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Stinging Nettle: A herb with tremendous pharmacological potential

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Abstract
Urticadioica L. commonly known as 'stinging nettle' is a perennial herb which belongs to the family Urticaceae. The plant is called Stinging Nettle because its leaves and stems contain hairs (trichomes) filled with a fluid that give severe sting when it comes in contact with the body. This herb is found in many South Asian Countries, Indian subcontinent and has been known in the world as a medicinal herb for a long time. The species has been a subject of recent scientific interest and product development all over due to its traditional usage as food, fibre and medicine. *U. dioica* is widely used by the traditional medicinal practitioners for curing various diseases such as nephritis, haematuria, jaundice, menorrhagia, arthritis and rheumatism. Phytochemical studies revealed the presence of many valuable chemical compounds like phytosterols, saponins, flavanoids, tannins, proteins, minerals and amino acids. *U. dioica* has been reported to have various pharmacological activities like antibacterial, antioxidant, analgesic, anti-inflammatory, antiviral, immunomodulatory, hepatoprotective, anti-colitis and anticancer effects. This paper aims to review and interpret up-to-date and comprehensive information regarding nutrition and health benefits, phytochemistry, pharmacology and toxicology of stinging nettle.

Keywords: Stinging Nettle, tremendous, potential

Introduction
Currently, research and development of new drugs from natural resources in a systematic and strategic manner has become the global trend. Natural product derived medicines are widely used today and account for more than 30% of therapeutic agents presently prescribed in clinics (Yang *et al*. 2008) [31]. These naturally derived medicines have been selected because of their great medicinal relevance. Within the recent years, infections have increased to a great extent and resistance against antibiotics becomes an ever-increasing therapeutic problem (Austin *et al*. 1999) [2].

Urticadioica L. one of the commonest plants on roadsides and wastelands, the common stinging nettle, (bichhubutti) is called *Soi* in Kashmir. It is a widespread annual plant from Urticaceae family. The plant is distinguished bythe stinging hairs on stem and leaves. These stinging trichomes contain a fluid which causes blistering upon contact with the skin. Nettle, or stinging nettle, is a perennial plant growing in temperate and tropical wasteland areas around the world. The genus name 'Urtica' comes from the Latin verb 'urere', meaning 'to burn,' because of these stinging hairs. The species name 'dioica' means 'two houses' because the plant usually contains either male or female flowers. Nettle has a well-known reputation for giving a savage sting when the skin touches the hairs and bristles on the leaves and stems (Upton, 2013) [29]. Since ancient times, people have taken advantage of this sting by flailing arthritic or paralytic limbs with fresh stinging nettle to stimulate circulation and bring warmth to joints and extremities in a treatment known as "urtication" (Green, 1824) [12]. Ancient Egyptians also reportedly used the infusion for the relief of arthritis and lumbago (Harrison, 1966) [14]. This practice of urtication or rubefaction became a standard in folk medicine as a remedy for arthritis, rheumatism, and muscular paralysis and is perhaps the most ancient medicinal use of stinging nettle. It has been used in traditional medicine since ancient times in the treatment of rheumatism and arthritis and as a tonic, astringent, and diuretic (Kavalali, 2003 [17]; Upton, 2013) [29]. In the last few years, *Urticadioica* L. has been accepted as a healing plant because of its considerable effects on human health in many countries all over the world. This plant is traditionally used in Morocco, Turkey, Brazil, Jordan and with much frequency in Northern Iran (Pourmorad *et al*. 2006) [21]. *U. dioica* herbs are used to treat stomachache in Turkish folk medicine (Gulçin *et al*. 2004) [13], and in Iran (Pourmorad *et al*. 2006) [21].

Besides, this herb is used to treat rheumatic pain and for colds and cough (Sezik *et al.* 1997) [25]. Nettle infusions and decocts are frequently used for the treatment of anemia and convalescing patients because its administration increases the iron binding capacity as well as the level of red cell folate and vitamin B12 in blood (Upton, 2013) [29]. Additionally, stinging nettle is used as a leaf vegetable, primarily in soups, vegetable pies, and salads (Kavalali, 2003) [17]. Some medicinal properties of stinging nettle have been confirmed by a modern research; thus, nowadays, it plays a major role in the treatment of benign prostatic hyperplasia (Chrubasik *et al*. 2007) [8] and rheumatoid arthritis (Upton, 2013) [29]. Considering notable medicinal and dietary applications of stinging nettle, there is a great need for detailed characterization and exploration of its chemical composition for therapeutic purposes.

Plant Description

U. dioica is originally from the colder regions of northern Europe and Asia, today this herbaceous shrub grows all over the world. It grows 2-4 meters high and produces pointed leaves and white to yellowish flowers. Stinging nettle grows well in nitrogen-rich soil, blooms between June and September of every year. The stem is erect and green, the leaves are opposite, cordate at the base, oblong or ovate, finely toothed, dark green above and paler beneath. The flowers are in reddish-brown to greenish-white colour. Usually, the plant has either male or female flowers, in separate inflorescences. Stinging nettle leaf, often mixed with stem and sometimes seed, is sold in fresh, dried, and freeze-dried forms. Both stems and leaves bear stinging hairs that are erect and bristly in nature. The hairs may be up to 70 mm in length. Both the leaves and stems are covered with erect and bristly glandular hairs that contain, among other compounds, acetylcholine, formic acid, 5-hydroxytryptamine, and histamine. (Ahmed and Parsuraman, 2014 [1]; Upton, 2013) [29].

Plant constituents and phytochemicals

The leaves of the stinging nettle contain a fairly wide variety of chemical constituents although only a few compounds belonging to various natural classes have been identified. The compounds responsible for the stinging/burning action of the hairs on the leaves of *Urticadioica* are acetylcholine, histamine, 5-hydroxytryptamine (serotonin), and small amounts of leukotrienes (Czarnetzki *et al*. 1990) [9]. The shikimic acid derived phenylpropanes, caffeic acid, and various esters of this acid such as chlorogenic acid and caffeoylmalic acid as well as the coumarin scopoletin have been identified (Schomakers *et al*. 1995) [24]. The distinctive constituents of the herb are the stinging constituents (acetylcholine, histamine, serotonin) and caffeoylmalic acid whereas *Urtica Dioica* Agglutinin (UDA) and ceramides are characteristic of the root.

Chemical constituents	Main compounds
Flavonoids	Patuletin, kaempferol, isorhamnetin, quercetin, and 3-rutinosides and 3-glycoside
Phenolics	Shikimic acid derivatives phenyl propanes, caffeic acid, and various esters of this acid such as chlorogenic acid and caffeoylmalic acid (upto 1.8%)
Essential oil	esters (14.7%), free alcohols (2%), and ketones (38.5%) identified as 2-methyl-2- hepten-2-one, acetophenone and ethylketone, and traces of nitrogenous substances, phenols, and aldehydes
Fatty acids	6.8% palmitic acid, 1.1% stearic acid, 3.6% oleic acid, 20.2% linoleic acid, and 12.4% linolenic acid
Carotenes	B-carotene (2.95-8 mg/100 g in fresh plants), 20.2 mg/100 g in dry young plants, hydroxy-α-carotene (0.9%), lutoxanthin (10.3%), lutein epoxide (13.1%), and violaxanthin (14.7%)
Vitamins	Ascorbic acid (36-269 mg%), VitaminB2-lactoflavin-1.5 mg/100g in dried, 0.25 mg in the fresh leaves, panthotenic acid, Vitamin-K1 0.64g/100g
Minerals	Silicates in a relative big quantity (1-4% SiO_2) calcium, iron, magnesium, phosphorus, potassium and sodium are also present.

Source: Upton, 2013 [29]; Joshi *et al*. 2014 [15]

Therapeutics of stinging nettle

Both the herb and the root of stinging nettle are used therapeutically, although in different capacities. The herb is primarily recommended as an adjuvant treatment of rheumatic conditions, lower urinary tract infections, as a nutritional tonic, and more recently, the fresh freeze-dried leaves for the treatment of allergies. The root is used to reduce complaints associated with benign prostate hyperplasia. For both, clinical, *in vitro*, and animal data have shed some light into the mechanism of action and provide support for some of these traditional uses. This review focuses on research regarding medicinal benefits of stinging nettle herb. Since then stinging nettle herb has been more subject to pharmacological than clinical research. It remains to be established if the pharmacological findings are surrogate markers for clinical improvements. Topical application of the fresh leaves has also been used traditionally and tested clinically (Upton, 2013) [29].

Anti-Inflammatory, analgesic, and local anesthetic activity

In an open uncontrolled study in two centers conducted by Wolf *et al*. 2001 [30], 20 patients suffering from acute exacerbations of osteoarthritis of the hip or knee received 2-3 capsules of 145 mg stinging nettle herb extract (IDS30; Strath 59) per day over 12 weeks. Pain scores assessed in a patient diary decreased by 42%. No Adverse events were observed.

Randall *et al*. (2008) [22] also conducted a small (n=42) randomized controlled pilot study to explore the feasibility of treatment of chronic knee pain with urtication by stinging nettle and found a mean reduction in pain score at the end of treatment in the stinging nettle groups of 1.7 and in the controls 1.6. Both groups reduced pain scores significantly.

There are mixed preclinical data regarding an anti-inflammatory effect of stinging nettle herb preparations. However, for the 50% ethanolic stinging nettle extract (IDS23) anti-inflammatory action was demonstrated in rats in which gonarthritis was induced with 100 g bovine gammaglobulin and 500 g silicon particles. The reduction of paw circumference by the stinging nettle extract relative to that of diclofenac (100%) were 12%, 36%, and 67% for the

3 doses, respectively. The potential for anti-inflammatory activity was studied for the major compound patuletin isolated from the dwarf stinging nettle. When administered orally, patuletin (10 mg/kg) reduced the carageenan-induced edema volume significantly ($P<0.05$) to the same degree as an equivalent dose of diclofenac and reduced carageenan-induced pleural fluid volume to a greater degree than diclofenac (Saeed *et al*. 1995) [23].

Dendritic cells (DCs) are important antigen presenting cells. They play an important role in the initiation of rheumatoid arthritis. The *in vitro* results showed the suppressive effect of the stinging nettle extract on the maturation of human myeloid DC, leading to a reduced induction of primary T-cell responses (Broer and Behnke, 2002) [4]. The authors concluded that this effect might contribute to the therapeutic effect of stinging nettle extract on T-cell-mediated inflammatory diseases such as rheumatoid arthritis.

Effect on Benign Prostatic Hyperplasia (BPH)

The effect of *Urticadioica* root on testosterone induced BPH has been studied by in‐ vitro studies for assessing the 5α‐ reductase inhibitory potential. The administration of petroleum ether, ethanolic extracts 10, 20 and 50 mg/kgand isolated β‐ sitosterol 10 and 20 mg/kg has been under taken for BPH studies. There was decrease in prostate/body weight ratio weekly urine out‐ put and serum testosterone levels, Prostate‐ specific antigen levels carried out which conclude that *Urticadioica* can be used for the management of BPH (Nahata and Dixit, 2012) [19].

Platelet anti-aggregation activity

The ability of stinging nettle preparations to inhibit platelet aggregation has been reported in various *in vitro* models. Crude aqueous stinging nettle extract inhibited thrombin-induced aggregation dose-dependently (at 1 mg/mL by 17%). The more lipophilic the solvent, the more potent the effect. Ethyl acetate extract exhibited the greatest anti-aggregation effect (77% inhibition at 1 mg/mL) (Upton, 2013) [29].

Antioxidant activity

Cetinus *et al*. (2005) [7] investigated the potential role of stinging nettle for prevention of oxidative stress in muscle tissues generated by tourniquet application in Wistar rats. Homogenized stinging nettle leaf or 1.15% KCl aqueous solution was given to each group of 8 rats once a day for 5 days through esophageal gavage. The authors concluded that stinging nettle has a potential antioxidant effect on ischemic muscle tissues. The protective effects of stinging nettle infusions (2.5 g dried herb/L boiled water) against chemical carcinogen trichloroacetic acid (TCA) exposure in rats has also been tested by Celik and Tuluce (2007) [6]

Anti-Cancer and immunomodulatory activity

Evidence regarding the use of stinging nettle herb in cancer is limited. However, in Turkey, stinging nettle is among the most prevalent herbal complementary and alternative medicines used by cancer patients (Kav *et al*. 2008) [16]. According to another survey in Turkey, stinging nettle, either as tea or eaten as a steamed or boiled green, was reportedly used by more than 93% of children receiving conventional therapies at a pediatric oncology unit (Gozum *et al*. 2007) [11]. Immunomodulatory activity of an aqueous stinging nettle extract was observed in mouse splenocytes. There is some evidence that the compounds quercetin-3-O-rutinoside, kaempherol-3-O-rutinoside, and is orhamnetin-3-O-glucoside present in the methanolic extract of the aerial parts of the plant contribute to the immunomodulatory activity of stinging nettle.

Hypotensive Effect

Of the reported cardiovascular actions of stinging nettle, the most notable is the potential for stinging nettle herb to lower blood pressure. An adrenolytic effect as well as an effect on potassium has been reported by various authors (Legssyer *et al*. 2002 [18]; Tahri *et al*. 2000) [26]. The authors concluded that the cardio- vascular effects might be based on the high potassium content in stinging nettle. The authors hypothesized a possible direct effect of stinging nettle herb on the cardiovascular system besides an action on renal function. They concluded that higher stinging nettle leaf dose is toxic because of the persistence of its hypotensive action.

Antidiabetic Activity

Two potential hypoglycemic activities of stinging nettle herb that have been reported include a decrease in intestinal glucose absorption through an inhibition of intestinal glucosidases (Onal *et al*. 2005) [20] and an increase in serum insulin (Farzami *et al*. 2003) [10]. These data are limited and their application to human use is unclear.

Diuretic Potential

Stinging nettle herb has traditionally been used as a diuretic. The aqueous extract of whole plant has been reported to produce diuretic and natriuretic effects in rabbits. The aqueous extract of aerial part of the plant was administered. At low dose (4 mg/kg/h) and high dose (24 mg/kg/h) which shows diuresis effect by increase diuresis (11 and 84% respectively) and natriuresis (28 and 143% respectively). Hence, the plant has shown to have potential diuretic effect. (Tahri *et al*. 2000) [26] Carceres *et al*. 1987 [5], reported an increase in urine production by 20% after 1g/kg oral dose in 10% decoction in rats. The diuretic effect of stinging nettle was approximately 25% of that achieved with hydrochlorothiazine (25 mg/kg). This diuretic effect may explain the traditional use of stinging nettle herb internally as an anti-rheumatic, not as a direct analgesic, but as an antidyscratic. Water-based nettle herb preparations (infusion and decoction) are the preferred diuretic treatment to prevent recurrence of kidney stones (Tita *et al*. 1999).

Erythropoiesis

One of the primary uses of stinging nettle herb among medical herbalists is as a nutritional tonic for the treatment of anemia. There are some studies that support this belief. Persistent anemia via bleeding was produced in rabbits and stinging nettle herb juice (10 mL per day) was administered resulting in a resolution of the anemia within 20 days compared to 6 weeks for untreated animals. The beneficial effect on the erythropoiesis was similar to that of iron-containing preparations. The excretion of porphyrins (chlorophyll metabolites) was increased. The author suggested that the improvement of well-being during stinging nettle juice treatment was based on these effects (Upton *et al*. 2013) [29].

Toxicological Results

The fixed oil of *Urticadioica* was completely non-lethal even at doses reaching 12.8 mL/kg and considered non-toxic (Joshi, *et al*. 2014) [15]. Acute and chronic toxicity of stinging nettle herb was studied by determining the (Lethal Dose) LD_{50}. Intravenous doses greater than 500 mg/kg caused transient hypotension and cardiac arrhythmias. Following intravenous injection the LD_{50} was 19,286 mg/kg for a stinging nettle infusion 100 mg/mL and 17,213 mg/kg for an aqueous extract (3:1) 109 mg/mL in mice. Whereas, oral administration of an infusion of the roots can be tolerated up to 1.310 g/kg body weight (Bombardelli and Morazzoni, 1997) [3]. Its toxicity has been attributed to the presence of hydro soluble constituents, (suspected to have a pyran-coumarin structure), a substance eliminated by boiling. The risk for adverse events during nettle root treatment is very low. Standardized nettle extract (at doses up to 50% concentration) showed no mortality in mice (Chrubasic *et al*. 2007) [8].

Safety Profile

The Botanical Safety Handbook (1997) [27] of the American Herbal Products Association (AHPA) assigns *Urtica dioica* as a Class 1 herb: Can be safely consumed when used appropriately. With the exception of the contact urticaria commonly associated with fresh stinging nettle, generally speaking, internal consumption of dried or cooked stinging nettle preparations is very safe as the irritating principles of the trichomes are mostly or completely dissipated with processing. There is a very long history of the use of stinging nettle as a steamed vegetable, soup ingredient, tea, juice, and a variety of dried preparations. This lack of irritating principles does not rule out the potential for idiosyncratic reactions to other compounds of stinging nettle (Upton, 2013) [29].

Conclusion and future scope

Keeping in view the long traditional and recent pharmacological usage, *U. dioica* has demonstrated a strong potential for food, health-maintaining and therapeutic purposes. The information as presented in this review on the pharmacological and various biological properties of the plant will provide evidence for the use of this plant in various ailments. The plant is reported to contain mainly kaempferol, is orhamnetin, quercetin, isoquercitrin, andrutin which might be useful in the development of new drugs to treat various diseases because of their potent antioxidant property. Literature findings indicate that *in-vitro*, *in-vivo* and clinical researches are validating its use in traditional and herbal medicines. Although the species is claimed to be beneficial for curing arthritis, diabetes, anemia, asthma, blood pressure, kidney problem, cancer, etc. however at times, there is inconsistency among the results. There is a need to further standardize the efficacy of stinging nettle and validation is required. It is suggested that more research needs to be done with relation to protein, minerals, vitamins and other bioactive compounds in fresh and dried nettles.

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