounds, such as polyphenolics, phenolic acid, flavonoid, and chlorogenic acid (Faulkner, King, 1976). Chlorogenic acids exhibit hypoglycemic activity besides reducing triglyceride and cholesterol levels (Cao *et al.,* 2012). AE is a flavonoid-abundant extract. Flavonoids exhibiting insulin-like behavior have been separated from the plant. Some sorts of flavonoids can delete the lipid synthesis and release from hepatocytes (Hii *et al.,* 1985). The cholesterol-diminishing activity of burdock is mainly in consequence of the reduction of its absorption in the intestinal tract via lowering pancreatic lipase, elevating lipoprotein lipase activity, and increase

TABLE II - Effect of Arctium lappa L extract on total cholesterol, TG, LDL, HDL and VLDL levels in metabolic syndrome (MS) rats

Groups	Control n = 8	MS n = 8	Extract (50 mg/kg) n = 8	Extract (100 mg/kg) n = 8	Extract (200 mg/k) n = 8	p-value
Cholesterol (mg/dL)	57.83 ± 4.6	87 ± 5.63	61.85 ± 4.37	57.71 ± 3.23	52.23 ± 3.99	acde***
TG (mg/dL)	67.16 ± 15.2	102.66 ± 13.2	73.71 ± 19.55	65.71 ± 3.77	60.57 ± 8.95	acde***
LDL (mg/dL)	45.4 ± 11	43.8 ± 11	37.06 ± 5.05	35.67 ± 3.6	22.35 ± 5.3	cd** e***
HDL (mg/dL)	45.83 ± 4.6	32.33 ± 5.37	47.71 ± 4.97	52.61 ± 4.12	64.42 ± 3.49	acd**e***
VLDL (mg/dL)	13.6 ± 3	20.53 ± 2.46	14.74 ± 3.91	13.14 ± 1.75	12.11 ± 1.79	ac*de***

a = comparison between control group with MS group. c = comparison between extract at 50 mg/kg group with MS group. d = comparison between extract at 100 mg/kg group with MS group. e = comparison between extract at 200 mg/kg group with MS group. Triacylglycerol(TG), low density lipoprotein (LDL), high density lipoprotein (HDL), and very low density lipoprotein (VLDL).One-way analysis of variance (ANOVA) and post-hoc least significant difference (LSD) tests were performed for the differences among groups n = 8; mean ± SD, *p < 0.05, **= p < 0.01, ***= p < 0.001.

TABLE III - Effect of *Arctium lappa* L extract on hepatic enzymes in metabolic syndrome (MS) rats

Groups	Control n = 8	MS n = 8	Extract (50 mg/kg) n = 8	Extract (100 mg/kg) n = 8	Extract (200 mg/kg) n = 8	p-value
AST(u/l)	112.42 ± 8.28	159.85 ± 21.58	142.85 ± 7.04	120.83 ± 9.51	113.16 ± 7.83	a**b*e**
ALT(u/l)	62.42 ± 3.16	74 ± 2.63	71.28 ± 6.16	59 ± 5.71	36 ± 6.72	de**
ALP(u/l)	125 ± 15.14	590.5 ± 62.52	489.57 ± 63.21	396.42 ± 47.2	430.16 ± 51	a***de**

a = comparison between control group with MS group. c = comparison between extract at 50 mg/kg group with MS group. d= comparison between extract at 100 mg/kg group with MS group. e = comparison between extract at 200 mg/kg group with MS group. Alanine aminotransferas(ALT), aspartate aminotransferase(AST) and alkaline phosphatase (ALP). One-way analysis of variance (ANOVA) and post-hoc least significant difference (LSD) tests were performed for the differences among groups. n = 8; mean ± SD, *p < 0.05, **= p < 0.01, ***= p < 0.001.

in liver secretion. Polyphenolics may perform their hypolipidemic activity via the elevation of liver LDL receptors (Samah *et al.,* 2016).

Effect of AE on hepatic enzymes

Arctium lappa L extract AST, ALT, ALP (100, 200 mg/kg) levels (P < 0.01) AST at 50 mg/kg (P < 0.05) was significantly decreased serum (Table III).

The increase in the level of these enzymes in hyperlipidemic rats depicts an elevation in oxidative agents in consequence of the high plasma lipid level. The results of this study are in agreement with those of various previous investigations that demonstrate elevated plasma lipids, decreased antioxidant defenses, and elevated lipid peroxidation in the liver (Ghosian Moghaddm, Roghani, Maleki, 2016). Our results show that ALT and AST activity in the burdock-administered rats had decreased. The antioxidant effects of burdock have been demonstrated in terms of MDA, CAT, and GSH-Px tests in high-fat-diet rats (Wang *et al.,* 2016).

The hepatoprotective mechanism of burdock might be related, in part, to its antioxidative effect, which reduces the oxidative stress in liver cells. This result is supported via previous studies on the hepatoprotective effect related to reducing fat accumulation, lipid peroxidation, and free radical scavenging effects of the plant (Lin *et al.,* 2002). ALP accumulates in the bile duct and is frequently used to detect the integrity of the liver plasma membrane. Rising total ALP levels in plasma is associated with the elevated osteoplastic effect and described via some level of cholestasis. The present investigation reveals that the ALP level of HS-diet-fed rats were elevated. This increase is caused by de novo synthesis in hepatocytes and a reduction in the biliary release of bile acids and glutathione, which is a credible marker of liver disorder (Zagorova *et al.,* 2015). Administering burdock caused reduced plasma ALP levels in MS rats. The reduction of the enzyme level is a clear sign of the hepatoprotective effect (Saleh *et al.,* 2015).

Further investigations are needed to recognize the exact molecular mechanisms by which AE improves hepatic enzymes and blood lipids in MS rats.

In conclusion, this study showed that the burdock aqueous extract exhibits hypolipidemic activity in hyperlipidemic rats. This activity is practically that of a triple-impact antioxidant, hypolipidemic, and hepatoprotective. The burdock can defend cells from fat accumulation and oxidative stress. These effects are clearly derived from its high levels of flavonoids and polyphenolics.

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