

# The effect of *Urtica dioica* extract on glycemic control of patients with type I diabetes: a randomized, double-blind clinical trial

## Abstract

Type 1 diabetes mellitus is the most common endocrine and metabolic disorder of childhood and adolescence. Its only current treatment is insulin therapy. Some herbs are traditionally used in treatment of diabetes mellitus such as *Urtica dioica*. Several Studies on animal models and few clinical trials have shown hypoglycemic effect for *Urtica dioica* leaves extract. This study aimed to evaluate hypoglycemic effect of *Urtica dioica* leaves extract in patients with type 1 diabetes (T1DM). A randomized double-blind placebo control clinical trial was done on 64 T1DM patients. Patients were randomly divided into placebo and control group. Along with injection of their usual daily insulin dose, they received 100mg/m<sup>2</sup> of *Urtica dioica* leaves extract or placebo orally for 3months. HbA1C level and daily dose of injected insulin were compared at the beginning and end of study in each and between 2groups. At the end of study, mean HbA1C level in case group was 9.7and in control group was 9.3 which was not statically significant (P value=0.17). Mean daily use of insulin in case group was 1.02IU/Kg and in control group was 1.17IU/Kg which was not statically significant (P value=0.13). In our study, use of *Urtica dioica* leaves extract did not have a significant hypoglycemic effect in patient with T1DM, neither it was effective to decrease daily insulin dose. We do not recommend use of *Urtica dioica* leaves extract in patients with T1DM as concomitant treatment with insulin for better Glycemic control.

**Keywords:** T1DM, *Urtica dioica* extract, Glycemic control, HbA1c

Volume 6 Issue 2 - 2019

Nasim Movahedi,<sup>1</sup> Hosein Zaeri,<sup>1</sup> Maryam Razzaghy Azar<sup>2</sup>

<sup>1</sup>Department of Pediatrics, Golestan University of Medical Sciences, Iran

<sup>2</sup>Department of Pediatrics, Iran University of Medical Sciences, Iran

**Correspondence:** Nasim Movahedi, Department of Pediatrics, Golestan University of Medical Sciences, Iran, Tel +98 9112770024, Email movahedi.nasm@gmail.com

**Received:** March 08, 2019 | **Published:** April 03, 2019

## Introduction

Type I diabetes is increasing in some regions of the world and this indicates the increasing prevalence of the diabetes in young ages. Because type I diabetes results in serious long-term complications in young ages, prognosis of the disease and intensity of its complications are directly related to glycemic control.<sup>1</sup> Today the only treatment for type I diabetes is insulin injection which necessitates multiple daily injections for years and this is a difficult and stressful task for the patient and families. Many attempts and experiments were carried out to find an alternative treatment for insulin so that diabetes could be controlled through simpler ways such as inhaled insulin. In this regard, herbal plants were considered to be used to control the blood sugar. This field has drawn the attention of numerous researchers within past few years due to previous history of herbal drugs usages in different societies and people's higher inclination towards traditional medicine and it has provided the environment for conducting multiple studies in different parts of the world. In Iranian traditional medicine, Stinging nettle has been used for treating different diseases such as diabetes. The liquid herbal extract of the nettle has been used as a complement for treating diabetes, in Iran and other countries of the region and it was affordable for patients and could be easily used. Considering the results of previous studies on the effect of extract of nettle on animals and some other limited studies on humans and lack of extensive and controlled study on children with type I diabetes, the present study aims to examine the effects of extract of nettle leaf on improvement of glycemic control of patients with type I diabetes in an extensive and controlled clinical trial design.

## Methods

### Participants and study design

This study is a randomized double-blind placebo controlled clinical trial on 64children within the age range of 6 to 17years who had been diagnosed with type 1 diabetes. The inclusion criteria for the present study are: children with type 1 diabetes who were diagnosed by ADA criteria and at least 6months passed since the diagnosis of diabetes, treatment with insulin, ages between 6 to 17years, and lack of underlying disease. The exclusion criteria include lack of proper consumption of *nettle extract* during the study, lack of necessary cooperation for orderly visits, suffering from another disease during the study, certain side effects preventing from consumption of the extract, consumption of other drugs such as herbal mixtures and vitamin supplements during the study. To blind the study, the researchers and patients were not informed of their allocated group (i.e. intervention or control group) and content of the drug prescribed for patients (Figure 1).

### Extract specifications

Stinging nettle (*Urtica dioica* L.) was identified, planted and harvested by Giah Essence Pharmaceutical Company in Gorgan (Iran). The aerial parts of the plants were removed and powdered. Extracting was done using percolation method at 25±2°C within three days (the selected solvent was 70percent pure ethanol). Then, the solvent was evaporated at 40°C in a vacuum evaporator and the remaining materials were placed in a vacuum oven set at room

temperature to be dried. Following microbial culture and confirmation of microbial laboratory, nettle granules had to be made for filling in the capsules. To do so, dry nettle and neutral material of microcrystalline cellulose were used through dry granulation method. Considering the determined dosage, each 350mg capsule contained 40mg of dry nettle material. The nettle-containing and placebo capsules were not different in terms of appearance, color, and weight and packaging. The drug containers were labeled A and B and only the pharmacist was aware of content of each container.

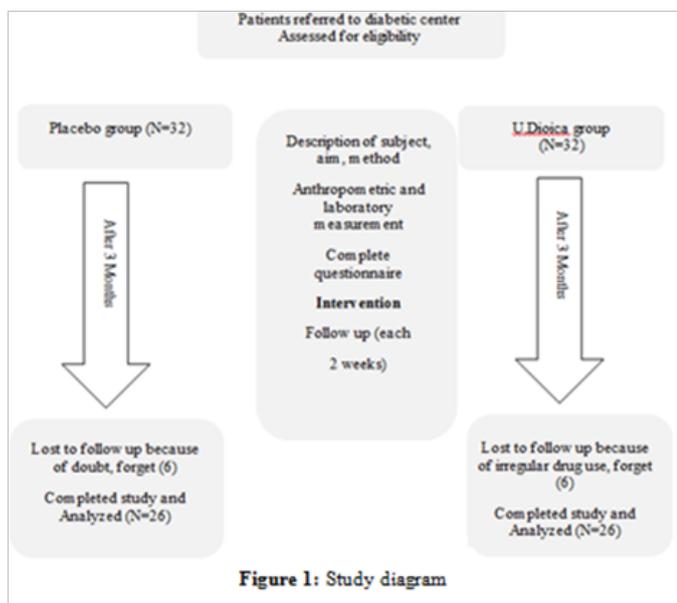


Figure 1 Study diagram.

### Intervention and measurements

Clinical and laboratory assessments (i.e. FBS, HbA1C, LFT, electrolytes, lipid profile, CBC, CPK and U/A) were done to evaluate the possibility of patient's enrollment in the study. The patients' diabetes files used for registering their blood sugar were controlled and necessary procedures were taught about the administration of insulin, blood sugar check-up with glucometer at home and noting it down in diabetes files. The insulin dosages were precisely recorded for each patient every day. The patients were randomly allocated to intervention group (*nettle extract*) and control group (placebo). In the first group, herbal extract of nettle leaf was administered orally with daily dosage of 100mg/m<sub>2</sub>. The dose was prescribed in two sessions (morning and evening) as a supplement to insulin for 3months. In the control group, placebo was administered along with insulin at similar dosage and time with intervention group. Determination of the dosage of the extract of nettle leaf was done based on the recommendation of PDR for Herbal Medicine (4th Edition, 2007). During the study, patients were precisely monitored in terms of consistent and timely use of drug, insulin injection, blood sugar check-up, side effects and lack of change in diet and physical activity. All patients and parents were recommended to stop taking the capsules and contact their physicians immediately if they saw any unusual symptoms.

During the study, patients were visited once every week for the first month and once every two weeks for the second and third month. The daily insulin dosage and blood sugar values were reviewed in the relevant files. If it was necessary, the insulin dosage was modified. At the end of study, complete examinations were done and previous basic tests were done again and obtained results were analyzed.

### Ethical consideration

The study was recorded in Iranian Registry of Clinical Trials (ID Code: IRCT201412084585N7) and confirmation letter was received from the center. The project administrator offered a complete explanation of the purpose and the methodology of the project to parents and patients. Before study starts, they signed the written agreement forms. Patients and their parents were authorized to refuse cooperation with project at any time during the study and for any reason.

### Statistical analysis

Data analysis was done through SPSS Software (version 16). First, the normality of data was verified using Kolmogorov-Smirnov test. The normality of variables of HbA1C, daily insulin dosage, and difference of HbA1C were confirmed in before and after steps but the difference of daily insulin dosage did not show a normal distribution in before and after step. In order to compare HbA1C and daily insulin dosage in the two steps, paired t-test was used. In addition, comparison between the two groups was done through independent t-test. Variation of HbA1C and insulin for the two groups were statistically analyzed through independent t-test and Mann Whitney test. To compare the represented side effects such as headache and stomachache between the two groups for three months, chi-square test was conducted. In this regard, the significance level of tests was regarded as 0.05.

### Results

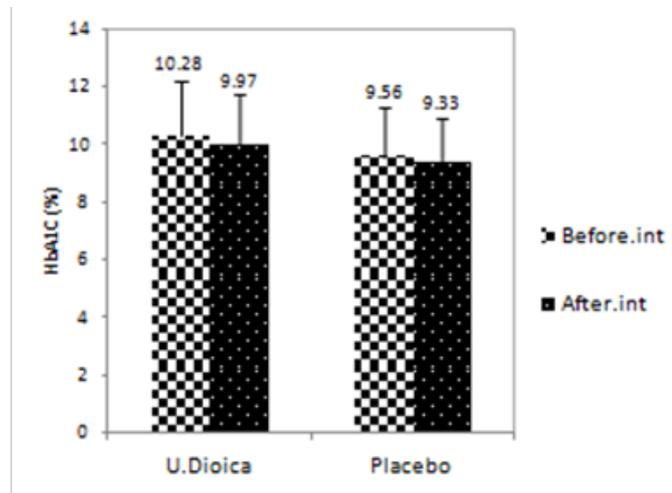
In this study, 64patients with type I diabetes who were compliant with inclusion criteria participated in the study. Out of those patients, 52participants continued their cooperation with the project to the end. As a result, 26patients were in intervention group and 26patients were included in control group. It should be noted that 5patients did not cooperate because of not attending the scheduled visits, 4patients denied to continue as they were concerned with the effects of nettle and 3patients were excluded from the study due to unorderly use of the capsules. The patients' demographic characteristics are represented in Table 1.

Table 1 Demographic Information of Examined Patients

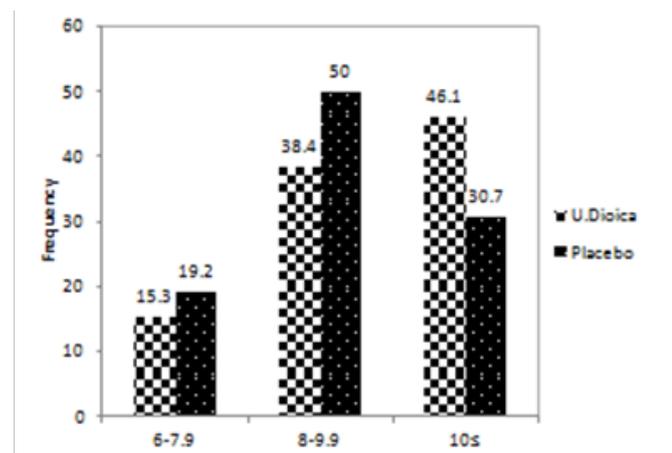
Variable	Group	U. Dioica	Placebo	P-Value
Age (yrs)		11.7±0.2	10.6±0.2	0.12
Gender (Male N-%)		12 (46.1%)	8 (30.7%)	0.09
Disease Duration (months)		44.19±29.8	48.15±24.8	0.6
BMI (kg/m <sub>2</sub> )		18.2±2.6	18.01±3.7	0.7
Insulin Dosage (U/Kg)		1.05±0.3	1.17±0.4	0.2
HbA1C (%)		10.2±1.9	9.56±1.7	0.1
HbA1C Category (N-%)	Good (6-7.9)	4 (15.4%)	5 (19.2%)	0.2
	Fair (8-9.9)	7 (26.9%)	12 (46.2%)	
	Poor (10≤)	15 (57.7%)	9 (34.6%)	
	NPH/Regular	6 (23%)	6 (23%)	
Insulin Regime (N-%)	Basal/Bolus	20 (76%)	19 (73%)	0.7
	Novomix	0 (0%)	1 (3.8%)	

After 3months from taking the capsules containing the extract of nettle leaf and placebo, mean A1C at the end of the study reduced. The

difference was 0.31 (P=0.09) for intervention group and 0.22 (P=0.7) for control group. In addition, variance of HbA1C did not suggest significant statistical difference when control and intervention groups were compared at the end of intervention (9.97 for intervention group and 9.33 for control group, P=0.174; Figures 2 and Figure 3).



**Figure 2** Mean HbA1C at start and end of study for intervention and control groups.



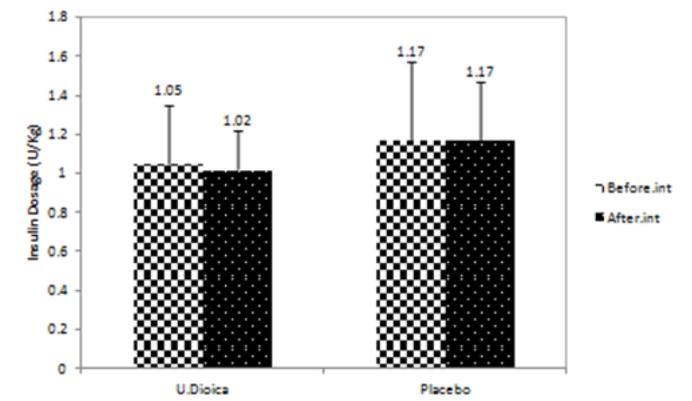
**Figure 3** Frequency distribution of Hemoglobin A1C at end of study for both groups.

As the results suggest, 3 patients in intervention group had poor control level of hemoglobin A1C at the beginning of the study. However, better glycemic control decreased hemoglobin A1C level to fair level at the end of the study. Mean hemoglobin A1C levels for this group of patients were 11.59 and 11.02 at the start and end of the study respectively (P-value=0.05). In control group, 9 patients had poor control of hemoglobin A1C level at the beginning of the study (10<), mean hemoglobin A1C levels for these patients at the beginning and end of the study were 11.51 and 10.66 respectively (P-value=0.02).

After three months of taking nettle leaf extract, average reductions of daily insulin administration for intervention and control groups were 0.03 and 0 respectively. Based on results of Mann-Whitney U test, one could suggest that the two groups did not have any significant statistical differences (P>0.05; Figure 4).

During the study, no case of severe medical allergy was found among the patients. No specific complain which required cessation

of drug administration or hospitalization were occurred. Some patients reported infrequent abdominal pain and headache which were intermittent and relatively mild but none of the cases stopped using the drug. It should be noted that 30.8 percent of patients in intervention group and 15.4 percent of patients in control group have reported side effects such as abdominal pain, undesirable smell of the drug after administration, dizziness, non-symptomatic increase of liver enzymes and stomachache accompanied with increase of liver enzymes (P=0.188).



**Figure 4** Mean insulin dosage before and after intervention for intervention and control groups.

## Discussion

The results of the present study suggest that use of 100mg/m<sup>2</sup> nettle extract twice a day for 3 months could improve glycemic control and reduce patient's insulin requirement but these changes were not statistically significant.

In this study, the patients of the two groups characterized with poor blood sugar control at the beginning of the study had improved blood sugar control at the end of the study. However, the intervention group did not show significant improvement of blood sugar control in comparison with control group. Therefore, the improvement is the outcome of another factor rather than the use of the nettle. Psychological-mental factors are among the ones exerting significantly high influence on glycemic control of patients. Considering the age group of this survey, the effect increases to a higher extent. Frequent physician's visits, parents' higher control and monitoring of insulin intake and children's diet could justify the improved control of blood sugar in this group of patients.

In most previous studies such as Shabani,<sup>2</sup> Karimiani,<sup>3</sup> Hassani et al.,<sup>4</sup> Farzami et al.,<sup>7</sup> Bnouham,<sup>12</sup> Kavalali et al.,<sup>21</sup> Yousefi et al.,<sup>5</sup> and Gotalipur et al.,<sup>8</sup> experimentation on diabetic rats were done through Streptozotocin. The findings suggested that the extract of nettle leaf affects the reduction of blood sugar significantly. However, Mobasheri et al.<sup>9</sup> suggested that complete alcoholic nettle extract could stimulate the insulin expression and C-peptide from pancreatic beta cells of rats. The extract could also add the sensitivity of human muscle cells to insulin.<sup>11</sup> Kazemian et al.<sup>6</sup> studied the effect of nettle extract on blood sugar of patients with type I diabetes. Their study was conducted on 10 patients for 2 days. In the second day, 30CC nettle water per square meter body surface area was administered. The findings of their study suggested that statistically significant reduction of insulin occurred in the second day but except for blood sugar level at 10th night no change in patients' blood sugar was observed.<sup>13-21</sup>

Reviewed this effect in a three-day period. They divided patients to 10 groups, each of which included 3 patients. The first group was prescribed 15ml/mT nettle extract which was administered once a day and the prescribed amount for each group increased 15ml/m<sub>2</sub> in comparison with previous groups. They suggested that the extract of nettle leaf has significant delay effect. It also reduces blood sugar and improves glycemic control of patients with type I diabetes while it has no significant side effects.<sup>10</sup> A major difference between the above mentioned study and this study is the prescription time of nettle extract. Maybe, nettle has short-term effect on blood sugar regulation but as Zaeri et al.<sup>10</sup> suggested that it does not exert any long-term effect.

In addition, another factor affecting anti-diabetic effects of nettle is the prescribed dosage. In this study, the minimum dosage was used which was recommended in herbal pharmacology books while Zaeri et al.<sup>10</sup> prescribed nettle extract by adopting ascending dose. Kezemian et al.<sup>10</sup> administered 30CC per square meter of nettle extract. This might be another reason for different results of the present study.

In a clinical trial, Namazi et al.<sup>23</sup> studied the effect of hydro-alcoholic extract of nettle leaf on blood sugar and resistance to insulin in patients with type II diabetes after they took the extract for 8 weeks. At the end of 8th week, the intervention group has significantly lower HbA1C and FBS than the control group. But, significant difference between fasting insulin concentration and resistance to insulin was not observed.<sup>23</sup> In another clinical trial, Kianbakht et al.<sup>24</sup> used 500mg nettle capsules for treating patients with type II diabetes. They found out that HbA1C, 2hpp and FSB of the intervention group were significantly lower than those of the control group. The difference between results of this study and findings of above-mentioned two studies could be justified through anti-diabetic mechanisms of medicinal herbs (i.e. regulation of gene expression and insulin synthesis, increase of insulin expression and reduction of glucose uptake) and different pathophysiologies of type I and II diabetes.<sup>25</sup>

## Conclusion

Prescribing 100mg/m<sub>2</sub> of *Urtica dioica* leaf extract twice a day for 3 months did not significantly improve glycemic control of patients with type I diabetes. Although the extract does not have any significant side effects, the researchers do not recommend the extract for better control of blood sugar in patients with type I diabetes.

## Funding details

This research supported financially by Neonatal and Children's Health Research Center, Golestan University of Medical Sciences and Endocrinology and Metabolism Research Institute Tehran University of Medical Sciences, Iran (Grant number #93041041870). This article is extracted from residential thesis of The Effect of *Urtica dioica* Extract on Glycemic Control of Patients with Type I Diabetes.

## Acknowledgment

The authors would like to thank all the staffs of the Taleghani Hospital in Gorgan. The authors also gratefully acknowledge the cooperation of the participating patients, without whom this investigation would not have been possible.

## Conflicts of interest

Authors declare that there is no conflict of interest.

## References

1. Behrman R, Kliegman R, Jenson H, et al. Nelson Textbook of Pediatrics. 19th ed. Philadelphia Saunders Elsevier. 2011:1968–1689.
2. Shabani M. Evaluating the function of urtica extracts on lowering blood glucose level. [Dissertation]. Tehran uni. 1374.
3. Karimani M. Identifying the molecular structure of glucose lowering elements in nettle. [Dissertation]. Tarbiat modarres uni. 1375.
4. Hasani SH. Identifying the place of effective glucose lowering elements of nettle. [Dissertation]. Tehran uni. 1376.
5. Yusefi M. Identifying the LD50 of *Urtica dioica*. [Dissertation]. Shahid Beheshti uni. 1376.
6. Kazemian A. Evaluating the effects of nettle on glycemic control of type one diabetic patients [Dissertation]. Tehran uni. 1381.
7. Farzami B. Induction of insulin secretion with nettle extracts. Tehran University. 1382.
8. Golalipor M. Protective effects of nettle extract on Blood glucose and pancreas beta cells of streptozocin induced diabetic rats. Golestan University of medical sciences. 1386.
9. Mobaseri A. Evaluating the effect of nettle extracts on muscle cells [dissertation]. Tehran uni. 1388.
10. Zaeri H. Evaluating the effects of aqueous extract of nettle on glycemic control of type one diabetic patients [dissertation], Tehran uni. 1389.
11. Swanston S, Day C, Flatt P, et al. Glycemic effects of traditional European plant treatment for diabetes studies in normal and Streptozotocin diabetic mice. *Diabetes Res.* 1989;10(2):69–73.
12. Bnouham M, Merhafour FZ, Ziyat A, et al. Anti-hyperglycemic activity of the aqueous extract of *Urtica dioica*. *Fitotrapia.* 2003;74(8):677–681.
13. Onal S, Timur S, Okutucu B, et al. Inhibition of Alpha-glucosidase by aqueous extracts of some potent antidiabetic medicinal herbs. *Prep Biochem Biotechnol.* 2005;35(1):29–36.
14. Kraus R, Spiteller G. Phenolic components from roots of *urtica dioica*. *Phytochemistry.* 1990;29(5):1653–1659.
15. Hiranto T, Homma M, Oka K. effect of stinging nettle root extracts and their steradiol components on the Na/K/ATPase of the benign prostatic hyperplasia. *Planta Medica.* 1994;60(1):30–33.
16. Krstic P, Pzamic R. Astringent and mineral component in leaves of nettle (U.D) from much natural location. 1985;3:191–198.
17. Otoom S, Al SS, Kerem Z, et al. The use of medicinal herbs by diabetic Jordanian patients. *J Herb Pharmacother abs.* 2006;6(2):31–41.
18. Fodor J, Keve T. New phytotherapeutic opportunity in the prevention and treatment of type 2 of diabetes mellitus. *Acta Pharm Hung.* 2006;76(4):200–207.
19. Said O, Fulder S, Khalil K. Maintaining a physiological blood glucose level with 'glucoselevel', a combination of four anti-diabetes plants used in the traditional arab herbal medicine. *Evid Based Complement Alternat Med.* 2008;5(4):421–428.
20. Kultur S. Medicinal plants used in kirklareli (Turkey). *J Ethnopharmacol abs.* 2007;111(2):341–364.
21. Kavalali G, Tuncel H, Goksel S, et al. Hypoglycemic activity of *Urtica pilulifera* in streptozotocin-diabetic rats. *J Ethnopharmacol.* 2003;84(3):241–245.
22. Domola MVV, Robson DC, Sweeney G, et al. Insulin mimetics in *Urtica dioica*: structural and computational analyses of *Urtica dioica* extracts. *Phytother Res.* 2010;24(2):233–234.

23. Namazi N, Esfanjani AT, Bahrami A, et al. Effect of Hydroalcoholic extract of Nettle (*Urtica Dioica*) on Glycemic Index and Insulin Resistance Index in Type 2 Diabetic Patients. *Iranian Journal of Endocrinology and Metabolism*. 2012;13(6):561–569.
24. Kianbakht S1, Khalighi SF, Dabaghian FH. Improved glycemic control in patients with advanced type 2 diabetes mellitus taking *Urtica dioica* leaf extract: a randomized double-blind placebo-controlled clinical trial. *Clin Lab*. 2013;59(9):1071–1076.
25. Tabatabaei MO, Larijani B, Abdollahi M. A systematic review of *in vitro* studies conducted on effect of herbal products on secretion of insulin from langerhans islets. *Journal pharm pharmaceutscience*. 2012;15(3):447–466.