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**FILE: ■ Nettle Root (*Urtica dioica*)
■ BPH (Benign Prostatic Hyperplasia)
■ Systematic Reviews**

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RE: Review of Stinging Nettle Root Extract Efficacy for BPH

Chrubasik JE, Roufogalis BD, Wagner H, Chrubasik S. A comprehensive review on the stinging nettle effect and efficacy profiles. Part II: urticae radix. *Phytomed.* Aug 2007;14(7-8):568-579.

In this systematic review, the authors examine the evidence on the effects and efficacy of stinging nettle root extract preparations in the treatment of benign prostate hyperplasia (BPH). The authors have systematically searched Medline via Pubmed through July 2006 for controlled and uncontrolled clinical trials and pre-clinical studies on stinging nettle root preparations and BPH. Contact with experts, hand searches through the authors' own files, and bibliographies from all included papers were searched for additional publications. Studies on preparations made from multi-plant mixtures were excluded from the review.

Stinging nettle root preparations have been used in European folk medicine for urinary tract complaints for many years. Germany's Commission E recommends 4-6 g/day of stinging nettle root (*Urtica dioica*, *U. urens*) preparations in the treatment of "Difficulty in urination in benign prostatic hyperplasia stages 1 and 2."¹ Studies on stinging nettle root use daily doses of 4-6 g/day of the infusion, 300-600 mg (DER [drug-extract ratio] 7-14:1, solvent-20% methanol) to 378-756 mg (DER 12-16:1, solvent- 70% ethanol) of the dried native stinging nettle extracts, and 4.5-7.5 ml (DER 1:1, solvent- 45% ethanol) or 15 ml (DER 1:5, solvent- 40% ethanol) of the fluid extracts. The active constituents include phytosterols, lignans, polysaccharides, and the lectin UDA (*Urtica dioica* agglutinine).

Published clinical research on stinging nettle root extract and BPH date back to 1950, but there are very few double-blind randomized controlled clinical trials. A case report from 1950 describes a beneficial effect of stinging nettle root tea. A total of 40,000 men with BPH have been treated with stinging nettle root preparations in 34 clinical trials. Of these 34 clinical trials, 24 are open and uncontrolled, 2 are open and controlled, and 6 are randomized placebo-controlled clinical trials. Only 1 of the 6 randomized placebo-

controlled clinical trials includes a hypothesis. All of the clinical trials have examined methanolic stinging nettle root extracts.

Two double-blind human pharmacological studies have shown that stinging nettle root extract BAZ (1,200 mg/day) decreases levels of sex hormone binding globulin (SHBG), compared with placebo. Two studies on stinging nettle root extracts demonstrated conflicting results on its hormonal effects. One showed an increase in levels of testosterone, 5-alpha-dehydroxytestosterone, and estradiol over seven months of treatment. Conversely, a 9-week trial on the BAZ extract (600 mg/day) showed no difference in levels of testosterone, androstadiol, and acid phosphatase. Open uncontrolled clinical trials provide conflicting evidence on the effects of stinging nettle root extract on sex hormones, and more research is needed. Human pharmacological studies have also examined the effect of stinging nettle root extract on prostate cell proliferation with inconclusive results. Nine weeks of treatment with BAZ (600 mg/day) resulted in treatment-induced glandular cell death and reactive inflammation. Twenty weeks of BAZ extract treatment (1,200 mg/day) resulted in reduced prostate cell metabolism. After six months of BAZ treatment (1,200 mg/day), the volume density of cytoplasmic secretion granula increased and the volume density of lysosomes decreased. These results suggest decreasing autophagy and increasing secretion of glandular cells. An additional study showed "an increase in the proportion of large-volume nuclei." After one year of treatment, stinging nettle root constituents or their metabolites are detectable in glandular cells, compared to controls. Stinging nettle constituents are not found following incubation of BPH tissue with stinging nettle extract. More research is needed on the possible effect of stinging nettle root extract on prostate cell growth.

All together, these clinical trials provide "some evidence of effectiveness of methanolic nettle root extracts in improving BPH complaints in the short-term; however, in order to calculate the effect size, more rigorous data are necessary." Future clinical trials should take into consideration the suggestions of the World Health Organization International Consultation on BPH and the consensus index (International Prostate Symptom Score). These authors write that more rigorous clinical research is needed "before nettle root extract may be considered in the BPH treatment guidelines." The clinical importance of pure stinging nettle root extract in the treatment of BPH has decreased because the combination of stinging nettle root and saw palmetto (*Serenoa repens*) extract are more effective. So, fewer studies are being conducted on stinging nettle root extract alone. There are a total of 699 adverse events for stinging nettle root; however, the numbers of adverse events may be higher because many studies did not report adverse events. The most common adverse effects are impotence and decreased libido. The majority of studies were conducted with a 20% methanolic extract. They indicate that this extract has a good short-term safety profile. Trials with longer treatment periods are needed to establish long-term safety; however short-term treatment is safe and associated with low toxicity levels.

In vitro experiments have provided insight into possible mechanisms of action for the effect of stinging nettle root extracts on BPH. An aqueous stinging nettle root extract inhibited SHBG binding to human prostatic membrane receptors. Isolated polar lignans, including secoisolariciresinol, interfered with SHBG binding to steroids, probably through

competitive inhibition. Structurally, "...a low polarity in the aliphatic part and a 3-methoxy-4-hydroxy substitution pattern in the aromatic part resulted in higher binding affinity for SHBG." Constituents of stinging nettle root displaced free steroid hormones from their SHBG binding sites and prevented the interaction of SHBG with prostate receptors. More research is needed to establish which constituents are responsible for these effects.

In addition, research suggests that stinging nettle root extract "...interferes with the conversion of testosterone into estrogens." Ethanolic stinging nettle root extract WS1031 (W. Schwabe Pharmaceuticals, Karlsruhe, Germany) inhibited the aromatization of androstenedione in vitro, and this effect has been attributed to lipophilic constituents. The addition of saw palmetto berry extract, used in the treatment of symptoms related to BPH, increased this effect. Ethanolic stinging nettle extract LI 166 (Lichtwer Pharma, Berlin, Germany) and a methanolic extract also inhibited aromatase. The activity of the methanolic extract increased with the addition of an extract made from the bark of the African prune (*Pygeum africanum*). Stinging nettle root extracts from a variety of producers inhibited aromatase. Aqueous stinging nettle root extract BNO 1250 (Bionorica, Neumarkdt, Germany) inhibited estradiol formation in a time- and dose-dependent manner. Common fatty acids, (10E, 12Z)-9-hydroxy-10,12-octadecadienoic acid, and other lignans are some of the constituents responsible for this effect. However, stinging nettle root contains only low levels of these constituents. Therefore, other active constituents remain to be identified. In addition to inhibiting aromatase, stinging nettle root extract may also inhibit aromatase gene expression.

In vitro evidence shows an anti-inflammatory effect for stinging nettle extracts. Ethanolic stinging nettle root extract WS1031 inhibited bovine leukocyte elastase. Methanolic stinging nettle root extract BAZ inhibited the alternative pathway of complement activation. A polysaccharide fraction and isolated nettle root polysaccharides, including rhamnogalacturanes, also inhibited complement activation. The commercial stinging nettle extract Bazoton® (Kanoldt Arzneimittel GmbH, Germany) contains 1.7% polysaccharides, which could exert an anti-inflammatory effect.

Cultured fibroblasts from the rat ventral prostate are used to screen for prostatotrophic compounds in vitro, and stinging nettle root extracts demonstrated activity. Nettle root extract BAZ (0.01%) reduced the proliferation of prostatic stromal fibroblasts by 50%. Fractions of methanolic BAZ extract reduced proliferation to various degrees, possibly through an androgen-independent mechanism of action. Conversely, another study on the methanolic BAZ extract showed a significant concentration- and time-dependent anti-proliferative effect on epithelial cells, but not stromal cells. The effect is attributed to a polysaccharide fraction. When cells from normal and BPH biopsies were incubated with the methanolic BAZ nettle extract, prostate metabolism was not affected and homogenous granules decreased. The stinging nettle root lectin UDA inhibited the binding of epithelial growth factor (EGF) to its receptor. This effect is antagonized by the oligosaccharide chitotriose, which has an affinity for the EGF receptor site. Another study showed that stinging nettle root extracts "may suppress prostate cell metabolism and growth by interaction with prostate steroid membrane receptors." Therefore, further research is needed on the effect of stinging nettle root extract on prostate cell growth.

In vivo studies provide further information. One in vivo study showed that stinging nettle root extract may exert an anti-inflammatory effect. Stinging nettle root extract LI 166 and its polysaccharide fraction showed an anti-inflammatory effect in the carageenin-induced rat paw edema test. More research is needed to determine if this anti-inflammatory effect translates to an anti-prostatic effect. The stinging nettle root extract BAZ reduced prostate size and serum testosterone levels in dogs. Hecogenin acetate is one of the active constituents.

It is clear that more pre-clinical and clinical research is warranted to identify the active constituents, effects on prostate cell growth, and anti-inflammatory effects of stinging nettle root in the treatment of BPH.

—*Marissa N. Oppel, MS*

References

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