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# A Systematic Review about Effects of Aerial Portions of *Urtica dioica* (Nettle) on Some Cardiovascular Risk Factors in Diabetes Mellitus

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**Abstract:** This study focuses on effects of aerial portions of *Urtica dioica* (Nettle) on some cardiovascular risk factors in diabetes mellitus. Databases including Pubmed, Science direct, Scopus, Google scholar and IranMedex, were searched for terms: lipid profile, glucose, Insulin Resistance, Oxidative stress, Inflammation, Cardiovascular disease, Blood Pressure, Diabetes and Nettle from 2000 till December 2011. Studies on Nettle root, mixed herbs, unpublished and review articles were excluded. Three human, 18 animal and 7 *in vitro* or *in vitro* studies were reviewed. More studies showed positive effects of nettle on decreasing cardiovascular risk factors in diabetes or non-diabetes. Available evidences suggest that *Urtica dioica* can prevent patients with diabetes from cardiovascular disease with different mechanisms. Because of different dosage, Nettle type and duration of intervention, comparison of studies are difficult. So Further studies need to determine effective dosage of *Urtica dioica* for decreasing cardiovascular risk factors in patients with diabetes mellitus.

**Key words:** Nettle, lipid profile, oxidative stress, inflammation, cardiovascular disease, diabetes mellitus

## INTRODUCTION

Diabetes mellitus is a common disease that involves the relative, absolute deficiency of insulin or insulin resistance that lead to increasing blood glucose. Disturbances in carbohydrate, fat and protein metabolism occur in this metabolic disease. Diabetes mellitus leads to acute and chronic complications if not controlled. Atherosclerosis is the most common long-term problems of diabetes that leads to Cardiovascular Disease (CVD) (Patel *et al*., 2011; Noroozi *et al*., 2011).

Also, Oxidative stress and inflammation can dependently or independently promote risks of CVD. Risk of death from heart disease in patients with diabetes mellitus is 2-4 times greater than non-diabetic patients, So It is important to prevent factors that increase risk of CVD in diabetes patients (Ismail-Beigi, 2011). Controlling of glucose level is the best way for prevention of short or long-term diabetes complications (Chokrungvaranon *et al*., 2011). Figure 1 showed risk factors in patients with diabetes mellitus that lead to CVD.

Due to the relatively side effects of chemical drugs and high interest of people to medicinal plants compare to chemical drugs, discovering of beneficial herbs is important (Egede *et al*., 2002).

One medicinal plant that is used to control glucose in traditional medicine is *Urtica dioica* (Nettle). Nettle from the Urticaceae family, found in south of Asian regions. leaves, flower, seed and root of nettle are used in treatment of various diseases by general people. All portions of nettle plant contain various micronutrients such as histamine, formic acid, acetylcholine, flavonoids, leukotrienes and 5-hydroxytryptamine.

Dose of biochemical Components in each part of nettle is different, So medical consumptions of each part of plant (root or aerial portions) are different (Anonymous, 2007).

Nettle leaves have been used traditionally for treatment bladder infection, inflammation of urinary tract, hypertrophy of prostate, Seasonal allergies especially in children, dandruff, acne, rheumatic pain treatment, hair loss and mild hemorrhage (Namazi *et al*., 2011a). Besides widespread usage of nettle in traditional medicine, nettle is used for only a few diseases in modern medicine like hypertrophy of prostate and rheumatoid arthritis (Chrubasik *et al*., 2007).

Studies showed effects of nettle on some risk factors of CVD in diabetes such as: blood glucose indexes, lipid profile, oxidative stress and hypertension. Due to importance of CVD prevention in patients with diabetes mellitus and no review articles about this subject, the aim of present study was to review effects of aerial portions of Nettle plant on some cardiovascular risk factors in diabetes mellitus.

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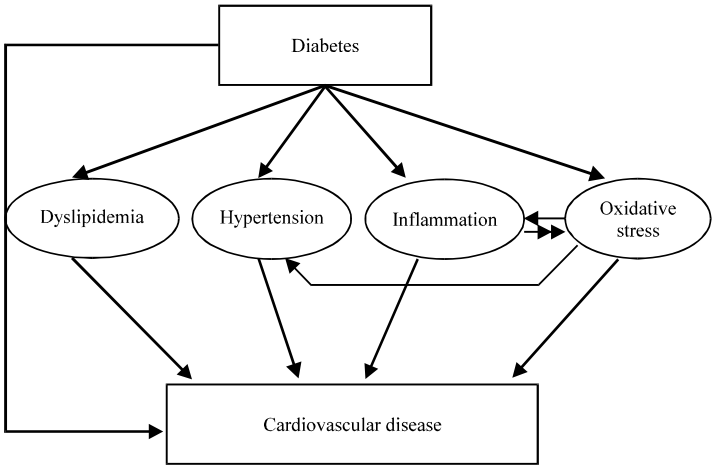


Fig. 1: Risk factors in patients with diabetes mellitus that lead to CVD

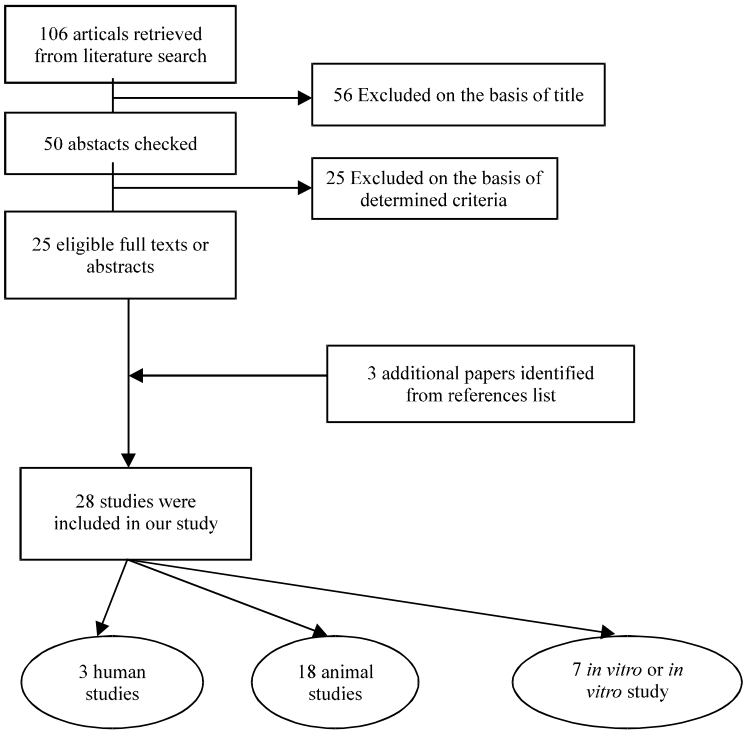


Fig. 2: Algorithm of literature search and selection

## MATERIALS AND METHODS

Data bases of Pubmed, Science Direct, Scopus, Google scholar and IranMedex were searched from 2000 till December 2011. Key words were: *Urtica dioica* (Nettle) plus glucose, lipid profile, blood pressure, oxidative stress, inflammation, insulin and cardiovascular disease on diabetes or non-diabetes. Two reviewers, independently extracted data and examined titles, abstracts and references of each article to eliminate duplication data. All abstracts or full text articles, with no language restriction were applied. Studies on nettle root, mixed herbs, review articles, abstract articles represented in congresses or unpublished results of dissertation were excluded.

Diagram showed steps of choosing articles for this review study (Fig. 2).

Searching lead to find 28 articles (abstract or full text) from 106 articles with criteria. 3 articles were found from references of articles. At the end of assessment, 29 articles were chosen and classified in three groups: human, animal, *in vitro* and *in vivo* studies. Characteristic and outcome of studies were summarized in Table 1.

## RESULTS AND DISCUSSION

Investigation of 28 chosen articles showed that 13 articles on glucose indexes, 6 articles on lipid profile and atherogenic index, 3 articles on Blood pressure, 6 articles on antioxidant and anti-inflammatory characteristic of

Table 1: Brief review of studies till December 2011

| Author/date | Sample size | Groups | Nettle type/dose | Duration of study | Outcome | Suggested mechanisms |
|---|---|---|---|---|---|---|
| **Human study** | | | | | | |
| Namazi *et al.* (2011) | 50 men and women | 2 diabetic group (25 case, 25 control) | 100 mg/kg/day Hydroalcholic extract | 8 weeks | ↓FBS, HbA1C, SBP, TG, IL6, hsCRP ↓LDL/HDL, Log TG/HDL ↑HDL-C, SOD, TAC -Fasting insulin, insulin resistance, Insulin sensitivity, TC, LDL-C, DBP | - |
| **Animal study** | | | | | | |
| Tahri *et al.* (2000) | 14 male Wistar rats | 3 groups 6 rats in each intervention group and 4 rats in control | 4, 24 mg/kg/h Aqueous extract | 1.25 h | ↓Arterial blood pressure ↑Water and sodium exertion | Effects on renal function |
| Ozen *et al.* (2003) | 24 Swiss albino mice | 3 groups (2 intervention, 1 control) 8 rats in each groups | 50 and 100 mg $kg^{-1}$ Hydroalcholic extract | 14 days | ↑SOD and catalase activity, DT-diaphorase Inducing glutathione S-transferase | Antioxidant components that scavenge liver from free radicals |
| Bnouham *et al.* (2003) | Male Wistar rats | - | 250 mg $kg^{-1}$ Aqueous extract | 30 min before glucose loading and 1, 3 h after it | ↓FBS-hypoglycemia | ↓glucose intestinal absorption |
| Kanter *et al.* (2003) | 56 Wistar albino rats | 4 groups (3 intervention, 1 control) 14 rats in each group | 0.8 mL $kg^{-1}$ Diethyl ether extract | 60 days | ↓lipid peroxidation, liver enzymes ↑Antioxidant defence system in tetrachloride carbon treated rats | Antioxidant components and their hepatoprotective effects |
| Fathi-Azad *et al.* (2005) | 10 Wistar rats | In first stage: 4 groups of healthy rats In second stage: 3 groups of diabetic rats | 500 and 1000, 2000 mg $kg^{-1}$ Hydroalcholic extract | 48 h | ↓Glucose level in diabetes rats -Insulin concentration | - |
| Khouri and Golalipour (2006) | 30 Wistar rats | 3 groups (healthy rats: control group; diabetic rat: case groups) | 100 mg $kg^{-1}$ Hydromethanolic extract | 4 weeks | ↓Glucose level -Glucose tolerance test | Protective effects on pancreatic beta cells |
| Golalipour *et al.* (2006) | 30 Wistar rats | 3 groups (Normal, diabetic, treatment groups) | 100 mg/kg/day Hydro alcoholic extract | 4 weeks | -hypoglycemia Regenerate beta cells | Antioxidant components that improve regenerating pancreatic beta cells |
| Daher *et al.* (2006) | 60 male rats | 2 groups | 150 mg/kg/day, 20 mg/kg/day Aqueous extract Petroleum ether extract | 30 days | -increasing liver enzymes ↓TC, LDL-C, LDL/HDL | - |
| Golalipour and Khori (2007) | 30 Wistar rats | 3 groups (Normal, diabetic, treatment groups) | 100 mg/kg/day Hydroalcoholic extract | 4 weeks | -glucose level in diabetic rats Protective effects in healthy rats | Antioxidant components |
| Alisi *et al.* (2008) | 40 albino Wistar rats | 4 groups (healthy rats in control and diabetic rats in intervention groups) | 100, 200, 300 mg/kg/day Aqueous extract | 41 days | ↓TC, TG, LDL-C, LDL/HDL, Total Non-HDL-C-HDL-C | Antioxidant components improve lipid metabolism in liver |
| Das *et al.* (2009) | 20 male rats | 3 groups (2 control, 1 intervention) : Control groups (6 rats) use Glibenclamide or deiodinazed water | 1.25 g $kg^{-1}$ Aqueous extract | 14 days | ↓FBS | Improvement in histological and functional of β-cells with the consequence of improved insulinemic status |
| Yener *et al.* (2009) | 18 rats | 3 groups | 2 mL $day^{-1}$ *Urtica dioica* seed | 90 days | Hepatoprotective effect ↑antioxidative defense | Antioxidant components |

Table 1: Continue

| Author/date | Sample size | Groups | Nettle type/dose | Duration of study | Outcome | Suggested mechanisms |
|---|---|---|---|---|---|---|
| Nassiri *et al.* (2009) | 50 Wistar rats | 5 groups (control groups used 10 mg $kg^{-1}$ lovastatin) | 100, 300 mg $kg^{-1}$ Hydroalcholic extract | 4 weeks | ↓TC, LDL-C | - |
| Shahraki *et al.* (2009) | 28 male Wistar albino rats | 3 groups (9 rats in control groups, 10 rats in intervention and group that consumed fructose) | Nettle decoction 40-60 insulin unit | 4 weeks | ↓FBS<br>↑Insulin<br>-TG, TC, LDL-C, HDL-C | - |
| Toldy *et al.* (2009) | 68 male Wistar rats | 8 groups | 1% w/w standard rat chow | 7 weeks | ↓Inflammatory transcription processes D-aspartate in N-methyl compare to sport | Antioxidant effects of components |
| Bitiren *et al.* (2010) | 50 male albino rats | 5 groups (10 rats in each groups) | 200 mg $kg^{-1}$ Hydroalcholic extract | 7 week | ↓Oxidative stress, DNA damage | Antioxidant effects of components |
| Morshed *et al.* (2011) | 18 male Long-Evans rats | 3 groups (2 control groups: healthy and diabetic rats) 5-8 rats in each groups | 1.25 g $kg^{-1}$ Aqueous extract | 8 days | ↓FBS, TG<br>↑Insulin | Anti-inflammatory effects |
| Qujeq *et al.* (2011) | 45 rats | 6 groups (7-8 rats in each groups) | 50 mg/kg/day Aqueous extract and Hydroalcholic extract | 2 weeks | ↓FBS<br>↑Insulin secretion in hydroalcoholic extract group | - |
| ***In vivo* and *in vitro* studies** | | | | | | |
| Petlevelski *et al.* (2001) | - | - | Aqueous extract 50 g $L^{-1}$ | - | -Transporting glucose within digestive tube | - |
| Farzami *et al.* (2001) | 12 albino Wistar rats | 2 groups | Aqueous extract 10 g leaves in 200 mL water | 60, 120 min | ↑Insulin secretion<br>↓glucose level | Simulating pancreatic beta cells |
| Legssyer *et al.* (2002) | - | - | Isolated rat aorta | 1 and 2 g $L^{-1}$ Aqueous extract | Caused vasoconstriction of aorta | Activation alpha 1-adrenergic receptors Antioxidant components |
| Gulcin *et al.* (2004) | - | - | - | 50, 100, 250 mcg Aqueous extract | Inhibited peroxidation of alpha linoleic acid emulsion | |
| Onal *et al.* (2005) | - | - | - | Aqueous extract | Inhibit α-glucosidase enzyme | - |
| Haurari *et al.* (2007) | 27 Blood samples of healthy and diabetic patients | | | 0.05-3 mg $mL^{-1}$ Aqueous extract | | |
| Shaebani *et al.* (2009) | - | - | - | Aqueous extract | Decreased glucose level | UD1 component that accelerate glucose uptake by permeable pores |

Nettle. Discussion about effects of nettle and its potential mechanism classified in three parts as follow:

**Human studies:** Only one human research was found according to the criteria till December 2011, Results of this research were represented in three articles. This double blinded randomized control clinical trial on 50 patients (24 men, 26 women) with type 2 diabetes, showed that 100 mg/kg/day of hydro alcoholic extract of Nettle had positive effects on Fasting Blood Glucose (FBS), glycated hemoglobin ($HbA_1c$), Triglyceride (TG), High Density Lipoprotein Cholesterol (HDL-C), Systolic Blood Pressure (SBP), Interleukin-6, high-sensitive C-Reactive Protein (hs-CRP), Super-Oxidase Dismutase (SOD) and Total Antioxidant Capacity (TAC) after 2 months intervention (Namazi *et al*., 2011b).

Although results showed 5.9, 1.5, 5.1% decreasing effect of nettle on LDL-C, TC and insulin resistance, respectively but there were not significant. On the other hands nettle extract (45% ethanol, 55% water) showed no significant changes on fasting insulin and insulin sensitivity. So it seems that hydroalcoholic nettle extract improved glucose level in patient with type 2 diabetes by other mechanisms (Namazi *et al*., 2012).

**Animal studies**

**Glucose indexes and insulin status:** 18 animal studies investigated the effects of *Urtica dioica* on risk factors of CVD. One study showed no effects of *Urtica dioica* on diabetes treatment but it showed protective effects of nettle in diabetic rats (Golalipour and Khori, 2007). Golalipour and Khori (2007) suggested that

hydroalcoholic extract of nettle regenerate beta cell of pancreas. Antioxidant component of nettle may be responsible for improving beta cell function by free radical damage.

Other animal studies showed decreasing effect of Nettle on glucose by increasing effect of nettle on insulin secretion (Shahraki *et al*., 2008; Morshed *et al*., 2011).

Qujeq *et al*. (2011) showed that alcoholic extract of nettle increased insulin secretion but aqueous extract did not effect on insulin secretion after 2 weeks. It showed that type of solvent can be an effective factor on extracting components of plants.

Extraction type, temperature and duration of extraction are other effective factors in extraction of components (Samsam-Shariat, 2000).

**Lipid profile:** Studies about effect of nettle on lipid profile can be classified in two groups: (I) diabetic rats (Shahraki *et al*., 2008; Das *et al*., 2009; Morshed *et al*., 2011) (II) non-diabetic rats. In studies that assessed effects of nettle on non-diabetic rats, they were under high fat diet (Qujeq *et al*., 2011; Alisi *et al*., 2008; Daher *et al*., 2006; Nassiri-Asl *et al*., 2009).

All of studies on non-diabetic rats showed beneficial effect of nettle on at least one of lipid factors. But One (Shahraki *et al*., 2008) of three studies that were done on diabetic rat did not showed any effects of decoction nettle on lipid profile.

Differences between Das *et al*. (2009) and Morshed *et al*. (2011) studies were in duration of study. Type and dose of nettle extract were similar in these two studies. Maybe longer duration of intervention caused significant decreasing in TC level in Das *et al*. (2009) study.

Daher *et al*. (2006), Nassiri-Asl *et al*. (2009) and Alisi *et al*. (2008) injected nettle extract intravenously but in Das *et al*. (2009) nettle extract was used orally. Difference in method may cause different results.

Only two studies investigated effects of nettle on plasma atherogenic index (Daher *et al*., 2006; Alisi *et al*., 2008). Aqueous extract of nettle decreased LDL-C to HDL-C ratio after 1 month. Significant reduction in LDL-C level, decreased the ratio (Daher *et al*., 2006) and reduction in TG, TC and LDL-C levels, decreased Non-HDL and LDL/HDL ratio after 41 days (Alisi *et al*., 2008). Nevertheless differences in sample size, dose and duration of intervention, both studies showed beneficial effect of nettle on decreasing plasma atherogenic Indexes. Potential mechanism that were suggested in these studies were: effects of antioxidant components such as: Quercitin, caffeic acid, carotenoids and other Flavonoids components in nettle. Studies showed these components destroyed free radicals, so lipid metabolism was performed better. Decreasing in Apo B48 lead to decreasing TG level and Inhibiting HMG COA Reductase caused decreasing in TC level (Skottova *et al*., 2003; Takechi *et al*., 2004).

**Oxidative stress:** All animal studies (Kanter *et al*., 2005; Ozen and Korkmaz, 2003; Yener *et al*., 2009; Toldy *et al*., 2005; Bitiren *et al*., 2010) that investigated antioxidant effects of nettle, were done on healthy rats. Kanter *et al*. (2005) showed that hydroalcoholic nettle extract decreased brain peroxidation and inhibited xanthine oxidase. Another study showed significant effect of hydroalcoholic nettle on catalyse, SOD, GPX and glutathione reductase.

Increasing GLUT4 expression, decreasing phosphoenol pyruvate reductase enzyme by polyphenols component were suggested as potential mechanism for improving glucose level in diabetes (Valentova *et al*., 2007; Manach *et al*., 2005).

Few studies that were done on nettle seeds, showed improving effect of nettle on oxidative stress status (Kanter *et al*., 2005; Yener *et al*., 2009). All studies showed beneficial effects of aerial parts of nettle on oxidative stress status, independently of their properties.

**Inflammation:** Only one animal study was founded. Morshed *et al*. (2011) showed that aqueous extract of nettle decreased CRP level after 8 days in type 1 diabetic rats. They suggested that anti-inflammatory effects of nettle improved histology of beta cells and insulin secretion. Adenine, nicotine amide and caffeic acid are known anti-inflammatory component in nettle (Daher *et al*., 2006).

**Blood pressure:** Limited studies were investigated effects of nettle on blood pressure. Only one animal study was done (Tahri *et al*., 2000). Tahri *et al*. (2000) showed diuretic characteristic of nettle. They compared effects of nettle on blood pressure, water and sodium excretion to furosemide. 4 and 24 mg $kg^{-1}$ nettle showed increasing in water and sodium excretion and decreasing effect on blood pressure irreversibly.

***In vitro* and *in vivo* study**

**Glycemic index:** One study showed that hydroalcoholic nettle extract can not increase insulin sensitivity in muscle cell but it increased insulin and C-peptide secretion from pancreatic cells (Mobasseri *et al*., 2009). Mobasseri *et al*. (2009) suggested increasing effect of nettle on insulin resistance.

On the other hands *in vivo* and *in vivo* study of Farzami *et al*. (2003) showed that active component of nettle can increase insulin secretion 5 times in normal and diabetic rats compare to the baseline.

*In vitro* studies assessed different mechanism of nettle on decreasing glucose (Petlevski *et al*., 2001; Onal *et al*., 2005).

Domola *et al*. (2010) isolated antidiabetic component from aqueous extract, named UD, UD did not effect on insulin secretion. UD consists of two particles, UD-1 and UD-2. UD-1 is N cyclical peptide that facilitate glucose uptake by forming unique glucose permeable pores, so it can improve blood glucose status.

Other potential mechanism is inhibitory effect of nettle on alpha glucosidase or alpha-amylase (two digestive enzymes) (Tadera *et al*., 2006; Onal *et al*., 2005). Inhibiting these enzymes caused decreasing glucose intestinal absorption. Antioxidant component such as: quercitin and tannin may play this role (Tadera *et al*., 2006) .

**Blood pressure:** *In vitro* study of Legssyer *et al*. (2002) showed that 1 and 2 g $L^{-1}$ aqueous extract of nettle decrease heart rate and BP in left ventricle.

**Oxidative stress:** Only one *in vitro* study investigated effects of aqueous extract of nettle on oxidative stress (Gulcin *et al*., 2004). They showed that antioxidant characteristic of nettle increased depend on dosage. Nettle extract inhibited peroxidation of alpha-linoleic acid stronger than alpha-tocopherol.

**Other risk factor of CVD:** There were not found any *in vivo* or *in vitro* studies about effect of nettle on lipid profile and inflammation status.

## CONCLUSION

Some studies showed effectiveness of Nettle on some risk factors of CVD in diabetic or non-diabetic models. Antioxidant effects of nettle were clear in those studies but effect of nettle on other risk factors of CVD need more studies in same condition.

It is difficult to conclude about effective dose of nettle on preventing from CVD in patients with diabetes mellitus. Because of Differences in method, duration of intervention, dosage, nettle type (extract, dried leaves) and solvent.

For future researches, it is suggested to study on effects of nettle as randomize clinical trial by larger sample size that compare different dose and solvent to each other in same condition.

To clarify precise mechanism and finding the best form of nettle supplement for patients with diabetes, *in vivo* and *in vitro* studies are suggested.

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