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Quran and Singular: Protective Effects of Extract of Urtica dioica Leaf on Mucosa of Intestine in Diabetic Rats

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ABSTRACT

Background: In Quran, the great, Surah Baghareh, Verse 255, it is stated: " Who is he aware of everything and the limited knowledge of humankind originates in His unending and unlimited knowledge". One of these sciences is the science of Pharmaceutical plants. Recognizing these plants plays an important role in the improvement of human society health. Herbal therapy is one of the supplement methods for improving the health rate. In Al-Rahman, verse 11, the significance of plants and fruits is mentioned. One of the mentioned plants is Urtica dioica, which is anti-diabetic.

Objectives: The objective of this study is to determine the protective effect of extract of Urtica dioica leaf on small intestine structure in order to find its anti-diabetic effect.

Materials and Methods: At first, the rats were injected 50 kg. mg-1ofStreptozotocin via their tail vane. The fasting animals with more than 250 mg dl-1 blood sugar was diagnosed as diabetic. One diabetic group was under therapy of blue extract of Urtica dioica leaf (daily injection of 4 cc kg -1 in Peritoneum). The blood sample and tissue of the intestine were prepared after two months of therapy and killing animals. The Histologist saw the samples tissue. The quality of parameters of tissue was assessed in both the therapeutic and non-therapeutic groups.

Results: The blood sugar decreased from 400 ± 54.2 mg dl -1 to 78.9 ± 11.9 dl ($P > 0.0004$) in therapeuticgroup while the blood sugar was not found in diabetic group. The mononuclear cells and destructive tissues were found in necrosis and infiltration of diabetic group, also epithelium and Lieberkuhn glands were destructed and the villain became short and atrophy 9 and the high level of blood shedding and exudate were found. In contrast, necrosis were not found in therapeutic group and infiltration of mononuclear cells and inflammation tissues were found slightly. There were not shorted villain and atrophy. Consuming Urtica dioica prevents the intestinal side effects of diabetes.

Conclusions: Urtica dioica protects themucosa of small intestine. This may lead to recovery of blood transfusion with decreasing end product mechanism (Advanced glicosylation end product) or improving the function of the nervous system by decreasing Sorbitol production. Further studies are needed for determining the major mechanisms.

Implication for health policy/practice/research/medical education:
Today, the traditional medicine is considered as an alternative one for completing treatment in common medicine. Application of Quran, The great, and documenting the statements of Muslim physicians can play an important role for improving the health.

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1. Background

In Quran, the great, Surah Baghareh, Verse 255, it is stated: "Who is he aware of everything and the limited knowledge of humankind originates in His unending and unlimited knowledge"(1). One of these sciences is the science of Pharmaceutical plants. Recognizing these plants plays an important role in the improvement of human society health. Herbal therapy is one of the alternative methods for improving health rate. In Al-Rahman, verse 11, the significance of plants and fruits is mentioned (2). One of the mentioned plants is Urtica dioica, which is anti-diabetic (3). There are two kinds of diabetes: Diabetes mellitus which includes prevalent metabolic disorders and their common point is hyperglycemia phenotype. Disorder in metabolism adjustment resulting from diabetes causes secondary pathophysiological changes in various organs of body. These changes cause a lot of problems for diabetic people and the health system in society (4, 5). Most of the chemical drugs originate in natural and herbal substances. Furthermore, there is proper climate setting for Pharmaceutical plants in Iran. One of the known Pharmaceutical and most-used plants in Iran is Urtica dioica. Urtica dioica is herbaceous perennial plant with straight stems which is half to one meter tall or more. Itself grows in abundance in ruined places, gardens and moist regions in countryside, shaded places and the animal farms. One of the applications of Urtica dioica is diabetes treatment (3). Urtica dioica has Tanin, Musylar, a kind of waxy substance, Formic acid, one Phytosterin, Potassium Nitrate, Ferriferouscompounds and a kind of Glucosidewith skin reddening effect. Knezaurek is made of Urticine, the colorful material (3). In medieval, there had been various therapeutic specificities for Urtica dioica and its other types. In 12th A.D, St Hildegard had applied Urtica dioica for stomachache healing, and other physicians applied it for angina therapy, blood phlegm, cancer and the diseases related to spleen (3). Fortunately, Urtica dioica has not any severe side effects. Its only side effects are contact Urticaria (6) and allergy to Urtica dioica pollen (7). The best time to harvest and collect the leaves of this plant is from Ordibehesht to Shahrivar (May-September) (3). Urtica dioica effects on increasing and activity of beta cells and plays its anti-diabetic role by this way (8, 9). The blue extract of Urtica dioica with its effect on rats and increasing the Insulin secretion causes blood sugar reduction (10, 11). Thus, the aim of this study is to examine the effect of Urtica dioica on blood sugar reduction and its relation to damage changes and histology of small intestine.

2. Objectives

The objective of this study is to determine the protective effect of extract of Urtica dioica leaf on small intestine structure in order to the anti-diabetic effect.

3. Materials and Methods

In this study, the female rats weighing 250-300 kg were applied. All the arts were kept under the standard conditions, 12 hours in lightness and 12 hours in darkness, enough food and water, 25 ± 1cg temperature and in each cage were 3 rats. Regarding that the death rate is high among diabetic animals, the number of samples were selected in such a way that seven animals were remained to assess in each group at the end of the study. At first, the Pilot study was done. The rats were injected 50 kg.mg^{-1} of Streptozotocinvia their tail vena. The blood sugar level was measured one week later. The fasting animals with more than 250 mg. dl^{-1} blood sugar was diagnosed as diabetic. The fasting animals with less than 250 mg.dl^{-1}blood sugar were omitted from the study. In the first study, the diabetic animals were classified in three groups in order to determine the necessary dose. The blue extract of two Urtica dioicae in three doses, 1cc. kg^{-1}, and 2cc. kg^{-1} and 4cc. kg^{-1} was injected in Peritoneumtothree groups of animals daily. The blood sugar level was measured one month after injecting the blue extract and there was an obvious reduction in group 4cc kg^{-1}. Also, the small intestine of every three groups was dismantled and Lam was made of them after fainting the rats with Ketamine. Based on the pilot study, 4 cc.mg^{-1} dose of the blue extract (w/v%) of Urtica dioica was proper to continue research. For doing the major research, two groups including seven animals, one is a control group and the other is treated with extract of Urtica dioica, were examined.

3.1. Instructions for Making Boiled Extract

Firstly, the fresh Urtica dioica was prepared in northern regions of Iran. Pharmacology of Tehran University has approved its scientific term. Urtica dioica was dried in shaded settings of laboratory and crushed into small pieces. Fifty grams of the material with 1000 cc distilled water was put on the mild heat for 30 minutes until it reached to spot welding. It was boiled for 10 minutes and cooled in room temperature for 2 hours. The liquid was passed from several gas layers for several times. Finally, to make the transplant extract, the liquid was centrifuged.

3.2. Determining the Remaining of Dried Extract

To determine the remaining of dried extract, a small amount of equiponderant liquid was selected and was put in 100 cc Avon and consecutive weighing of dried extract was acquired.

3.3. Diabetes Induction Method

To induce diabetes, Streptozotocin with 50 mg. kg^{-1} was injected in tail vena. The STA was dissolved in Physiology serum and used freshly. To reach better results, the animal must be kept fasting for 24 hours before testing, the

injection must be done fast and the amount of injection must not be high. Thus the drug was dissolved in Physiology serum and the amount of injection was not more than 0.3 cc. Blood sampling was made from the tail of animals ten days after the diabetes induction. The blood sugar level was measured by glucometer. The animals with more than 250 mg.dl $^{-1}$ were diabetic. Injection of extract to Peritoneum has been done for one month in specified time. In the first study, the animals were classified into three groups in order to determine the drug dose. One group has taken 1 mg.kg $^{-1}$ of extract; another group 2 mg.kg $^{-1}$ of extract and other group 4mg. kg $^{-1}$ of extract. Regarding the results of the study, the research on 4 mg.kg $^{-1}$ continued.

3.4. Measuring the Blood Sugar Level

The tail of the animals kept fasting last night was scratched with a scalpel. A drop of blood was put on a special strip of glucometer. By this way, the level of blood sugar was measured. This was done on the tenth day and at the end of the first month after the therapy.

3.5. Method of Preparing the Textural Sample for Researching about Histopathology

At the end of the study, the small intestine of rats were sampling by injecting 55 mg.kg $^{-1}$ of Ketamine to the Peritoneum after the rats fainted and were kept in 10% of formalin. 5-micron- slices were prepared after proving the sampling and making the blocks of them. Then haematoxylin-eosin staining (H&E) was done to differentiate between the internal structure of tissues and cellular components.

3.6. Data Analysis

SPSS software and t-test were used for investigating and analyzing data.

4. Results

At first, the pilot study was done for this research. On the basis of pilot study, cc. mg $^{-1}$ from blue extract of Urtica dioica was proper. The effects of various doses of Urtica dioica extract on intestine were presented qualitatively in *Table 1*.

To do the main research, two groups including seven diabetic animals, one control group and the treated group with Urtica dioicawere considered. One month after getting the extract, the blood sugar level reduced significantly. In data analysis, the blood sugar after diabetes induction was 400 ± 54.2.Blood sugar level reached to 78.9 ± 11 one month after the therapy by Urtica dioica extract which decreased significantly ($P = 0.0004$) (*Figure 1*).

The studies on intestine histology were done qualitatively. That qualitative parameter includes inflammation tissue, necrosis, transpiration of mononuclear cells, shorting the villain, exudate in Lumen, Muccose ulceration, epithelium destruction, Hemorhage congestion shortening the villain. Epithelium rehabilitation and rehabilitation of liber Kuhn glands. Necrosis and infiltration of mononuclear cells and destructive tissues were shown enormously in a therapeutic diabetic group. In contrast, necrosis were not shown in therapeutic diabetic group and the infiltration of mononuclear cells and inflammation tissue were shown slightly. Also villain shorted and atrophy, destructive epithelium and hyperemia and a lot of exudate in Lumen were found in the untreated group. Villain shorted and atrophy was not found in under therapy group and epithelium destruction and, blood shedding and exudate were not shown. The villain of liberkuhn glands and epithelium were not found in other apeuticdiabetic group (*Figure 2-1, 2-2*) while there were villian substantially in under therapeutic group (*Figure2-3, 2-4*).

In summer, therapy by blue extract of Urtica dioica leaf

Table 1. Comparison of Parameters of Tissues in Three Groups of 1 cc.kg $^{-1}$, 2 cc.kg $^{-1}$, 4 cc.kg -1 and The Untherapeutic Group [a,b]

	Diabetic	Under Therapy cc/kg	Group 2 (cc/kg^{2})	Group 3 (cc/kg $^{-1}$)
Inflamation Tissue	+++	+	++	++
Necrosis	++	-	-	+
Infiltration of Mononuclear	+++	+	++	++
Villous athrophy	+++	-	+	+
Exudate in Lumen	+++	-	+	+
Muccosa ulceration	+++	-	+	+
Epithelium Destruction	+++	-	+	+
Hemorhage Congestion	+++	-	+	+
Villiane Shorted	+++	-	+	++
Destruction of Liberkuhn Gland	+++	-	+	++

No change -; Mild changes+;Moderate changes++; Severe changes+++

[a] Data were reported as Mean ± SE

[b] Significant Difference ($P < 0.001$)

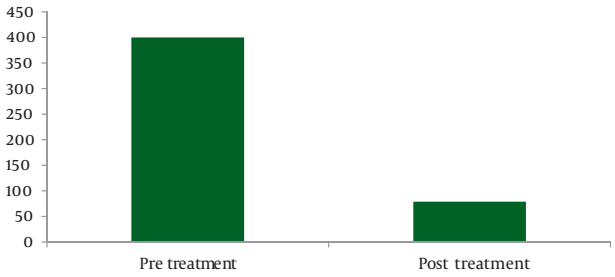

Figure 1. Comparison of Blood Sugar Means After and Before the Therapy in The Diabetic Group Under the Treatment by Blue Extract of Urtic adioica.

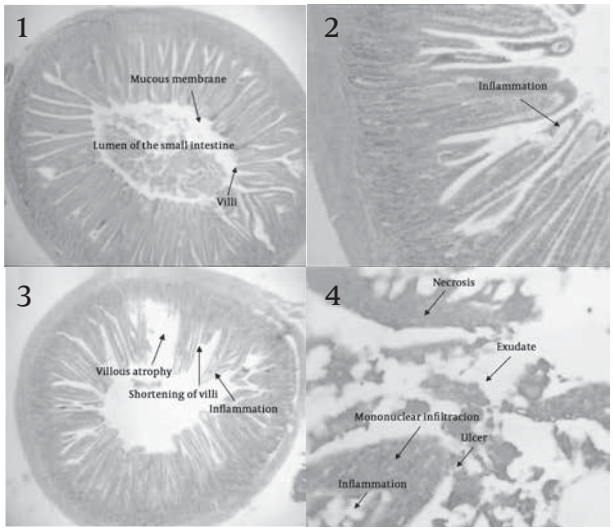

Figure 2. Microscopic parts of small intestine. 1, 2 under therapy group. Epithelium of small intestine has its own natural structure. 3, 4 Un therapeutic group. In these figures, destructive epithelium, inflammation, necrosis, mucosa ulceration, exudate, atrophy and shortening of villain with transpiration of mononuclear cells were found. H &R staining zooming out ×40.

controls the blood sugar and has a protective effect on the texture of small intestine of diabetic rats.

5. Discussion

Regarding the verses of Quran related to Pharmaceutical plants and examining one of them on animal sampling, prescription of a blue extract of Urtica dioica that leads to blood sugar reduction is specified in this study. Other researchers applied Urtica dioica for blood sugar reduction. Various studies include different mechanisms in this case. In one study, extracted Lectin from Urtica dioicais applied to remedy diabetic animal. Lectin causes insulin secretion from beta cells of the Islets of Langerhans or release of insulin from its reserves and therefore leads to blood sugar reduction (3, 12). Farzami, PhD *et al*., Examined the effect of Urtica dioica on isolated pancereatic islets of rats and considers the insulin secretion as the reason of blood sugar reduction (6, 13). Petlevski, *et al*, has used an Etanolic extract of Urtica dioicaas a reducer of blood sugar and the effective mechanism in this study was reduction of Glycatedalbumin and fructose Amin (14, 15).

Also Bnouham, *et al*. Proved that a blue extract of Urtica dioica plays its anti-diabetic role by reducing the intestinal glucose absorbing (16, 17) SecilOnal, *et al*. examine the effect of some of the pharmaceutical plants such as Urtica dioica on Alfa-glycoside of small intestine of rabbits and found the inhibition of Alfa-glycoside as a factor of blood sugar reduction (18). In another study, blue extract of Urtica dioica rehabilitates the pancreas texture on STZ-diabetic rats as well as blood sugar reduction (19). The probable mechanisms of blood sugar reduction by Urtica dioica are as follows:

Increasing the insulin secretion from beta cells and release of insulin from its reserves.

Reducing the Glycatedalbumin and fructose Amin

Inhibiting the intestinal Alfa-glycoside and reducing the blood sugar absorbing.

Diabetes induction by STZ causes morphologic changes like proliferation of epithelial cells, hypertrophy of mucus and destructing of intestine structure. In other words, it causes the same changes as the diabetic patients (20, 21). In this study, rehabilitation effects on destructive small intestine structure and blood sugar was examined as well. With regard to the acquired results, 4 $cc.kg^{-1}$ of blue extract of Urtica dioica causes rehabilitation of librekuhn glands and destructive epithelium. As mentioned before, diabetes mellitus effects appear following the chronic hyperglycemia. The studies show that reduction of hyperglycemia leads to prevention or delay in retinopathy, neuropathy and nephropathy (4). Various mechanisms have been mentioned for relation between hyperglycemia and long-term side effects, of which two mechanisms are more important (22): Non-enzyme glycosylation and intra cellular hyperglycemia associated with disorders in polyol metabolic pathways. The probable reason of positive effects of Urtica dioica can be justified in this study; Urtica dioica prevents increasing glucose in cells which leads to forming advanced glycosylation end products by blood sugar reduction, so it prevents destruction and leads to recovery of blood transfusion and rehabilitation of destructive textures. In other words, it prevents congestion of glucose and sorbitol in nerve cells which causes destruction of these cells and doesn't let neuropathy appear. Thus the function of nerve cells entering the villain improves and their atrophy recovers slightly.We can justify the longing of these villian by these two mechanisms. In addition to the mentioned positive effects, Urtica dioica causes the reduction of inflammation tieeue. The mucosa of digestion system is protected by adherent epithelium which prevents entering the microbe. Destruction of this epithelium causes activation of inflammatory factors (23, 24). We can suggest that Urtica dioica has a role in recovery of blood transfusion by the mentioned mechanism

in rehabilitating of mucus of intestine and can turn the adherence of mucus to the former state. By this way, entering the pathogenic factors which causes activation of the immune system is prevented and thus the activity of inflammation factors and the its side effects such as exudate, destruction, blood shedding and necrosis reduces. The study on histology show that blue extract of Urtica dioica causes rehabilitation of intestine mucus.

Controlling the blood sugar is the most important factor in preventing the acute and chronic side effects resulting from diabetes, thus Urtica dioica can prevent the appearing of these side effects by blood sugar reduction.

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Authors' Contribution

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