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A Systematic Review of Efficacy and Safety of *Urtica dioica* in the Treatment of Diabetes

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Abstract: This review focuses on the efficacy and safety of *Urtica dioica* which has been utilized in traditional medicine for management of diabetes. All relevant databases including Pubmed, Google Scholar, Web of Science, Scopus, Iranmedex and MD Consult were searched for the terms diabetes mellitus and *Urtica dioica* without limitation up to 15th September 2010. All the animal studies with the outcome of change in blood glucose or other relevant complications of diabetes and all available abstracts were included. Review articles and letters to the editor were excluded. Search of databases resulted in 724 articles which 87 were potentially relevant studies on *Urtica dioica* and diabetes. On the basis of inclusion/exclusion criteria, 21 studies were finally included. One human and 20 animal studies were reviewed for the efficacy of *Urtica dioica*. Most of these studies showed significant decrease in blood glucose and complications of diabetes by use of *Urtica dioica*. *Urtica dioica* can affect both pancreatic and extra pancreatic pathways. Available evidences suggest that *Urtica dioica* can be used to treat diabetes and its long-term complications. Of course, further experiments would help determine exact mechanisms of action, effects and side effects of this herbal medicine.

Key words: Diabetes, *Urtica dioica*, treatment, traditional medicine, medicinal plants, herbal medicine

INTRODUCTION

Diabetes is one of the most common chronic diseases in the world. The number of people with diabetes is increasing dramatically due to population growth, aging, urbanization, and increasing prevalence of obesity and physical inactivity that is finally associated with major health and socio-economic problems. The extent and severity of these problems are reflected in extra mortality and at-risk people. For example, according to the last International Diabetes Federation (IDF) report, about 2566000 people (6% total population) are suffering from diabetes in Iran and its prevalence is increasing like other developing countries expecting to reach 5114900 in 2025 (Sicree *et al*., 2007). Current estimates demonstrate that the world prevalence of diabetes will increase to 7.7% (439 million) adults by 2030. Between 2010 and 2030, there will be a 69% increase in number of diabetic patients in developing countries and 20% in developed countries (Shaw *et al*., 2010). So, with regard to the issue of socioeconomic burden of diabetes, discovery of more effective and less side effect therapies are necessary. In the recent years good data have been obtained from traditional medicines indicating usefulness of many herbal medicines (Hasani-Ranjbar *et al*., 2008, 2009). For a very long time, plants have been an important role part of treatment of many diseases. The use of plants to treat diabetes is a centuries-old practice. More than 400 traditional plant treatments for diabetes have been recorded, but only a small number of these have received scientific and medical evaluation to assess their efficacy. Hypoglycemic action from some treatments has been confirmed in animal models, and various hypoglycemic compounds have been identified. Traditional treatments may provide valuable clues for the development of new oral hypoglycemic agents and simple dietary adjuncts. *Urtica dioica* (Stinging Nettle) has been used for centuries for food and medical purposes. The genus name Urtica comes from the Latin verb urere, meaning to burn because of stinging hairs of the herb. The species name dioica means two houses because the plant usually contains either male or female flowers. It is abundant in North America, Northern Europe and most of Asia, usually found in the rural area. It contains flavonoides (0.7-1.8%), silicic acid (1-4%), potassium-ions (0.6%), nitrates (1.5-3%), volatile oil, histamine, serotonin,

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acetylcholine, formic acid and leukotrienes (LTB4, LTC4, LTD4). The blood sugar lowering effect of *Urtica dioica* has been mentioned in old script such as those written by Avicenna. There have been other reports indicating the benefits of using the infusion or the extract of the leaves or other parts of this plant for the use in diabetes (Ramos *et al*., 1992; Swanston-Flatt *et al*., 1989). Moreover, it is used internally and externally as supportive therapy for prostatic hyperplasia (Hirano *et al*., 1994; Krzeski *et al*., 1993; Kayser *et al*., 1995), inflammation (Obertreis *et al*., 1996), rheumatoid arthritis, hypertension and allergic rhinitis (Mittman, 1990).

The present systematic review aimed to evaluate the efficacy and safety of *Urtica dioica* in diabetes by reviewing all animal and human studies.

MATERIALS AND METHODS

Databases of Pubmed, Google Scholar, Web of Science, Scopus, Iranmedex, and MD Consult were searched up to 15th September 2010, for studies examined *Urtica dioica* in prevention or treatment of diabetes. The search terms were diabetes and *Urtica dioica* without limiting search elements. A Flow diagram of the search process has been shown in Fig. 1. Among the studies, there were only one human study and the rest of them were animal ones. All of animal studies with the outcome of change in blood glucose and other relevant complications of diabetes with available abstracts were included. Review articles and letters to the editor were examined to ensure inclusion of all relevant studies. Unpublished data such as dissertations were not included. Two reviewers independently examined the title, abstract and references of each article to eliminate duplication. The reference lists of articles were also reviewed for additional relevant studies. The reviewers summarized data on *Urtica dioica* for dose, treatment duration, grouping, main outcome, probable mechanism and side effects (Table 1).

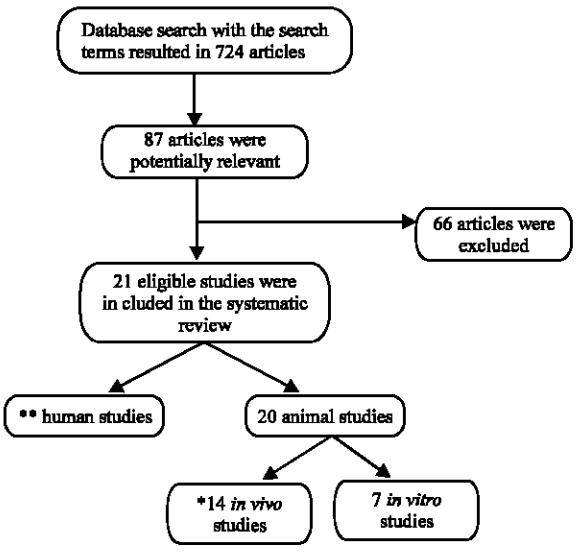

Fig. 1: Flow diagram of the search process.*There was one study which had both *in vivo* and *in vitro* sections. **There was one study which had both animal and human parts

RESULTS

The electronic database search identified 724 articles which 87 were potentially relevant studies on *Urtica dioica* and diabetes. Finally, based on our inclusion and exclusion criteria, 21 studies were included (Table 1) (Ramos *et al*., 1992; Swanston-Flatt *et al*., 1989; Said *et al*., 2008; Bnouham *et al*., 2010; Bnouham *et al*., 2003; Bijan *et al*., 2003; Petlevski *et al*., 2001; Shahraki *et al*., 2009; Fathi-Azad *et al*., 2005; Khouri and Golalipour, 2006; Golalipour *et al*., 2009a; Golalipour *et al*., 2010; Gunes *et al*., 1999; Neef *et al*., 1995; Jahanshahi *et al*., 2009; Fazeli *et al*., 2008; Fazeli *et al*., 2010; Golalipour *et al*., 2007a; Golalipour and Khouri, 2007b; Petlevski *et al*., 2003; Golalipour *et al*., 2009b). Only one human study was found which applied *Urtica dioica* in combination with *Juglans regia* L. *Olea europea* L. and *Atriplex halimus* L. in the form of Glucolevel tablets. This study revealed that acceptable glucose level was achieved in patients treated with Glucolevel (Said *et al*., 2008). Besides, animal studies showed significant decrease in blood glucose after treatment with *Urtica dioica* (Said *et al*., 2008; Bnouham *et al*., 2010; Bnouham *et al*., 2003; Bijan *et al*., 2003; Petlevski *et al*., 2001; Shahraki *et al*., 2009; Fathi-Azad *et al*., 2005; Golalipour *et al*., 2009a; Golalipour and Khouri, 2007b). One animal study showed ineffectiveness of *Urtica dioica* in treated animals (Khouri and Golalipour, 2006) and another study showed that *Urtica dioica* can aggravate diabetes (Swanston-Flatt *et al*., 1989). One animal study showed that the active component of *Urticadioica* can increase insulin content of blood in normal and streptozotocin-induced diabetes (Bijan *et al*., 2003). A suggested mechanism for action of *Urtica dioica* in reducing hyperglycemia is illustrated in Fig. 2. There were reports investigated intracellular changes in animals receiving *Urtica dioica*. Two studies showed that hydroalcoholic extract of Urtca Dioica reduces density of astrocytes in dentate gyrus in the diabetic rats (Jahanshahi *et al*., 2009; Fazeli *et al*., 2008). Another

Table 1: Human and animal studies considering antidiabetic effect of *Urtica dioica*

Authors	Target	Herbs (Scientific name)	Dose/Duration	Groups	Main outcomes	Other relevant effects and complications	Suggested mechanisms
Human studies							
Said *et al*. (2008)	Diabetic patients (n=16)	Dry extract of leaves of the *Juglans regia* L. *Olea europea* L. *Urtica dioica* L. *Atriplex halimus* L.	Glucolevel tablets 1 x 3 daily for a period of 4 weeks	-Treatment	Clinically acceptable glucose levels	-No side effect -Significant reduction in hemoglobin A_1C in six patients	-Augmentation of glucose uptake -Inhibition of glucose intestinal absorption
Animal studies (*in vivo*)							
Bnouham *et al*. (2010)	Neonatal streptozotocin induced-diabetic rats	Water extract of: -Arbutus unedo (Au) -Ammoïdes pusilla(Ap) -Thymelaea hirsute (Th) -*Urtica dioica*(Ud)	400 mg L^{-1}, drink water for 5 weeks	-Healthy controls -Neonatal STZ-induced diabetic rats - Neonatal STZ + tolbutamide -4 groups of n-STZ + water extract of plants	The percentages of plasma glucose lowering effect were, respectively for Au, Ap, Th, Ud and tolbutamide: 31.6, 27.4, 38.2, 13 and 33.9 % when compared with diabetic controls	-	-
Bnouham *et al*. (2010)	Neonatal STZ-induced diabetic rats	Water extract of -A: Ammoïdes pusilla(Ap) + *Urtica dioica* (Ud) -B: Arbutus unedo (Au) + *Thymelaea hirsuta* (Th)	A: 150 mg kg^{-1} for 5 weeks B: 150 mg kg^{-1} for 5 weeks	-Treatment -Control	Significant reduction in glycemia after glucose overload compared with controls	The effect of water extract of Au and Th was not significant	-
Said *et al*. (2008)	Diabetic rats	Dry extract of leaves of the *Juglans regia* L. *Olea europea* L. *Urtica dioica* L. *Atriplex halimus* L.	25 g kg^{-1} for 2-3 weeks	-Treatment -Control	Significant reduction in glucose levels [above 400 ±50 mg dL^{-1} to 210 ±22 mg dL^{-1}]	Significantly improved sugar uptake during the glucose tolerance test	-
Bnouham *et al*. (2003)	Diabetic rats	Aqueous extract of *Urtica dioica*	500 mg kg^{-1} of nettle extract	-Control: distilled water -Treatment: extract, orally	The decrease of glycemia has reached to 33±3.4% of the control value 1 h after glucose loading	LD50 was 3.5 g kg^{-1} intraperitoneally	Reduction of intestinal glucose absorption
Bijan *et al*. (2003)	Diabetic rats	Aqueous extract of *Urtica dioica* leaves	-	-Control: normal saline -Treatment: active ingredient fraction Fraction of *Urtica dioica* (F1) and normal saline	Increase in insulin level and the decrease in glucose level	-	Enhancement of insulin secretion by Langerhance Isletes
Petlevski *et al*. (2001)	NOD mice (n=66)	*Vaccinium myrtillus* L. *Taraxacum officinale* Web., *Cichorium intybus* L. *Juniperus communis* L. *Centaurium Umbellatum Gilib*., *Phaseolus vulgaris*, *Achillea millefolium* L. *Morus nigra* L. *Valleriana officinalis* L. *Urtica dioica* L.	Extract 1: ethanol Extract extract 2: Ethanol extract from which ethanol was evaporated on a rotator evaporator at a temperature of 45°C. 20 mg kg^{-1} for a period of 7 days	-Group A: extract 1 -Group B: extract 2 -Group C: normal without treatment -Group D: control extract 2 -Group F: acarbose	-Significantly lower glucose and fructosamine levels were recorded in extract 2-treated NOD mice as compared with NOD mice -Significantly decrease in the level of -Group E: fructosamine in alloxan-induced NOD mice	Decrease the blood level of glucose and fructosamine in the acarbose group (group F) comparison to the control group of NOD mice (group D) glucose and	-

Table 1: Continue

Authors	Target	Herbs (Scientific name)	Dose/Duration	Groups	Main outcomes	Other relevant effects and complications	Suggested mechanisms
Swanston-Flatt *et al*. (1989)	Diabetic mice	Nettle (*Urtica dioica*)	Administered in the diet (6.25% by weight) and/or as decoctions or infusions in place of drinking water for a period of 28 days	-normal -STZ diabetic	Nettle aggravated the diabetic condition	-	-
Shahraki *et al*. (2009)	Wistar-Albino healthy male rats (n=28)	Boiling solution of *Urtica dioica*	-	-Control: usual diet -Treatment A: 66% fructose-enriched diet (66%) then 40-60 mL boiling of *Urtica dioica* B: fructose-enriched diet (66%) then 40-60 mL distilled water	Significant decrease in blood glucose and insulin on fructose-fed male rats that received *Urtica dioica* boiling	Decrease in water and food intake on fructose-fed male rats that received *Urtica dioica* boiling	*Urtica dioica* - boiling induced decreased insulin resistance in fructose-fed male rats
Fathi-Azad *et al*. (2005)	Diabetic rats	Hydroalcoholic extract of *Urtica dioica* either i.p. or orally		500 and 1000 mg kg^{-1}	Two groups: -Normal: divide in to two groups -Diabetic: divided in to two groups	Both oral and i.p. administration extract decreased glucose level action only in diabetic rats effect in normal rats	*Urtica dioica* did not show hypoglycemic
Khouri and Golalipour (2006)	Diabetic Wistar rats (n=30)	Hydroalcoholic extract of *Urtica dioica*	for 4 weeks i.p.	100 mg kg^{-1} day^{-1} -Hyperglycemic -Treatment	-Normal Chronic administration of extract has no hypoglycemic effect and regeneration of β-cells of langerhans	-	-
Golalipour *et al*. (2009a)	STZ diabetic rats: renal morphometric and histological alterations in (n=30)	Hydroalcoholic extract of *Urtica dioica*	100 mg kg^{-1}, for 5 days before diabetes induction in animals by STZ	-Normal control group -Diabetic group -Protective group	*Urtica dioica* had protective effects on blood glucose, renal morphometric and histological alterations in STZ diabetic rats.	-	-
Golalipour *et al*. (2010)	STZ diabetic rats: quantitative changes of β-cells	Hydroalcoholic extract of *Urtica dioica*	100 mg kg^{-1} day^{-1} for 4 weeks i.p.	-Normal: saline -Diabetic: saline then induction of diabetes -Treatment: extract -Protective: extract before inducing diabetes	An association between decrease of blood glucose, increase of number of β-cells and administration of Urtica before induction of diabetes were seen	-	*Urtica dioica* may have antioxidant or free radical scavenger properties

Table 1: Continue

Authors	Target	Herbs (Scientific name)	Dose/Duration	Groups	Main outcomes	Other relevant effects and complications	Suggested mechanisms
Gunes *et al*. (1999)	STZ diabetic rats: blood and urine parameters and liver and kidney histology	Water extract of *Rumex patientia* grains and *Urtica dioica*	-Duration:10 days -Group (2): 0.3 mL^{-1} rat citrate buffer i.v. and water orally -Group (3): 2% decoction of the grain of *R. patientia* orally -Group (4): 0.5% infusion of the leaf of U. dioica orally -Group (5): 65 mg kg^{-1} STZ i.v. and water orally -Group (6): 65 mg kg^{-1} STZ i.v. and 2% *R. patientia* orally -Group (7): 65 mg kg^{-1} STZ i.v. and 0.5% U. dioica orally	-group (1): control -Groups (2-7): treatment groups	*Urtica dioica* had no protective effect, and it even caused an increase in nephrotoxicity	-	-
Ramos *et al*. (1992)	Rabbits after induction of temporary hyperglycemia	-	-Treatment -Control	-	*Urtica dioica* increased glycemia slightly	-	-
Neef *et al*. (1995)	Male Swiss mice	*Urtica dioica*	Oral gavage of ethanol extract	-	*Urtica dioica* had no effect on glucose profile	-	-
Animal studies (*in vitro*)							
Jahanshahi *et al*. (2009)	Diabetic rats: number of astrocytes in dentate gyrus of diabetic rats (n=21)	Hydroalcoholic extract of *Urtca dioica*	100 mg kg^{-1} for 4 weeks	-Control -Nettle-untreated diabetic -Nettle-treated diabetic	*Urtica dioica* extract helped compensate for astrocytes in the treatment rats dentate gyrus in comparison with diabetic rats	-	-
Fazeli *et al*. (2008)	Diabetic Wistar rats: diabetic encephalopathy and the granule cell density of the dentate gyrus of diabetic rats (n=24)	Hydroalcoholic extract *Urtica dioica* L. stinging nettle	100 mgkg day^{-1} for 4 weeks i.p.	-Normal -Diabetic -Preventive -Treatment	The densities in the treated rats were higher than in the diabetic rats *Urtica dioica* can help compensate for granule cell loss in the diabetic rat dentate gyrus	Preventive use of the extract showed no significant benefit	-

Table 1: Continue

Authors	Target	Herbs (Scientific name)	Dose/Duration	Groups	Main Outcomes	Other relevant effects and complications	Suggested Mechanisms
Fazeli *et al*. (2010)	Diabetic rats: neuroprotective efficacy of nettle extract on pyramidal cell density in the CA3 hippocampal (n=20)	Hydroalcoholic extract of *Urtica dioica*	100 mg kg^{-1} day^{-1} for 4 weeks	-Normal control -Diabetic model -Preventive: received extract 5 day before diabetes induction -Treatment: received extract one week afler diabetes induction	No significant neuroprotective benefits in diabetes-induced loss of pyramidal cells in the CA3 hippocampal subfields	-	-
Golalipour *et al*. (2007a)	Diabetic rats: effect of *Urtica dioica* on Morphometric indices of kiduey	Hydroalcoholic extract of *U. dioica*	100 mg kg^{-1} for	-control 4 weeks -Treatment: *Urtica dioica*	No effect on renal -Diabeti morphometric indices in induced diabetic rats	-	-
Golalipour and Khouri (2007b)	Diabetic rats: hyperglycemia and beta-cells (n=30)	Hydroalcoholic extract of *Urtica dioica*	for five days	100 mg kg^{-1} day^{-1} -Diabetic -Treatment	-normal *Urtica dioica* had hypoglycemic effect and protective activity of β-cells of Langerhans	-	-
Petlevski *et al*. (2003)	Diabetic rats: antioxidant effect of *Urtica dioica* (n=18)	Centaurii herba 12.3%, Cichorii radix 17.7%, Juniperi fructus 6.2%, Millefolii herba 3.5%, Myrtilli folium 6.6%, Phaseoli Pericarpium 14.4%, Taraxaci radix 9.7%, *Urtica dioica* L. 14.7, Valerianae radix 7.8%, Mori folium 7.4%	20 mg/kg/day, mixed with laboratory chow treated for 7 days with	-Group A: Normal NOD mice -Group B: Diabetic NOD mice -Group C: Diabetic NOD mice plant extract	Influences lipid peroxidation and increases the antioxidative activity of glutathione S-transferases in the liver of diabetic NOD mice	-	Reduction in hyperglycemia, which leading to a delay in the development of late diabetic complications associated with hyperglycemia.
Golalipour *et al*. (2009b)	Diabetic rats: quantitative morphometric changes in parenchymal cells of the livers rats (n=30)	Hydroalcoholic extract of *Urtica dioica*	over four weeks	100 mg kg^{-1} day^{-1} -Diabetic -Treatment	-Normal *Urtica dioica* can cause a little modulating in the main morphometric indices of liver such as area of hepatocytes, nuclei and nucleolus in periportal and perivenous zones.	-	-

STZ: Streptozotocin, i.v: Intravenous, i.p: Intraperitoneal, NOD: Non-obese diabetic

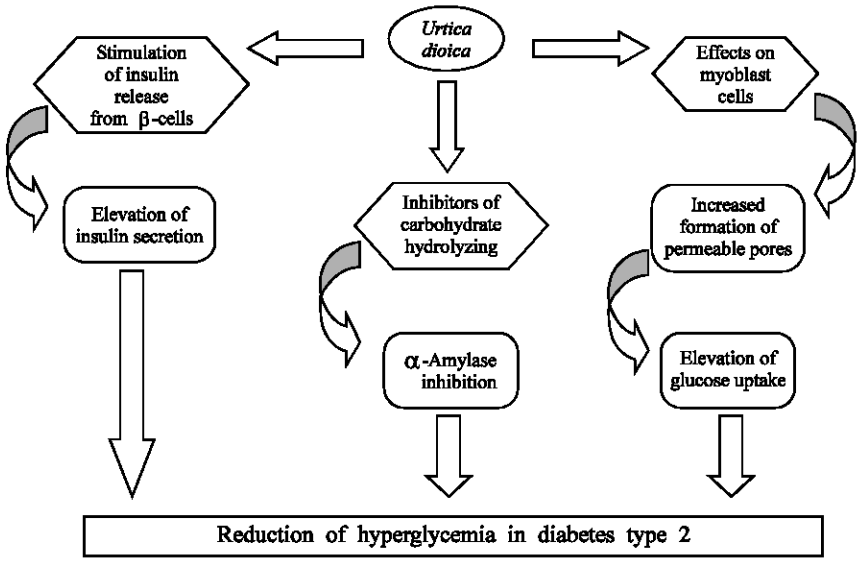

Fig. 2: Suggested mechanisms of action of *Urtica dioica* in reducing hyperglycemia

study demonstrated that this extract has no significant neuroprotective benefit in diabetes-induced loss of pyramidal cells in the CA3 hippocampal subfields of young diabetic rats (Fazeli *et al*., 2010). Three studies pointed the effect of *Urtica dioica* on renal complications of diabetes. In another study, the protective effect of *Urtica dioica* on morphometric and histological alterations in streptozotocin diabetic rats were reported (Golalipour *et al*., 2009a). Another study showed that *Urtica dioica* has no protection on renal complication of diabetes and even causes nephrotoxicity (Gunes *et al*., 1999). Another research revealed that Urtica has no effect on morphometric indices in diabetic rats (Golalipour *et al*., 2007a). One study noticed that *Urtica dioica* can modulate the main morphometric indices of liver such as area of hepatocytes, nuclei and nucleolus in periportal and perivenous zones (Golalipour *et al*., 2009b). Another study showed that *Urtica dioica* has antioxidant effect in diabetes which influences lipid peroxidation and antioxidative activity of glutathione S-transferases in the liver of diabetic NOD mice (Petlevski *et al*., 2003). Scientists in 2007 showed protective activity of *Urtica dioica* in beta-cells of Langerhans in hyperglycemic rats (Golalipour and Khouri, 2007b).

DISCUSSION

Looking back demonstrates that natural remedies have played an important role in people's daily life in most parts of the world. Some herbs are traditionally used in treatment of type 2 diabetes. *Urtica dioica* has been used traditionally in Morocco, Turkey, Brazil, Jordan, Iran and many other countries. The present study reviewed the effects of *Urtica dioica* on diabetes. Most of the included studies concluded that *Urtica dioica* can significantly reduce blood sugar. Researchers have proposed several mechanisms for this process. Possible effects of *Urtica dioica* could be categorized into two groups of pancreatic and extrapancreatic. Regarding to pancreatic effects, they have been suggested that *Urtica dioica* enhances the secretagogue function of islets of Langerhance and it is a potent stimulator of insulin release from β-cells (Bijan *et al*., 2003). Urtica has shown protective effect on β-cells in hyperglycemic rats (Fazeli *et al*., 2008).

Extra-pancreatic mechanisms that *Urtica dioica* affects glucose homeostasis include inhibition of intestinal absorption of glucose (Bnouham *et al*., 2003), inhibitory effects on the alpha amylase activity in a dose dependent-manner (Nickavar and Yousefian, 2010) and forming unique glucose permeable pores to facilitate glucose uptake (Domola *et al*., 2010).

On the other hand, investigators found that *Urtica dioica* has benefits on complications of diabetes and can cause a delay in development of late complications associated with hyperglycemia. They showed that Urtica can compensate granule cells in dentate gyrus after diabetes-induced cell loss, so it can ameliorate cognitive impairment in diabetes (Jahanshahi *et al*., 2009; Fazeli *et al*., 2008). A further effect of *Urtica dioica* is in the liver. Urtica has shown antioxidant effect in the liver, which can influence lipid peroxidation and increase the antioxidative activity of glutathione S-transferases in the liver (Petlevski *et al*., 2003) and can cause a little modulation in the main morphometric indices of liver

(Golalipour *et al*., 2009b). Meanwhile, platelet hyperaggregability is one of the pathogenesis of diabetes which Urtica can reduce and thus prevents cardiovascular complications of diabetes (El-Haouari *et al*., 2007). Its effects on kidney have been controversial. Among studies conducted in this field, only one showed protective effects of *Urtica dioica* on renal morphometric and histological alterations of diabetes (Golalipour *et al*., 2009a).

Besides in some in vivo and in vitro studies, *Urtica dioica* had no effects on diabetes or vice versa showed toxic effects on kidney and liver (Ramos *et al*., 1992; Swanston-Flatt *et al*., 1989; Gunes *et al*., 1999). And its mechanism of action is still controversial (Mobaseri *et al*., 2010).

In conclusion, considering all available evidences, the integration of chemical drugs with *Urtica dioica* may be possible and recommendable for management of diabetes. As a matter of fact, antioxidant composition of *Urtica dioica* should be noted as an excellent influencing element in management of diabetes and its complications (Rahimi *et al*., 2005; Momtaz and Abdollahi, 2010; Sarkhail *et al*., 2007; Mohseni-Salehi-Monfared *et al*., 2009; Milani *et al*., 2005; Malihi *et al*., 2009). In the recent years, *Urtica dioica* in combination with Rosa canina, Tanacetum vulgare and selenium and electromagnetic processing (named and patented as IMOD) has been tested in rat diabetes 1 model and found to improve oxidative and immunological distresses of type-1 immunogenic diabetes but could not normalize blood glucose (Mohseni-Salehi-Monfared *et al*., 2010). Of course evidence-based supports on the efficacy and safety of Urtica in diabetes are too few and needs further well-designed clinical trials. IMOD containing *Urtica dioica* is a good example of this hypothesis that has been found useful in experimental colitis (Baghaei *et al*., 2010), in human sever sepsis (Mahmoodpoor *et al*., 2010) and as an immunomodulator (Khairandish *et al*., 2009).

Meanwhile better experimental studies should be conducted to elucidate exact mechanism of action of *Urtica dioica* in diabetes.

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