13

New Botanical Materials with Anti-Androgenic Activity

Tomoyuki Koyama
Tokyo University of Marine Science and Technology
Japan

1. Introduction

Enlargement of prostate, which affects 50% of men aged 60 and 90% of men by age 80, is commonly referred to as benign prostate hyperplasia (BPH) (Russell & Wilson, 1994). BPH is a slow, progressive enlargement of the fibromuscular and epithelial structures of the prostate gland (Cristoni et al., 2000). Substantial evidence indicates that the androgens testosterone (T) and dihydrotestosterone (DHT) contribute to the production of BPH (Lowe et al., 2003). The principal serum androgen T is converted by 5alpha-reductase (5aR) to DHT. DHT binds to androgen receptor (AR) in the prostate, where it initiates DNA synthesis (Marks, 2004). This action, in turn induces protein synthesis and abnormal growth of prostate. Current clinical evidence indicates that either the inhibition of 5aR or the inhibition of the binding of DHT to AR reverses the symptoms of BPH in human males.

The effective drugs, finasteride as a 5aR inhibitor and flutamide as a binding inhibitor to AR are utiliezed clinically for treatment of BPH. Alternatively functional foods are eclectic selection as dietary approaches to prevent BPH in middle-aged men. Natural products are frequently used to care BPH in preference to therapeutic agents that can cause severe side-effects. Plant extracts such as the lipid extracts of saw palmetto berry extract (SPE) have also been found to reduce the conversion of testosterone (T) to dihydrotestosterone (DHT) by inhibiting 5alpha-reductase (5aR) both in vitro and in vivo (Elliot, 2001). However, few products of natural origin besides SPE are believed to be effective against enlargement of the prostate. The scientifically-proven food materials are expected to be of benefit for prevention of BPH.

In our preliminary study, the suppressive effects of natural food materials have been found in BHT model mice. We introduce here the suppressive effects against BHT of two materials, i.e., “banana peel” and “leaf of *Houttuynia cordata*”. The effects of these materials in the androgen-responsive LNCaP human prostate cancer cell line and in effects of BHT model mice were examined. These data presented here demonstrate that these materials inhibit the growth of the prostate and HCE has anti-androgenic activity.

2. Experimental

2.1 Drugs and chemicals

The chemicals used and their sources were as follows: testosterone propionate and dihydrotestosterone from Wako Pure Chemical Industries (Osaka, Japan); flutamide from

Sigma–Aldrich Japan (Tokyo); finasteride from LKT Labs. (St. Paul, MN); and pentobarbital from Dainippon Sumitomo Pharma (Osaka, Japan). Other chemicals were of analytical grade.

2.2 Animal experiments

Male ddY mice (6-8 weeks of age) were purchased from SLC Inc., Shizuoka, Japan. The room was maintained at 24±1°C and 50±10% humidity under a 12 h light/dark cycle (lights on from 8:00 AM to 8:00 PM), and the animals had free access to water and food. Animal studies were conducted according to the 2006 guidelines entitled Notification No. 88 of the Ministry of the Environment in Japan and Guidelines for Animal Experimentation of Tokyo University of Marine Science and Technology with the approval of the Animal Care and Use Committee of Tokyo University of Marine Science and Technology.

2.3 Growth suppression of mouse prostates and seminal vesicles in testosterone-induced BPH model mice

Assay of growth suppression in castrated mouse prostates and seminal vesicles was performed based on the OECD protocol. (Yamasaki et al., 2003) The testes of ddY mice were removed at 7 weeks of age under anesthesia by intraperitoneal injection of pentobarbital (50 mg/ml/kg). After 1 d, testosterone propionate (TP) was injected intraperitoneally into the mice once daily for 10 d. Enlargement of the reproductive organs in the mice was demonstrated dose-dependently due to TP in our preliminary studies as shown in Fig. 1A. The growth of these organs is androgen-dependent (Franck-Lissbrant et al., 1998).

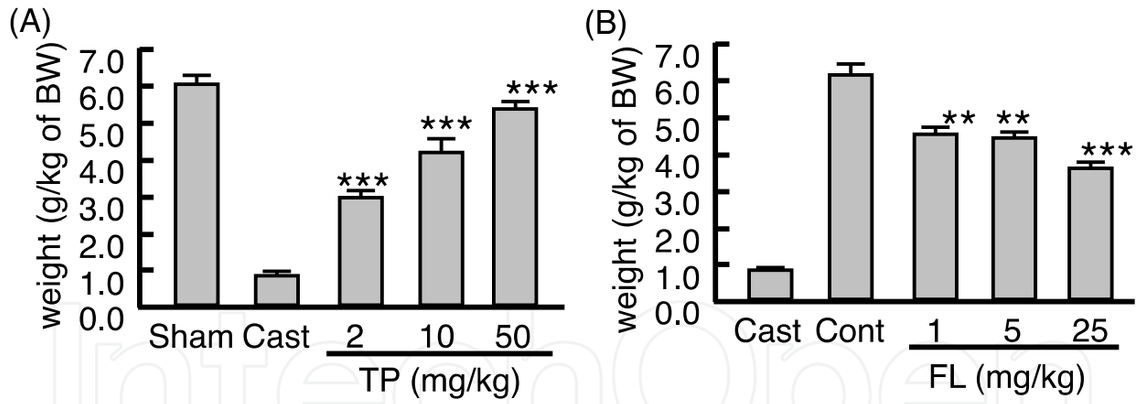


Fig. 1. TP-induced regrowth of seminal vesicles (A) and its suppressive effects by flutamide (B) in castrated mice

Testosterone propionate (TP; 2, 10, and 50 mg/kg) was injected i.p. into castrated mice (7-weeks-old) once daily for 10 days. Flutamide (1, 5, and 25 mg/kg) suspended in 1% ethanol and orally administered once daily. The seminal vesicles were removed and weighed and compared with castrated mice as a control. Cast: castrated control, Cont: control (TP-treated), and FL: flutamide. Each value represents the mean ± S.E., n=5. **: p<0.01,***: p<0.005 *vs* control.

To evaluate the effects on reproductive organs, each of various doses of sample extract was suspended in 1% ethanol and orally administered to the BPH model mice once daily. After 10 d, the mice were weighed, and sacrificed by cervical dislocation. The lengths of the short

and long axes of the prostates were then measured with vernier calipers, and the seminal vesicles were removed and weighed. In particular, the weights of the seminal vesicles were sensitive to androgenic effects in our mice model. Finasteride (FI, 2 mg/kg) and flutamide (FL, 10 mg /kg) were used as positive control for the assay system. As shown in Fig. 1B, orally administration of flutamide suppressed weight of the seminal vesicles in BPH model mice with dose dependent manner (1-25 mg/kg/day) for 10 d.

2.4 Cell culture and growth studies of human prostate cancer cells

The LNCaP human prostate cancer cell line is a well-established androgen-dependent cell line. (Goldman et al., 2004) AR-positive human prostate cancer LNCaP cells were obtained from the Riken BRC Cell Bank (Tsukuba, Japan). The cells were plated onto a 96-well plate at a density of 2×10^5 /well and supplemented with 10% charcoal stripped fetal bovine serum (CSFBS) obtained from Invitrogen Japan (Tokyo). Twenty-four h later, the cells were treated with either vehicle control or androgens (T or DHT) in the presence and the absence of each concentration of assessed samples for another 3 d. Sample was dissolved in ethanol and added to the cells after further dilution so that the final volume of ethanol was 1% or less. After culture, cell proliferation was determined to measure cell viability by 3-[4,5-dimethyl thiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) assay. (Hamid et al., 2004) The cells were treated with 1 mg/ml of MTT for 2 h, and precipitated dye was dissolved into dimethylsulfoxide. The absorbance of each well was measured at 570 nm.

2.5 Statistical analysis

Data were analyzed statistically by Student's *t*-test to determine significant differences in the data among the groups. The *p* values less than 0.05 were considered significant. The values were expressed as mean ± S.E.

3. Banana peel

Fig. 2. Banana peel extract (BPEx) prepared from fresh peel part from organically-cultivated bananas showed suppressive effects for enlargement of prostate in BPH model mice

3.1 Source material

The common banana (Musa spp.) is a tropical fruit that grows in the western hemisphere. Primarily viewed as a food source, the banana has a fleshy inside portion surrounded by an outer typically yellow peel (Fig. 2). The fleshy inside portion, or pulp, is edible when raw, and the peel is usually discarded. When ripe, bananas have a deep yellow rind with brown spots, and a creamy pulp, which is easily digested. Bananas are rich in carbohydrates and contain relatively large amounts of vitamins A, B and C and the minerals potassium and phosphorous (Proteggente et al., 2002; Blades et al., 2003). However, banana peel has not been studied nutritionally and pharmaceutically as a source of bioactive compounds. In this report, we examined the effects of banana peel extract (BPEx) on androgen-induced enlargement of accessory reproductive organs in castrated mice. To elucidate the mechanisms of action, the effects of BPEx on the androgen-responsive LNCaP human prostate cancer cell line were investigated. The data presented here indicate that BPEx inhibits growth of the prostate and that BPEx has anti-androgenic activity through inhibition of 5aR.

Fresh banana peel (2.4 kg) of organically-cultivated bananas were cut and extracted with methanol at room temperature for 2 days. The extracts were filtered, concentrated under a vacuum, and freeze-dried. BPEx (56 g) was stored in a refrigerator before assay.

3.2 Suppressive effect of benign prostate hyperplasia in mouse

Our research group has been shown that BPEx treatment (10 d of administration at 0, 50, 100, and 200 mg/kg per orally) dose-dependently reduced the prostate size and the weights of seminal vesicles in the BPH model mice. Then, the effects of BPEx on the growth of mouse prostates and seminal vesicles were studied as compared with those of flutamide and finasteride in the BPH model mice for 10 d. The short and long axes of the ventral prostates and the weights of the seminal vesicles were severely reduced, and when TP (2 mg/kg i.p.) was injected, significant growth of prostates and seminal vesicles was induced. BPEx (200 mg/kg) produced a reduction in prostate weight. Finasteride (2 mg/kg) and flutamide (10 mg/kg), well-known anti-androgens, showed larger reductions in prostate weight. Similar results were observed with regard to seminal vesicle weights. When DHT (6 mg/kg, i.p.) was injected in place of T, significant growth of the prostate and seminal vesicles was induced. BPEx did not inhibit these effects of DHT (Akamine, 2009). These results indicate that orally treatment of BPEx suppress the action of testosterone against enlargement of the reproductive organs in vivo.

3.3 Effects of parts of banana fruit on mouse prostate and seminal vesicles

Testosterone propionate (TP, 2 mg/kg, i.p.) and sample solution (p.o.) were treated to castrated mice once daily for 10 d (Fig. 3). The lengths of the long axes (A) of the prostates of mice were measured vernier calipers, and seminal vesicles (B) were removed and weighed. Cast, castration only; Cont, control; Pe, banana peel (200 mg/kg); Ed, edible part (200 mg/kg). Each value represents the mean ± S.E., n=5. *: p<0.05; **: p<0.01 *vs*. control (TP-treated without samples).

Fresh banana fruits separated into two parts, peel and edible part to evaluate suppressive effects of the extracts (“Pe” and “Ed”, respectively) on BPH model mice. The inhibitory effects of BPEx on the growth of mouse prostates and seminal vesicles were estimated after 10 d of administration. BPEx dose-dependently reduced the prostate size and the weights of

seminal vesicles, and showed almost maximal effect at 200 mg/kg. These results indicate that some components in banana peel will be required to suppress prostate enlargement in this model.

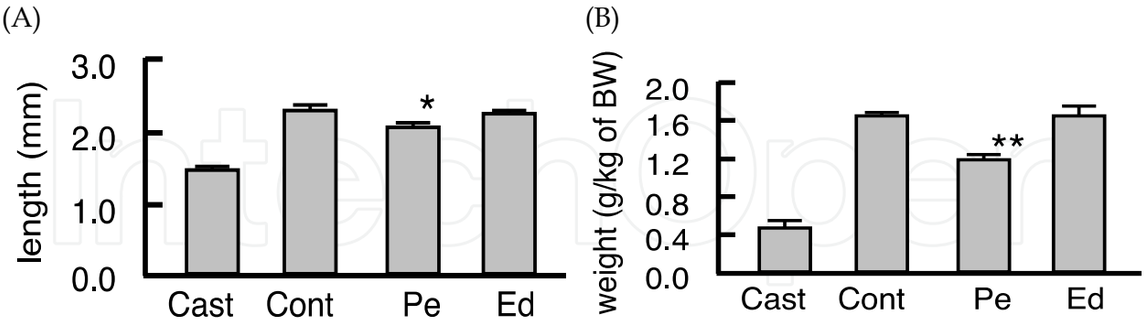


Fig. 3. Effects of extracts of peel (Pe) and edible part (Ed) of banana fruit on TP-induced regrowth of prostates and seminal vesicles in castrated mice

3.4 Inhibitory effects of BPEx on prostate cancer cells

The effects of BPEx on the proliferation of prostate cancer cells (LNCaP cells) were investigated. LNCaP cells show most of the characteristics of human prostatic carcinoma, such as dependence on androgens, the presence of ARs, and the production of acid phosphatase and prostate-specific antigen. The LNCaP cell line is used as an attractive model for in vitro studies of the biology of human prostate cancer. LNCaP cells were incubated with different concentrations of BPEx (3.13–100 μg/ml) with and without T or DHT for 3 d. In the absence of BPEx, T alone stimulated LNCaP cell number about 20.5 ± 0.5 x 10^5 /well, and DHT alone stimulated LNCaP cell numbers to about 30.4 ± 2.1 x 10^5 /well.

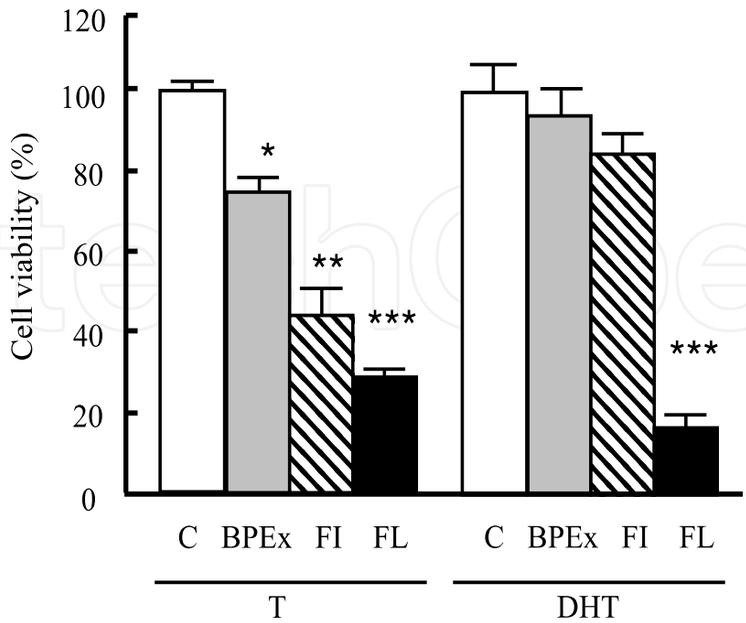


Fig. 4. Inhibitory effects of BPEx on the proliferation of LNCaP cells induced by testosterone (T) or dihydrotestosterone (DHT)

Treatment of LNCaP cells with BPEx in the presence of T resulted in dose-dependent inhibition of cell growth. In the presence of T, both finasteride and flutamide inhibited cell proliferation. However, in the presence of DHT, while flutamide inhibited cell proliferation, finasteride did not. These results indicate that BPEx will suppress on T did not affect on DHT in vivo and in vitro experiments. Fig. 4 showed the inhibitory effects of anti-androgenic samples at 25 μg/ml on LNCaP cells. Scince BPEx showed similar profile with that of FI and not FL, BPEx was estimate to inhibit BPH by its inhibitory activity against 5aR.

Proliferation of prostate cancer cells (LNCaP) were evaluated cell viability (% of control) by MTT assay after 3 days incubation with or without samples at 25 μg/ml in the presence of testosterone (T: 10 mg/ml) or dihydrotestosterone (DHT: 10 mg/ml). BPEx: banana peel extract; FI: finasteride; FI: flutamide. Each data presents as mean±S.E. (n=4).

4. Leaf of *Houttuynia cordata*

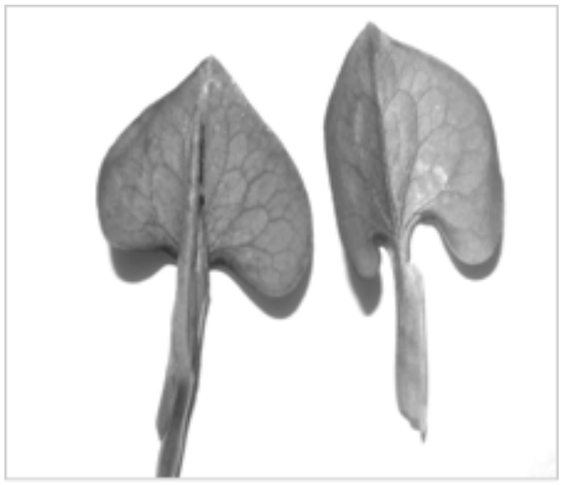


Fig. 5. *Houttuynia cordata* extract (HCE) prepared from fresh leaf part showed suppressive effects for enlargement of prostate in BPH model mice

4.1 Source material

Houttuynia cordata Thunb., which is called dokudami in Japanese, is widely distributed in eastern Asia, and it has a thin leafstalk and heart-shaped leaf (Fig. 5). It is used in folk medicine for diuresis and detoxification. Thus far, it has been reported that *H. cordata* contains many flavonoids (quercitrin, isoquercitrin, rutin, etc.), alkaloids (aristolactam B, norcepharadione B, splendidine, etc.), and volatile components of essential oils (methyl-n-nonyl ketone, lauraldehyde, β-myrcene, etc.) (Meng et al., 2005; Kim et al., 2001; Xu et al., 2005). The extracts and components exhibit diuretic, anti-obesity (Miyata et al., 2009), antioxidative (Kusirisin et al., 2009), antibacterial (Kim et al., 2008), anti-inflammatory (Lu et al., 2006), and apoptotic effects (Tang et al., 2009). The effects for benign prostate hyperplasia (BPH) of this material have been not investigated.

The fresh *Houttuynia cordata* were cut and extracted with 99.5% methanol at room temperature for 2 days. The extract were filtered, and concentrated under a vacuum. The extract was stored in the refrigerator before assay.

We examined the effects of *H. cordata* extract (HCE) in the androgen-responsive effects in BPH model mice and LNCaP human prostate cancer cell line. The data presented here demonstrate that HCE inhibits the growth of the prostate with anti-androgenic activity.

4.2 Suppressive effect of benign prostate hyperplasia in mouse

Testosterone propionate (TP, 2 mg/kg, i.p.) and sample solution (p.o.) were treated to castrated mice once daily for 10 d. The seminal vesicles were removed and weighed. Cast, castration only; Cont, TP treated control; HCE: *Houttuynia cordata* extract (20, 100, and 500 mg/kg). Each data presents as mean±S.E., n=6, *: p<0.05, **: p<0.01, ***: p<0.005 vs control (Cont) as shown in Fig. 6.

The suppressive effects of HCE on reproductive organs were investigated in testosterone-induced BPH model mice. The assay to evaluate the effects of HCE on castrated mice prostates and seminal vesicles was performed based on the Hershberger assay as a mean of rapidly developing in vivo. The testes of ddY mice were removed at 7 weeks of age under anesthesia with intraperitoneal injection of pentobarbital (50 mg/ml/kg). After one day of orchiectmy, testosterone propionate (TP) 2 mg/kg was injected intraperitoneally (i.p.) into the mice once daily for 10 days. HCE was administered once daily. After 10 days, mice were weighted and sacrificed by cervical dislocation. The lengths of the long axes of prostate were measured by vernier calipers, and seminal vesicles were removed and weighed.

As shown in Fig. 6, HCE suppress prostates and seminal in a dose-dependent manner at 20, 100, and 500 mg/kg.

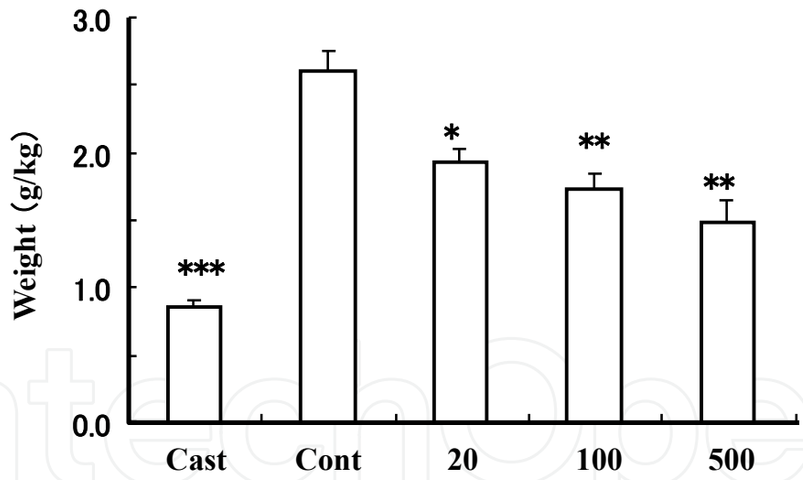


Fig. 6. Effects of extracts of HCE on TP-induced regrowth of prostates and seminal vesicles in castrated mice

In the further experiments, the suppressive effects of HCE were compared with flutamide (FL, 10 mg/kg/day) and finasteride (FI, 2 mg/kg/day) in BPH model mice. As shown in Fig. 7, the size of long-axis length of prostates (A) and the weight of seminal vesicles (B) were severely reduced by HCE ingestion, and when T was injected, a significant growth of prostates and seminal vesicles was induced. Flutamide and finasteride are well known anti-androgen drugs, showed a larger reduction in prostate and seminal vesicle. HCE showed suppressive effect on reproductive organs as same as these medicine at these experimental conditions.

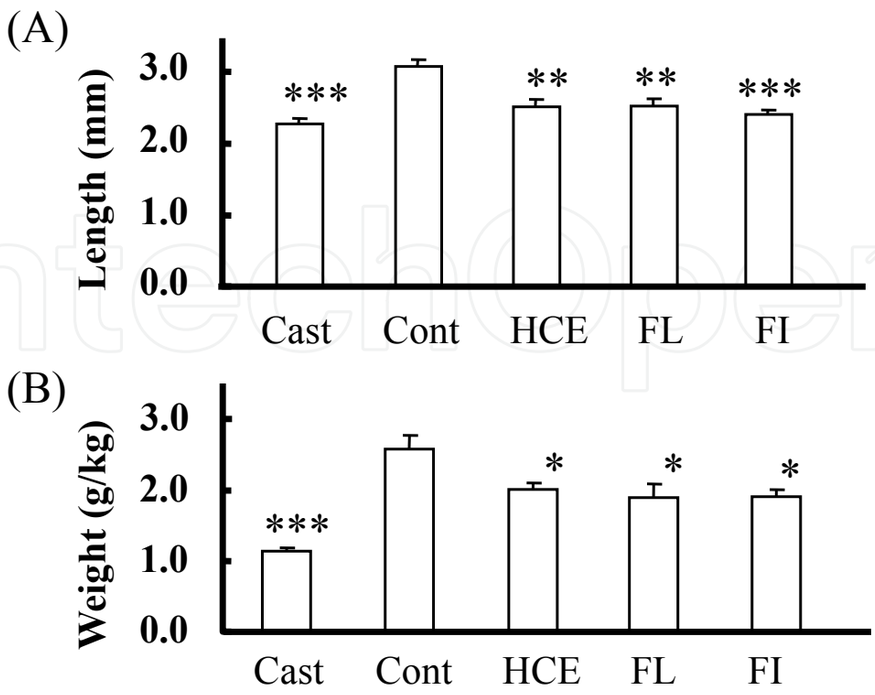


Fig. 7. Evaluation of HCE on T-induced regrowth in castrated mouse prostates and seminal vesicles. (A) long-axis length of prostates, (B) weight of seminal vesicles.

Testosterone propionate (TP, 2 mg/kg, i.p.) and sample solution (p.o.) were treated to castrated mice once daily for 10 d. The lengths of the long axes (A) of the prostates of mice were measured vernier calipers, and seminal vesicles (B) were removed and weighed. Cast: Castration without T-treatment (50 mg/kg, i.p.), Cont: Control, HCE: *H. cordata* extract (100 mg/kg), FI : Finasteride 2 mg/kg, FL: Flutamide 10 mg/kg. Each value represents the means±S.E., n=5. *:p<0.05, **:p<0.01, ***:p<0.005 vs Control.

4.3 Inhibitory effects of HCE on LNCaP cells

The effects of HCE on the proliferation of prostate cancer cells (LNCaP cells) were investigated. After incubation, the cell numbers in T-treated and DHT-treated groups were defined as 100%. As shown in Fig. 8 finasteride, 5aR inhibitor, showed dose-dependent inhibition in T-treated and DHT-treated LNCaP cells. However, its inhibitory effects on DHT-treated group are relatively weak. In contrast, flutamide, androgen receptor antagonist, showed inhibition both in T alone and DHT alone groups at the similar concentrations. On the other hand, the treatment of HCE to LNCaP cells in the presence of T and DHT resulted in the concentration-dependent inhibition of cell proliferation at the same concentrations as same as case of flutamide treatment. These results indicate that HCE suppress enlargement of prostate with a different mechanism with finasteride, 5aR inhibitor. Proliferation of prostate cancer cells (LNCaP) were evaluated cell viability (% of control) by MTT assay after 3 days incubation with or without samples at 6.25, 25, 100 μg/ml in the presence of testosterone (T: 10 mg/ml) or dihydrotestosterone (DHT: 10 mg/ml). HCE: *Houttuynia cordata* extract; FI: finasteride; FI: flutamide. Each data presents as mean±S.E. (n=4).

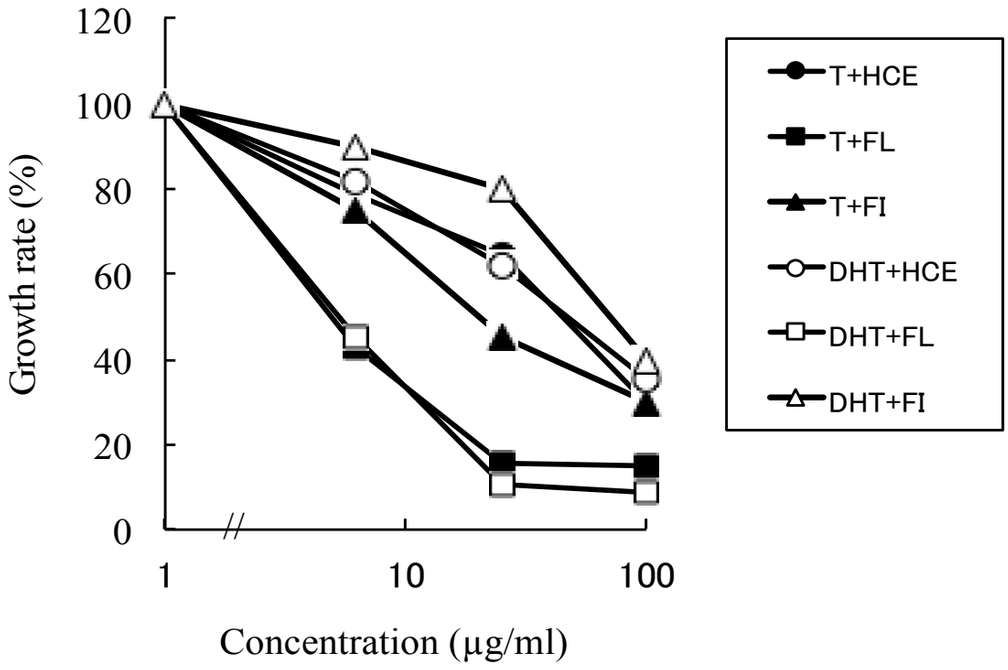


Fig. 8. Inhibitory effects of HCE, Flutamide (FL), and Finasteride (FI) on LNCaP cell proliferation in the presence of testosterone (T) or dihydrotestosterone (DHT). Each point shows the mean of the separated duplicate experiments.

5. Discussion

We studied the in vivo potency of BPEx and HCE, as new botanical materials in immature castrated mice. We evaluated these biological effects in the androgen-responsive LNCaP human prostate cancer cell line and in effects of BHT model mice.

BPEx inhibited TP-induced growth of prostates and seminal vesicles in castrated mice, although it was less potent than finasteride at the same doses. While BPEx inhibited the action of TP, it did not inhibit DHT-induced organ growth. In addition, BPEx inhibited cell proliferation in the presence of T, but not in the presence of DHT. These results suggest that BPEx suppressed the growth of prostates and seminal vesicles by inhibiting the conversion of T to DHT, rather than by blocking the binding of androgen and its receptor. BPEx may have reduced prostate size and seminal vesicle weight by inhibiting 5aR. In further study, we found that treatment of LNCaP cells with BPEx inhibited T-induced cell proliferation (Akamine et al., 2009). The inhibition of this effect of T might have be due, at least in part, to inhibition of 5aR or to antagonism of androgen binding to the AR (Lazier et al., 2004). Since 25 μg/ml of BPEx inhibited 5aR activity by about 30%, we expected to find that this dose would inhibit T action. Similar results have been found with finasteride, a well-known inhibitor of 5aR (McConnell et al., 1992; Sudduth & Koronkowski, 1993), at doses above 25 μg/ml. Similar results were also found with flutamide, an antagonist of androgen binding to the AR (Bergman, & Eriksson, 1996; Sundblad et al., 2005). On the other hand, treatment of LNCaP cells with BPEx in the

presence of DHT did not result in a dose-dependent inhibition of cell growth. These results suggest that inhibition of cell growth in the presence of BPEx was not the result of a cell cytotoxic effect, but rather was due to an anti-androgen effect, such as inhibition of 5aR. According to a previous report describing discrimination between cytotoxic and cytostatic effects of integrants on LNCaP cells (Romijn et al., 1988), cytotoxic effects are detectable as a decrease in MTT conversion to a level below that of the starting cells. In our experiment, growth of androgen-induced LNCaP cells was suppressed without decreasing from the starting level in the presence of BPEx during the experimental period. Therefore, a cytostatical effect was estimated for suppression of BPEx on LNCaP cell growth. However, since no index markers related to apoptotic signaling were measured in our experiments, the possibility of a non-cytostatical effect should be considered and confirmed in further detailed investigation. There are generally two ways to suppress prostate regrowth in animal experiments: by inhibiting 5aR activity, and through the use of an androgen receptor antagonist (Imperato-McGinley et al., 1992). An androgen antagonist can suppress DHT-induced prostate and seminal vesicle regrowth (Geller et al., 1981) Therefore, blocking DHT from binding to androgen receptors in the prostate and seminal vesicle is considered to be a possible mechanism of action (other than 5aR inhibition) (Nakayama et al., 1997). To examine this possibility, the effects of BPEx on prostate growth induced by DHT were investigated. If the suppression of prostate growth is caused only by inhibition of 5aR, DHT-induced prostatic regrowth should not be suppressed. Ten d after castration, the weights of mouse prostates were markedly reduced, and prostate size was restored by i.p. injections of TP or DHT. BPEx had no effect on the sizes of the prostate and seminal vesicle of castrated mice that received DHT, whereas flutamide, an androgen receptor antagonist, significantly reduced prostate weight (Fig. 3). In our study, blood levels of testosterone and samples were not measured, but in vivo and in vitro experiments gave mutually correlated results with regard with their mechanism of action. These results suggest that BPEx inhibited prostate growth by inhibiting 5aR activity rather than by exerting a direct effect on the androgen receptor, although the detailed mechanism including bioavailability remains unclear. Recently, there is research reports on components of the banana peel: dietary fiber and pectin (Happi Emaga et al., 2008), and phytosterol from unripe pulp and peel (Oliveira et al., 2008) have been reported. In particular, phytosterols are able to be the active principle in BPEx, due to their anti-androgen activity based on structural similarity. Investigation to elucidate the active components in banana peel is in progress. In this study, we found that BPEx can have anti-androgenic activities through in vitro 5aR inhibitory activity and in vivo growth suppression of prostates and seminal vesicles from castrated mice.

In this study, we have shown that HCE inhibited the T-induced growth of prostates and seminal vesicles in castrated mice and that HCE inhibited T- and DHT-induced cell proliferation in NLCaP cells at the same concentration. The inhibition of this effect of T may be due, at least in part, to the inhibition of 5aR or to antagonism of androgen binding to the AR. And treatment of LNCaP cells with HCE in the presence of DHT result in the dose-dependent inhibition of cell growth. These results were seen with flutamide, which is an antagonist of androgen binding to the AR. These results suggested that the inhibition of cell proliferation in the presence HCE was not the result of a cell cytotoxic effect, but rather was

due to an anti-androgen effect, such as inhibition of AR. These results suggest that HCE suppressed the growth of prostates and seminal vesicles by blocking the binding to AR, rather then by conversion of T to DHT. HCE may have reduced prostate size and seminal vesicle weight by blocking the binding of androgen and its receptor.

There are generally two ways to suppress prostate regrowth in animal experiments: by inhibiting 5aR activity and by blocking the binding of androgen and its receptor. An androgen antagonist can suppress DHT-induced prostate and seminal vesicle regrowth. Therefore, blocking DHT from binding to androgen receptors in the prostate and seminal vesicle was considered to be possible mechanism of action (other than 5aR inhibition) of the extract of HCE. To examine this possibility, the effects of HCE on LNCaP cells growth induced by DHT were investigated. These results suggest that HCE inhibited prostate growth by inhibiting androgen receptor rather than by having a direct effect on the 5aR, although the detailed mechanism unclear. In this study, we found that HCE may have anti-androgenic activities through in vitro androgen binding to the AR and in vivo growth suppression of prostate and seminal vesicles from castrated mice. Active compounds showing anti-androgen activity in HCE are of scientific interest. Since, the clinical implications of this activity are currently unknown, further research is needed before is needed before HCE can for the treatment of BPH.

For several years, SPEx has been used as a popular phytotherapeutic agent in the treatment of BPH, but its active component and mechanism of action have not been fully elucidated (Hill & Kyprianou, 2004). Banana peel is usually considered useless and is discarded, but the anti-androgenic activity of BPEx might be useful in the treatment of BPH patients. And leaf of H. cordata have been used as folk medicine, however, never used for treatment BPH with suppressive effect of androgenic functions. Since the clinical implications of this activity are currently unknown, further research is needed before BPEx can be used in the treatment of BPH.

6. Conclusion

In this chapter, the androgen-responsive effects of the two natural extracts from banana peel extract (BPEx) and leaf of *H. cordata* extract (HCE) were shown in BPH model mice and LNCaP human prostate cancer cell line. The data presented here revealed that BPEx was estimated to inhibit the growth of the prostate in BPH model mice by its inhibitory activity against 5-alpha reductase (5aR). And HCE was estimated to inhibit BPH in mice by its anti-androgenic activity different from 5aR inhibition. Therefore, these new botanical materials can be promising most likely candidates as potential material for preventing benign prostate hyperplasia, and it is able to continue to be one of the best preventive medicinal foods to keep our good health in the future.

7. References

Akamine, K.; Koyama, T. & Yazawa, K. (2009) Banana peel extract suppresses prostate gland enlargement in testosterone-treated mice. *Biosci. Biotech. Biochem*. Vol. 73, No. 9, pp. 1911-1914, ISSN: 0916-8451

Bergman, L. & Eriksson, E. (1996) Marked symptom reduction in two women with bulimia nervosa treated with the testosterone receptor antagonist flutamide. *Acta Psychiatrica Scandinavica*, Vol. 94, pp. 137-139, ISSN: 0001-690X

Blades, B. L.; Dufficy, L.; Englberger, L.; Daniells, J. W.; Coyne, T.; Hamill, S. & Wills, R. L. (2003) Bananas and plantains as a source of provitamin A. *Asia Pac J Clin Nutr.*, Vol. 12, pp. S36, ISSN: 0964-7058

Cristoni A.; Di Pierro F. & Bombardelli E. (2000). Botanical derivatives for the prostate. *Fitoterapia*, Vol. 71, pp. S21-S28, ISSN: 0367-326X

Elliot, F. & Franklin, C. L. (2001) Saw Palmetto Berry as a Treatment for BPH. *Rev Urol.*, Vol. 3, pp. 134-138, ISSN: 1523-6161

Franck-Lissbrant, I.; Haggstom, S.; Damber, J. E. & Bergh, A. (1998) Testosterone stimulates angiogenesis and vascular regrowth in the ventral prostate in castrated adult rats. *Endocrinology*, Vol. 139, pp. 451-456, ISSN: 0013-7227

Geller, J.; Albert, J. & Nachtsheim, D. A. (1981) The effects of flutamide on total DHT and nuclear DHT levels in the human prostate. *Prostate*, Vol. 2, pp. 309-314, ISSN: 0270-4137

Goldman, W. H.; Sharma, A. L.; Currier, S. J.; Johnston, P. D.; Rana, A. & Sharma, C. P. (2004) Saw palmetto berry extract inhibits cell growth and Cox-2 expression in prostatic cancer cells. *Cell Biol Int.*, Vol. 25, pp. 1117-1124, ISSN:1065-6995

Happi Emaga, T.; Robert, C.; Ronkart, S. N.; Wathelet, B. & Paquot, M. (2008) Dietary fibre components and pectin chemical features of peels during ripening in banana and plantain varieties. *Bioresour Technol.*, Vol. 99, pp. 4346-4354, ISSN: 0960-8524

Hamid, R.; Rotshteyn, Y.; Rabadi, L.; Parikh, R. & Bullock, P. (2004) Comparison of alamar blue and MTT assays for high through-put screening. *Toxicology in Vitro*, Vol. 18, pp. 703-710, ISSN: 0887-2333

Hill, B. & Kyprianou, N. (2004) Effect of permixon on human prostate cell growth: Lack of apoptotic action. *Prostate*, Vol. 61, pp. 73-80, ISSN: 0270-4137

Imperato-McGinley, J.; Sanchez, R. S.; Spencer, J. R.; Yee, B. & Vaughan, E. D. (1992) Comparison of the effects of the 5 alpha-reductase inhibitor finasteride and the antiandrogen flutamide on prostate and genital differentiation: dose-response studies. *Endocrinology*, Vol. 131, pp. 1149-1156, ISSN: 0013-7227

Kim, G. S.; Kim, D. H., Lim, J. J., Lee, J. J.; Han, D. Y.; Lee, W. M.; Jung, W. C.; Min, W. G., Won, C. G.; Rhee, M. H.; Lee, H. J. & Kim, S. (2008). Biological and antibacterial activities of the natural herb *Houttuynia cordata* water extract against the intracellular bacterial pathogen salmonella within the RAW 264.7 macrophage. *Biol Pharm Bull,* Vol. 31, 2012-2017, ISSN: 0918-6158

Kim, S. K.; Ryu, S. Y.; No, J.; Choi, S. U.; & Kim, Y. S. (2001). Cytotoxic alkaloids from *Houttuynia cordata*. *Arch Pharm Res,* Vol. 24, 518-521, ISSN: 0253-6269

Kusirisin, W; Srichairatanakool, S.; Lerttrakarnnon, P.; Lailerd, N.; Suttajit, M.; Jaikang, C. & Chaiyasut, C. (2009). Antioxidative activity, polyphenolic content and anti-glycation effect of some Thai medicinal plants traditionally used in diabetic patients. *Med Chem,* Vol. 5, No. 2, pp. 139-147, ISSN: 1573-4064

Lu, H. M.; Liang, Y. Z.; Yi, L. Z.; Wu, X. J. (2006). Anti-inflammatory effect of *Houttuynia cordata* injection. *J Ethnopharmacol,* Vol. 104, 245-249, ISSN: 0378-8741

Lazier, C. B.; Thomas, L. N.; Douglas, R. C.; Vessey, J. P. & Rittmaster, R. S. (2004) Dutasteride, the dual 5 alpha-reductase inhibitor, inhibits androgen action and promotes cell death in the LNCaP prostate cancer cell line *Prostate*, Vol. 58, pp. 130-144, ISSN: 0270-4137

Lowe, F. C.; McConnell, J. D.; Hudson, P. B.; Romas, N.A.; Boake, R.; Lieber, M.; Elhilali, M.; Geller, J.; Imperto-McGinely, J.; Andriole, G. L.; Bruskewitz, R. C.; Walsh, P. C.; Bartsch, G.; Nacey, J. N.; Shah, A.; Pappas F.; Ko, A.; Cook, T.; Stoner, E. & Waldstreicher, J. (2003) Long-term 6-year experience with finasteride in patients with benign prostatic hyperplasia. *Urology* Vol. 61, pp. 791-796. ISSN: 0090-4295

Marks. L. S. (2004) 5alpha-reductase: history and clinical importance. *Rev Urol*. Vol. 6, pp. S11-S21, ISSN: 1523-6161

McConnell, J. D.; Wilson, J. D.; George, F. W.; Geller, J.; Pappas, F.; Stoner, E. (1992) Finasteride, an inhibitor of 5 alpha-reductase, suppresses prostatic dihydrotestosterone in men with benign prostatic hyperplasia. *Journal of Clinical Endocrinology and Metabolism*, Vol. 74, No. 3, 505-508, ISSN: 0021-972X

Meng, J.; Leung, K. S.; Jiang, Z.; Dong, X.; Zhao, Z. & Xu, L. J. (2005). Establishment of HPLC-DAD-MS fingerprint of fresh *Houttuynia cordata*. *Chem Pharm Bull,* Vol. 53, 1604-1609, ISSN:

Miyata, M.; Koyama, T. & Yazawa, K. (2010). Water extract of *Houttuynia cordata* Thunb. leaves exerts anti-obesity effects by inhibiting fatty acid and glycerol absorption. *J Nutr Sci Vitaminol,* Vol. 56, No. 2, 150-156, ISSN: 0301-4800

Nakayama, O.; Hirosumi, J.; Chida, N.; Takahashi, S.; Sawada, K.; Kojo, H. & Notsu, Y. (1997) FR146687, a novel steroid 5 alpha-reductase inhibitor: In vitro and in vivo effects on prostates. *Prostate*, Vol. 31, pp. 241-249, ISSN: 0270-4137

Oliveira, L.; Freire, C.S.; Silvestre, A. J. & Cordeiro, N. (2008) Lipophilic extracts from banana fruit residues: a source of valuable phytosterols. *J Agric Food Chem*. Vol. 56, pp. 9520-9524, ISSN: 0021-8561

Proteggente, A. R.; Pannala, A. S.; Paganga, G.; Van Buren, L.; Wagner, E.; Wiseman, S.; Van De Put, F.; Dacombe, C. & Rice-Evans, C. A. (2002) The antioxidant activity of regularly consumed fruit and vegetables reflects their phenolic and vitamin C composition. *Free Radic Res*., Vol. 36, pp. 217-233, ISSN: 1071-5762

Romijn, J. C.; Verkoelen, C. F. & Schroeder, F. H. (1988) Application of the MTT assay to human prostate cancer cell lines in vitro: establishment of test conditions and assessment of hormone-stimulated growth and drug-induced cytostatic and cytotoxic effects. *Prostate,* Vol. 12, pp. 99-110, ISSN: 0270-4137

Russell, D. W. & Wilson J. D. (1994). Steroid 5 alpha-reductase: two genes/two enzymes. *Annual Review of Clinical Biochemistry*, Vol 63, pp. 25-61, PMID: 7979239

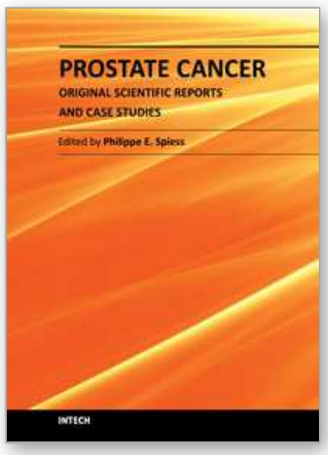
Sudduth, S. L. & Koronkowski, M. J. (1993) Finasteride- The first 5-alpha-reductase inhibitor. *Pharmacotherapy*, Vol. 13, pp. 309-329, ISSN 0277-0008

Sundblad, C.; Landen, M.; Eriksson, T.; Bergman, L. & Eriksson, E. (2005) Effects of the androgen antagonist flutamide and the serotonin reuptake inhibitor citalopram in bulimia nervosa: a placebo-controlled pilot study. *Journal of Clinical Psychopharmacology*, Vol. 25, pp. 85-88, ISSN: 0271-0749

Tang, Y. J.; Yang, J. S.; Lin, C. F.; Shyu, W. C.; Tsuzuki, M.; Lu, C. C.; Chen, Y. F. & Lai, K. C. (2009). *Houttuynia cordata* Thunb extract induces apoptosis through mitochondrial-dependent pathway in HT-29 human colon adenocarcinoma cells. *Oncol Rep,* Vol. 22, 1051-1056, ISSN: 1523-3790

Xu, C. J.; Liang, Y. Z.; Chau, F. T. (2005). Identification of essential components of *Houttuynia cordata* by gas chromatography/mass spectrometry and the integrated chemometric approach. *Talanta,* Vol. 68, 108-115, ISSN: 0039-9140

Yamasaki, K.; Sawaki, M.; Ohta, R.; Okuda, H.; Katayama, S.; Yamada, T.; Ohta, T.; Kosaka, T. & Owens, W. (2003) OECD validation of the Hershberger assay in Japan: Phase 2 dose response of methyltestosterone, vinclozolin, and *p,p'*-DDE. *Environ Health Perspect*, Vol. 111, pp. 1912-1919, ISSN: 0091-6765



Prostate Cancer - Original Scientific Reports and Case Studies
Edited by Dr. Philippe E. Spiess

ISBN 978-953-307-342-2
Hard cover, 238 pages
Publisher InTech
Published online 21, November, 2011
Published in print edition November, 2011

This book encompasses three sections pertaining to the topics of cancer biology, diagnostic markers, and therapeutic novelties. It represents an essential resource for healthcare professionals and scientist dedicated to the field of prostate cancer research. This book is a celebration of the significant advances made within this field over the past decade, with the hopes that this is the stepping stone for the eradication of this potentially debilitating and/or fatal malignancy.

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen