Journal of Medicinal Plants Research Vol. 6(46), pp. 5714-5719, 3 December, 2012
Available online at http://www.academicjournals.org/JMPR
DOI: 10.5897/JMPR12.540
ISSN 1996-0875 ©2012 Academic Journals

Review

Phytochemistry and pharmacologic properties of *Urtica dioica* L.

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Accepted 10 July, 2012

***Urtica dioica* is known as Stinging Nettle. *U. dioica* extracts are important areas in drug development with numerous pharmacological activities in many countries. For a long time *U. dioica* has been used in alternative medicine, food, paint, fiber, manure and cosmetics. *U. dioica* has recently been shown to have antibacterial, antioxidant, analgesic, anti-inflammatory, antiviral, anti-colitis, anticancer and anti-Alzheimer activities. Flavonoids, tanins, scopoletin, sterols, fatty acids, polysaccharides, isolectins and sterols are phytochemicals which are reported from this plant. Due to the easy collection of the plant and being widespread and also remarkable biological activities, this plant has become both medicine and food in many countries especially in Mediterranean region. This paper presents comprehensive analyzed information on the botanical, chemical and pharmacological aspects of *U. dioica*.**

Key words: *Urtica dioica*, Urticaceae, pharmacology, phytochemistry.

INTRODUCTION

Urtica dioica L. commonly known as Stinging Nettle is an herbaceous perennial plant that grows in temperate and tropical wasteland areas around the world (Krystofova et al., 2010). Stinging Nettle has been among the key plants of the European pharmacopoeia since ancient times. It belongs to Urticaceae family in the order of Rosales that contains about 60 genera and more than 700 species. *U. dioica* has been known as “Gazaneh” in Iran and distributed in North, North-West and central parts of Iran. *U. dioica* is a dioecious herbaceous perennial, reaches to 1-2 m high (Figure 1). It has widely spreading rhizomes and stolons, which are bright yellow as are the perennial roots (Figure 2). The soft green leaves are 3-15 cm long and are borne oppositely on an erect wiry green stem. The leaves have a strongly serrated margin, a cordate base and an acuminate tip with a terminal leaf tooth longer than adjacent laterals (Figure 3). It bears small greenish or brownish numerous flowers in dense axillary inflorescences (Figure 4). The male flowers have stamens only, and the female ones have only pistil or seed-producing organs. Usually a plant will bear either male or female flowers throughout (Zargari, 1998). The leaves and stems are very hairy with non-stinging hairs and also bear many stinging hairs or trichomes (Figure 5), whose tips come off when touched, transforming the hair into a needle that will inject several chemicals including acetylcholine, histamine, 5-HT (serotonin), moroidin, leukotrienes and possibly formic acid (Casarett et al., 2008; Greenberg, 2003). After contacting human skin, the irritant is released and produces pain, wheals or a stinging sensation which may last for even more than 12 h (Oliver et al., 1991). The burning property of the juice is dissipated by heat, enabling the young shoots of the Nettle, when boiled, to be eaten as a pot-herb.

For a long time, in folklore medicine, *U. dioica* has been used as a diuretic agent and to treat arthritis and rheumatism. Nowadays it is an important medical herb and consumed as a component of the human diet due to its content of minerals, chlorophyll, amino acids, lecithin, carotenoids and vitamins. A number of chemical constituents such as flavonoids, tanins and sterols have been isolated from different parts of the plant (Krystofova et al., 2010).

From current pharmaceutical studies, additional pharmaceutical applications of *U. dioica* have revealed antioxidant (Mavi et al., 2004), anti-inflammatory, anti-ulcer (Gulcin et al., 2004), antiviral (Krystofova et al., 2010), anticancer (Koch, 2001), antibacterial, antifungal (Meepagala et al., 2005), antiandrogenic (Khouri and El-

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Figure 1. *Urtica dioica* L. (Stinging nettle).

Figure 2. *Urtica dioica* roots.

Akawi, 2005), insecticide (Barbosa et al., 2011), effects among others.

Since review and systemic analysis of chemistry, pharmacology and clinical properties of *U. dioica* have not been reported, we prompted to provide the currently available information on traditional and local knowledge, ethno biological and ethno medicinal issues, identification of pharmacologically important molecules and pharmacological studies on this useful plant. The aim of this paper is to introduce *U. dioica* as a potent medicinal plant by highlighting its traditional applications as well as the recent findings for novel pharmacological and clinical applications.

Figure 3. *U. dioica* leaf.

Figure 4. *U. dioica* flowers.

CHEMICAL COMPOSITION

The commonly known phytochemical compounds from *U. dioica* are flavonoids, tanins, volatile compounds and sterols (Krystofova et al., 2010; Gul et al., 2005).

Three smooth-muscle stimulating substances including acetylcholine, histamine, and 5-hydroxytryptamine (5-HT) have been identified in *U. dioica* (Collier and Chesher, 1956). Formic acid, histamine and serotonin are also identified as the pain-inducing agents in the stinging hairs of *U. dioica* (Fu et al., 2006). Carvacrol (38.2%), carvone (9.0%), naphthalene (8.9%), (E)-anethol (4.7%), hexahydrofarnesyl acetone (3.0%), (E)-geranyl acetone (2.9%), (E)-β-ionone (2.8%) and phytol (2.7%) are characterized as the main components of *U. dioica* essential oil (Gul et al., 2005).

Figure 5. *U. dioica* trichomes.

Rhizomes of *U. dioica* contain other biological active compounds such as scopoletin, sterols, fatty acids, polysaccharides and isolectins (Krystofova et al., 2010). These rhizomes contain a complex mixture of agglutinin isolectins which are differ definitely with respect to their amino acid composition. It is likely that at least some of them are different polypeptides coded for by different genes (Van Damme et al., 1988).

ANTI-INFLAMMATORY AND ANALGESIC PROPERTIES

Although a number of steroidal or non-steroidal anti-inflammatory drugs have been developed, researchers are changing their focus to natural products to develop new anti-inflammatory agents due to the side-effects of chemical drugs (Hyun and Kim, 2009; Shokrzadeh and Saeedi Sarvari, 2009). As a result, the search for other alternatives seems necessary and beneficial. *U. dioica* is an open door for new and effective compounds. Many cells and mediators are involved in proceeding inflamemation. For example, macrophages are representative inflammatory cells involved in acute or chronic inflammatory responses by over-production of pro-inflammatory cytokines [for example, tumor necrosis factor (TNF)-a, interleukin (IL)-1b and granulocyte/ macrophage colony stimulating factor (GMCSF)] and inflammatory mediators (Rhee et al., 2009; Lundberg, 2003; Walsh, 2003). *U. dioica* sting seems a safe treatment for musculoskeletal pain. It contains serotonin and histamine that are involved in the cascade of stimulation affecting levels of nerve growth factor which in turn increases activation of nociceptive pain neurons (McMahon, 1996). The mechanism of this plant analgesia could be hyper stimulation of the sensory nociceptors causing a TENS-like effect (Melzack and Wall, 1965), a substance P depletion effect similar to that of capsaicin (Frucht-Pery et al., 1997), an acupuncture-like effect (Lewith and Kenyon, 1984), or a counter irritant effect (Turner, 1984). A stinging rash might also have a powerful effect on patients cognitive perception of pain (Weisenberg, 1998).

Leaf extracts from *U. dioica* acts by switching Th1 derived responses to Th2; therefore it may inhibit inflammatory events of rheumatoid arthritis (Riehemann et al., 1999). The combination of 50 mg *U. dioica* with 50 mg diclofenac showed similar effectiveness to 200 mg diclofenac and this is important for patients suffering from non steroidal anti-inflammatory drugs (Chrubasik et al., 1997).

Type 2 diabetes is a metabolic disorder that is strongly associated with cardiovascular risk. Inflammation is a potential risk factor for cardiovascular disease. Hydro alcoholic extract of *U. dioica* has also shown effectiveness on some inflammatory indicators in type 2 diabetic patients. Patients were adjusted by age, sex and duration of diabetes, then randomly divided into two groups, an intervention and control group. They received, 100 mg kg^{-1} nettle extract or placebo in three portions a day for 8 weeks. Interleukin 6 (IL-6) and High Sensitive C-Reactive protein (hs-CRP) showed a significant decrease in patients with type 2 diabetes after eight weeks intervention (Namazi et al., 2007).

Phytalgic®

Phytalgic® consists of capsules containing fish oils, *U. dioica*, zinc, and vitamin E. The medicinal treatment of osteoarthritis (OA) is mostly symptomatic to relieve pain and incapacity with analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), drugs with well-known risks. Complementary medicines might reduce the symptoms of OA and decrease the need for NSAIDs. A randomized double-blind parallel-groups clinical trial compared Phytalgic® to a placebo for three months, in 81 patients with OA of the knee or hip using NSAIDs and/or analgesics regularly. The food supplement tested appeared to decrease the need for analgesics and NSAIDs and improve the symptoms of osteoarthritis. The effect size (ES) of this supplement for pain reduction was -1.27, which corresponds to a very large ES and indicated that Phytalgic® is 76% more efficacious than intra-articular corticosteroid therapy for knee OA (Zhang et al., 2007). Osteoarthritis experts who endorse nutraceuticals would probably agree that a nutraceutical with an ES above 0.5 is rarely seen and it has never been seen anything as efficacious as Phytalgic® (Bliddal and Christensen, 2009).

HEPATOPROTECTIVE PROPERTIES

U. dioica has a protective effect on hepatic damage created

with ischemia-reperfusion. Since *U. dioica* is known to be a strong antioxidant, breaking up free radicals, it is expected to be protective in hepatic ischemia-reperfusion injury of rats. *U. dioica* exhibited liver protection effect by increasing the activity of paraoxonase, arylesterase, and liver tissue catalase activity. Treatment with *U. dioica* reduced oxidative stress resulting in a decrease in ceruloplasmin levels. Also, it was found that treatment with *U. dioica* decreased the lipid hydroperoxide activity, indicating that the antioxidant effect of *U. dioica* had prevented the emergence of an oxidant agent such as LOOH with creation of hepatic ischemia-reperfusion (Kandis et al., 2010).

A histopathological examination detected no pathological changes. Also, evaluation of liver enzymes and histopathological findings of liver tissue indicated that UD had beneficial effects on the liver, so UD can be considered a preventive treatment agent in hepatic ischemia-reperfusion injury (Kandis et al., 2010).

U. dioica extract has shown hypocholesterolemic effects in animal models at doses of 100 and 300 mg/kg and significantly reduced the levels of total cholesterol and LDL and also markedly decreased liver enzymes and weight in animals with a high cholesterol diet (Nassiri-Asl et al., 2009).

U. dioica treatment for 60 days has exhibited significant reduction in liver enzyme levels and also has increased the reduced antioxidant enzyme levels in CCl4-treated rats (Kanter et al., 2005). *U. dioica* has also shown a protective effect against oxidative damage in isolated rat hepatocytes (Daba and Abdel-Rahman, 1998). It was found that the fixed oil of this plant has both antioxidant and anti-eicosanoid effects greater than thymoquinone which is its active constituent (Houghton et al., 1995). Furthermore, *U. dioica* has antioxidant activity by suppressing the chemiluminescence in phagocytes (Haq et al., 1995). Recently, it is observed that *U. dioica* has a significant hepatoprotective effect in CCl4-administrated rabbits, and that hepatocellular degenerative and necrotic changes are slight without advanced fibrosis and cirrhotic process (Turkdogan et al., 2003). However, it is found that *U. dioica* can prevent liver fibrosis and cirrhosis, suggesting that this plant protects liver against fibrosis possibly through immunomodulator and antioxidant activities (Turkdogan et al., 2001). *U. dioica* extract prevented CCl4-induced hepatotoxicity in rats by decreasing the lipid peroxidation and increasing the antioxidant defense system activity (Kanter et al., 2005).

U. dioica leaves extract (100 mg/kg/day for 5 days) before inducing diabetes in rats could prevent reduction of hepatocyte area in the periportal zone and increase in the nucleus area in the perivenous zone in the protective group.

Since the *U. dioica* extract has antioxidant properties, it can possibly affect the mechanisms of STZ and modulate or limit the effects of diabetes on the liver tissue (Golalipour et al., 2010).

ANTIVIRAL ACTIVITY

Mannose-binding proteins derived from several plants inhibit human immunodeficiency virus (HIV) replication and select for drug-resistant viruses that show profound deletion of N-glycosylation sites in the GP120 envelope. The N-acetylglucosamine-binding protein from *U. dioica* (UDA) prevented HIV entry and eventually selected for viruses in which conserved N-glycosylation sites in GP120 were deleted. In contrast to the mannose-binding proteins, which have a 50 to 100-fold decreased antiviral activity against the UDA-exposed mutant viruses, UDA has decreased anti-HIV activity to a very limited extent, even against those mutant virus strains that lack at least 9 of 22 glycosylation sites in their GP120 envelope. UDA represents the prototype of a new conceptual class of carbohydrate-binding agents with an unusually specific and targeted drug resistance profile. It forces HIV to escape drug pressure by deleting the indispensable glycans on its GP120 (Balzarini et al., 2005).

U. dioica EFFECTS ON BPH

Effects of *U. dioica* on benign prostatic hyperplasia (BPH) induced by testosterone have been exhibited. In vitro studies were conducted to assess the 5α-reductase inhibitory potential of this plant. Hyperplasia was induced in rats by subcutaneous administration of testosterone (3 mg/kg sc.) for 28 days. Simultaneous administration of petroleum ether and ethanolic extracts (10, 20 and 50 mg/kg po.) and isolated β-sitosterol (10 and 20 mg/kg po.) was undertaken. Measurement of prostate/body weight ratio, weekly urine output and serum testosterone levels, prostate-specific antigen levels (on day 28) and histological examinations carried out led to conclude that *U. dioica* can be used as an effective drug for the management of BPH. These effects are related to two biochemical markers, β-sitosterol and scopoletin (Nahata and Dixit, 2002).

U. dioica EFFECTS ON PROSTATIC CANCER

Various extracts of *U. dioica* were commonly used in the treatment of prostatic disease. Some extracts from *U. dioica* roots were demonstrated to exert proliferation-reducing effects in an *in vivo* animal model. It has been observed that some sterols and hydroxyl fatty acids, even they exist at low concentrations in this plant can inhibit aromatase, which is a key enzyme in steroid hormone-metabolism mediation the conversion of androgens into estrogens. The aqueous extract of *U. dioica* roots demonstrated a dose dependent inhibition of the binding globulin to its receptor and directly inhibits cell proliferation of HeLa cells and block binding of epidermal growth factor to its receptor. The aqueous extract of *U.*

dioica leaves also caused significant inhibition on ADA activities in prostate tissues from prostate cancer patients (Durak et al., 2004).

Cisplatin (CP) is a widely used cytotoxic agent against cancer, and high doses of CP have been known to cause nephrotoxicity and hepatotoxicity. The hepatoprotective, nephroprotective, and antioxidant activities of *U. dioica* methanolic extract against CP toxicity in Erhlich ascites tumor-bearing mice have been demonstrated. After a single dose of CP administration on day 1, the extract was given at the doses of 50, 100, 200, and 400 mg/kg body weight daily during 6 days. Almost all doses of the extract performed a significant preventive role against CP toxicity by decreasing aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, blood urea nitrogen, creatinine, lipid peroxidation, protein oxidation levels, and myeloperoxidase activity, as well as increasing reduced glutathione content, superoxide dismutase, catalase, glutathione S-transferase, and glutathione peroxidase activities. This suggests that methanolic extract of this plant has a protective capacity and antioxidant activity against CP toxicity in EAT-bearing mice, probably by promoting antioxidative defense systems (Ozkol et al., 2000).

CONCLUSION

The objective of this paper has been to show the recent advances in the exploration of *U. dioica* as phytotherapy and to illustrate its potential as a therapeutic agent. With the current information, it is evident that *U. dioica* has pharmacological functions including anti-inflammatory, analgesic, antiandrogenic, antihyperglycemia, anti-hyperlipidemia, antiviral and anticancer activities, among others. As the current information shows, it is also possible that Scopoletin, polysaccharides, isolectins and sterols might be useful in the development of new drugs to treat various diseases. However, the present results suggest a possibility that scopoletin, polysaccharides and isolectins can be further developed as potential disease-curing remedy. It must be kept in mind that clinicians should remain cautious until more definitive studies demonstrate the safety, quality and efficacy of *U. dioica*. For these reasons, extensive pharmacological and chemical experiments, together with human metabolism will be a focus for future studies. Last but not the least, this article emphasizes the potential of *U. dioica* to be employed in new therapeutic drugs and provide the basis for future research on the application of transitional medicinal plants.

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