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Effects of coconut oil on testosterone-induced prostatic hyperplasia in Sprague–Dawley rats

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Abstract

Benign prostatic hyperplasia (BPH) is the benign uncontrolled growth of the prostate gland, leading to difficulty with urination. Saw palmetto lipid extracts (SPLE), used to treat BPH, have been shown to inhibit prostate 5α-reductase, and some major components, such as lauric, myristic and oleic acids also inhibit this enzyme. Coconut oil (CO) is also rich in fatty acids, mainly lauric and myristic acids. We investigated whether CO prevents testosterone-induced prostate hyperplasia (PH) in Sprague-Dawley rats. Animals were distributed into seven groups (10 rats each). A negative control group were injected with soya oil; six groups were injected with testosterone (3 mg kg^{-1}) to induce PH: a positive control group, and five groups treated orally with SPLE (400 mg kg^{-1}), CO or sunflower oil (SO) (400 and 800 mg kg^{-1}). Treatments were given for 14 days. Rats were weighed before treatment and weekly thereafter. Rats were then killed and the prostates were removed and weighed. CO (400 and 800 mg kg^{-1}), SPLE (400 mg kg^{-1}) and SO at 800 mg kg^{-1}, but not at 400 mg kg^{-1}, significantly reduced the increase in prostate weight (PW) and PW:body weight (BW) ratio induced by testosterone (% inhibition 61.5%, 82.0%, 43.8% and 28.2%, respectively). Since CO and SPLE, but not SO, contain appreciable concentrations of lauric and myristic acids, these results could be attributed to this fact. In conclusion, this study shows that CO reduced the increase of both PW and PW:BW ratio, markers of testosterone-induced PH in rats.

Introduction

Benign prostate hyperplasia (BPH) is the benign and uncontrolled growth of the prostate gland; it leads to bladder outflow obstruction and lower urinary tract symptoms. BPH is common in men over 50 years of age, and frequency increases with age (Clifford & Farmer 2000; Barry & Roehrborn 2001; Thorpe & Neal 2003; Bhargava et al 2004).

The aetiology of BPH, although not fully elucidated, involves hormonal changes in the aging man. The development and growth of the prostate gland depends on androgen stimulation, mainly by dihydrotestosterone (DHT), which is formed in the prostate, as in other tissues, through the enzymatic conversion of testosterone into its more active metabolite DHT, catalysed by prostate 5α-reductase. DHT binds to androgenic receptors and promotes protein synthesis and cellular growth. With aging, the production and accumulation of DHT in the prostate increases, encouraging cell growth and causing hyperplasia (Bartsch et al 2000; Carson & Rittmaster 2003). Therefore, anti-androgenic drugs, mainly prostate 5α-reductase inhibitors, are indicated for the treatment of BPH, improving the enlarged prostate and reducing complications, although their impact on BPH symptoms is modest (Bartsch et al 2002; Lam et al 2003; Sandhu & Te 2004).

BPH also involves augmented adrenergic tone in prostate smooth muscle, regulated through α_1-adrenoceptors (Michel et al 1998); α_1-adrenoceptors blockers are therefore also leading drugs in the treatment of BPH and are particularly effective for relaxing the smooth muscle and improving BPH symptoms (Oelke et al 2002).

Herbal drugs, mainly saw palmetto (*Serenoa repens*) lipid extracts (SPLE) (Lowe et al 1998; Plosker & Brogden 1996; Wilt et al 2000; Aliaev et al 2002), are commonly used to treat BPH. The efficacy of SPLE has shown to be similar to that of finasteride and tamsulosin (Carraro et al 1996, Debruyne et al 2002), although some placebo-controlled trials found no differences when SPLE was compared with placebo (Willetts et al 2003; Bent et al 2006).

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The mechanisms contributing to the efficacy of *S. repens* in BPH are multiple (Plosker & Brogden 1996), but most studies (Sultan et al 1984; Liang & Liao 1992; Niederprum et al 1994; Weisser et al 1996; Bayne et al 1999; Raynaud et al 2002; Habib et al 2005), although not all (Rhodes et al 1993), have shown that inhibition of 5α-reductase activity plays a role, and that fatty acids, major components of SPLE, also cause enzyme inhibition, lauric acid being the most effective (Liang & Liao 1992; Niederprum et al 1994). More recently, SPLE and the free fatty acids lauric acid, oleic acid and myristic acid, but not esterified fatty acids, alcohols or sterols, have been shown to inhibit 5α-reductase. While palmitic acid and stearic acid were inactive, SPLE, lauric acid and oleic acid inhibited the activity of both 5α-reductase isoforms. Oleic acid was more active on type 1 than on type 2 isoenzyme. Myristic acid was also active but was evaluated on the type 2 isoform only (Raynaud et al 2002).

Coconut oil (CO), extracted from coconut (*Cocos nucifera*) and used in food, is composed mainly of medium-chain fatty acids. Although the exact composition of CO can vary according to the source, lauric acid has been shown to be its most abundant component (Akpan et al 2006). There have been conflicting reports on the cardiovascular effects of CO, such as atherogenic effects due to some long-chain fatty acids and advantageous effects due to medium-chain fatty acids. However, absorbed intact, CO may be a ready source of energy (Garcia-Fuentes et al 2003; Müller et al 2003; Nevin & Rajamohan 2004) but, because of the absence of the essential fatty acid linolenic acid, it should not be used as the only source of oil in daily nutrition (Pehowich et al 2000). CO has not been shown to have preventive effects against BPH or prostate enlargement caused by androgens (PubMed database up to March 2007).

Prostate enlargement induced by testosterone has been used to assess the effects of potential treatments for BPH, since it reproduces adequately, although not fully, the major features of human BPH, including functional and histological changes, supporting the theory that testosterone actually produces prostate hyperplasia (PH) (Pandita et al 1998; Mitra et al 1999; Noa et al 2005). This study investigated whether oral dosing with CO could prevent PH induced by testosterone in rats.

Materials and Methods

Animals

Adult (12 weeks old) male Sprague–Dawley rats, weighing 380–400 g, were obtained from the National Centre for Laboratory Animals Production (CENPALAB, Havana, Cuba), and adapted to laboratory conditions (temperature 25 ± 3°C, relative humidity 60 ± 5%, light/dark cycles of 12 h) for 7 days. Free access to food (rodent chow from CENPALAB) and water was allowed.

Animal handling was conducted in accordance with the Cuban regulations for the use of laboratory animals and ethical principles of animal management. The study protocol and animal use were approved by an independent board of animal use.

Oils

Extra-virgin CO (Sunvalley Foods International Pharmaceuticals Inc. Tingub, Mandaue, Thailand), saw palmetto (Proseren, Blackmores Ltd, Balgowlah, Australia), and sunflower oil (SO) (Ideal, Buenos Aires, Argentina) were used. Fatty acid composition was assessed by gas chromatography. Table 1 shows the fatty acid content of SPLE, CO and SO used in the experiments. In brief, the fatty acid methyl esters were prepared by methylation, using acetyl chloride:methanol (10:90 v/v). Gas chromatography was conducted using a Fisons (Manchester, UK) gas chromatograph 8000 series, with a flame ionization detector and a Solgelwax column (SGE, Austin, TX, USA) (30 m × 0.25 μm film thickness, 0.25 m internal diameter). The oven was heated from 80°C to 180°C at 20° per min, and from 180°C to 280°C at 4° per min. The injector and detector were set at 270°C and 275°C, respectively. Hydrogen at 1.3 mL min^{-1} was used as the carrier gas.

The identity of each peak observed was confirmed using standards of each fatty acid (all from Sigma Chemicals, St Louis, MO, USA). Concentrations were calculated from peak areas, using tridecanoic acid as the internal standard.

Administration and dosage

For dosing, oils were suspended in Tween 65/water (2%) and administered orally by gastric gavage (1 mL kg^{-1}). Testosterone propionate (Cuban Medical Pharmaceutical Industry, IMEFA, Havana, Cuba), was diluted in soya oil and injected subcutaneously at 3 mg kg^{-1}, daily for 14 days, as described previously (Pandita et al 1998; Arruzazabala et al 2004; Carbajal et al 2004, 2005; Noa et al 2005).

Rats were randomly distributed into seven groups (10 rats in each group): the negative control received daily subcutaneous injections of soy oil (i.e. vehicle) and six groups received daily subcutaneous injections of testosterone. Of the latter, one group were treated with the vehicle (positive control) and the other five received SPLE (400 mg kg^{-1}), CO (400 and 800 mg kg^{-1}) or SO (400 and 800 mg kg^{-1}). Treatments were given orally for 14 days.

The doses were selected on the basis that SPLE (400 mg kg^{-1}) administered orally prevented PH in rats (Carbajal et al 2005), and that, according to its lauric acid content, CO at the same dose should display a similar effect in this model. SO was administered at the same doses for comparison.

Table 1 Fatty acid composition (%) of the saw palmetto lipid extract (SPLE), coconut oil and sunflower oil used in the study

Fatty acids	Coconut oil	Sunflower oil	SPLE
Caprylic acid ($C_{8:0}$)	6.3	0.0	1.4
Capric acid ($C_{10:0}$)	5.8	0.0	0.9
Lauric acid ($C_{12:0}$)	45.4	0.0	16.5
Myristic acid ($C_{14:0}$)	17.4	0.0	6.2
Palmitic acid ($C_{16:0}$)	7.8	5.7	9.0
Palmitoleic acid ($C_{16:1}$)	0.0	0.1	0.1
Stearic acid ($C_{18:0}$)	2.1	3.2	2.6
Oleic acid ($C_{18:1}$)	5.0	27.6	29.8
Linoleic acid ($C_{18:2}$)	0.9	55.8	23.2
Linolenic acid ($C_{18:3}$)	0.0	0.1	2.3
Total content	90.5	92.5	92.1

Body and prostate weight

Animals were weighed at the start of experiment, on the day before drug administration started, and weekly thereafter. At study completion, animals were killed under ether anaesthesia, and their prostates immediately removed and weighed. Although biological responses to testosterone stimulation may be different in the two prostate lobes (Tsai et al 2006), we weighed the whole prostate, since a previous study in rats with testosterone-induced prostate enlargement found histological evidences of PH not only in the ventral but also in the dorsolateral lobes (Mitra et al 1999; Noa et al 2005). Prostate weight (PW) and PW to body weight ratios (PW/BW) were recorded.

Percentage inhibition was calculated as follows: $100 - [(TG - NC)/(PC - NC) \times 100]$, where PC, NC and TG were the values of the positive control, negative control and treated group, respectively.

Statistical analysis

Comparison between study groups was performed using the Kruskal–Wallis one-way test. Differences between individual treatment groups and the positive or negative control groups were compared using Dunn's test. $P < 0.05$ was considered significant. Statistical analysis were performed using Pathtox system software (version 4.2.2; Xybion Corp; Cedar Knolls, NJ, USA).

Results

Table 2 summarizes the effects of the treatment on testosterone-induced prostate enlargement. PW and PW/BW ratio increased in the positive control compared with the negative control group. Compared with the positive controls, CO (400 and 800 mg kg^{-1}) significantly decreased the PW gain induced with testosterone by 61.5% and 82.0%, respectively, and decreased the PW/BW ratio by 50.5% and 74.3%, respectively. As expected, SPLE (400 mg kg^{-1}) significantly decreased the testosterone-induced prostate enlargement and increase of PW/BW ratio – by 43.8% and 42.5%, respectively. SO at 800 mg kg^{-1}, but not at 400 mg kg^{-1}, significantly inhibited the increase in PW and PW/BW ratio, producing modest inhibitions of 28.2% and 22.7%, respectively.

The final values of PW and PW/BW ratio achieved with CO (400 mg kg^{-1}) and SPLE (400 mg kg^{-1}) were similar, although the percentage inhibition achieved with CO (61.5%) was greater than that reached with SPLE (43.8%). Also, final values of PW and PW/BW ratio in the CO groups were lower than in those treated with either dose of SO.

There were no significant differences in BW between groups. Thus, oral dosing with CO, SO or SPLE did not affect BW gain significantly (Table 3).

Discussion

This study shows that CO (400 and 800 mg kg^{-1}) administered orally for 14 days significantly and dose-dependently inhibited the increase in PW (by 61.5% and 82.0%, respectively) and PW/BW ratio (by 50.5% and 74.3% respectively) induced by testosterone in rats. The effect achieved with the 400 mg kg^{-1} dose was comparable to, or even slightly greater than, that reached with SPLE, a herbal drug used to treat BPH (Plosker & Brogden 1996; Wilt et al 2000; Aliaev et al 2002).

Since previous studies have shown that PW gain induced by testosterone in rats is accompanied by histological changes indicative of PH, and that treatments that prevented PW increase also lowered histological scores of PH (Mitra et al 1999; Noa et al 2005), the effects of CO on PW increase and increase in PW/BW found here can be interpreted as preventive effects on testosterone-induced PH in rats.

The effects of CO found here are consistent with its high content of lauric and myristic acids (mainly lauric acid), since both inhibit prostate 5α-reductase activity (Liang & Liao 1992; Niederprum et al 1994; Raynaud et al 2002). This result, although suspected, was amazing, since we did not find any report of the effects of CO on testosterone-induced PH in rodents or in BPH (PubMed database, up to March 2007). Some studies have shown other biological effects of CO (Pehowich et al 2000; Garcia-Fuentes et al 2003; Müller et al 2003; Nevin & Rajamohan 2004). The effects of CO on lipid markers are controversial. A CO-supplemented diet (10–20%) for 12 weeks produced hypercholesterolaemia in chicks (Garcia-Fuentes et al 2003), whereas diets with either high or low levels of saturated fatty acids from CO have beneficially decreased levels of lipoprotein (a) compared with a diet rich in highly unsaturated acids (Müller et al 2003). Also, virgin CO has

Table 2 Effects of treatments on prostate enlargement in rats treated with testosterone

Group	PW (g)	% Inhibition	PW/BW ($\times 10^{-3}$)	% Inhibition
Negative control	0.76 ± 0.06	–	1.88 ± 0.14	–
Positive control	1.15 ± 0.03*	–	2.89 ± 0.05	–
CO (400 mg kg^{-1})	0.91 ± 0.02+	61.5	2.38 ± 0.07+	50.5
CO (800 mg kg^{-1})	0.83 ± 0.03+	82.0	2.14 ± 0.07+	74.3
SO (400 mg kg^{-1})	1.09 ± 0.04	15.4	2.79 ± 0.13	11.8
SO (800 mg kg^{-1})	1.04 ± 0.04†	28.2	2.72 ± 0.13†	22.7
SPLE (400 mg kg^{-1})	0.98 ± 0.06‡	43.8	2.46 ± 0.15‡	42.5

PW, prostate weight; BW, body weight; CO, coconut oil; SO, sunflower oil; SPLE, saw palmetto lipid extract. Data are mean ± s.d. Between-group comparisons: PW: $P = 0.0006$; PW/BW $P = 0.0011$ (Kruskal–Wallis test); *$P < 0.01$ vs negative control; †$P < 0.05$; ‡$P < 0.01$; +$P < 0.001$ vs positive control (Dunn's test).

Table 3 Effects of treatments on body weight (g) of rats treated with testosterone

Group	Baseline	Final
Negative control	340.4 ± 8.6	401.2 ± 10.1
Positive control	344.6 ± 9.6	397.2 ± 10.8
CO (400 mg kg^{-1})	337.7 ± 7.6	385.8 ± 6.3
CO (800 mg kg^{-1})	346.9 ± 7.9	397.2 ± 7.2
SO (400 mg kg^{-1})	341.1 ± 5.0	391.6 ± 6.1
SO (800 mg kg^{-1})	344.9 ± 6.0	398.7 ± 7.1
SPLE (400 mg kg^{-1})	340.2 ± 7.1	391.4 ± 6.8

CO, coconut oil; SO, sunflower oil; SPLE saw palmetto lipid extract. Data are mean ± s.d. There were no significant differences between the groups (Kruskal–Wallis test).

shown to control BW gain, to lower serum levels of cholesterol, triglycerides, phospholipids, low-density lipoprotein (LDL) cholesterol, and to increase high-density lipoprotein cholesterol, while its polyphenol fraction has prevented LDL oxidation in-vitro (Nevin & Rajamohan 2004). To the best of our knowledge, this result is the first evidence of the preventive effect of CO on prostate enlargement induced by testosterone.

Both CO and SPLE treatments, administered at 400 mg kg^{-1}, were effective in preventing testosterone-induced PW gain in the rat, whereas only the higher dose of SO (800 mg kg^{-1}) achieved a significant but modest reduction in prostate enlargement (28.2%).

Although SPLE is commonly used to treat BPH, there are no guidelines to regulate the composition of SPLE. The total content of fatty acids in the SPLE assessed here was 92.1%, and sterol content was 0.35%. The fatty acid content matches the US Pharmacopeia recommendations (US Pharmacopeial Forum 2005), and is similar to that of CO and SO (90.5% and 92.5%, respectively). Thus, differences in the total content of these acids do not explain their effects in this model; differences are probably related mainly to the relative content of lauric acid and myristic acid. CO had the highest concentrations of lauric acid (45.4%) and myristic acid (17.4%), which could explain its greater effects in this model, followed by SPLE (16.5% lauric acid and 6.2% myristic acid); the lack of these acids in SO emphasizes their relevance in producing the effect here assessed. However, the fact that a modest effect on PW was achieved with the higher dose of SO (800 mg kg^{-1}) indicates the contribution of other fatty acids/compounds. Both oleic acid (Liang & Liao 1992; Niederprum et al 1994; Raynaud et al 2002) and linoleic acid (Raynaud et al 2002) have been shown to inhibit 5α-reductase. Oleic acid was present in SO and SPLE at similar proportions and linoleic acid was present at double the level in SO compared with SPLE. Thus, the modest efficacy of SO was a little unexpected, and it is not clear why SO had so little effect in preventing PH even though it contains these two acids. Reduced biovailability of oleic acid and linoleic acid in the target organ (the prostate) could not explain the lack of effect, since labelled oleic acid added to SPLE has been shown to effectively reach the prostate (Chevalier et al 1997).

These facts suggest that the identity and relative content of each acid is relevant to the inhibition of testosterone-incuced PH in-vivo, since individual components/acids may potentially either compete and/or have additive effects, cancelling out or increasing their pharmacological effects.

Although the effects of treatments on PW gain were evident, they should theoretically be related to BW changes; the PW/BW ratio has therefore been used as the main marker of the effects of treatments on this model. However, since in this study the treatments did not significantly affect BW, effects on PW/BW ratios can be attributed to effects on PW gain.

How promising or clinically relevant are the effects of CO reported here remains to be answered. These results need to be reproduced, and higher doses and longer treatments need to be tested, and also in different models to determine whether it is worth assessing such effects in men with BPH. We do not expect that these benefits would be seen with the use of CO in food, since the doses here used were relatively high compared with the quantities of CO commonly used in food and nutritional products.

Conclusions

CO (400 and 800 mg kg^{-1}) administered orally for 14 days markedly, significantly and dose-dependently inhibited prostate enlargement induced by testosterone in rats. As expected, SPLE at 400 mg kg^{-1} was also effective. Oral treatment with SO at the same dose, however, did not prevent PH in this model, and was only modestly effective when administered at 800 mg kg^{-1}. Since CO had higher concentrations of lauric and myristic acids, effective inhibitors of 5α-reductase, this could explain the greater efficacy of CO compared with SPLE, while the lack of these acids in SO could explain its lesser activity. Further experimental studies should confirm the present results before deciding whether they are meaningful enough to be explored in men with BPH.

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