Avicenna J Med Biochem. 2014 September; 2(1): e18782. DOI: 10.17795/ajmb-18782

Published online 2014 September 25. **Research Article**

Urtica dioica Effect on Malonyl-CoA Decarboxylase

Durdi Qujeq [1,2,*]; Mohsen Tatar [2]; Farideh Feizi [3]; Hadi Parsian [1,2]; Sohrab Halalkhor [2]

[1]Cellular and Molecular Biology Research Center, Department of Biochemistry and Biophysics, Faculty of Medicine, Babol University of Medical Sciences, Babol, IR Iran
[2]Department of Biochemistry and Biophysics, Faculty of Medicine, Babol University of Medical Sciences, Babol, IR Iran
[3]Department of Anatomical Sciences, Faculty of Medicine, Babol University of Medical Sciences, Babol, IR Iran

*Corresponding author: Durdi Qujeq, Cellular and Molecular Biology Research Center, Department of Biochemistry and Biophysics, Faculty of Medicine, Babol University of Medical Sciences, Babol, IR Iran. Tel: +98-1112229591-5, Fax: +98-1112226109, E-mail: d.qujeq@mubabol.ac.ir

Received: April 30, 2014; **Accepted:** June 2, 2014

Background: The malonyl-CoA decarboxylase (MCD, EC.4.1.1.9) enzyme regulates malonyl-CoA levels. The effect of aerial parts extracts of *Urtica dioica* (UD) on MCD is poorly understood.
Objectives: The present experiment was undertaken to evaluate the effect of UD aerial parts extracts on MCD level.
Materials and Methods: In this experimental study, two groups of rats were used: normal and hyperglycemic group. Then UD aerial parts extracts (5 mg /500 μL) administrated to the hyperglycemic group of rats and finally, the MCD and insulin levels were measured in both groups.
Results: Interestingly, we observed that the UD aerial parts extracts powder caused a significant ($P < 0.05$) increase in insulin level during the experiment, from the base level of 0.36 ± 0.07 μg/L to the peak value of 0.52 ± 0.15 μg/L. Also, it caused a significant ($P < 0.05$) decrease in MCD level, from the base level of 29.68 ± 1.29 pg/mL to the bottom value of 22.12 ± 2.41 pg/mL.
Conclusions: The results of the present study indicate that UD aerial part extracts would decrease MCD level in hyperglycemic rats.

Keywords:Urtica dioica; Malonyl Coenzyme A Decarboxylase; Streptozotocin

1. Background

Malonyl-CoA is not only a key intermediate for fatty acid synthesis, but also a key metabolic sensor (1). Much evidence has accumulated in recent years, indicating that malonyl-CoA is a cytosolic signal of glucose abundance (2, 3). Earlier studies also indicated that MCD could be an important site for intervention in diabetic status (3). Many studies showed that MCD is ubiquitously distributed in all organisms (4).

The enzyme malonyl-CoA decarboxylase (MCD, EC 4.1.1.9) catalyzes the conversion of malonyl-CoA to acetyl-CoA (4, 5). Furthermore, MCD balances the energy intake and expenditure (6). According to the literature, *Urtica dioica* has been known as a medicinal plant (7). Previous studies have also demonstrated that *U. dioica* is known for its antidiabetic effects in folk medicine (8-10).

Several experimental studies revealed that UD possesses hypoglycemic properties (11). Alcoholic and aqueous extracts of UD leaf can repair pancreatic tissue in streptozotocin-induced diabetic models (12). UD leaves extracts (given parenterally) possess a hypoglycemic effect on alloxan hyperglycemic rats (13). UD affects on the liver enzymes activity (14). Preliminary studies revealed that UD administration could prevent atherosclerosis by protecting liver enzymes (15). UD is shown to prevent low density lipoprotein (LDL) oxidation and has an antihypotensive effect (16).

Despite this knowledge about UD, there is little information about the effect of UD aerial parts extracts on MCD level. Given the above findings, it is worthwhile to study the possible effect of UD aerial parts extracts on MCD level. Based on the mentioned studies, we proposed the following hypothesis that administration of UD aerial parts extracts might contribute to the control of MCD.

2. Objectives

This study aimed to evaluate the effect of UD aerial parts extracts on MCD level.

3. Materials and Methods

3.1. Urtica dioica Aerial Parts

Urtica dioica aerial parts were collected from Babol City, Iran. The aerial parts were isolated and dried at laboratory temperature (20-25°C) in shadow and then were grounded into powder as described by Qujeq et al. (12, 17).

3.2. The Aqueous and Ethanolic Extract of Aerial Parts of Urtica dioica

In order to prepare the aqueous and ethanolic extract

of the aerial parts of *Urtica dioica*, we used the methods as described by Qujeq et al. (12, 13, 17).

3.3. Isolation and Purification of Aerial Parts of Urtica dioica Extracted by Chromatography

One-tenth gram of crude extract was loaded onto the column chromatography. The whole fractions were collected and used in the next steps. *Urtica dioica* aeri administration dose was 5 mg / 500 μL.

3.4. Animals

Male adult Wistar rats (n = 12) weighting between 180 to 225 g were used. The rats were divided into two groups: control group and hyperglycemic group. All protocols involving animals were approved by Babol University Animal Care and Use Committee. All experimental manipulations were carried out with the animal under ether inhalation anesthesia.

3.5. Induced Hyperglycemic Status

Streptozotocin (STZ) was dissolved in cold 0.9% saline solution just before use and injected intraperitoneally (IP) to the rats as described by Qujeq et al. (12, 17, 18). Hyperglycemic state was induced by a single IP injection of STZ (120 mg/kg body weight) to overnight fasted rats. Hyperglycemic state was confirmed by measuring the glucose concentration using a kit.

3.6. Experimental Design

A total amount of 5 mg / 500μL of aerial parts of *Urtica dioica* was administrated IP to hyperglycemic rats. At the end of the experiment, blood samples were collected and biochemical factors were assayed by the spectrophotometric method.

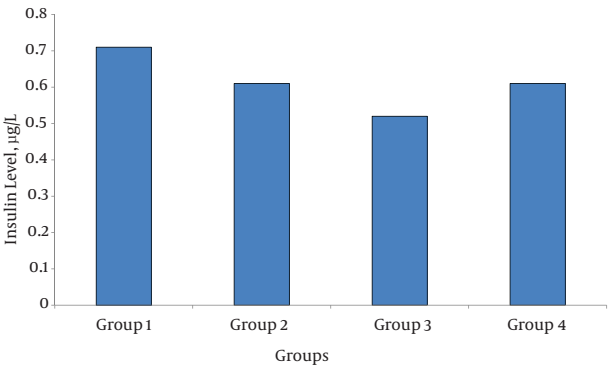
3.7. Experimental Procedure

Blood glucose level was determined by using a glucose kit (Jenway, Model 6505, UK, Pars Azmon Co., Tehran, Iran). Insulin level was measured by an enzyme immunoassay ELISA kit specific for rats made by Mercodia Rat insulin ELISA (10-1250-01, Mercodia AB, Uppsala, Sweden). The malonyl-CoA decarboxylase level was determined by ELISA method using a rat malonyl-CoA decarboxylase (MCD) ELISA kit (CSB-E11337r, Cusabio Biotech Co. LTD) as previously described (17, 18).

3.8. Statistical Analysis

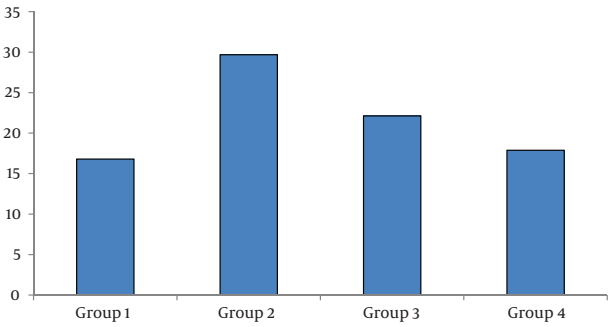
Data have been presented as mean ± standard error. All tests were carried out in triplicate. Statistical analysis were done using SPSS version 18.0. The significance of differences between the mean values was determined by analysis of variance, and a P value of less than 0.05 was considered statistically significant.

Figure 1. Serum Insulin Level (μg/L) With Administration of *Urtica dioica* Aerial Parts Extracts



Column 1, control; column 2, hyperglycemic; column 3, with aqueous extract; column 4, with ethanolic extract.

Figure 2. Serum MCD Level (pg/mL) With Administration of *Urtica dioica* Aerial Parts Extracts



Column 1, control; column 2, diabetic; column 3, with aqueous extract; column 4, with ethanolic extract.

4. Results

Aerial parts of UD extract increased insulin secretion compared to the untreated hyperglycemic group (0.52 ± 0.15 vs. 0.36 ± 0.07 μg/L, [P < 0.05]) (Figure 1). By administration of UD aerial parts extracts, MCD level was reduced compared to the untreated hyperglycemic group (22.12 ± 2.41 vs. 29.68 ± 1.29 pg/mL, [P < 0.05]). According to our findings, UD aerial parts extracts can increase insulin secretion. The results of the present study indicate that UD aerial parts extracts decrease MCD level in the animals made hyperglycemic with STZ (Figure 2).

5. Discussion

In hyperglycemic rats treated with UD aerial parts extracts, we observed a decrease in MCD level and increase in insulin level. Our data suggest that MCD can be targeted for the treatment of hyperglycemic state. This phenomenon is very important, because at cellular level, malonyl-CoA is a key factor in energy homeostasis (19).

On the other hand, MCD plays a key role in the balance of energy intake and expenditure through the regulation of malonyl-CoA and acetyl-CoA levels in the cellular metabolism. Malonyl-CoA is a signal for glucose content, which regulates fuel partitioning and metabolic signal transduction. Also, malonyl-CoA has been considered as an important site of intervention in a hyperglycemic state.

Generally, in situations where MCD level is elevated, the malonyl-CoA content is low, which results in elevated rates of fatty acid oxidation. In this regard, growing scientific and medical data supports the fact that MCD inhibitor decreases the pancreatic malonyl-CoA level (15).

Interestingly, our results showed that it may be possible to develop therapies for hyperglycemic state by changing malonyl-CoA levels (with plant materials effect on MCD). Our study provided the evidence that UD aerial parts extract regulated MCD level in hyperglycemic rat. While there has been great interest in the using activator or inhibitor of MCD as a highly selective tool, but the effects of such agents on insulin release from pancreatic tissue are disputed.

Many investigators reported that UD aerial parts extract has hypoglycemic activity and β-cell regenerative potency (20). Investigators showed that UD aerial parts extract was a potent stimulator of insulin release from β-cells (21). On the other hand, our findings are in contrast to the previous study (22), regarding nohypoglycemic activity of aqueous extract of UD. Our results indicated that increased insulin level by UD aerial parts extracts might be due to the regeneration in the β-cells.

This switch in energy substrate improves pancreatic function during hyperglycemia, suggesting that pharmacological inhibition of MCD may be a novel approach into treating hyperglycemia (23). However, other pancreatic mechanisms such as enhanced glucose transport into the cells, and inhibition of the endogenous glucose production cannot be rolled out. Therefore, administration of UD aerial parts extracts after inducing hyperglycemia in rats could increase insulin.

We provided the evidence of UD aerial parts extracts in the control of MCD level in hyperglycemic rats. Our data demonstrated that UD aerial parts extracts decrease MCD level. Our data also indicated that MCD inhibition may accelerate glucose oxidation, and improves functional recovery in hyperglycemic rat. Insulin is important in hyperglycemic activity of UD.

This can be considered as one of the mechanisms by which this extract can regulate the glucose homeostasis. The effect of MCD requires further evaluation; our data suggest that pharmacological inhibition of MCD may be a viable approach to the treatment of clinical pathologies associated with hyperglycemia. However, this result does not exclude the other involved mechanisms. The biochemical relevance of these findings is unclear and need to clarify.

Acknowledgements

We would like to thank Mr. Shikhzadeh for his excellent technical assistance.

Authors' Contributions

Study concept and design: Durdi Qujeq; acquisition of data: Mohsen Tatar; analysis and interpretation of data: Durdi Qujeq; drafting of the manuscript: Farideh Feizi; critical revision of the manuscript for important intellectual content: Hadi Parsian; statistical analysis: Sohrab Halalkhor; administrative, technical, and material support: Hadi Parsian; study supervision: Durdi Qujeq.

Funding/Support

This study was funded by the Research Council of Babol University of Medical Sciences.

References

1. Saha AK, Ruderman NB. Malonyl-CoA and AMP-activated protein kinase: an expanding partnership. *Mol Cell Biochem.* 2003;**253**(1-2):65–70.
2. McGarry JD, Brown NF. The mitochondrial carnitine palmitoyltransferase system. From concept to molecular analysis. *Eur J Biochem.* 1997;**244**(1):1–14.
3. Voilley N, Roduit R, Vicaretti R, Bonny C, Waeber G, Dyck JR, et al. Cloning and expression of rat pancreatic beta-cell malonyl-CoA decarboxylase. *Biochem J.* 1999;**340 (Pt 1)**:213–7.
4. Zhou D, Yuen P, Chu D, Thon V, McConnell S, Brown S, et al. Expression, purification, and characterization of human malonyl-CoA decarboxylase. *Protein Expr Purif.* 2004;**34**(2):261–9.
5. FitzPatrick DR, Hill A, Tolmie JL, Thorburn DR, Christodoulou J. The molecular basis of malonyl-CoA decarboxylase deficiency. *Am J Hum Genet.* 1999;**65**(2):318–26.
6. Folmes CD, Lopaschuk GD. Role of malonyl-CoA in heart disease and the hypothalamic control of obesity. *Cardiovasc Res.* 2007;**73**(2):278–87.
7. Gunther RT. *The Greek Herbal of Dioscorides.*NewYork: Hafner Publishing; 1959.
8. Petlevski R, Hadzija M, Slijepcevic M, Juretic D, Petrik J. Glutathione S-transferases and malondialdehyde in the liver of NOD mice on short-term treatment with plant mixture extract P-9801091. *Phytother Res.* 2003;**17**(4):311–4.
9. Burrowes JD, Van Houten G. Herbs and dietary supplement use in patients with stage 5 chronic kidney disease. *Nephrol Nurs J.* 2006;**33**(1):85–8.
10. Grover JK, Vats V, Rathi SS, Dawar R. Traditional Indian anti-diabetic plants attenuate progression of renal damage in streptozotocin induced diabetic mice. *J Ethnopharmacol.* 2001;**76**(3):233–8.
11. Newall CA, Anderson LA, Phillipson JD. *Herbal medicines: a guide for health-care professionals.*London: The pharmaceutical press; 1996. pp. 201–2
12. Qujeq D, Tatar M, Feizi F, Parsian H, Sohan Faraji A, Halalkhor S. Effect of Urtica dioica Leaf Alcoholic and Aqueous Extracts on the Number and the Diameter of the Islets in Diabetic Rats. *Int J Mol Cell Med.* 2013;**2**(1):21–6.
13. Qujeq D, Davary S, Moazzi Z, Mahjoub S. Effect of Urtica dioica leaf extract on activities of nucleoside diphosphate kinase and acetyl coenzyme, a carboxylase, in normal and hyperglycemic rats. *Afr J Pharm Pharmacol.* 2011;**5**:792–6.
14. Ozen T, Korkmaz H. Modulatory effect of Urtica dioica L. (Urticaceae) leaf extract on biotransformation enzyme systems, antioxidant enzymes, lactate dehydrogenase and lipid peroxidation in mice. *Phytomedicine.* 2003;**10**(5):405–15.
15. Kanter M, Meral I, Dede S, Gunduz H, Cemek M, Ozbek H, et al. Effects of Nigella sativa L. and Urtica dioica L. on lipid peroxidation, antioxidant enzyme systems and some liver enzymes in CCl4-treated rats. *J Vet Med A Physiol Pathol Clin Med.* 2003;**50**(5):264–8.
16. Domola MS, Vu V, Robson-Doucette CA, Sweeney G, Wheeler MB. Insulin mimetics in Urtica dioica: structural and computational

analyses of Urtica dioica extracts. *Phytother Res.* 2010;**24 Suppl 2**:S175–82.
17. Qujeq D, Tatar M, Feizi F, Parsian H, Halalkhor S. Effects of Teucrium polium aerial parts extracts on Malonyl-CoA decarboxylase level. *Mol Biol Res Commun.* 2013;**2**(4):101–7.
18. Qujeq D, Tatar M, Feizi F, Parsian H, Halalkhor S. Effects of Teucrium polium leaf extracts on AMPK level in isolated rat pancreases. *Res Mol Med.* 2013;**1**(3):32–28.
19. Bandyopadhyay GK, Yu JG, Ofrecio J, Olefsky JM. Increased malonyl-CoA levels in muscle from obese and type 2 diabetic subjects lead to decreased fatty acid oxidation and increased lipogenesis; thiazolidinedione treatment reverses these defects. *Diabetes.* 2006;**55**(8):2277–85.
20. Kavalali G, Tuncel H, Goksel S, Hatemi HH. Hypoglycemic activity of Urtica pilulifera in streptozotocin-diabetic rats. *J Ethnopharmacol.* 2003;**84**(2-3):241–5.
21. Farzami B, Ahmadvand D, Vardasbi S, Majin FJ, Khaghani S. Induction of insulin secretion by a component of Urtica dioica leave extract in perifused Islets of Langerhans and its in vivo effects in normal and streptozotocin diabetic rats. *J Ethnopharmacol.* 2003;**89**(1):47–53.
22. Roman Ramos R, Alarcon-Aguilar F, Lara-Lemus A, Flores-Saenz JL. Hypoglycemic effect of plants used in Mexico as antidiabetics. *Arch Med Res.* 1992;**23**(1):59–64.
23. Tang H, Yan Y, Feng Z, de Jesus RK, Yang L, Levorse DA, et al. Design and synthesis of a new class of malonyl-CoA decarboxylase inhibitors with anti-obesity and anti-diabetic activities. *Bioorg Med Chem Lett.* 2010;**20**(20):6088–92.