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Review Article

Urtica Dioica, An Emerauld in the Medical Kingdom

Sadegh Fattahi[1, 2], Monireh Golpour[2], Haleh Akhavan-Niaki[1, 3*]

1. North Research Center-Pasteur Institute of Iran, Amol, Iran.

2. Cellular and Molecular Biology Research Center, Babol University of Medical Sciences, Babol, Iran.

3. Department of Genetics, Faculty of Medicine, Babol University of Medical Sciences, Babol, Iran.

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Urtica dioica is a perennial plant used as herbal medicine due to its many pharmacological and clinical effects. Because of its antioxidant activity, it is widely used in traditional diabetes treatment but is also known as antimicrobial, anti inflammatory or anti prostate cancer agent. Extensive studies have been conducted on different parts of this plant and their biological effects. Here we reviewed the effect of different parts of this plant including leave, seed, root and aerial part extracted with various methods in treatment of diseases. Various beneficial effects were reported on animal models without apparent side effects, which led us to consider it as an emerald to be more deeply discovered in the kingdom of health.

Keywords: *Urtica dioica*, diabetes, cancer, antioxidant, anti-inflammatory

In traditional medicine, plants and herbs are widely used in treatment of the disease for their benefits such as having low side effects, being natural sources with low cost. *Urtica dioica* is one of the herbs to be widely used as a medicine due to many pharmacological and clinical effects. *Urtica dioica* or stinging nettle is a member of Urticaceae family, herbaceous perennial plants which have many little hairs and contain histamine, formic acid, acetylcholine, acetic acid, etc… on the leaves and stalks that cause skin irritation after contact. In Iran, it is named gazaneh which means stinging. It is also known as Anonhasquara among native Americans, or Grande ortie among French people (1). Alkaloids, saponins, tannins, flavonoids, steroids and terpenes, polyphenols and cardiac glycosides are present in the leaves of *Urtica dioica* (2). The investigation of polyphenolic acids in male and female forms of stinging nettle showed that the male has higher polyphenolic acids content than female form and these compounds increase at the stage of full blooming in both forms (3). Regarding a variety of uses of *Urtica dioica* in improving human health, we extensively reviewed the effect of different sections of this plant including leave, seed, root and aerial part extracted with various methods in treatment of diseases.

Root aqueous extract

An anti prostate cancer effect of the aqueous root extract which is accomplished by inhibition of

*Correspondence: Department of Genetics, Faculty of Medicine, Babol University of Medical Sciences, Babol, Iran.
E-mail: halehakhavan@yahoo.com

the binding of 125I-SHBG (human sex hormone binding globulin) to its receptor was reported (4). In fact, pinoresinol, dehydrodiconiferyl alcohol, (-)-secoisolariciresinol, (+)-neoolivil, isolariciresinol, lignans, and 3,4- ivanillyltetrahydrofuran, from the aqueous root extract of *Urtica dioica* bind to SHBG (5). Moreover, this aqueous extract diminishes nocturia in men suffering from prostatic adenoma (6). Wagner et al. showed that aqueous root extract contains a polysaccharide mixture that can be used by some stimulated T lymphocytes and others for influencing the complement system or triggering the secretion of tumor necrosis factor-α (TNF-α) *in vitro*. They also indicated an extended anti-inflammatory activity while performing the rat paw edema assay (7). This extract can induce hypotensive responses due to negative inotropic effect, potassium channels opening and the production of endothelial nitric oxide (8). Patients receiving *Urtica dioica* improved their international prostate symptom score, lower urinary tract symptoms, and the maximum rate of urinary flow with modest decrease in prostate size. Moreover, *Urtica dioica* decreased postvoid residual urine volume (PVR) but did not change serum prostate-specific antigen (PSA) and testosterone levels (9).

Root non-aqueous extract

Antiprostatic effect of GlcN-Ac-(N-acetylg-lucosamine), a specific lectin from the rhizomes of stinging nettle , also called urtica dioica agglutinin (UDA), exerted by inhibiting the attachment of 125I-EGF (epidermal groth factor) to its receptor (EGF-R) in prostate tissues was demonstrated (10). UDA inhibits the activity of respiratory syncytial virus, cytomegalovirus (CMV), influenza A and human immunodeficiency virus types 1 and 2 (11). It also inhibits the development of the systemic lupus erythematosus-like pathology in Murphy Roths Large (MRL) mice homozygous for the *lpr* (lymphoproliferation) mutation (12). The combination of *Urtica dioica* root and *Pygeum africanum* bark extracts reduce urine flow as well as residual urine and nocturia in men showing benign prostatic hyperplasia (13). Non-aqueous root extract of *Urtica dioica* inhibits the membrane Na+, K(+)-ATPase activity in prostatic tissue showing hyperplasia (14). Petroleum ether and ethanol extracts of Urtica dioica have 5α-reductase inhibitory activity *in vitro*. Moreover b-sitosterol, a molecule used in prostatic hyperplasia therapy, and scopoletin, an anti-inflammatory molecule, are present as major constituents of the extract (15). The combination of extracts of stinging nettle root and *Serenoa repens* fruit showed an efficiency similar to finasteride, an inhibitor of 5α-reductase, This efficiency was independent of the prostate volume (16). A combination of extracts of roots of stinging Nettle and *Sabal serrulata* fruits improves the symptoms observed in lower urinary tracts of elderly men (17).

Root hydroalcoholic extract

The hydr alcoholic extract of stinging nettle root has a cytotoxic activity on human prostatic epithelial cells (18). Aromatase inhibition by the methanolic extract of *Urtica dioica* root was also observed (19).

Leave aqueous extract

In vivo studies showed that aqueous leaf extract of *Urtica dioica* is helpful in different aspects of diabetes treatment in rats. This extract affects Langerhans islets in diabetic rats and subsequently leads to an increase of insulin secretion and decrease of blood sugar (20). Similarly, simultaneous increase of insulin and decrease of blood glucose after treatment of diabetic rats with *Urtica dioica* accompanied by an increase of the activity of coenzyme acetyl A carboxylase and nucleoside diphosphate kinase in the alloxan induced diabetic rats was reported (21). Antihyperglycemic effect of leaf aqueous extract of

Urtica dioica in the streptozotocin treated hyperglycemic rats as well as significant decrease of the level of lipids, cholesterol but not triglyceride and low density lipoprotein (LDL) was demonstrated (22). Inhibition of, protein tyrosine phosphorylation, Ca2+ mobilization and oxidant production which cause platelet hyperaggregability in type 2 diabetes mellitus is caused by *Urtica dioica* extracts (23). The aqueous leaf extract has also an antiplatelet activity *in vitro* (24). Investigation of the effect of aqueous extract in the prostate cancer showed a significant decrease of adenosine deaminase, an important enzyme in nucleotide synthesis (25). *In vitro* studies showed apoptosis induction in MCF-7 breast cancer cell line after exposure to aqueous leave extract of *Urtica dioica* (26). Finally, an antibacterial effect of aqueous extract against pseudomonas and psychrotrophic bacteria present in the ground beef was reported (27).

Leave non-aqueous extract

The non aqueous leave extract of *Urtica dioica* have various clinical effects. The ethanolic leave extract have an anti inflammatory effect on rheumatoid arthritis via inhibition of the proinflammatory transcription factor NF-κB (28). This extract was also shown to be efficient in allergic rhinitis treatment (29). An antimicrobial effect of extracts on fish and human pathogenic bacteria was demonstrated by disc diffusion method. Considerable antibacterial activity against both Gram negative and positive bacteria was reported (30-32) with hexane extracts showing better antimicrobial activity on Gram negative bacteria (31) and ethyl acetate and hexane extracts exhibiting better antimicrobial activity on Gram-positive bacteria (30). Ethyl acetate extracts were demonstrated to be more efficient than methanol extracts in preventing *in vitro* rat platelet aggregation induction by thrombin (24). The investigation of ethanolic extract efficiency against four main plant pathogenic fungi, demonstrated that it exert an important antifungal activity. Therefore the ethanolic extract of *Urtica dioica* could be substituted to chemical products routinely used for preventing fungal infections in plants (33). The study of antioxidant, hepatoprotective and anti helminthic activity of methanol extract of leaves of *Urtica dioica in vitro* and *in vivo* showed a significant antioxidant activity comparable to traditional antioxidant compounds such as α - tocopherol, ascorbic acid and butylated hydroxyanisole (BHA). Pretreatment of animals with this extract had a significant increase in superoxide dismutase level and inhibited lipid peroxidation (34). *Urtica dioica* leaf homogenized in 1.15% KCl decreased malonyldialdehyde level therefore preventing oxidative stress induced by tourniquet in rats (35). The methanolic extract also decreased the levels of alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and total bilirubin of serum which indicates its hepatoprotective effect. Antihelminthic activity of the methanolic extract was also reported in *Pheretima posthuma* and mice naturally infected with *Aspiculuris etraptera* (36).

Leave hydroalcoholic extract

The hydroalcoholic extract of *Urtica dioica* has an anti allergic rhinitis effect exerted by preventing prostaglandin formation through inhibiting hematopoietic prostaglandin D2 synthase cyclooxygenase-1 and cyclooxygenase-2 which all play essential roles in pro-inflammatory pathways. It also inhibits the activity of mast cell tryptase and histamine-1 receptor (37). The examination of antioxidant activity of hydroalcoholic extract by means of different antioxidant evaluation methods demonstrated an antioxidant effect comparable with traditional antioxidants such as α-tocopherol, butylated hydroxytoluene (BHT) and BHA (38).

Using carrageenan-induced paw edema, formalin test and acetic acid-induced writhing, an anti-inflammatory and antinociceptive effect of the hydroalcholic leaf extract was demonstrated in Swiss mice and Wistar rats. Therefore, the hydroalcoholic leaf extract may reduce pain and inflammation by suppressing histamine release from mast cells and also suppressing arachidonic acid metabolism (39). *In vivo* evaluation of extract's effect on lactate dehydrogenase, lipid peroxidation and antioxidant enzymes showed a significant increase of superoxide dismutase, glutathione S-transferase, glutathione reductase, NADH-cytochrome b5 reductase, cytochrome b5, DT-diaphorase, glutathione peroxidase, catalase activities in the liver and a decrease of NADPH-cytochrome P450 reductase activities, cytochrome P450, total sulfhydryl groups, as well as a decrease of lactate dehydrogenase, protein bound sulfhydryl groups and nonprotein sulfhydryl groups (40). Injection of this extract before inducing diabetes by streptozotocin in rats, has a hypoglycemic and protective effect on the β-cells of Langerhans islets as well as morphometric features of hepatocytes and seminiferous tubules (41-46). This extract also decreased the number of astrocytes in the dentate gyrus of hyperglycemic rats (47). In fructose-induced insulin resistance rats, treatment with this extract caused a decrease of insulin, LDL, leptin, fasting insulin resistance index (FIRI), serum glucose, LDL/HDL ratio and increase of very low density lipoprotein (VLDL), AST and triglyceride (TG) but no ALP of serum (48). In hypercholesterolemic rats a decrease of the level of total cholesterol, LDL, ALT, AST and weight was shown (49) while a decrease of blood glucose and increase of insulin, acetyl coenzyme A carboxylase and nucleoside diphosphate kinase activities was reported in alloxan induced diabetic rats (21). This extract increased aniline 4-hydroxylase activity, cofactor requirement (NADH and NADPH) and metal ions (Mg2+ and Ca2+) in mice (50). The combination of *Urtica dioica* with *Atriplex halimus*, *Olea europea* and *Juglans regia* decreased glucose levels and improved sugar uptake during glucose tolerance test (51).

Seed non-aqueous extract

The diethyl ether extract of *Urtica dioica* seed decreased serum aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, ceruloplasmin and lipid hydroperoxides levels and increased serum arylesterase, paraoxonase, and catalase levels in rats (52). The diethyl ether seed extract alone or in combination with *Nigella sativa* decreased liver enzyme levels and malonedialdehyde in rats and increased their weight as well as the levels of the reduced antioxidants during 60 days treatment (53). The extract showed moderate anti inflammatory effects in tissue inflammation model induced by carrageenan (54). The methanol extract of seeds of *Urtica diocia* was highly effective against *Xanthomonas vesicatoria*, a plant-borne pathogen (55).

Seed hydroalcoholic extract

The hydroalcoholic extract of *Urtica dioica* seeds had a good antioxidant effect compared to traditional antioxidants α-tocopherol, BHT and BHA as demonstrated by different antioxidant evaluation methods such as reducing power, total antioxidant activity, hydrogen peroxide scavenging, superoxide anion radical scavenging, metal chelating activity and free radical scavenging (38).

Aerial aqueous extract

Oral pretreatment of rats with the aqueous extract of aerial part of stinging nettle enabled a decrease of glucose level during oral glucose tolerance test (OGTT) (56). This extract was shown to produce a vasoconstriction of the aorta by activating α1-adrenergic receptors and caused a

strong bradycardia through non-cholinergic and non-adrenergic pathways (57). Total LDL, cholesterol, LDL/HDL ratio and plasma total AST, lactate dehydrogenase (LDH), ALT and apo B decreased after treatment of rats with aqueous extract of aerial part of stinging nettle (58). This extract affects also arterial blood pressure in rats by increasing diuresis and natriuresis (59).

Antimicrobial, antiulcer, antioxidant and analgesic activities of *Urtica dioica* were investigated by Gülçin et al. who showed that aqueous extract of aerial part of this plant has a remarkable antioxidant activity comparable to standard antioxidants and has antibacterial effect on both Gram-negative and positive bacteria. Nevertheless, pre-treatment of this extract with metamizol and famotidine inhibits the acetic acid-induced writhing and ethanol-induced gastric mucosal injury in rats, respectively (60). The extract increased T lymphocytes proliferation with a moderate increase of CD4+ T cells proportion and due to their scavenging activity inhibited peritoneal macrophages, NO2 production without affecting cell viability (61). Cytotoxicity and antioxidant effect of this extract was reported on MCF-7 cell line (62).

Aerial non-aqueous extract

Non-aqueous extract exhibited good antibacterial activity on both Gram negative and positive bacteria. Ethyl acetate and hexane extract demonstrated better antimicrobial activity against the Gram-positive bacteria (30). Total LDL, LDL/HDL, cholesterol ratio and plasma total apo B decreased after treating rats with petroleum ether extract of aerial parts of the plant (58).

Aerial hydroalcoholic extract

The hydroalcoholic extract of aerial part of *Urtica dioica* increased HDL, total antioxidant capacity and superoxidant dismutase and decreased FBS, HBA1C, TG, Log (TG/HDL-c) and systolic blood pressure without any changes in malondi-aldehyde and glutathione peroxides in type 2 diabetes patients after eight weeks treatement (63, 64). This extract unabled glucose utilization enhance either directly or by increasing the insulin sensitivity *in vitro* (65). Treatment with *Urtica dioica* reduced densities of CA3 hippocampal pyramidal cells in diabetic rats (66).

Conclusion

Various parts of *Urtica dioica* with different modes of extraction have many pharmacological effects. As shown in Table 1, greatest attentions have been conducted on the leaves, roots, seeds and aerial parts of the plant, respectively. The nettle roots, regardless of the extraction method, due to the presence of specific N-acetyl glucosamine have an anti-cancer, especially anti prostate cancer property. The aerial parts and leaves of *Urtica dioica* have anti-diabetic, anti-thrombosis, anti-allergic, anti-microbial, antioxidant properties in addition to anti-cancer. The seed of *Urtica Dioica* which belongs to aerial parts of this plant has antioxidant and anti-microbial properties. Contrary to pharmaceutical drugs which regardless of their side effects have been synthesized for a specific disease, the whole plant of *Urtica Dioica* not only has no side effects, but has many medicinal properties against various diseases. So, this plant perhaps accessible mostly in small traditional drugstores, despite all its benefits, was suggested by authors to be considered as an emerald in the kingdom of health and not as just a simple weed.

Conflict of interest

The authors declared no conflict of interest.

Table 1. Various effects of extracts from different parts of *Urtica dioica*

Part of plant	Extraction method	Diseases or conditions	References
Root	Aqueous	Prostate cancer Anti inflammatory Hypotensive	(3-8)
	Non-aqueous	Prostate cancer Systemic lupus rythematosus	(9-16, 66)
	Hydroalcoholic	Prostate cancer Aromatase inhibitor Breast cancer	(17-18)
Leave	Aqueous	Anti diabetic Thrombosis Atherosclerosis Breast cancer Antimicrobial	(19-24, 26)
	Non-aqueous	Rheumatoid arthritis Allergic rhinitis Antimicrobial Antifungal Antioxidant Antihelminthic Anti diabetic	(23, 27-35)
	Hydroalcoholic	Allergic rhinitis Anti diabetic Antioxidant Anti nociceptive Anti inflammatory	(20, 36-50)
Seed	Non-aqueous	Ischemia/reperfusion injury Sepsis Hepatoprotective Antioxidant Anti-inflammatory Antibacterial	(51-54)
	Hydroalcoholic	Antioxidant	(37)
Aerial part	Aqueous	Anti diabetic Hypotensive Cardiovascular disease Antioxidant Antimicrobial Antiulcer Analgesic T lymphocyte proliferation Antioxidant Breast cancer	(55-61)
	Non-aqueous	Antimicrobial Cardiovascular disease	(29, 57)
	Hydroalcoholic	Anti diabetic	(62-65)

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