

## *Urtica dioica*; *Urtica urens* (Nettle)

### Description

*Urtica dioica* (stinging nettle) and *Urtica urens* (dwarf nettle) are members of the Urticaceae family native to Eurasia, and are considered therapeutically interchangeable.<sup>1</sup> The term nettle is used in this article to refer simultaneously to stinging and dwarf nettle.

*Urtica* prefers wet, rich soil and tends to grow in large patches. Stinging nettle is taller than dwarf nettle and is perennial; dwarf nettle is an annual. Both plants have fleshy, drooping, serrated, roughly heart-shaped leaves. The leaves and stems are covered with stinging hairs (dwarf nettle leaves are smooth and more delicate). Both produce inconspicuous green-white flowers in late spring or summer. The leaf, flower, seed, and root of nettle are used differently and contain different chemical constituents.



### Constituents and Mechanisms of Actions

Like all green vegetables, nettle leaf is a micronutrient dense, nutritious food; however, it should be steamed or cooked before ingestion to destroy the stinging hairs, which contain histamine, formic acid, acetylcholine, acetic acid, butyric acid, leukotrienes, 5-hydroxytryptamine, and other irritants.<sup>2,3</sup> Contact with the hairs leads to a mildly painful sting, development of an erythematous macule, and itching or numbness for a period lasting from minutes to days. Medicinal extracts of nettle do not cause this reaction as the hairs are destroyed in processing.

The hydrophilic components of nettle, including lectins and polysaccharides, appear to be important, particularly in prostate disease;<sup>4</sup> however, hydrophobic constituents have not been ruled entirely unimportant.<sup>5</sup> Each constituent may have individual effects, with the combination acting differently than any one constituent in isolation.

The importance of nettle root lignans, such as (-)-3,4-divanillyltetrahydrofuran, in benign prostatic hyperplasia (BPH) and other androgen- and estrogen-sensitive conditions may be due to interference with binding of sex hormone binding globulin (SHBG) to testosterone, the testosterone receptor, and/or the SHBG receptor.<sup>6,7</sup> Nettle lectins and sterols did not show anti-SHBG effects in these studies.

The steroidal compounds stigmasterol, stimast-4-en-3-one, and campesterol have been shown to inhibit the prostatic sodium/potassium pump, which might contribute to nettle's effects in BPH.<sup>5</sup> The small quantity of beta-sitosterol in nettle root (<0.01% of total mass) is unlikely to have an effect on BPH, given that 60 mg beta-sitosterol daily is the usual amount necessary to reduce symptoms.<sup>8</sup>

*Urtica dioica* agglutinin (UDA) is a heat- and acid-resistant lectin found in stinging nettle, primarily the root. UDA induces a pattern of T-lymphocyte activity not seen with any other known plant lectin.<sup>9</sup> UDA appears to prevent formation of a systemic lupus erythematosus-like condition in mice, and has diverse antiviral effects *in vitro*.<sup>10,11</sup> UDA antagonizes the epidermal growth factor receptor, an effect that may be of benefit in interfering with the pathogenesis of BPH.<sup>12</sup>



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Testosterone, its metabolite dihydrotestosterone (DHT), and estrogen are hormones commonly associated with prostate disease. Testosterone is converted to estrogen via the enzyme aromatase. Aromatase levels increase as men age, testosterone levels decline (as higher aromatase levels convert testosterone to estrogen), and the prostate gland becomes enlarged. Aromatase inhibitors are used in BPH to prevent the age-related rise in estrogen and associated prostate enlargement. 9-hydroxy-10-trans-12-cis-octadecadienic acid (HOA) from nettle root inhibits aromatase in prostate tissue.<sup>13</sup> A botanical formula consisting of whole herb *Urtica dioica* and *Pygeum africanum* bark was found to inhibit both aromatase and 5-alpha reductase.<sup>14</sup> Inhibition of 5-alpha reductase interferes with conversion of testosterone to DHT, high levels of which are associated with BPH and prostate cancer.

Polysaccharides and caffeic malic acid (CMA) are both found to some extent in all parts of nettle. Polysaccharides stimulated T-lymphocyte activity and complement activation *in vitro*.<sup>2</sup> *Urtica* polysaccharides and CMA demonstrated anti-inflammatory activity *in vitro* and in animal studies, via cyclooxygenase and lipoxygenase inhibition.<sup>2,15</sup> Isolated polysaccharides promoted tumor necrosis factor (TNF) production *in vitro*, while whole plant extracts inhibited TNF.<sup>2,16</sup>

## Clinical Indications

### Benign Prostatic Hyperplasia

The best-researched indication for nettle is use of the root for men with symptomatic BPH, something nettle is not known for traditionally. At least four double-blind clinical trials confirm the efficacy of nettle root for BPH symptoms alone or in combination. Earlier research on a combination with *Pygeum* extract at two dose levels, a combination with alpha-adrenergic antagonists, and a combination with *Serenoa repens* (saw palmetto) fruit extracts all show the benefits of nettle root.<sup>17-19</sup> In perhaps the most persuasive trial, a combination of nettle and saw palmetto was just as effective as finasteride (Proscar®) in improving symptoms of BPH in a 48-week, double-blind trial, with fewer and milder adverse effects in the herbal group than the drug group.<sup>20</sup> Uncontrolled trials have also demonstrated nettle's effectiveness for BPH.<sup>21</sup>

Several other randomized, double-blind, placebo-controlled clinical trials have investigated the effect of *Urtica dioica* (UD) root extracts on lower urinary tract symptoms (LUTS) associated with BPH. In the largest study, 558 symptomatic subjects (ages 55-72) received either 120 mg aqueous extract of UD root (n=287) or placebo (n=271) three times daily for six months.<sup>22</sup> After six months subjects were evaluated, crossed over to the alternate group, and the trial continued for another 18 months. Eighty-one percent (n=232) of the treatment group reported improved LUTS compared to 16 percent (n=43) in the placebo group. Subjects in the treatment group also exhibited decreased International Prostate Symptom Score (IPSS) (from 19.8 at baseline to 11.8 at six months, compared to a decline from 19.2 to 17.7 for placebo). After six months, improvements in peak flow rate (Q<sub>max</sub>) of 8.2 mL in the UD group, compared to 3.4 mL for placebo, and significant decreases in postvoid residual volume (PRV) compared to placebo were also noted. No significant differences were observed between groups for PSA or testosterone levels, but those in the treatment group experienced a moderate decrease in prostate size. All improvements were maintained at the 18-month follow up.<sup>22</sup>

In a group of 226 patients, researchers investigated the efficacy of 459 mg dry UD root extract (n=114) or placebo (n=112) for one year. Decreases in IPSS reached statistical significance in the UD group (18.5±3.0 to 13.8±0.5) compared to placebo, without significant differences in Q<sub>max</sub> or PRV. Subjects in the treatment group experienced fewer adverse events than the placebo group.<sup>23</sup>

Clinical trials have also examined the effects of UD in combination with *Sabal serrulata* for relieving LUTS in patients with BPH. In a multicenter, double-blind, placebo-controlled trial, 253 men were assigned to treatment (n=127) with 160 mg Sabal fruit extract and 120 mg UD root or placebo (n=126). After a two-week run-in phase, subjects were randomized to double-blind treatment for 24 weeks and then to an open control period of 24 weeks with all study subjects receiving the herbal extract. At 24 weeks, patients in the treatment group experienced a significantly greater reduction in IPSS scores (decrease of six points) compared to the placebo group (decrease of four points), reflecting improvement in both obstructive and irritative symptoms.

Subjects switched from placebo to herbal treatment also reported a marked improvement in LUTS (as measured by IPSS). The combination extract formula was well tolerated.<sup>24</sup>

Subsequently, this same combination formula was compared to tamsulosin, an alpha1-adrenoceptor antagonist used to treat LUTS. Subjects (n=140) with BPH and IPSS scores  $\geq 13$  were randomized to receive either two capsules (240 mg) herbal extract or 0.4 mg tamsulosin daily for 60 weeks. IPSS scores were evaluated at baseline, 8, 16, 24, 36, 48, and 60 weeks. Over the 60-week period the IPSS scores were reduced by a median of nine points in both groups; 32.4 percent in the botanical group and 27.9 percent in the tamsulosin group responded to treatment. The authors concluded both treatments were effective (the herbal preparation slightly more effective), and both were well tolerated with almost no side effects.<sup>25</sup>

### **Other Urinary Tract Conditions**

The German Commission E approves the use of nettle leaf as supportive therapy in patients with lower urinary tract infections (combined with immune and antimicrobial therapy) and to prevent and treat formation of urinary gravel.<sup>1</sup>

### **Arthritis, Neuralgia, and Related Conditions**

Topical application of fresh nettle leaves has a long history as a counter-irritant for patients with various pain syndromes. Weiss mentions using topical nettle for lumbalgia, sciatica, chronic tendonitis, sprains, and osteoarthritis.<sup>26</sup> This approach is safe if individuals are not allergic to nettle.

Two case studies suggest topically applied *Urtica* reduces osteoarthritis pain.<sup>27</sup> In a double-blind study, topical applications of *Urtica* and *Lamium album* (white nettle; a plant that has evolved to look like nettle but does not have stinging hairs) were compared.<sup>28</sup> Only *Urtica* was associated with relief of arthritic symptoms.

Oral dosing of nettle leaf preparations has also been investigated for rheumatic conditions. In one open trial, a leaf extract was associated with symptom reduction comparable to that achieved with non-steroidal anti-inflammatory drugs (NSAIDs).<sup>29</sup> In another open

study, nettle leaf (50 g of stewed leaves daily with food) was shown to potentiate the efficacy of sub-therapeutic doses of the NSAID diclofenac.<sup>30</sup>

### **Cardiovascular Disease**

Animal studies indicate UD extracts markedly inhibit platelet aggregation and improve lipid profiles.<sup>31,32</sup> An aqueous extract of UD leaves given to rats at 1 mg/kg body weight inhibited thrombin-induced platelet aggregation by  $17.1 \pm 4.2$  percent, while an ethyl acetate extract inhibited thrombin-induced platelet aggregation by  $76.8 \pm 6.1$  percent. Flavonoids appear to be the constituent responsible for this potent inhibition.<sup>31</sup> Aqueous extracts of 150 mg/kg UD daily given with a high-fat diet for 30 days improved lipid profiles in rats. Significant decreases were noted in total and LDL cholesterol, plasma Apo B, and the LDL/HDL ratio. Liver function was assessed and no liver damage was noted.<sup>32</sup>

### **Allergic Rhinitis**

Anti-inflammatory effects of nettle leaf suggest it may be useful for allergic diseases of all types. An open trial of 69 patients with allergic rhinitis found 600 mg freeze dried nettle leaf daily was effective for symptom relief. Fifty-eight percent reported relief of most symptoms and 48 percent stated it was more effective than other over-the-counter medications.<sup>33</sup> More rigorous trials are needed to confirm this finding.

### **Other Traditional Uses**

Nettle leaf has traditionally been used for numerous other conditions, although confirmatory clinical trials have not been conducted. Gout, hair loss, and mild bleeding (particularly mild menorrhagia), are some of the traditional indications for nettle leaf.<sup>34</sup>

### **Side Effects and Toxicity**

Internal use of nettle is not associated with any significant adverse effects. Fresh nettle causes stings and can rarely lead to severe allergic reactions in susceptible individuals.





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### Dosage

Typical daily dosages of *Urtica* (used in studies cited above) include 360 mg aqueous extract, 460 mg dried extract, and 600 mg freeze-dried nettle. One study used 50 g stewed nettle leaf daily for rheumatic conditions. Some nettle root products are standardized to their scopoletin content, but since this substance is not established as an active ingredient, the significance of this standardization is unclear.

Dosages for other nettle preparations include 1 tablespoon nettle juice (15 mL) in 4-6 oz water three times daily. Steamed (for 10-15 minutes) leaves can be eaten or added to soup. Vinegar or lemon improves flavor and may improve absorption of minerals. Tincture of the leaf or root is taken at a dose of 1/2-1 tsp (2-5 mL) three times daily, or as part of a formula with other herbs. Nettle leaf tea can be made by steeping 2-3 tsp herb in 1 pint of boiled water for 10-15 minutes.

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