Clinical Update

trials with animal studies examining potential fetotoxicity due to ginger.

The success of this trial brings back into focus the controversy surrounding ginger's safety during pregnancy. As noted in the monograph on ginger in Herbal Medicine: Expanded Commission E Monographs, the German Commission E listing of ginger (1 g/day) as a contraindication during pregnancy is based on rather weak evidence. The Commission's warnings about ginger appear to be based on in vitro studies that found mutagenic activity for high amounts of 6-gingerol, one of the pungent constituents in ginger root. However, this data is countered by the fact that the same researcher found that other constituents in ginger root are antimutagenic and that studies of the whole root also indicate antimutagenic properties.

Dr. Joshua Backon from Mount Pleasant Hospital in Jerusalem also raised concern about ginger's use during pregnancy in 1991. Based on in vitro evidence showing ginger's ability to inhibit thromboxane synthetase (which is thought to contribute to ginger's ability to inhibit platelet aggregation), Dr. Backon suggests that the herb may affect testosterone receptor binding in the fetus and theoretically alter sex steroid differentiation in the fetal brain. The relevance of this hypothesis to the oral consumption of ginger has been questioned.

A literature review of all available data on ginger published in 1996 in HerbalGram could find no scientific or medical evidence to support either the Commission E or Dr. Backon's concerns. As noted in Herbal Medicine: The Expanded Commission E Monographs, Prof. Dr. Heinz Schilcher, vice president of Commission E, agrees with this assessment of ginger's presumed safety during pregnancy.

Practice Implications: For women with nausea of pregnancy (morning sickness), with or without vomiting, 250 mg of ginger root four times per day, appears to be effective for reducing nausea and the incidence of vomiting. According to the results of this trial and the one with women suffering from hyperemesis gravidarum found no adverse effects on pregnancy outcome, safety studies in animals would help allay fears of potential fetotoxicity for ginger. Finally, assuming negative results for these animal studies, future trial with pregnant women should test different dosages of ginger to see if the anecdotal choice of 1 g/day is optimal for treating symptoms.

—Donald J. Brown, N.D.

References

Prostate Hormonal Actions for Saw Palmetto Becoming Clearer


Summary: Using prostate tissue samples obtained by needle biopsy, researchers compared tissue levels of testosterone (T) and dihydrotosterone (DHT) in men with symptomatic benign prostatic hyperplasia (BPH) taking finasteride, placebo, or a saw palmetto herbal blend (SPHB). Tissue samples were obtained from three groups of men participating in different clinical trials: (1) 15 men receiving finasteride (Proscar) treatment (5 mg/day) for 3 months or longer versus 7 untreated controls; (2) 22 men undergoing prostate adenomectomy (surgical excision of the gland) to rule out cancer; (n = 18) or transurethral resection (a surgical technique used to allow relief of prostatic obstruction of urine flow in men with BPH) for the relief of obstruction; (n = 4); (3) 44 men receiving either the SPHB (n = 21) or placebo (n = 23) for six months. Serum levels of T and DHT were also measured for each patient. The SPHB used in the original clinical trial is a combination supplying 106 mg of saw palmetto (Serenoa repens [W. Bartram] Small, Arecaceae) extract, stinging nettle (Urtica dioica L. ssp. dioica, Urticaceae) root extract (80 mg), pumpkin (Curcurbita pepo L., Cucurbitaceae) seed extract (160 mg), flavonoids extracted from lemon (Citrus x limon

Saw palmetto Serenoa repens
Photo © 2001 stevenfoster.com
Clinical Update

[L. Ostbeck, Rutaceae) (33 mg), and vitamin A (190 mg) per capsule (supplied by Nutrilite, of Buena Park, California). One capsule of the product was taken three times per day.

A total of 244 prostate samples were analyzed — 40 from the prostate adenomectomy group, 44 from the finasteride study, and 160 from the SPHB trial. In men taking finasteride, prostate tissue levels of DHT were decreased significantly when compared to untreated men (p < 0.01). Conversely, prostate tissue levels of T were significantly decreased — five to ten times — in those taking finasteride compared to untreated controls (p < 0.01). While serum (i.e., bloodstream) levels of T remained similar, serum levels of DHT were also significantly reduced in men taking finasteride compared to controls (p < 0.01).

Men taking SPHB had a significant decrease in prostate tissue levels of DHT from baseline to 6 months of treatment (p = 0.005). However, this reduction was not statistically significant when compared to the placebo group. The 6-month decline in DHT for the SPHB group was 32%. In comparison, the finasteride effect on prostate tissue levels of DHT was an 80% reduction compared to untreated men. Treatment with SPHB led to no changes in prostate tissue levels of T or in serum levels of T or DHT. Of particular interest, serum levels of prostate-specific antigen (PSA) decreased by approximately 50% in men taking finasteride compared to no change in men taking SPHB.

The authors of the study conclude that compared to finasteride, the SPHB-induced suppression of prostatic DHT levels is modest but significant enough to support the hypothesis that inhibition of the enzyme 5-alpha reductase (5-AR), which is responsible for the conversion of T to DHT, may be a mechanism for saw palmetto and the SPHB used in the study.

Comments/Opinions: Directed by Leonard Marks, M.D., head of the Urological Sciences Research Foundation, this is the first American study to explore potential mechanisms of action for saw palmetto. While a meta-analysis of clinical trials published in the Journal of the American Medical Association in 1998 concluded that saw palmetto preparations are safe and effective in treating many of the symptoms associated with BPH,¹ there has been little consensus on the how saw palmetto achieves this clinical effect.

DHT is the major androgenic hormone in the prostate and is needed throughout life for the growth and maintenance of the gland. It is derived from T and this conversion is catalyzed by 5-AR. As excessive accumulation of DHT is thought to be a potential contributor to the development of BPH in middle age and older males, drugs that inhibit 5-AR (i.e., finasteride) have been developed to treat BPH. Some herbal experts and European researchers have suggested that this action may partially explain how saw palmetto works.

In vitro and animal studies have suggested an antiandrogenic action for the liposterolic extract of saw palmetto.² In vitro studies have shown inhibition of the enzymes 5-AR and 3-ketosteroid reductase as well as inhibition of the binding of DHT to prostate cells.³ In addition, in vitro as well as in vivo research has found that saw palmetto extract inhibits the production of basic fibroblast growth factor and epidermal growth factor.⁴ In addition to DHT, these growth factors are also thought to contribute to BPH.

There have been conflicting results regarding the ability of saw palmetto extracts to inhibit 5-AR — particularly when compared to finasteride. One in vitro study found minimal 5-AR inhibition when compared directly to finasteride.⁵ However, one study showed that at the therapeutic dose of 320 mg/day, saw palmetto extract does inhibit 5-AR,⁶ and other studies have shown inhibition of both type I and type II isoenzymes of 5-AR.⁷ One in vitro study found that inhibition of 5-AR was limited to only prostate cells and not cells from other parts of the body.⁸ Unlike other 5-AR inhibitors, saw palmetto has not shown inhibition of prostate-specific antigen (PSA) secretion, even after stimulation with testosterone in vivo.⁹ As noted below, PSA is a serum marker used to detect possible prostate cancer. Inhibition of PSA secretion may, in some cases, block early detection of prostate cancer. One in vitro study found that decreased levels of DHT were significant only in the periurethral area. This may suggest a more localized effect for the extract and may partly explain why in clinical trials administration of saw palmetto extracts have not resulted in significant reduction in prostate size. In fact, the current study found no reduction in prostate size for men taking SPHB while those taking finasteride had a 20% reduction.

While the study by Dr. Marks and colleagues suggests that inhibition of 5-AR (likely far more modest than that noted for finasteride) may partially explain the modest reduction in DHT levels noted for men taking the SPHB product, further studies are needed to confirm the earlier European studies noted above.

Finally, the results of this study may be viewed critically as the product used contains not only saw palmetto but also nettle root and pumpkin seed oil, two other products sometimes used for the symptomatic treatment of BPH and both approved by the German Commission E for this use (albeit with much less clinical evidence than saw palmetto).¹⁰ Interestingly, an earlier Italian study using a monopreparation of saw palmetto (Permixon®, Pierre Fabre, Paris) found a 50% reduction in prostate tissue levels of DHT in men with BPH taking 320 mg of the extract per day.¹¹ The daily dosage of saw palmetto extract used in the current study equals that used in the Italian study. Could some ingredient in the combination product counter some of the effect of saw palmetto? This could only be answered with a comparison study of the two products.

Practice Implications: The results of this study confirm that a saw palmetto herbal combination product does reduce prostate tissue levels of DHT — an effect that may partially explain the clinical effectiveness of saw palmetto for the treatment of mild to moderate BPH. Further studies are needed to determine the degree to which saw palmetto inhibits 5-AR, the likely explanation for the effect noted in this study. Perhaps most notable to the healthcare professional is the lack of effect on PSA levels noted in the study. An important serum marker for prostate cancer, the findings of this study confirm the lack of effect for saw palmetto on PSA noted in earlier clinical trials.¹²¹³

While the liposterolic extract of saw palmetto at a daily dosage of 320 mg appears to be a safe and effective alternative to finasteride, future clinical trials should compare the herbal extract to the class of BPH drugs known as alpha-blockers (e.g. Cardura®, Flomax®, and Hytrin®) which are far more commonly prescribed than finasteride.

—Donald J. Brown, N.D.
Clinical Update

References

Ginkgo Ginkgo biloba Photo © 2001 stevenfoster.com

Ginkgo Extract Fails to Treat Tinnitus in Flawed Study


Summary: In a double-blind clinical trial, 1,121 adults (ages 18 to 70 years) with a diagnosis of tinnitus were recruited by phone and were randomized to receive either 150 mg of ginkgo (Ginkgo biloba L., Ginkgoaceae) extract (LI 1370, Lichtwer Pharma, Berlin, Germany sold as Ginkai® in the U.S.) or placebo three times per day for 12 weeks. Tinnitus was assessed using subjective questionnaires and no audiological measures were taken. The questionnaire was completed at baseline and at weeks 4 and 12, as well as two weeks after treatment (week 14) was completed. The questionnaire contained 21 questions on the severity of tinnitus as well as changes in tinnitus. Of the 1,121 participants entered in the trial, 956 were paired for the final analysis. The mean duration of tinnitus for both groups was approximately 10 years.

There were no significant differences between the two groups at weeks 4, 12, and 14 on the primary outcome measure of changes in tinnitus. This was also the case for the secondary measures of severity of tinnitus. Adverse events such as gastrointestinal upset, dizziness, and mouth dryness were the same for both groups.

Comments/Opinions: This is the largest clinical trial to date studying the effects of a standardized extract of ginkgo leaves (GBE) on tinnitus. Unfortunately, the results add little to current understanding about the efficacy of GBE for treating tinnitus as the investigators surprisingly chose to complete the study using only subjective feedback that was gathered by phone interviews. The lack of objective audiological measures, used in most trials studying tinnitus, makes the results of this trial inconclusive.

Tinnitus is defined as the perception of sound when no external sound is present. Although often described as ringing in the ears, it is sometimes described as hissing, roaring, whistling, chirping, or clicking. It can be sporadic in nature or constant. It is a very common condition that is estimated to affect 10% of the world’s population with about 0.5% considering it a problem that severely impacts their quality of life. More than 50