Comparison of Saw Palmetto (extract and whole berry) and Cernitin on prostate growth in rats

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Abstract

Pharmaceuticals such as finasteride and alpha blockers are used to treat symptoms of benign prostatic hyperplasia (BPH) and are known to cause severe adverse reactions. Accordingly, a search for safer, natural products has been undertaken. Two natural agents (nutraceuticals) have come under recent scrutiny; because natural products, in general, often have evidence of long term safety. The present study compares the *in vivo* effects on androgen-induced prostatic enlargement in rats of two nutraceuticals – the widely recognized Saw Palmetto (*Serenoa repens*) and the less well-known Cernitin (defined pollen extract). Non- castrated rats, had a mean prostate weight of 124 mg ± 8.8 (S.E.M) compared to the 24.5 ± 1.9 (S.E.M.) of the castrated rat followed under the same regimen ($p<0.01$). When castrated rats were given testosterone, the mass increased significantly to 250.0 mg ± 31.7 (S.E.M.) ($p<0.01$). In the five remaining groups, castrated rats receiving testosterone were given finasteride, an extract of Saw Palmetto, crushed whole berry derived from Saw Palmetto fruit, a water soluble and fat soluble extract of Cernitin or a combination of the Saw Palmetto extract and Cernitin. All treatments decreased the size of the prostate to roughly the same size as in the non-castrated rats, a size that was significantly smaller than castrated rats treated with testosterone in the same manner ($p<0.01$). A second study examining non-castrated rats treated with very high doses of testosterone showed similar results. In both studies, the nutraceuticals generally decreased body weight. In conclusion, these studies show the ability of Saw Palmetto (whole berry and extract) and Cernitin to influence prostatic hyperplasia via effects on androgen metabolism. (Mol Cell Biochem **250**: 21-26, 2003)

Keywords: benign prostatic hyperplasia (BPH), finasteride, alpha blockers, Saw Palmetto, Cernitin, androgen-induced prostatic hyperplasia; castrated and non-castrated rats

Introduction

Benign prostatic hyperplasia (BPH) is the most common non-cancerous tumor in men and ranks with prostate cancer as the two most common prostate disorders affecting middle-aged and older men [1]. BPH is basically enlargement of the prostate, which is common in older men. Epidemiological studies have revealed that when a man reaches approximately 40 years of age the prostate gland starts enlarging. More than 50% of men ages 60 years have BPH, while 90% of men in their 70's and 80's have BPH. BPH is a secret, silent disease which progresses with aging and the irritating symptoms of BPH are prevalent throughout our society [1-3]. Common symptoms of this prostate perturbation include a weak urinary

stream, incomplete bladder emptying, difficulty in starting urination, frequent urination (especially at night), nocturia (excess urination at night), urgency (difficulty in postponing urination), painful and difficult urination (dysuria), and interruption of the stream (stopping and starting) [1].

In the past, treatment options for prostate enlargement focused mainly on surgery [4]. Over the last few years, prescription drugs have also been used to initiate therapy against prostatic perturbations in their early stages. One highly recognized pharmaceutical (finasteride, Proscar™) works chiefly to inhibit the activity of 5-alpha reductase and the formation of dihydrotestosterone (DHT), which is considered a major cause of prostatic hyperplasia [5-7]. Another agent (terazosin, Hytrin™) is an alpha blocker that relaxes the muscle tissue of the prostate and thus relieves the pressure around the urethra [8,9]. However, surgery and pharmaceuticals carry a high monetary cost and the added risk of developing potentially debilitating side effects [1,3]. Accordingly, there is a need to develop safer and better therapeutic agents. One potential is avenue is the use of natural products to treat BPH a concept that has been pioneered in Europe and Japan [10-13].

The present study compares the *in vivo* effects of the widely recognized Saw Palmetto (*Serenoa repens)* and the less well-known Cernitin (defined pollen extract) on prostatic enlargement in rats. Furthermore, we also compared the effects of a standard Saw Palmetto extract against crushed whole berries from the Saw Palmetto tree.

Materials and methods

Saw Palmetto, Cernitin, and other chemicals

The Saw Palmetto extract (lot code 199633 – 45% fatty acids) and the Saw Palmetto berry powder (lot code 9809555 – 8.49% fatty acids) were obtained from Rexall/Sundown (Boca Raton, FL, USA). Cernitin (T63) 20:1 mixture of water-soluble T60 and alcohol-soluble GBX, was obtained from Graminex (Saginaw, MI, USA). Finasteride was obtained from Georgetown University Medical Center Pharmacy (Washington, DC, USA). All other chemicals used in this study were obtained from Sigma Chemical Company (St. Louis, MO, USA) and were of analytical grade or the highest commercial grade available.

Animals and treatment

To examine the ability of phytochemicals to influence androgen-stimulated prostate growth, six regular and 42 castrated male Sprague-Dawley rats, weighing between 50-100g were purchased from Taconic Farms, Germantown, NY, USA. The *in vivo* assay used to determine androgen-stimulated prostate growth was patterned as described earlier [11]. Throughout the study, rats were fed standard rat chow and drank water *ad libitum.* Six rats were assigned to one of eight groups based upon their daily protocol. The Saw Palmetto extract dosage was selected based on the studies conducted by Rhodes *et al.* [13]. No previous determination study was conducted for Cernitin T63, we used a dosage similar to that of Saw Palmetto extract.

The regimen for the first 7 days among eight different groups was as follows:

Group 1 Normal, non-castrated rats receiving the vehicle, methylcellulose, alone via gavage

Group 2 Castrated rats receiving the vehicle, methylcellulose, alone via gavage

Group 3 Castrated rats gavaged with methylcellulose similar to the second group

Group 4 Castrated rats gavaged with 10mg of finasteride in methyl cellulose

Group 5 Castrated rats gavaged with Saw Palmetto extract (200 mg) in methylcellulose

Group 6 Castrated rats gavaged with a preparation of crushed berries obtained

from Saw Palmetto fruit (200 mg) in methylcellulose

Group 7 Castrated rats gavaged with Cernitin T63 (200 mg/ day) in methylcellulose

Group 8 Castrated rats gavaged with Saw Palmetto extract (200 mg/ day) plus Cernitin T63 (200 mg/ day) in methylcellulose

From days 8-17, rats in groups 1 and 2 received a daily subcutaneous injection of 0.1 ml of saline, while the rats in groups 3-8 received a daily injection of 20 µg testosterone enanthate in a 0.1 ml volume. Groups 2 and 3 were distinguished by the injection of saline or testosterone. All groups (1-8) were continued on their same daily oral regimens. Body weights were measured on day 8 and the last day of the study, which was 10 days later.

Upon completion of the study, prostates were removed and wet/dry prostate weights were measured. DNA and RNA concentrations were measured using a Qiagen RNA and DNA Kit (Qiagen, Valencia, CA, USA) and a BioRad Smatspec 3000 Spectrometer.

On day 8, we injected each rat's right paw with 0.1 ml of incomplete Freund's adjuvant after initial measurements of paw thickness were made with sensitive calipers (day 0). Thereafter, the right and left paws (control) of each rat were measured 1 day, 3 days, and 7 days after testosterone dosing was initiated.

In a separate study, 35 non-castrated rats were injected daily with either saline or testosterone enanthate, 20 mg. This was a 1000-fold increase in the dose of testosterone. Treatment groups received the same doses by gavage of finasteride, whole berry Saw Palmetto, Saw Palmetto extract, Cernitin and a combination of Cernitin and Saw Palmetto extract as in the initial study.

Statistical analyses

Results from the two studies are presented as mean ± S.E.M. The statistics were performed by one-way analysis of variance (ANOVA). Where a significant effect of treatment was detected by ANOVA ($p<0.05$), the Dunnett *t*-test was used to establish which differences between means reached statistical significance ($p<0.05$) [14].

Results

In the first experiment the non-castrated rats gavaged with only methylcellulose had a mean prostate weight of 124 mg ± 8.8 (S.E.M.) compared to the 24.5 mg ± 1.9 (S.E.M.) of the castrated rat followed under the same regimen, i.e. approximately a 5-fold difference in size at the end of the trial period (Table 1). When castrated rats receiving only methylcellulose were given testosterone enanthate, the mean increase in size was almost 10 fold, i.e. 250.0 mg ± 31.7 (S.E.M.). In the five remaining groups, castrated rats receiving testosterone were given finasteride, an extract of Saw Palmetto (SPE), crushed whole berry derived from Saw Palmetto fruit (WBSP), a water soluble and fat soluble extract of defined pollen extract in a 20:1 ratio (Cernitin T63), or a combination of the SPE and Cernitin T63. All treatments decreased the size of the prostate to roughly the same size as in the non-castrated, control rats. At the doses used, finasteride decreased prostate size the most, but the decreased size was not statistically different from the other groups receiving the natural therapies. Two additional points of interest stand out: first, the crushed whole berry of Saw Palmetto fruit was as effective as the extract and the combination of the SPE and Cernitin T63 was no better in reducing prostate size than each alone in this model.

When the prostatic tissues were examined further, the concentrations of DNA and RNA in the prostate were essentially similar. In addition, the dry/wet weight ratio of the prostates among the groups were virtually similar.

In Figure 1, we examined more closely the effects of the various regimens on body weight changes over the 10 day experimental period

when the rats were receiving different therapeutic regimens. Compared to the untouched control rats (group 1), those receiving the castration procedure and no testosterone (group 2) showed a similar mean body weight gain. The addition of testosterone caused an increased body weight (group 3) as did the rats given finasteride in addition to testosterone (group 4). These increases, however, were not statistically significant. Comparing natural products to regular or castrated controls, the groups gavaged with SPE (group 5) and WBSP (group 6), and Cernitin T63 plus SPE (group 8) showed significantly reduced body weight gain. This was not seen with the group receiving Cernitin T63 alone (group 7).

In this same study, the effects of the various therapeutic agents on paw edema were also examined (Table 2). Using the left paw as control, we found no consistent differences in response of the edema when the animals were receiving SPE, Cernitin T63, or a combination of both over the course of the various regimens.

In a second, separate study, where groups of five non-castrated rats were challenged with the 20 times more testosterone than in the original studies (20 mg), the prostate sizes increased markedly, i.e. from a mean of 90 mg ± 16.5 (S.E.M) to 621 mg ± 57.0 (S.E.M.). The addition of finasteride, SPE, WBSP, Cernitin T63 and the combination of SPE plus Cernitin T63 all decreased prostate size significantly when compared to the group gavaged with the carrier alone. In the contrast to the first study, the combination of Cernitin T63 plus SPE caused a greater reduction in weight when compared to the additions of each ingredient alone (Table 3).

When changes in body weight over the study period were examined, rats gavaged with finasteride, WBSP, Cernitin T63, and the combination of Cernitin T63 and SPE showed less gain when compared to control.

Discussion

Standard treatment options for symptoms emanating from prostatic enlargement focus principally on surgery and pharmaceuticals such as finasteride (Proscar™) and alpha blockers (Hytrin™) [1]. However, many patients seek to avoid these treatments, partially due to adverse reactions associated with these regimens. Finasteride, a synthetic 4-azasteroid compound and a specific inhibitor of 5-alpha-reductase, converts the androgen testosterone into dihydrotestosterone (DHT). It is worthwhile to mention that DHT is a potent stimulator of prostate gland growth and is responsible for the overproduction of prostate cells, which ultimately results in prostate enlargement. Finasteride

Table 1. Androgen stimulation of prostate in castrated rats

Group	In BW (g)	F BW (g)	Pros Size (mg)	DNA (μg/10 mg)	RNA (μg/10 mg)	Dry/wet (%)
Baseline	121.4 ± 8.8	169.5 ± 5.0	124.0 ± 8.8	10.4 ± 0.8	38.8 ± 1.8	0.27 ± 0.059
Cas	124.7 ± 2.5	178.5 ± 2.1	24.5 ± 1.9	10.4 ± 0.8	37.6 ± 1.9	0.26 ± 0.037
Cas + T	133.7 ± 4.3	194.0 ± 4.6	250.0 ± 31.7	10.3 ± 0.9	36.9 ± 1.9	0.23 ± 0.007
Cas + T + Pros	137.3 ± 2.5	197.0 ± 4.9	77.5 ± 11.0*	10.7 ± 0.9	41.6 ± 4.2	0.27 ± 0.012
Cas + T + SPE	130.3 ± 5.1	169.3 ± 7.8	103.0 ± 13.6*	8.9 ± 0.5	38.2 ± 2.6	0.24 ± 0.014
Cas + T + SPWB	132.8 ± 4.2	170.8 ± 7.3	122.6 ± 11.2*	9.5 ± 1.3	36.9 ± 2.5	0.29 ± 0.060
Cas + T + T63	132.3 ± 3.3	190.4 ± 6.4	141.4 ± 17.2*	9.0 ± 0.4	42.9 ± 3.1	0.26 ± 0.059
Cas + T + Comb	128.7 ± 3.7	173.9 ± 5.3	122.3 ± 10.6*	9.5 ± 1.6	38.8 ± 2.2	0.25 ± 0.024

Each value is the mean ± S.E.M. from 6 rats. See 'Materials and methods' for details. *Statistically significantly different from C + T. C – castrated; T – testosterone enanthate (20 μg subcu daily); Pros – finasteride (0.15 mg po daily); SPE – Saw Palmetto extract (200 mg po daily); SPWB – whole berry Saw Palmetto (200 mg po daily); T63 – Cernitin (200 mg po daily); Comb – same dose of SPE and T63 together.

has been demonstrated to cause a number of adverse events including decreased libido, ejaculatory disorders, impotence, reduced sex drive, and increases in the overall testosterone level, which results in increased body hair [15,16]. In Europe and Japan, use of natural products derived from plants has been used to treat prostatic perturbations in order to derive a favorable ratio between therapeutic benefits and adverse reactions. A major attractiveness of natural compounds, for the most part, lies in their fewer serious adverse side effects compared to drugs. Two potentially useful natural products could be useful therapeutic agents – SPE [10] and the relative newcomer on

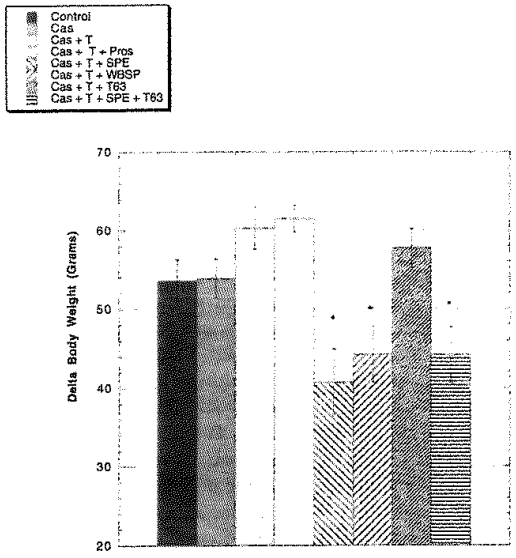

Fig. 1. Effects of nutraceuticals alone and combined on body weight during a 10 day study period in the first experiment. Mean ± S.E.M. is depicted ($p < 0.01$).

the block, Cernitin T63 [11]. Many large trials have found that SPE and Cernitin T63 improved

prostatic symptomatology and even compared favorably with finasteride when compared head to head [17-31]. Recently, combining both natural products was shown to have therapeutic effects in a randomized, placebo-controlled, double-blind trial [32].

Interestingly, the hypothesized mechanisms of action for Saw Palmetto and Cernitin T63 are essentially similar [1]. Among other mechanisms, benefits of both are attributed to their ability to affect the androgen metabolism. Saw Palmetto and perhaps Cernitin T63 simulate finasteride by preventing conversion of testosterone to DHT. DHT is the androgen associated with undesired prostate growth during aging. Saw Palmetto and Cernitin T63 not only lower the rate of DHT formation but block the ability of DHT to bind cells, preventing the action of hormone [31] (Table 1). SPE may also demonstrate potent anti-inflammatory activity as it has been shown to reduce prostate inflammation and pain [32]. Furthermore, inhibition of prolactin and growth factor induced cell proliferation may be another mechanistic avenue of cytoprotection of enlarged prostate by Saw Palmetto.

The ability of Saw Palmetto to influence androgen metabolism has been well studied (Table 4). SPE was found to inhibit 5-alpha

Table 2. Effect of various regimens on raw paw edema

Group	Day 0	Day 1	Day 3	Day 7
Regular	31.6 ± 0.3/31.5 ± 0.4	33.9 ± 0.4/62.2 ± 1.4	30.9 ± 0.4/54.8 ± 1.0	33.4 ± 0.8/50.5 ± 0.9
Cas	31.7 ± 0.7/31.7 ± 0.6	35.0 ± 0.6/54.5 ± 1.9	30.0 ± 0.5/47.5 ± 1.3	30.8 ± 0.7/44.7 ± 1.4
Cas + T	32.0 ± 0.3/32.1 ± 0.3	35.7 ± 0.7/57.8 ± 1.3	30.3 ± 0.5/45.8 ± 1.8	33.8 ± 0.8/47.3 ± 1.0
Cas + T + Pros	32.2 ± 0.3/32.2 ± 0.3	35.6 ± 0.6/59.6 ± 1.5	29.2 ± 0.8/44.8 ± 2.3	32.4 ± 0.8/46.4 ± 1.1
Cas + T +SPE	30.2 ± 0.8/30.0 ± 0.4	35.2 ± 0.9/57.7 ± 2.2	31.8 ± 0.2/46.3 ± 1.6	30.0 ± 0.4/43.0 ± 1.8
Cas + T +SPWB	31.3 ± 0.2/31.3 ± 0.2	35.0 ± 0.9/61.0 ± 1.4	31.1 ± 0.3/57.4 ± 1.8	29.8 ± 0.8/44.3 ± 0.6
Cas + T +T63	30.3 ± 0.2/30.2 ± 0.2	34.5 ± 0.4/59.5 ± 2.0	33.7 ± 0.4/53.5 ± 4.2	30.6 ± 0.4/45.6 ± 0.9
Cas + T +Comb	30.7 ± 0.2/30.3 ± 0.4	34.0 ± 0.7/57.7 ± 0.6	30.5 ± 0.8/54.2 ± 1.3	28.2 ± 0.6/43.2 ± 0.9

Each value is the mean ± S.E.M. from 6 rats. See 'Materials and methods' for details. Cas – castrated; T – testosterone enanthate (20 μg subcu daily); Pros – finasteride (0.15 mg po daily); SPE – Saw Palmetto extract (200 mg po daily); SPWB – whole berry Saw Palmetto (200 mg po daily); T63 – Cernitin (200 mg po daily); Comb – same dose of SPE and T63 together.

Comparison of Saw Palmetto (extract and whole berry) and Cernitin on prostate growth in rats

Table 3. Androgen-stimulation of prostate in regular non castrated rats

Group	Number	Initial BW (g)	Final BW (g)	Prostate size (mg)
Control	5	141 ± 7.7	186 ± 8.7	90 ± 16.5
T	5	150 ± 1.3	200 ± 4.2	621 ± 57.0
T + Pros	5	144 ± 8.4	179 ± 7.6	401 ± 18.0*
T + SPE	5	146 ± 3.8	188 ± 6.0	454 ± 53*
T + SPWB	5	142 ± 9.5	166 ± 11.7	453 ± 11.3*
T + T63	5	162 ± 9.0	197 ± 5.7	514 ± 52.6*
T + SPE + T63	5	147 ± 5.9	176 ± 5.4	368 ± 11.4*#*

Each value is the mean ± S.E.M. from 6 rats. See 'Materials and methods' for details. *Significantly different from T; #significantly different from T + SPE, T + WBSP and T + T63. T – testosterone enanthate (20 µg subcu daily); Pros – finasteride (0.15 mg po daily); SPE – Saw Palmetto extract (200 mg po daily); T63 – Cernitin (200 mg po daily); WBSP – whole berry Saw Palmetto (200 mg po daily).

reductase and receptor binding of androgens in cultured human foreskin fibroblasts [31]. In contrast, Rhodes *et al.* [13] found different results when comparing the effects of *Sereona repens* (Permixon) and finasteride using an antiandrogen assay. While finasteride inhibited 5-alpha reductase activity and not the binding of DHT to prostatic androgen receptors, *Sereona repens* did neither. Kamijo *et al.* [33] had examined the effects of Cernitin T63 on experimental nonbacterial prostatitis in rats but not androgen-stimulated prostate growth.

In the present study, we compared the abilities of finasteride, Saw Palmetto and Cernitin T63 to influence androgen metabolism in the prostate. We corroborated that injections of testosterone into castrated and non-castrated rats increased prostate mass via hyperplasia. We found that the oral intake of finasteride; Saw Palmetto, either as an extract or crushed whole berries; and Cernitin T63 (combined T60 water soluble and GBX oil soluble extracts) overcame much of the androgen-stimulated prostate growth in castrated and non-castrated rats. When massive doses of testosterone were given in the second study, the combination of both Saw Palmetto and Cernitin T63 overcame the androgen effect more than either one alone. However, this may be a dose-dependent effect, i.e. increasing the dose of either agent alone might have produced similar results as the combination. Nevertheless, the potential for additive effects of independent agents is plausible.

Table 4. Hypothesized major mechanisms of action of Saw Palmetto and Cernitin on androgen metabolism

1.	Inhibits 5 alpha reductase
2.	Inhibits 3 alpha reductase
3.	Inhibits binding of DHT to cytosolic receptors Inhibits translocation of the DHT-receptor to the nucleus
4.	Demonstrates anti-inflammatory activity
5.	Inhibits prolactin and growth factor induced cell proliferation

The two natural ingredients are also postulated to have anti-inflammatory and smooth muscle relaxant effects through a dose-related effect on the arachidonic acid cascade through a double blocking of cyclooxygenase and lipoxygenase pathways [34,35]. We did not see this in our anti-androgen model. The similar and unchanging dry to wet prostate weight ratios suggest no difference in tissue water content among any group over the course of study (Table 1). Also, the rat paw assay showed no effects of any gavaged substance on the produced edema (Table 2).

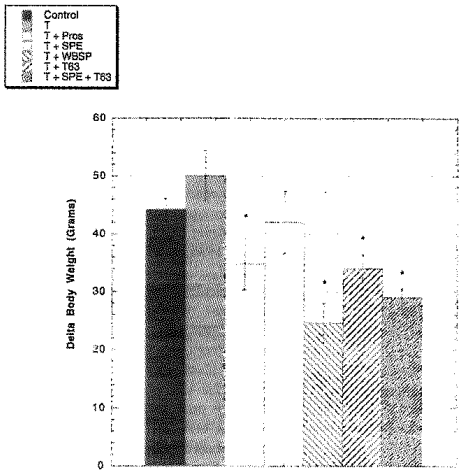

Fig. 2. Effects of nutraceuticals alone and combined on body weight during a 10 day study period in the second experiment where excessive doses of testosterone were given. Mean ± S.E.M. is depicted ($p < 0.01$).

It is unclear why Saw Palmetto and Cernitin T63 appeared to slow body weight gain. We surmised this by examining both Figs 1 and 2 (Cernitin T63 did not have any effect in the first study on castrated rats, but did in the second study on non-castrated rats: SPE decreased weight gain in the first study but not in the second). Unfortunately, we did not measure the food intake in either study to determine if varying weight changes could be due to different food intakes.

In conclusion, these studies corroborate the potential of Saw Palmetto (whole berry and extract) and Cernitin T63 to influence prostatic hyperplasia via effects on androgen metabolism

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